Gemelli

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Le polmoniti dei pazienti immunocompromessi

Livio Pagano

UOC di Ematologia Geriatrica ed Emopatie Rare

Roma

Sorveglianza Epidemiologica Infezioni Fungine nelle Emopatie Maligne

EHA EUROPEAN HEMATOLOGY ASSOCIATION

ECL

ECMM

EORTC The future of cancer therapy

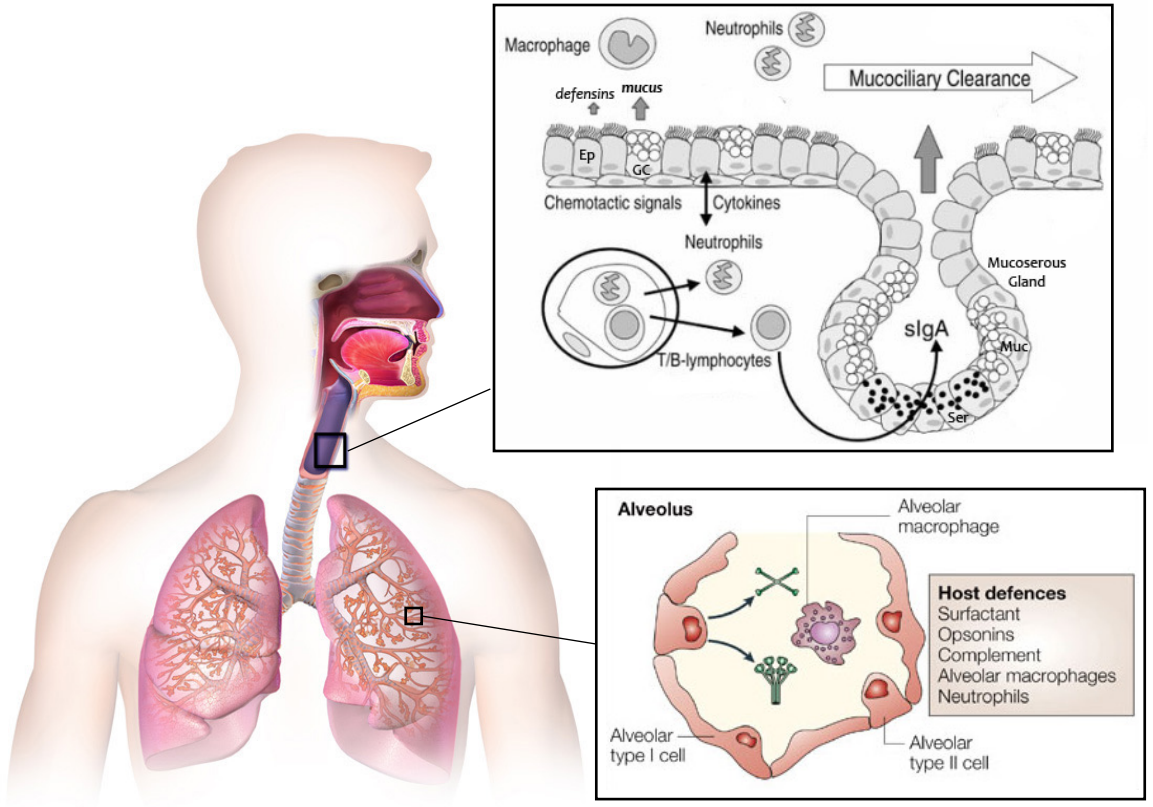
fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

Invited Speaker – Consultant – Research grants

PNEUMONIA

Microbes constantly enter airways but many factors prevent colonization:

- mucous entrapment
- ciliary clearance
- immune surveillance
- intact epithelial barrier
- secreted factors such as:
  - secretory IgA
  - surfactant proteins (SP-a, SP-d)
  - defensins



Disrupting or overwhelming these defense mechanisms can allow microbes to colonize the lungs, resulting in PNEUMONIA

Pathogenesis and manifestations

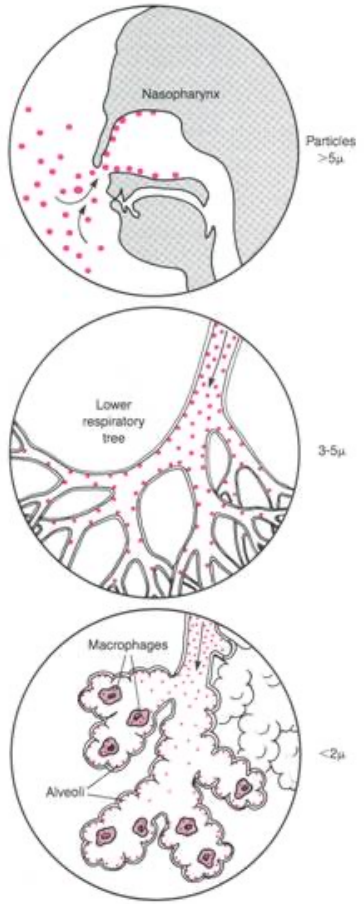
Defense mechanisms

normal lung is free of bacteria

- nasal clearance
- tracheobronchial clearance
- alveolar clearance

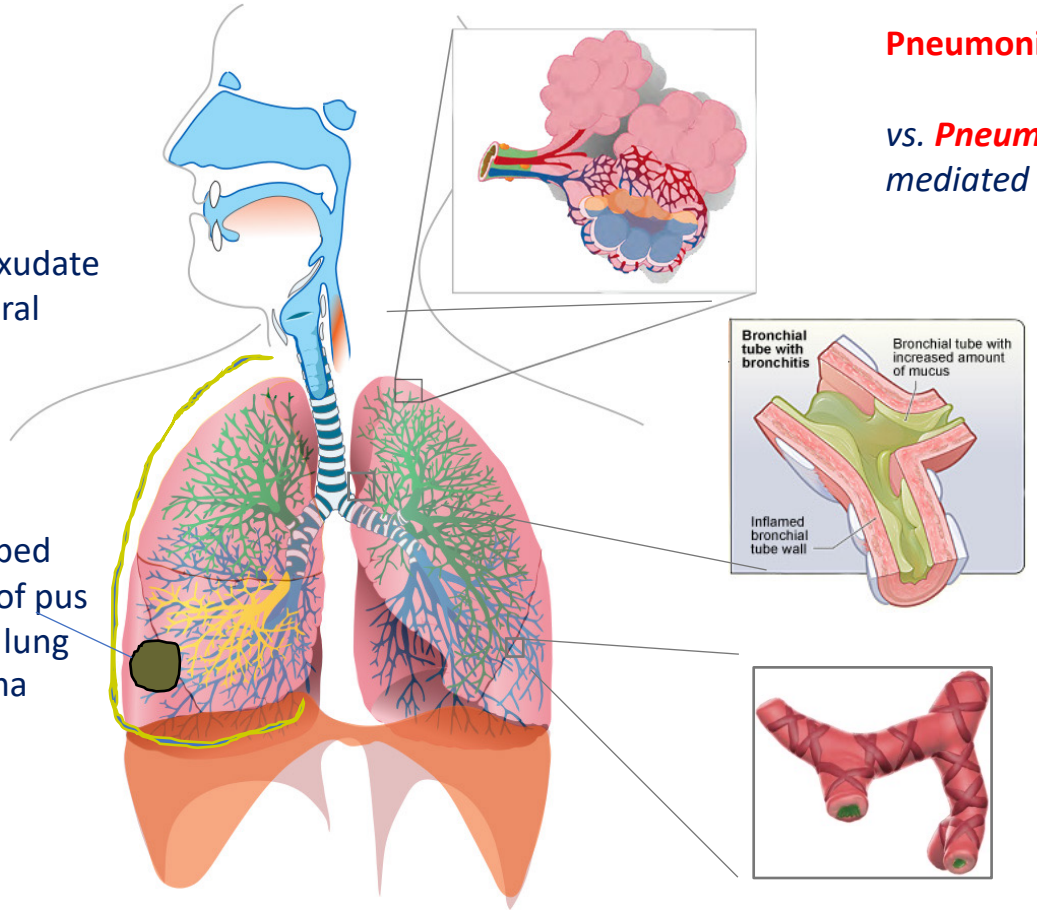
impaired defense

- chronic disease, immunologic defects, **immunocompromised**



Empyema: purulent exudate in the pleural cavity

Abscess: circumscribed collection of pus within the lung parenchyma

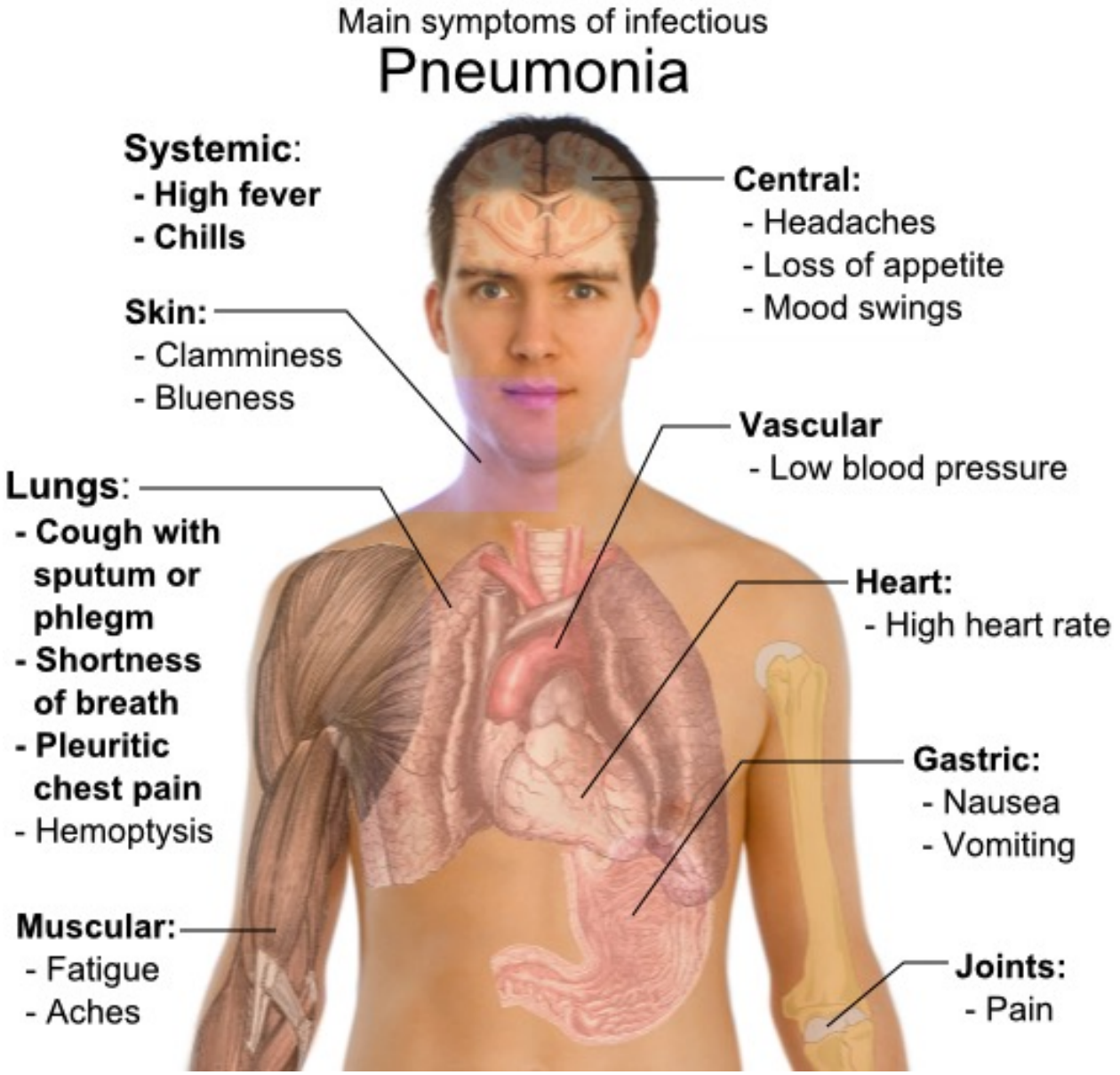


Pneumonia -- infection of alveoli (viral or bacterial)
vs. ***Pneumonitis*** *-- immune-mediated inflammation of alveoli*

Bronchitis -- inflammation of bronchi, may be **immune-mediated**, e.g. asthma, COPD, or **infectious** (usually viral but can be bacterial)

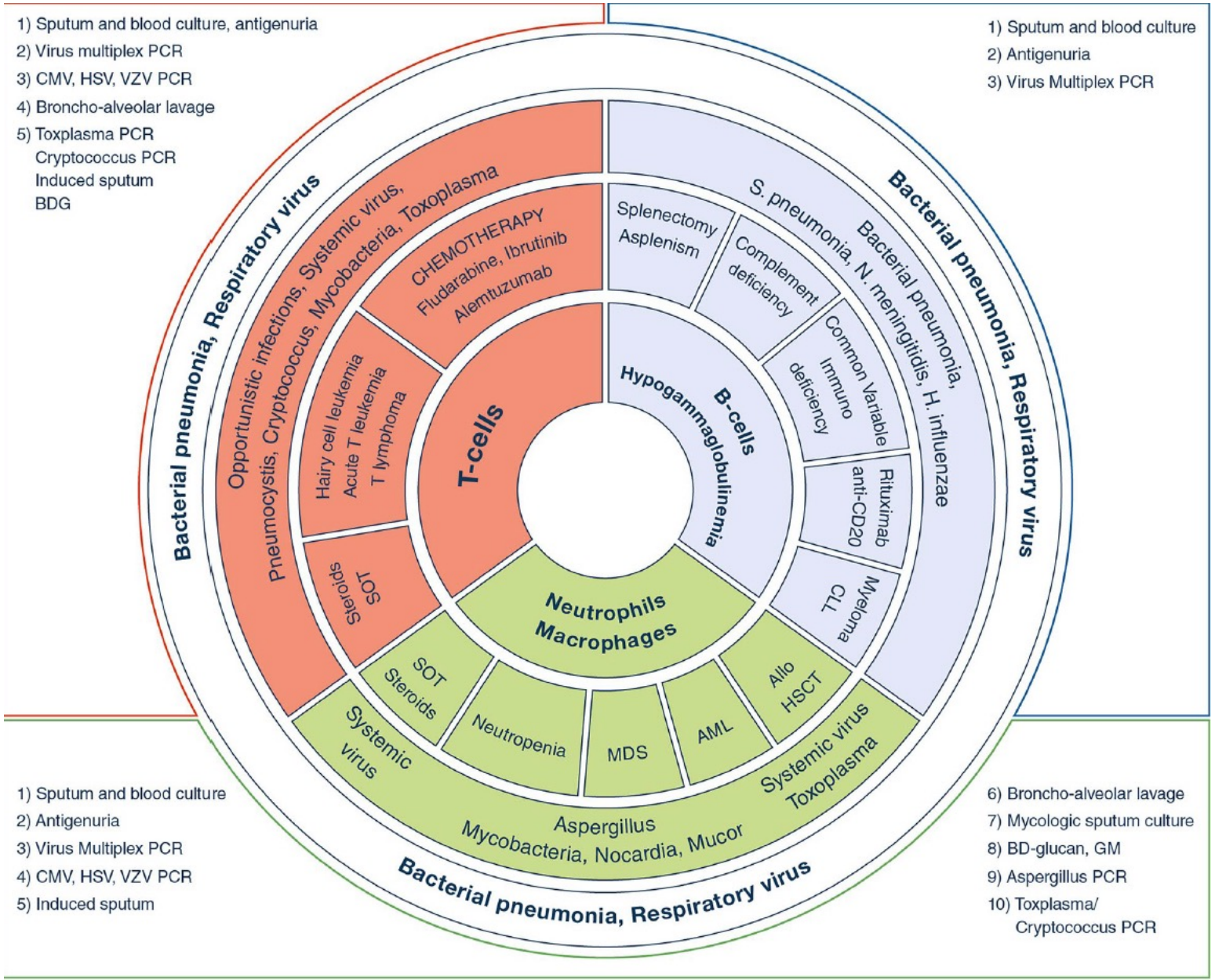
Bronchiolitis: inflammation of bronchioles (often viral but can be bacterial)

Clinical Manifestations



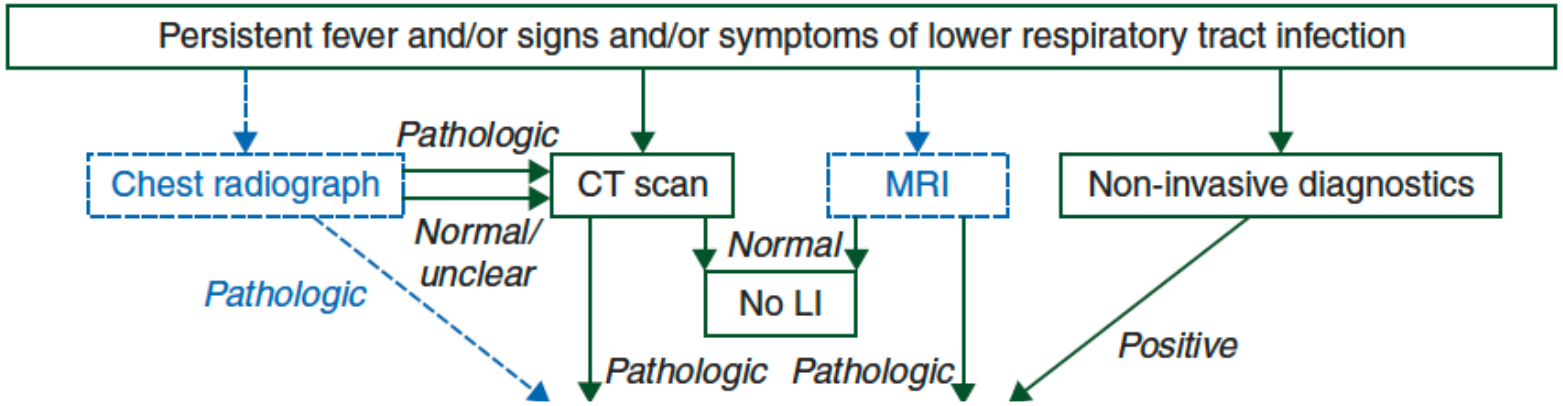
Diagnosis of severe respiratory infections in immunocompromised patients

Azoulay et al, Int Care Med 2020



- Nel paziente immunodepresso (PID) il polmone è l'organo più spesso colpito da complicanze (70%), che sono per lo più infettive (70-90%) e gravate da un'elevata mortalità.
- Gli agenti responsabili di infezioni possono essere patogeni comuni, rari, o germi opportunisti.
- La presentazione clinica è spesso subdola, atipica, aspecifica.
- Nel 15-40% delle polmoniti, è un controllo radiologico di routine a rivelare la presenza di una patologia polmonare non sospettata in precedenza.
- Il limite della radiologia è che non è in grado di definire nella maggior parte dei casi l'agente etiologico

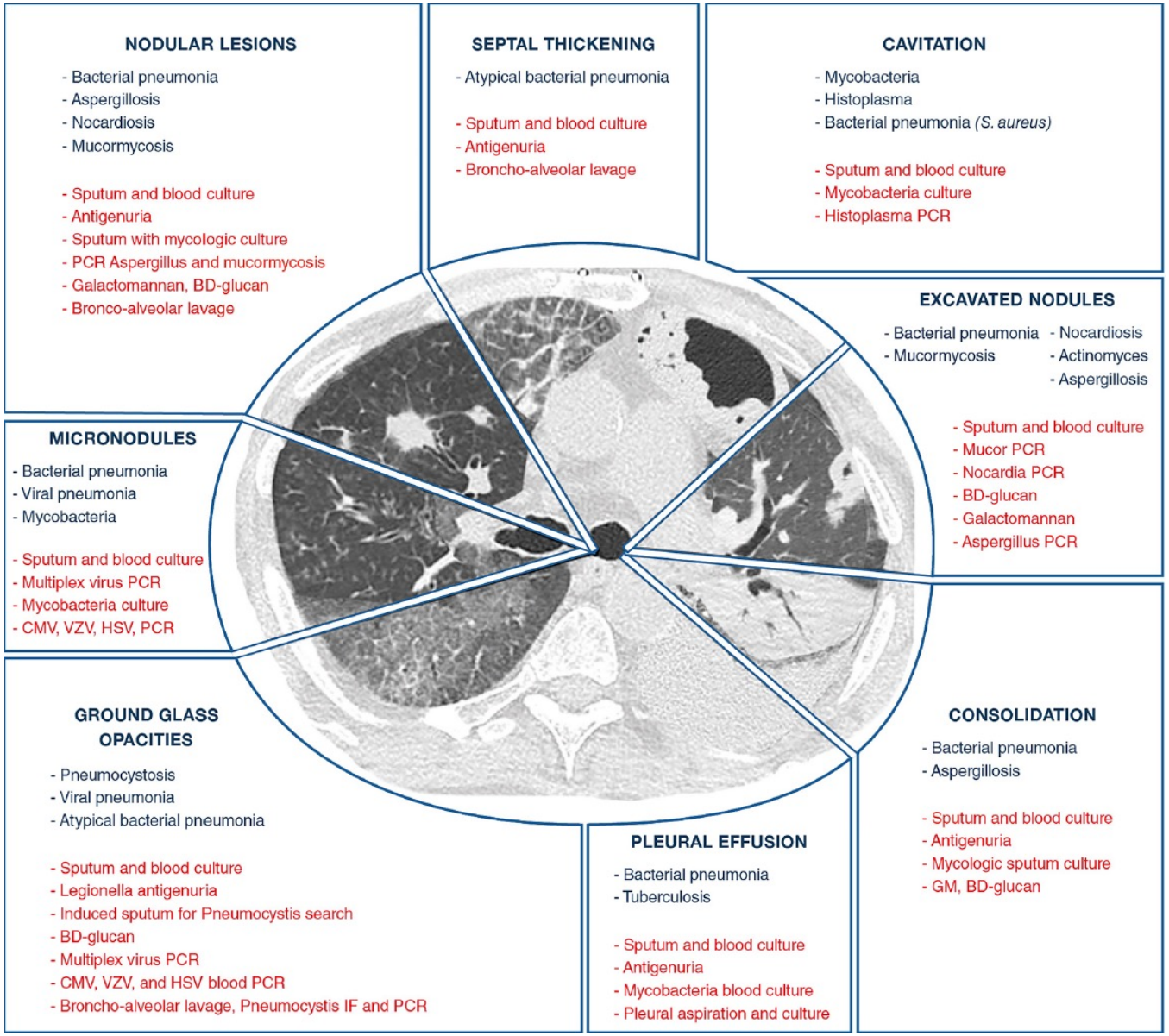
Diagnosis and antimicrobial therapy of lung infiltrates in febrile neutropenic patients (allogeneic SCT excluded): updated guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO



Maschmmeyer G et al. Ann Oncol 2015

Diagnosis of severe respiratory infections in immunocompromised patients

Azoulay et al, Int Care Med 2020



RX Torace

Di primo impiego nella patologia toracica

Può essere negativo in presenza di patologia

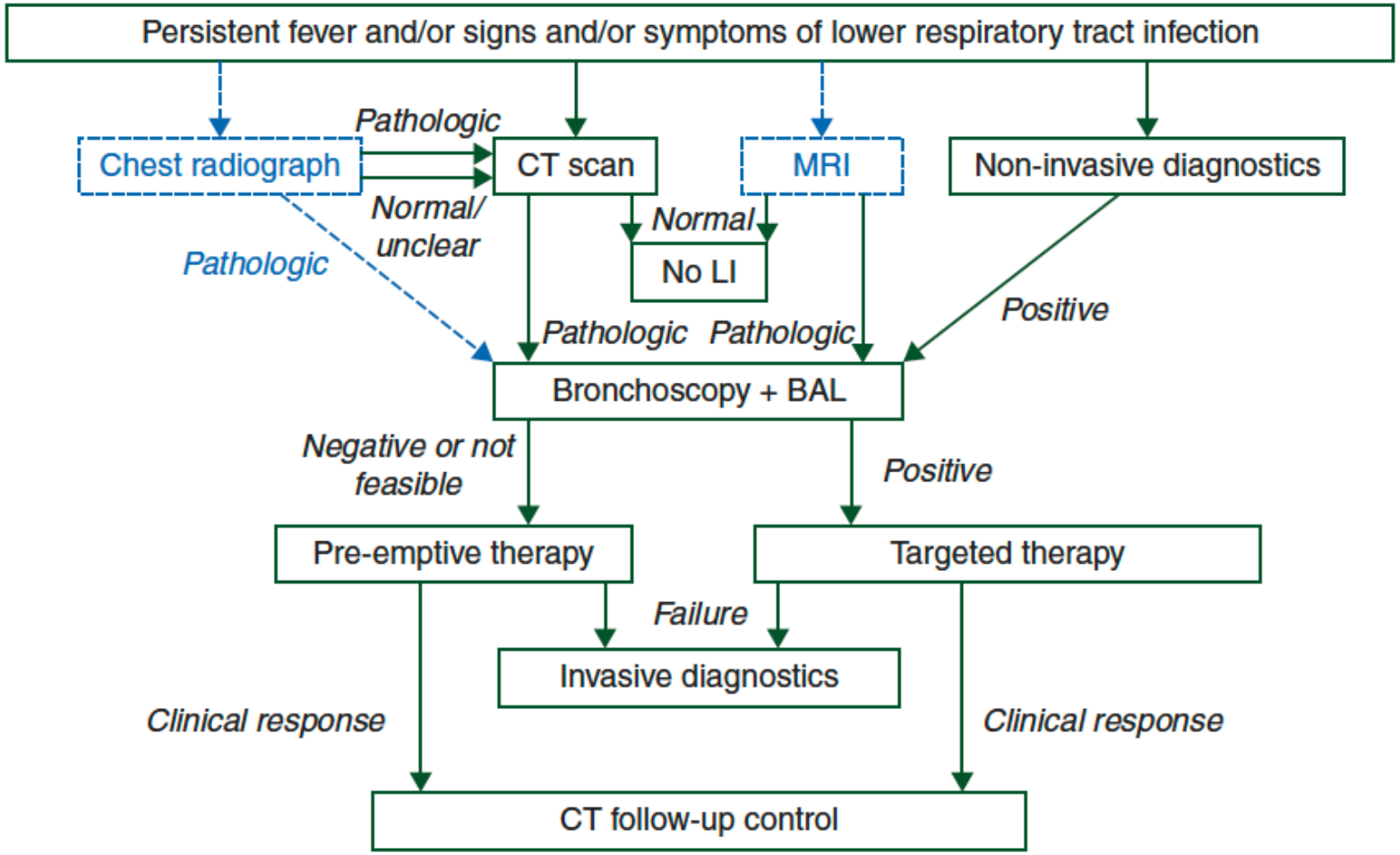
Rararemete fornisce una diagnosi precisa

TC/ HRCT

Maggiore sensibilità (elevatissimo valore predittivo negativo)

Maggiori informazioni per un orientamento diagnostico (variazioni della terapia nel 40%)

Diagnosis and antimicrobial therapy of lung infiltrates in febrile neutropenic patients (allogeneic SCT excluded): updated guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO



Maschmmeyer G et al. Ann Oncol 2015

Recommendations for bronchoscopy

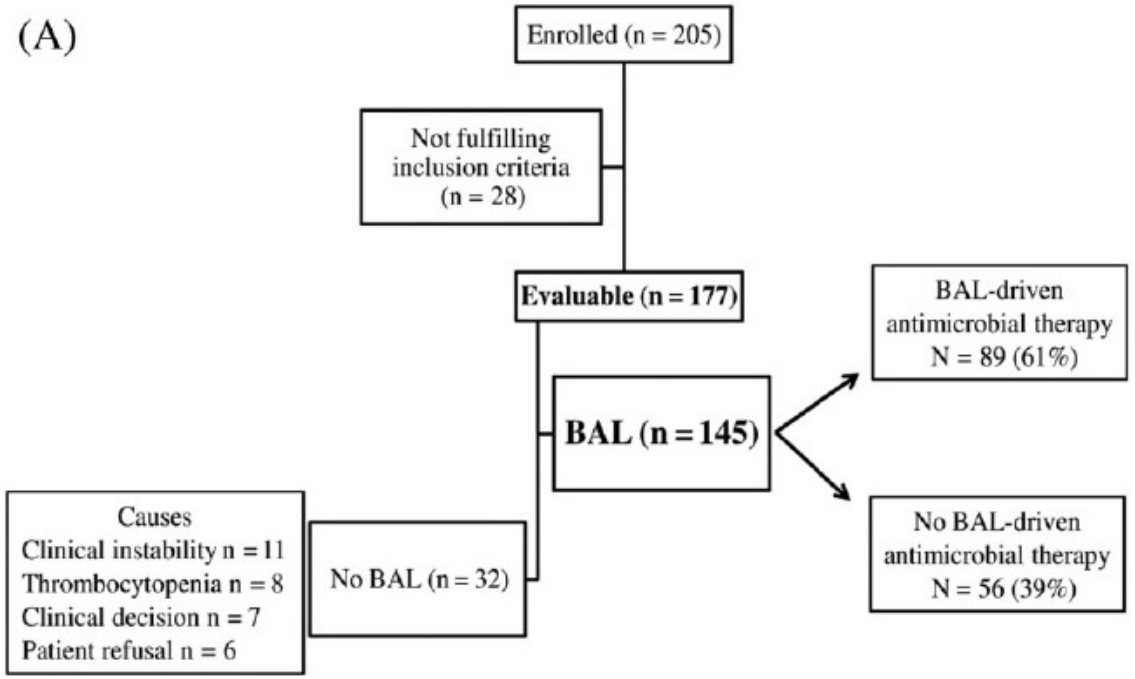
The detection rate of potential pathogens from BAL samples has been described to be 25%-50% or even higher

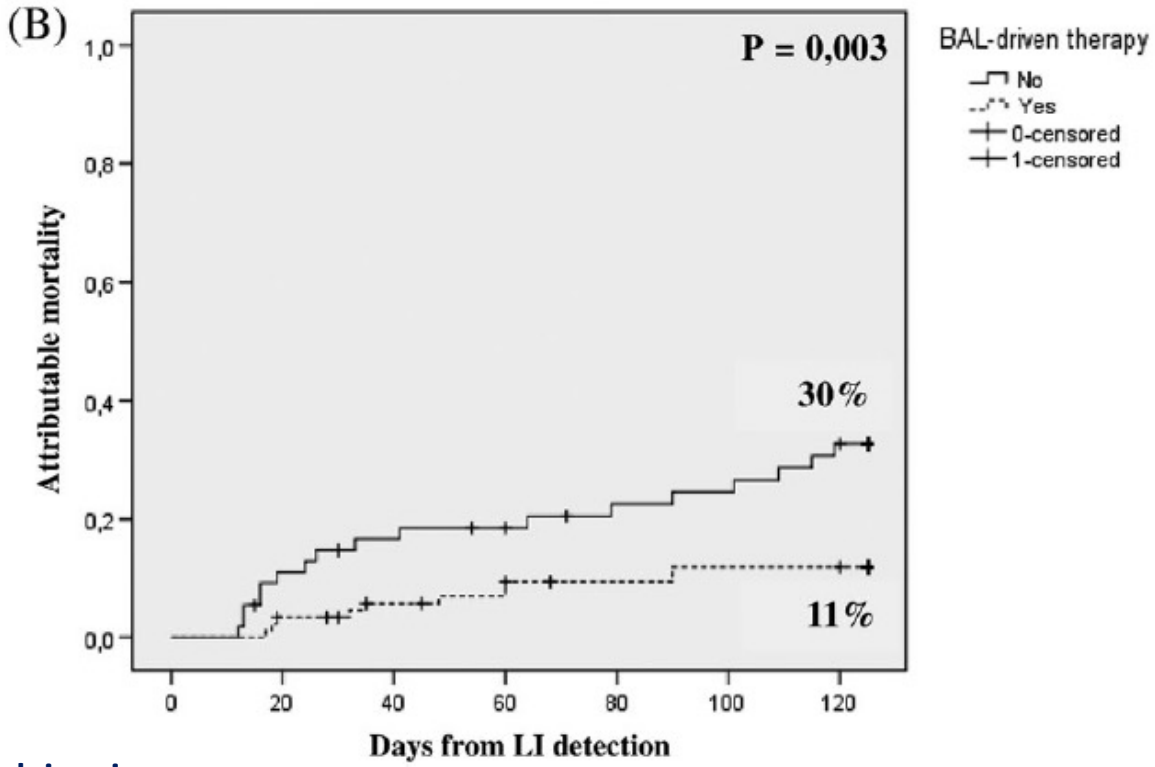
Recommendation	Strength
Bronchoscopy and BAL should be available within 24 h after clinical indication has been established	B-III
Urgent need to start or modify antimicrobial therapy should not be postponed by bronchoscopy and BAL	A-II
Bronchoscopy and BAL should only be carried out in patients without critical hypoxemia	B-II

Maschmmeyer G et al. Ann Oncol 2015

SEIFEM

A bronchoalveolar lavage-driven antimicrobial treatment improves survival in hematologic malignancy patients with detected lung infiltrates: A prospective multicenter study of the SEIFEM group



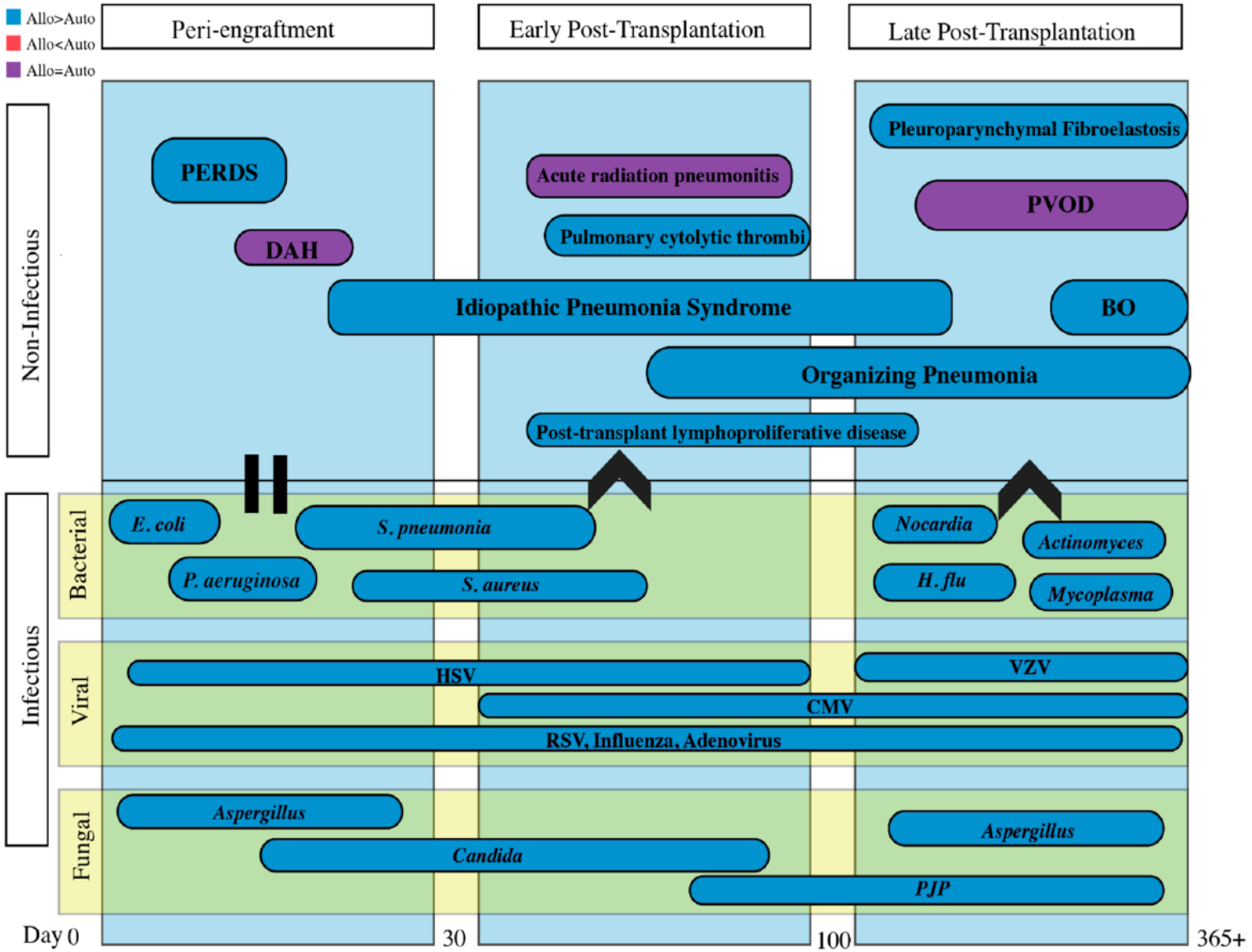


- Il BAL permette di identificare un agente microbiologico causale nel **75% dei casi**
- Il BAL è una procedura sicura anche in questa popolazione "difficile"
- **Una terapia antimicrobica BAL-driven è fattibile nel 61% dei casi e consente di migliorare l'outcome clinico in termini di sopravvivenza**

Marchesi et al. Am Hematol 2019

Pulmonary Complications in Hematopoietic Stem Cell Transplant Recipients—A Clinician Primer

Astashchanka et al, J Clin Med 2021



PERDS = peri-engraftment respiratory distress syndrome;
DAH = diffuse alveolar hemorrhage;
PVOD = pulmonary veno-occlusive disease;
BO = bronchiolitis obliterans;

Hematological malignancies Chemotherapy- HSCT

Soggetti a rischio di infezione polmonare

Pneumonia

Consolidamento, Versamento, Interstiziopatia

Bacterial

Più frequente

Fungal

Più pericolosa

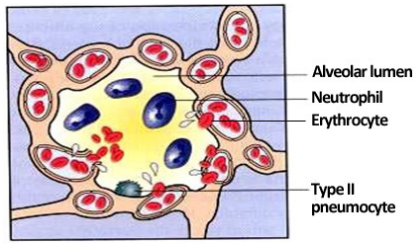
Viral

Più insidiosa

Effects and patterns of microbial colonization

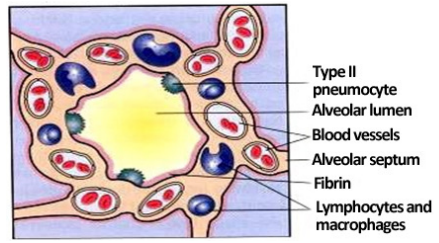
Alveolar

- In alveolar **lumen**
- Purulent exudate of RBCs and PMNs



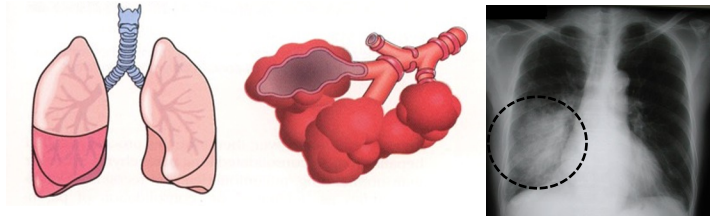
Interstitial

- Mostly in alveolar **wall**
- Mononuclear WBCs
- Fibrinous exudate



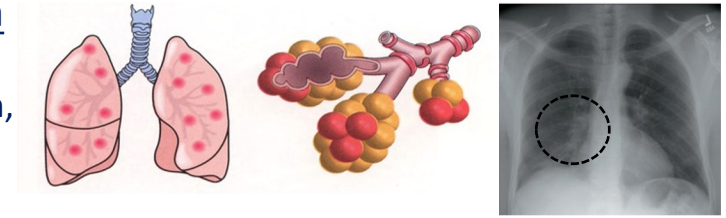
Lobar pneumonia

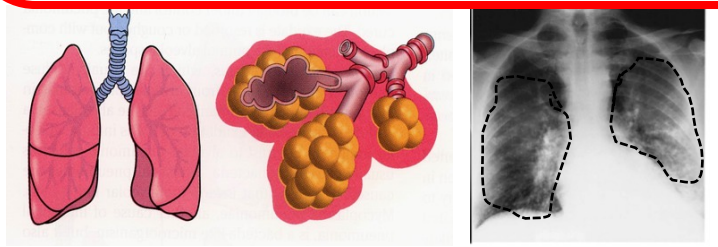
- lobar distribution
- "typical" CAP
- *S. pneumo, H. flu.*



Bronchopneumonia

- patchy distribution
- aspiration, intubation, bronchiectasis
- *Staph, enterics, Pseudomonas*





Atypical pneumonia

- diffuse infiltrate w/ perihilar concentration
- *Mycoplasma, Chlamydophila, Legionella*
- Respiratory viruses, e.g. influenza

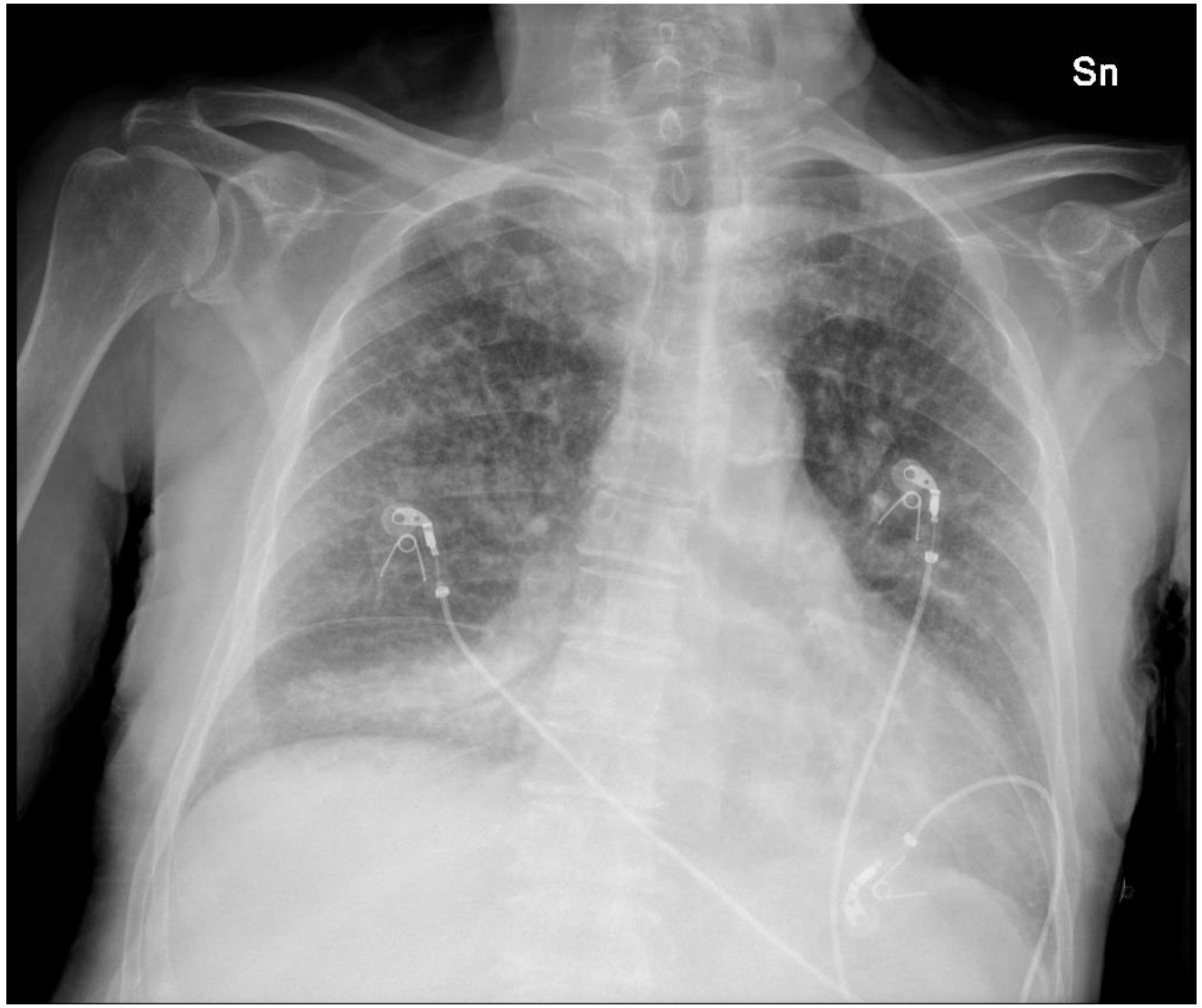
Quadri di Interstiziopatia

Non infettive

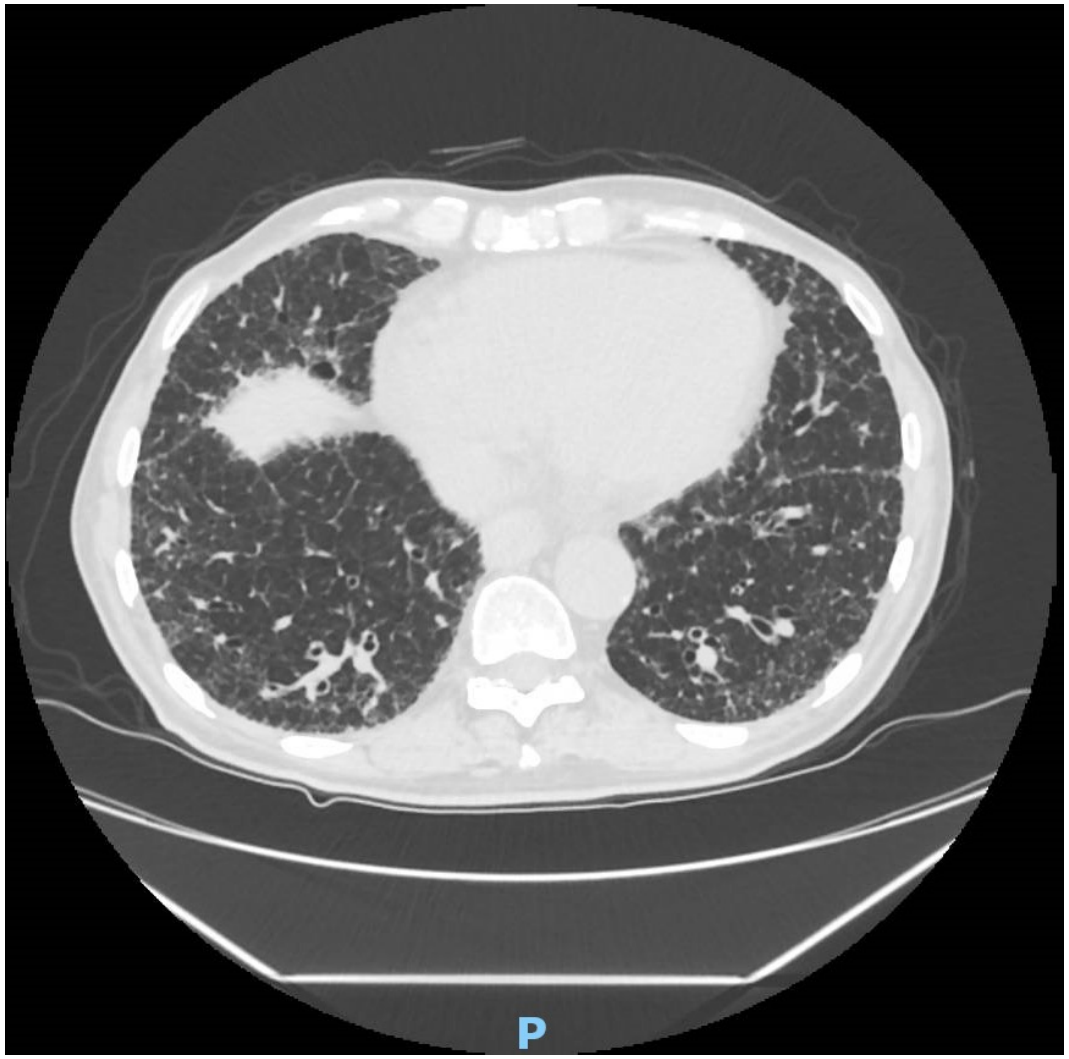
- Leucostasi polmonare
- Tossicità da farmaci
- Edema polmonare (emodinamico o lesionale)
- Emorragia alveolare
- Bronchiolite obliterante (tipica della GVHD nei HSCTs)

Infettivi

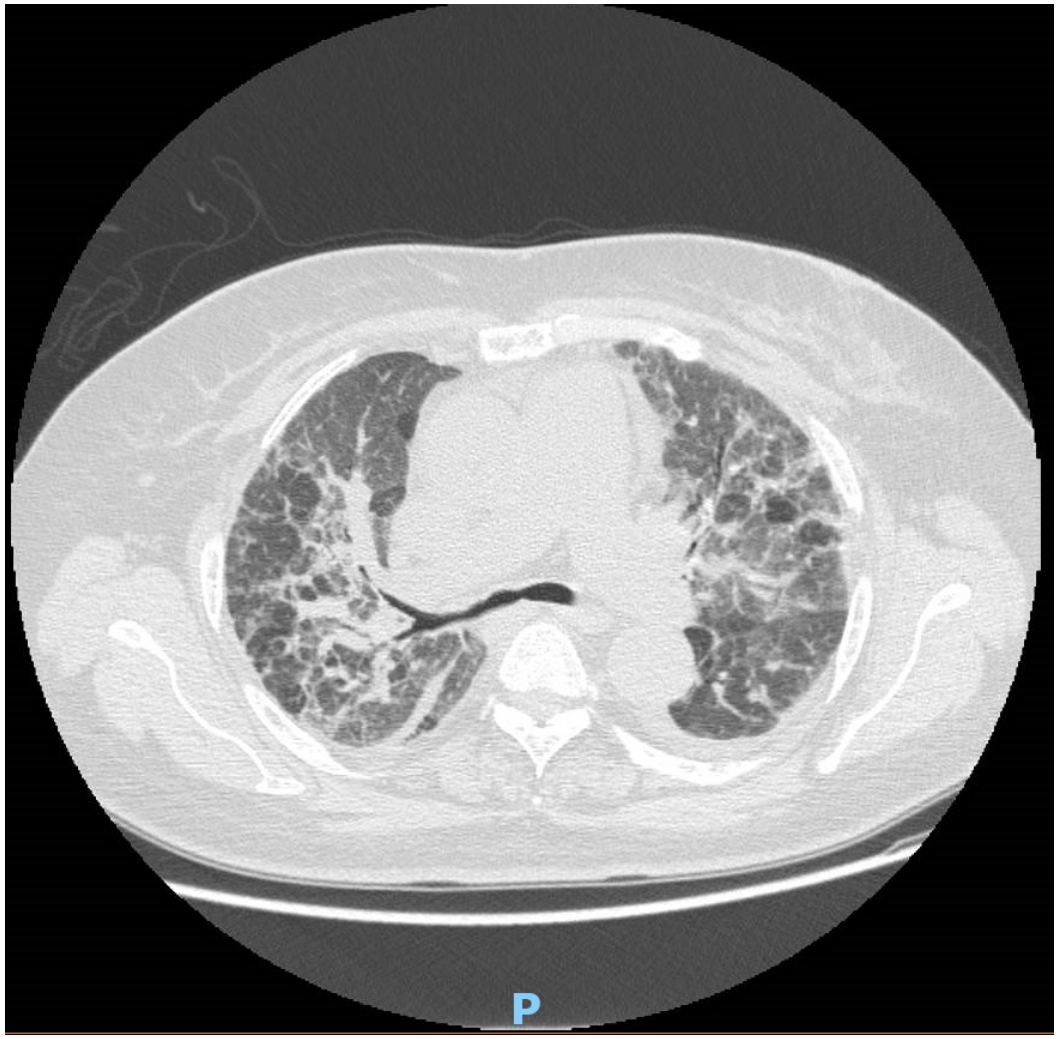
- PJP
- TBC-micobatteri atipici
- Miceti
- Emboli settici
- Virus !!!



Rx torace compatibile con interessamento interstizio-alveolare da leucostasi polmonare in paziente affetto da leucemia mieloide acuta monoblastica ipercitemica (GB 360000/mmc).



Quadro TC torace compatibile con polmonite interstiziale in iniziale evoluzione fibrotica relato a Bleomicina in paziente affetto da linfoma Hodgkin sottoposto a regime terapeutico a tipo ABVD

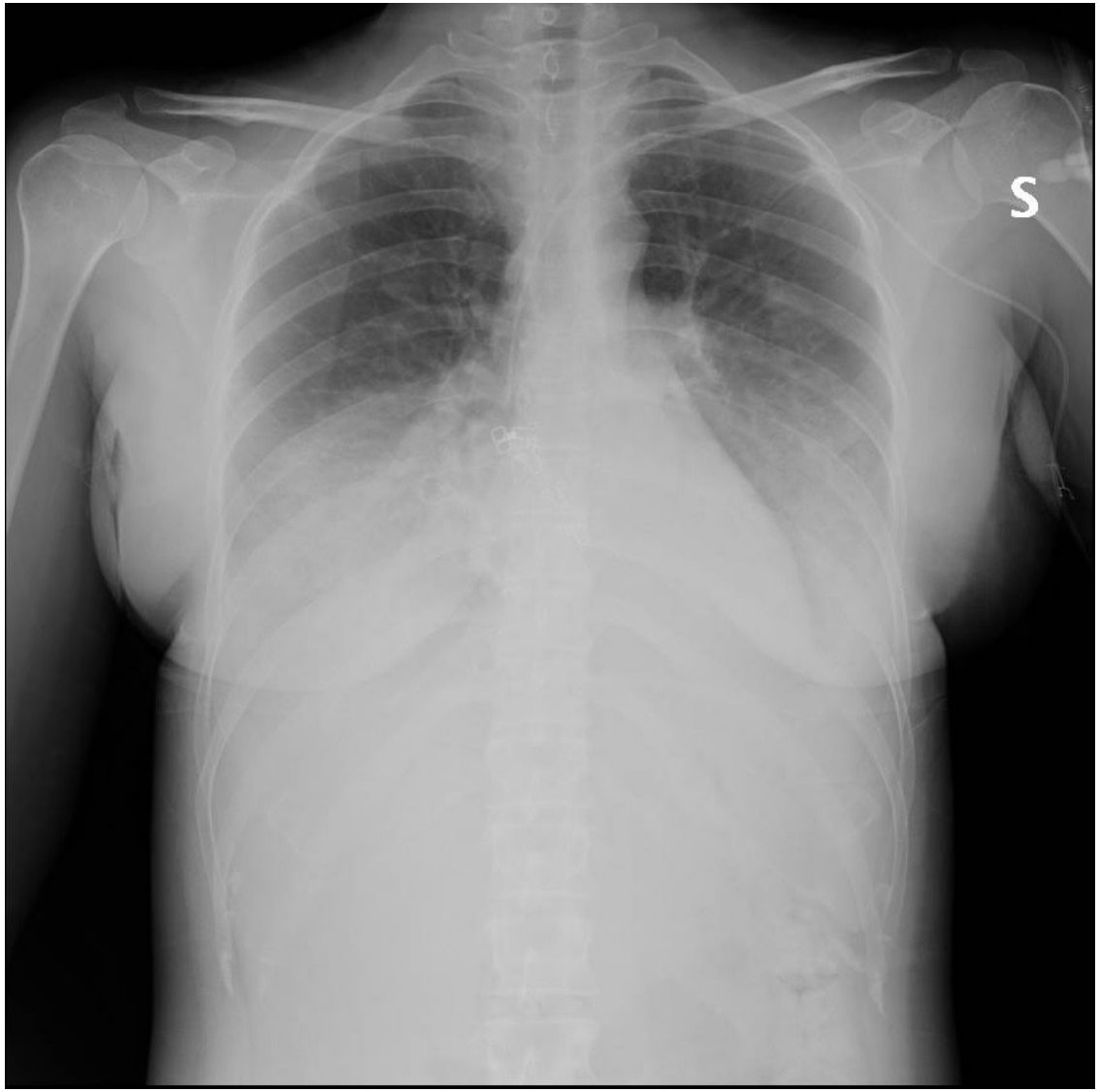


Quadro TC torace compatibile con polmonite interstiziale in chiara evoluzione fibrotica in paziente affetta da mieloma multiplo in trattamento con Bortezomib (regime VTD)

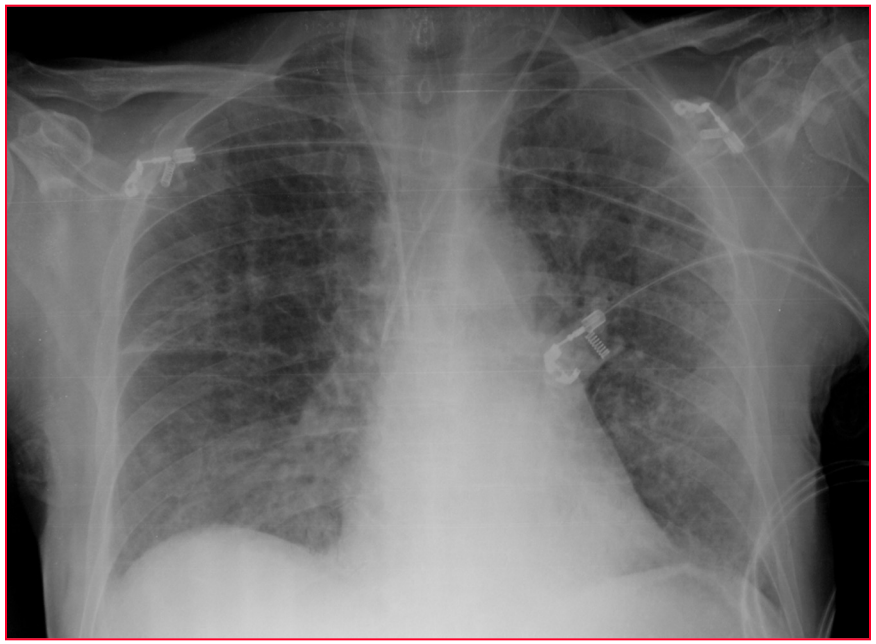
Nivolumab cause PD-1 block with a reduced activity of T-lymphocyte. Usually administered in Hodgkin's relapsed/refractory

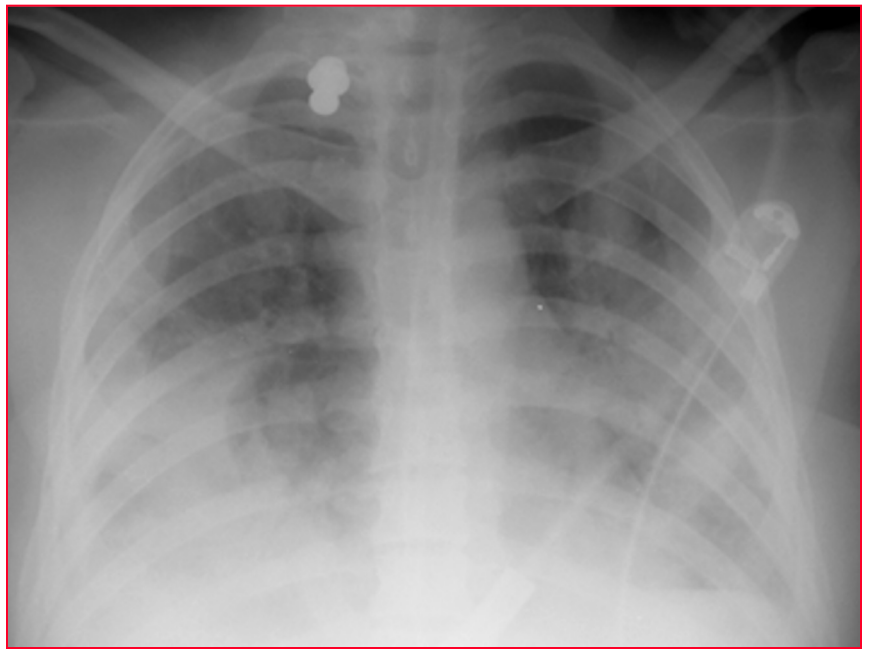
✧ **Immunological mechanisms is related to pro-inflammatory activation of the innate immune system, mediated by effects on monocytes or macrophages and upregulation of nuclear factor kB**

✧**The adaptive immune system is also affected leading to enhanced CD8 memory T-cell responses to foreign antigens, and the recruitment and activation of macrophages and other inflammatory cells possibly via a T-cell-mediated, delayed-type hypersensitivity mechanisms**

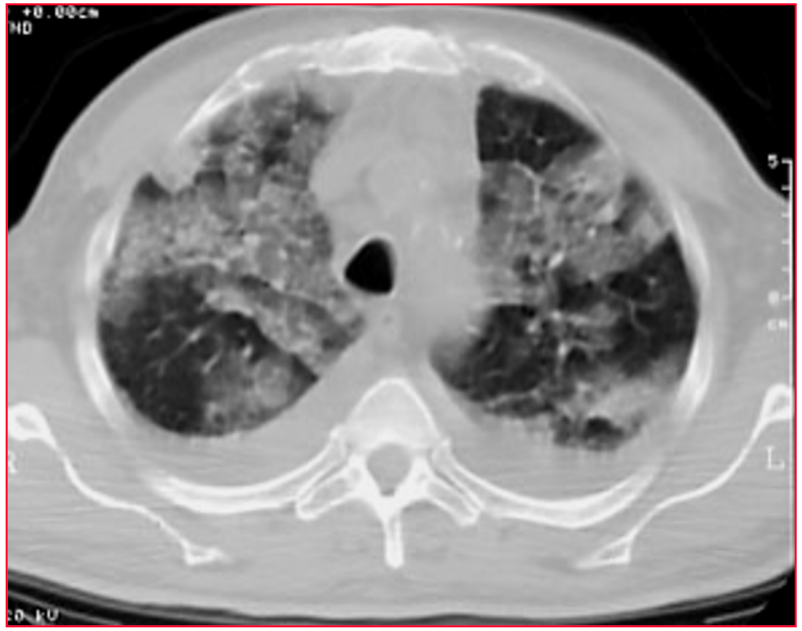


Sindrome da ATRA. Quadro RX torace compatibile con versamento pleurico bilaterale ed edema polmonare in fase interstizio alveolare in paziente in trattamento con ATRA e Triossido di arsenico affetta da leucemia acuta promielocitica

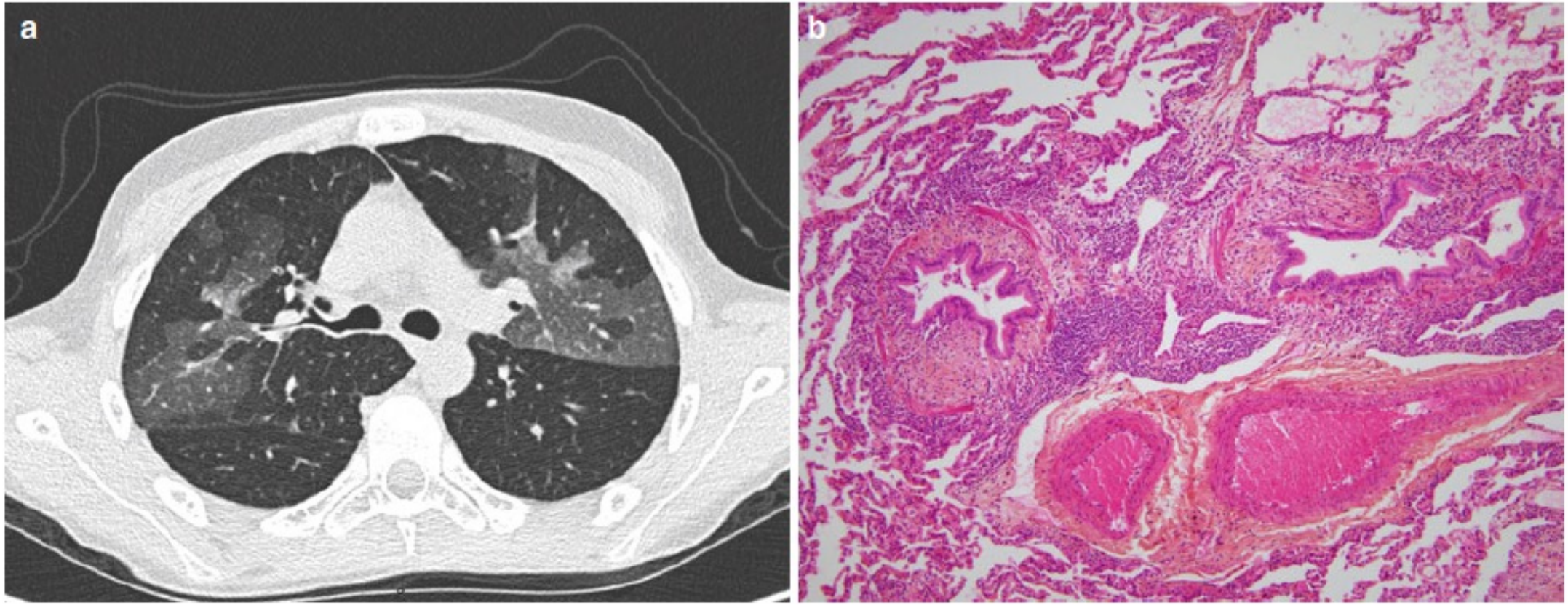




Emorragia polmonare in AML



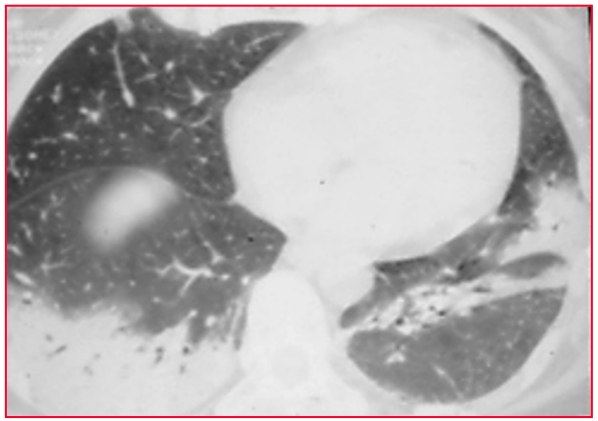
Pulmonary Manifestations of Hematological Malignancies: Focus on Pulmonary Chronic Graft-Versus Host Disease

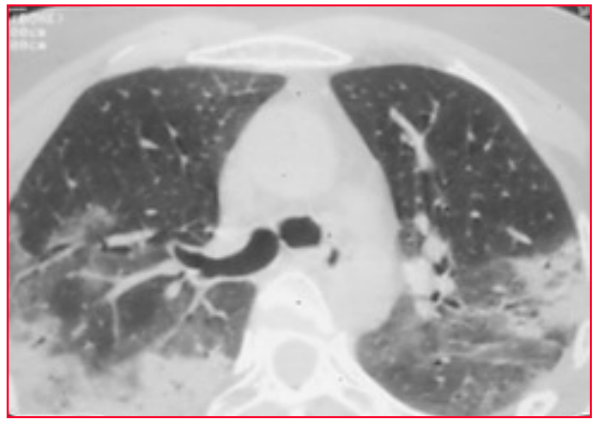


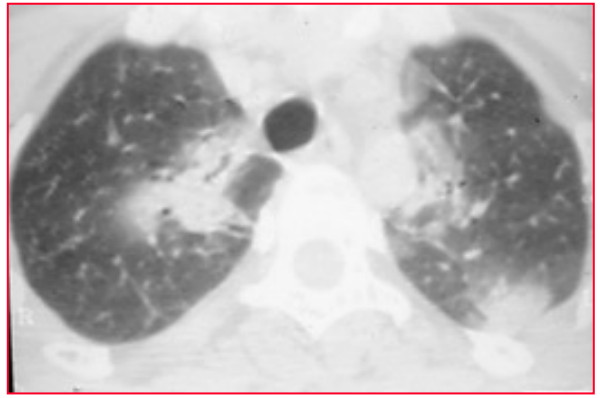
Bronchiolite obliterante dopo HSCT

Chagnon et al, Orphan Lung Diseases. 2014

Bronchiolite Obliterante



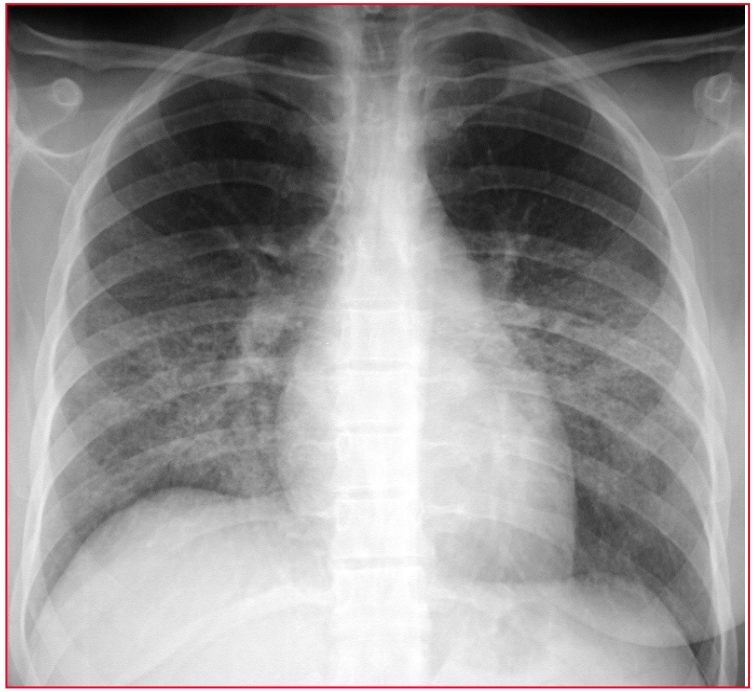


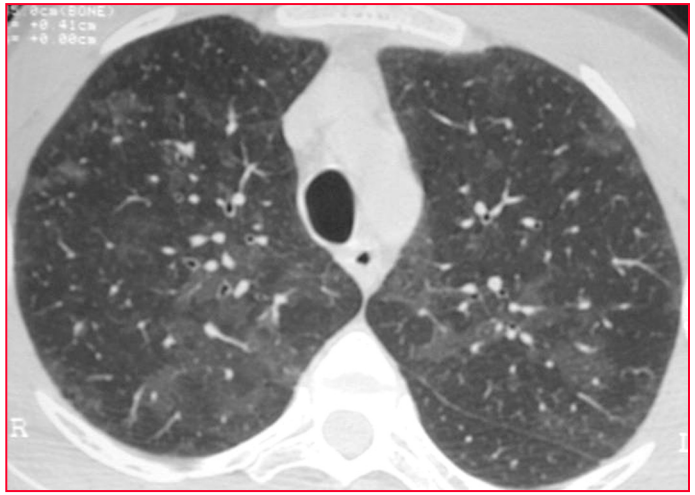


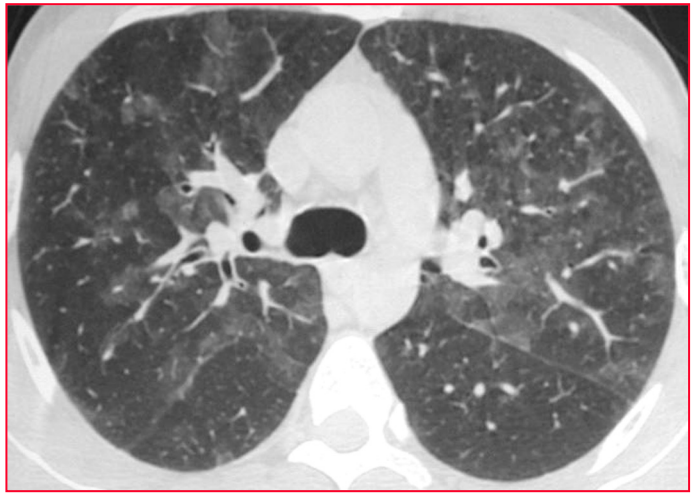
Infiltrati Polmonari Infettivi

Pneumocystis jirovecii

- RX: processo interstiziale perilare, bilaterale → consolidazione alveolare
- HRCT: ground-glass con RX negativo





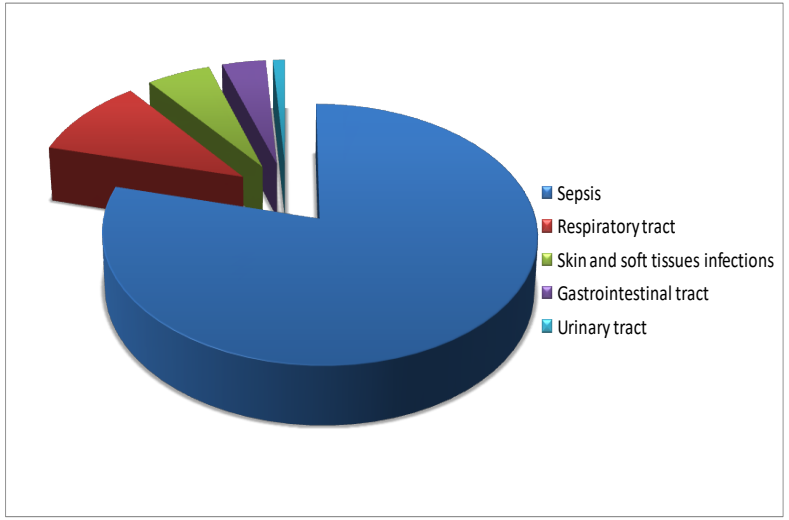


A prospective survey of febrile events in hematological malignancies

Pagano et al, Ann Hematol (2012) 91:767–774

- **19 EVALUABLE CENTERS for Epidemiological Analysis**
- **3197 NEWLY DIAGNOSED PATIENTS**

Underlying Malignancy	
Acute Lymphoblastic Leukemia	205
Acute Myeloid Leukemia	861
Chronic Myeloid Leukemia	64
Chronic Lymphocytic Leukemia	172
Lymphoma	953
Hodgkin's Lymphoma	138
Myelodysplastic Syndromes	190
Multiple Myeloma	410
Chronic Myeloprolipherative Diseases	204
Total	**3197**



	EVT	%
Bacterial	**301**	**34.6**
Fungal	**95**	**10.9**
Viral	**7**	**0.8**
DTRF	**48**	**5.5**
FUO	**386**	**44.4**
Mixed infections	**32**	**3.6**
Fungi/Bacteria	**23**	
Bacteria/Virus	**6**	
Fungi/Virus	**2**	
Bacteria/Fungi/Virus	**1**	
TOTAL	**869**	

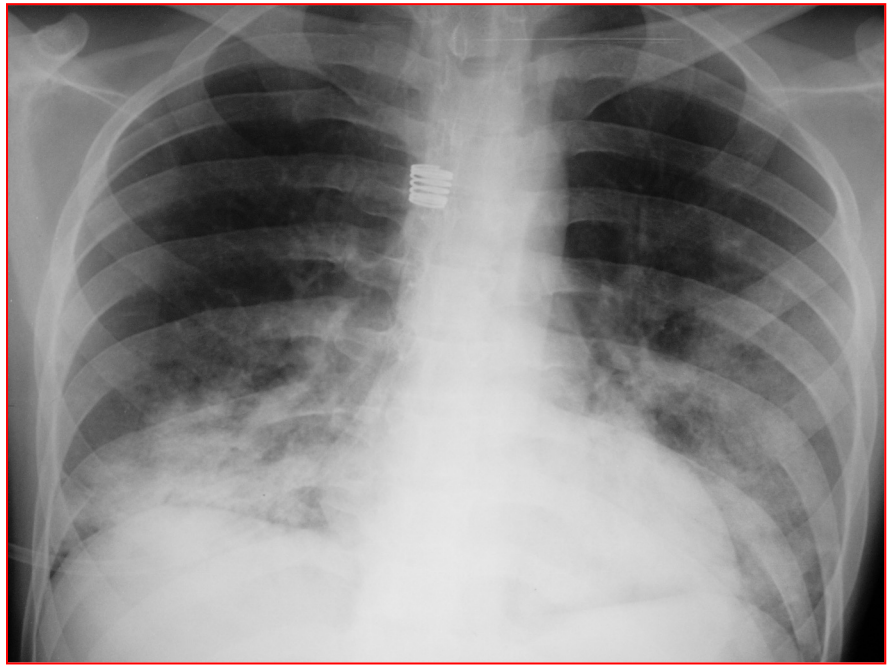
598 FE (70%) in AML

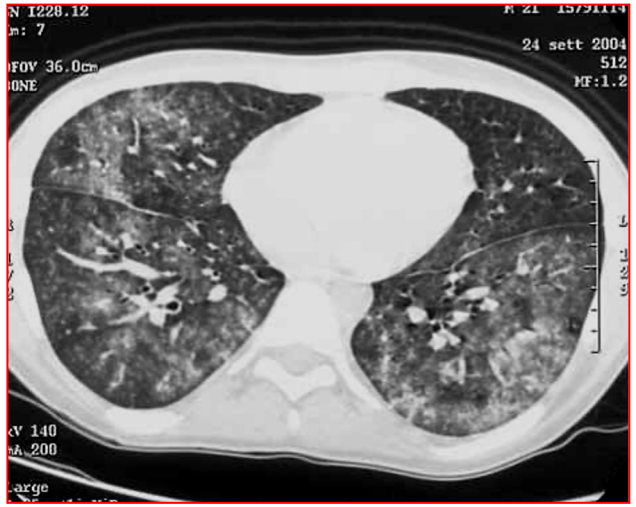
869 FEBRILE EVENTS = 27.1%

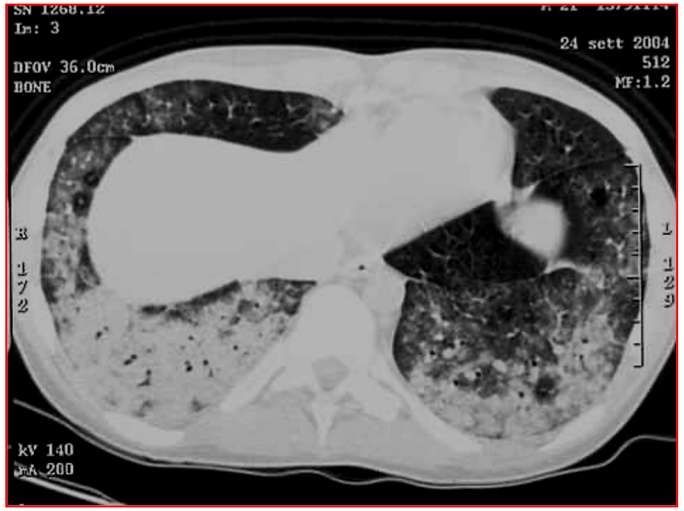
Infiltrati Polmonari Diffusi

Cytomegalovirus (CMV)

- RX: opacità lineari e nodulari diffuse, a partenza dalle basi.
- HRCT: piccoli noduli parenchimali ed aree di ground-glass







Diagnosis of severe respiratory infections in immunocompromised patients

Azoulay et al, Int Care Med 2020

Type	Family	Genus	Virus
RNA viruses	Orthomyxoviridae	*Influenza A*	All Influenza A subtypes
		Influenza B	Influenza B
	Paramyxoviridae	*Rubulavirus*	Human parainfluenza virus type 2 (PIV-2) Human parainfluenza virus type 4a (PIV-4a) Human parainfluenza virus type 4b (PIV-4b)
		Respirovirus	Human parainfluenza virus type 1 (PIV-1) Human parainfluenza virus type 3 (PIV-3)
	Pneumoviridae	*Metapneumovirus*	Human metapneumovirus (hMPV)
		Orthopneumovirus	Human orthopneumovirus/Respiratory syncytial virus A (RSV-A) Human orthopneumovirus/Respiratory syncytial virus B (RSV-B)
	Coronaviridae	*Betacoronavirus*	Middle East respiratory syndrome-related coronavirus (MERS-CoV) Severe acute respiratory syndrome-related coronavirus (SARS-CoV) Human coronavirus NL63 Human coronavirus 229E Human coronavirus HKU1 Human coronavirus OC43
	Picornaviridae	*Enterovirus*	Enterovirus A-L Rhinovirus A, B, C

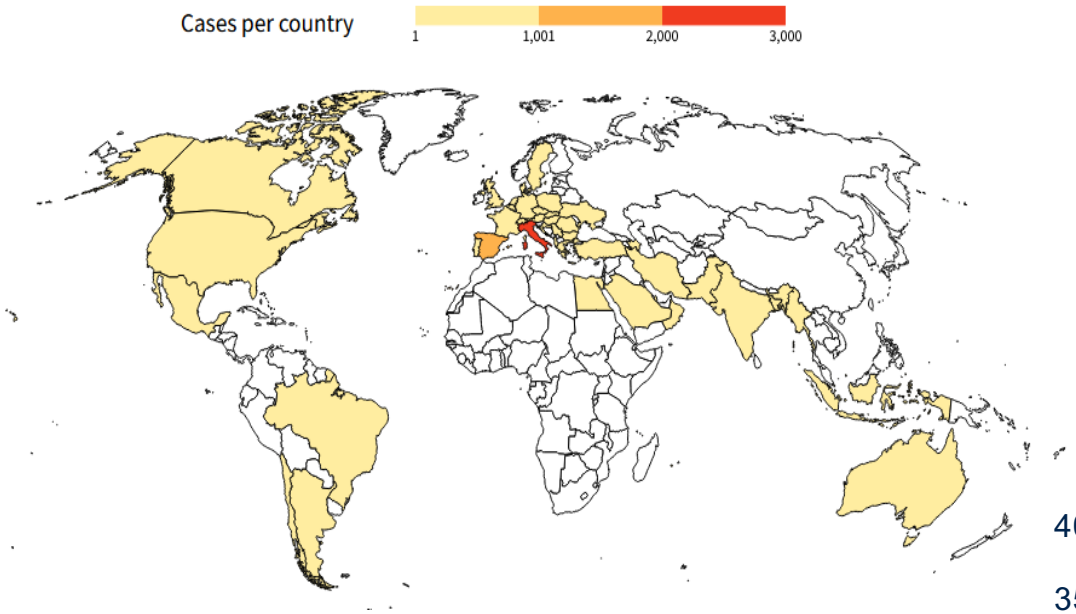
Influenza infections after hematopoietic stem cell transplantation: risk factors mortality, and the effect of antiviral therapy

Garrett et al. Clin Infect Dis 2004

Table 2. Risks for influenza acquisition, progression to pneumonia, and 1-year mortality in multivariable models.

Parameter	OR or HR (95% CI)[a]	*P*
Risk for acquisition of influenza		
Female sex	1.72 (1.03–2.88)	.038
Advanced disease	2.04 (1.23–3.38)	.006
Risk for influenza pneumonia		
Lymphocyte count of <100 lymphocytes/μL	4.17 (1.21–14.4)	.024
Steroid use at time of diagnosis	0.22 (0.063–0.79)	.020
Risk for 1-year mortality[b]		
No influenza	1.0	
Influenza URI	0.77 (0.43–1.40)	.39
Influenza LRI	2.60 (1.40–4.86)	.003

COVID-19 Infection in adult patients with hematological malignancies: A European Hematology Association Survey (EPICOVIDEHA)



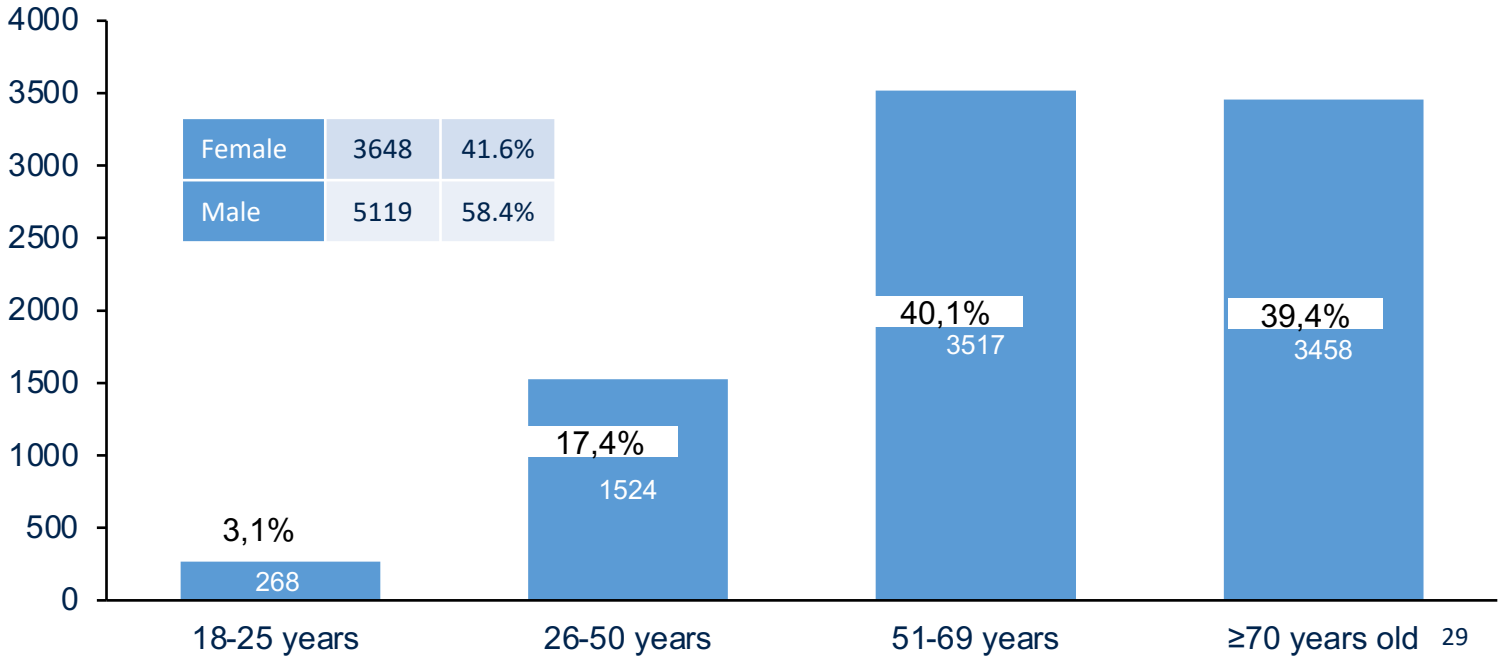
152 centres in 41 countries

2020-2022

9416 cases registered in the EPICOVIDEHA platform

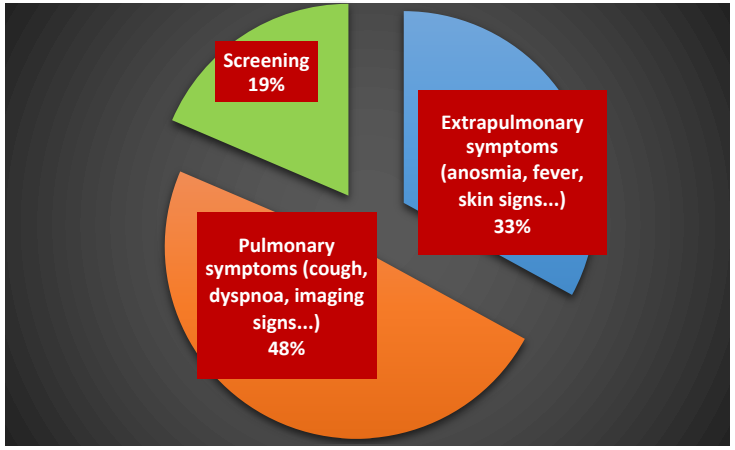
649 cases excluded
- Age <18 years
- Clinical diagnosis of COVID-19
- Double entry
- Haem diseases/solid cancer
- Haem malignancy after COVID
- Incomplete information
- More than 5 years off therapy

8767 valid cases

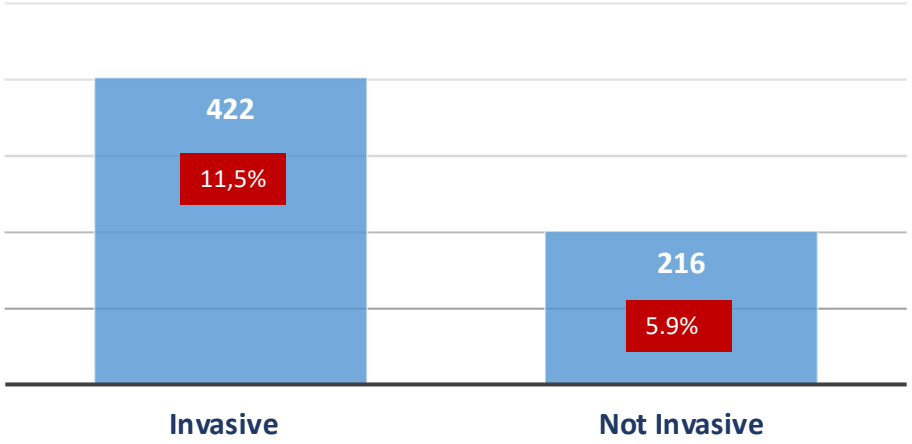


Pulmonary involvement during COVID-19

Pagano et al, J Hematol Oncol 2021



Mechanical ventilation



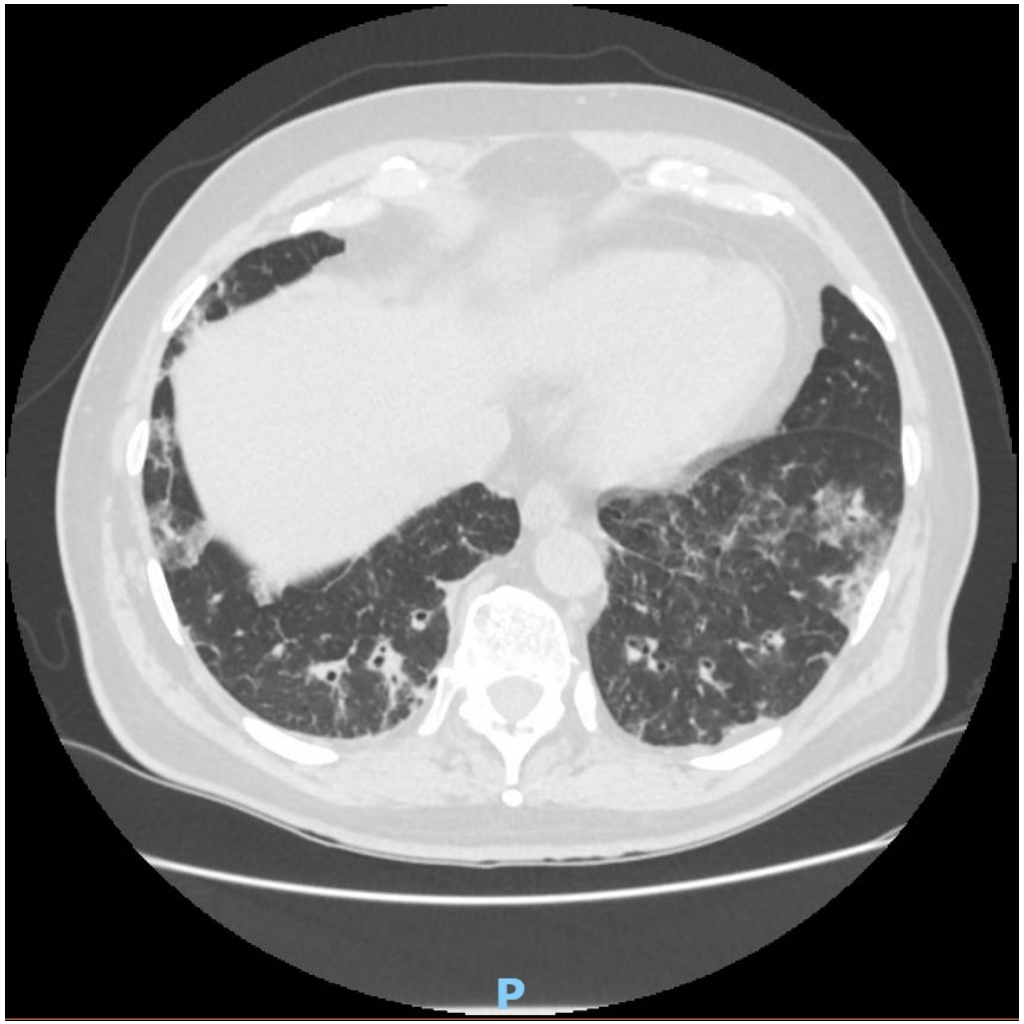
	Univariable				Multivariable			
	p value	HR	95% CI		p value	HR	95% CI	
			Lower	Upper			Lower	Upper
Sex								
• Female	-	-	-	-	-	-	-	-
• Male	0.081	1.100	0.988	1.223	0.987	1.001	0.899	1.115
Age	<0.001	1.037	1.033	1.041	<0.001	1.037	1.032	1.042
• Comorbidities								
• 0-1	-	-	-	-	-	-	-	-
• 2+	<0.001	1.917	1.726	2.130	<0.001	1.244	1.117	1.386
Malignancy status at COVID-19 diagnosis								
• Controlled malignancy	-	-	-	-	-	-	-	-
• Stable malignancy	<0.001	1.394	1.187	1.637	0.212	1.115	0.94	1.321
• Active malignancy	<0.001	2.731	2.418	3.085	<0.001	1.832	1.617	2.075
• Unknown	<0.001	3.631	2.888	4.564	<0.001	2.117	1.679	2.671
Vaccine doses before COVID-19								
• 0	-	-	-	-	-	-	-	-
• 1-2	<0.001	0.503	0.421	0.601	<0.001	0.681	0.546	0.85
• 3+	<0.001	0.286	0.233	0.350	<0.001	0.451	0.35	0.582
COVID-19 diagnosis								
• January-June 2020	-	-	-	-	-	-	-	-
• July-December 2020	<0.001	0.577	0.506	0.657	0.001	0.802	0.701	0.917
• January-June 2021	<0.001	0.618	0.517	0.740	0.016	0.796	0.662	0.958
• July-December 2021	<0.001	0.470	0.388	0.567	0.585	0.938	0.745	1.18
• January-June 2022	<0.001	0.322	0.273	0.381	0.078	0.833	0.679	1.021
• July-December 2022	<0.001	0.132	0.089	0.197	<0.001	0.427	0.282	0.647
COVID-19 symptoms at onset								
• Screening	-	-	-	-	-	-	-	-
• Extrapulmonary only	0.488	0.928	0.751	1.146	0.129	0.848	0.685	1.049
• Extrapulmonary + pulmonary	<0.001	2.131	1.794	2.530	0.087	1.168	0.978	1.396
• Pulmonary only	<0.001	2.149	1.821	2.535	0.003	1.299	1.095	1.541
Stay during COVID-19 episode								
• Home	-	-	-	-	-	-	-	-
• Hospital, no ICU	<0.001	22.360	15.342	32.589	<0.001	12.767	8.723	18.684
• Hospital, ICU	<0.001	57.020	39.015	83.335	<0.001	33.684	22.915	49.514

Comparison of COVID-19 and influenza characteristics

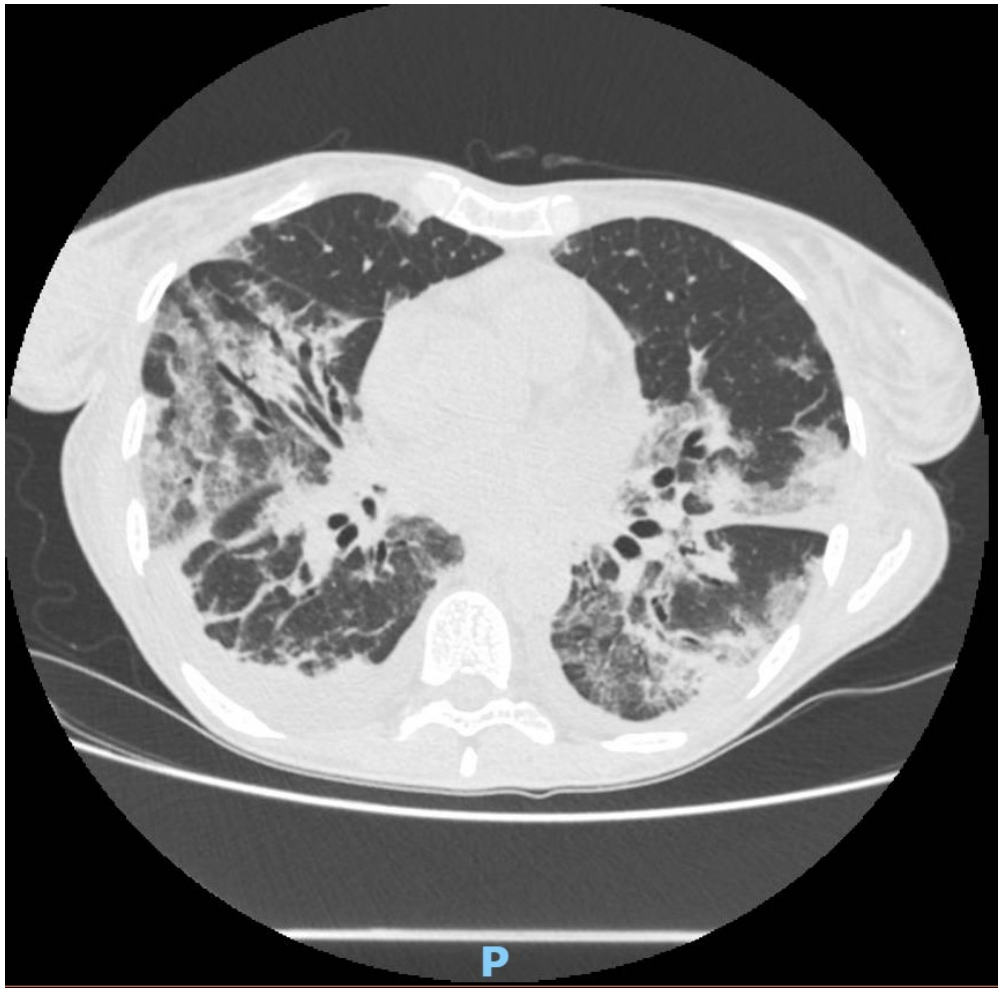
Bai et al, J Zhejiang Un 2021

Disease	Mortality (%)	Median age (year)	Sex	Respiratory symptom
COVID-19	1.40–3.67	44–56	Male biased	Similar to the common cold in early stages; nonproductive cough and shortness of breath are relatively large
Influenza	0.13–1.36	H7N9: 62; H5N1: 26; and 2009-H1N1: 25	Male biased	Cough is the common symptom

Disease	Other symptom	Hematology	Pulmonary CT
COVID-19	Fever, chemical sensory disturbance, damage to the reproductive system, constitutional symptoms and rash	Lymphocytopenia is predominant	Ground-glass opacity mostly located in the periphery and involved the lower lobe
Influenza	High fever and eye symptoms	Lymphocytopenia is predominant	Shadows tend to present centrally, peripherally, or randomly, often involving the five lobes and mediastinal emphysema and pneumothorax were reported



Quadro TC polmonare documentante multiple e sfumate aree a densità mista, prevalentemente "a vetro smerigliato» in parte anche di aspetto consolidativo in paziente affetto da mieloma multiplo e influenza (H1N1 variant)



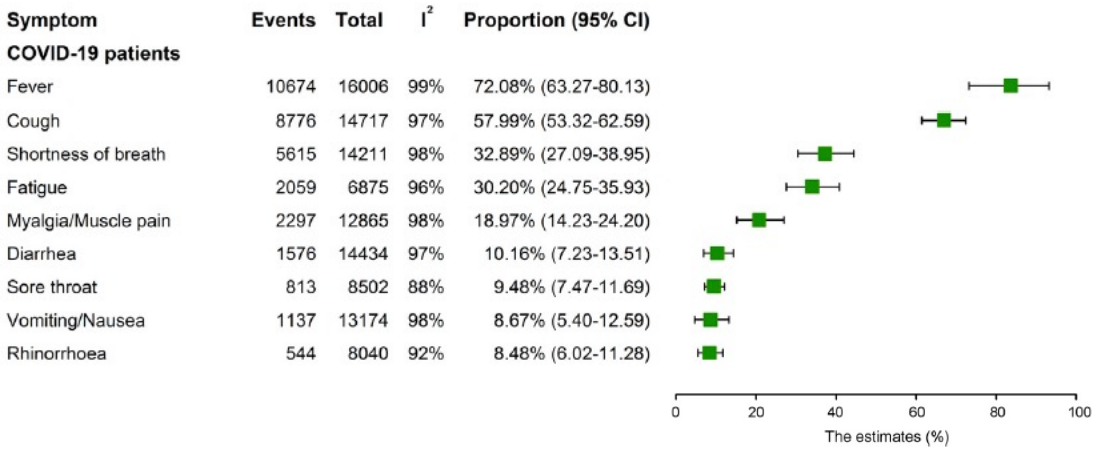
Quadro TC in paziente affetta da leucemia mieloide acuta post mielofibrosi affetta da COVID-19

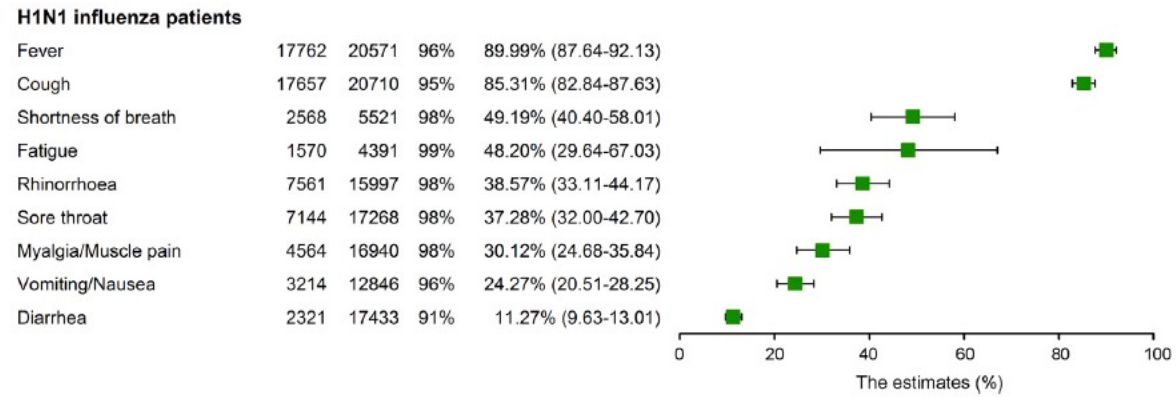
Systematically comparing COVID-19 with the 2009 influenza pandemic for hospitalized patients

Li et al, Int J Inf Dis 2021

	COVID-19 pandemic			2009 influenza pandemic			
Characteristics	Estimates (95% CI)	Study No.	Patient No.	Estimates (95% CI)	Study No.	Patient No.	*p*-value
Sex (male%)	20,425 (56.08%)	113	36,422	12,556 (54.20%)	84	23,167	/
Age, years (mean ± SD, range)	52.11 ± 16.93 (0.2–96)	37	5085	26.27 ± 15.57 (0–94)	47	12,347	/
Management							
Antibiotics use	67.44% (51.91–81.27)	23	5350	60.45% (47.93–72.31)	13	2569	0.3081
Mechanical ventilation	27.10% (20.91–33.75)	46	17,101	14.70% (6.65–25.12)	13	4975	0.0603
ECMO	3.10% (1.45–5.25)	19	6644	5.79%	2	863	/
ICU admission	17.74% (13.93–21.89)	35	15,636	16.03% (11.55–21.06)	36	9083	0.4416
Outcome							
Death	12.94% (10.93–15.10)	54	25,390	9.63% (6.05–13.90)	28	5075	0.1682

Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.



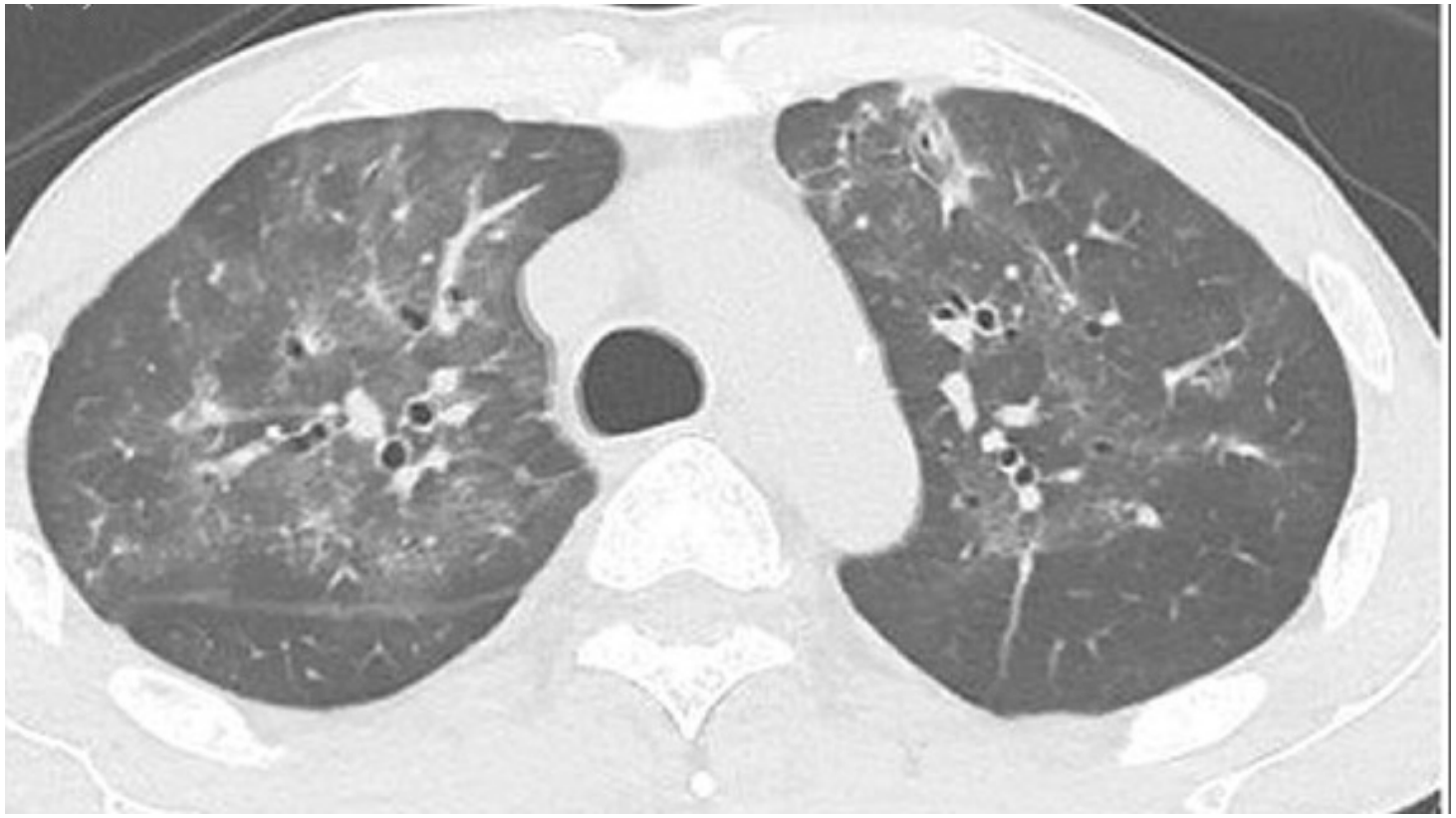


Are Community Acquired Respiratory Viral Infections an Underestimated Burden in Hematology Patients?

Popescu et al, Microorganisms 2019

Virus	General Population		Hematologic Malignancy/HSCT		Risk Factors
	Incidence	Mortality	Incidence	Mortality	
RSV	2005 estimates: 33.8 million episodes (22% of all LRTIs) in children <5 years old	2005 estimates: 66,000–199,000 in children <5 years old	0.3–14% (pediatric), 1–31% (adult)	32%	Host-related; ISI: neutropenia, lymphopenia, age <40 years, graft-versus-host disease, corticosteroid use, myeloablative chemotherapy, time from HSCT
HMPV	2–7%	Self-limiting	2.5–9%	6%; 27% in patients who develop HMPV LRTI	Host- and virus-related: prematurity, female sex, genotype B virus (immunocompetent children); hypoxia, nosocomial acquisition, hematologic malignancy (cancer patients)
HRV	52–80% of common colds	Self-limiting	23–62% of URTIDs, 65% of LRTIDs (children) 22.3% (adults)	6% (URTID), 41% (LRTID)	Low monocyte count, oxygen requirement at diagnosis, corticosteroid use ≥ 1 mg/kg
HCoV	10–30% of common colds	10.8% (SARS), 35.67% (MERS); otherwise self-limiting	11.1%	54% in patients with LRTI and require oxygen at diagnosis	High viral load, high-dose steroids and myeloablative conditioning (for prolonged viral shedding)
HBoV	2–19% of all RTIs	Self-limiting	8% of all RTIs with found etiology, 19% of diagnosed LRTIs	0% in found studies	Difficult to ascertain due to frequency of copathogens
HPiV	12% of 500,000–800,000 patients <18 years old admitted with LRTIDs	Typically self-limiting	2–7% of symptomatic RTIs, 1/3 of which manifest as LRTID	17–35% (and as high as 75%, with high frequency of coinfection)	With progression to LRTI: Temporal proximity to HSCT, steroid use, low ALC at onset With mortality: African-American ethnicity, low ALC, LRTI, steroid use, mechanical ventilation

HMPV human metapneumovirus
HRV human rhinoviruses
HBoV human bocavirus
HCoV human coronavirus
HPiV human parainfluenza virus
RSV respiratory syncytial virus
HRV human rhinoviruses
U/L/RTID upper/lower/respiratory tract infectious disease



Quadro TC compatibile con polmonite da virus respiratorio sinciziale (RSV) in paziente affetto da leucemia mieloide acuta in tratpianto di cellule staminali allogenico

New survey EPICOVIDEHA/EPIFLUEHA

- Inclusion criteria
  - Active malignancy within the last five years
  - ≥18 years old
  - Laboratory-based diagnosis of viral infection
- Exclusion criteria
  - Solid tumours
  - Non-malignant haematological diseases
  - Inactive/Off-therapy malignancy within the last five years
- Additional viruses
  - Influenza
  - Metapneumovirus
  - Parainfluenza virus
  - Respiratory syncytial virus (RSV)
  - Rhinovirus
  - SARS-CoV-2

EPICOVIDEHA - EPIFLUEHA

Epidemiology of viral infection in patients with haematological malignancies: A European Hematology Association Survey