ISBMT
Indian Society for Blood & Marrow Transplantation

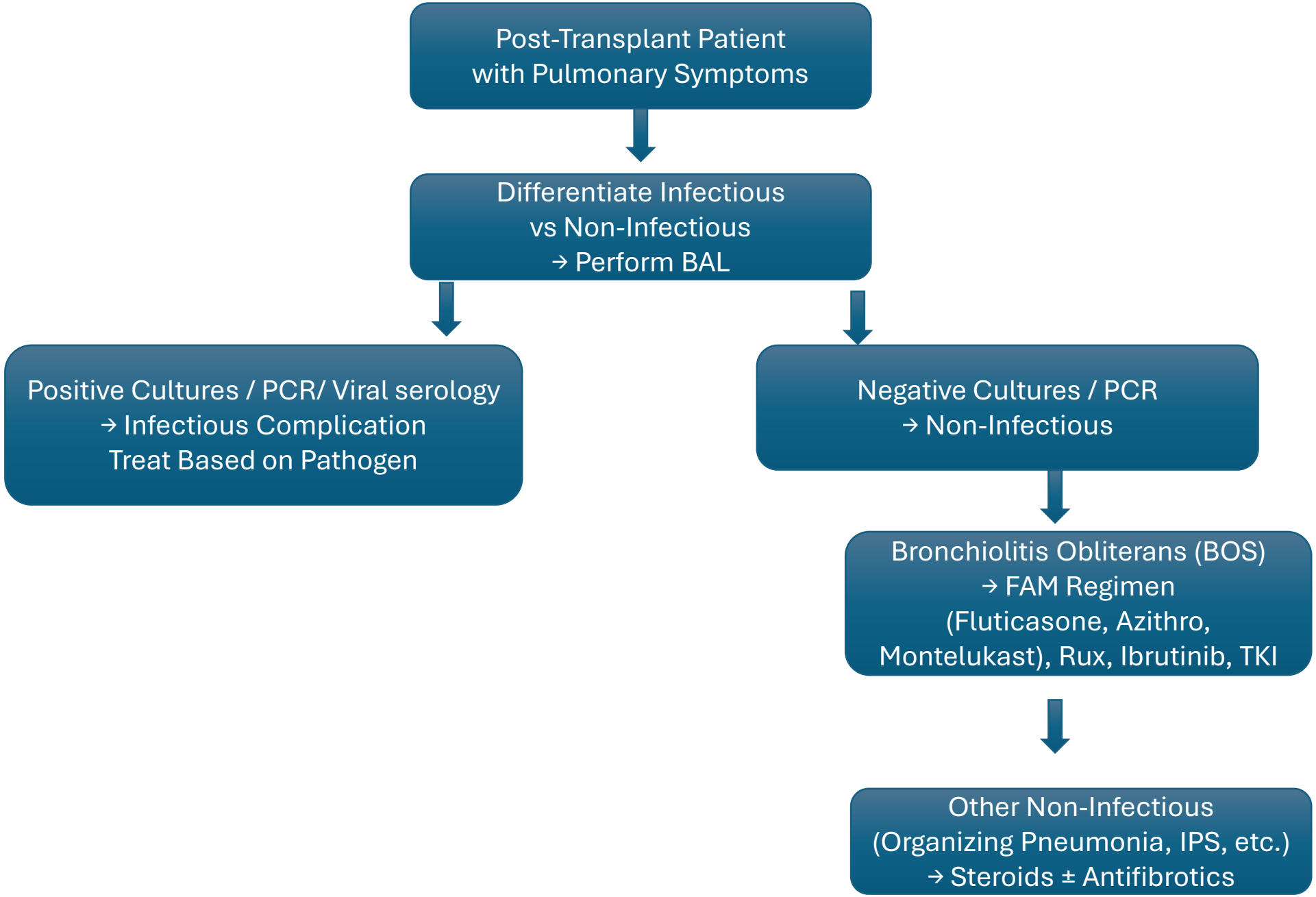
BMT MASTER CLASS

December 2025

Non infectious pulmonary complications post transplant

Dr Pravas Mishra

Amrita Hospital Faridabad

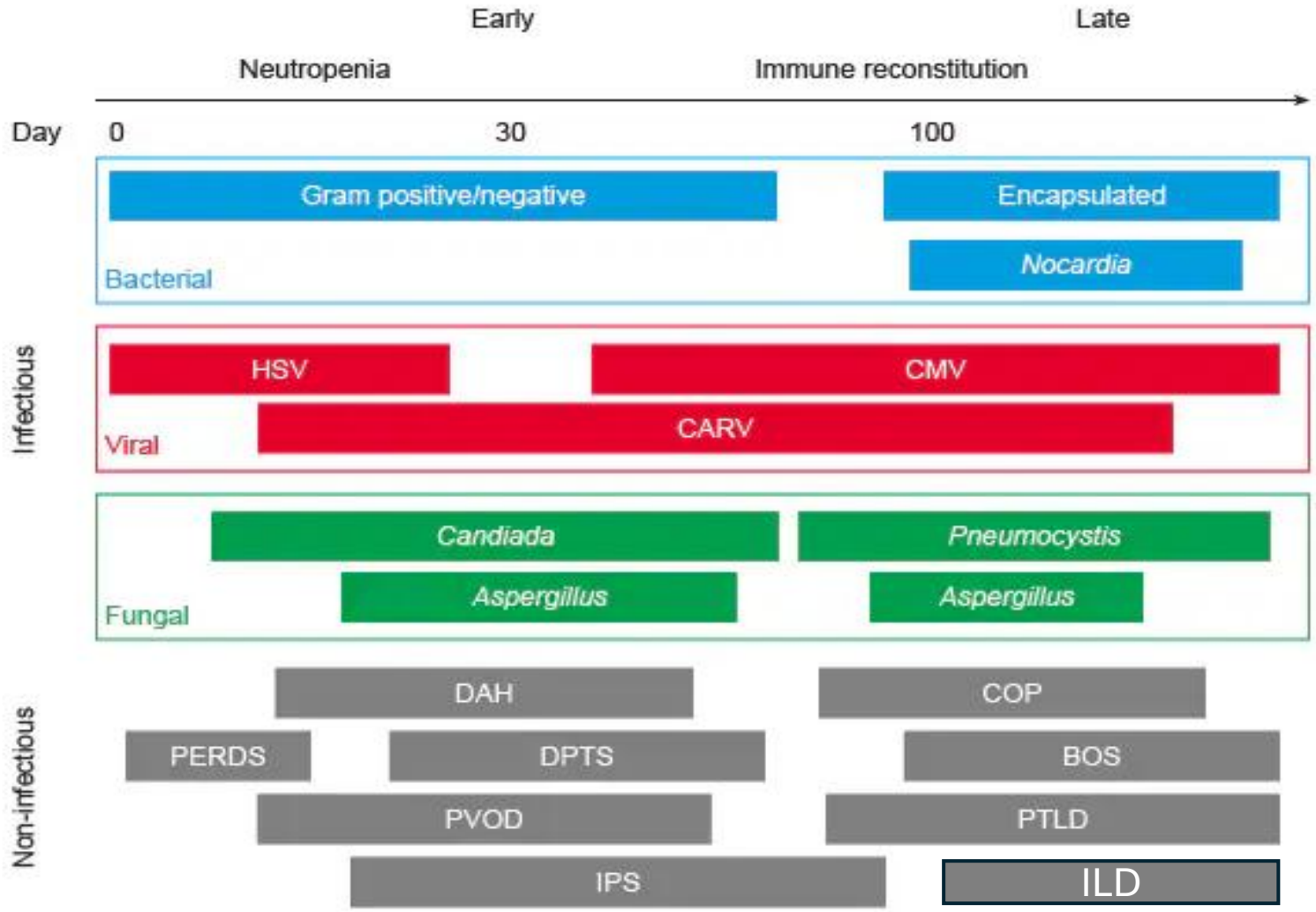

Post-Transplant Patient
with Pulmonary Symptoms
Differentiate Infectious
vs Non-Infectious
→ Perform BAL
Positive Cultures / PCR/ Viral serology
→ Infectious Complication
Treat Based on Pathogen
Negative Cultures / PCR
→ Non-Infectious
Bronchiolitis Obliterans (BOS)
→ FAM Regimen
(Fluticasone, Azithro,
Montelukast), Rux, Ibrutinib, TKI
Other Non-Infectious
(Organizing Pneumonia, IPS, etc.)
→ Steroids ± Antifibrotics

BAL – Cultures and serology	Routine bacterial culture; Acid-fast bacilli; Fungal Culture; BAL Galactomannan
Molecular / Serologic Tests	Biofire PCR: human metapneumovirus, rhinovirus, coronavirus, HHV-6; PCR: CMV Serum galactomannan ELISA (Aspergillus) Serum Beta D Glucan
Histopathology (if feasible)	Transbronchial lung biopsy
Noninfectious Causes	No cardiac dysfunction; No acute renal failure; No iatrogenic fluid overload

ARDS

30%-40% of recipients will have a pulmonary complication

5% have an ARDS with 60% mortality.



Early

PERDS = Peri-engraftment respiratory distress syndrome;
DAH = diffuse alveolar hemorrhage;
DPTS: Delayed pulmonary toxicity syndrome
PVOD: Pulmonary Vaso occlusive disease
IPS = idiopathic pneumonia syndrome;

Late/ delayed

BOS = bronchiolitis obliterans syndrome; Not to be confused with BOOP
ILD : Interstitial lung disease/ late onset interstitial Pneumonia
HCT-OP/COP/ BOOP = HCT or cryptogenic-organizing pneumonia;
PTLD: Post-transplant lymphoproliferative disorder


P

Early Complications	Incidence & Risk Factors	Pathophysiology	Imaging Findings (CXR / HRCT)	Mortality	Management
Hydrostatic pulmonary edema / TACO-type volume overload	Fluid overload	Volume overload ± Increased capillary permeability from chemotherapy, radiation, sepsis.	CXR: bilateral perihilar/alveolar opacities, vascular congestion, Kerley B lines, pleural effusions. HRCT: **interlobular septal thickening + bilateral GGOs ± effusions**.	Reversible with adequate fluid management	Careful fluid balance
Transfusion-related acute lung injury (TRALI)	Occurs within **6 h of plasma-rich blood products** (platelets, FFP, cryo)	Recipient primed neutrophils in pulmonary microvasculature + donor antibodies → neutrophil activation, capillary endothelial injury → noncardiogenic pulmonary edema.	Acute bilateral alveolar infiltrates similar to ARDS; Normal **LV function** .	5–20% in non-HSCT cohorts; likely higher in HSCT because of comorbid illness	Prevention: Nulliparous/male-only plasma donor strategies.

Early Complications	Incidence & Risk Factors	Pathophysiology	Imaging Findings (CXR / HRCT)	Mortality	Management
Idiopathic pneumonia syndrome (IPS)	**2–15%** Occurs typically **2–6 weeks** post-transplant. Risk factors: MAC TBI Pre-existing lung disease, GVHD, Possibly prior pulmonary toxic chemotherapy.	Widespread alveolar injury. Cytokine storm (TNF-α, other inflammatory mediators)	Diffuse or patchy **bilateral GGOs and consolidations**,	**High mortality**, often **50–80%** .	High-dose systemic steroids (eg methylpred); ?Etanercept.
Diffuse alveolar hemorrhage (DAH)	F**irst 4 weeks** post-HCT, Incidence **2–14%**. MAC TBI Cord blood Thrombocytopenia	Acute **diffuse alveolar-capillary membrane injury** with intra-alveolar bleeding; BAL shows **progressively bloodier aliquots** ± hemosiderin-laden macrophages.	IPS like	**Mortality 64–100%** in series.	**High-dose IV steroids** (eg pulse methylpred), ± **antifibrinolytic** (aminocaproic acid, tranexamic acid)
Peri-engraftment respiratory distress syndrome (PERDS) (engraftment syndrome-associated lung injury)	Occurs **around neutrophil recovery** (often days 0 to +7) in auto- and allo-HCT. Risk factors: higher CD34+ cell dose, prior radiation, female sex, myeloablative regimens	Systemic **capillary leak** linked to engraftment cytokine surge (IL-1, IL-6, TNF-α) → non-cardiogenic pulmonary edema + fever, rash, weight gain, sometimes hepatic/renal dysfunction	IPS like	**10–30%** mortality	**Steroids**

Late onset non infectious pulmonary complication : LONIPC

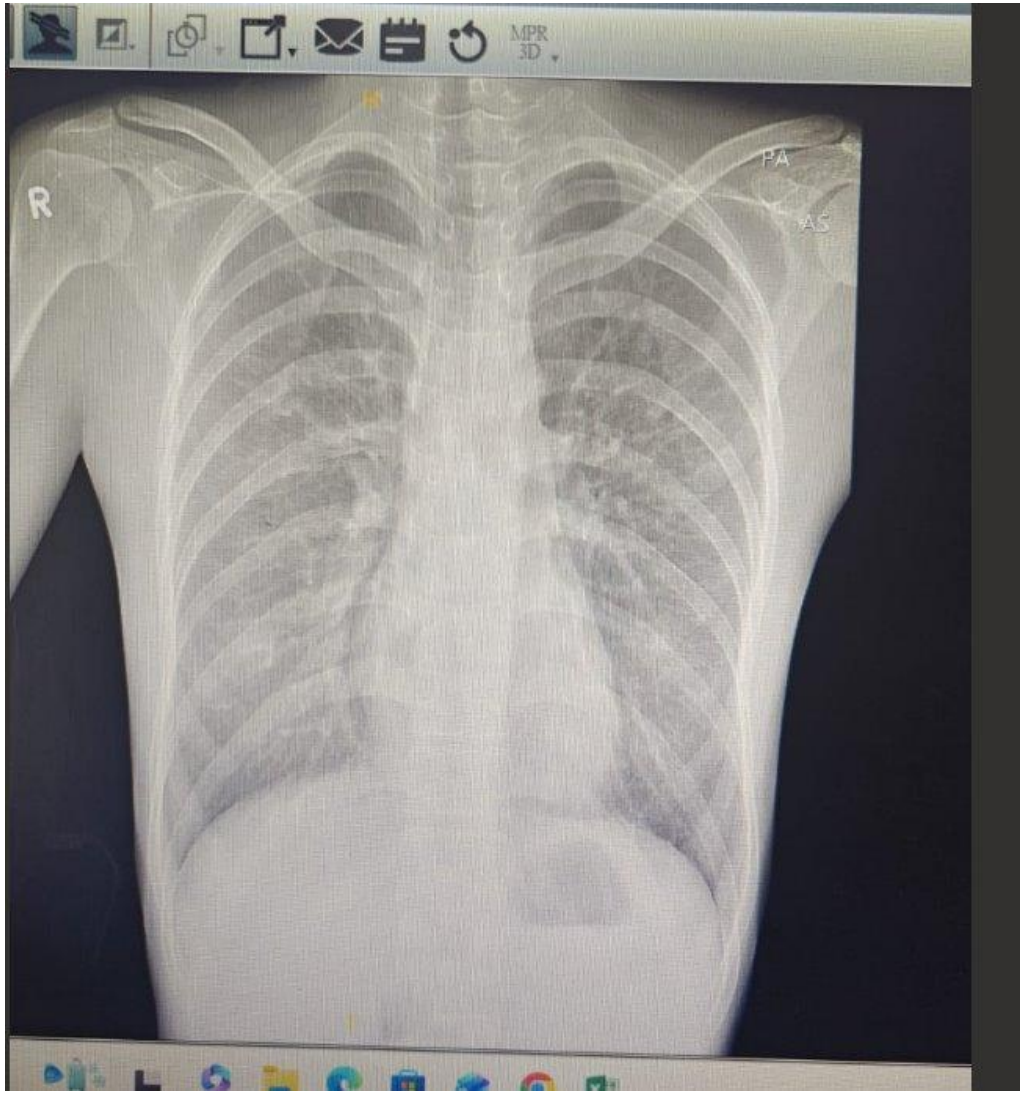
AML, 23 year old

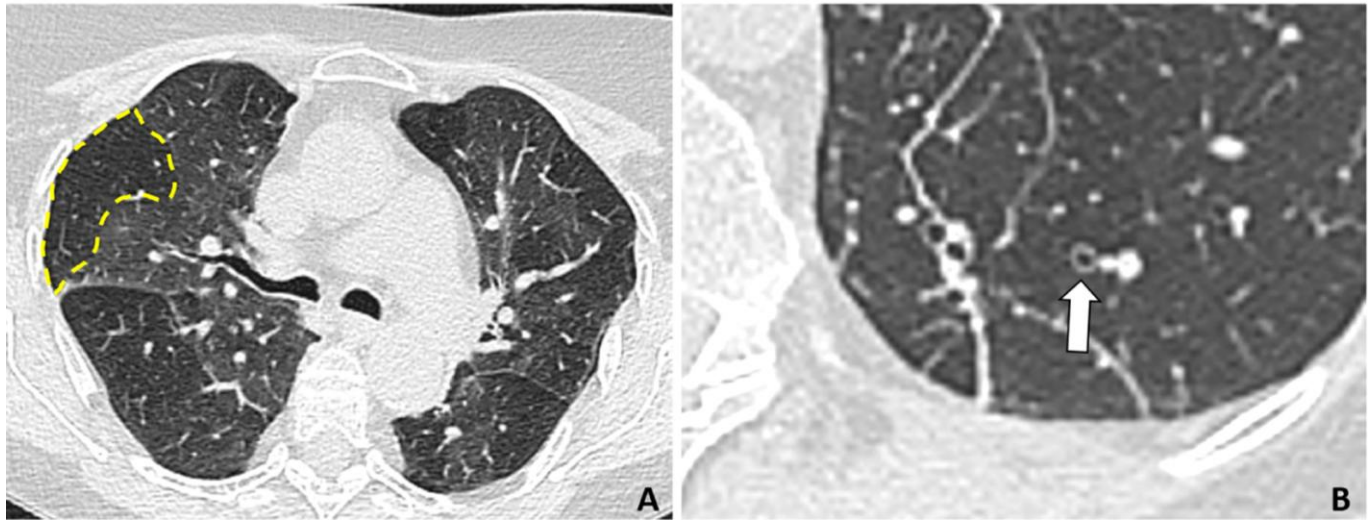
- Fludarabine Busulfan
- 2020
- Oral GVHD
- 6 months post transplant
- January 2021 ? COVID
- Progressive insidous breathlessness
- Oxygen requirement
- Ibrutinib, Ruxolitinib, Imatinib
- No improvement: died after 4 months of breathlessness

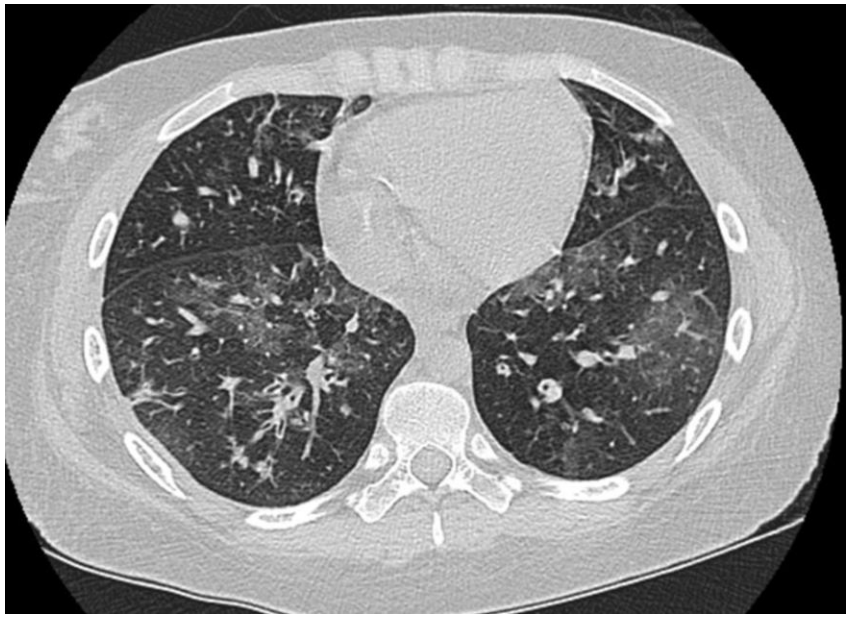
Aplastic anemia: 20 year old

- Fludarabine Cyclophosphamide
- Post engraftment : TMA cyclosporine --> Mycophenolate
- Skin and liver GVHD
- 18 months post Tx: Breathlessness on exertion
- SIGNIFICANT Weight loss
- Progressive dyspnea
- Required increasing oxygen support
- Died

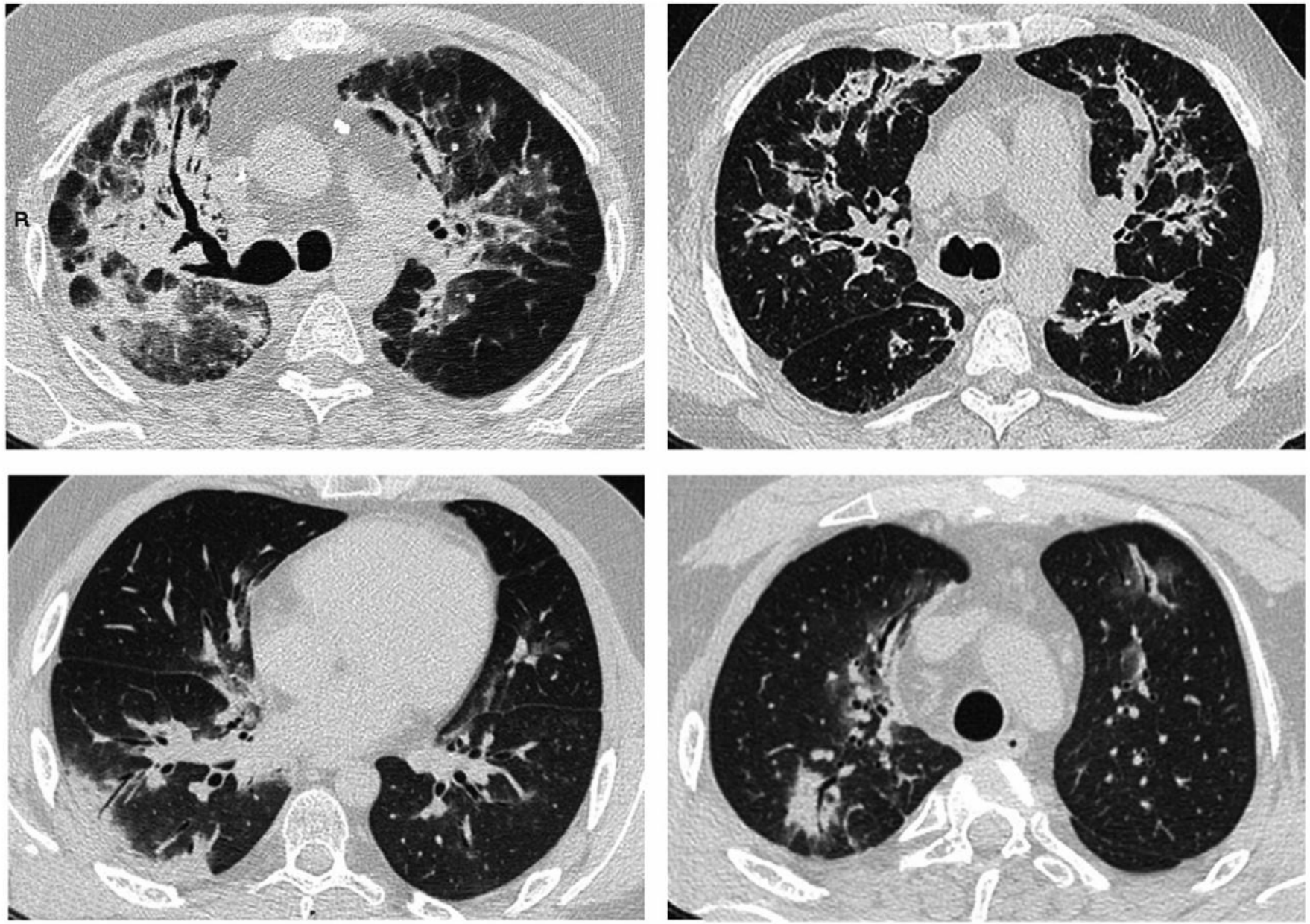
Category	LONIPC Entity	Key Features
Airway	**Bronchiolitis obliterans / Bronchiolitis obliterans syndrome (BOS)**	
Parenchymal	**Transplant-associated Organizing Pneumonia (T-OP/BOOP)**	
	Late-onset Interstitial Pneumonia / Interstitial Lung Disease (IP/ILD)	
	Pleuroparenchymal Fibroelastosis (PPFE)	
	Pulmonary Alveolar Proteinosis (PAP)	Surfactant accumulation due to macrophage dysfunction; CT “crazy paving” (GGO + septal thickening), Post-HSCT cases linked to drugs (e.g., ruxolitinib, sirolimus) and chronic GVHD; diagnosed on BAL (milky PAS-positive material).
Vascular	**Pulmonary Arterial Hypertension (PAH)**	Rare; risk with cyclophosphamide, busulfan, GVHD, prior VOD; Progressive dyspnea, RV failure; diagnosed by echo + right heart cath; treat with PAH-targeted therapy (NO, prostacyclin, endothelin-pathway agents); delays increase mortality.
	Venous Thromboembolism (VTE: DVT/PE)	1-year incidence ~4–7%; often within first 3–6 months but can be late;
	Pulmonary Cytolytic Thrombi (PCT)	Rare; usually 2–6 months post-HSCT, predominantly pediatric; nodular infiltrates; biopsy shows leukocyte-rich thrombi with basophilic cytolytic debris in pulmonary capillaries; considered lung GVHD manifestation; responds well to systemic steroids, good prognosis.


MPR
3D
R
PA
AS





BOS: Transplant Cell Ther. 2024 Sep;30(9S):S585-S596.

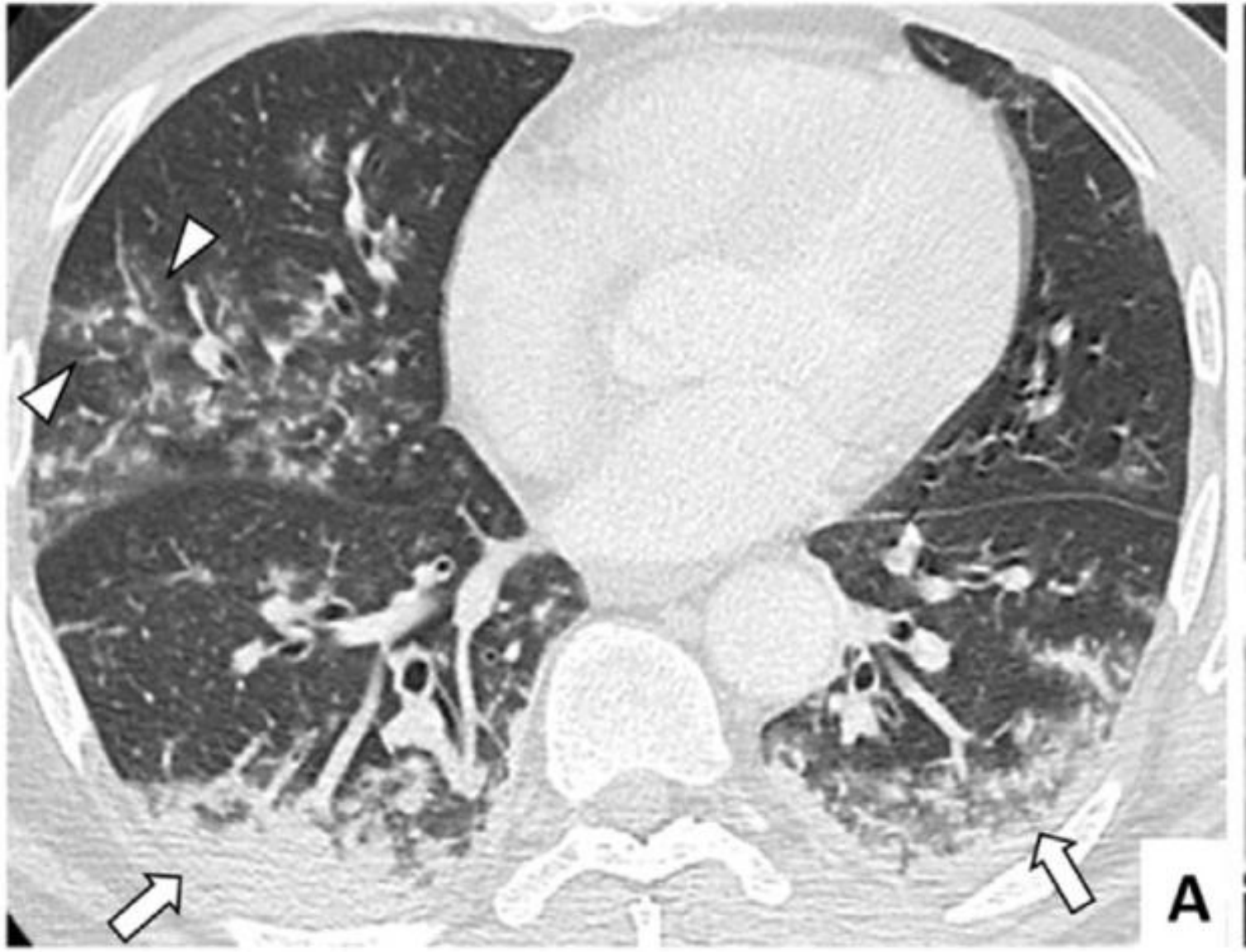


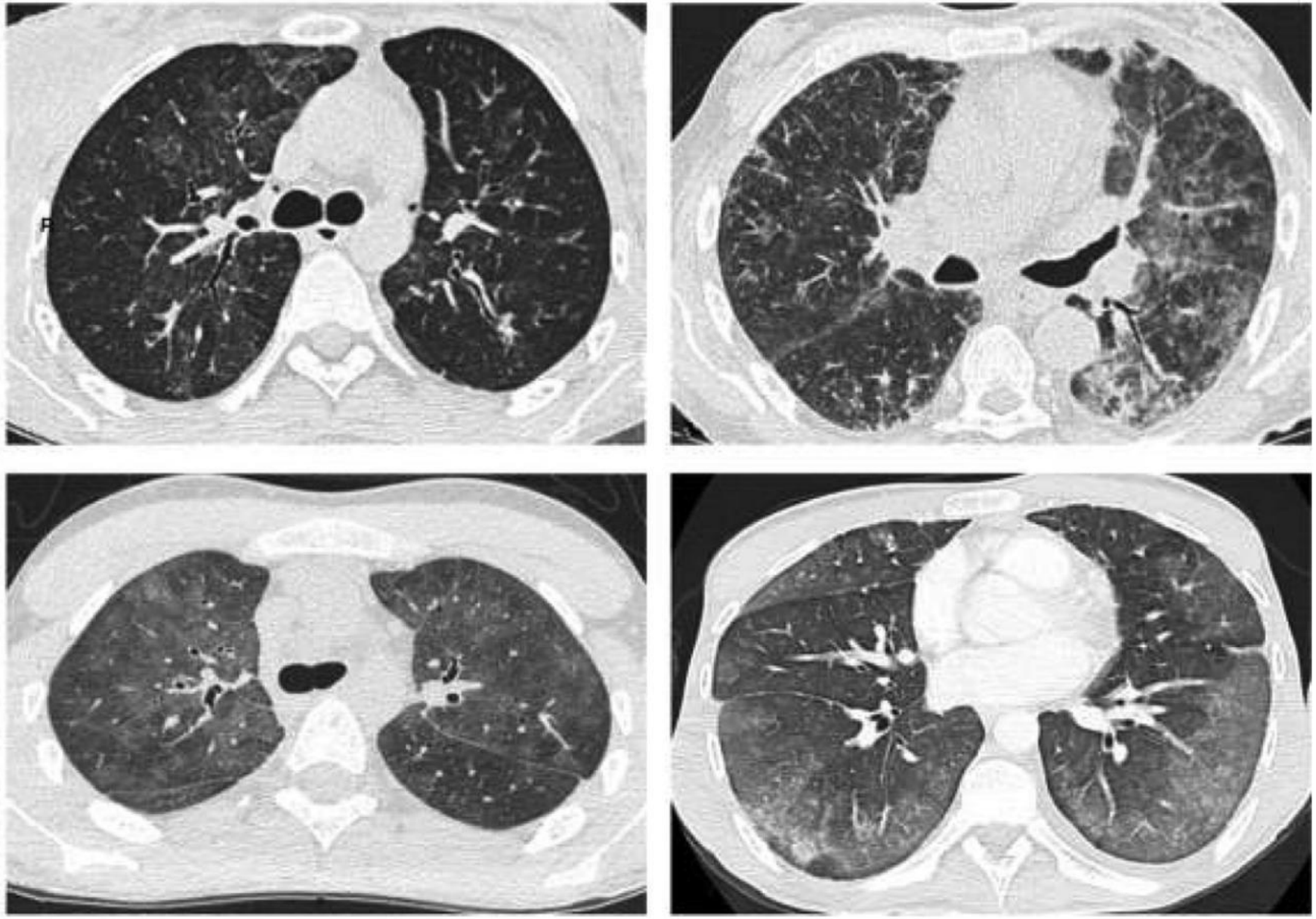
ILD/ late onset interstitial pneumonia :Respir Med. 2014 Oct;108(10):1525-33.

Interstitial pneumonia

Subpleural consolidative opacities (Arrows)

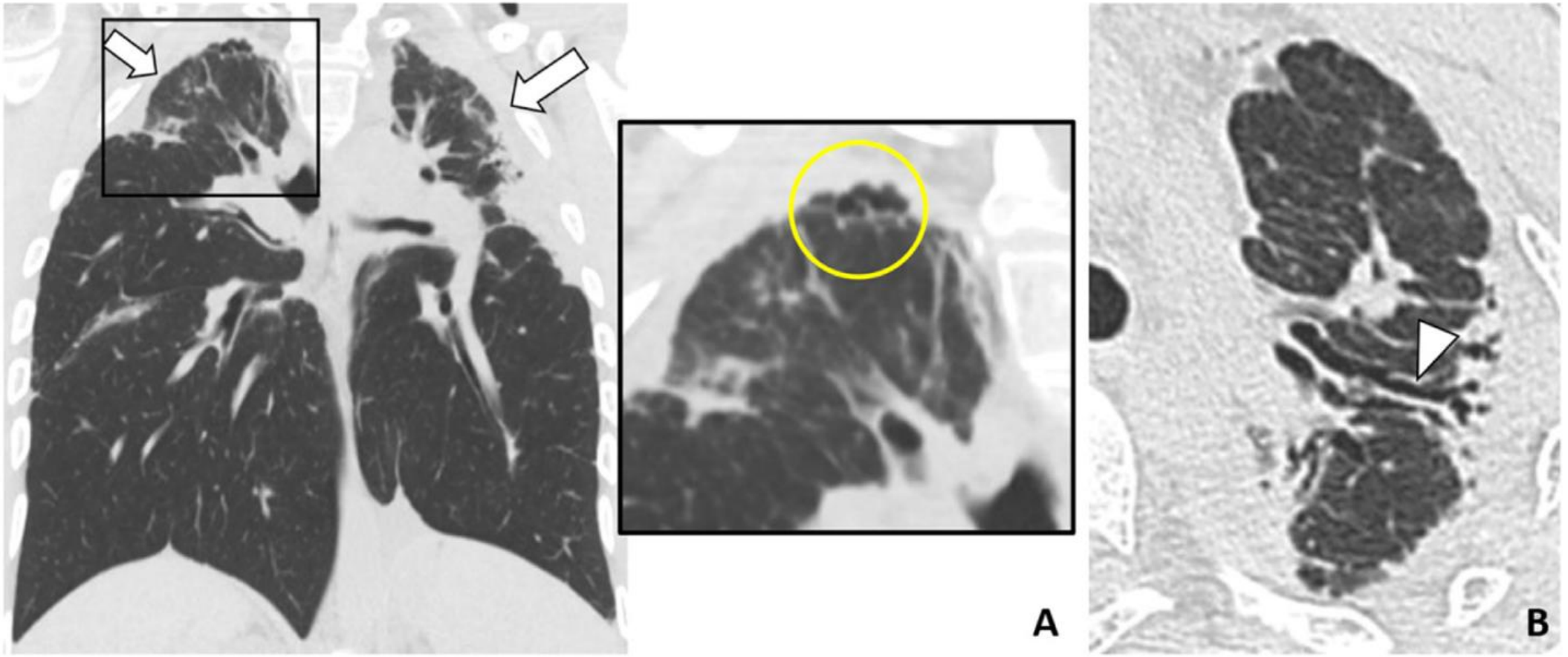
Peri-bronchial ground glass opacities (Arrowheads)





ILD/ late onset interstitial pneumonia :Respir Med. 2014 Oct;108(10):1525-33.

Pleuroparenchymal Fibroelastosis



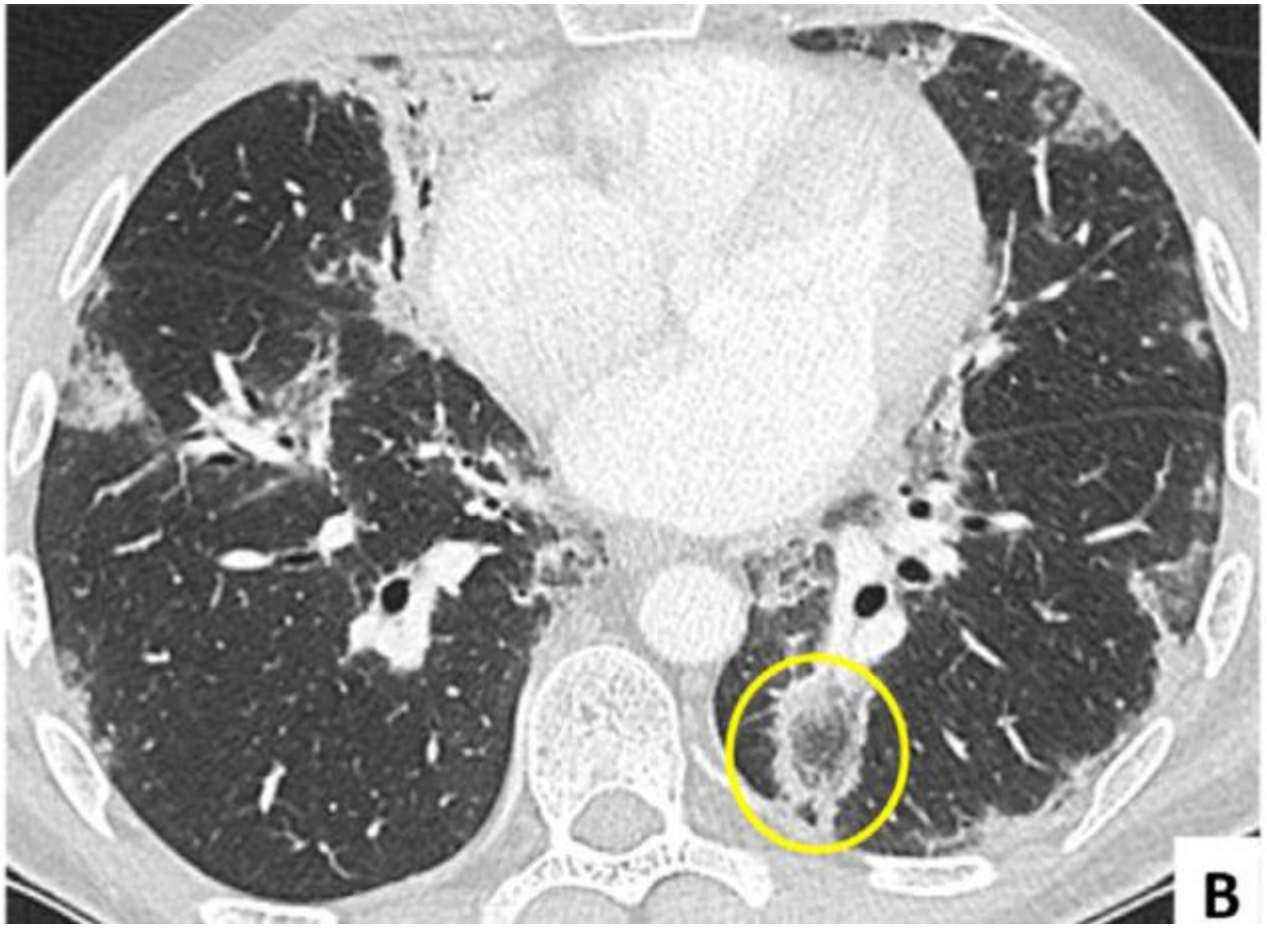
Organizing pneumonia

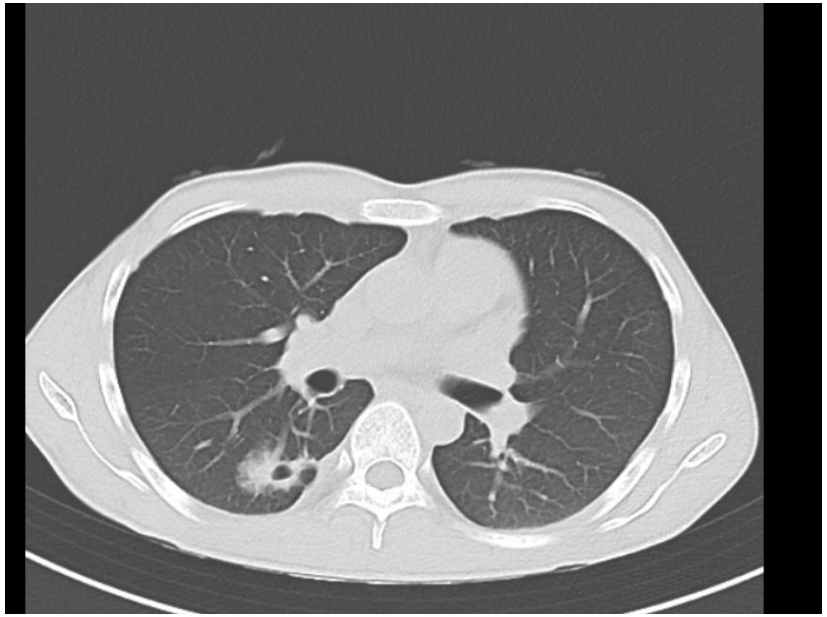
Ground Glass opacities: Not peri bronchial unlike ILD

Peripheral distribution

Subpleural lesions

Reverse halo: Central ground glass with peripheral consolidations





24 year old

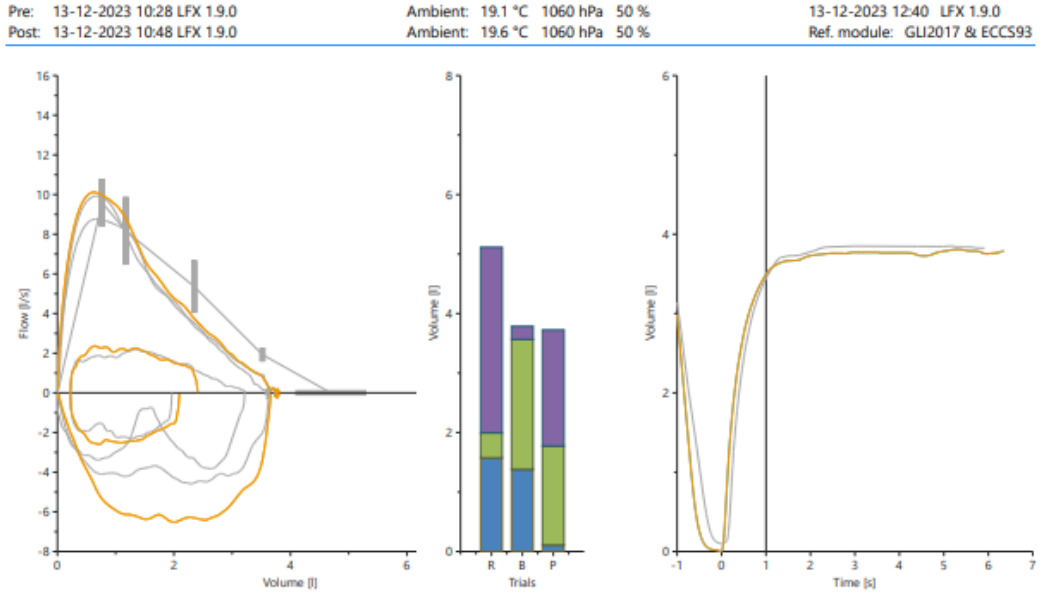
Philadelphia positive ALL

Poor Graft function

8 Months post transplant : fever , cough

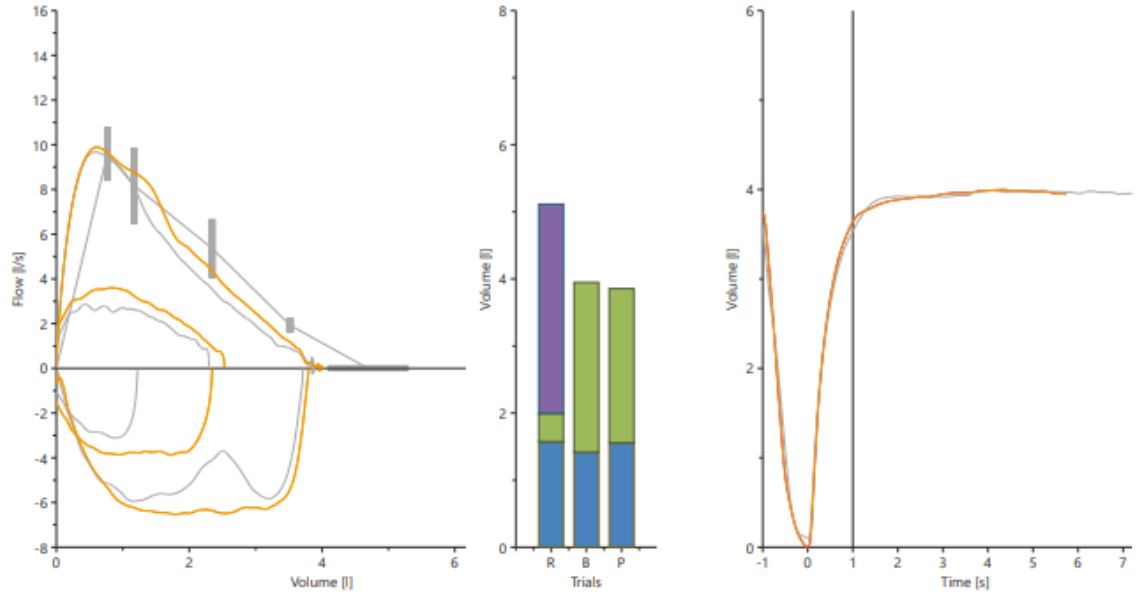
No dypnea

BAL, LDH, fungal biomarkers : No pathogen



		Pred	Pre	Pre % Pred	LLN	Post	% Pred	Z-Score	% Change
VC IN	[L]	4.55	3.63	80 %	3.63	3.66	80 %	-1.6	1 %
FVC	[L]	4.69	3.72	79 %	3.84	3.78	81 %	-1.7	2 %
FEV 1	[L]	3.98	3.48	88 %	3.19	3.53	89 %	-0.9	1 %
FEV1%VCin	[%]	82.53	95.86	116 %	70.77	96.52	117 %	1.9	1 %
MEF 75	[L/s]	8.17	9.55	117 %	5.36	9.70	119 %	0.9	2 %
MEF 50	[L/s]	5.36	4.97	93 %	3.20	5.20	97 %	-0.1	5 %
MEF 25	[L/s]	1.93	2.39	124 %	1.06	2.41	125 %	0.7	1 %
MMEF	[L/s]	4.30	4.51	105 %	2.72	4.70	109 %	0.4	4 %
PEF	[L/s]	9.59	9.93	103 %	7.61	10.12	105 %	0.4	2 %

		Pred	Pre	% Pred	Z-Score
DLCO	[mmol/min/kPa]	11.36	6.14	54 %	-3.7
KCO	[mmol/min/kPa/L]	1.70	1.13	67 %	-1.3
VA	[L]	6.51	5.41	83 %	
TLC	[L]	6.66	5.76	86 %	-1.3
VC IN	[L]	4.55	3.78	83 %	-1.4
RV	[L]	1.60	1.88	118 %	0.7
FRC	[L]	3.17	2.88	91 %	-0.5
RV%TLC	[%]	24.10	32.68	136 %	1.6



		Pred	Pre	Pre % Pred	LLN	Post	% Pred	Z-Score	% Change
VC IN	[L]	4.55	3.72	82 %	3.63	3.80	84 %	-1.3	2 %
FVC	[L]	4.69	3.86	82 %	3.84	3.95	84 %	-1.4	2 %
FEV 1	[L]	3.98	3.53	89 %	3.19	3.69	93 %	-0.6	5 %
FEV1%VCin	[%]	82.53	95.09	115 %	70.77	97.19	118 %	2.1	2 %
MEF 75	[L/s]	8.17	9.04	111 %	5.36	9.10	111 %	0.5	1 %
MEF 50	[L/s]	5.36	4.78	89 %	3.20	5.46	102 %	0.1	14 %
MEF 25	[L/s]	1.93	2.19	114 %	1.06	2.58	134 %	0.9	17 %
MMEF	[L/s]	4.30	4.26	99 %	2.72	4.93	115 %	0.6	16 %
PEF	[L/s]	9.59	9.67	101 %	7.61	9.89	103 %	0.2	2 %

- 3 months of tapering steroids
- The CT scan cleared out
- No recurrence on stopping the steroids
- Note : the DLCO remains reduced

		Pred	Pre	% Pred	Z-Score
DLCO	[mmol/min/kPa]	11.36	6.99	62 %	-3.1
KCO	[mmol/min/kPa/L]	1.70	1.32	78 %	-0.8
VA	[L]	6.51	5.28	81 %	
TLC	[L]	6.66	6.06	91 %	-0.9
VC IN	[L]	4.55	4.10	90 %	-0.8
RV	[L]	1.60	1.96	123 %	0.9
FRC	[L]	3.17	3.76	119 %	1.0
RV%TLC	[%]	24.10	32.33	134 %	1.5

Test Name: Pneumoniae Plus Panel
Equipment: Film Array
Sample Type: BAL
Method: Multiplex PCR

Detection Summary:
Viruses : DETECTED ----Human Rhinovirus/Enterovirus

Result Summary

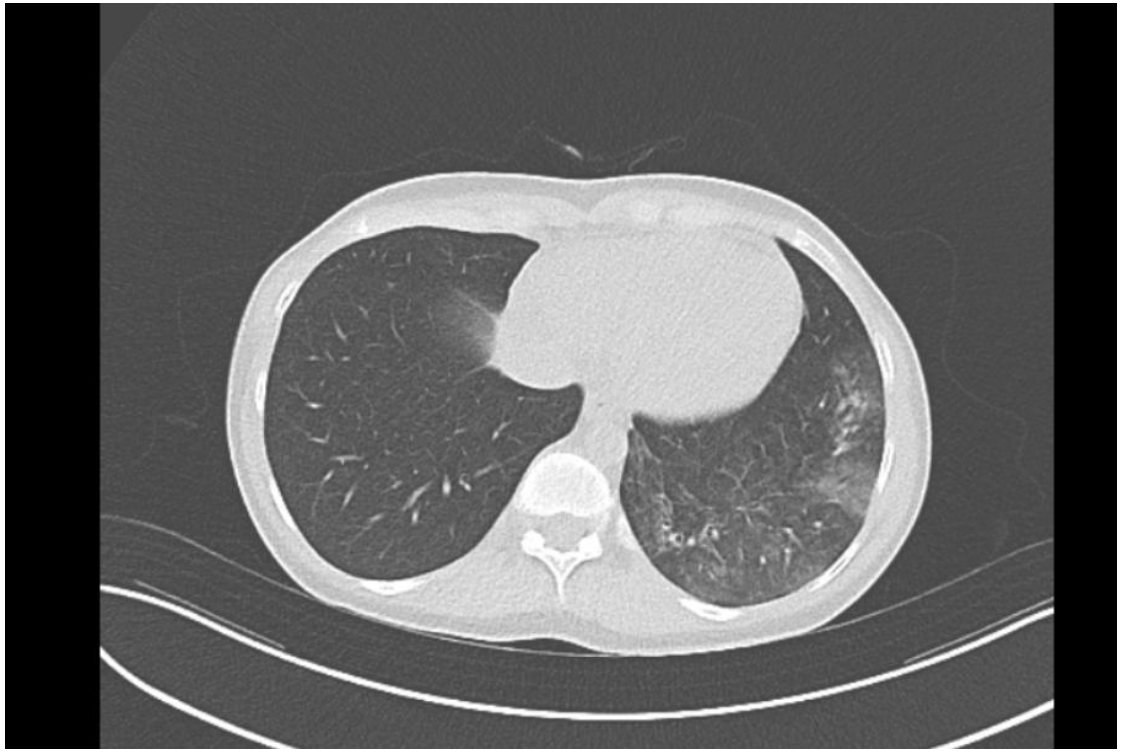
Result	Pathogen	Bin(copies/mL)

BACTERIA
Not Detected ----Acinetobacter calcoaceticus baumannii - complex
Not Detected ----Enterobacter cloacae complex
Not Detected ----Escherichia coli
Not Detected ----Haemophilus influenza
Not Detected ----Klebsiella aerogenes
Not Detected ----Klebsiella oxytoca
Not Detected ----Klebsiella pneumoniae group
Not Detected ----Moraxella catarrhalis
Not Detected ----Proteus spp.
Not Detected ----Pseudomonas aeruginosa
Not Detected ----Serratia marcescens
Not Detected ----Staphylococcus aureus
Not Detected ----Streptococcus agalactiae
Not Detected ----Streptococcus pneumoniae
Not Detected ----Streptococcus pyogenes

ATYPICAL BACTERIA
Not Detected ----Chlamydia pneumoniae
Not Detected ----Legionella pneumophila

Not Detected ----Mycoplasma pneumoniae

VIRUSES
Not Detected ----Adenovirus
Not Detected ----Coronavirus(HKU1, NL63, 229E or OC43)
Not Detected ----Human metapneumovirus
DETECTED ----Human Rhinovirus/Enterovirus
Not Detected ----Influenza A
Not Detected ----Influenza B



Sample Collected D & T: 19/11/2025 11:26 **Sample Recd. D & T:** 19/11/2025 11:33 **Result Certified D & T:** 19/11/2025 15:26

Findings:

Test Name: Respiratory Panel
Equipment: QIAstat
Sample Type: Nasopharyngeal swab
Method: Multiplex PCR

Detection Summary: Human Rhinovirus/Enterovirus
Bacteria: None
Viruses: Human Rhinovirus/Enterovirus

Result Summary

Result	Pathogen

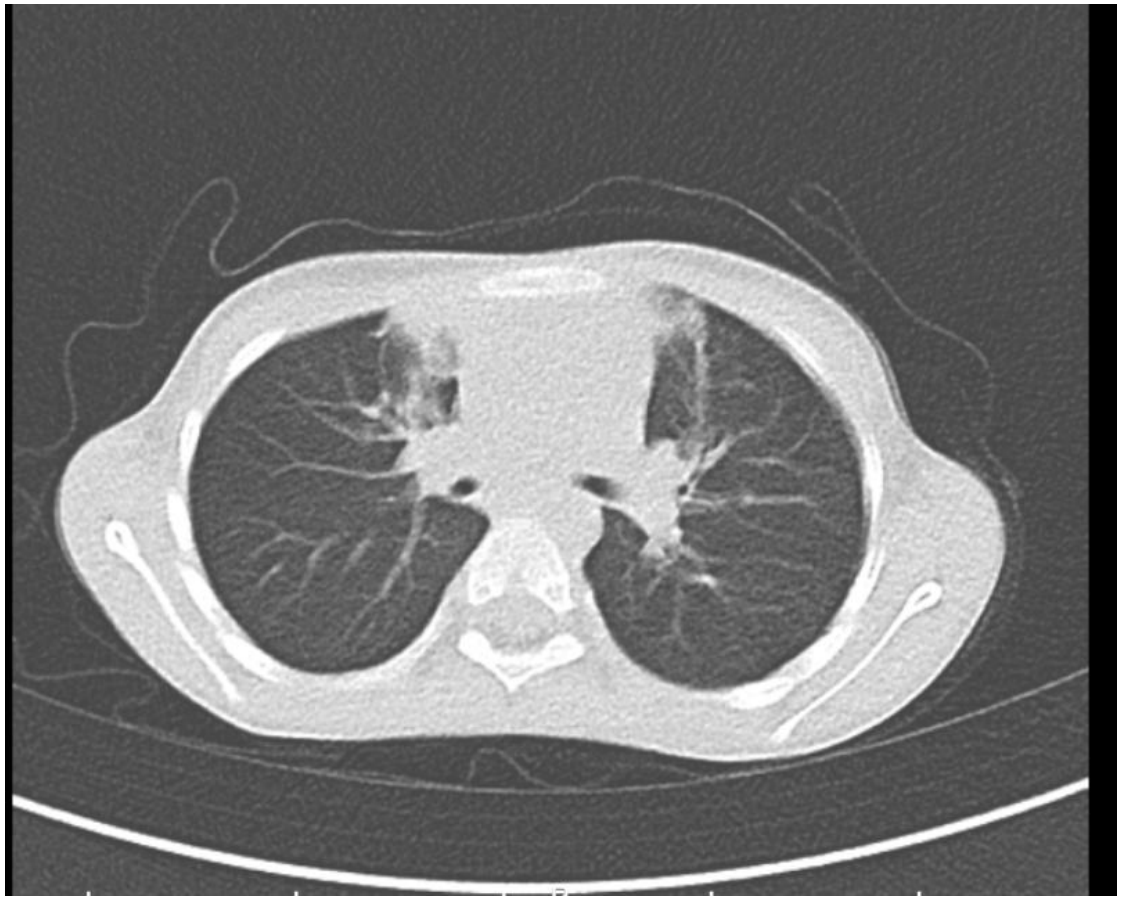
VIRUSES

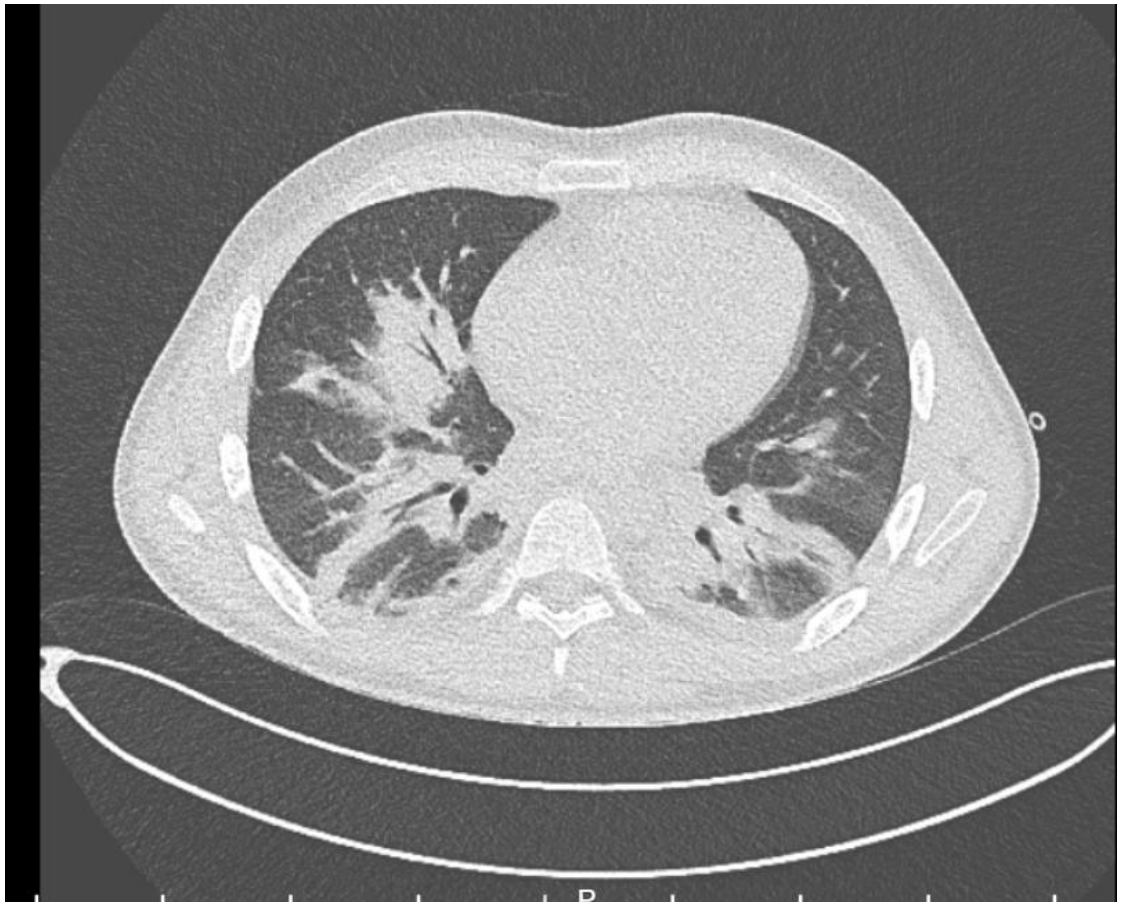
Not Detected ----Adenovirus
Not Detected ----Coronavirus 229E
Not Detected ----Coronavirus HKU1
Not Detected ----Coronavirus NL63
Not Detected ----Coronavirus OC43
Not Detected ----Human Metapneumovirus A+B
Detected ----Human Rhinovirus/Enterovirus
Not Detected ----Influenza A
Not Detected ----Influenza B
Not Detected ----Influenza A H1N1 pdm09
Not Detected ----Parainfluenza Virus 1
Not Detected ----Parainfluenza Virus 2
Not Detected ----Parainfluenza Virus 3
Not Detected ----Parainfluenza Virus 4
Not Detected ----Influenza A H1
Not Detected ----Influenza A H3

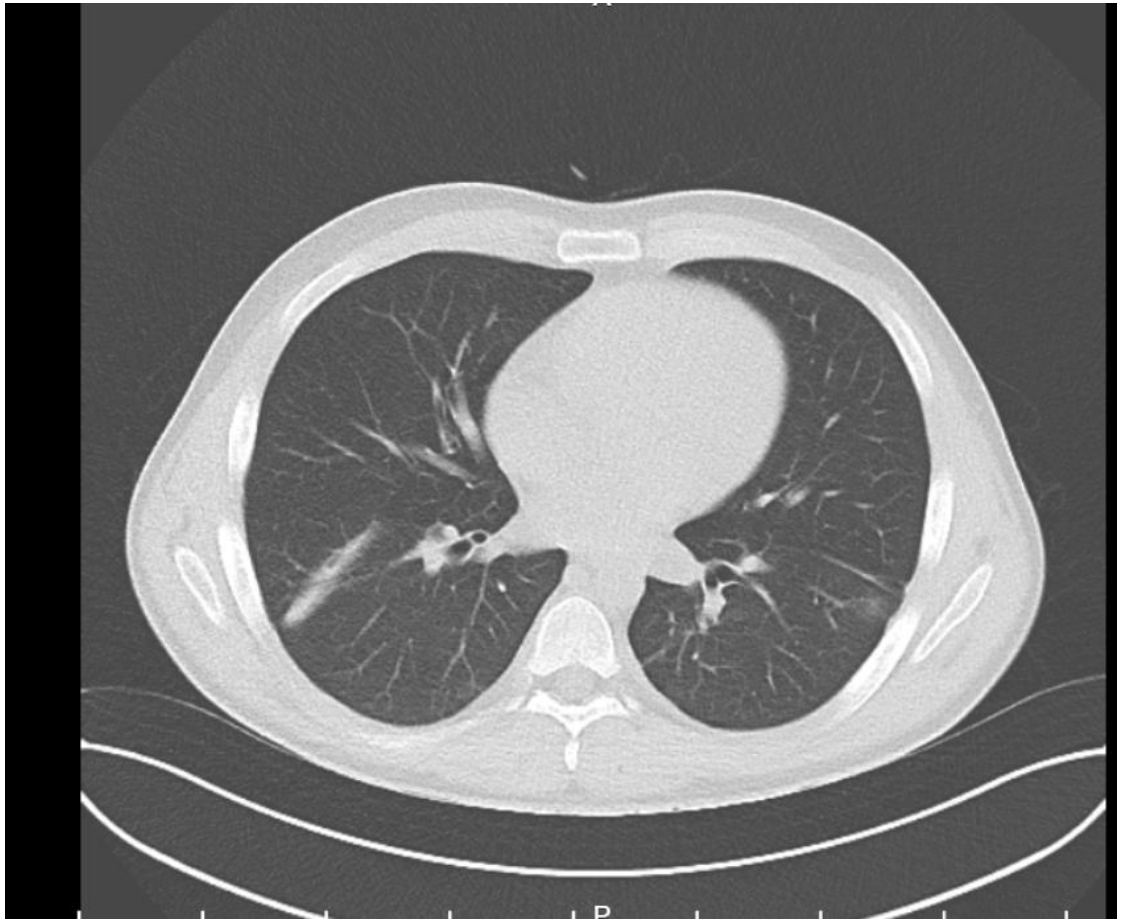
Not Detected ----Respiratory Syncytial Virus A+B
Not Detected ----Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)
Not Detected -----Bocavirus

BACTERIA

Not Detected ---- Bordetella pertussis
Not Detected ---- Mycoplasma pneumoniae
Not Detected ---- Legionella pneumphila

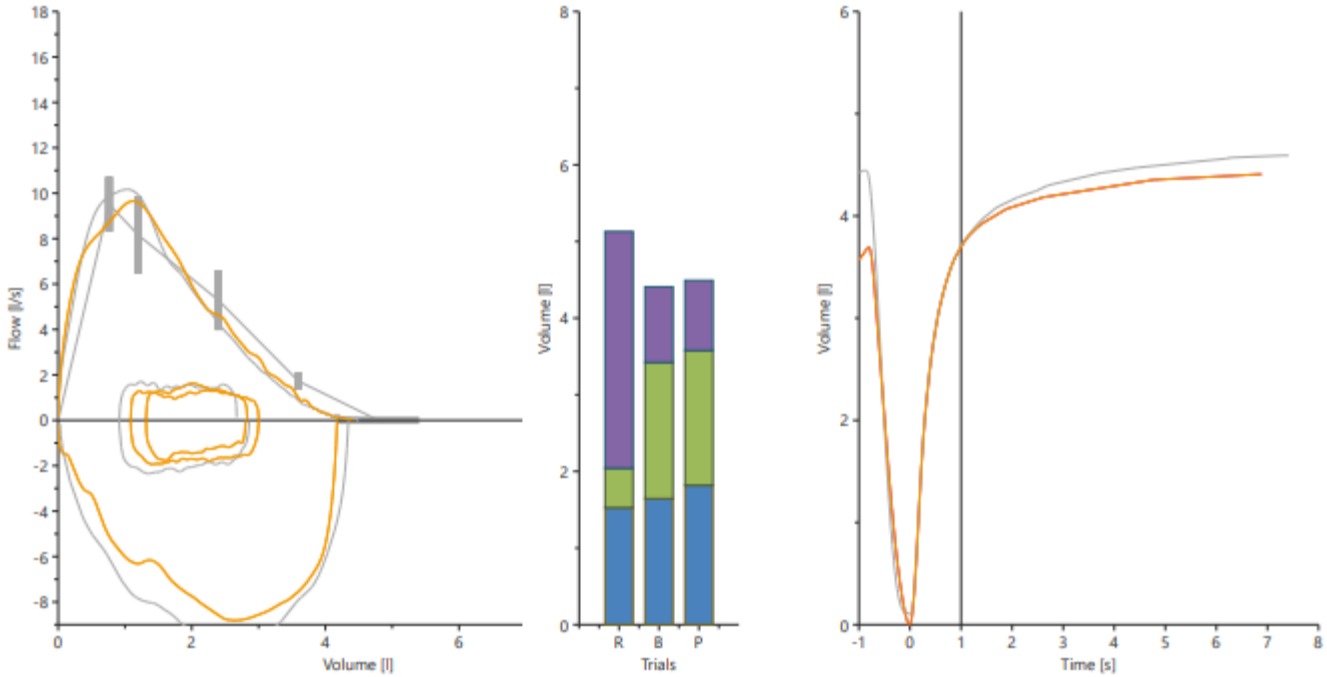






Patient Id	205056	Gender	male	Technician	Mr.Prashant Pathak

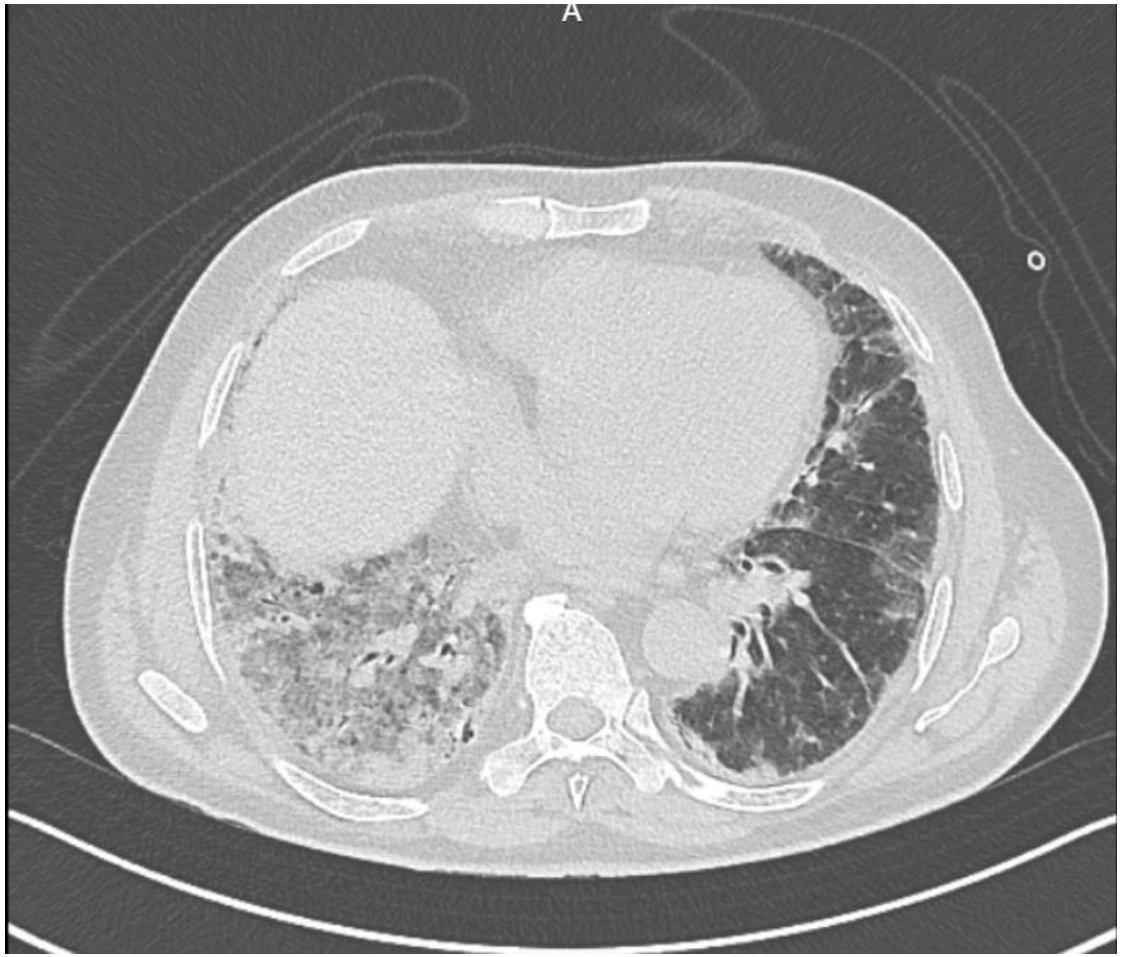
Pre: 24-10-2025 11:43 LFX 1.9.0 Ambient: 25 °C 1013 hPa 40 %
Post: 24-10-2025 11:52 LFX 1.9.0 Ambient: 25.1 °C 1013 hPa 40 %
24-10-2025 16:23 LFX 1.9.0
Ref. module: GLI2017 & ECCS93

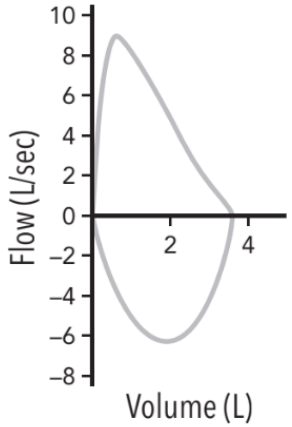
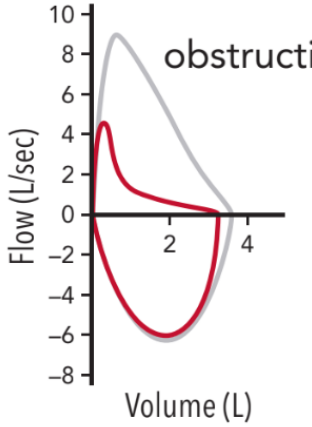
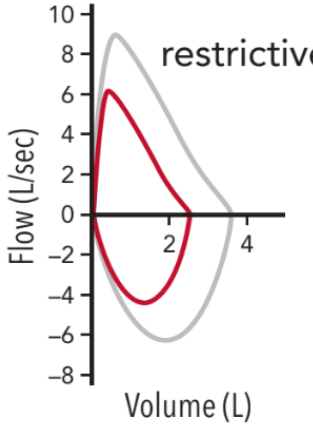
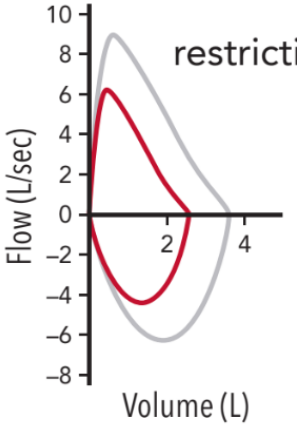


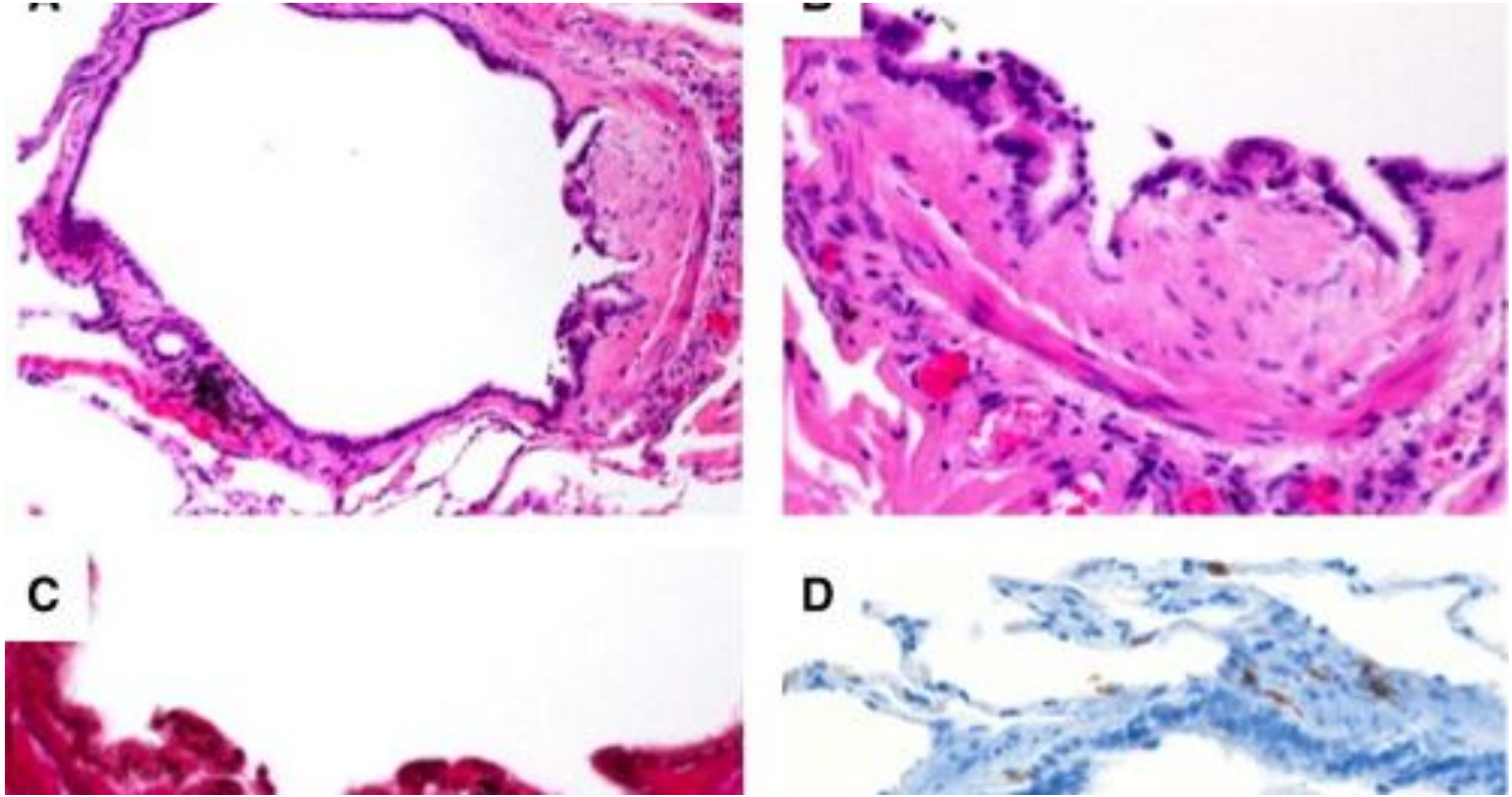
		Pred	Pre	Pre % Pred	LLN	Post	% Pred	Z-Score	% Change
VC IN	[L]	4.56	4.34	95 %	3.65	4.17	91 %	-0.7	-4 %
FVC	[L]	4.79	4.49	94 %	3.90	4.41	92 %	-0.7	-2 %
FEV 1	[L]	3.99	3.66	92 %	3.17	3.74	94 %	-0.5	2 %
FEV1%VCin	[%]	81.45	84.34	104 %	69.69	89.62	110 %	1.5	6 %
MEF 75	[L/s]	8.16	10.14	124 %	5.35	9.62	118 %	0.9	-5 %
MEF 50	[L/s]	5.29	4.88	92 %	3.12	5.02	95 %	-0.2	3 %
MEF 25	[L/s]	1.72	1.41	82 %	0.92	1.82	106 %	0.2	29 %
MMEF	[L/s]	4.13	3.78	92 %	2.53	4.33	105 %	0.2	15 %
PEF	[L/s]	9.52	10.17	107 %	7.53	9.65	101 %	0.1	-5 %

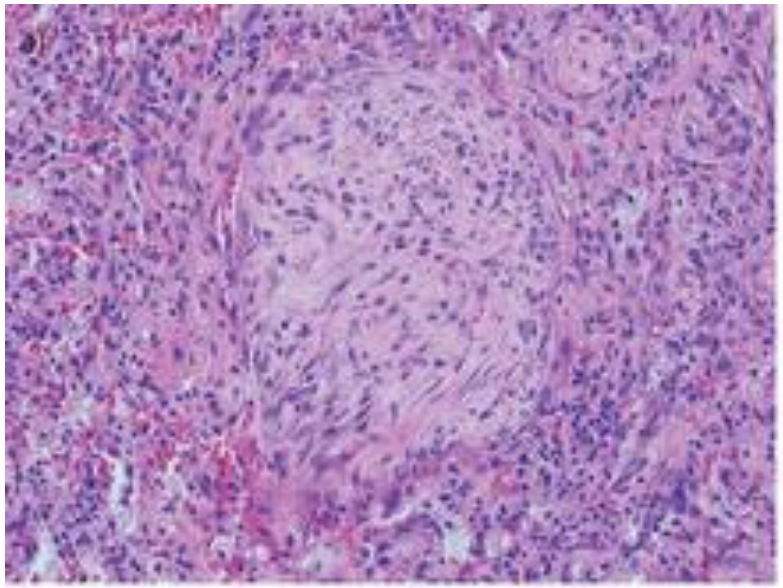
		Pred	Pre	% Pred	Z-Score
DLCO	[mmol/min/kPa]	11.30	10.10	89 %	-0.8
KCO	[mmol/min/kPa/L]	1.64	1.68	102 %	0.1
VA	[L]	6.75	6.03	89 %	
TLC	[L]	6.90	6.32	92 %	-0.8
VC IN	[L]	4.56	4.20	92 %	-0.7
RV	[L]	1.77	2.10	119 %	0.8
FRC	[L]	3.29	3.66	111 %	0.6
RV%TLC	[%]	26.44	33.19	126 %	1.2

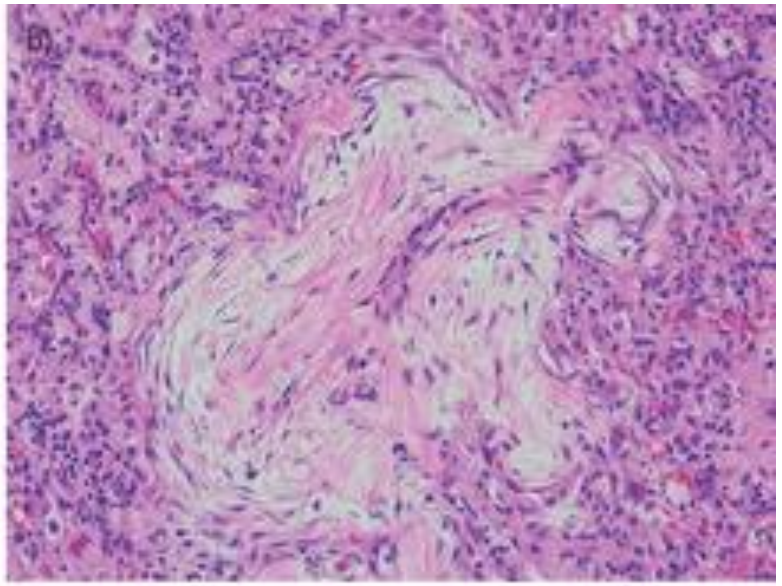

P

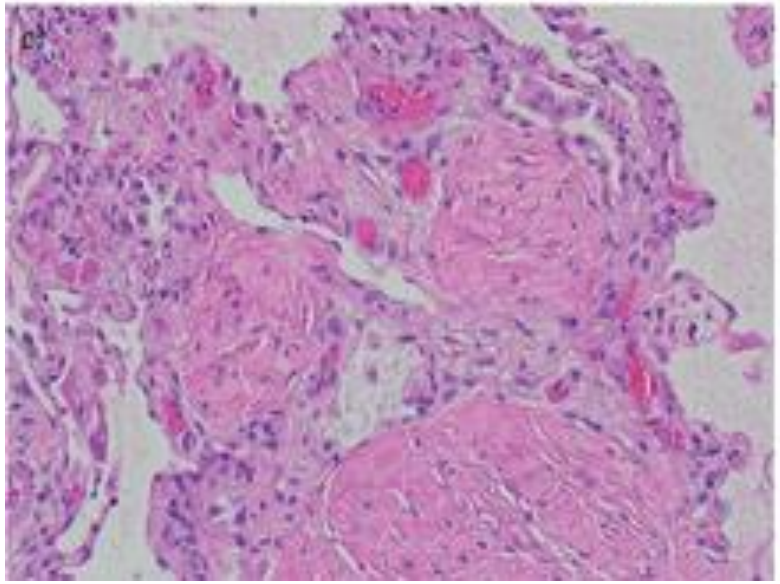

A

PFT		Normal	BOS	HCT-OP	Truncal Sclerosis
	Flow-volume Loop/ Spirometric Pattern				
	FEV_1	>80%	↓	↓	↓
	FVC	>80%	Normal or ↑	↓	↓
	FEV_1/FVC	>70%	↓	Normal or ↑	Normal or ↑
	DLCO	>80%	Normal or ↓	↓	Normal or ↓


C
D







Masson body (intraluminal plug of mucopolysaccharide-rich fibroblast proliferation without evidence of collagenous fibrosis)

ORGANIZING PNEUMONIA

BOS NIH CRITERIA

- **A (Airflow obstruction):** FEV_1 <75% with ≥10% decline in predicted FEV1 with FEV_1/FVC <0.7
- **B (Exclude infection):** Negative BAL/PCR; no active infectious pneumonia
- **C (Small airway disease):** Air trapping on CT **or** RV >120% **or** histologic OB or pre existing diagnosis of chronic GVHD

	Bronchiolitis Obliterans / BOS	Late-Onset Interstitial Lung Disease (ILD / IP)	Transplant-Associated Organizing Pneumonia (T-OP / BOOP)
Incidence (allo-HSCT)	3–11% of allo-HSCT recipients. median onset ~11 months.	2% of allo-HSCT recipients; median onset ~11 months post-transplant.	Incidence ~1–11%; usually >100 days post-HSCT (median >100 days; range 41–538 days).
Typical timing	Late; usually >100 days	Late; median ~11.3 months	Late >100 days).
Risk factors / associations	GVHD; TBI conditioning; Infections	Acute/chronic GVHD, Older age, comorbidities; Prior pulmonary insults	Acute and chronic GVHD, Prior CMV infection, TBI-based conditioning; Sometimes post viral infection
Clinical presentation	Insidious onset. Later: exertional dyspnea, tachypnea, dry cough, wheeze New O_2 requirement.	Dyspnea most common; Cough frequent;	1–2 weeks of cough (≈87%), dyspnea (≈46%), fever (≈50%);
PFT pattern	Screening PFT can detect earlier **Obstructive pattern**	R**estrictive** but can be mixed.	Usually **restrictive**: sometimes mixed pattern;
Imaging – CT / HRCT	Air-trapping with mosaic attenuation, Small airway thickening, bronchiectasis. HRCT shows patchy low-attenuation regions adjacent to normal lung.	GGOs often with areas of consolidation; diffuse interstitial changes.	Bilateral, often migratory **alveolar infiltrates**: Peripheral/subpleural: GGOs and consolidations, reversed halo (“atoll”) sign is relatively specific.

Transplant Cell Ther. 2024 Sep;30(9S):S585-S596

	Bronchiolitis Obliterans / BOS	Late-Onset Interstitial Lung Disease (ILD / IP)	Transplant-Associated Organizing Pneumonia (T-OP / BOOP)
Histopathology	Concentric peribronchiolar fibrosis Luminal narrowing with fibrous and cellular lesions;	Interstitial inflammation/fibrosis, Diffuse alveolar damage Variable fibrosis;	Intraluminal plugs of loose fibroblastic connective tissue (“Masson bodies”) Underlying lung architecture preserved
Diagnostic approach: Exclude infections in all	Clinical + PFT + HRCT **PFT : Can detect earlier** Every 3 months post 100 days	Often diagnosed when OP-like picture does not fully explain course or response.	Suspect when “pneumonia”-like picture with negative microbiology and poor antibiotic response.
First-line treatment	FAM (inhaled fluticasone / Formoterol± azithromycin, montelukast) Short pulse of systemic steroids (e.g., ~1 mg/kg prednisone tapered over ≈1 month)	Systemic corticosteroids GVHD immunosuppression. .	Systemic corticosteroids are mainstay: Symptomatic improvements usually within 1–2 weeks, Radiologic resolution over weeks–months. Long, slow steroid taper (2–12 months); .
Prognosis	Chronic, often progressive; 5-year survival ≈50%. Lung transplant: 5-year survival ≈67% in selected patients.	Worse than T-OP: Many patients die of respiratory failure	Generally favorable

Transplant Cell Ther. 2024 Sep;30(9S):S585-S596

Inhaled long acting bronchodilators/ inhaled corticosteroids along with systemic immunosuppression

Adults

- Budesonide 800 mcg plus Formoterol 24 mcg BD inhaler (Symbicort 400/12 Turbohaler), OR Fluticasone 500 mcg plus Salmeterol 50 mcg BD : rinse mouth
- 2. Azithromycin 250 mg 3 days per week (Monday/Wednesday/Friday) PO.
- 3. Montelukast 10 mg once at night.

Children

- Inhaled fluticasone propionate 250 µg twice a day for children 6–11 years, and 500 µg twice a day for children over 12.
- Azithromycin at a dose of 5 mg/kg bw (max 250 mg) once a day, three days a week,
- Anti-leukotriene drug (montelukast) at a dose of 5 mg for children 6–14 years and 10 mg for children >15 years once a day at night

FAM Mechanism

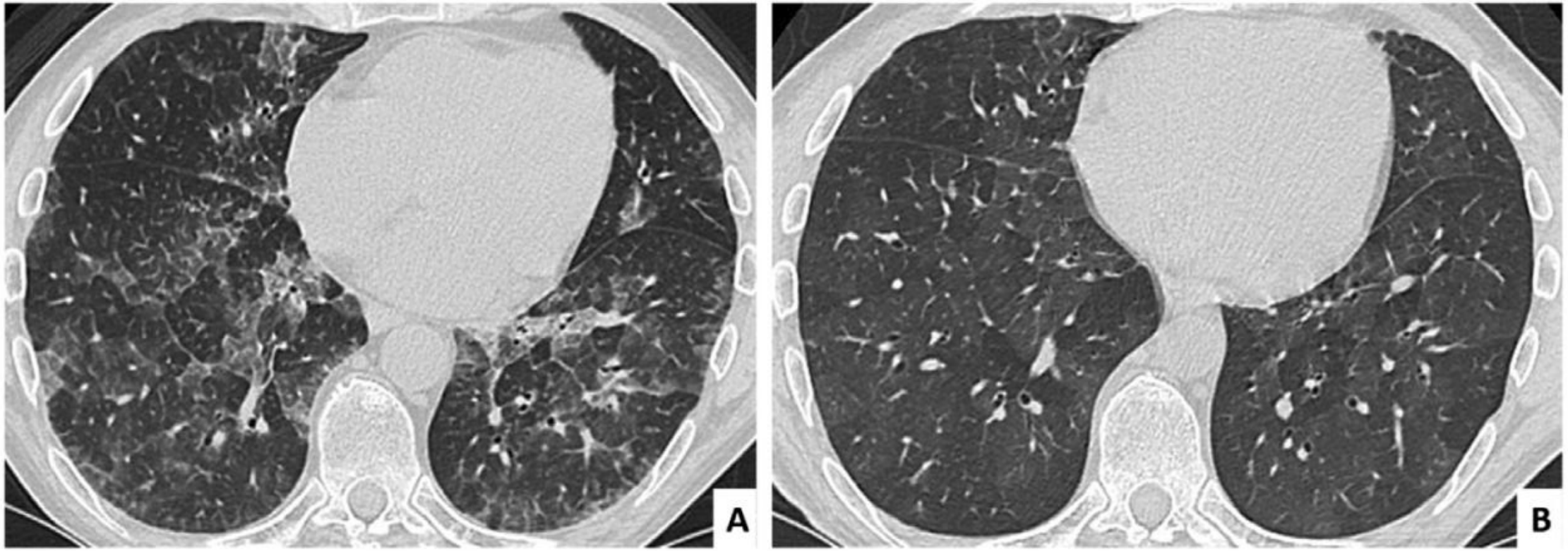
- Inhaled steroids provide local anti-inflammatory effects
- Azithromycin **impairs interleukin-8 (IL-8)** production and neutrophilia,
- Montelukast blocks leukotriene activity, impairing cellular homing and activation and possibly **blocking fibroblast proliferation** and collagen deposition

INFECTIOUS PROPHYLAXIS & MONITORING	**Antibacterial prophylaxis**	• **Penicillin** for Streptococcus spp.	Amoxycillin, Erthromycin
	Antifungal prophylaxis	• Broad-spectrum azoles with activity against **aspergillus** (voriconazole or posaconazole).	
	PJP prophylaxis	• **TMP-SMX**	
	Evaluation for infections	• Extensive testing if new PFT decline or symptoms.• Rule out: gram-negative bacteria, nocardia, NTM, fungi, PJP, viral infections.• BAL recommended; biopsy if suspicion remains.	25% had identifiable infection on BAL in prospective study.
	Recurrent bacterial infections	• Consider **inhaled aminoglycoside prophylaxis** or **rotating systemic antibiotics** (CF-based strategies) when bronchiectasis present.	

SECOND-LINE & LATER THERAPIES	**FDA-approved agents**	• **Ibrutinib**, **Ruxolitinib**, **Belumosudil** for steroid-refractory or steroid-dependent chronic GVHD.	BOS responses to second-line therapy are **poor (<50%).**
	Extracorporeal Photopheresis (ECP)	• Used for chronic GVHD, though not FDA-approved.• BOS response rates remain low relative to other organs.	
END-STAGE OPTIONS	**Lung Transplantation**	• Consider when progressive decline despite therapy. • 5-year survival after lung transplant post-HSCT ≈ **67%**, comparable to other lung diseases.• Higher mortality when done **within 2 years** of HSCT.	

Transplant Cell Ther. 2024 Sep;30(9S):S585-S596

Pulmonary Alveolar Proteinosis



Quiz

- All of the following are true of LONIPC except:
  a. Masson bodies are typical of interstitial lung disease
  b. Lung biopsy is not essential in the NIH criteria
  c. FAM therapy is the treatment of choice for BOS
  d. Impedance oscillometry is useful in children where PFT is not possible

Impedance oscillometry

Quiz

- Following are true of non infectious complications except
  a. Early onset PERDS is more common with autologous transplant
  b. Late onset non complications are exclusively allogenic
  c. Reverse halo sign is seen in organizing pneumonia
  d. Cryptogenc organizing pneumonia finally requires lung transplant

Summary

- Non-infectious pulmonary complications are rare but potentially fatal
- Regular PFT could atleast detect early onset of BOS.
- Prevention is possibly the key
- Inputs from radiology and respiratory team with microbiology/ infectious disease team are essential