LA GVHD POLMONARE

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HIGHLIGHTS IN EMATOLOGIA
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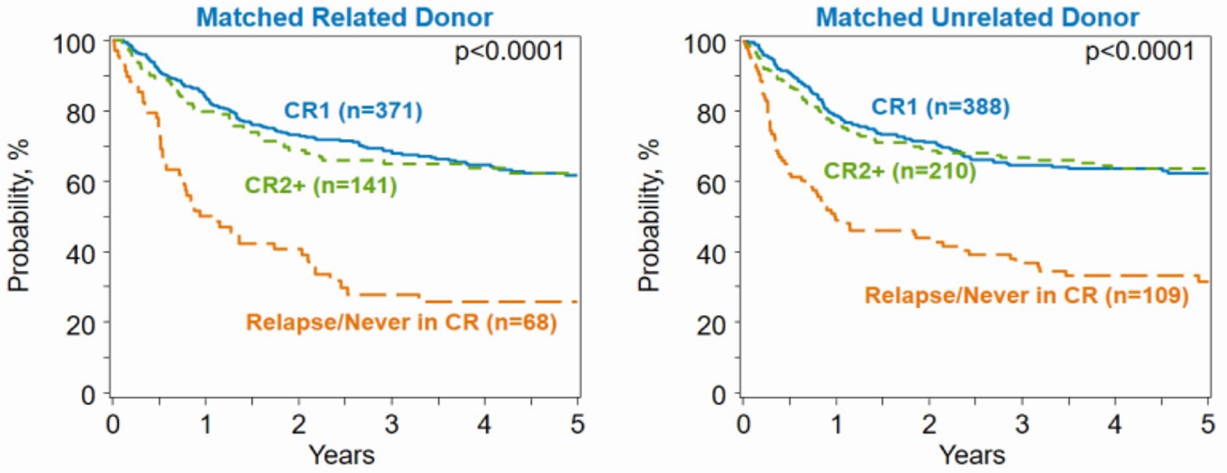
AGENDA

- Pathophysiology
- Which risk factors are most important?
- Diagnostic challanges
- Therapeutic options

THE IMPORTANCE OF NON-INFECTIOUS PULMONARY COMPLICATIONS (NIPCs) FOR ALLOGENEIC HSCT

- Mortality after HSCT has declined over the last 30 years
- cGVHD occurs 30-70% of patients after HSCT.
- Non-Infectious Pulmonary Complications (NIPCs) affect approximately 20% of HSCT recipients
- NIPCs increase the rate of death 2-fold

Survival after Allogeneic HCTs for Acute Myeloid Leukemia (AML), Using Matched Donors, Age <18 Years, in the U.S., 2010-2020



CIBMTR CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Abbreviation – CR: Complete remission.

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PATHOPHYSIOLOGY

Impaired immune regulation

Thymus dysfunction

Immune suppression

↓ T reg

Immune activation + Non-specific lung injury

cytokines
chemokines
growth factors

Pulmonary Injury

obstructive lung disease

OLD

A

Acute inflammation

restrictive lung disease

RLD

Lymphocytic bronchiolitis

BrOb

B

C

D

E

Interstitial pneumonitis

Interstitial Fibrosis

Phase one

Inflammation

Phase two

Dysregulation

Phase three

Fibrosis

Cooke et al, Biol Blood Marrow Transplant 2017
Bos et al, Lancet Respir Med 2022

THE CONCEPT OF NIPCs

when do they occurs?		how do they affect the lung?	
EARLY *first 3 months*	**LATE** *after 3 months*	**OBSTRUCTIVE** *hard to get air out*	**RESTRICTIVE** *hard to get air in*
Diffuse Alveolar Hemorrhage	Organizing Pneumonia	**Bronchiolitis Obliterans Syndrome (BOS)**	Diffuse Alveolar Hemorrhage
Idiopathic Pneumonia Syndrome	**Bronchiolitis Obliterans Syndrome (BOS)**		Interstitial Pneumonia
Organizing Pneumonia			Organizing Pneumonia
Pulmonary Veno-Occlusive Disease			Lymphocytic Interstitial Pneumonia
			Pluroparenchymal Fibroelastosis

NIH CLASSIFICATION SYSTEM FOR CHRONIC GVHD

Mild	• 1 or 2 organs or sites (except lung) with score 1
	  • Mild oral symptoms, no decrease in oral intake
	  • Mild dry eyes, lubricant eyedrops ≤ 3x/day

Moderate	• 3 or more organs with score 1
	• At least 1 organ or site with score 2
	  • 19-50% body surface area involved or superficial sclerosis
	  • Moderate dry eyes, eyedrops > 3x/day or punctal plugs
	• Lung score 1 (FEV1 60-79% or dyspnea with stairs)

Severe	• At least 1 organ or site with score 3
	  • > 50% body surface area involved
	  • Deep sclerosis, impaired mobility or ulceration
	  • Severe oral symptoms with major limitation in oral intake
	  • Severe dry eyes affecting ADL
	• Lung score 2 (FEV1 40-59% or dyspnea walking on flat ground)

Lee J, Blood 2017

BRONCHIOLITIS OBLITERANS SYNDROME

- Most common form of pulmonary GVHD
- Generally, develops in the first 2 years
- Occurs in:
  - 5% of all HCT recipients within 5 years
  - 14% of patients with GVHD
  - the true prevalence is probably higher
- Defined by progressive disease of small airways
- 5-year survival rate 40-60% and 10-year survival rate 20%
- Prognosis has improved in the last two decades with better screening and recognition

Cheng et al, Ann Am Thor Soc 2016
Arai et al Biol Blood Marrow Transplant 2015
Kwok et al Respirology 2019
Hakim et al, BMT 2019
Bos et al, Lancet Respir Med 2022

RISK FACTORS FOR BOS

Risk factor	OR	95% CI	*P* value
Busulfan	6.37	[2.37,17.13]	<0.001
ATG	0.08	[0.02, 0.27]	<0.001
Unrelated donor	4.01	[1.55,10.42]	0.004
Female donor	4.20	[1.63, 10.86]	0.003
Reduced pretransplant FEV_1%	1.04	[1.01, 1.07]	<0.01
CMV positive	3.44	[1.34, 8.87]	0.01
Acute GVHD	3.34	[1.29, 8.67]	0.01
Pretransplant history of lung disease	9.99	[1.66, 59.80]	0.01
High-risk disease	2.76	[1.02, 7.45]	<0.05

Gazourian L et al, Am J Hematol 2015
Au et al Biol Blood Marrow Transplant 2011
Versluys et al Biol Blood Marrow Transplant 2010
Hakim et al, BMT 2019

"Listen to your patient,
he is telling you the diagnosis."

Sir William Osler
(1849 – 1919)

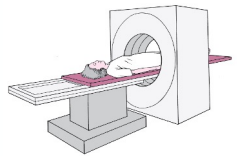
SYMPTOMS

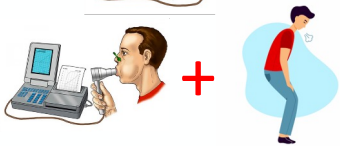
- DRY COUGH 60-100%
- WHEEZING 40%
- DYSPNEA 50-70%
- ASYMPTOMATIC 20%

Earlier diagnosis is associated with better outcomes

DIAGNOSTIC TOOLS

Modality	Description
PULMONARY FUNCTION TESTS (PFTs)	FEV_1 FEV_1/FVC
PULMONARY CT	Air trapping Bronchiectasis Rule out infections
PARAMETRIC RESPONSE MAPPING	HR CT upon inspiration and expiration (children and during infection)
SIX-MINUTE WALK TEST	Early suspicion (obstructive pattern)
MULTIPLE BREATH WASHOUT	Early perifery airways pathology
FORCED OSCILLOMETRY	Similar to FEV_1
NIH CHRONIC GVHD SCORE	PFTs + symptoms

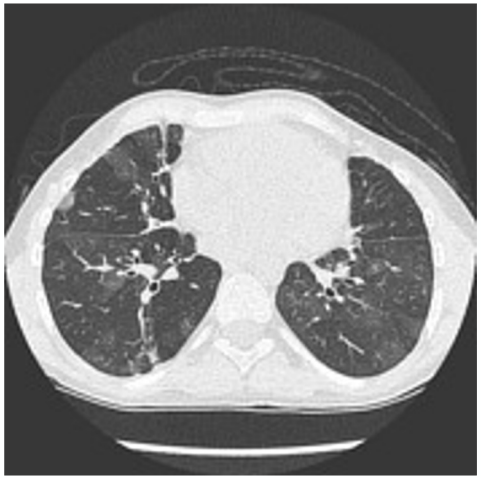




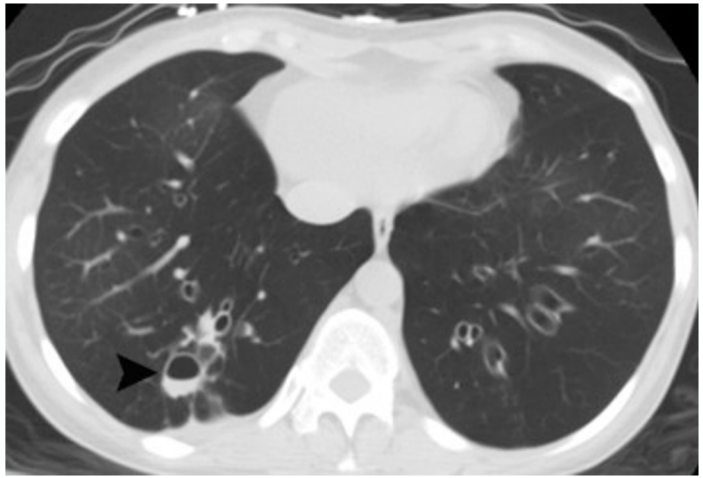
PULMONARY FUNCTION TESTs

Parameters		Rif	% Rif	
SPIROMETRY				
FEV_1 (liters)	forced expiratory volume in one second	3.72	>80	OBSTRUCTION
FVC (liters)	forced vital capacity	4.46	>80	
FEV_1/FVC (%)	-	>0.7	>85	
FEF_{25-75} (L/sec)	forced expiratory flow rate	4.36	>70	
LUNG VOLUME				
TLC (liters)	total lung capacity	4200-6400	>90%	RESTRICTION
DLCO (mL/min/mmHg)	diffusing capacity of carbon monoxide	21	>75	

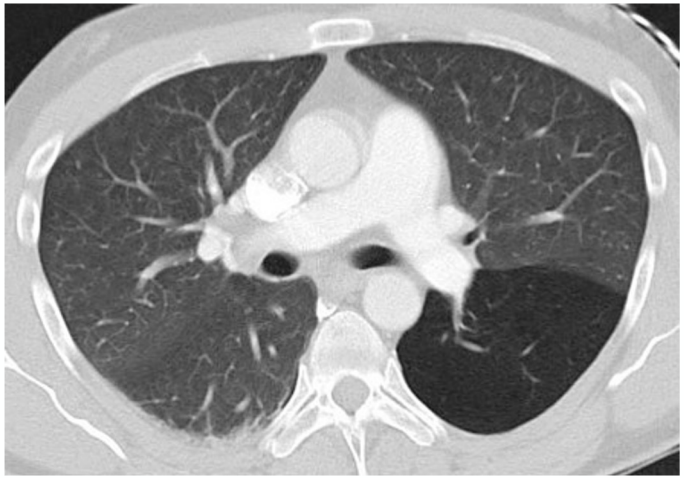
CT FINDINGS



Air trapping bronchiolitis
TREE IN BUD



Bronchiectasis



Air trapping

DIAGNOSIS CRITERIA

Clinical diagnosis is based on pulmonary function studies and imaging:

1. Evidence of progressive airflow obstruction:

- Fall in FEV_1
- Evidence of air trapping all'imaging (CT)

2. Absence of infection in the respiratory tract:

- Imaging (CT)
- Microbiological tests
  - cultures
  - testing for viral infections (NAAT preferred)
  - sputum culture
  - BAL

NIH CRITERIA FOR CLINICAL TRIALS IN CHRONIC GVHD

1) FEV_1/FVC ratio <0.7 or 5th percentile of predicted
2) FEV_1 <75% of predicted with ≥10% decline over less than 2 years
3) Absence of respiratory tract infections
4) One of the 2 supporting features of BOS: - Air trapping by expiratory CT or small airway thickening or bronchiectasis by HR CT - Air trapping by PFTs (Residual Volume > 120% of predicted or RV/TLC elevated outside the 90% confidence interval)

If other organs are involved ⇒ first 3 criteria are required
If no other organ are involved ⇒ biopsy is required

Jagasia et al Biol Blood Marrow Transplant 2015

NIH GRADING FOR CLINICAL TRIALS IN LUNG CHRONIC GVHD

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* **Yes** **No** **Not examined**	No symptoms	Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				
GI Tract ***Check all that apply:*** Esophageal web/ proximal stricture or ring Dysphagia Anorexia Nausea Vomiting Diarrhea Weight loss ≥5%* Failure to thrive	No symptoms	Symptoms without significant weight loss* (<5%)	Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				
LIVER	Normal total bilirubin and ALT or AP < 3 x ULN	Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	Elevated total bilirubin > 3 mg/dL
Abnormality present but explained entirely by non-GVHD documented cause (specify):				
LUNGS**				
Symptom score:	No symptoms	Mild symptoms (shortness of breath after climbing one flight of steps)	Moderate symptoms (shortness of breath after walking on flat ground)	Severe symptoms (shortness of breath at rest; requiring 0_2)
Lung score: **% FEV1** ☐	FEV1≥80%	FEV1 60-79%	FEV1 40-59%	FEV1 ≤39%
Pulmonary function tests Not performed				
Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				

NO GVHD	FEV_1 ≥80% of predicted asymptomatic
MILD	FEV_1 60-79% of predicted shortness of breath after climbing one flight of steps
MODERATE	FEV_1 40-59% of predicted shortness of breath after walking on flat ground
SEVERE	FEV_1 ≤39% of predicted shortness of breath at rest - requiring O_2

Jagasia et al Biol Blood Marrow Transplant 2015

COMPARISON BETWEEN NIH AND ISHLT CRITERIA

Table 1. Comparison of the 2014 NIH cGVHD consensus criteria, the 2019 ISHLT CLAD criteria, and the adapted criteria

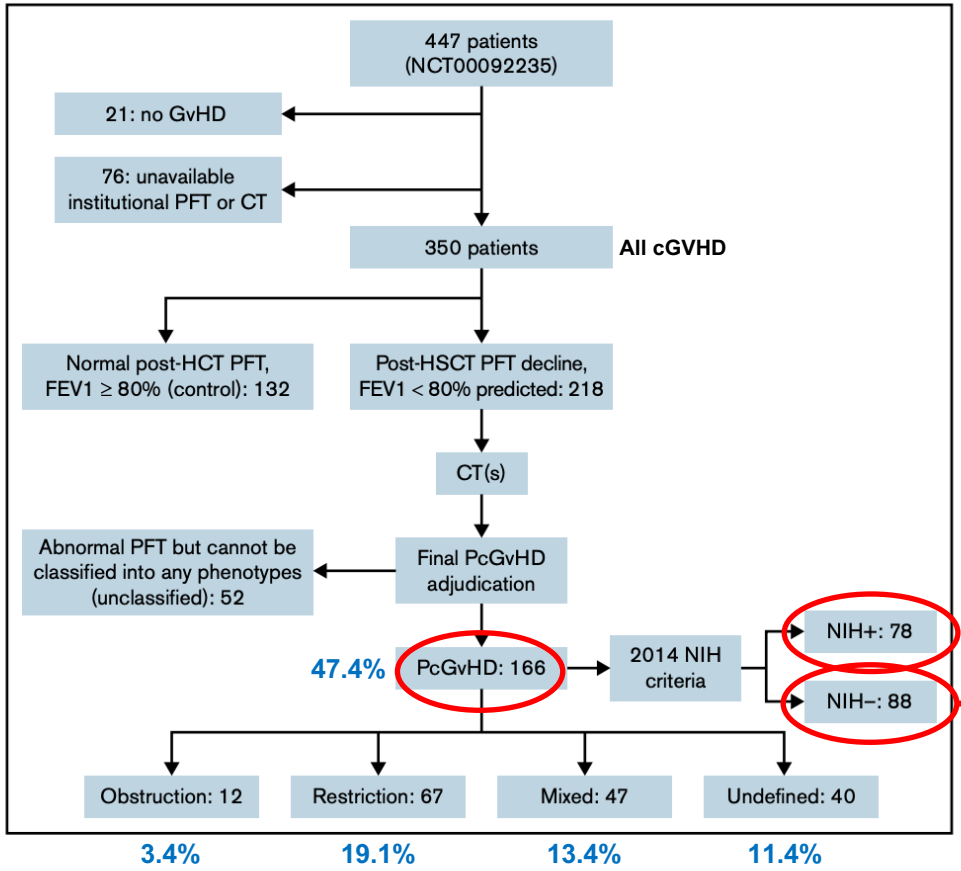
Criteria	NIH criteria	ISHLT CLAD criteria	Adapted criteria
Diagnosis	FEV1/VC < 0.7 or the 5th percentile predicted based on population-based reference; VC is either FVC or SVC, whichever is greater; FEV1 < 75% predicted with ≥ 10% decrease over less than 2 y, not corrected with albuterol	Persistent decline (> 3 mo, ≥ 20%) of FEV1 from the reference baseline; baseline is the mean of the best 2 post-transplant FEV1 measurements taken 3 wk apart	Abnormal pulmonary function after transplant (FEV1 < 80% predicted based on population-based reference), able to be classified into 1 of the 4 CLAD-PcGVHD subtypes, rule out other causes of pulmonary dysfunction
Phenotype	BOS: FEV1/VC < 0.7 or the 5th percentile predicted based on population-based reference; VC is either FVC or SVC, whichever is greater; evidence of air-trapping by expiratory CT or airway thickening or bronchiectasis by high-resolution CT, or air-trapping by PFT	BOS: obstruction (FEV1/FVC < 0.7), without restriction or CT opacity; RAS: restriction (TLC < 90% baseline) + CT opacity, FEV1/FVC ≥ 0.7; mixed: FEV1/FVC < 0.7, TLC < 90% baseline, with CT opacity; undefined: A. FEV1/FVC < 0.7, TLC < 90% baseline, NO CT opacity; B. FEV1/FVC < 0.7, TLC ≥ 90% baseline, WITH CT opacity	Obstruction: obstruction (FEV1/FVC < 0.7), without restrictive findings on PFT or CT; restriction: restriction (TLC < 90% predicted), with restrictive CT findings,* FEV1/FVC ≥ 0.7; mixed: FEV1/FVC < 0.7, TLC < 90% predicted, restrictive CT findings; undefined: A. FEV1/FVC < 0.7, TLC < 90% predicted, NO restrictive CT findings; B. FEV1/FVC < 0.7, TLC ≥ 90% predicted, WITH restrictive CT findings

RAS, restrictive allograft syndrome.

*Restrictive CT scan findings include ground glass opacities, parenchymal consolidation, traction bronchiectasis, lobar volume loss, usual interstitial pneumonitis pattern, and pleural abnormalities.

Pang et al, Blood Adv 2022

ADAPTED CRITERIA



- Increased risk of death compared to non-GVHD patients (HR 1.88; p=0.006)
- Same risk of death compared to NIH GVHD patients (p=0.678)

Pang et al, Blood Adv 2022

DIAGNOSTIC CHALLENGES

Early diagnosis is associated with better outcomes

Why can't we diagnose BOS consistently earlier?

1. ***Symptoms appear when the disease is advanced***
2. ***Symptoms are subtle and hard to distinguish from other post-HCT problems*** *(COPD, fibrosis)*
3. ***Lack of serial PFTs at well-defined intervals***
   (occurs every few months, while BOS can occur within a few weeks)
4. ***It does not show up on chest imaging until it is very severe***
5. ***Consider pre-existing lung disease***

Palmer et al Biol Blood Marrow Transplant 2014
Bos et al, Lancet Respir Med 2022

RESPONSE TO DIAGNOSTIC PROBLEMS

PFTs are recommended:

- baseline, d +100, each 3 months in the first year post-allo
- at cGVHD diagnosis
- each 3 months thereafter cGVHD diagnosis

Monitoring for FEV_1 trajectory decline:

- FEV_1 decline >10% from baseline
- FEV_1 decline >5%/year

Assessment of the FEF_{25-75}:

- decline >25% pre-HCT baseline (prediction 85%; NPV 98%)
- more representative of small airways function
- usually deteriorate before FEV_1 (early stage)

FEV_1 can be altered by other causes:

- infections
- deterioration of the general conditions
- technical issues or noise

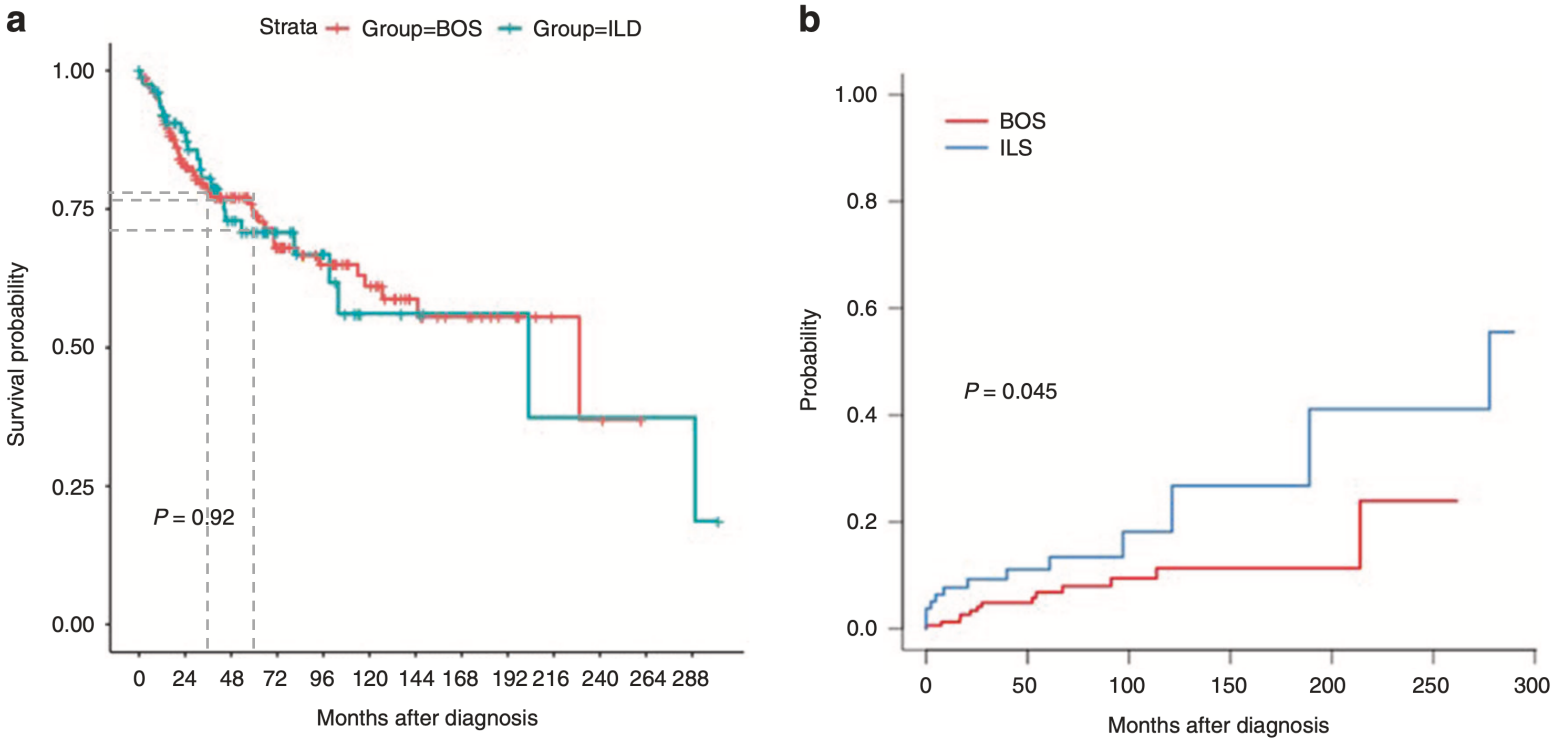
Bos et al, Lancet Respir Med 2022
Jamani et al, Biol Blood Marrow Transplant 2020
Kitko et al, Transplant Cell Ther 2021

RESTRICTIVE PULMONARY CHRONIC GVHD

- Not «officially» recognized as part of pulmonary cGVHD.
- Prevalence unknown (3-year cumulative incidence 5%).
- CT imaging can be useful:
  - bilateral interstitial lung disease
  - ground-glass, consolidations
  - pleural attraction and thickening
  - bronchiectasis
- PFTs are useful (DLCO)
- Can be seen after:
  - drug exposure
  - radiation
  - HD chemotherapy

Bos et al, Lancet Respir Med 2022
Archer et al, BMT 2023

OUTCOMES ACCORDING TO THE TYPE OF DIGNOSIS: BOS vs. ILD

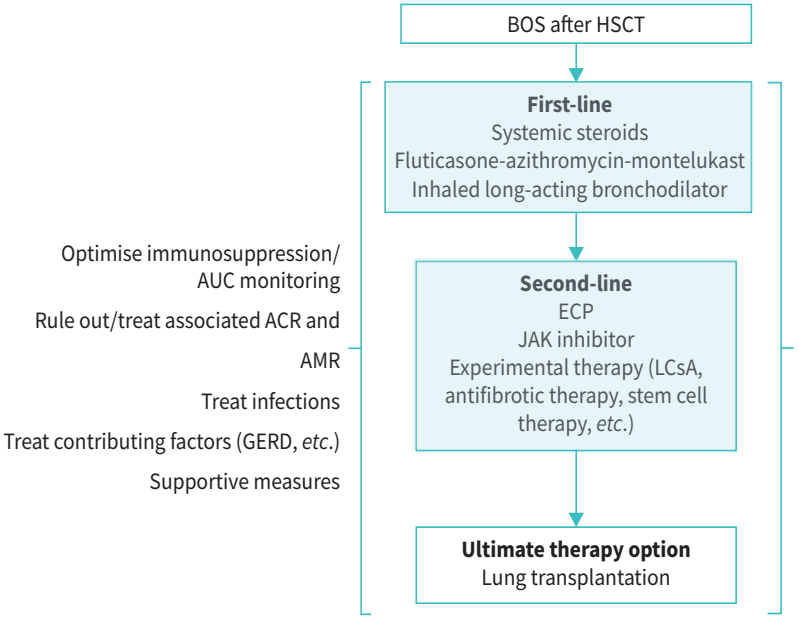


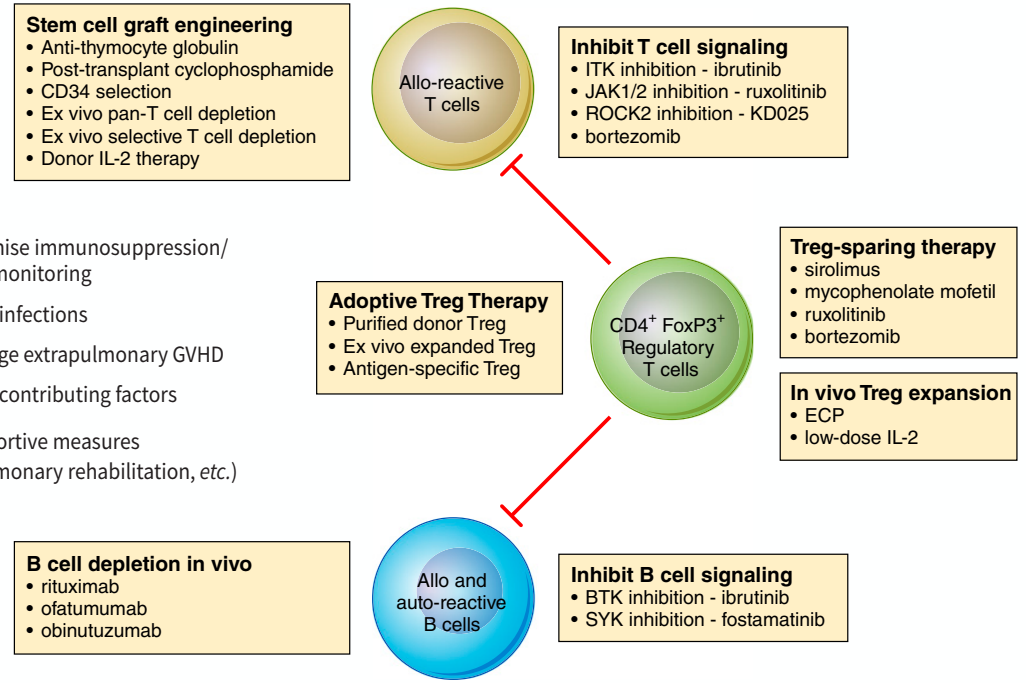
OVERALL SURVIVAL

HEMATOLOGICAL RELAPSE

Archer et al, BMT 2023

TREATMENT





Glanville et al, ERJ Open Res 2022
Cutler et al, Blood 2017

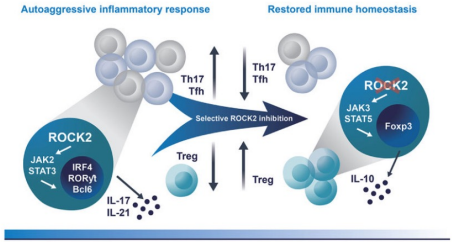
STUDIES ON BOS THERAPY

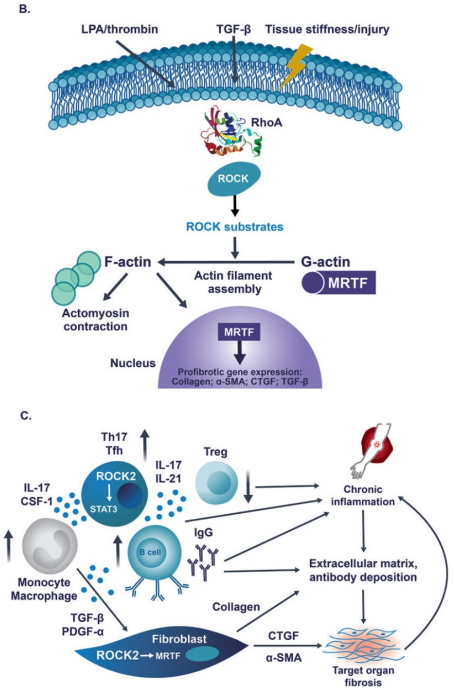
Author	Study type	Intervention	Size	Response definition	Response
Child 1999	retrospective	ECP	5	PFTs	40%
Khalid 2005	prospective	Azithromycin	8	symptomatic and PFTs	87%
Ratejan 2005	retrospective	HD steroids	9	-	CR=20%; PR=30%
Zaja 2007	retrospective	Rituximab	9	CR=100% resolution; PR=50% improved	CR=0; PR=37%
Kim 2010	prospective, open label, phase II	Rituximab	11	CR=100% resolution; PR=clinical score	CR=0; PR=9%
Ueda 2010	retrospective	Steroids	44	symptomatic and radiologic	?
Lucid 2011	retrospective	ECP	9	symptomatic and PFTs	67%
Lam 2011	prospective, randomized, DB, placebo-controlled	Azithromycin	12	symptomatic and PFTs	0
Norman 2011	retrospective	FAM+steroids	9	symptomatic, PFTs, lung function score	0
Yanik 2012	prospective, open label	Etanercept	22	PFTs	32%
Del Fante 2016	retrospective	ECP	20	symptomatic and PFTs	76%
Williams 2016	prospective, open label, single-arm	FAM	36	PFTs	94% → 64%

RUXOLITINIB FOR CHRONIC PULMONARY GVHD

Author	Trial design	Treatment	Lung response	Sample size
Redondo, 2022	Retrospective	RUXO+CS	ORR 33%	48
Zeiser, 2021	Open-label, randomized, multicenter, Phase III	RUXO+CS vs BAT+CS	ORR 9%	329
Wel, 2021	Retrospective	RUXO+CS	ORR 44%	32
Moiseev, 2020	Prospective	RUXO+CS vs other IS	No response	43
Gomez, 2020	Retrospective, multicenter	RUXO+CS	ORR 61.5%	27
Modi, 2019	Retrospective	RUXO+CS vs other IS	12-mo ORR 10%	46

ROCK2 INHIBITORS





THE ROLES OF ROCK2 IN PULMONARY cGVHD

- Controls the balance between pro-inflammatory and Treg
- Regulates cytoskeletal dynamics
- Regulates profibrotic gene expression
- Drives chronic inflammation
- Enhances fibrosis in cGVHD.

Zhanin-Zharov et al, Clin Immunol 2021

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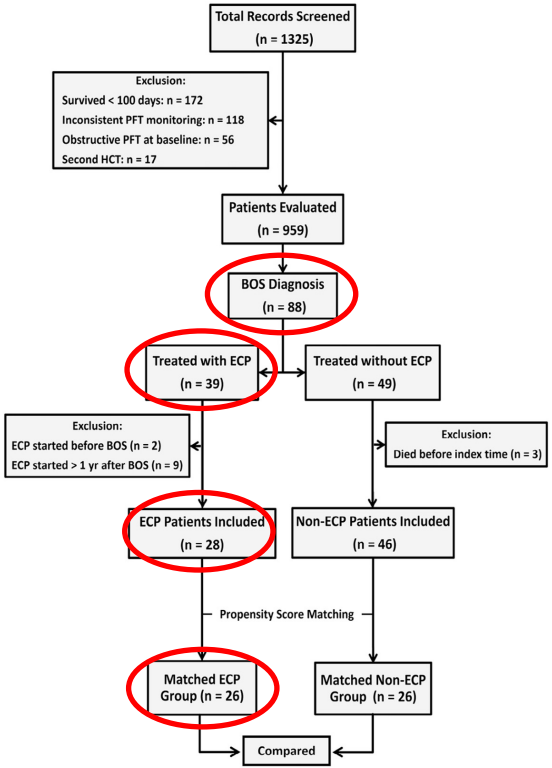

Figure 1. Flow diagram of the study cohort.

Table 3
PFT Data for the ECP and Non–ECP-Treated Groups before and after PSM

	Unmatched Cohort			Matched Cohort		
	ECP (n = 28)	No ECP (n = 46)	*P*	ECP (n = 26)	No ECP (n = 26)	*P*
PFT data before HCT						
FEV_{1PP}	86 (64-109)	96 (68-124)	.05	87 (64-109)	91 (68-110)	.72
FEV_1/FVC ratio	.7 (.6-.9)	.7 (.6-.9)	.76	.7 (.6-.9)	.7 (.6-.9)	.49
DL_{COPP}	84 (55-106)	82 (55-116)	.91	84 (55-106)	81 (55-116)	1.0
PFT data at BOS diagnosis						
FEV_{1PP}	56 (23-74)	63 (16-74)	.22	56 (23-74)	54 (16-74)	.87
FEV_1/FVC ratio	.6 (.3-.7)	.6 (.4-.7)	.40	.7 (.3-.7)	.6 (.4-.7)	.37
DL_{COPP}	63 (42-102)	66 (38-113)	.24	63 (42-78)	67 (38-96)	.18
PFT data at ECP/index date						
FEV_{1PP}	42 (20-79)	64 (14-94)	.001	43 (23-79)	52 (14-94)	.20
FEV_1/FVC ratio	.6 (.3-.8)	.6 (.3-.9)	.22	.6 (.3-.8)	.5 (.3-.9)	.86
DL_{COPP}	60 (43-84)	65 (20-113)	.03	60 (46-84)	61 (20-96)	.40
PFT data at last follow-up						
FEV_{1PP}	40 (14-74)	54 (10-94)	.007	43 (17-74)	46 (10-86)	.43
FEV_1/FVC ratio	.5 (.3-.8)	.6 (.3-.9)	.17	.5 (.3-.8)	.5 (.3-.9)	.74
DL_{COPP}	53 (27-75)	62 (29-96)	.05	48 (27-75)	62 (29-95)	.08
Rate of decline in FEV_{1PP} per month						
Before ECP/index date	−4.5 (−16 to .5)	−3.1 (−15 to −.7)	.83*	−4.5 (−16 to .5)	−3.6 (−15 to −.7)	.33*
After ECP/index date	−.3 (−7.5 to 1.3)	.0 (−3.1 to 19)		−.2 (−2.3 to 1.3)	−.5 (−2.5 to 3)	

Values are median (range).
* Wilcoxon signed-rank test for comparison of paired data (*before* and *after* ECP/index date) between ECP and non-ECP groups.

Hefazi et al Biol Blood Marrow Transplant 2018

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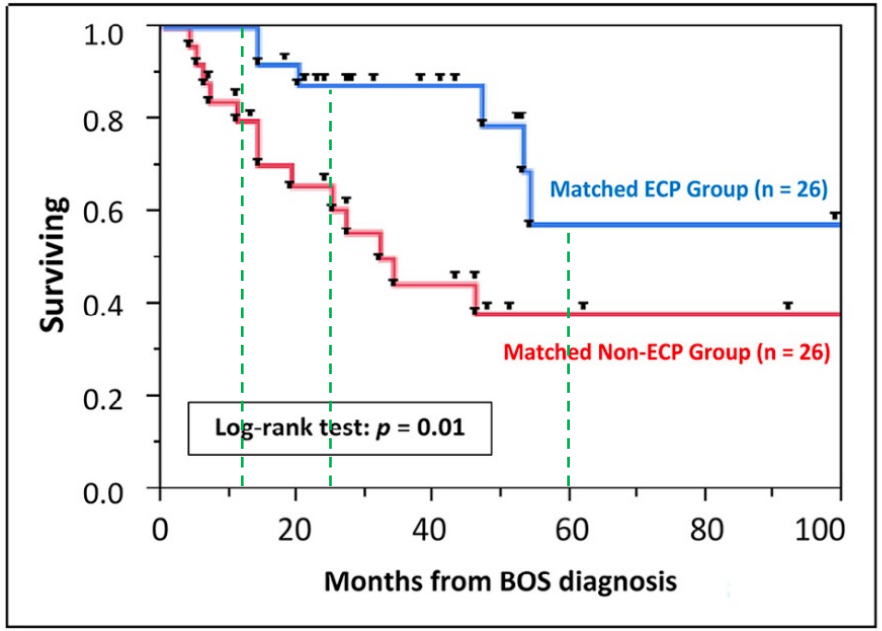


Figure 2. Kaplan-Meier survival curves for the matched ECP and non–ECP-treated patients.

Hefazi et al Biol Blood Marrow Transplant 2018

NEW TARGET: AEROSOLISED LIPOSOMIAL CYCLOSPORINE

TABLE 2 Clinical trials with aerosolised liposomal cyclosporine

Study	Clinical trial registration number	Phase	Design (n)	Treatments	Primary end-point	Completion date
BOS after single or double lung transplantation						
Iacono *et al.* 2019 (single or double LTx) [118]	NCT01650545	IIb	Open-label, parallel (21)	LCsA 5 or 10 mg +SOC *versus* SOC	1) A composite of BOS PFS, defined as time from randomisation to ⩾20% decline in FEV_1, re-transplantation or death, whichever occurred first (prolonged mechanical ventilation and irreversible respiratory failure equivalent to ⩾20% decline of FEV_1), and 2) BOS grade progression by grade changes from randomisation to study completion	Sep 2017
BOSTON-1 (single LTx)	NCT03657342	III	Randomised, single-blind (110)	LCsA 5 mg+SOC *versus* SOC	Mean change in FEV_1 from baseline to week 48	July 2023
BOSTON-2 (double LTx)	NCT03656926	III	Randomised, single-blind (152)	LCsA 10 mg +SOC *versus* SOC	Mean change in FEV_1 from baseline to week 48	July 2023
BOSTON-3 (OLE for BOSTON-1 and -2)	NCT04039347	III	Open-label (220)	LCsA 5 mg or 10 mg	Mean change in FEV_1 from baseline to week 24	Apr 2024
BOS after HSCT						
BOSTON-4	NCT04107675	II	Randomised, single-blind (24)	LCsA 2.5, 5 or 10 mg *versus* placebo	Safety and tolerability	May 2022

BOS: bronchiolitis obliterans syndrome; LTx: lung transplantation; LCsA: aerosolised liposomal cyclosporine; SOC: standard of care; OLE: open-label extension; PFS: progression-free survival; FEV_1: forced expiratory volume in 1 s; HSCT: haematopoietic stem cell transplant.

Glanville et al, ERJ Open Res 2022

NEW TARGET: ANTIFIBROTIC TREATMENT

TABLE 3 Clinical trials with antifibrotic treatments

Clinical trial registration number (name)	Patients (target n)	Phase	Design	Treatments	Primary end-point	Completion date
Nintedanib						
NCT03805477	BOS after HSCT (40)	II	Open-label	Nintedanib 150 mg twice daily	Adverse events leading to treatment interruption or discontinuation	Feb 2021
NCT03283007 (INFINITY study)	Grade 1–2 BOS after LTx (80)	III	Randomised, quadruple-blind	Nintedanib 150 mg twice daily *versus* placebo	Reduction in the rate of FEV_1 decline from baseline to month 6	Jun 2023
Pirfenidone						
NCT03315741	BOS after HSCT (30)	I	Open-label	Pirfenidone $\leqslant$2403 mg·day^{-1}	Number of patients requiring a dose reduction for >21 days due to adverse events	Feb 2022
NCT03473340 (STOP-CLAD)	CLAD after LTx (60)	II	Randomised, double-blind	Pirfenidone 801–2403 mg·day^{-1} *versus* placebo	Per cent change in functional small airways disease as measured by parametric response mapping (HRCT) at week 24	Mar 2022
NCT02262299 (EPOS)	Grade 1–3 BOS after LTx (90)	II/III	Randomised, double-blind	Pirfenidone 801–2403 mg·day^{-1} *versus* placebo	Change in FEV_1 decline from baseline to month 6	Dec 2019

BOS: bronchiolitis obliterans syndrome; HSCT: haematopoietic stem cell transplant; LTx: lung transplantation; FEV_1: forced expiratory volume in 1 s; CLAD: chronic lung allograft dysfunction; HRCT: high-resolution computed tomography.

Glanville et al, ERJ Open Res 2022

WHAT IS PULMONARY REHABILITATION?

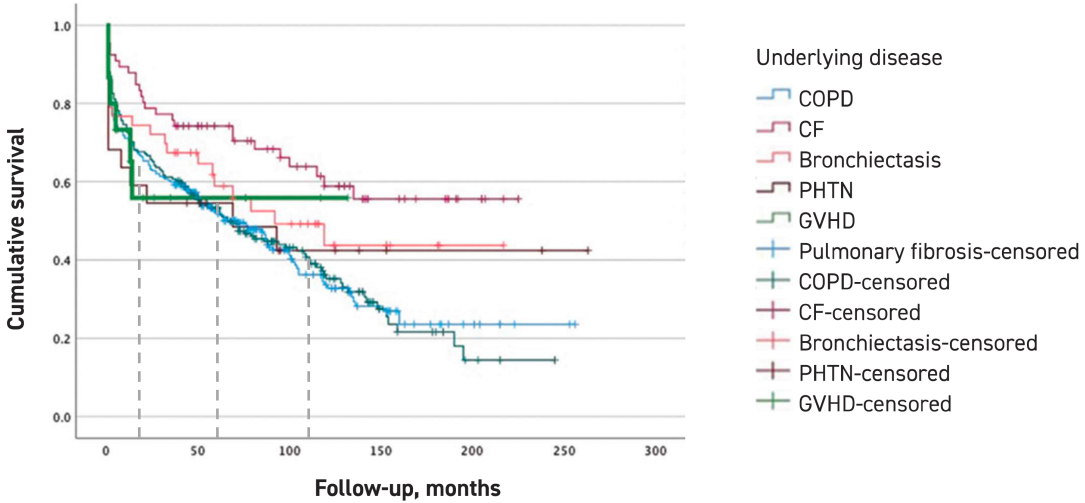
- **Comprehensive, multimodal rehab approach intended to:**
  - Improve aerobic conditioning
  - Improve muscle strength and balance
  - Teach patients how to lessen symptoms of shortness of breath
  - Individually tailored progression plan (like a personal trainer!)
- **Requires 2-3 sessions per week, usually 60-90 minutes in length for 2-6 months**
- **In one study, 10/11 patients with BOS who completed pulmonary rehabilitation walked an average of 307 feet longer in 6 minute walk testing, had less shortness of breath and better perceived physical function**

Palmer et al Biol Blood Marrow Transplant 2014

LUNG TRANSPLANTATION FOR LUNG GVHD

Figure 1: Survival by indication

CF = cystic fibrosis, COPD = chronic obstructive pulmonary disease, GVHD = graft-versus-host disease, PHTN = pulmonary hypertension

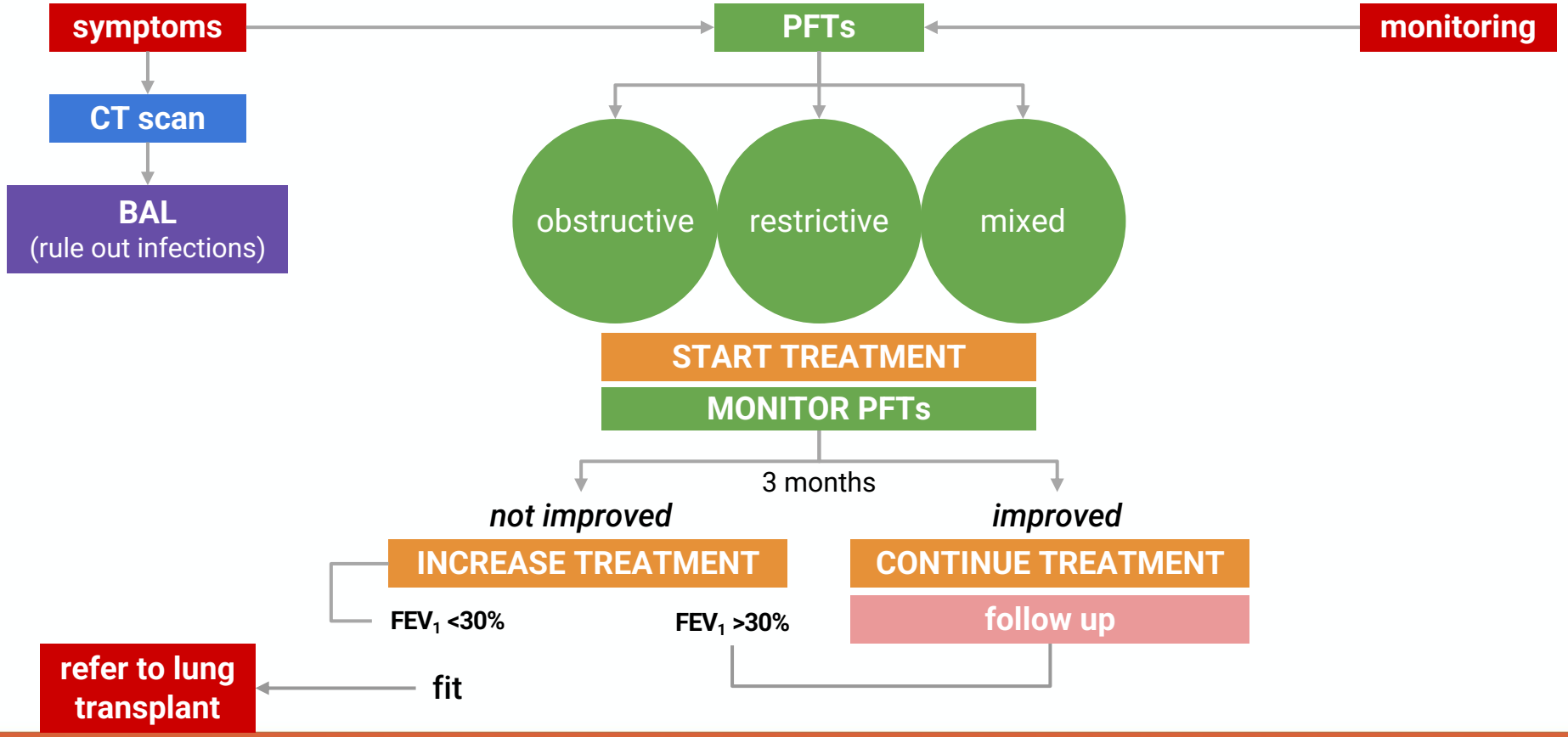


Hakim et al, BMT 2019
Shitenberg et al, IMAG 2023

Author	Study type	Size	Outcome
Koeneck 2010	multicenter	13	5-year OS 63%
Chen 2011	retrospective	19	ar OS 100%
Yousef 2012	multicenter		year OS 80% 5-year OS 60%
Holm 2013	retrospective		1-year OS 90% 5-year OS 75%
Cheng 2016	retrospe	9	1-year OS 89% 5-year OS 37%
Yung 2016	sin	9	1-year OS 68%
Gao 2017	enter	6	OS 100%
Chen-Yoshika 2018	lticenter	62	1-year OS 85% 5-year OS 64%
Greer 2018	multicenter	105	1-year OS 85% 5-year OS 67%
Kilman 2019	multicenter	18	5-year OS 80%
Shitenber 2023	singlecenter	15	1-year OS 80%

5 year survival rates: 63-80%

MANAGEMENT OF PULMONARY CHRONIC GVHD



TAKE HOME MESSAGES

- Polmonary cGVHD shows a 10-year survival <20%.
- Early diagnosis is associated to better outcome.
- Periodic surveillance with PFTs is reccomanded.
- Consider all therapeutic options.
- Patients who undergo to lung transplant for cGVHD have similar survival to lung transplant recipient for other indications.

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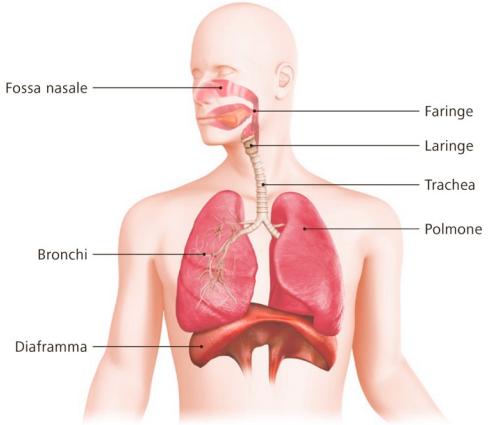
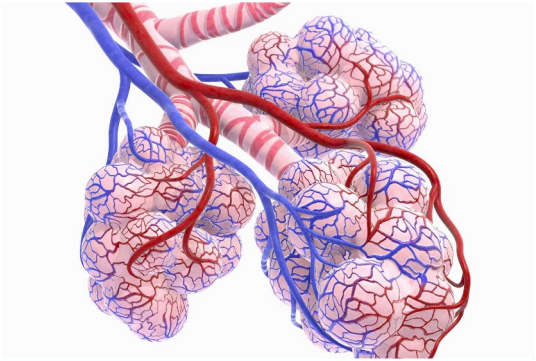
HOW DOES THE LUNG WORK?

- Breath is initiated by diaphragm contraction that expands the thoracic cavity.
- The lung passively expands and inflates with air because the pressure inside is lower than outside.
- This continues until these pressures equalize at full inspiration.

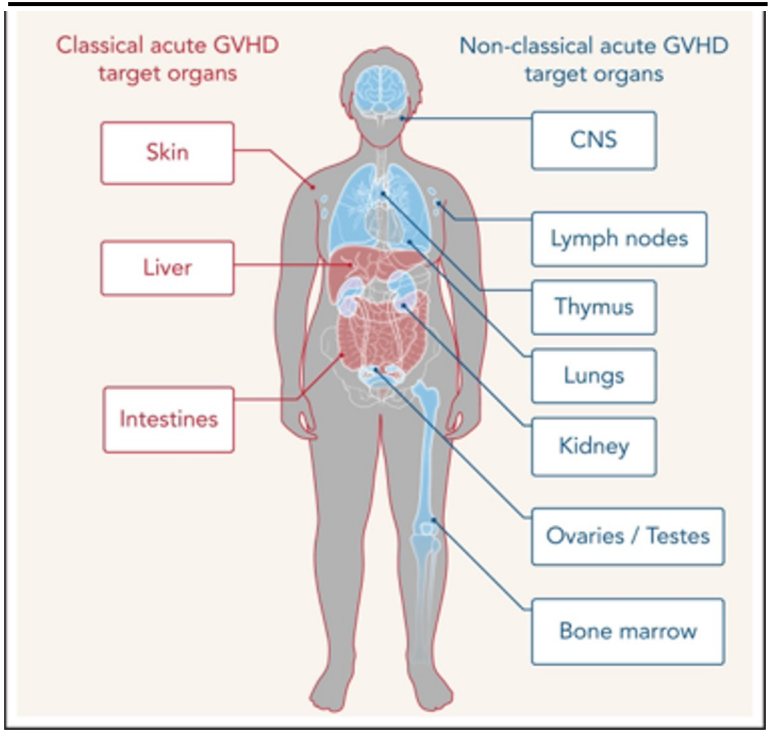




- Air enters the airways and eventually into the alveoli.
- Oxygen diffuses into the blood while carbon dioxide diffuses out of the alveoli.
- Finally, the blood is oxygenated and carbon dioxide is removed.

Nonclassical manifestations of acute GVHD

Emerging evidence indicates that acute GVHD can target non-classical organs



Zeiser et al Blood 2021

TREATMENT

Treatment type	Bronchiolitis Obliterans Syndrome	Restrictive Pulmonary cGVHD
PREEMPTIVE No azithromicyn	compliance with IS anti-infective vaccinations IVIG prevention	compliance with IS anti-infective vaccinations IVIG prevention

Bos et al, Lancet Respir Med 2022

TREATMENT

Treatment type	Bronchiolitis Obliterans Syndrome	Restrictive Pulmonary cGVHD
INHALED	steroind ± long-acting β agonist	steroind ± long-acting β agonist

Bos et al, Lancet Respir Med 2022

TREATMENT

Treatment type	Bronchiolitis Obliterans Syndrome	Restrictive Pulmonary cGVHD
SYSTEMIC	pulse corticosteroids (FIRST LINE) azithromycin + montelukast ruxolitinib ibrutinib/imatinib belumosudil rituximab calcineurin inhibitor mycophenolate mofetil	pulse corticosteroids (FIRST LINE) azithromycin + montelukast antibiotic agents

Bos et al, Lancet Respir Med 2022

TREATMENT

Treatment type	Bronchiolitis Obliterans Syndrome	Restrictive Pulmonary cGVHD
SYMPTOMATIC	oxygen therapy rehabilitation	oxygen therapy rehabilitation

Bos et al, Lancet Respir Med 2022

TREATMENT

1. The mainstay of BOS treatment is systemic immunosuppression and inhaled corticosteroids

2. No accepted gold-standard therapy, but, historically, we used FAM + systemic steroids:

- **F** → Fluticasone
- **A** → Azithromycin
- **M** → Montelukast

3. No recommendation for preemptive therapy with azithromycin:

- interference with anti-tumor immune surveillance ⇒ relapse and new neoplasm risk
  (FDA black box warning and the cessation of azithromycin for BOS at many institutions)

4. Second-line therapies (e.g. ruxolitinib, belumosudil) generally do not work as well for lung GVHD as for other types of GVHD

5. ECP showed an ORR <30% and it is used in combo

6. Consider pulmonary rehabilitation

Palmer et al Biol Blood Marrow Transplant 2014
Bos et al, Lancet Respir Med 2022

Hakim et al, BMT 2019

TREATMENT

Treatment type	Bronchiolitis Obliterans Syndrome	Restrictive Pulmonary cGVHD
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OTHER	ECP lung transplantation	lung transplantation
SYMPTOMATIC	oxygen therapy rehabilitation	oxygen therapy rehabilitation

Bos et al, Lancet Respir Med 2022