2026 California Thoracic Society Annual Educational Conference

& Chronic Obstructive Pulmonary Disease Symposium

Thursday March 12, 2026-Sunday March 15, 2026

Earn up to 19 CME/CEU/MOC Credits

Jointly Provided by AKH Inc., Advancing Knowledge in Healthcare and the California Thoracic Society

PORTOLA HOTEL & SPA
AT MONTEREY BAY

Thursday March 12, 2026 (6 CME/CEU/MOC Credits)
COPD Symposium
Friday March 13, 2026 (6.5 CME/CEU/MOC Credits):
Advances in Interventional Pulmonary, Remote Monitoring in Pulmonary and Sleep Medicine, Approach to Symptom Management in Chronic Lung Disease and Critical Care
Saturday March 14, 2026 (6.5 CME/CEU/MOC Credits)
Sepsis and Shock, Extracorporeal Membrane Oxygenation, Inpatient Pulmonary Complications of Cancer Care
Sunday March 15, 2026
Fellow and Resident Track Symposium

California Thoracic Society
ATS Chapter Serving California and Arizona

AKH INC.
ADVANCING KNOWLEDGE IN HEALTHCARE

California Thoracic Society
Annual Conference
March 12-15, 2026
Portola Hotel and Spa, Monterey, CA

Saturday March 14, 2026

Advances in Management of the Patient with Sepsis

8:00 am – 8:10 am: Welcome and Introduction

8:10 am – 8:55 am: Keynote Address – Phenotyping and Personalized Medicine in Sepsis

- **Angela Rogers, MD (Stanford)** - This speaker will discuss phenotyping in the patient with sepsis and septic shock and how close we are to precision medicine in managing sepsis.

8:55 am – 9:20 am: Incorporating Artificial Intelligence Decision Making in Identifying Sepsis

- **Gabriel Wardi, MD (UC San Diego)** - This speaker will describe how artificial intelligence can be used to identify the septic patient before they present with end stage symptoms to impact care earlier in the course of illness.

9:20 pm – 9:35 pm: Pro: The Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) Bundle Saves Lives

- **Sean Townsend, MD (CPMC-Sutter)**- This speaker will argue the benefits of the SEP-1 Bundle/how it saves lives.

9:35 pm – 9:50 pm: Con: : The Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) Bundle Does Not Save Lives

- **Natalie Achamallah, MD, MS (Cottage Health)** - This speaker will argue the against the SEP-1 Bundle/highlight its limitations.

9:50-10:00 am Question and Answer

10:00 am – 10:30 am: Break

Extracorporeal Membrane Oxygenation

10:30 am – 10:55 am: When to refer to an ECMO center and when to deploy ECMO

- **Nida Qadir, MD (UC Los Angeles)** - This speaker will discuss the evidence behind the use of ECMO in patients with respiratory failure and when providers should consider referral to an ECMO center and when centers should use ECMO.

10:55 am – 11:20 am: What about ECMO to go?

- **Mazen Odish, MD (UC San Diego)** - This speaker will discuss the advent of mobile ECMO services, how they can help improve patient care, and the use of extracorporeal cardiopulmonary resuscitation.

11:20 am – 11:45 pm: Ventilator Strategies for the patient on ECMO

- **Abirami Kumaresan, MD (Cedars-Sinai)** - This speaker will discuss the how ventilator strategies may differ in the patient on ECMO and how different ECMO configurations impact which ventilator strategy to use.

11:45 pm – 12:10 pm: What you need to know about pediatric ECMO

- **Kathleen Ryan, MD (Stanford)** - This speaker will discuss the utility of ECMO in neonates and children, and the complexities of management in children who needs mechanical support.

12:10 pm – 12:20 pm: Question and Answer

12:20 pm – 1:20 pm: Lunch

Hands-On Session:

1:20 pm – 2:20 pm: Non-Invasive Cardiac Output Monitors **Speaker Abirami Kumaresan, MD (Cedars-Sinai)** ECMO Machines **Mazen Odish, MD (UC San Diego)** ECMO Placement **David Gordon, DNP (UC San Francisco) & Brianna Zuckerman, NP (UC San Francisco)** Ventilator Settings and Portable ventilators **Joe Van Vleet, RT (UC Los Angeles) & Theresa Cantu, RT (Valley Children's)**

2:20 pm – 2:45 pm: Break

Inpatient and Pulmonary Complications of Cancer Care

2:45 pm – 3:10 pm: Pulmonary Complications of Hematopoietic Stem Cell Transplantation

- **Husham Sharifi, MD (Stanford)** - This speaker will discuss the pulmonary complications that arise after HCT, in particular the development of bronchiolitis obliterans syndrome and approaches to management.

3:10 pm – 3:35 pm: Pulmonary Vascular Complications of Malignancy

- **Naomi Habib, MD (Norton Thoracic Institute)**- This speaker will discuss the Pulmonary Vascular Disease complications of malignancy including PA sarcoma, pulmonary tumor thrombotic microangiopathy, and medications that can cause PAH.

3:35 pm – 4:00 pm: Drug induced Interstitial Lung Disease and Pneumonitis During Cancer Therapy

- **Weijia Chua, MD (Stanford)** - This speaker will discuss the pulmonary complications of interstitial lung disease and pneumonitis that develop after chemotherapy and targeted immunotherapy

4:00 pm – 4:25 pm: Respiratory Complications of Acute Leukemia

- **Hugh Davis, MD (City of Hope)** - The speaker will discuss various oncologic emergencies, how they are recognized, and how they are managed in the acute setting.

4:25 pm – 4:35 pm: Question and Answer

5:30 pm – 7:30 pm: Trainee Poster Competition (NON-CME) – Food and beverages will be served

I am a Clinical Assistant Professor in the Division of Pulmonary, Allergy, and Critical Care Medicine in Stanford University School of Medicine. In addition to seeing patients in the intensive care unit (ICU), I focus my research and clinical practice on transplant-related pulmonary fibrosis, which includes fibrotic lung disease after lung transplant or after hematopoietic cell transplant. My research applies advanced computational analysis to clinical metadata and quantitative imaging data, domains that draw on my training in engineering and bioinformatics. In the clinical setting I see patients in a Lung Graft-versus-Host-Disease (GVHD) Clinic for individuals with pulmonary complications after life-saving hematopoietic cell transplant. Our clinic is part of a national Lung GVHD Consortium comprising Stanford, Fred Hutchinson Cancer Center, University of Michigan, and MD Anderson Cancer Center. In this context I am the site co-Principal Investigator for two national clinical trials through the Lung GVHD Consortium that are funded by the National Institutes of Health. The first trial uses a home spirometry device and monitoring system to study the association of Lung GVHD with respiratory viral infections. The second trial studies the diagnostic and prognostic utility of quantitative CT scans of the chest for Lung GVHD. My goal is to fuse detailed, communicative patient care with the advances of data science in medicine that I research and study.

Pulmonary Complications After HCT

BOS & Organizing Pneumonia: A Guide for the Practicing Pulmonologist

Husham Sharifi
Stanford University
February 2026

Why This Matters to Community Pulmonologists

The growing burden landing in your clinic

39,000

Allogeneic HCTs performed yearly worldwide (Ref 5)

+7%

Annual growth rate in HCT incidence (Ref 5)

≤20%

HCT recipients develop LONIPCs (Refs 1, 2)

50–60%

5-year survival once BOS is diagnosed (Ref 4)

Key Message for Your Practice

- Most HCT survivors return to community care — BOS will arrive in YOUR clinic
- BOS is frequently diagnosed at an advanced stage due to delayed recognition
- Early detection offers the best chance to mitigate morbidity and mortality

Source: Cheng et al., Am J Respir Crit Care Med 2025 | Ref: 1,2,4,5,13,14

Disclosures

- I have no relationships with ACCME defined ineligible companies.
- I **WILL** discuss off-label use and/or investigational use of certain drugs

What is BOS After HCT?

A pulmonary manifestation of chronic graft-versus-host disease

DEFINITION & CONTEXT

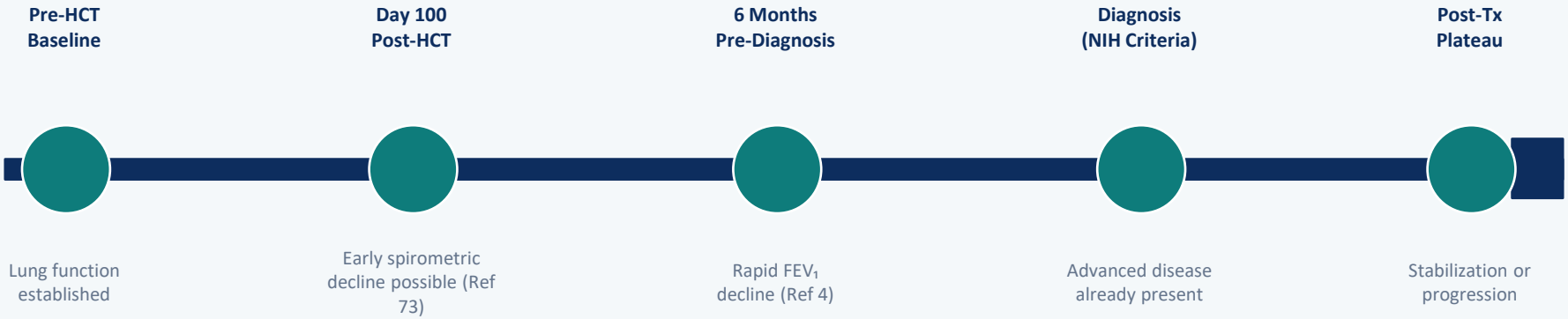
- Obliterative bronchiolitis (OB) — pathologic lesion of small airways
- Characterized by new-onset airflow obstruction
- Most common late-onset noninfectious pulmonary complication (LONIPC)
- Occurs within cGVHD context — alloimmune inflammation and fibrosis
- Small airways = 'silent zone' — advanced disease often present at symptom onset
- Incidence peaks within first 2 years post-HCT (Refs 1, 23, 24)

CLINICAL IMPACT

- Chronic respiratory impairment
- Increased susceptibility to lung infections
- 50–60% five-year survival rate (Ref 4)
- Response to therapy markedly lower than other cGVHD manifestations (Refs 8–12)
- Current corticosteroid treatment largely ineffective at restoring lung function (Ref 7)
- Advanced disease reflects irreversible structural airway changes

Source: Cheng et al., Am J Respir Crit Care Med 2025 | Ref: 1,3,4,7–12,23,24

Natural History & Clinical Course



Disease Phenotypes (Ref 4, 27, 28)

Rapid Progression

- FEV_1 decline within 3–6 months
- Onset <1 year post-HCT
- Poorer prognosis (Refs 25–27)

Indolent / Plateau

- Mild impairment with stabilization
- Often in context of cGVHD treatment
- Better prognosis (Refs 27, 28)

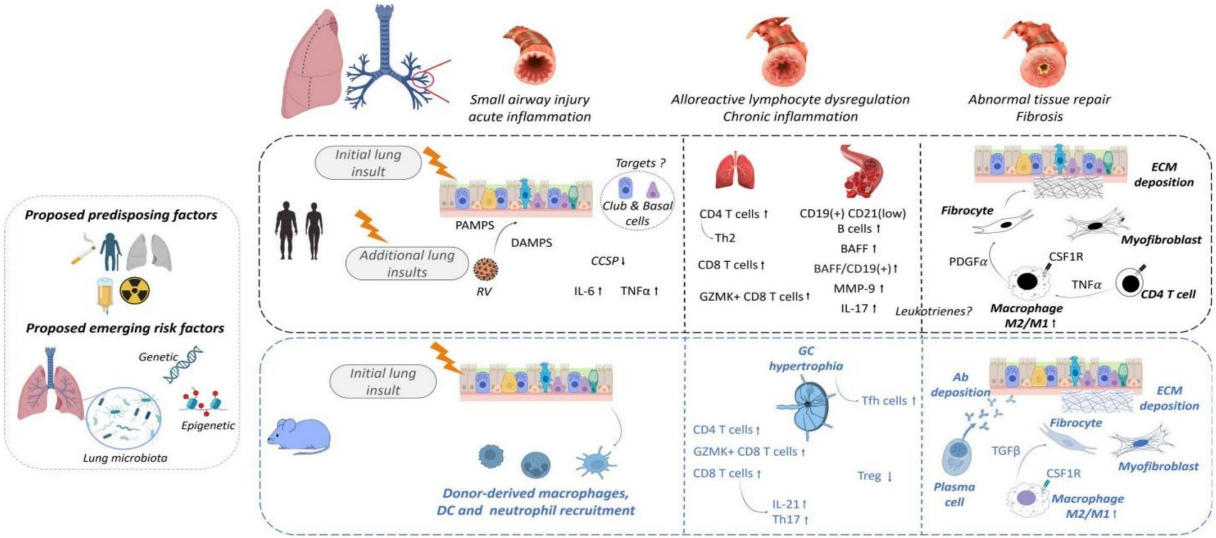
Lymphocytic Bronchiolitis

- Clinically identical to OB
- Much better prognosis (Ref 29)
- Different phenotype vs. earlier stage?

Source: Cheng et al., Am J Respir Crit Care Med 2025 | Ref: 4,25–29,73

Proposed Pathogenesis of BOS After HCT

From acute injury to irreversible fibrosis



THREE-STEP MODEL

① Acute inflammation from conditioning, infection, or toxicity

② Alloreactive lymphocyte dysregulation & chronic inflammation

③ Abnormal tissue repair → airway fibrosis (irreversible)

KEY CELLULAR PLAYERS

- Club cell (CC) loss → ↑ adaptive/humoral response
- Basal cell injury → profibrotic profile
- M2 macrophage infiltration → TGF-β → fibrosis
- Germinal center B cells → pathologic Ig deposition
- Granzyme K+ CD8 T cells (CCR5+) in BOS

Source: Cheng et al., Am J Respir Crit Care Med 2025 | Figure 1, p.1375

2014 NIH Diagnostic Criteria for BOS After HCT

The current standard — and its limitations

Criterion	Requirement	Details
1 — Airflow Obstruction	$FEV_1/FVC < 0.7$ or below LLN	Vital capacity = FVC or slow VC, whichever is greater
2 — Spirometric Threshold	FEV_1 ≤75% predicted + >10% decline over ≤2 years	FEV_1 must not correct to >75% with albuterol; absolute decrease must still remain >10%
3 — Exclude Infection	No active respiratory tract infection	Documented by CXR, CT, or microbiologic cultures
4 — Supporting Feature (at least 1 required)	A. Expiratory CT: air trapping or bronchial wall thickening/bronchiectasis	B. PFTs: RV ≥120% predicted OR RV/TLC ratio above 90th percentile

Adapted from Jagasia et al. (Ref 6) | Also requires: presence of a distinctive cGVHD manifestation in another organ

Source: Cheng et al., Am J Respir Crit Care Med 2025 | Ref: 6,30

Critical Limitations of the NIH BOS Criteria

Why we miss early disease

52%

of biopsy-proven OB cases actually met NIH spirometric criteria (Ref 31)

AND: 24% who DID meet NIH criteria had non-OB entities (Ref 31)

Sensitivity Problem

- ppFEV$_1$ threshold of ≤75% insensitive to early disease
- Small airways are the 'silent zone' — BOS may not reflect in FEV$_1$ until significant burden
- Patients with high baseline FEV$_1$ may not reach threshold even with real disease (Ref 32)

Bronchodilator Pitfall

- Requirement for post-bronchodilator ppFEV$_1$ ≤75% is misleading
- Improvement from 73% → 76% would FAIL the criterion — not truly normal!
- A bronchodilator response is seen in some patients with BOS (Ref 7)

Missing PRISM Pattern

- Preserved-ratio impaired spirometry (PRISM) pattern not captured
- PRISM associated with small airway dysfunction
- May precede fulfillment of NIH BOS criteria in HCT recipients (Refs 1, 27, 34–36)

Specificity Gaps

- Non-BOS conditions (organizing pneumonia, NSIP) can fulfil criteria
- Infection exclusion criterion ignores that infection can coexist with and trigger BOS
- Leads to diagnostic odyssey and treatment delay (Refs 37–40)

Source: Cheng et al., Am J Respir Crit Care Med 2025 | Ref: 7,31–40

The Screening Gap: Are We Doing Enough?

Implementation of PFT recommendations remains poor

30–40%

of allogeneic HCT recipients undergo routine post-transplant PFTs
despite 2 decades of recommendations (Refs 165, 166)

CURRENT RECOMMENDED SCREENING INTERVALS (Ref 168)

Every 3 months — Year 1 post-HCT
Every 6 months — Year 2 post-HCT
Annually — Years 3–5 post-HCT
Every 3 months — For active cGVHD patients, with full PFTs annually

Barriers to Screening Implementation

Perception Burden
Many HCT physicians stop ordering PFTs after early post-transplant period

Competing Priorities
cGVHD of other organs, hematologic relapse risk dominate clinical attention

Asymptomatic Disease
BOS is clinically silent — 'onset' is the time of diagnosis, not true start of disease

Criteria Limitation
Fixed ppFEV$_1$ threshold doesn't encourage early trending of lung function (Ref 32)

Source: Cheng et al., Am J Respir Crit Care Med 2025 | Ref: 32,165,166,168

Identifying Patients at Risk for BOS

Temporal framework for risk assessment

PRE-TRANSPLANT

- Preexisting airflow limitation / obstructive disease (asthma, tobacco history)
- Older recipient age
- Male recipient with female donor (H-Y antigen mismatch) (Refs 1, 64, 117)
- Lower pre-HCT FEV_1 / FEV_1/FVC ratio (even in normal range)

PERI-TRANSPLANT

- Myeloablative conditioning (especially busulfan-based)
- Peripheral blood stem cell source
- Unrelated donor transplant
- Note: T-cell depletion (ATG, alemtuzumab, post-Cy) reduces BOS risk (Refs 63, 131–134)

POST-TRANSPLANT

- Extrapulmonary cGVHD — risk ↑ 2.9-fold (Ref 1); incidence ~15% in cGVHD vs ~5–10% overall
- Early lung infections / lower tract infections in first 100 days
- CMV or herpesvirus reactivation (CMV increases BOS risk by 70%) (Ref 142)
- FEV_1 decline >10% at Day 100 or early declines in FEF_{25-75} (Ref 73)

⚠ **Positive predictive value of any single risk factor is LOW — combinations are needed. BOS incidence is only ~5–15% even in high-risk groups.**

Source: Cheng et al., Am J Respir Crit Care Med 2025 | Ref: 1,23,63–65,73,116–118,131–134,142

Beyond Standard PFTs: Novel Diagnostic Approaches

Emerging tools for earlier detection

Quantitative CT (qCT)

- Density-mapping detects low attenuation years before CLAD-BOS (Ref 182)
- Parametric response mapping (PRM) quantifies functional small airway disease
- PRM correlates with FEV_1 and FEV_1/FVC (Ref 184)
- Combined radiologist + qCT analysis improves diagnostic accuracy (Ref 185)
- ML on qCT distinguishes normal vs. mild vs. severe BOS (Ref 186)

Advanced PFT Techniques

- FEF_{25-75} decline at Day 80 predicts future BOS better than FEV_1 (Ref 73)
- Multiple breath washout (MBW): lung clearance index correlates with BOS in pediatric HCT
- Oscillometry: measures airway impedance; investigational role
- FEV_3/FVC ratio and z-scores not yet applied to BOS (Ref 174)
- Home spirometry: >70% adherence achievable; can detect antecedent FEV_1 decline (Ref 172)

Biomarkers (Table 3 in ATS Statement)

- MMP-9 elevated at time of BOS onset (Ref 208)
- BAFF & CD19(+)CD21(low) B cells elevated at new diagnosis (Ref 212)
- CC16 (CCSP): reduced serum levels in HCT-BOS (Ref 97)
- KL-6: elevated at 1 month post-transplant in children who later develop BOS (Ref 213)
- NONE yet clinically validated for early detection — active research area

Source: Cheng et al., Am J Respir Crit Care Med 2025 | Ref: 73,97,172,174,182,184,185,186,208,212,213

Biomarkers for BOS: Current Evidence

Circulating and tissue markers — no clinically validated early-detection assay yet

The FDA defines three relevant biomarker categories for BOS research:

Risk / Susceptibility

Identifies potential for disease before it is clinically apparent

Diagnostic

Confirms presence of disease at time of suspicion

Prognostic

Predicts likelihood of progression or clinical events

Biomarker	Finding in HCT-BOS	n	Reference	Stage / Utility
MMP-9 (matrix metalloproteinase-9)	Elevated at time of BOS onset; higher than other cGVHD manifestations	33	Inamoto et al. (208)	Diagnostic
MMP-3	Elevated in HCT-BOS and CLAD	88	Liu et al. (209)	Diagnostic
BAFF + CD19(+)CD21(low) B cells	Elevated at new diagnosis; consistent with humoral immunity role	46	Kuzmina et al. (212)	Diagnostic / Risk
CC16 / CCSP (club cell secretory protein)	Reduced serum levels; marker of club cell loss	8	Mattsson et al. (97)	Diagnostic
KL-6 (Krebs Von Den Lungen-6)	Elevated at 1 month post-HCT in children who later developed BOS	6	Gassas et al. (213)	Risk (early)
CXCL9 / CXCL11	Higher in mild/moderate BOS in ruxolitinib trial	49	DeFilipp et al. (15)	Prognostic
Cathepsin D, EGFR, KIR3DL1, TNFSF14	Associated with FEV_1 improvement on pirfenidone	22	Matthaiou et al. (111)	Prognostic / Tx response

Source: Cheng et al., Am J Respir Crit Care Med 2025 | Ref: 15,97,111,208,209,212,213

Biomarkers: Critical Gaps & Research Priorities

From established disease markers toward early detection

WHERE WE ARE

- All published biomarkers reflect established or moderate-to-severe BOS — none validated for early detection
- Studies are small (n=6–88) and mostly single-center; limited replication
- KL-6 is the only biomarker showing pre-diagnosis elevation (at 1 month post-HCT) in a pediatric cohort (Ref 213)
- Insights from CLAD-BOS may guide HCT: low CCSP in BAL fluid predicts subsequent PFT decline after lung transplant (Ref 216)
- Serum MMP-9 and MMP-3 show the strongest cross-study consistency (Refs 208, 209)

RESEARCH PRIORITIES (ATS Road Map)

- Multi-omics discovery (proteomics, transcriptomics) in plasma and PBMCs at landmark HCT time points
- Bronchoscopy at initial BOS suspicion: BAL fluid for immune cells, microbiome, lung-specific markers
- Nasal / bronchial epithelial lining fluid sampling — minimally invasive alternative to BAL (Ref 218)
- Nasal markers of inflammation detected post-HCT may distinguish transient impairment from progressive BOS (Ref 219)
- Integrate biomarkers with qCT and spirometry into a clinical risk-stratification algorithm
- Validate biomarkers prospectively in multicenter cohorts before clinical implementation

Source: Cheng et al., Am J Respir Crit Care Med 2025 | Ref: 97,208,209,213,216,218,219

Quantitative CT (qCT): Seeing What Spirometry Misses

Imaging biomarkers for early small airway disease

HOW qCT WORKS

- Standard CT generates density maps of the lung on inspiratory and expiratory phases
- Density-mapping identifies areas of low attenuation (air trapping) that are invisible on standard radiologic review
- Parametric Response Mapping (PRM): automated algorithm that quantifies functional small airway disease vs. emphysema by comparing inspiratory/expiratory voxels
- PRM was originally developed for COPD — now validated for BOS (Ref 184)
- Co-inventor Craig Galban is a committee member of this ATS Statement

KEY FINDINGS IN BOS

- Density-mapping CT detects low-attenuation areas YEARS before CLAD-BOS diagnosis (Ref 182)
- PRM-derived small airway disease correlates with ppFEV$_1$ and FEV$_1$/FVC — results consistent across CT acquisition protocols (Ref 184)
- Combined radiologist assessment + qCT improves diagnostic accuracy vs. either method alone (Ref 185)
- Unsupervised ML on qCT successfully distinguishes normal vs. mild vs. severe HCT-BOS (Ref 186)
- qCT strain metrics (dynamic lung distortion) separate early BOS from NIH-BOS with high sensitivity and specificity (Ref 187)

EMERGING: ^{129}Xe MRI

- Hyperpolarized ^{129}Xe MRI generates diffusion metrics reflecting lung microstructure beyond airways
- Superior sensitivity for early structural-functional impairment in asymptomatic smokers without spirometric change (Ref 191)
- Ventilation deficits detected in pediatric HCT recipients with normal spirometry (ppFEV$_1$ ≥80%) (Ref 193)
- No study yet proves ^{129}Xe MRI detects early BOS more accurately than spirometry
- Prospective adult data being collected (NCT04029636)

Source: Cheng et al., Am J Respir Crit Care Med 2025

qCT + Machine Learning: From Research to Clinical Readiness

Where we are and what needs to happen

What Machine Learning on qCT Has Shown

Unsupervised ML

No patient labels needed — algorithm successfully distinguished normal lungs, mild BOS, and severe BOS on qCT alone (Ref 186)

Supervised ML Classification

Inspiratory + expiratory lung volume thresholds combined with quantitative air trapping identified HCT-BOS with high specificity and sensitivity (Ref 186)

Strain Metrics (ML)

Dynamic lung parenchymal distortion analysis distinguished early BOS from NIH-defined BOS and from normal — high sensitivity and specificity (Ref 187)

Clinical Readiness Assessment

✅ Validated

- PRM correlates with spirometric parameters across multiple CT protocols (Ref 184)
- Combined qCT + radiologist read improves BOS diagnostic accuracy (Ref 185)

⚠ Investigational

- ML strain metrics show promise but need prospective validation
- No ML model yet extended beyond radiomics to PFT or biomarker integration
- Routine implementation feasibility not yet established

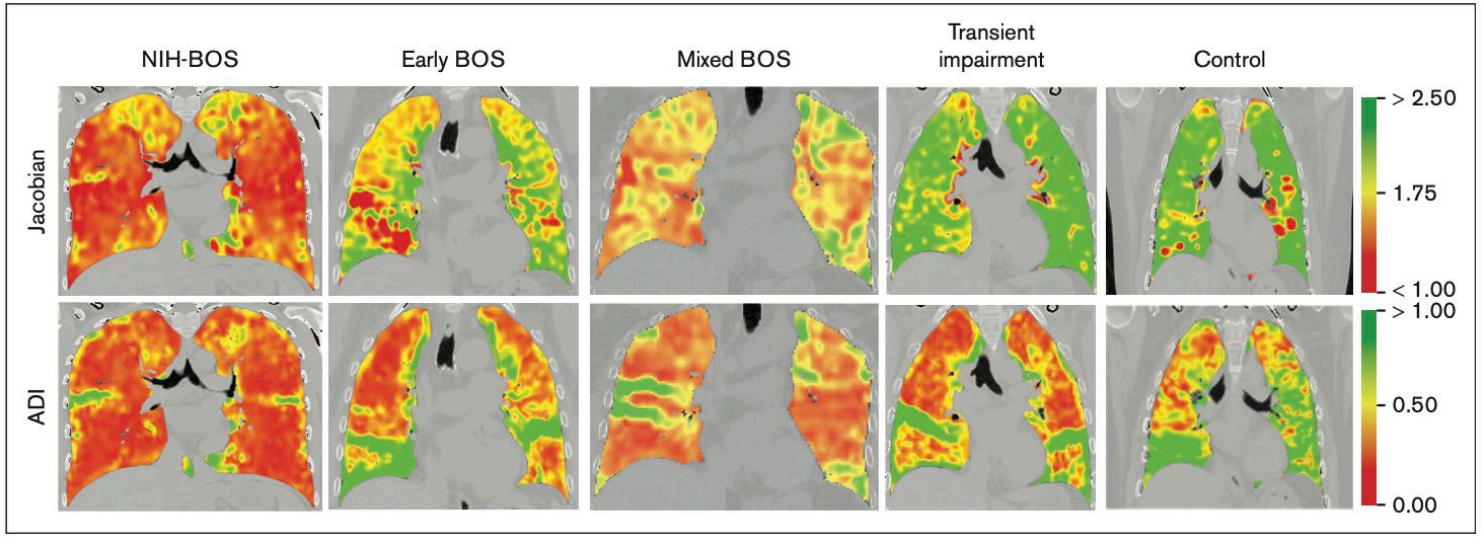
❌ Not Yet Ready

- No qCT technique formally validated as a standalone early BOS detection tool
- ^{129}Xe MRI: no study proves superiority over spirometry for early BOS

Source: Cheng et al., Am J Respir Crit Care Med 2025

Radiomic Biomarkers for LCAT Subtypes

Quantitative CT strain metrics distinguish BOS phenotypes

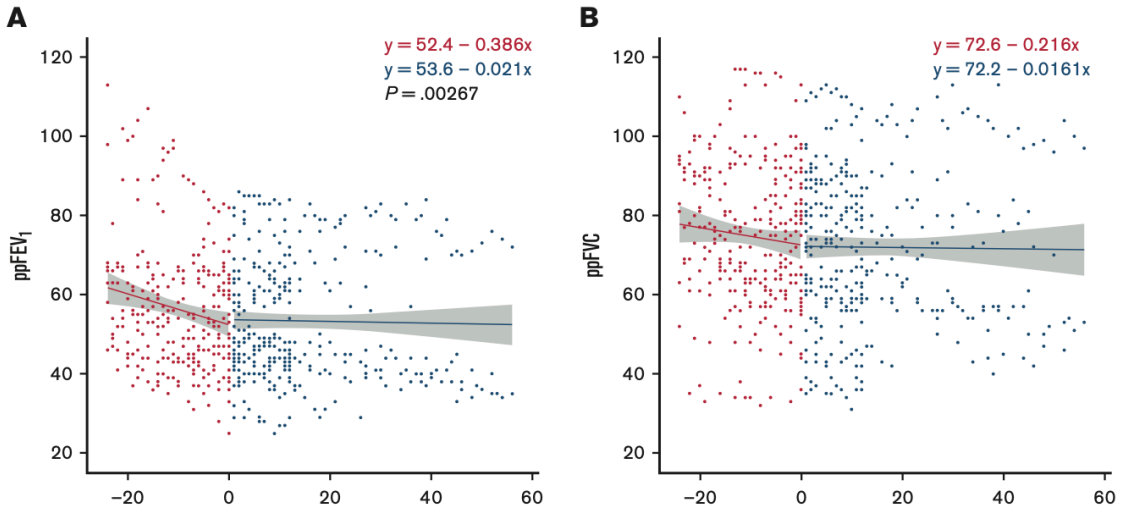


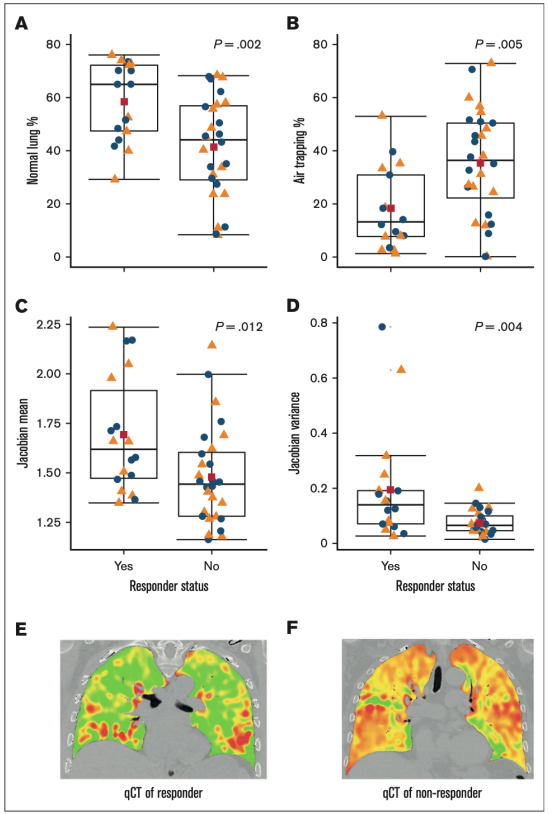
Key Findings (n=84 HCT patients, MDACC + Stanford):

- All strain metrics differentiated BOS from non-BOS ($P < 0.0001$); air trapping alone achieved $P = 0.002$ for early BOS
- Naïve Bayes ML classifier: early BOS detected with AUC 0.84 (95% CI 0.69–0.97), sensitivity 0.77, specificity 0.89
- PPV 0.83, NPV 0.84 — strong discriminatory performance for early BOS vs. transient impairment/controls

Source: Sharifi et al., Blood Adv 2024

STOP-BOS Trial: Pirfenidone & Biomarker Discovery



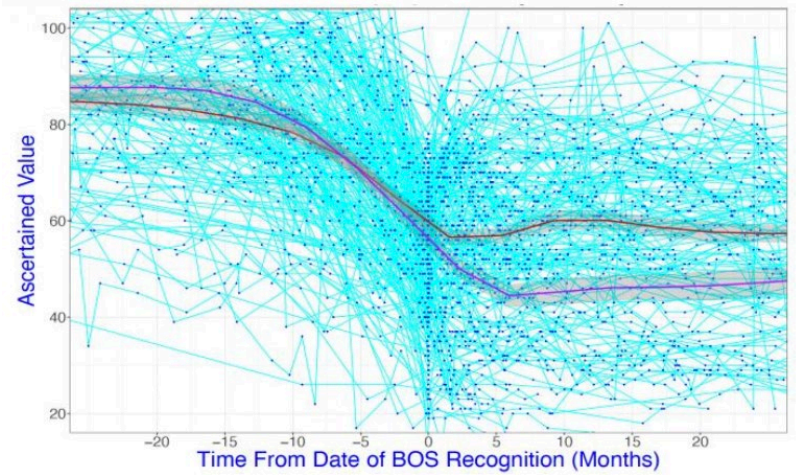


TRIAL RESULTS (n=30)

- 7-point annual ppFEV1 improvement (P = 0.029)
- 41% had significant positive FEV1 change vs baseline
- 4-year extension data confirm sustained benefit

Source: Sharifi, et al Blood Advances 2025

BOS Prognosis: FEV_1 Decline Predicts Mortality



KEY FINDINGS (n=217, FHCC 2000–2019)

- 33% experienced ≥10% FEV1 decline within 2 years
- Lowest 33rd %ile declined ≥5 pp at 1 year
- Each 10% FEV1 decrease → 67% ↑ mortality risk
  (HR 1.67; 95% CI 1.36–1.86, P < 0.0001)

CLINICAL IMPLICATION

- Average ppFEV1 at diagnosis: 51% (historical)
- With early detection emphasis: median 67% (IQR 52.5–76%)
- → Stage shift demonstrates feasibility of earlier Dx
- Therapy must halt FEV1 decline ASAP to avert mortality

PATIENT PERSPECTIVE (n=54 BOS patients surveyed)

#1 priority: Early diagnosis and prevention

#2 priority: Treatment

#3 priority: Biological mechanisms

Survey across 2 Consortium + 1 European site (6/2023)

Source: Preliminary Data

Treatment of BOS After HCT: Current Approach

Limited evidence base — all agents repurposed from other indications

Agent / Approach	Evidence	Key Finding	Ref
Inhaled budesonide / formoterol (FAD — Inhaled Corticosteroid + LABA)	RCT (new-onset BOS)	Milder / earlier disease can be halted or reversed; supports early recognition and treatment	7
Systemic corticosteroids	Standard of care; no RCT for BOS	Largely ineffective at restoring lung function; backbone of cGVHD Tx but limited lung benefit	7
Ruxolitinib (JAK1/2 inhibitor)	Single-arm trial (refractory cGVHD)	BOS response rate and QoL markedly lower than other cGVHD manifestations; CXCL9/11 higher in mild disease (Ref 15)	8,15
Belumosudil (ROCK2 inhibitor)	Phase 2 (steroid-refractory cGVHD)	BOS response lower than non-pulmonary cGVHD manifestations — advanced lung disease refracts targeted therapy	9
Pirfenidone (anti-fibrotic / TGF-β blocker)	Single-arm trial (22 patients)	FEV_1 improvement in a subset; biomarkers (cathepsin D, EGFR, TNFSF14) associated with response (Ref 111)	111,112
Montelukast (leukotriene receptor antagonist)	Single-arm trial (established BOS)	BAL showed bland cellular composition; $CD4^+$ Th2 predominance; all immune lineages expressed leukotriene receptors	195
FAD — Ibrutinib (BTK inhibitor)	FDA-approved for cGVHD 2017	Pulmonary responses seen; first targeted therapy approved for cGVHD including BOS manifestation	—

Source: Cheng et al., Am J Respir Crit Care Med 2025

Treatment: Why Early Detection Changes Everything

The Disease–Treatment Timing Mismatch

Subclinical Airway Injury

Possible Rx: anti-inflammatory

Early BOS (pre-NIH)

Possible Rx: ruxolitinib, inhaled Tx

NIH-Defined BOS (≥75% FEV_1)

Current standard practice starts here

Advanced / Refractory BOS

Targeted agents poorly effective (Refs 8–12)

← WINDOW OF OPPORTUNITY FOR INTERVENTION

Timing of Intervention

- Early inflammatory phase → target inflammation first (e.g. ruxolitinib)
- Fibrotic phase → anti-fibrotic agents (e.g. pirfenidone)

Design Requirements

- Randomized controlled design to separate drug effect from natural history
- Incorporate early detection endpoints (pre-NIH disease definition)

Endpoints by Disease Phase

- Inflammatory early BOS: improvement / resolution within 1 month
- Established BOS: FEV_1 stabilization short-term, improved trajectory long-term

Source: Cheng et al., Am J Respir Crit Care Med 2025

Section 2:
Organizing Pneumonia After HCT

Diagnosis, Treatment, and Management Challenges

What is HCT-OP?

Organizing pneumonia as a noninfectious pulmonary complication of cGVHD

OVERVIEW & PATHOLOGY

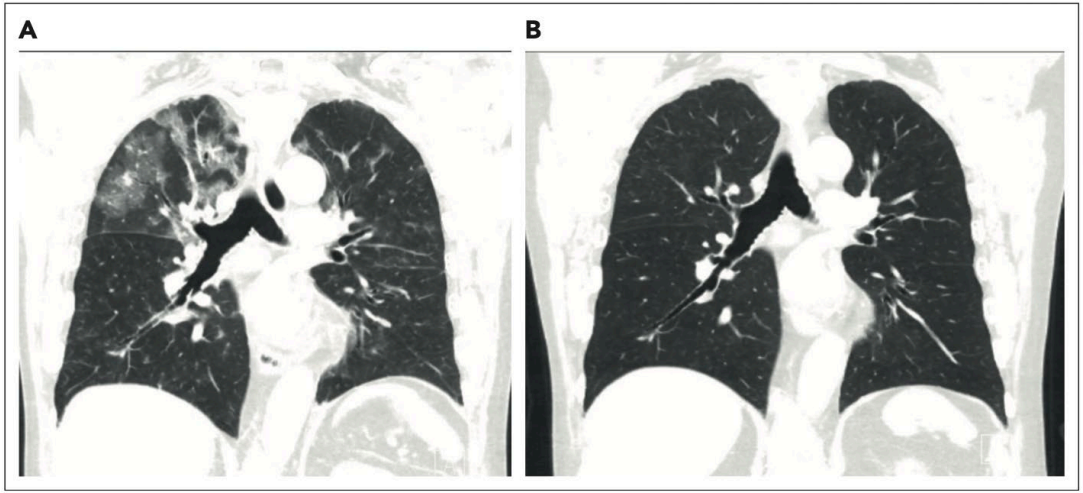
- Intraluminal granulation tissue filling distal bronchioles, alveolar ducts, and sacs
- Incidence: ~0.9% of allogeneic HCT recipients; strongly associated with cGVHD
- Risk factors: acute GVHD (OR 3.8), cGVHD (OR 3.1), myeloablative conditioning, high-dose irradiation
- Most HCT-OP occurs within 3 years post-HCT; late presentations described up to >7 years
- Temporally associated with new onset or exacerbation of extrapulmonary cGVHD (skin, GI, oral)
- Unlike BOS, HCT-OP is NOT recognized as a distinctive cGVHD manifestation in NIH guidelines

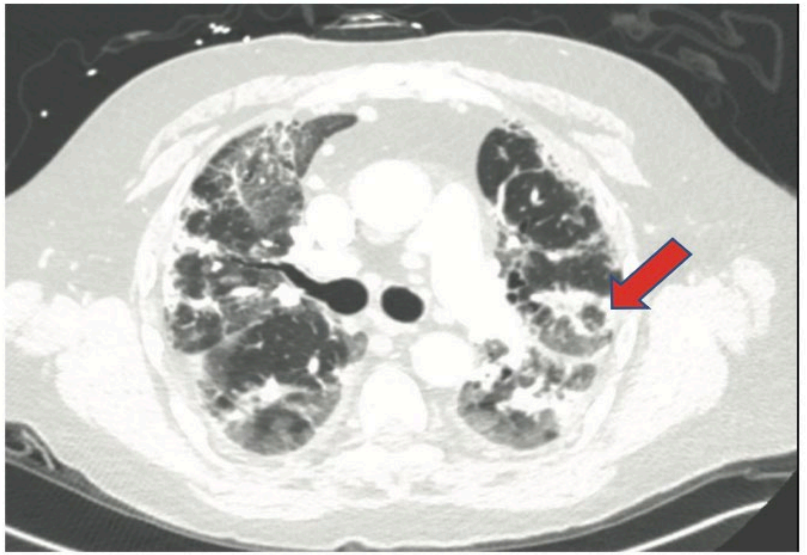
CLINICAL PRESENTATION

- Symptoms: dyspnea, nonproductive cough, pleuritic chest pain, low-grade fever
- CT: ground-glass opacities, consolidation in subpleural/peribronchovascular distribution; atoll sign
- PFTs: restrictive pattern with reduced DLCO (vs. obstructive pattern in BOS)
- Diagnosis often delayed due to similarity with infectious pneumonia
- 5-year overall survival ~70.8% (95% CI 60–83.5%), comparable to BOS
- Respiratory failure is the leading cause of death; spontaneous resolution is rare in HCT-OP

Source: Lai, Sharifi, Hsu. Blood 2024;144:1048–1060

HCT-OP: Radiographic Presentations



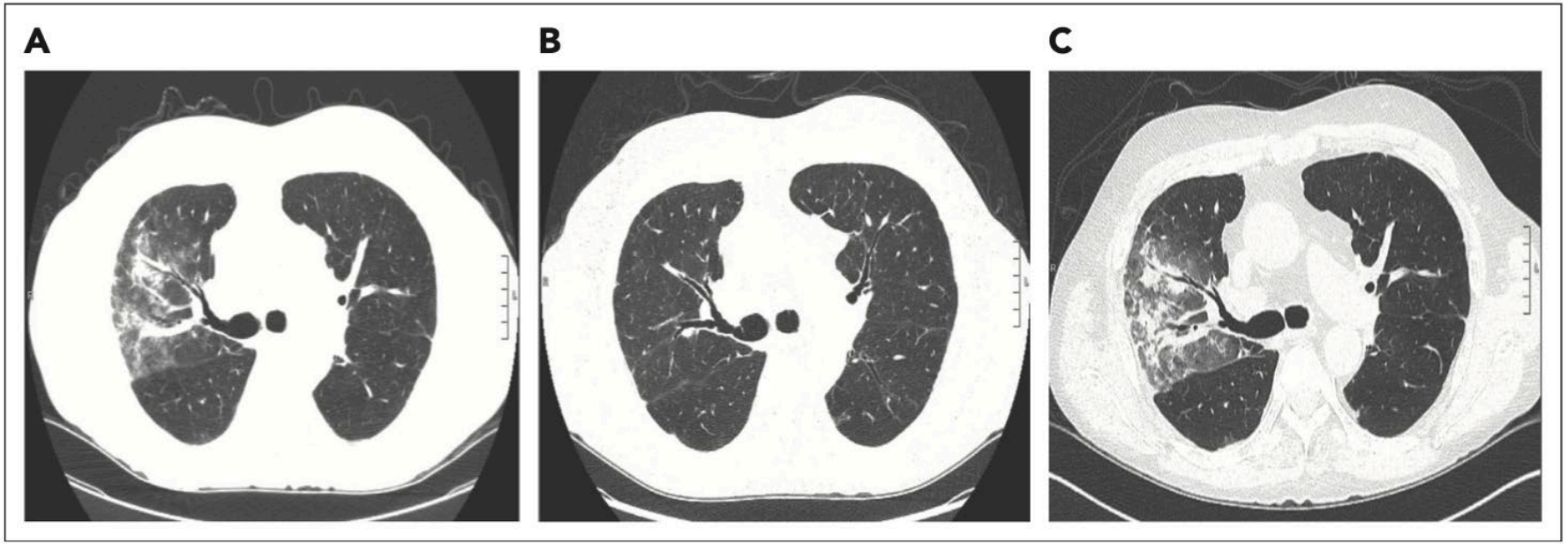


Key Radiographic Features of HCT-OP:

- Ground-glass opacities (GGO) and consolidation in subpleural or peribronchovascular distribution; no zonal preference
- Atoll sign (reversed halo): central GGO surrounded by dense consolidation — characteristic but not always present
- Recurrence tends to occur at the SAME anatomic location as index episode (unlike migratory COP)
- Findings may closely mimic infectious pneumonia or CMV pneumonitis → always exclude infection before treating

Source: Lai et al. Blood 2024;144:1048–1060 | Figures 1–3

HCT-OP: Radiographic Presentations



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Source: Lai et al. Blood 2024;144:1048–1060

Proposed Diagnostic Criteria for HCT-OP

REQUIRED CRITERIA

- 1. History of allogeneic HCT
- 2. Presence or history of acute or chronic GVHD in another organ
- 3. Chest CT findings consistent with OP (GGO, consolidation, atoll sign)
- 4. Decline in DLCO with restrictive spirometric pattern on PFT

DIAGNOSTIC WORKUP

- 5. Absence of infectious pathogen in cultures, or no improvement despite broad-spectrum antibiotics
- Bronchoscopy with BAL to exclude infection (bacteria, fungi, viruses, PCP, molds)
- Non-invasive tests: serum PCR for molds, β-D-glucan, galactomannan, respiratory viral PCR
- Exclude drug-induced pneumonitis: review medication list at www.pneumotox.com

WHEN TO BIOPSY

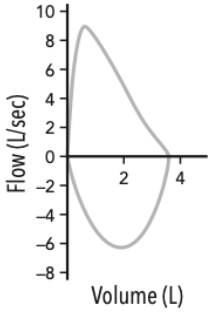
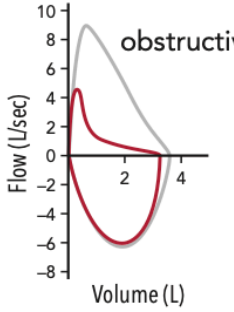
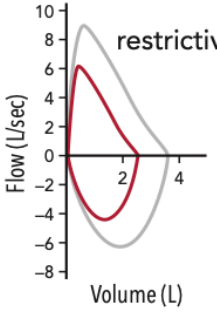
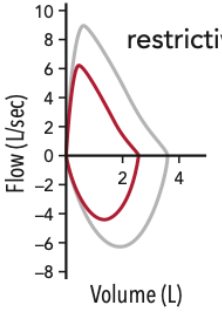
- Diagnosis remains elusive despite comprehensive evaluation
- No clinical improvement despite corticosteroid treatment
- Malignancy or invasive fungal disease high on differential
- 6. Lung biopsy compatible with OP (if performed; reserved for selective cases)

⚠ **Infectious causes must be VIGOROUSLY excluded before initiating immunosuppression. Involve pulmonology, HCT team, and infectious disease specialists early.**

Source: Lai et al. Blood 2024;144:1048–1060

HCT-OP vs BOS vs Truncal Sclerosis: PFT Patterns

Understanding PFT differences aids phenotyping and guides management — Lai et al. Blood 2024

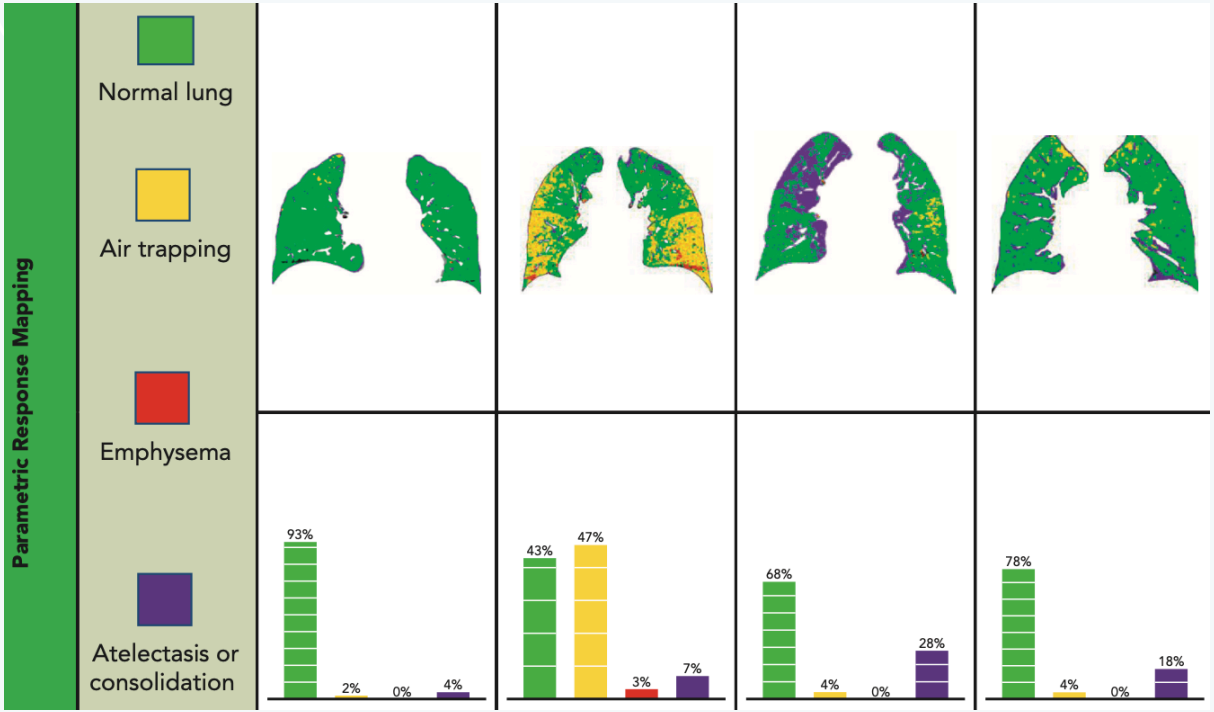
PFT		Normal	BOS	HCT-OP	Truncal Sclerosis
	Flow-volume Loop/ Spirometric Pattern				
	FEV_1	>80%	↓	↓	↓
	FVC	>80%	Normal or ↑	↓	↓
	FEV_1/FVC	>70%	↓	Normal or ↑	Normal or ↑
	DLCO	>80%	Normal or ↓	↓	Normal or ↓

Source: Lai et al. Blood 2024;144:1048–1060 | Cheng et al. Am J Respir Crit Care Med 2025

HCT-OP vs BOS vs Truncal Sclerosis: Quantitative CT Patterns

Understanding PFT differences aids phenotyping and guides management — Lai et al. Blood 2024

HCT-OP PATTERN



Treatment of HCT-OP: Corticosteroid Approach

INTENSIVE PHASE

- Start prednisone 1 mg/kg/day (0.5 mg/kg if not hypoxemic)
- For ICU/mechanical ventilation: methylprednisolone 1–2 mg/kg/day
- Assess response at 1–2 weeks; if improving, taper by 10 mg/week until 50–60 mg/day
- Monthly PFTs and clinic follow-up; repeat CT to confirm radiographic improvement

CONSOLIDATIVE PHASE

- At 50–60 mg/day: taper 5 mg every 2 weeks until 20 mg/day
- Monthly PFTs; imaging if clinical or PFT decline
- Monitor for extrapulmonary cGVHD flares, opportunistic infections, steroid complications (bone density, glucose, myopathy)
- Introduce corticosteroid-sparing agents if relapse occurs or rapid taper needed

COMPLETION PHASE

- At 20 mg/day: taper 5 mg every 2–4 weeks — slower, highest relapse risk in this phase
- Watch for adrenal insufficiency once prednisone <10 mg/day
- Obtain PFTs and chest imaging 1 month after steroid completion to establish new baseline
- Sparing agents: mycophenolate mofetil, ibrutinib (FDA-approved cGVHD), ruxolitinib, cyclosporine

⚠ **Relapse occurs in 30–50% of cases, often during taper. Recurrence tends to occur at the same radiographic location as the index episode (unlike cryptogenic OP). Maintain infection prophylaxis throughout.**

Source: Lai et al. Blood 2024;144:1048–1060

HCT-OP Treatment

CORTICOSTEROID-SPARING AGENTS

For HCT-OP:

- Mycophenolate mofetil
- Ibrutinib (FDA-approved for cGVHD)
- Ruxolitinib (FDA-approved for cGVHD)
- Cyclosporine
- Etanercept (prospective trial: 33% FVC improvement)

MONITORING ESSENTIALS

Multidisciplinary: BMT + Pulm + ID

- Monthly PFTs during intensive/consolidative phases
- Infection prophylaxis throughout (PCP, fungal, viral)
- Repeat CT if clinical or PFT decline
- Monitor steroid complications: bone density, glucose, myopathy
- Watch for adrenal insufficiency below prednisone 10 mg/d

Source: Lai et al. Blood 2024;144:1048–1060

HCT-OP vs Non-HCT-OP: Key Differences

HCT-OP has a distinct clinical course requiring tailored management

PATIENT & DIAGNOSIS

- HCT-OP: any allogeneic HCT recipient; non-HCT-OP: rarely in children; cryptogenic in adults
- HCT-OP: isolated occurrence without other GVHD is rare; non-HCT-OP: can be cryptogenic
- HCT-OP: no zonal preference on CT; non-HCT-OP: lower lung zone predominance
- HCT-OP: lung biopsy reserved for selective cases due to procedural risk in cGVHD patients

TREATMENT

- HCT-OP: immunosuppression almost always required; spontaneous resolution is rare
- HCT-OP: extended corticosteroid course >6–12 months often required
- Non-HCT-OP: spontaneous resolution can occur; corticosteroid course may be shorter (6–12 months)
- HCT-OP: multidisciplinary management (BMT + pulmonology + infectious disease) is essential

PROGNOSIS & RELAPSE

- HCT-OP relapse: 30–50%; non-HCT-OP relapse: 13–58%
- HCT-OP: relapse at same radiographic location; non-HCT-OP: migratory opacities common
- HCT-OP: mortality from respiratory failure significant; non-HCT-OP: <10% mortality, rarely from OP
- HCT-OP 5-year survival ~70.8%; non-HCT-OP 5-year survival >90%

⚠ **HCT-OP can also develop from causes UNRELATED to GVHD (viral infections, drug toxicity, aspiration, autoimmune disease). Always rule out these causes before attributing OP to GVHD**

Source: Lai et al. Blood 2024;144:1048–1060

Key Takeaways & Your Role as a Practicing Pulmonologist

01 BOS will reach your clinic — 39,000 HCTs/year globally, 7% annual growth, most survivors return to community care

02 Early detection is the best opportunity to limit damage — but the NIH criteria miss 48% of histologically proven cases

03 Only 30–40% of HCT recipients get routine PFTs — ask about transplant history and trend FEV_1 even when it is 'normal'

04 Know the high-risk profile: extrapulmonary cGVHD, unrelated donor, busulfan conditioning, early FEF_{25-75} decline, viral infections

05 HCT-OP presents with restrictive PFTs + GGO on CT; treat with prednisone 1 mg/kg/day. Relapse occurs in 30–50%; recurrence at same CT location is characteristic

06 Collaborate with HCT centers — multidisciplinary approach (pulmonology, HCT team, infectious disease) is essential for both BOS and HCT-OP management