

Graft-versus-Host Disease: What to Do When it Attacks the Lungs

**Celebrating a Second Chance at Life
Survivorship Symposium**

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Graft-versus-Host Disease: What to Do When It Attacks the Lungs

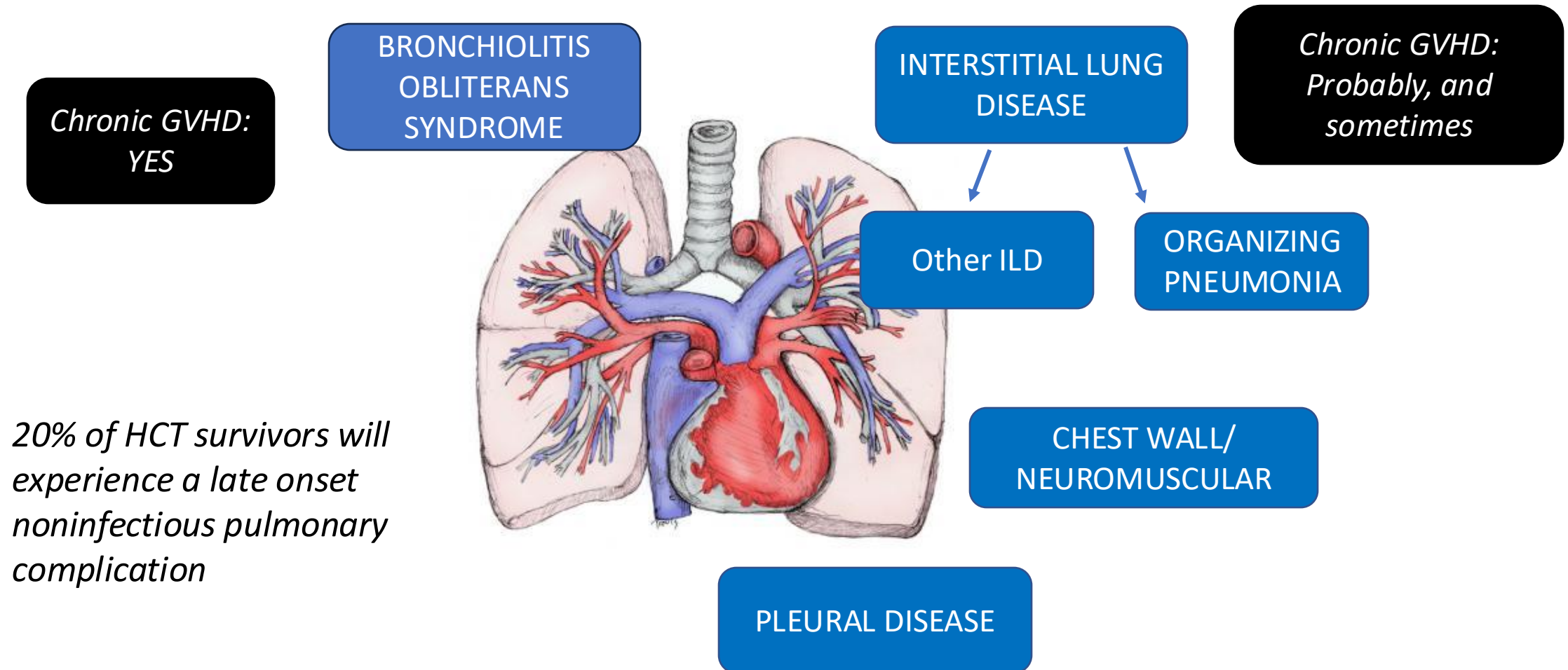
Learn how frequently GVHD affects the lungs, risk factors, symptoms,
and treatment options

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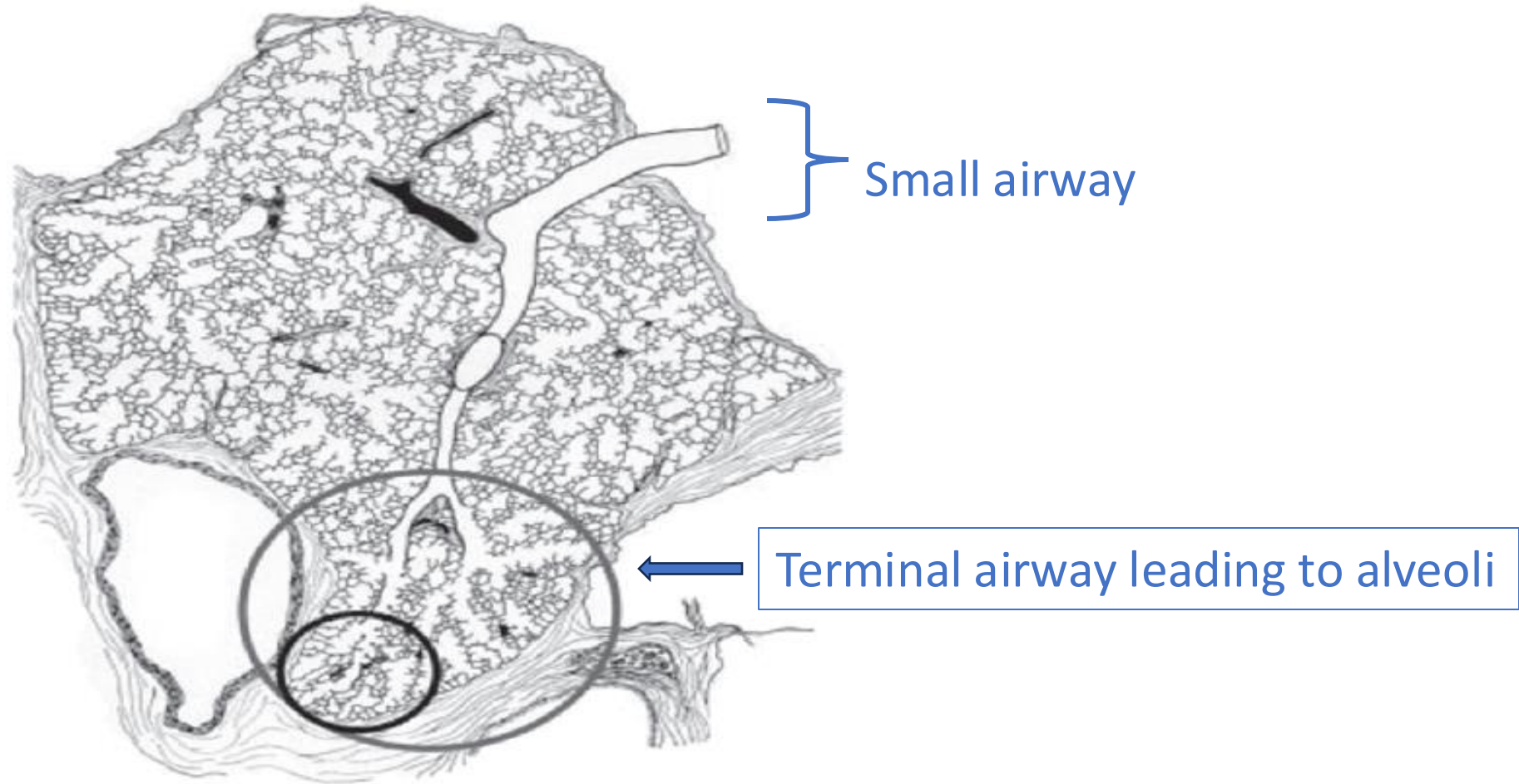
Outline

- I. Lung GVHD Basics: *Bronchiolitis obliterans syndrome*
- II. Treatment of bronchiolitis obliterans syndrome
- III. Other Lung Conditions related to GVHD

Late Onset Noninfectious Pulmonary Complications

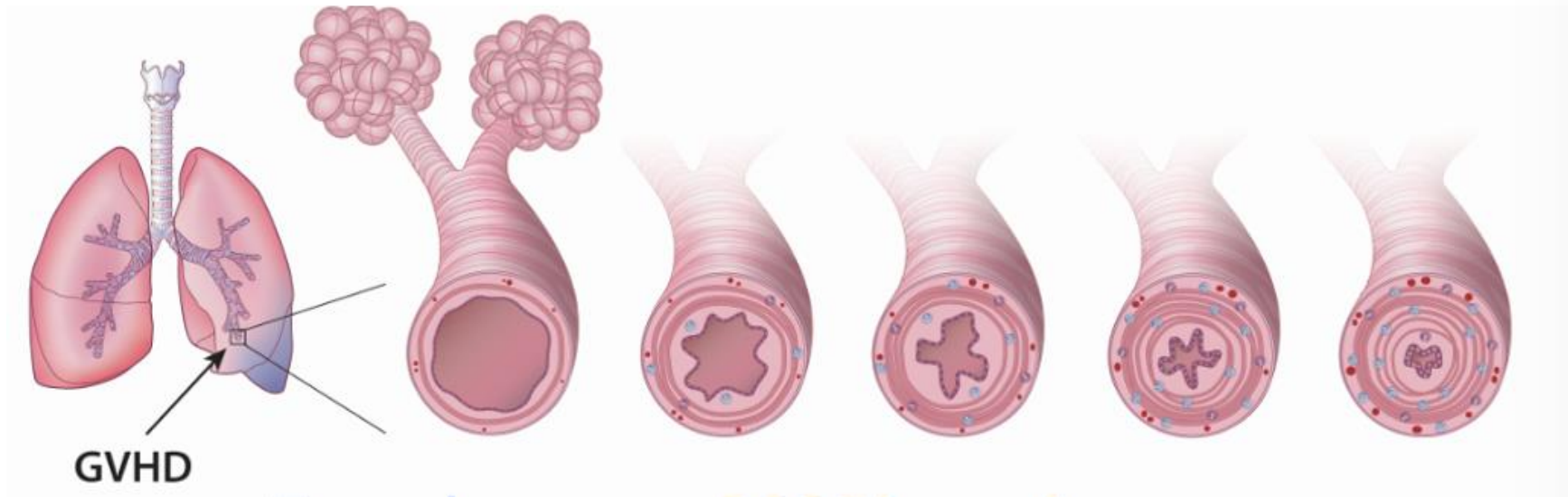


Anatomy of lung tissue

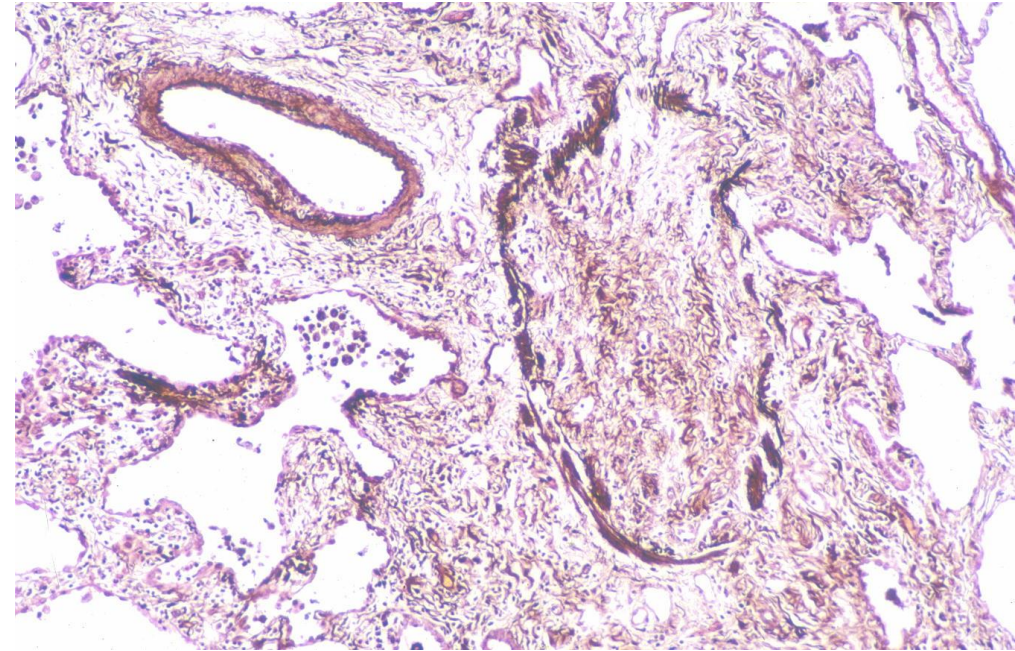
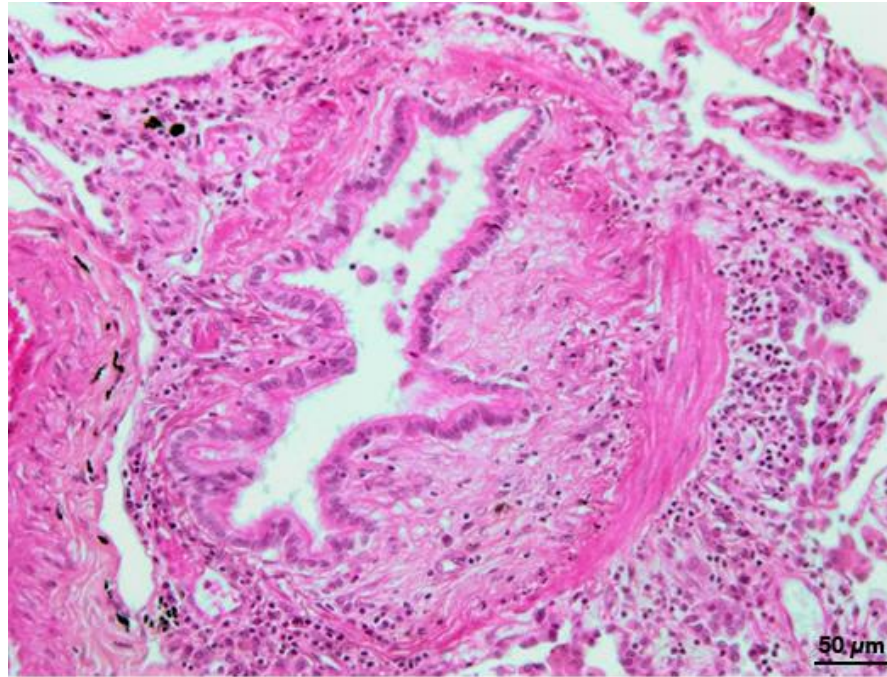


Bronchiolitis Obliterans Syndrome (BOS)

- Starts when the donor cells attack the airways
- Inflammation leads to airways obstruction and fibrosis of small airways
- This results in airflow decline and difficulty breathing



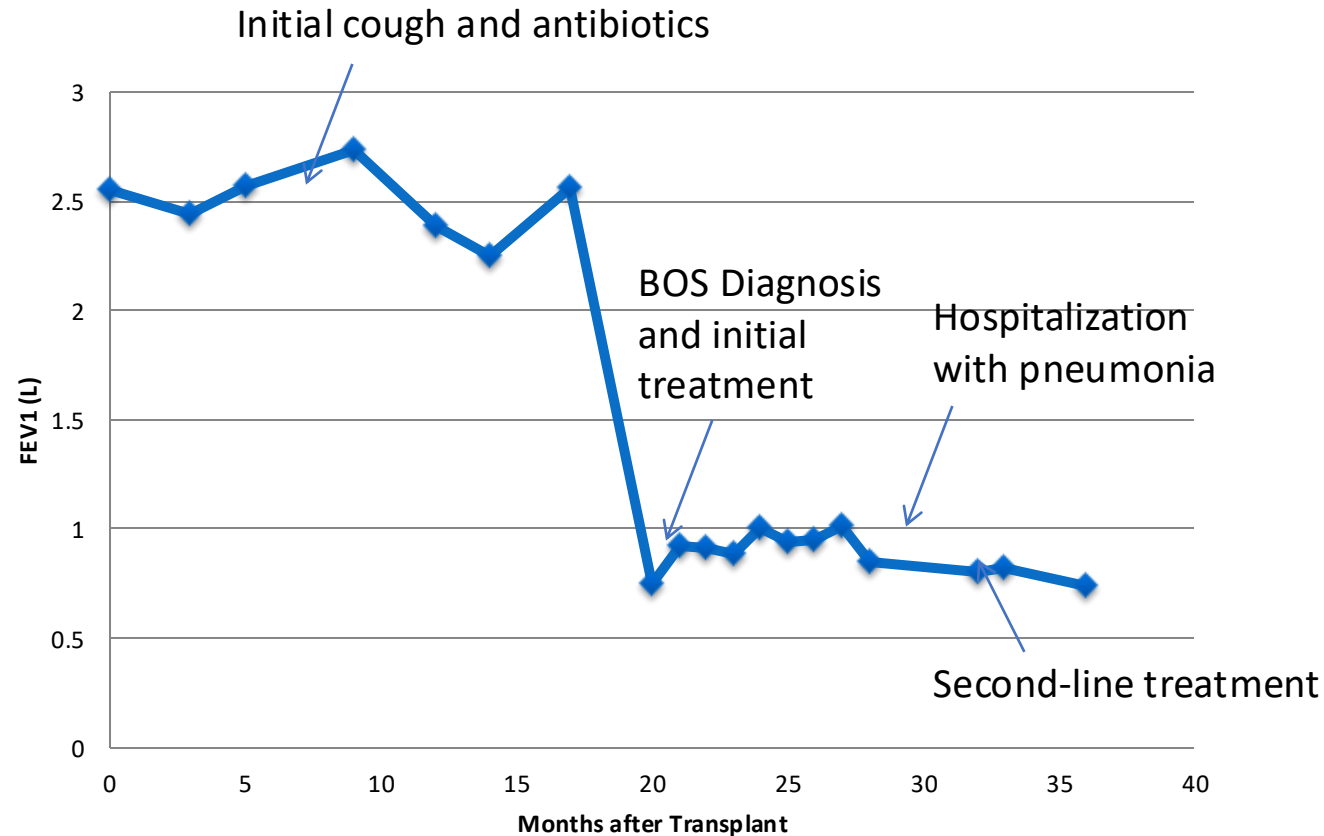
Pathology: Obliterative Bronchiolitis



- **Obliterative bronchiolitis:** fibrotic obliteration of small airways seen on lung biopsy
- Rare condition seen in other disease contexts, such lung transplantation

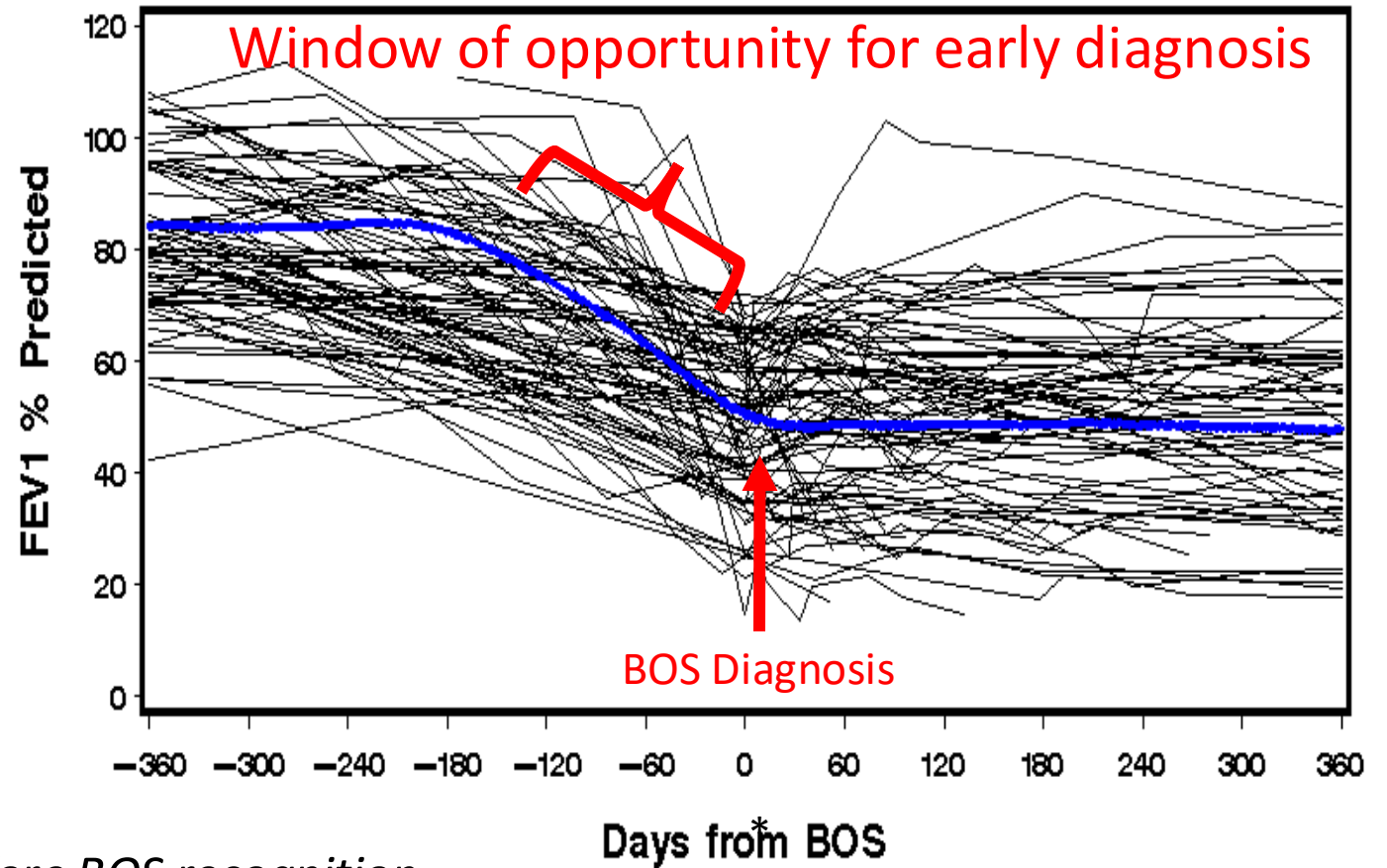
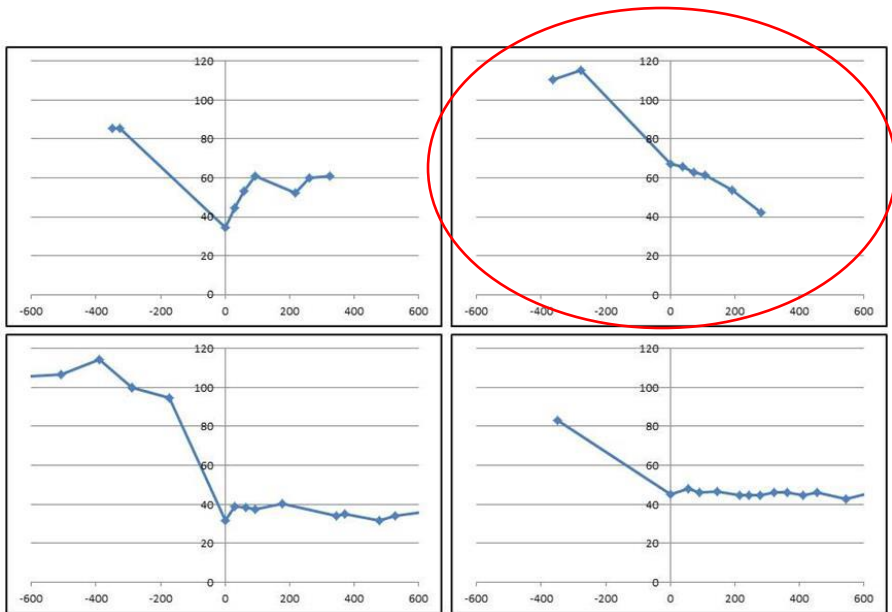
Micrographs courtesy of Dr Anne Bergeron and Dr. Robert Hackman

The clinical course of severe BOS



- Initial symptoms:
 - persistent cough
 - shortness of breath with exertion
- Treatment may help symptoms, but lung function usually doesn't recover fully
- Punctuated by periods of worsening symptoms, usually due to lung infections

BOS lung function trajectories are heterogenous, but generally plateau



Steepest decline in lung function occurs before BOS recognition

Cheng et al. AATS 2016

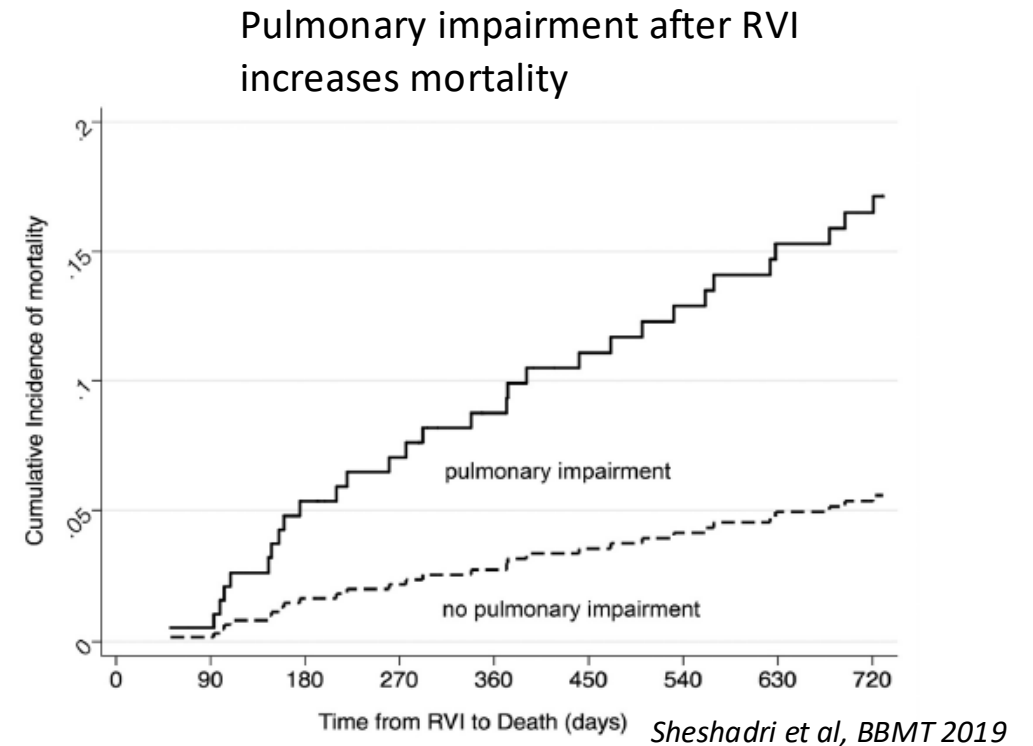
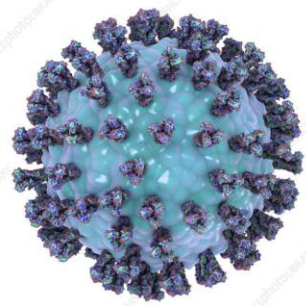
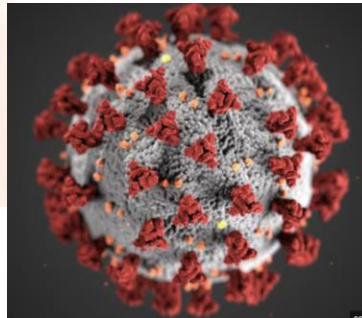
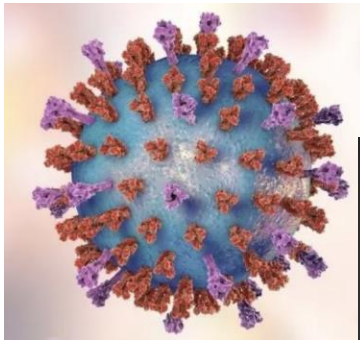
Risk factors for BOS

- Chronic Graft-versus-Host Disease (GVHD)
 - BOS occurs in 14% of patients
 - Usually diagnosed within 6 months of chronic GVHD diagnosis
- Changes in lung function measurements at day 80-100
- Some conditioning regimens (such as busulfan)
- Prior lung disease
- Low immunoglobulins

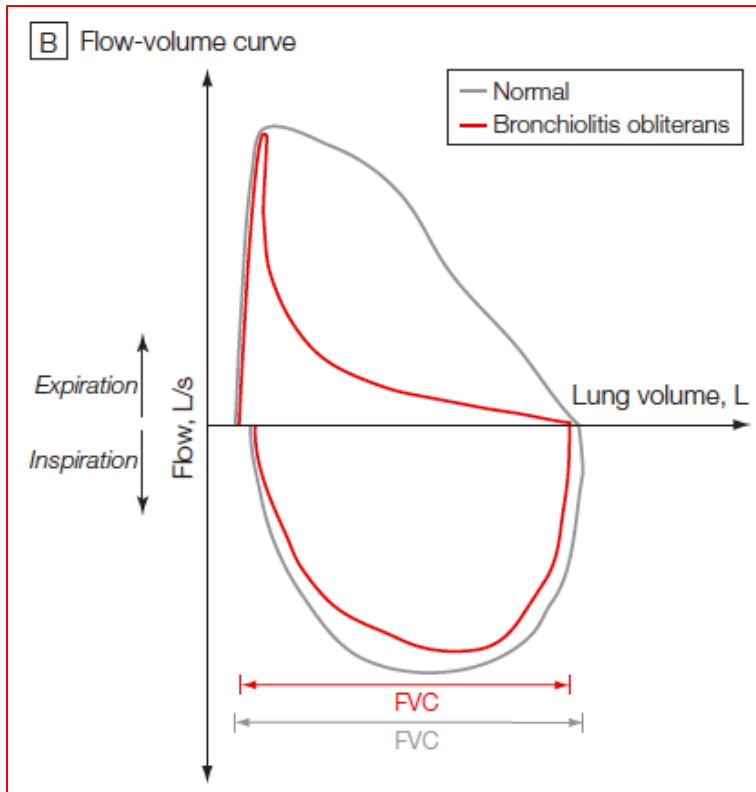


Specific respiratory viruses are thought to increase risk for BOS

- Respiratory syncytial virus
- Parainfluenza virus
- COVID-19 virus (SARS-CoV2)

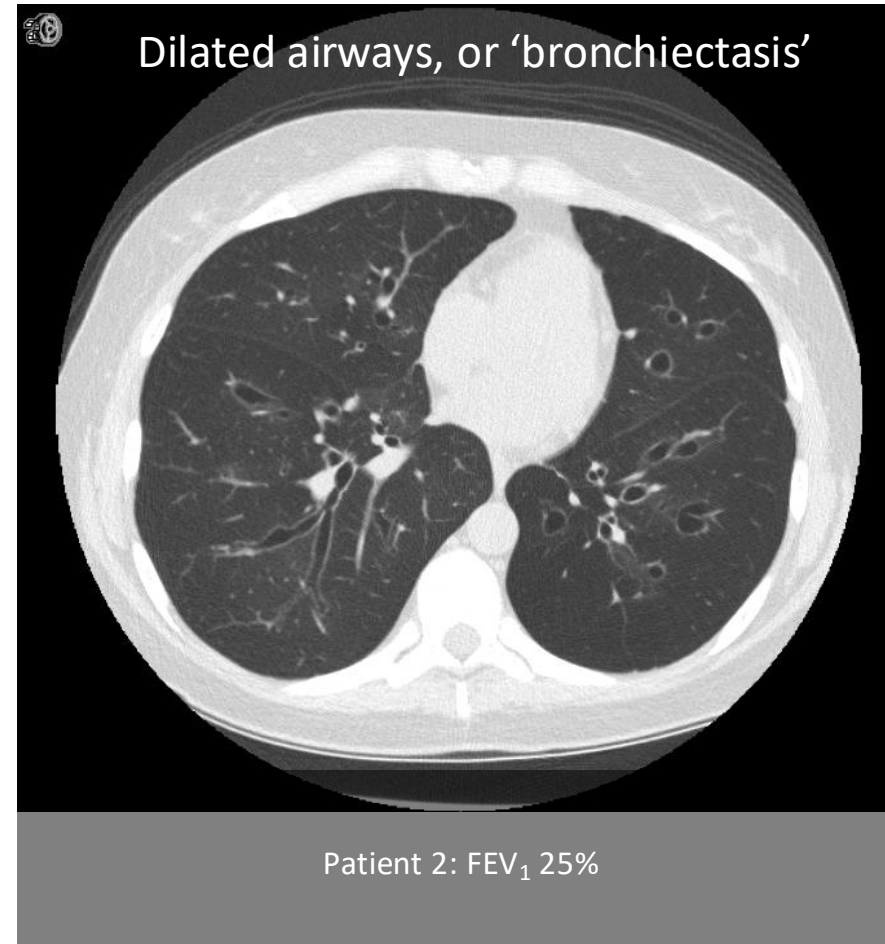
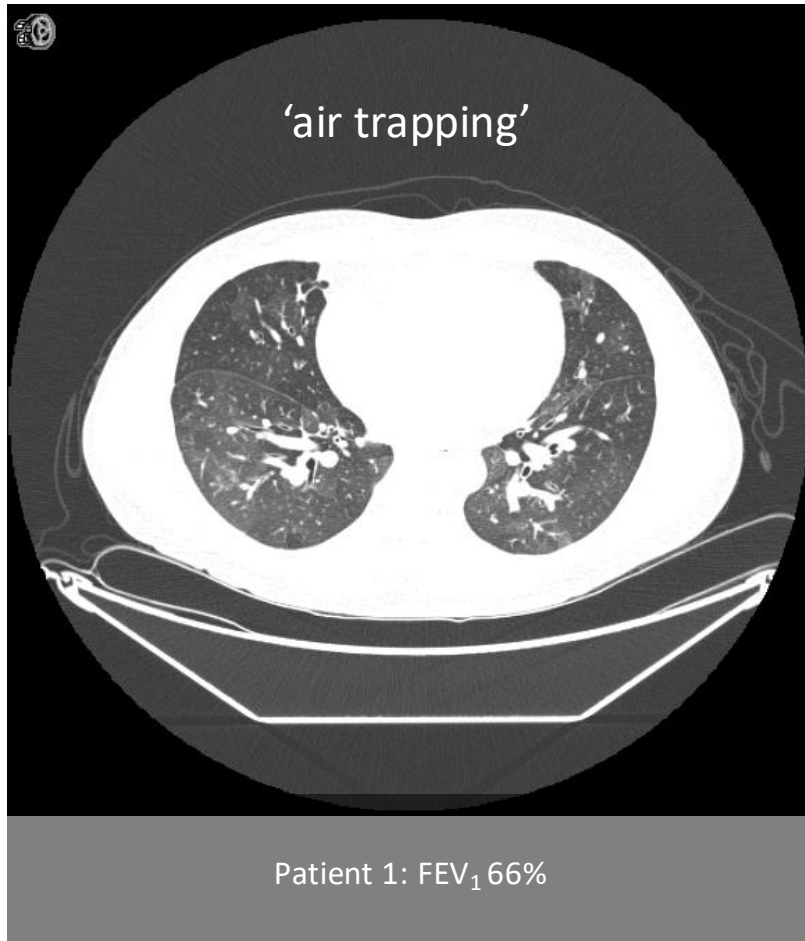


Diagnosis of BOS depends on Pulmonary Function Tests (PFTs)

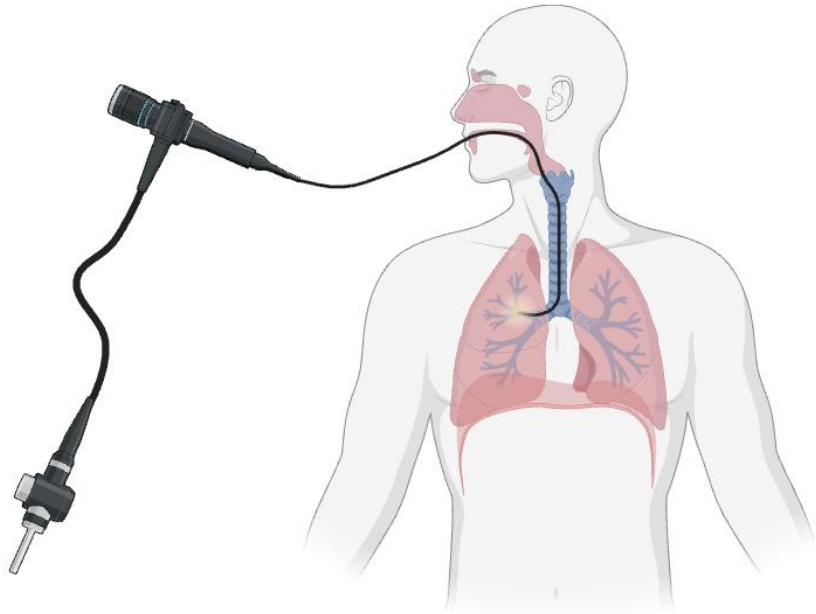


- New decline in spirometry compared with prior PFTs
- Evidence of airflow obstruction not due to other lung disease such as asthma
- Absence of active lung infection
- Usually accompanied by other cGVHD
 - If no other cGVHD, may require a lung biopsy

Chest CT scans that show signs of airways disease help confirm diagnosis



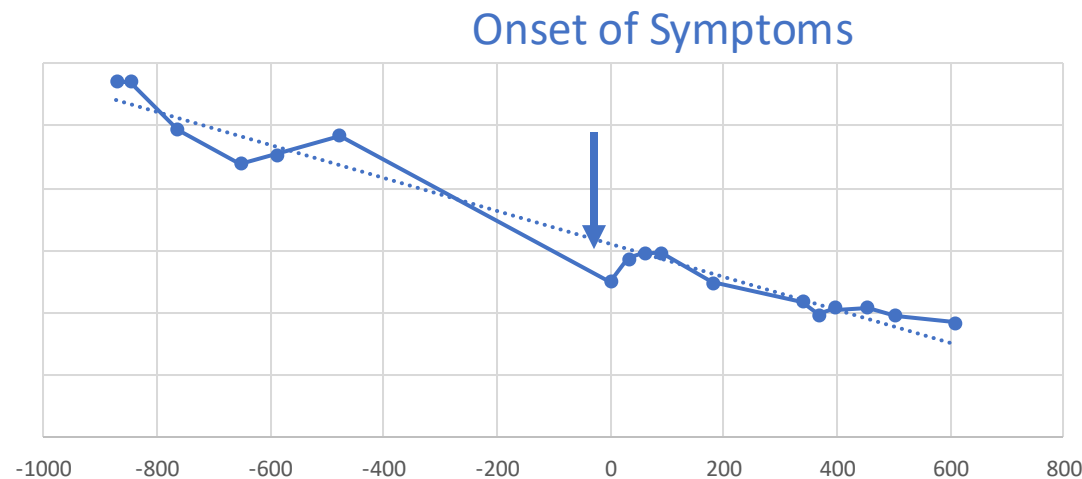
Bronchoscopy is often performed to rule out infection



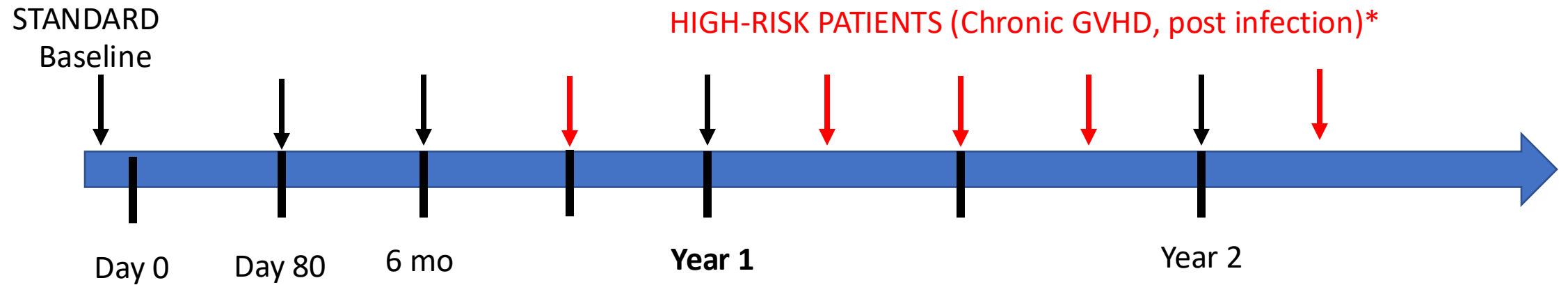
- Minimally invasive way to sample the lung tissue with instillation of saline (lavage)
- Biopsies can be performed if necessary
- Ambulatory or inpatient procedure

Early diagnosis of BOS depends on routine PFTs after transplant

- Symptoms don't develop until a lot of lung function has been lost!
- 10% decline is a good rule of thumb (though this requires further study)



Current recommendations for PFT monitoring after HCT



*Kitko et al. 2020 NIH Chronic GVHD Consensus Project: Early Diagnosis. JTCT 2021

Types of spirometry

SUPERVISED



UNSUPERVISED



Pulmonary Function Laboratory



Office Desktop



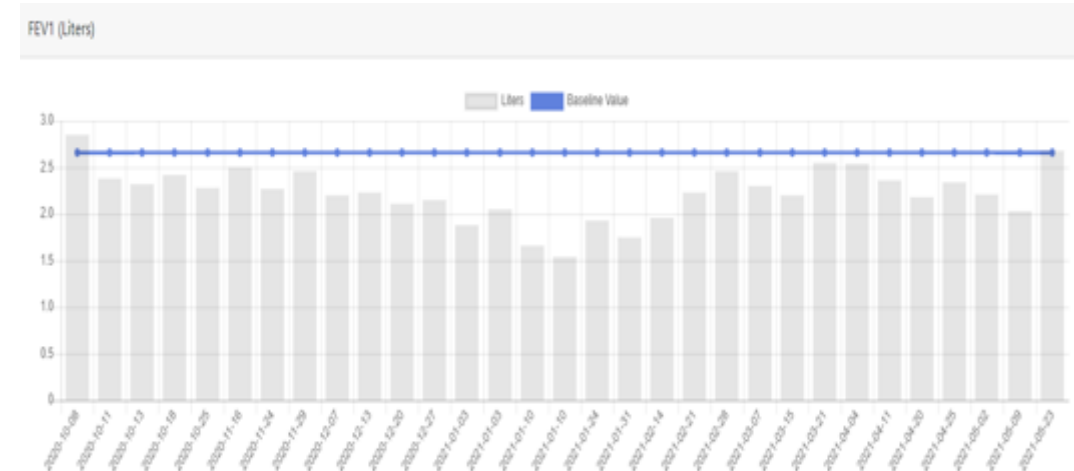
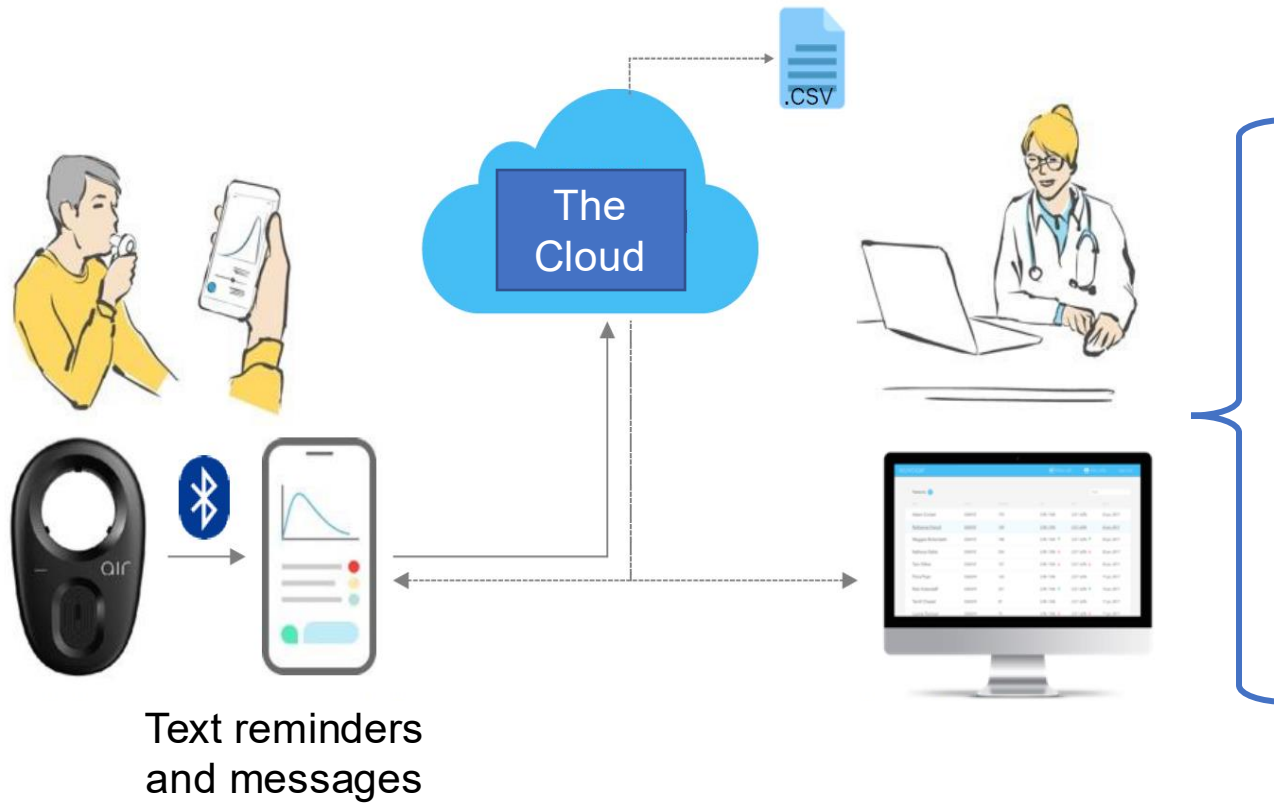
Handheld Portable



Wireless home spirometry makes it easier to monitor lung function



Cloud-based telemonitoring schema



Treatment



Current Backbone of BOS Treatment

FAM+ LABA

Fluticasone

Azithromycin

Montelukast

Long-acting beta-agonist (LABA)



Based on 2 clinical trials:
Bergeron et al., 2015
Williams et al., 2016

+/-

Prednisone 1mg/kg x 2 weeks
followed by taper over 4-6 weeks



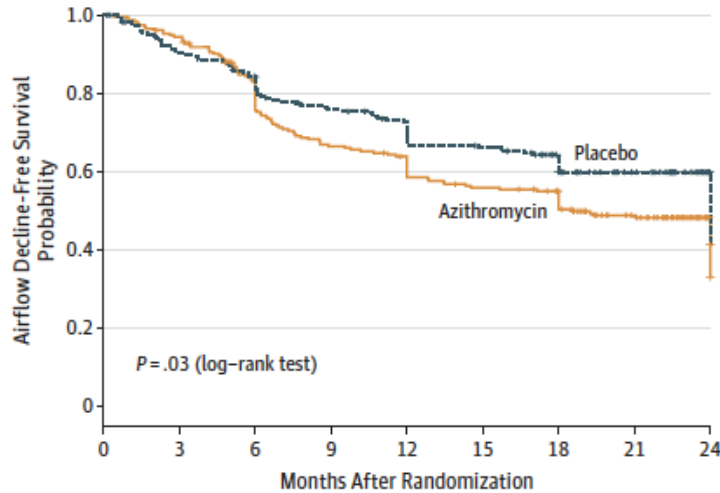
Azithromycin—is it safe for BOS?

JAMA | Original Investigation

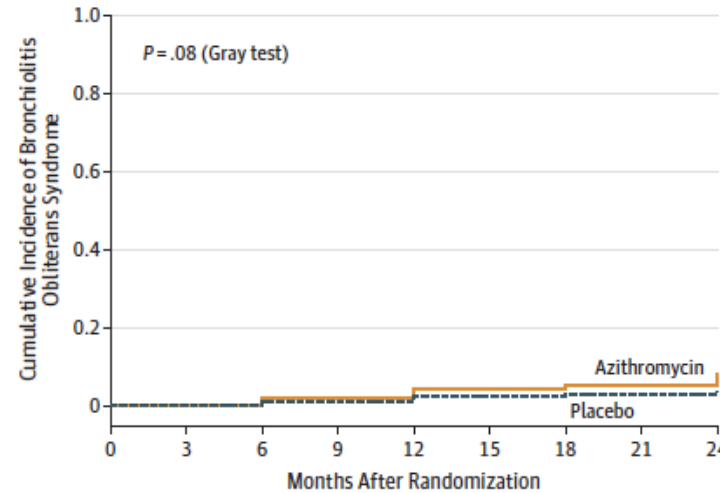
Bergeron et al JAMA Aug 2017

Effect of Azithromycin on Airflow Decline-Free Survival After Allogeneic Hematopoietic Stem Cell Transplant The ALLOZITHRO Randomized Clinical Trial

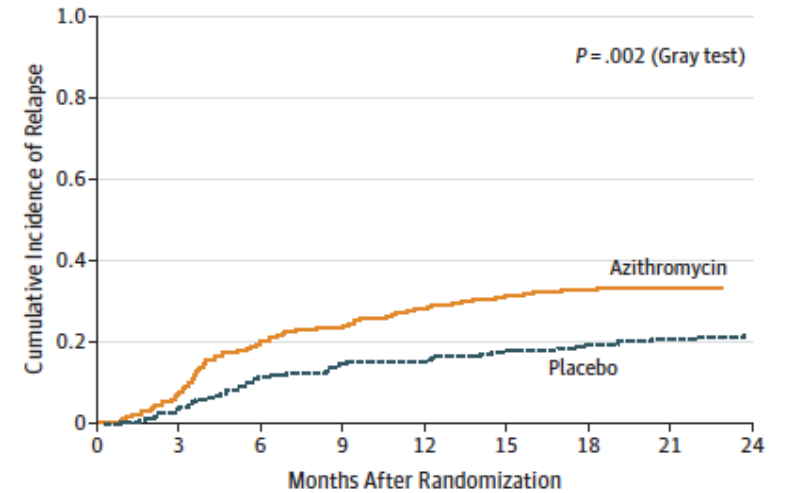
A Airflow decline-free survival



B Bronchiolitis obliterans syndrome



B Relapse



Considerations for FAM regimen

- Inhaled corticosteroid
 - Initial efficacy
 - Association with pneumonia in other obstructive airway diseases
 - Side effects
- Long-acting beta agonist
 - Probably not necessary after the first month
- Azithromycin
 - Risk of subsequent malignancy with little evidence of efficacy or reduction in cGVHD
- Montelukast
 - Unlikely to have a major effect



A practical approach @ initial BOS diagnosis

Assessment of FAM+LABA elements

1. Avoid azithromycin

- Prior to 1-year posttransplant
- High risk AML/ALL for relapse
- Discontinue @ 3-6 months

2. Discontinue montelukast @ 6-12 months

3. Ongoing use of bronchodilator depends on patient

Additional treatments for BOS

Graft-versus-host disease medications

- ECP (extracorporeal photopheresis)
- Ruxolitinib (Jakafi®)
- Belumosudil (Rezurock®)
- Axatilimab (Niktimvo™)

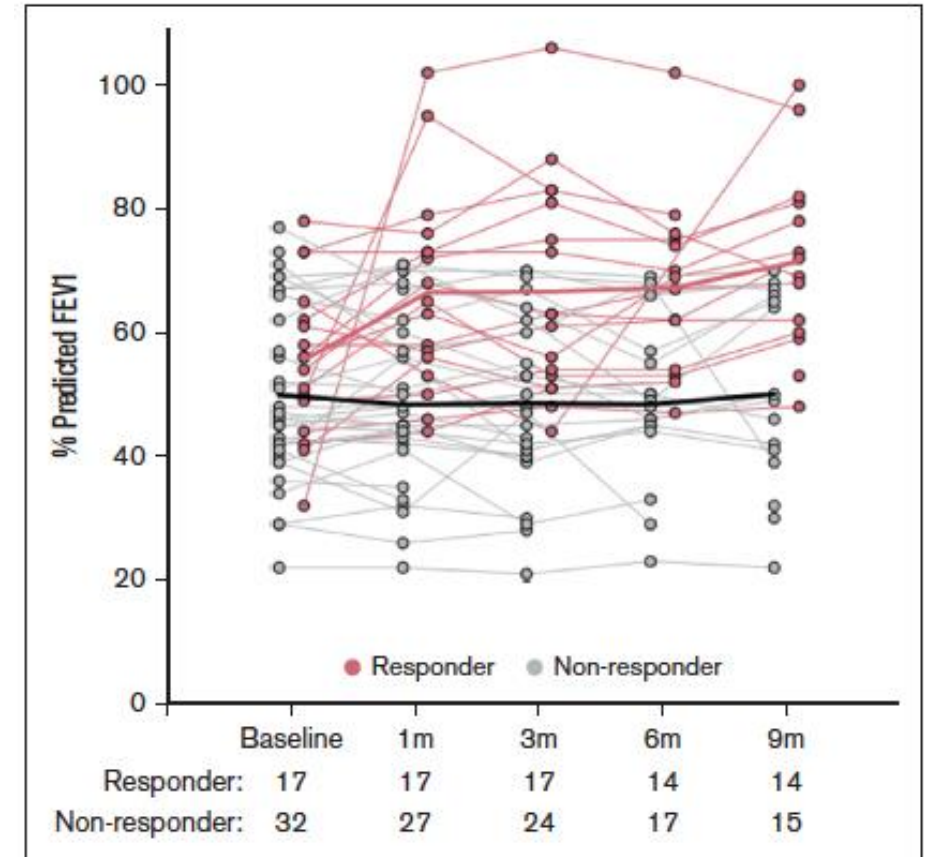
Pulmonary fibrosis medications

- Pirfenidone
- Nintendanib



Ruxolitinib (Jakafi®)

- Inhibits Jak pathway; anti-inflammatory
- Phase II Trial with 49 patients completed
- In patients with newly diagnosed BOS, 28% had improvement in their lung function at 3 months
- Those with established BOS were stable
- Reasonably tolerated



DeFilipp, Blood Advances 2025

Belumosudil (Rezurock®)

- Anti-inflammatory and antifibrotic activity
- Once a day pill
- FDA-approved for third-line GVHD treatment
- **BEBOP Trial is recruiting for new-onset BOS and BOS prevention**
 - Dana Farber Cancer Institute, Dr. Corey Cutler (LEAD Investigator)
 - Fred Hutchinson Cancer Center, Dr. Guang-Shing Cheng
 - University of Michigan, Dr. Greg Yanik

<https://www.clinicaltrials.gov/study/NCT05922761>



SCAN ME

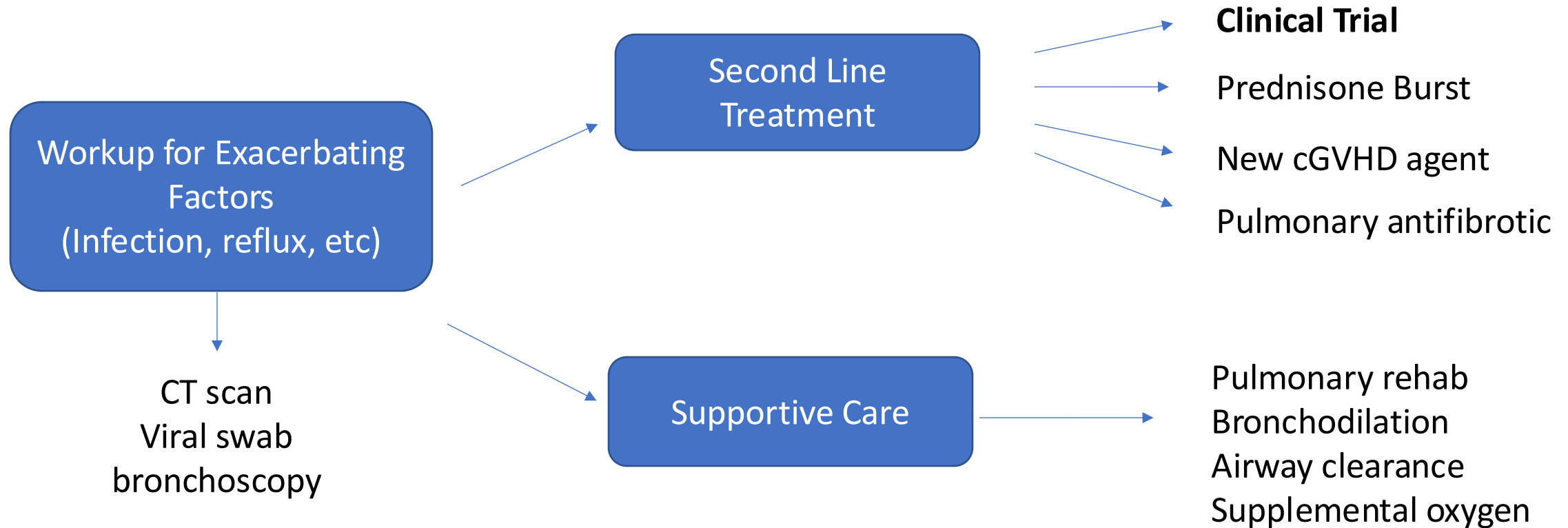
Pirfenidone

The safety and tolerability of pirfenidone for bronchiolitis obliterans syndrome after hematopoietic cell transplant (STOP-BOS trial)

- FDA-approved for the treatment of idiopathic pulmonary fibrosis since 2014
- 3 x daily pill
- In this single-arm trial, there was an Improvement in FEV1 trajectory in 41% of patients
- Generally well-tolerated; mild GI side effects for some

Matthiaou et al BMT 2022

An approach to progressive FEV₁ decline



Cheng GS. The Role of the Pulmonologist Ch37 in Pulmonary and Critical Care Considerations of Hematopoietic Stem Cell Transplantation, ed Soubani AO. Springer Intl 2023, pp472-481.

Adjunctive treatments for breathlessness

- Bronchodilators
 - Beta-agonists (e.g. albuterol, formoterol)
 - Muscarinic agonists (e.g. tiotropium)
- Supplemental oxygen for severe disease
 - With activity or around the clock
 - May only be needed at night



Supportive Care

- PREVENT and treat Infections
 - Vaccinations (Flu, COVID, RSV, pneumococcus)
 - General hygiene
 - Avoidance of sick contacts
- Treat other exacerbating conditions
 - Sinus disease
 - Aspiration
 - Reflux
 - Environmental allergies



Airway clearance

- Particularly for people who have recurrent lung infections and bronchiectasis
- Positive expiratory pressure devices (like a capella) help clear secretions



Pulmonary Rehabilitation

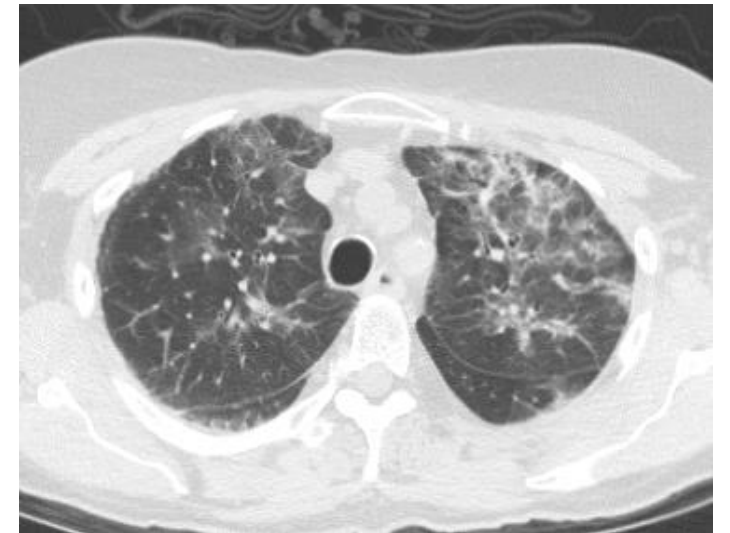
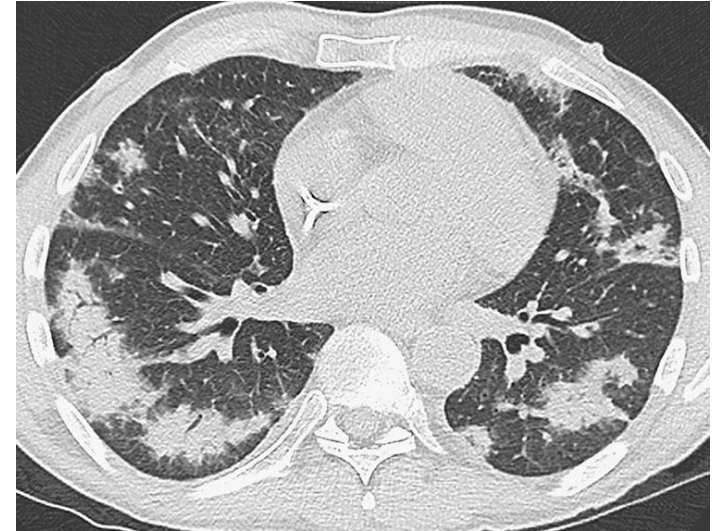
- Best for people who have a lot of limitations because of their lungs
- Consists of :
 - Education
 - fitness training
 - breathing exercises



Other Lung Conditions

Organizing pneumonia after HCT

- When alveoli are attacked and filled with inflammatory material
- Can present like infectious pneumonia
- Can occur after a lung infection, such as COVID-19, or other medical conditions
- Patients with a history of acute and chronic GVHD are at risk



Treatment of Organizing Pneumonia

First Line

Prednisone

- Start at higher dose
- Taper duration 4-6 mos
- Taper slowly to avoid relapse

Second Line

- Inhaled corticosteroids and/or bronchodilators
- Ruxolitinib Azathioprine
- Mycophenolate mofetil
- Macrolide antibiotic (azithromycin or clarithromycin)



Restrictive lung disease: Extrathoracic consequences of cGVHD

- Skin tightening of abdomen and chest (sclerosis)
- Respiratory muscle weakness
 - Inflammation affecting diaphragm and other muscles (myositis)
 - May be due to prolonged steroids
- Inflammation of the lining of the lungs, which causes fluid build-up (pleural effusions)



Martires KJ, Baird K, Steinberg SM et al. *Blood* 2011; 118 (15)



Courtesy of Stephanie Lee, MD



Lung transplantation is an option

What qualifies you for a lung transplant?

- **End-stage lung disease**, requiring home oxygen
- Cancer-free at least 5 years
- Minimal or no systemic immunosuppression
- No other organ problems
- Adequate weight
- Adequate social support
- Ability to do physical rehab



Summary

- Lung GVHD is uncommon but can limit people's activities and quality of life
- BOS starts out without symptoms, so routine lung function monitoring after transplant is important
- One is more likely to prevent lung function loss if treated early
- While rare, there are multiple additional lung complications related to GVHD that we are still learning about

Questions?



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Let Us Know How We Can Help You

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Email us: help@bmtinfonet.org

Phone: 888-597-7674 or 847-433-3313

