

Breath of Life: Your Lungs after Transplant

Celebrating a Second Chance at Life
Survivorship Symposium

July 11-17, 2020



Jane Turner, MD
Hamilton Health
Sciences/McMaster University

Breath of life: Your lungs after transplant



**BRIGHTER
WORLD**

Jane Turner MD
Assistant Professor
Division of Respiriology
McMaster University



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Contact: jane.turner@medportal.ca

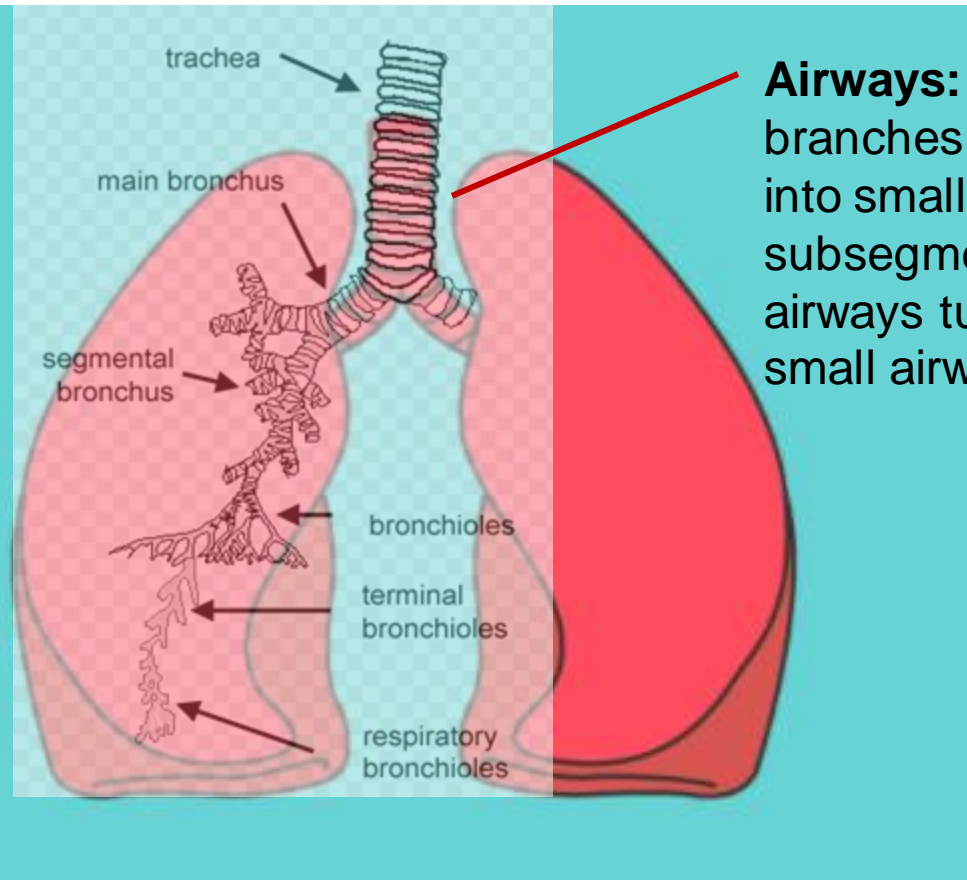


Objectives

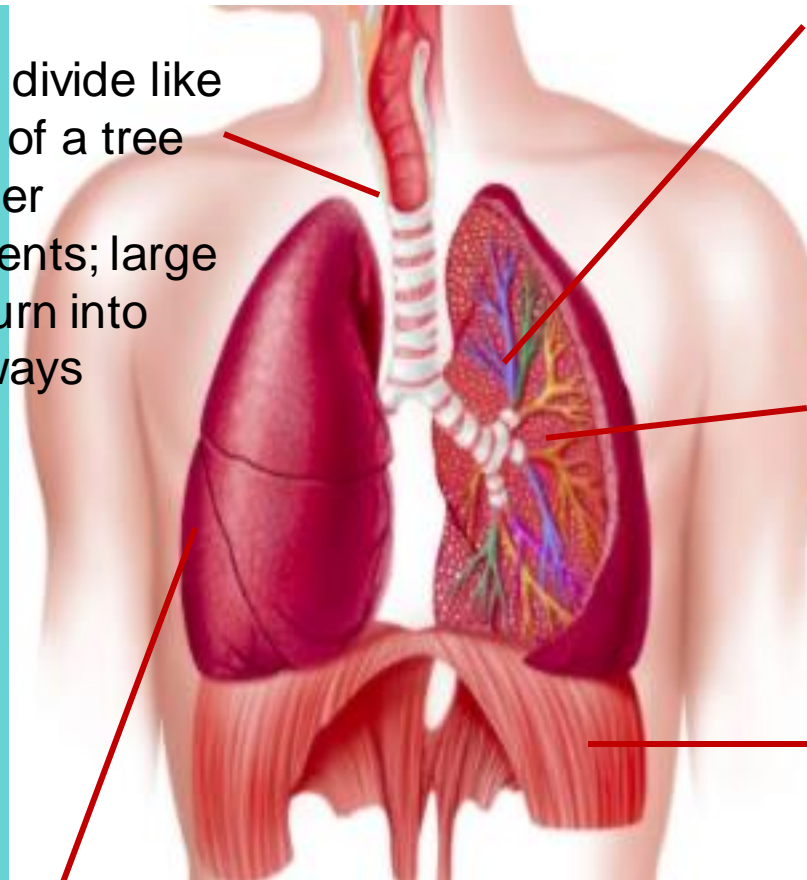
- 1) Respiratory anatomy and function review
- 2) What is lung GVHD?
 - Bronchiolitis Obliterans Syndrome (BOS)
 - Other possible types
 - Who is at risk?
- 3) Management and treatment strategies



Components of the respiratory system: How we breathe



Airways: divide like branches of a tree into smaller subsegments; large airways turn into small airways



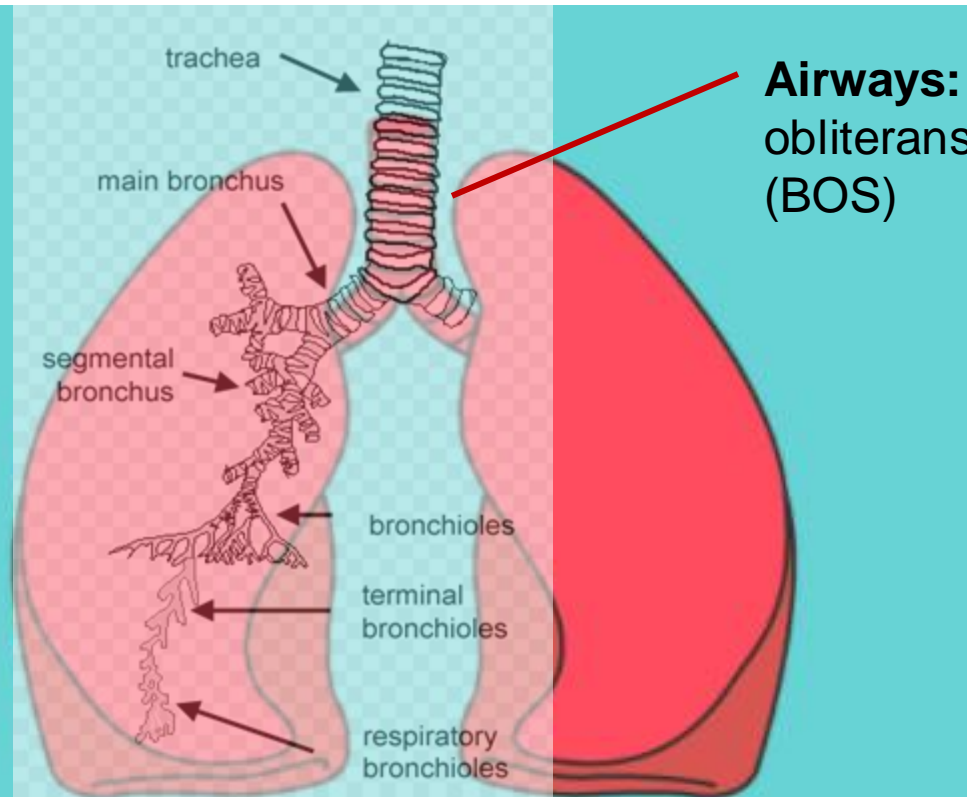
Blood vessels: carry blood from heart to lungs (to pick up oxygen) and back to heart

Lung tissue: tiny air sacs and blood vessels that perform gas exchange

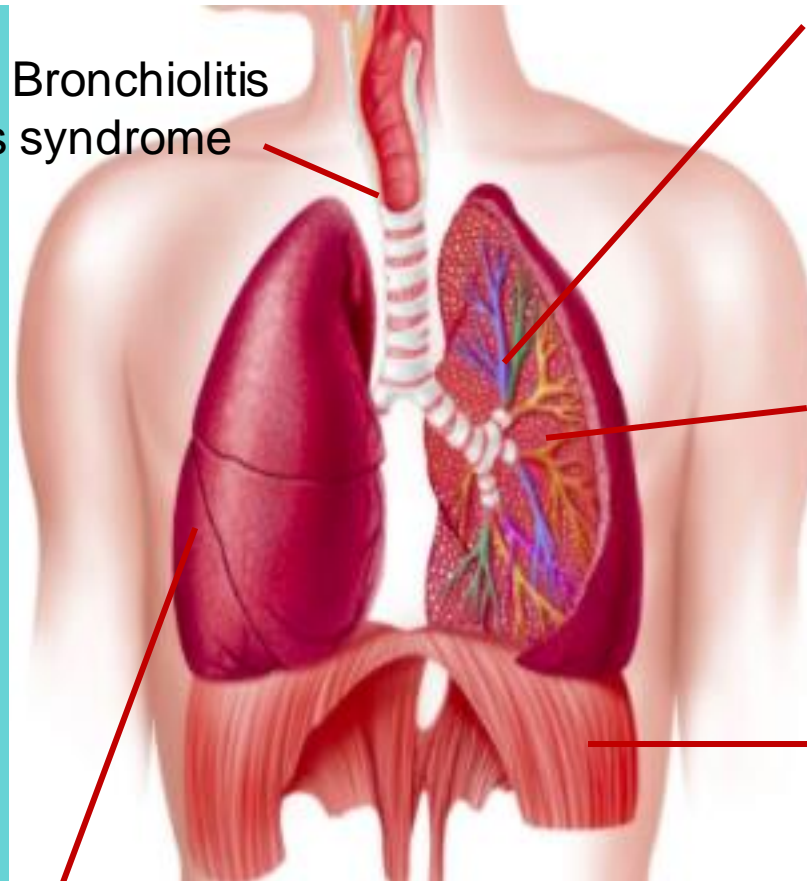
Muscles: Diaphragm, intercostal muscles (between ribs): allow our lungs to breathe in and out

Pleura: lining of the lung

The Spectrum of Lung Disease in Survivors of Stem Cell Transplantation



Airways: Bronchiolitis obliterans syndrome (BOS)



Pleura: pleural disease – thickening and restriction of the lung



Lung Problems in Survivors of Stem Cell Transplantation

Many post-transplant lung complications are associated with GVHD, but BOS is the only one that is part of the definition of cGVHD.

Incidence of late (>100 day) noninfectious pulmonary complications ~ 20%

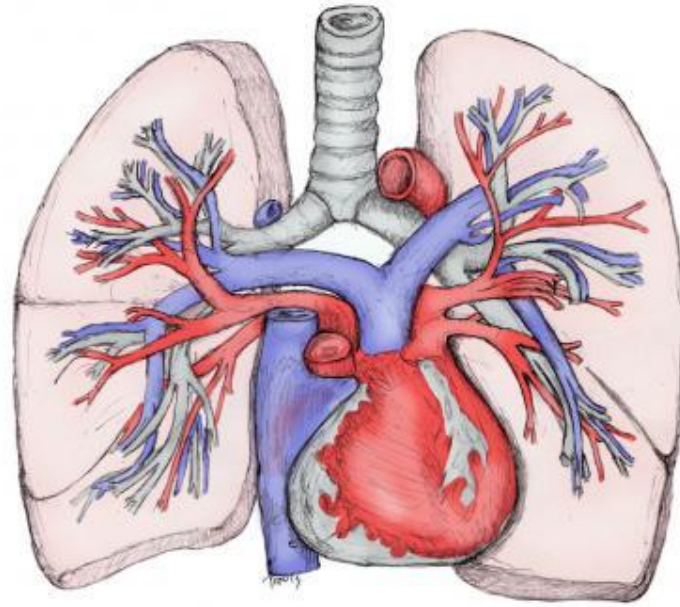
Respiratory problems are a major cause of hospitalizations and death



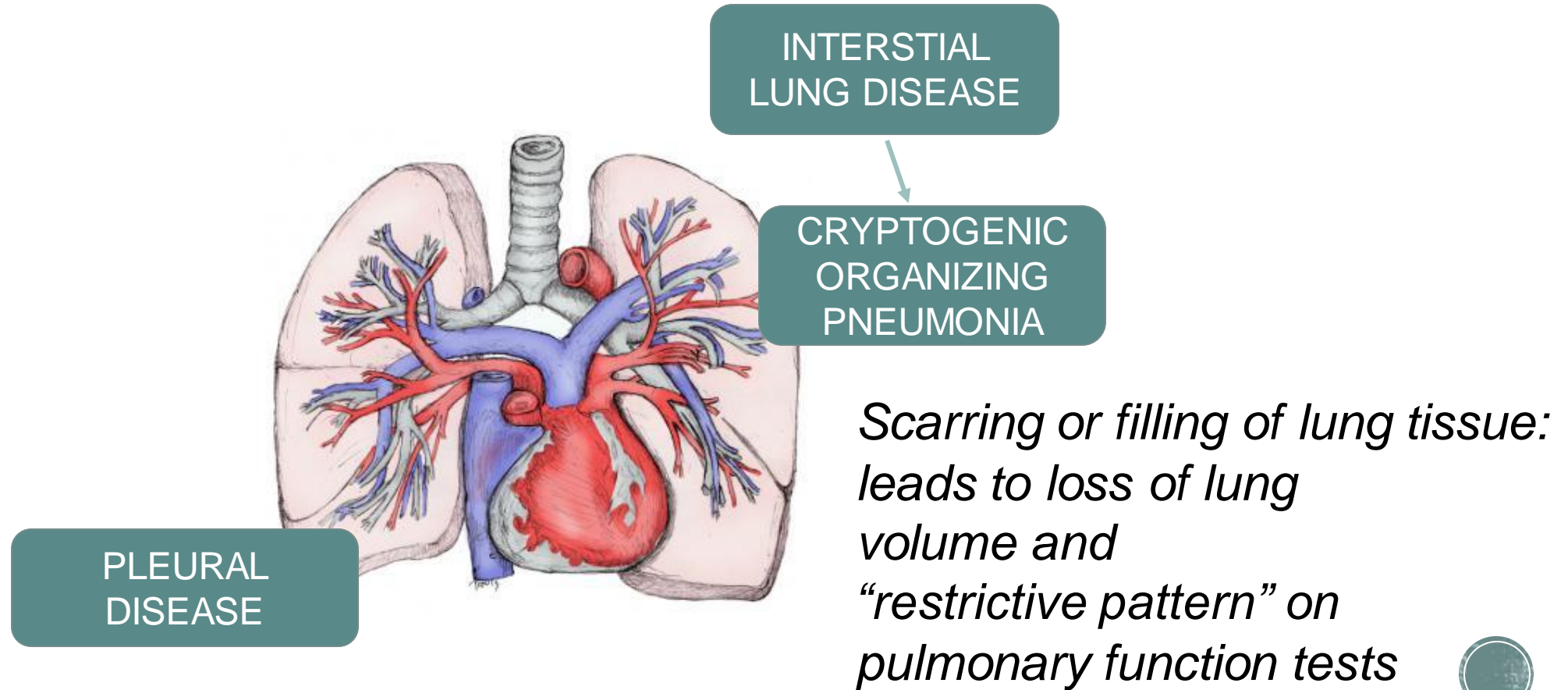
Lung disease due to chronic GVHD

BRONCHIOLITIS
OBLITERANS
SYNDROME

*Progressive
destruction/blockage of
small airways: “Obstructive
pattern” on pulmonary
function tests*

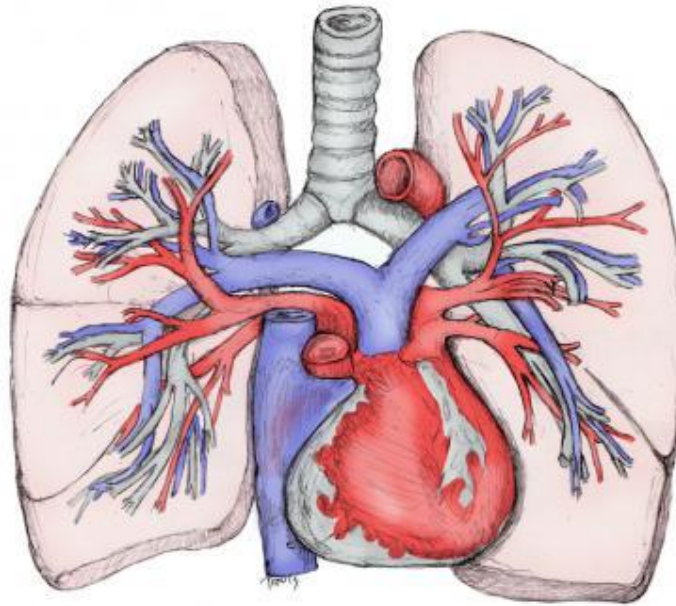


Lung disease *possibly* due to chronic GVHD



Lung problems due to chronic GVHD outside of the lung

NEUROMUSCULAR
WEAKNESS



CHEST WALL
RESTRICTION
FROM
SCLEROSIS

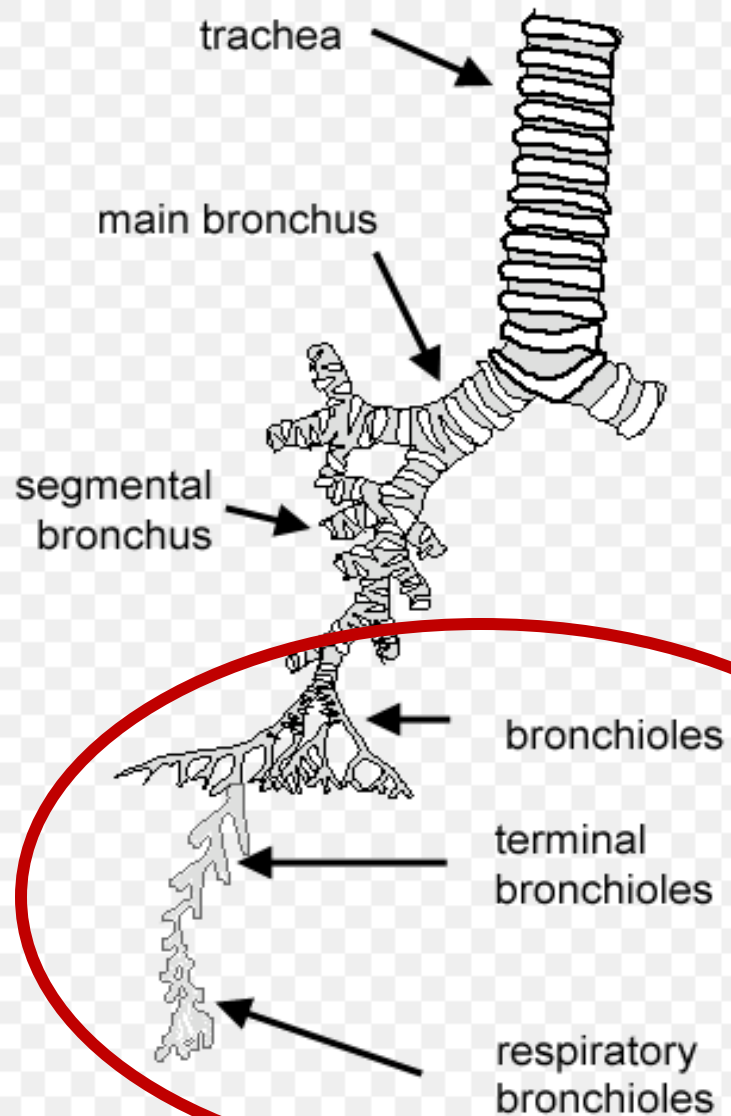


Bronchiolitis

- “Catchall” term: a broad definition for small airway inflammation
- May result from a variety of processes that cause injury

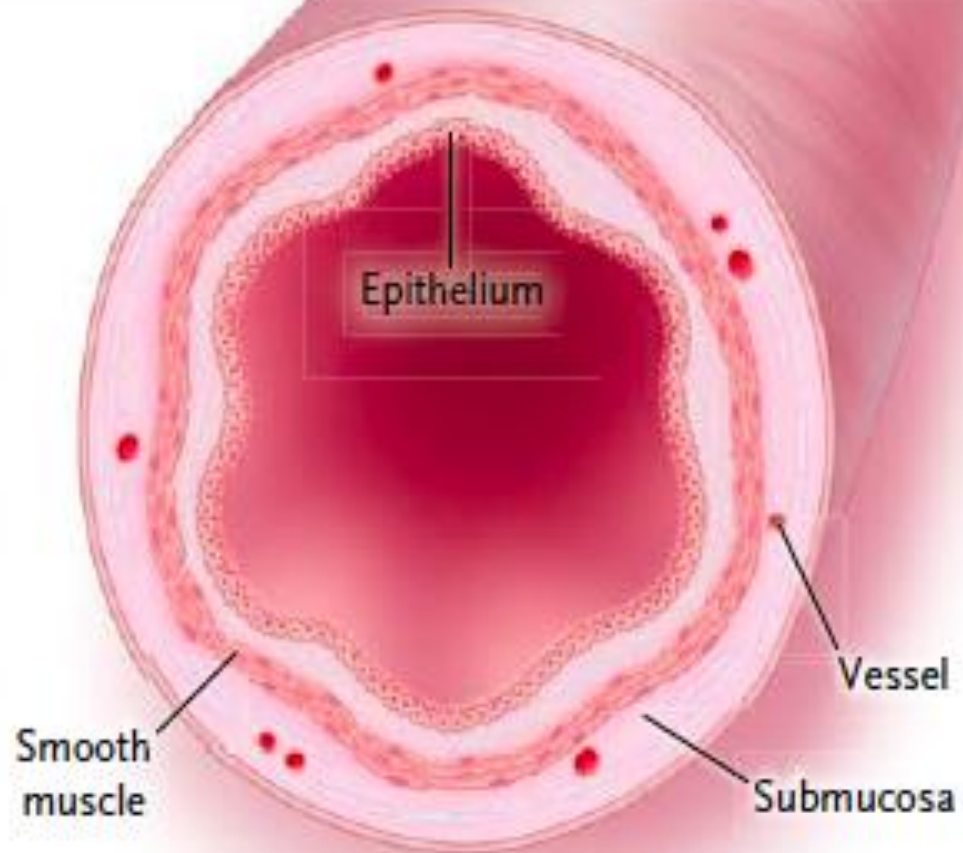


Bronchioles: the smallest airways

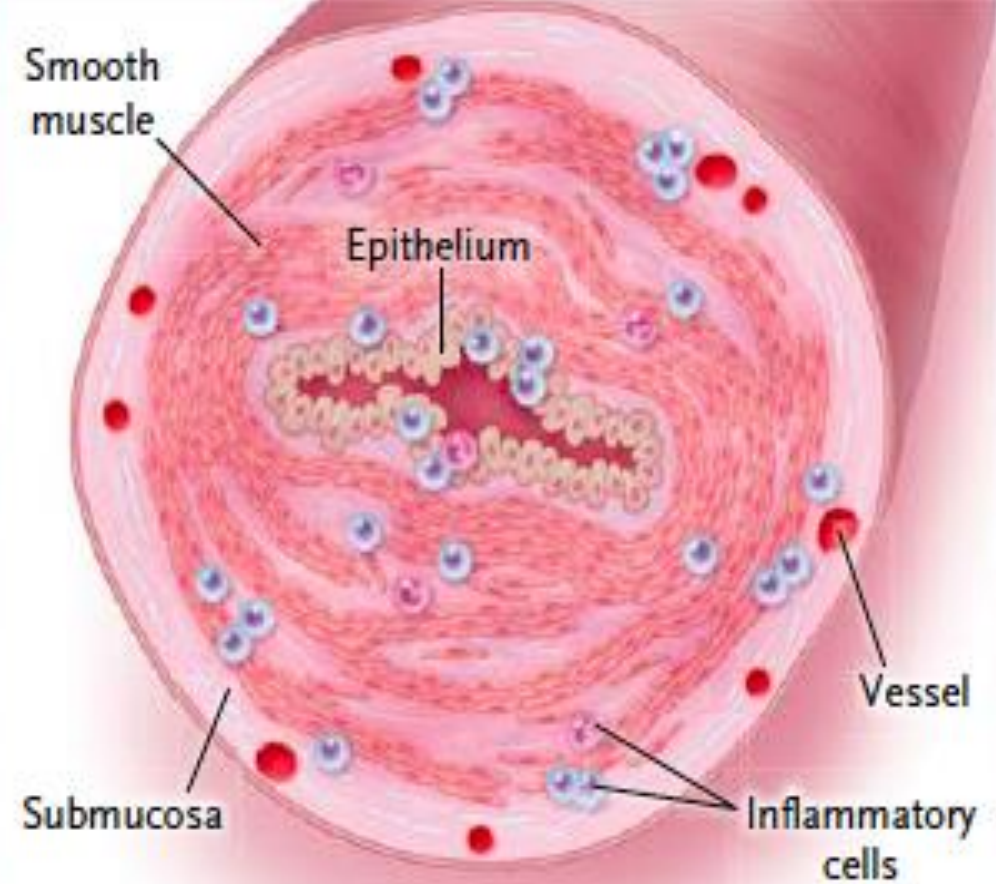


CONDUCTING AIRWAYS							RESPIRATORY UNIT							
Trachea	Bronchi				Nonrespiratory Bronchioles		Respiratory Bronchioles			Alveolar Ducts				
0	1	2	3	→	10	→	16	17	18	19	20	21	22	23

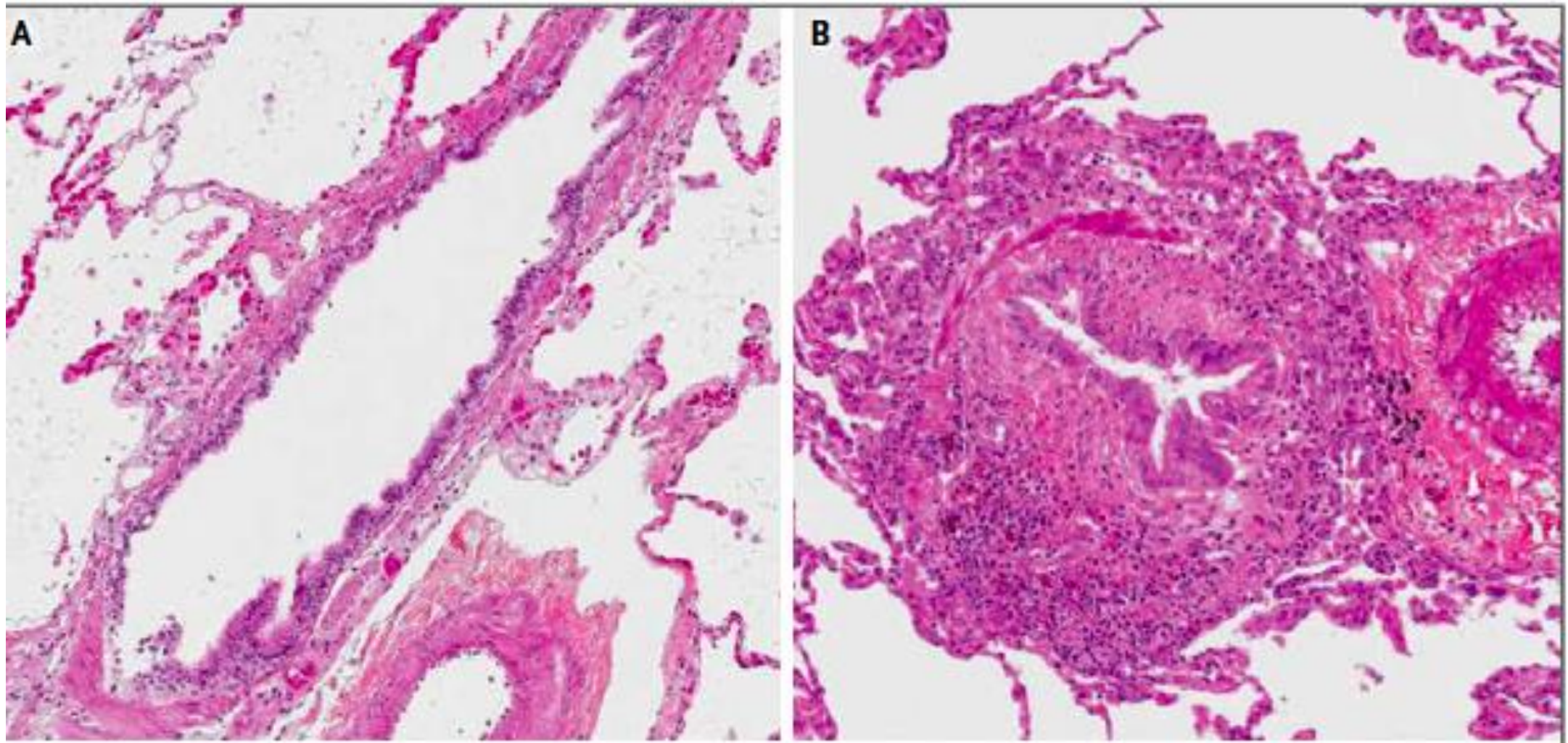
D Normal bronchiole



E Obliterative bronchiolitis

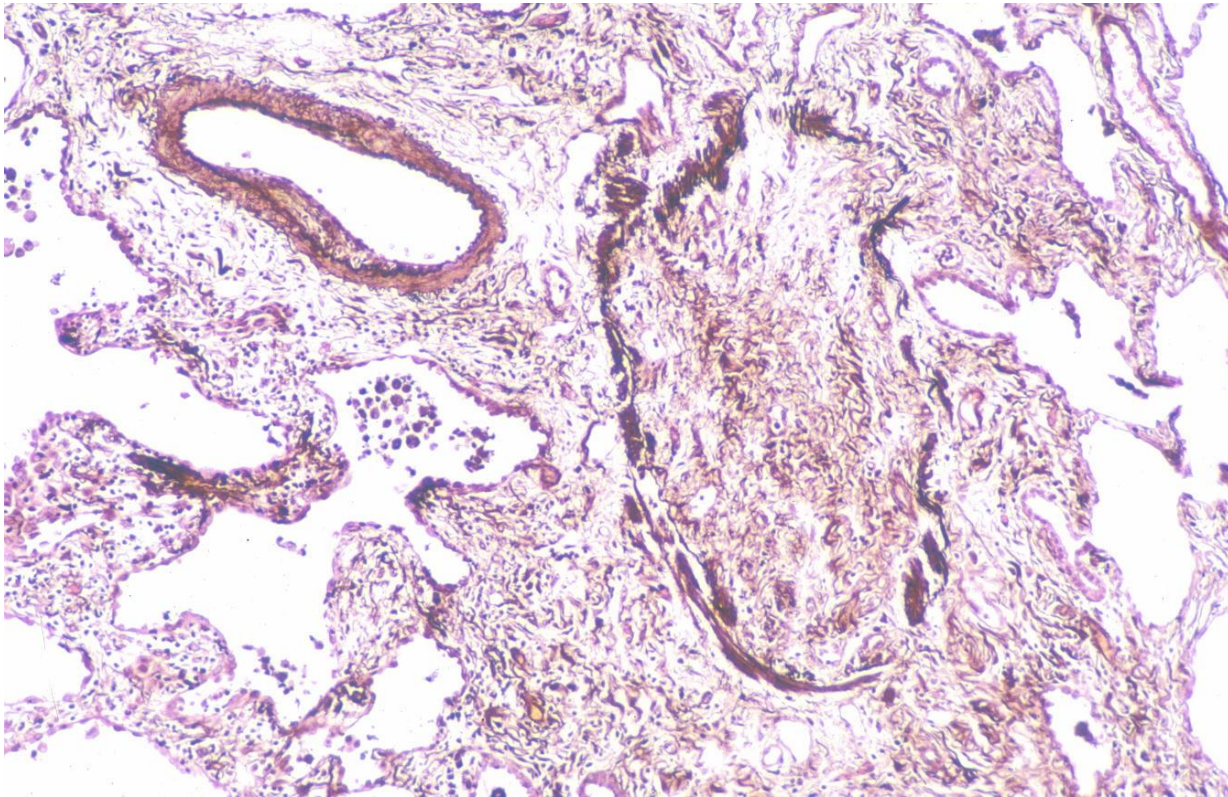


Circumferentially and externally compresses the bronchiolar lumen



BOS Pathology

Airway obliterated by fibrous material



Airflow obstruction



Breathlessness, cough,
lack of oxygen

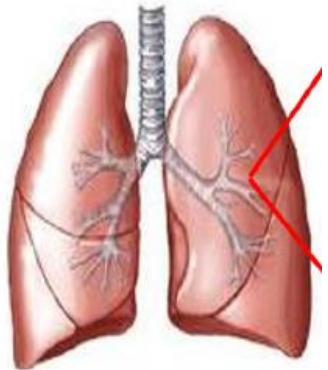
Courtesy of Robert Hackman, MD

Slide courtesy of Guang-Shing Cheng, MD

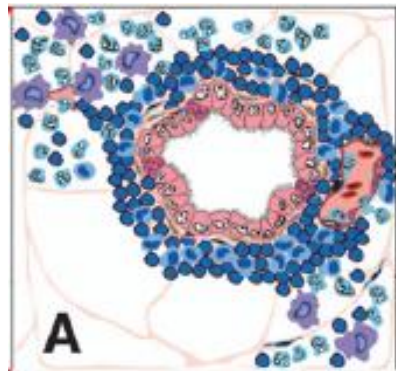


Hypothesis of how BOS happens

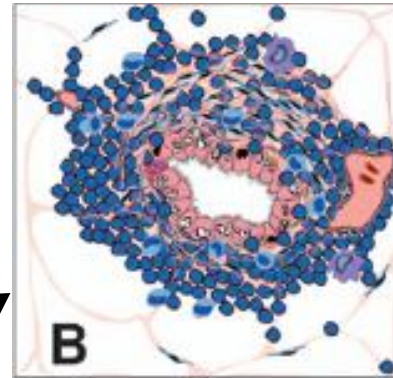
VIRAL INFECTION
TOXINS
REFLUX



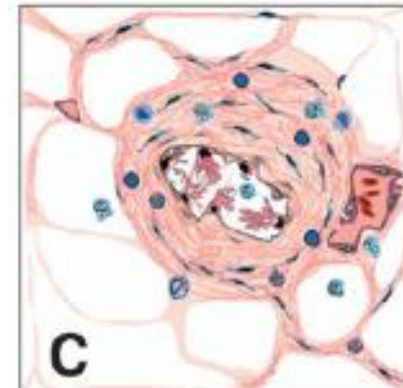
ACUTE INFLAMMATION



CHRONIC INFLAMMATION



FIBROSIS



AIRFLOW OBSTRUCTION



Bronchiolitis Obliterans Syndrome (BOS) vs. Cryptogenic Organizing Pneumonia (COP)



COP affects the airspaces (alveoli)

BOS affects the small airways (bronchioles)

BOS Facts

- How often does it occur?
 - 14% among patients with chronic GVHD
- When is it diagnosed?
 - 6 months to >5 years after transplant
- How is BOS diagnosed?
 - Pulmonary function tests
 - CT scan
 - Sometimes a bronchoscopy or biopsy is required



Who Gets BOS?

KNOWN RISK FACTORS

- **Chronic GVHD**
- Low immunoglobulin

POSSIBLE RISK FACTORS

- Lung problems before transplant
- Certain chemotherapy
- Radiation (for cancer treatment)
- *Viral infections*



Pulmonary Function Laboratory



Laboratory with technician and “body box”



Performing Spirometry



What do lung function tests measure?

- **FEV1:**

- The amount of air you can breathe out in the first second of a forced exhalation
- A measure of airflow: the primary measurement we follow with lung function
- Drops with airways disease, “airflow obstruction”



What do lung function tests measure?

■ FVC:

- The amount of air you can breathe out in the entire forced exhalation
- Can be a reflection of lung volumes: smaller lungs will have less air
- Drops with “restrictive” lung disease, which can be from lung tissue scarring or filling, or from a tight chest wall surrounding the lung e.g. pleural or chest wall disease (sclerosis)



What do lung function tests measure?

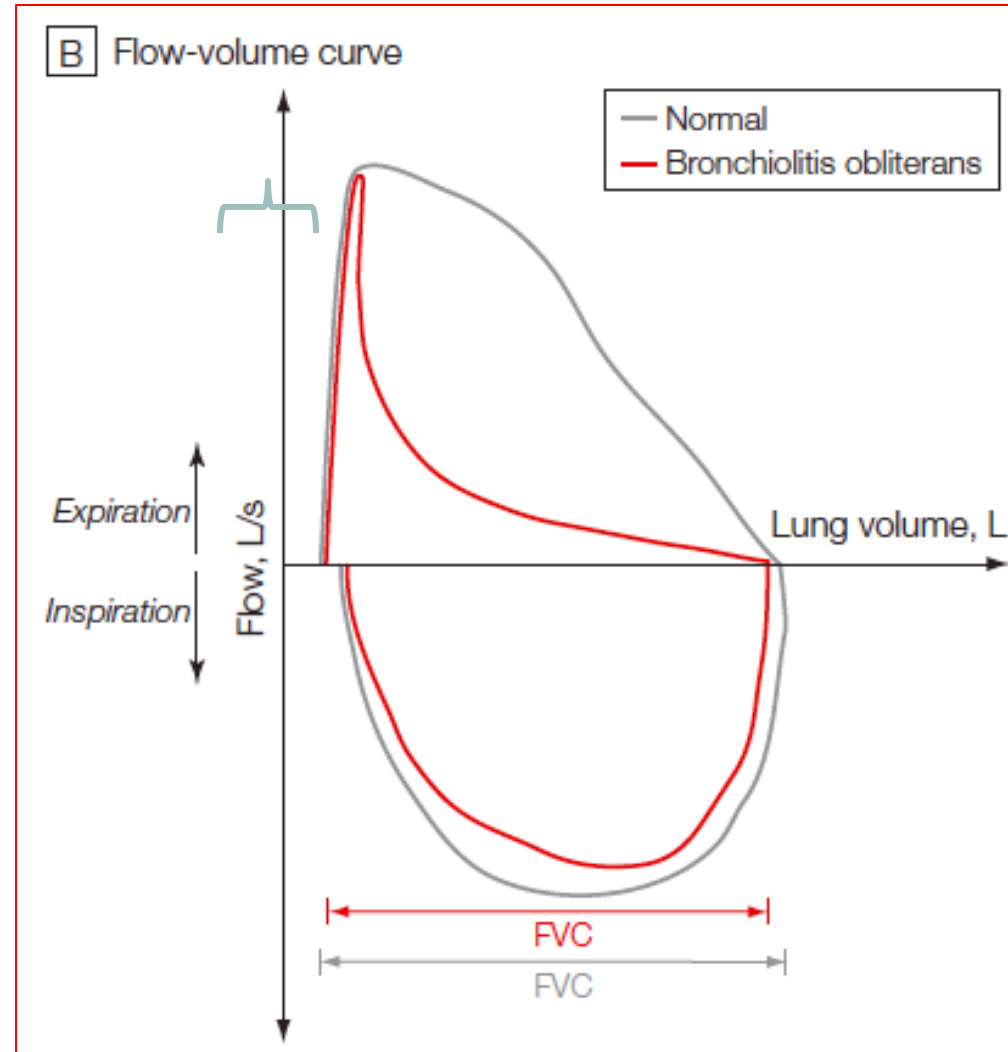
- **DLCO:**

- A measure of gas diffusion, i.e. how easily does oxygen get passed from the lung into the blood. Drops with lung tissue problems (fibrosis or COP), blood vessel problems
- Often see a non-specific drop post-transplant which may be from conditioning regimens
- The relevance of an isolated mild decrease is unclear: seen in up to 80% of all HSCT survivors



Airflow is obstructed on spirometry in BOS

→ FORCED EXPIRATORY VOLUME IN THE FIRST SECOND IS REDUCED



BOS diagnosis:

- The definitive diagnosis of BO is based on lung biopsy specimens: thickening of the bronchiolar wall under a microscope
- Not practical to obtain routine surgical lung biopsy
- Rely on clinical criteria: presence of a new-onset obstructive pattern on PFT, and CT scan findings



BOS Diagnosis:

2014 National Institutes of Health (NIH) consensus criteria for diagnosis and staging of chronic graft-versus-host disease

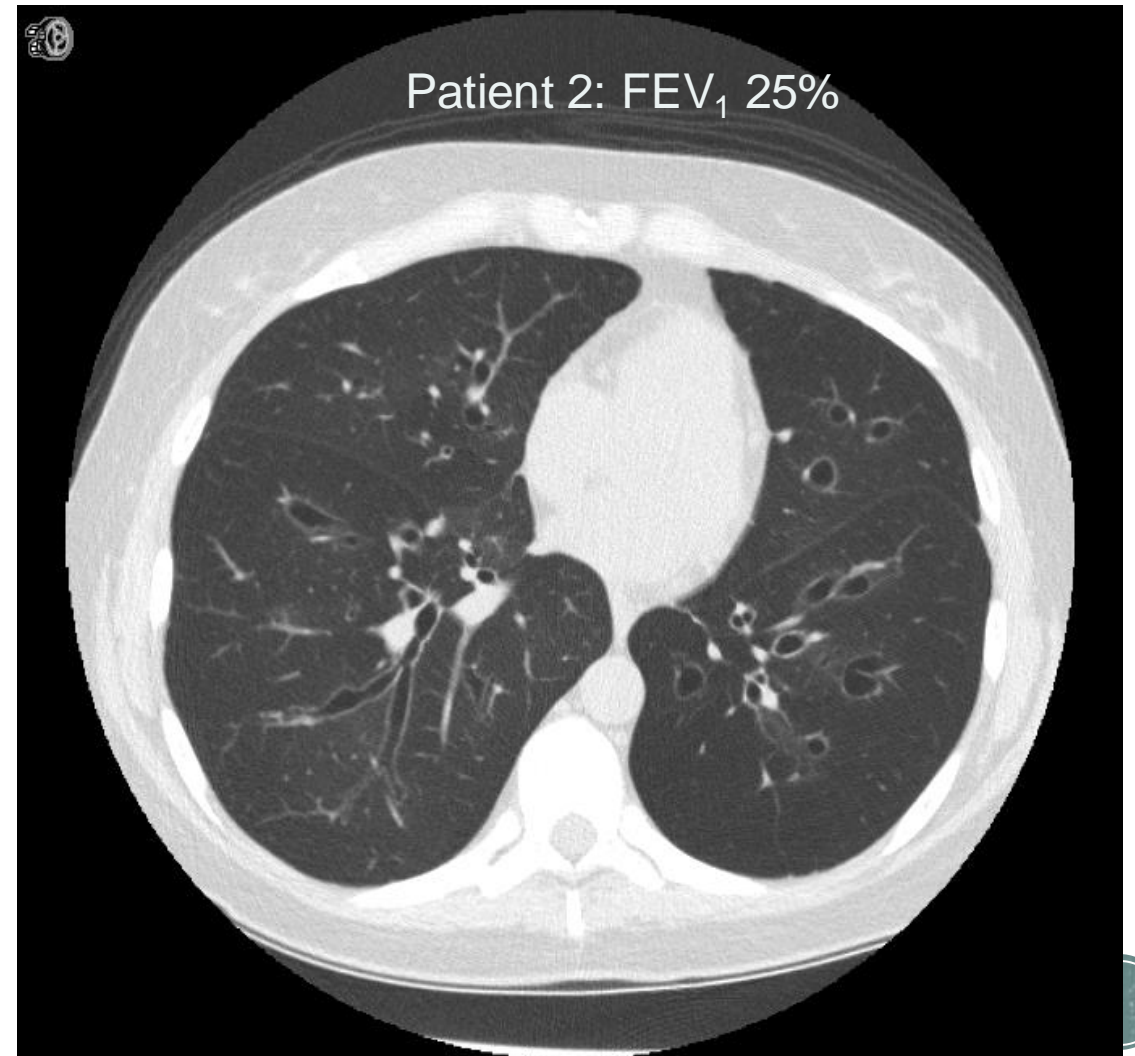
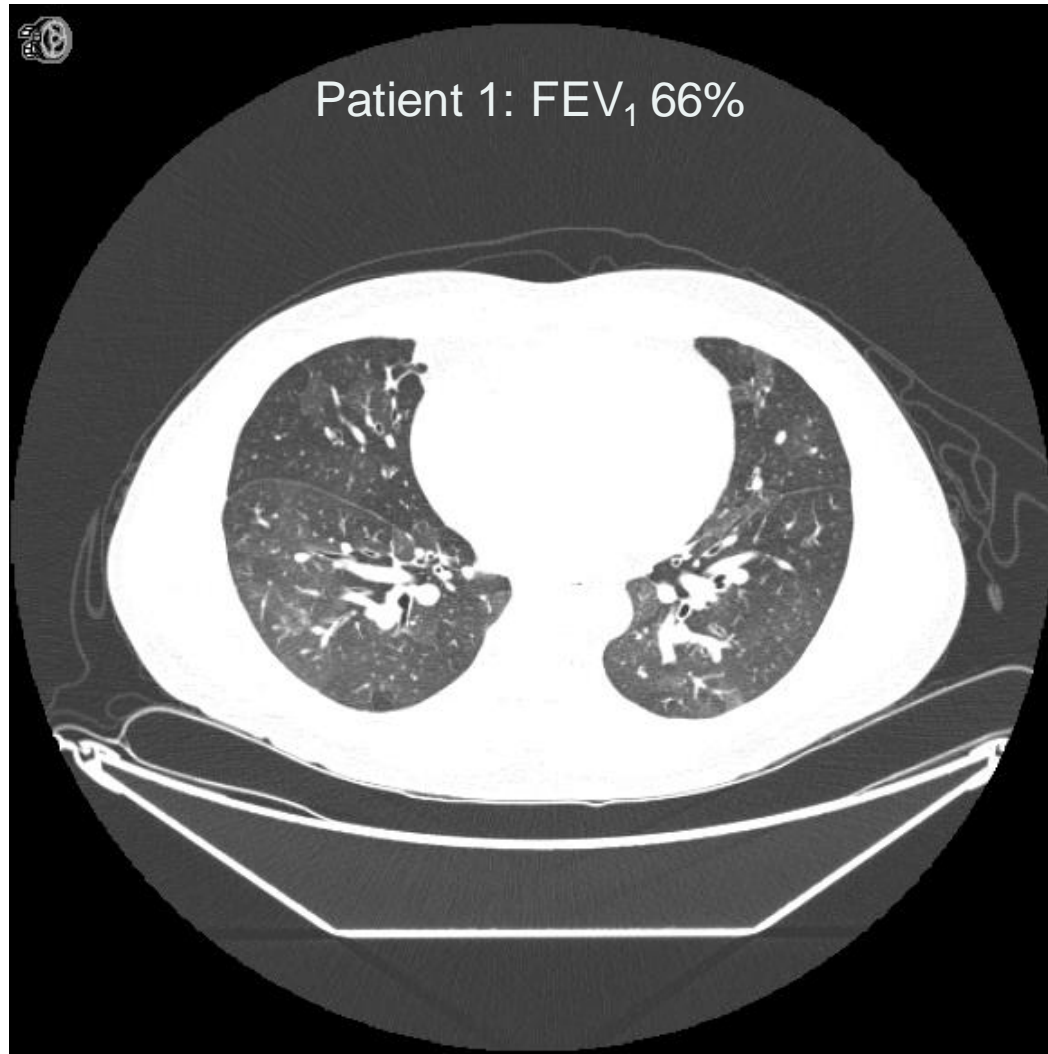
- 1) $FEV1/FVC < 0.7$ [airflow obstruction]
- 2) $FEV1 < 75\%$ predicted (post bronchodilator) with $>10\%$ decline over less than 2 years
- 3) Absence of respiratory tract infection
- 4) One of the two supporting features of BOS:
 - CT findings (air trapping on end-expiration, or small airway thickening/bronchiectasis)
 - Evidence of air trapping by PFTs: $RV > 120\%$ predicted, or $RV/TLC > 90^{th}$ CI



Gas trapping on end-expiration



Chest CT may show air trapping and dilated large airways



Lung function post transplant

- Lung function fluctuation post-HCT is common: up to 80% of the patients presented a significant PFT decrease at least once (Bergeron 2018)
- Many events following transplant can contribute to lung function fluctuation: respiratory infections, general deconditioning, conditioning regimen toxicity, scleroderma-like cGVHD or steroid treatment-related myopathy

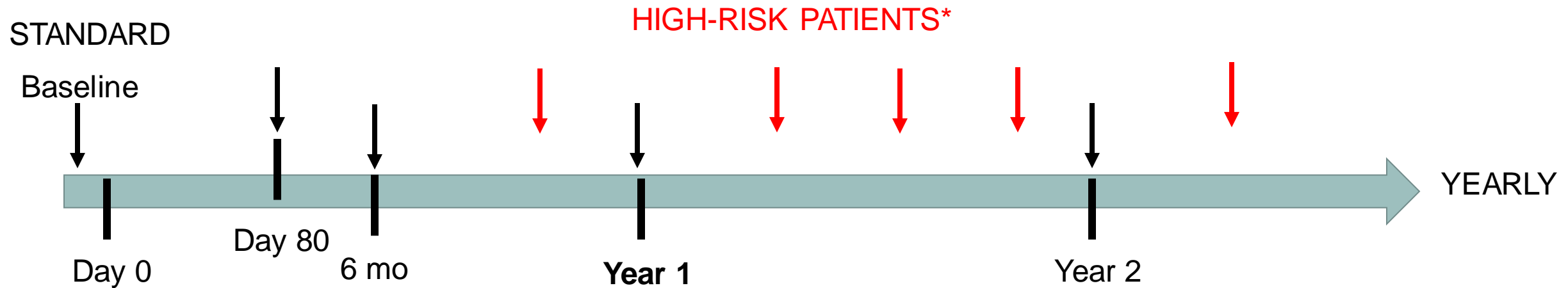


Monitoring lung function

- Q3-month screening for the first 1-2 years post HSCT
- Higher frequency or longer duration may be considered in those with cGVHD
- Include PFTs at the time of GVHD flare, or signs of other organ progression
- A sustained decline in FEV1, FVC, or both, should be considered significant



Current recommendations for PFT monitoring after transplant

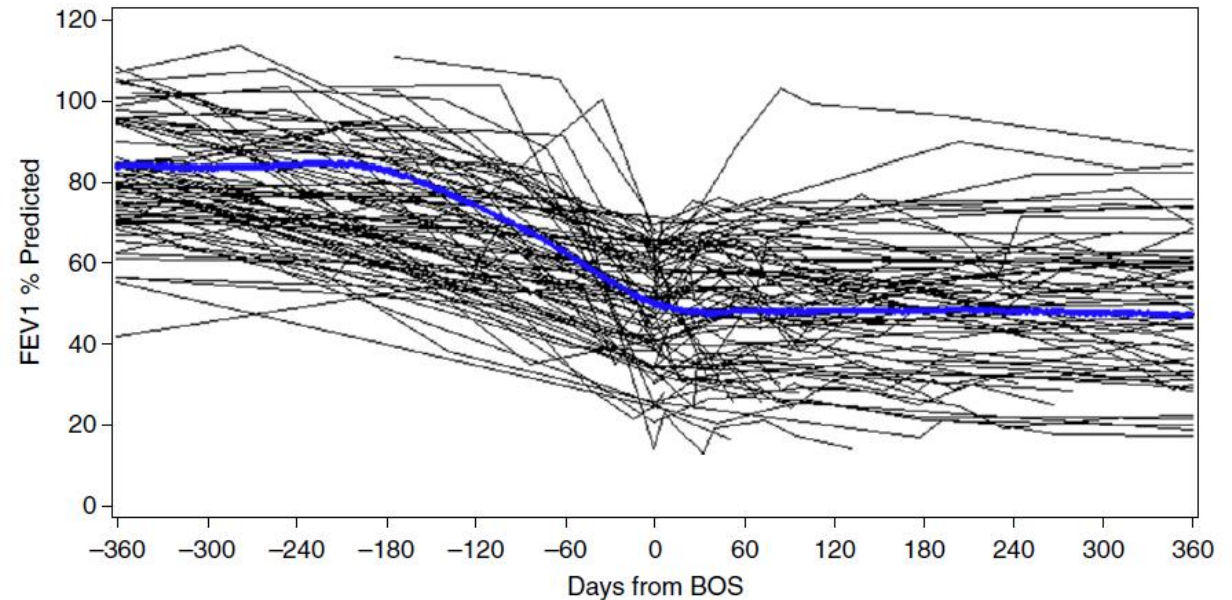


PFT monitoring after transplant varies from center to center



FAQ: What's the prognosis of Lung GVHD?

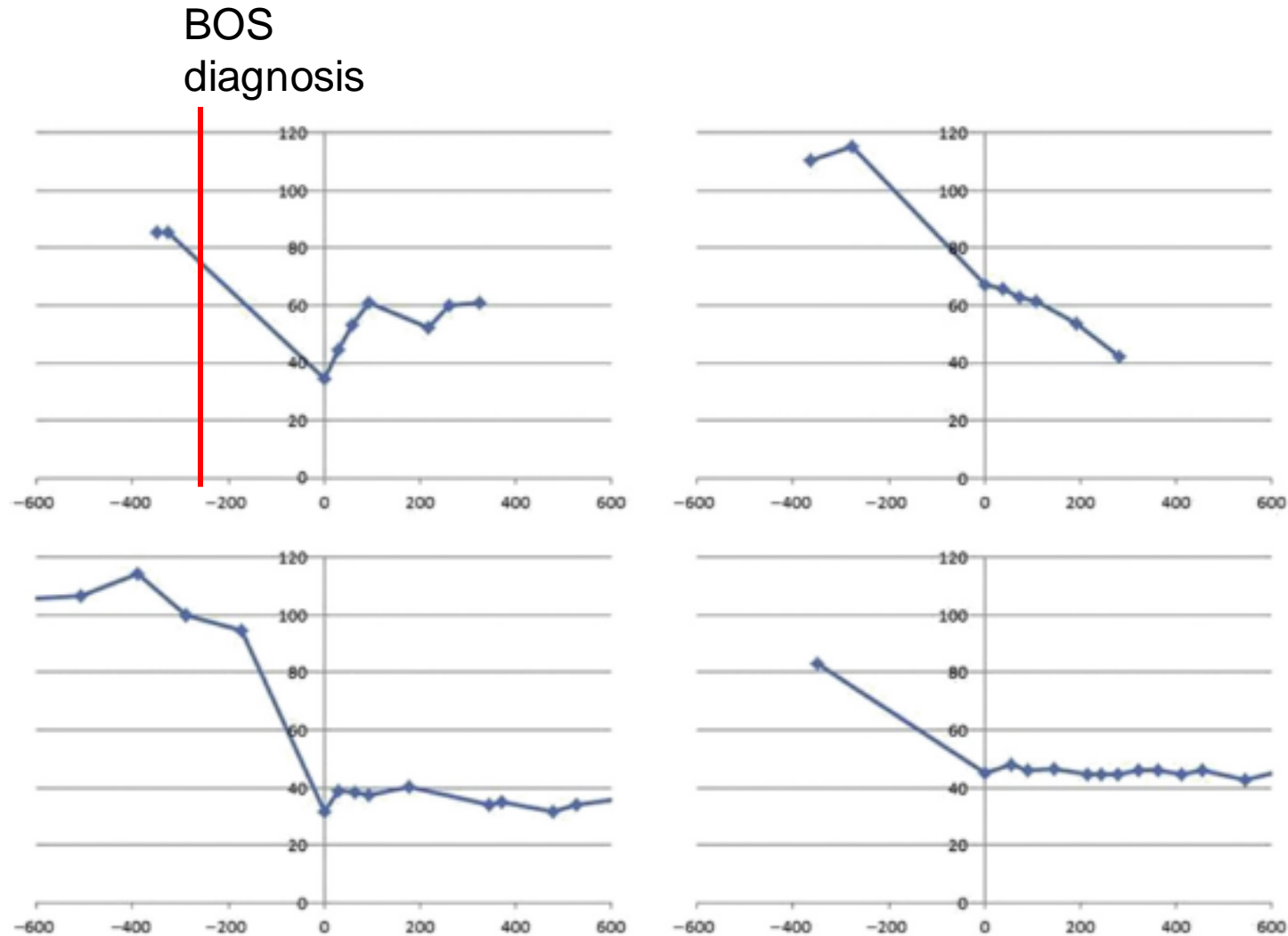
- Respiratory infections
- Overall survival
- Lung Function



Patients can survive many years even with poor lung function



Fev1 in HSCT-BOS; natural history



First Line Management

“FAM + LABA”

- Fluticasone or Budesonide
- Long-acting beta-agonist (LABA)
- (Azithromycin)
- Montelukast

Benefits based on trials:

- Possible stabilization of FEV1
- Reduced dose of systemic prednisone, minimizing prednisone-related side effects



Inhaled Corticosteroid and Bronchodilator Combos

Inhaled Corticosteroid/ Long-Acting Beta Agonists	Brand Name
Budesonide/ formoterol HFA	Symbicort
Fluticasone/salmeterol DPI	Advair Diskus or HFA
Mometasone/formoterol HFA	Dulera
Fluticasone/vilanterol DPI	Breo

Long-Acting Muscarinic Formulations	Brand Name
Tiotropium	Spiriva
Umeclidium	Incruse
Umedclidium/vilanterol	Anoro
Tiotropium/Olodaterol	Stiolto
Fluticasone/vilanterol/ umeclidium	Trelegy



Systemic Corticosteroids (Prednisone)

- Short burst may be used
- Prolonged prednisone course is not beneficial for BOS



Treatment of Exacerbating Factors

- Infections
- Sinus disease
- Aspiration
- Reflux
- Environmental



FAQ: Should I be taking azithromycin for lung GVHD?

JAMA | **Original Investigation**

Bergeron A et al. Aug 2017

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



Azithromycin for Lung GVHD

PRO

- No evidence for relapse in patients with BOS
- Potentially reduces infectious exacerbations
- Generally well tolerated

CON

- Risk of relapse early post-transplant
- Reduced tumor surveillance
- Associated with arrhythmias
- No effect on lung function



FAQ: What if my lung function gets worse?

- Investigate exacerbating factors: will often require a work-up including chest imaging (CT scan), and possibly bronchoscopy to rule out infection
- Specific Second Line Treatments:
 - Extracorporeal Photopheresis
 - Ruxolitinib
 - Ibrutinib



Agents currently being tested for BOS after transplant

Agent	Mechanism of Action	Clinical Trial Phase/Location
Ruxolitinib	Blocks inflammatory cytokine cascade	Multicenter Phase II, US NCT03674047
Pirfenidone	Anti-fibrotic	Single Center Pilot, Stanford NCT03315741
Nintendanib	Anti-fibrotic	Multicenter Phase II, Europe NCT03805477
Alvelestat	Neutrophil elastase inhibitor	NIH, Bethesda MD NCT02669251
Inhaled cyclosporine	Regulation of T cell activity	Multicenter Phase III, US Lung Transplant Only NCT03657342, NCT03656926

Supportive Care

- Supplemental Oxygen
- Airway Clearance
- Pulmonary rehabilitation
- Prevention of infections

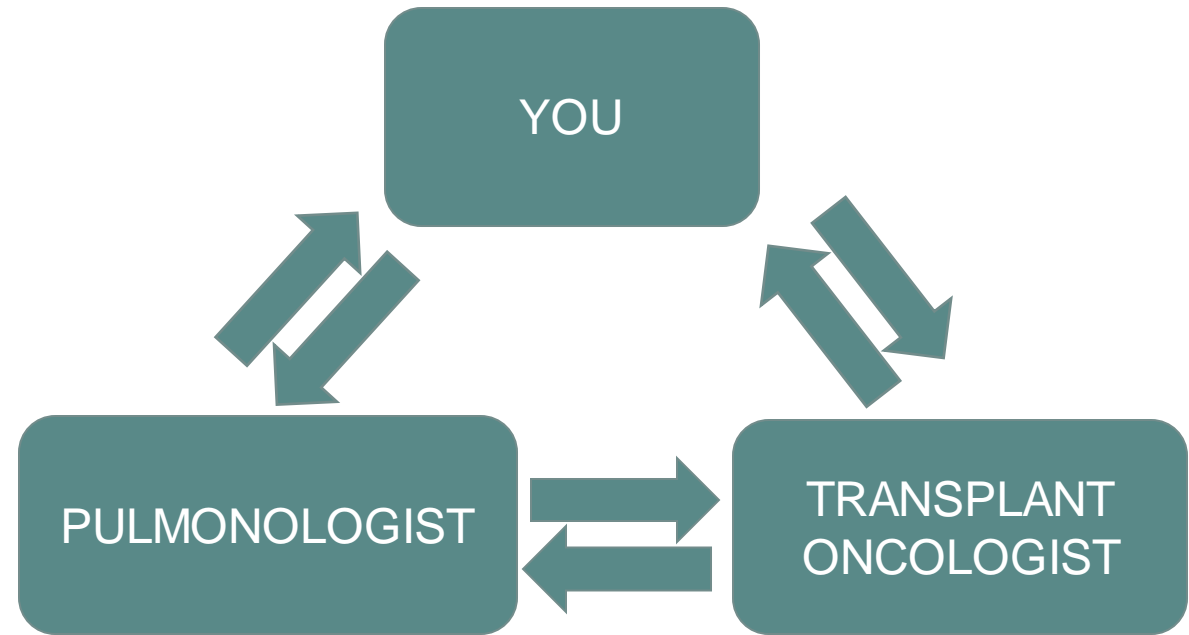
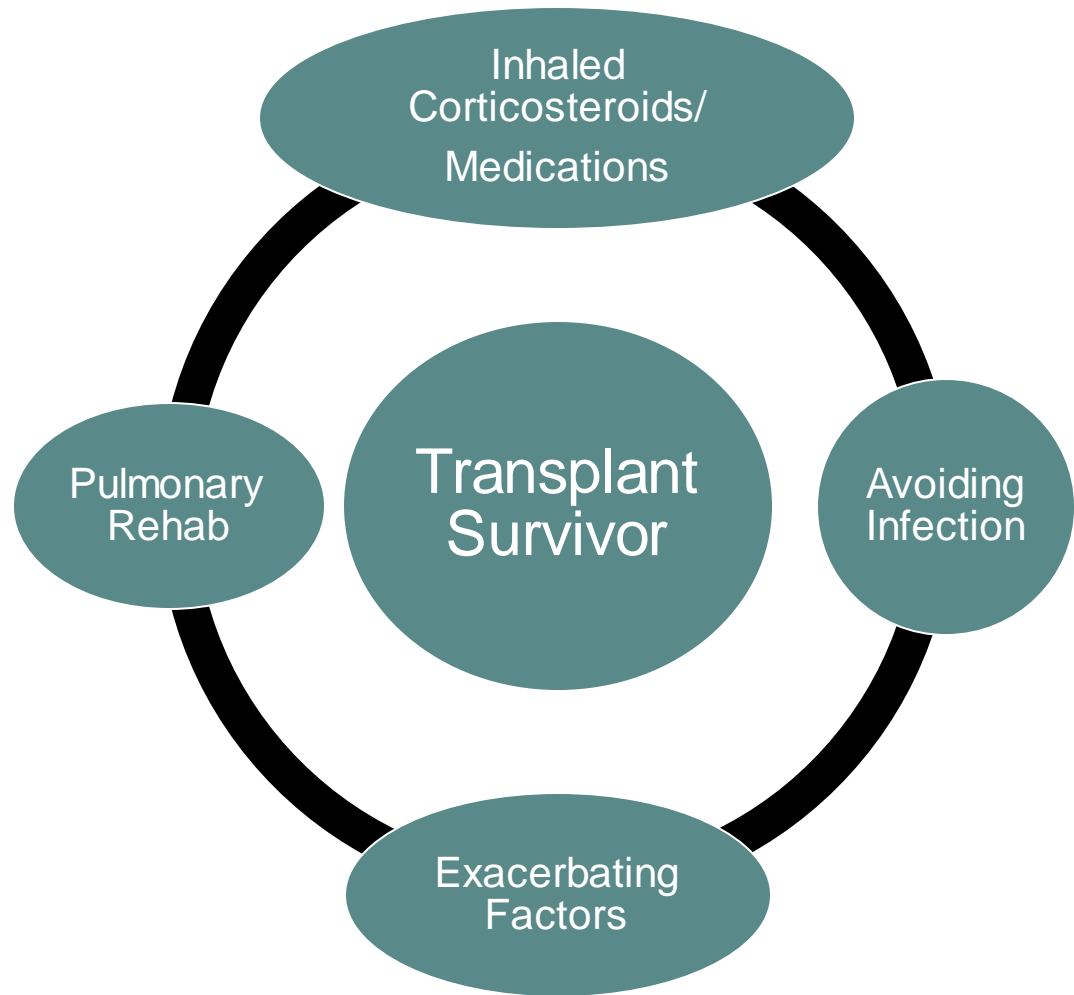


Lung Transplantation for Lung GVHD

- Who is eligible?
- What's the process?
- Will I get BOS again?



Living with Lung GVHD





Questions?



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