



## Take a Breath: Managing Lung Problems after Transplant

Celebrating a Second Chance at Life  
Survivorship Symposium

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## Disclosures

- Adjudication Committee, Enanta  
Pharmaceuticals



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## Learning Objectives

- The types of lung injury that can occur after transplant
- Risk factors for developing various types of pulmonary difficulties after transplant
- Treatment strategies
- How to find a specialist who can help manage pulmonary difficulties after transplant

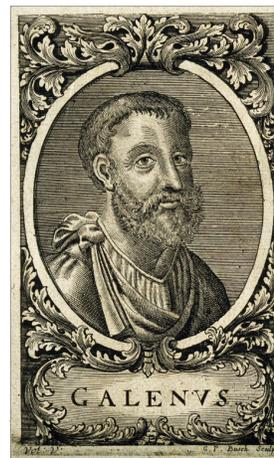


Photo by Carol M. Highsmith, Library of Congress

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## A brief history of breathing

- Early Greek philosophers recognized the importance of breath, but thought it represented the mortal soul.
- Later, scholars, such as Plato and Aristotle, conceived that the lung existed to cool the body, particularly the heart.
- Galen greatly advanced the science of diaphragmatic mechanics, but struggled to explain what exactly the lung did.



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## A brief history of breathing

- Ibn al-Nafis, an Egyptian doctor, first surmised the existence of the pulmonary circulation in 1288
- In 1644, the existence of air as matter was confirmed by Evangelista Torricelli, later confirmed by Robert Boyle
- In 1774, “oxygen” was discovered by Joseph Priestley and was confirmed to diffuse into the lungs by Marie Krogh in the early 1900’s
- The importance of the breath was recognized by many, leading the surgeon and inventor John Hutchinson to label the volume of inspired air (air breathed in) as “vital capacity”



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## We have come a long way....

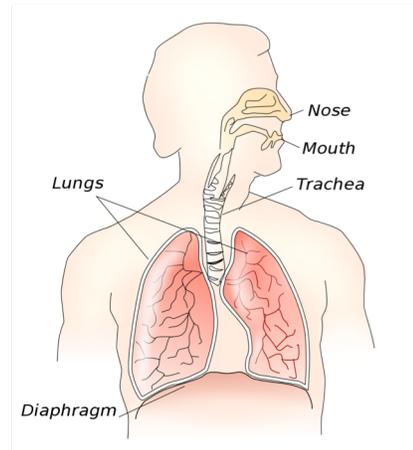
- It took:
  - 1,000 years to understand that blood circulated through the lung
  - Another 500 years to understand that air was not just a vacuum
  - Another 150 years to understand that oxygen was vital for human function
  - And another 150 years to understand how oxygen diffused into the lung

Further reading: Jean-William Fitting, "From Breathing to Respiration", *Respiration* 2015;89-82-87

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## So... how does the lung work?

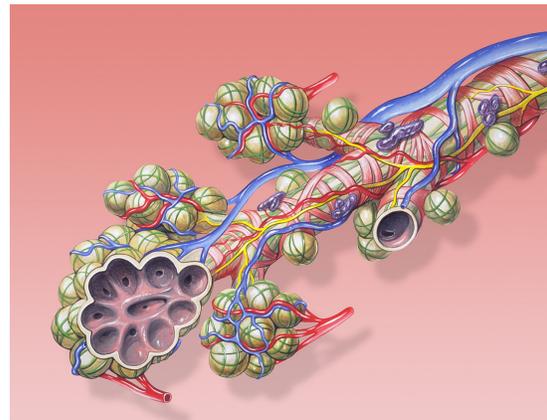
- Breath is initiated by sending a signal to the diaphragm to contract
- The diaphragm contracts and expands the thoracic cavity
- The lung passively expands and inflates with air because the pressure inside the lung is now lower than outside
- This continues until these pressures equalize at full inspiration



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## So... how does the lung work?

- Ambient air enters the airways and eventually into sacs at the end of the airways called alveoli.
- Oxygen diffuses into the blood while carbon dioxide diffuses out of the alveoli.
- The end result is that blood is oxygenated and carbon dioxide, a byproduct of metabolism, is removed.



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## Why is the lung so important for hematopoietic cell transplant (HCT) recipients?

- Mortality after hematopoietic cell transplantation (HCT) has declined substantially over the last 30 years.<sup>1</sup>
- However, non-infectious pulmonary complications (NIPCs) occur in about 20% of HCT recipients and increase the rate of death two-fold.<sup>2</sup>
- Other than relapse, NIPCs are collectively one of the biggest barriers to a healthy post-HCT life!

<sup>1</sup>Penack et al, Blood Adv 2020

<sup>2</sup>Bergeron et al, Eur Resp J 2018

## A simple Way to Conceptualize Non-Infectious Pulmonary Complications (NIPCs)

You can think about the various NIPCs by

- **when they occur**
  - **early** (in the first few months) vs.
  - **late** (after the first few months)
- **how they affect your breathing**
  - **obstructive** (hard to get air out) vs.
  - **restrictive** (hard to get air in)

## Early versus Late NIPCs

### Early (within 3-6 months of HCT)

- Diffuse Alveolar Hemorrhage (DAH)
- Idiopathic Pneumonia Syndrome (IPS)
- Cryptogenic Organizing Pneumonia (COP)
- Pulmonary Veno-Occlusive Disease (PVOD)

### Late (usually 6 months or more after HCT)

- Cryptogenic Organizing Pneumonia (COP)
- Bronchiolitis Obliterans Syndrome (BOS)

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## Restrictive versus Obstructive NIPCs

- Bronchiolitis Obliterans Syndrome (BOS) is the main **obstructive** disorder that occurs after HCT
- All other NIPCs are **restrictive** – patients have difficulty getting air into the lungs and oxygen into the blood
- Truncal sclerosis (tightening of skin around the chest) and weakness can restrict breathing but are not “true” lung conditions, despite affecting lung function

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## Diffuse Alveolar Hemorrhage (DAH)

- DAH is characterized by bleeding in the lung and difficulty with oxygenation
- The diagnosis is made by increasingly bloody return on bronchoalveolar lavage (BAL)



Figure, Samuel et al Respiratory Medicine  
Case reports 2020

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## Diffuse Alveolar Hemorrhage (DAH) cont'd

- Bleeding in lungs can be a result of low platelets or radiation injury
- DAH is usually treated with steroids (prednisone)
- However, the evidence for steroids and anti-clotting agents is limited
- DAH is a very serious NIPC and must be addressed promptly



Figure, Radiopedia

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## Idiopathic Pneumonia Syndrome (IPS)

- A severe NIPC that occurs within the first few months after HCT
- Looks like a severe infectious pneumonia but, by definition, there must be no evidence of infection
- Recent data suggest that around half of cases diagnosed as IPS had evidence of occult viral infection.<sup>1</sup>

<sup>1</sup>Seo et al, Blood 2015

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## Idiopathic Pneumonia Syndrome (IPS) cont'd

The American Thoracic Society defines IPS as:

- Evidence of alveolar injury
  - Multilobar alveolar infiltrates
  - Symptoms and signs of pneumonia
  - New lung restriction or hypoxemia (low oxygen)
- Absence of lower respiratory tract infection (ideally by BAL)
- Absence of cardiac or renal dysfunction

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## Idiopathic Pneumonia Syndrome (IPS) cont'd

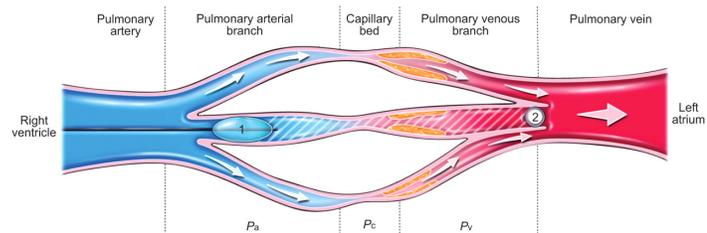
- Occurs in 3-4% of HCT recipients<sup>1</sup>
- Myeloablative conditioning is a major risk factor
- The treatment is high-dose steroids and other anti-inflammatory agents (etanercept)
- Is associated with high mortality; nearly 70% die within a year of HCT

<sup>1</sup> Wenger et al, Biol Blood Marrow Transplant 2020

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## Pulmonary Veno-Occlusive Disease (PVOD)

- A very rare NIPC caused by scarring of the pulmonary venules (small veins)
- Symptoms include shortness of breath, usually with hypoxemia, almost always in the presence of a severe skin rash and usually with weight gain or swelling
- There are some limited data on treatment with drugs that have been used for hepatic VOD (defibrotide)
- Mortality is very high

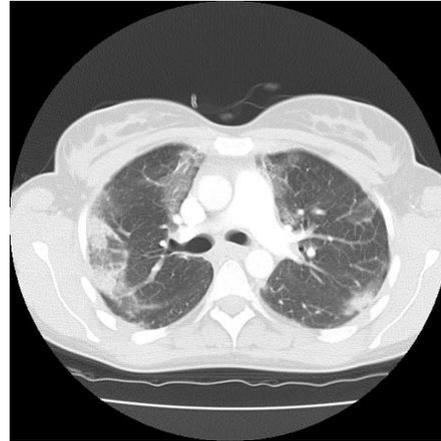


Figure, Montani et al, Eur Resp J 2009

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## Cryptogenic Organizing Pneumonia (COP)

- COP occurs in 1-2% of HCT recipients
- COP often manifests as a slow onset of shortness of breath or cough over weeks, though occasionally can occur rapidly and with more severity
- COP generally responds to steroids
- Respiratory viruses may be a trigger for COP<sup>1</sup>



Figure, Radiopedia

<sup>1</sup>Brownback et al Ann Hematol 2019

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## Cryptogenic Organizing Pneumonia (COP) - Treatment

- COP is usually treated with steroids (prednisone) over a period of usually 12 weeks
- Tapering off steroids too soon may result in recurrence of COP
- Very rarely, recurrent or severe cases of COP may require additional immunosuppression, such as mycophenolate mofetil, but data is limited
- Generally speaking, COP has a very favorable prognosis

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## Bronchiolitis Obliterans Syndrome (BOS)

- BOS is the most common form of graft-versus-host disease (GVHD) of the lung
- BOS occurs in about 5% of all HCT recipients and as many as 15% of patients with GVHD
- The prognosis for patients with BOS has drastically improved in the last two decades with better screening and recognition
- However, patients with a diagnosis of severe BOS have a mortality rate of nearly 80% 10 years after diagnosis<sup>1</sup>

<sup>1</sup> Cheng et al, Ann Am Thor Soc 2016

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## Bronchiolitis Obliterans Syndrome (BOS) – Risk Factors

- The two major risk factors for BOS are chronic GVHD of another organ and respiratory viral infections.
- Anecdotally, the incidence of BOS declined dramatically during COVID-based restrictions, in parallel with the absence of community respiratory viruses.
- Why viruses trigger BOS is not entirely clear.

<sup>1</sup> Au et al Biol Blood Marrow Transplant 2011

<sup>2</sup> Versluys et al Biol Blood Marrow Transplant 2010

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## Diagnosing Bronchiolitis Obliterans Syndrome

1. Evidence of airflow obstruction
  - a. FEV1/FVC or slow VC <70% or 5<sup>th</sup> percentile of predicted
  - b. Ratio should use the greater of FVC or slow VC
2. FEV1 < 75% of predicted values with  $\geq 0\%$  decline over two years
  - a. FEV1 should not correct to > 75% of predicted values after albuterol administration
  - b. Decline should be  $\geq 0\%$  despite albuterol administration
3. Absence of infection in the respiratory tract, documented by radiology or microbiological test
  - a. Radiology includes chest radiographs or computed tomography (preferred)
  - b. Microbiological tests include cultures from the upper airway, testing for viral infections (NAAT preferred), sputum culture, or BAL
4. One of the 2 support features of BOS
  - a. Evidence of air trapping by expiratory CT or small airway thickening or bronchiectasis on high-resolution CT, OR
  - b. Evidence of air trapping by PFTs (RV > 120% of predicted values or RV/TLC > 95<sup>th</sup> percentile)
5. If there is evidence of extrapulmonary chronic GVHD, only the first three criteria are necessary to diagnose BOS
6. In the absence of extrapulmonary chronic GVHD, histopathologic evidence of constrictive bronchiolitis is recommended prior to enrollment into clinical trials.

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## Diagnosing Bronchiolitis Obliterans Syndrome cont'd

- Diagnosing BOS early in its course is generally associated with better outcomes
- Why can't we diagnose early BOS consistently?
  - Symptoms are subtle initially and hard to distinguish from other post-HCT symptoms like fatigue, anemia, or viral infection<sup>1</sup>
  - Pulmonary function screening occurs every few months, while BOS can occur within a few weeks
  - BOS does not show up on chest imaging until it is very severe

<sup>1</sup> (Palmer et al Biol Blood Marrow Transplant 2014)

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## Bronchiolitis Obliterans Syndrome -Treatment

- The mainstay of BOS treatment is systemic immunosuppression and inhaled corticosteroids
- Historically, we used FAM:
  - F - Fluticasone, A - azithromycin, M - montelukast
- More recently there have been concerns that azithromycin may increase cancer relapse, leading to an FDA black box warning and the cessation of azithromycin for BOS at many institutions
- Second-line therapies (e.g. ruxolitinib, belumosudil) generally do not work as well for lung GVHD as for other types of GVHD
- If you have BOS, ask your docs about pulmonary rehabilitation!!!

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## 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<sup>1</sup>

<sup>1</sup> (Palmer et al Biol Blood Marrow Transplant 2014)

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## BOS in the Digital Age

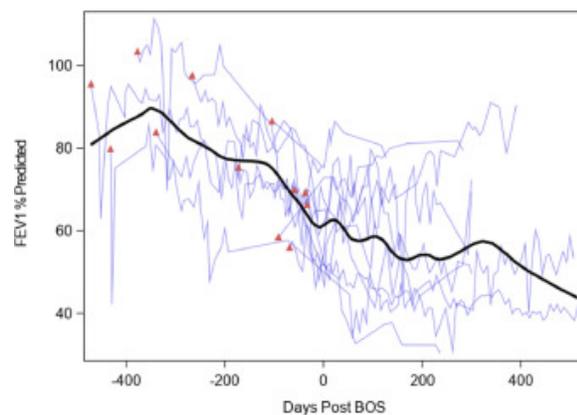
- We have recently started to use home spirometry to measure lung function more frequently
- Work from myself and Guang-Shing Cheng (Fred Hutchinson Cancer Research Center) has shown that home spirometry is easy, reproducible, and cost-effective



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## BOS in the Digital Age cont'd

- By measuring lung function more frequently, we can diagnose BOS early in its course
- 10% drop in spirometry usually indicates a “real” drop BUT
- Need to distinguish early BOS from:
  - Technical issues or noise
  - Weakness
  - Infection
  - And other conditions



Figure, Turner et al, ASTCT 2021

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## Possible Downsides of Home Spirometry

- **Cost** – hard to convince payors this is important (though it will likely save \$)
- **Burden on patients** – typically takes 5 minutes per session, but it is just one more thing to worry about
- **Overdiagnosis of BOS** – we don't have great biomarkers to diagnose early BOS (*active area of research*)
- **Coordinator/nursing time** to monitor patients and coordinate care
- Difficulty in **arranging proper follow-up** for patients who are not near cancer centers
- I would argue that, despite all this, **home spirometry is something that should be widely** implemented in HCT centers!

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## Finding your friendly neighborhood pulmonologist

- If you live near a cancer center, ask to be referred to a pulmonologist (lung doctor) who sees HCT recipients, because it takes experience and nuance to consider all possibilities
- If not, try to coordinate a tele-visit with a pulmonologist at your cancer center and get testing locally
- If that is not possible, try to find a pulmonologist listed in BMT InfoNet's GVHD Directory ([www.bmtinfonet.org/gvhd-directory](http://www.bmtinfonet.org/gvhd-directory)) and have him/her coordinate with your main pulmonologist
- If all else fails, please connect with BMTNet for help – we want to help you!

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# Questions?



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