

Pulmonary Complications of Non-Lung Transplant Patients

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Learning Objectives:

1. Review infectious and non-infectious complications of hematopoietic stem cell and solid organ transplant including bronchiolitis obliterans syndrome
2. Review diagnostic criteria and management of bronchiolitis obliterans syndrome

Scenario:

Patient X is a 24 year old male hematopoietic stem cell transplant (HSCT) recipient (received 14 months ago) who presents with progressive shortness of breath over the last 3 weeks.

Question 1: What factors do you need to consider when determining the likely differential diagnosis for this patient?

Pulmonary complications occur in 20-60% of HSCT recipients (Sakauda E, et al. Blood 2003). First, we must consider the timing since the HSCT as the potential etiologies vary greatly with time since transplant, in addition to the origin of the stem cells transplanted (autologous vs. allogenic and bone marrow vs. peripheral blood) also playing a significant role. The other consideration is infectious complications vs. non-infectious complications. Let's start with non-infectious pulmonary complications first. These phases after HSCT include:

- Phase 1: Pre-engraftment (neutropenic) phase (1-4 weeks post-transplant)
- Phase 2: Early post engraftment phase (engraftment to day 100)
- Phase 3: Late phase (beyond day 100)

Importantly, acute lung injury remains a major cause of early post-HSCT non-relapse mortality. Early post-transplant specific causes of lung injury include:

- idiopathic pneumonia syndrome
- acute graft versus host disease
- pulmonary cytolytic thrombi
- diffuse alveolar hemorrhage
- peri-engraftment respiratory distress syndrome
- engraftment syndrome (ES)
- drug-induced pneumonitis
- organizing pneumonia (OP, previously cryptogenic organizing pneumonia, COP)
- Transfusion Reaction Associated Lung Injury (TRALI)
- Acute Fibrinous Organizing Pneumonia (AFOP)
- pulmonary veno-occlusive disease (VOD)

Complications in the pre-engraftment and early post-engraftment time periods are typically dealt with as an inpatient.

Pre-transplant pulmonary testing can indicate those at risk of early respiratory failure, for instance those with reduced total lung capacity (Kovalzki et al. 2008)

	Phase I Pre-engraftment (0-30 days)	Phase II Post-engraftment (30-100 days)	Phase III Late Phase > 100 days)
Host immune system defect	Neutropenia, mucositis, catheters and lines, acute GVHD	Impaired cellular immunity Acute GVHD	Impaired humoral and cellular immunity chronic GVHD
Infectious	<div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">gram - bacteria</div> <div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">Gram + bacteria (Staph, Strep)</div> <div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">Candida</div> <div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">Aspergillus</div> <div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">HSV</div>	<div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">Aspergillus</div> <div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">Pneumocystis</div> <div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">CMV</div> <div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">CRV (RSV, influenza, adenovirus)</div>	<div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">Encapsulated bacteria</div> <div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">Nocardia</div> <div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">Aspergillus</div> <div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">HZV</div>
Non-infectious	<div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">CHF</div> <div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">ES</div>	<div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">VOD</div> <div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">DAH</div> <div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">IPS</div>	<div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">BO</div> <div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">COP</div> <div style="border: 1px solid black; padding: 2px; margin-bottom: 5px;">PTLPD</div>

From Chi et al. (2013). Figure 1. The timeline of pulmonary complications following hematopoietic stem cell transplantation (HSCT). BO = bronchiolitis obliterans; CHF = congestive heart failure; CMV = cytomegalovirus; COP = cryptogenic-organizing pneumonia; DAH = diffuse alveolar hemorrhage; ES = engraftment syndrome; GVHD =

graft-vs-host disease; HSV = herpes simplex virus; HZV = herpes zoster virus; IPS = idiopathic pneumonia syndrome; PTLPD = posttransplant lymphoproliferative disorder; RSV = respiratory syncytial virus; VOD = veno-occlusive disease.

Question 2: What are the important non-infectious long term (“late”) pulmonary complications of HSCT that we should consider in the outpatient setting?

Bronchiolitis obliterans syndrome (BOS) is the most well characterized late pulmonary complication and the only entity formally recognized as a manifestation of chronic graft-versus-host disease of the lung. The clinical correlate to obliterative bronchiolitis (OB), characterized by peribronchiolar fibrosis and varying degrees of intraluminal fibrous obliteration and circumferential narrowing of the terminal small airways, is termed BOS. Although the pathogenesis of OB is largely unknown, it is postulated that an insult to the small airway epithelium, such as aspiration or viral infection, induces an inflammatory infiltrate driven by alloreactive T cells, leading to an aberrant repair response that ultimately results in fibrosis.

The other primary long-term pulmonary manifestation of HSCT is interstitial lung disease. Diagnosis is usually based on relatively acute respiratory symptoms, new radiographic findings, and restrictive appearing PFTs. The appearance of ILD can vary widely, including organizing pneumonia and pleuroparenchymal fibroelastosis. Steroid responsiveness is widely variable based on radiographic appearance, type of disease, etc (von der Thusen, et al. Mod Pathol 2011), with organizing pneumonia typically but not always being steroid-responsive.

Pleural effusions are also unfortunately common after transplant, with a cumulative incidence of 9.9% at one year and 11.8% at 5 years. Most are large and bilateral and associated with poor outcomes (Modi D, et al. Am J Hematol, 2016).

Finally, we must consider pulmonary vascular disease (PVD). PVDs include different entities such as pulmonary veno-occlusive disease (often responsive to steroids), thrombotic microangiopathy (with normal ADAMTS-13 levels), and venous thromboembolic disease (Bunte MC, et al. Bone marrow transplantation 2008).

Question 3: What are the diagnostic criteria for diagnosing bronchiolitis obliterans syndrome? What are the typical symptoms?

Criteria for diagnosing BOS after HSCT – 2014 Consensus Criteria

1. FEV1/vital capacity < 0.7 or fifth percentile of predicted. Vital capacity includes FVC or slow vital capacity, whichever is greater.
2. FEV1 <75% predicted with ≥ 10% decline over less than 2 years. FEV1 should not correct to >75% of predicted with albuterol.
3. Absence of infection in the respiratory tract
4. One of the 2 supporting features of BOS: A) evidence of air trapping by expiratory CT or small airway thickening or bronchiectasis by high resolution chest CT, or B) Evidence of air trapping by PFTs: RV > 120% of predicted of RV/Total Lung Capacity > 90% confidence interval.

**Note: Only criteria 1-3 are required if the patient has a diagnosis of cGVHD by involvement in other organs.*

***Note: Lung biopsy is required to establish the diagnosis of cGVHD if BOS is the only clinical manifestation of cGVHD for the purposes of enrollment on general cGVHD trials.*

Table 1 above based on Jafasia MH, et al. *Biol Blood Marrow Transplant* 2014.

Patients with BOS after HSCT (allogenic most commonly) usually present with insidious or subacute symptoms of dyspnea on exertion or a persistent cough unresponsive to empiric antibiotics. Patients usually present after 100 days and often in the first two years after transplant. Clinical practice guidelines recommend (American Society for Blood and Marrow Transplantation) pulmonary function testing at 6 months and yearly post-HSCT. An asymptomatic decline on routine pulmonary function testing may alert the clinician to a diagnosis of BOS. Airflow decline may be marked at the time of diagnosis.

Question 4: What are the treatment options from bronchiolitis obliterans syndrome?

Some studies indicate treatment with fluticasone, azithromycin, and montelukast (FAM) may have benefit in delaying the progression of BOS. However, the ALLOAZITHRO trial showed that early administration of azithromycin, prior to the development of BOS and concurrent with the transplant, resulted in worse airflow decline-free survival than did placebo – largely driven by relapse of hematologic malignancy (Bergeron A, et al. *JAMA* 2017). This finding was not confirmed in a second study of azithromycin after HSCT, though a higher rate of secondary malignancy was seen (Cheng G-S et al, *BBMT* 2020). A study of budesonide-formoterol (compared to placebo) showed an increase in FEV₁ but no improvement in symptoms in HSCT patients with BOS (Bergeron A et al, *AJRCCM*, 2015). There is also evidence (poor or ongoing in most cases), of benefit from systemic steroids, extracorporeal photopheresis, imatinib, rituximab, ruxolitinib (a JAK2 inhibitor), and bortezomib. New data demonstrates a role for belumosudil, and oral rho-associated coiled-coil-containing protein kinase-2 (ROCK2) inhibitor, for treatment of refractory BOS (Cutler C et al, *Blood*, 2021).

Lung transplantation has been performed in select patients with BOS with variable results. Decisions for treatments should be made on case-by-case basis.

Question 5: What infectious complications should we consider in this patient (or in a solid organ transplant patient)?

Nosocomial infections, including bacterial pneumonia and community respiratory viral infections, can often occur post-transplant, and can increase morbidity and mortality. Infectious complications are more common in allogenic HSCT due to prolonged immunosuppressive therapy and graft vs host disease.

We will focus on non-typical bacterial processes for the sake of this discussion. First, let's consider mycobacterial disease. Donor derived mycobacterial disease is at most extremely rare; the one that must be considered is likely *Mycobacterium tuberculosis* with various organizations making recommendation about living donor surveillance programs. Latent tuberculosis infection (LTBI) is not uncommon in potential transplant recipients. Given the

severity of MTB in an immunosuppressed transplant recipient, the difficulty treating it, and the multiple drug interactions with immunosuppressive therapies, surveillance for LTBI is recommended as part of the evaluation for potential transplant recipients.

NTM infection in the post-transplant period is a significant risk to long term patient survival. Studies have demonstrated that heart and lung transplant recipients are at the highest risk for these types of infections. There have been several outbreaks in hospitals of NTM infection (including *M. abscessus*) linked to colonization of hospital water supplies (Doucette K, et al. Clin Infect Dis 2004). In HSCT patients, MAI is likely the most common non-tuberculous pathogen.

There is a significant increased risk of mortality in solid organ transplant recipients who are infected with mycobacterium in the post-transplant phase compared to non-infected patients.

CMV disease can occur post-transplant, and recipients who are CMV + are at greatest risk, particularly when donors are CMV – (lack of CMV donor-transferred CMV immunity). CMV status is determined prior to stem cell transplant, and reduction of CMV disease can be achieved by selecting CMV – donors for CMV – recipients whenever possible. CMV pneumonia is overall less common with pre-emptive treatment and prophylaxis post-transplant.

Lastly, let's consider fungal infections in this patient population. Respiratory fungal infections are associated with high morbidity and mortality in HSCT and solid organ (SOT) transplant recipients, and are caused primarily by molds. The primary organism of concern remains aspergillus, although the epidemiology has been changing due to changes in the use of prophylactic antifungal therapies (Minari A, et al. Transpl Infect Dis 2002; Worthy SA, et al. Radiographics 1997).

The incidence of invasive aspergillus (IA) varies according to the transplanted organ. Lung transplant recipients have the highest risk of IA, heart and liver recipients have moderate risk, and kidney recipients are considered low risk. Most cases of IA are pulmonary in origin, with the "halo sign" being a common radiographic presentation (indicating vascular invasion). Serum galactomannan has poor sensitivity in non-neutropenic patients while BAL galactomannan has better test characteristics.

Other molds are rising in incidence as more anti-aspergillus antifungal prophylaxis is used, including zygomycete infection. Cryptococcus is the third most common fungal infection - cryptococcosis has an overall prevalence rate of 0.26% to 8% in solid organ transplant recipients. Infections caused by *Fusarium* are rare and occur mainly in HSCT recipients, with sporadic cases in SOT, mostly lung recipients (Husain S, et al. Med mycol 2016; Pappas PG, et al. Clin Infect Dis 2010). Pneumocystis jirovecii pneumonia is rare in patients who receive appropriate prophylaxis.

Finally, we must consider endemic mycoses – these obviously vary based on geography. *Histoplasma capsulatum* occurs in the Mississippi and Ohio River valleys, Central and South America and certain areas of Africa and Asia. Coccidioidomycosis is endemic in the southwestern United States and northern Mexico. Blastomycosis occurs in the southeastern, south central and midwestern United States and the Canadian provinces that border the Great Lakes and the St. Lawrence Seaway. Most infections with endemic mycoses are secondary to reactivation of previous infection.

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