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Pulmonary Complications of Non-Lung Transplant Patients

An APCCMPD Ambulatory Care Curriculum Teaching Script

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Review Update Literature review current through June 2026
Last updated June 2026

Citation Diamond J. *Pulmonary Complications of Non-Lung Transplant Patients* [teaching script]. Brady AK, Cordova T, Petri C, McCutcheon M, Small B, assoc eds. Sodhi A, ed. Association of Pulmonary and Critical Care Medical Program Directors; Published 2026. https://apccmpd.memberclicks.net/assets/AmbulatoryCareWorkgroup/Year_2_Scripts/02%20Cystic%20Fibrosis_2026_Final.pdf

Pulmonary Complications of Non-Lung Transplant Patients

Scenario:

Mr. X is a 24-year-old male hematopoietic stem cell transplant (HSCT) recipient (received 14 months ago) who presents to clinic as an urgent referral from his hematologist with progressive shortness of breath over the last 3 weeks.

Question 1: How do timing and type of hematopoietic transplant help structure the differential diagnosis for this patient?

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

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

Question 4: What are the treatment options for BOS?

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

Pulmonary Complications of Non-Lung Transplant Patients

Educational Objectives: Review infectious and non-infectious complications of hematopoietic stem cell and solid organ transplant including bronchiolitis obliterans syndrome

1. Review diagnostic criteria and management of bronchiolitis obliterans syndrome

Scenario:

Mr. X is a 24 year-old male hematopoietic stem cell transplant (HSCT) recipient (received 14 months ago) who presents to clinic as an urgent referral from his hematologist with progressive shortness of breath over the last 3 weeks.

Question 1: How do timing and type of hematopoietic transplant help structure the differential diagnosis for this patient?

Pulmonary complications occur in 20-60% of HSCT recipients (Sakauda, 2003).

The origin of the stem cells transplanted (autologous vs. allogeneic and bone marrow vs. peripheral blood) plays a significant role in determining risk for particular conditions, especially those that are mediated by cellular interactions between the graft and the host. As such, in an autologous transplant, the risk of graft-versus-host disease and rejection is nil and reduces the need for post-transplant immunosuppression.

Timing since the HSCT is very important, as the potential etiologies, both infectious and non-infectious, vary greatly with time since transplant.

The 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)

Let's begin by considering non-infectious complications based on the phase of transplant.

Importantly, lung injury remains a major cause of early post-HSCT non-relapse mortality. Other, early post-transplant specific causes of lung injury which will not be covered in depth in this script but which are more relevant in the inpatient pulmonary consultative setting include:

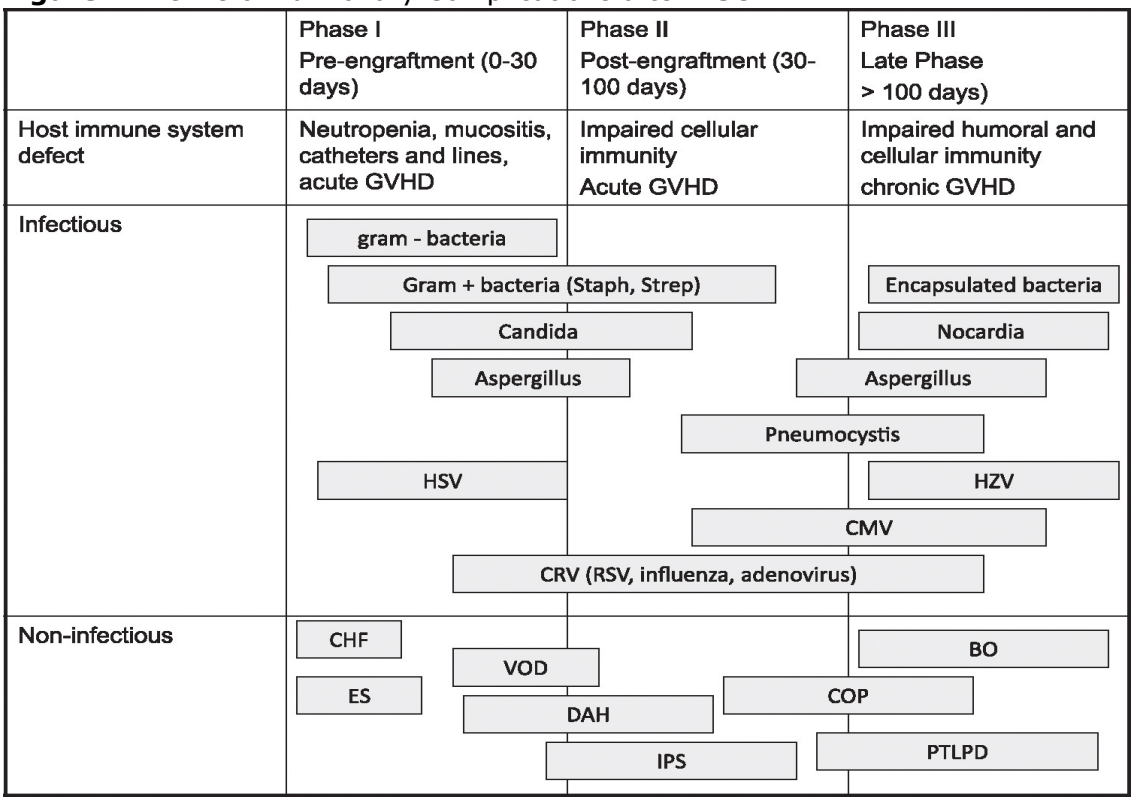
- idiopathic pneumonia syndrome (diffuse alveolar damage of unclear etiology)
- pulmonary cytolytic thrombi
- diffuse alveolar hemorrhage
- peri-engraftment respiratory distress syndrome / engraftment syndrome
- drug-induced pneumonitis
- organizing pneumonia (OP, previously cryptogenic organizing pneumonia, COP)
- Transfusion Reaction Associated Lung Injury
- Acute Fibrinous Organizing Pneumonia
- pulmonary veno-occlusive disease

Additional reading about these entities can be found at references below (Chi, 2013).

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

The Figure illustrates the risk of non-infectious and infectious complications of HSCT based on the phase of transplant.

Figure. Timeline of Pulmonary Complications after 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.

Figure adapted from Chi, 2013.

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 BOS 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. Five-year mortality is 12% but higher in patients with rapidly declining lung function (Chi, 2013).

The other primary long-term pulmonary manifestation of HSCT is interstitial lung disease (ILD). Diagnosis is usually based on subactue to chronic respiratory symptoms, new radiographic findings, restrictive PFTs, and the absence of an infectious cause. 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, 2011), with organizing pneumonia typically, but not always, being steroid-responsive.

Pleural effusions are 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, 2016).

Finally, we must consider pulmonary vascular disease including pulmonary veno-occlusive disease, thrombotic microangiopathy (with normal ADAMTS-13 levels), and venous thromboembolic disease (Bunte, 2008).

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

Patients with BOS after HSCT usually present with insidious or subacute symptoms of dyspnea on exertion or a persistent cough unresponsive to empiric antibiotics. BOS presents most commonly between 100 days and two years after transplant. Clinical practice guidelines from the American Society for Blood and Marrow Transplantation and expert opinion recommend pulmonary function testing at 100 days, 6 months, and yearly post-HSCT. An asymptomatic decline on routine pulmonary function testing may be the first sign of BOS. There are a 2014 set of consensus criteria often referenced in diagnosing BOS, shown in the Table below.

Table. Criteria for Diagnosing BOS after HSCT – 2014 Consensus Criteria*

1. Forced expiratory volume in 1 second (FEV_1)/vital capacity < 0.7 or lower limit of normal. Vital capacity includes forcesd or slow vital capacity, whichever is greater.
2. FEV_1 <75% predicted with ≥ 10% decline over less than 2 years. FEV_1 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 computed tomography, or B) Evidence of air trapping by lung function testing: residual volume > 120% of predicted or residual volume/Total Lung Capacity > 90% confidence interval.

**Only criteria 1-3 are required if the patient has a diagnosis of chronic GVHD in other organs besides the lung.*
Based on Jafasia, 2014.

These consensus criteria use percent predicted rather than Z-scores but can be adapted based on the reporting of the pulmonary function laboratory at your institution. New airflow obstruction, lack of a bronchodilator response, and presence of air trapping are the most important findings to look for on pulmonary function testing.

Mr. X has newly reduced FEV_1 of 69% predicted for age, height, and sex, and FEV_1/VC ratio below the lower limit of normal, compared to his pre-transplant testing, which was all within normal limits. You are concerned he has BOS and order lung volumes and a high resolution chest computed tomography to look for air trapping or other causes of obstruction such as bronchomalacia.

Question 4: What are the treatment options for BOS?

There is little high-quality evidence for BOS treatment. A single arm study of 36 patients suggested that treatment with fluticasone, azithromycin, and montelukast may have benefit in delaying the progression of BOS and allowing for tapering of oral prednisone (Williams, 2016). A study of budesonide-formoterol (compared to placebo) showed an increase in FEV_1 but no improvement in symptoms in HSCT patients with BOS (Bergeron, 2015). 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, 2017). This finding was not confirmed in a second study of azithromycin after HSCT, though a higher rate of secondary malignancy was seen (Cheng, 2020). 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, an oral rho-associated coiled-coil-containing protein kinase-2 (ROCK2) inhibitor, for treatment of refractory BOS (Cutler, 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, 2004). In HSCT patients, mycobacterium avium intracellulare 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.

Cytomegalovirus (CMV) disease can occur post-transplant, and recipients who are CMV positive are at greatest risk, particularly when donors are CMV negative (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 negative donors for CMV negative 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, 2002; Worthy1997).

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, 2017; Pappas, 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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