

## Complications After Lung Transplantation: Infections

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### Educational Objectives:

1. Be able to review the timing of onset of infections following lung transplantation
2. Identify the testing required for infectious donor screening prior to lung transplantation
3. Describe a stepwise approach to prophylaxis, screening, and treatment for cytomegalovirus (CMV) infection and disease
4. List the possible manifestations of fungal infections post-transplant and antifungal prophylaxis

### Scenario one:

**Mrs. X is a 56-year-old female s/p bilateral lung transplant for COPD (CMV D-/R-) who was readmitted to hospital 5 days after her initial lung transplant admission with respiratory distress and recurrent sternal instability. Peri-transplant she received standard immunosuppression with anti-thymocyte globulin, and maintenance immunosuppression with tacrolimus, mycophenolate mofetil and methylprednisolone. Her post-operative course was complicated by sternal malunion and she underwent surgical repair on POD 10. Mrs. X was discharged to rehabilitation POD 14 on prophylactic trimethoprim-sulfamethoxazole, itraconazole and acyclovir.**

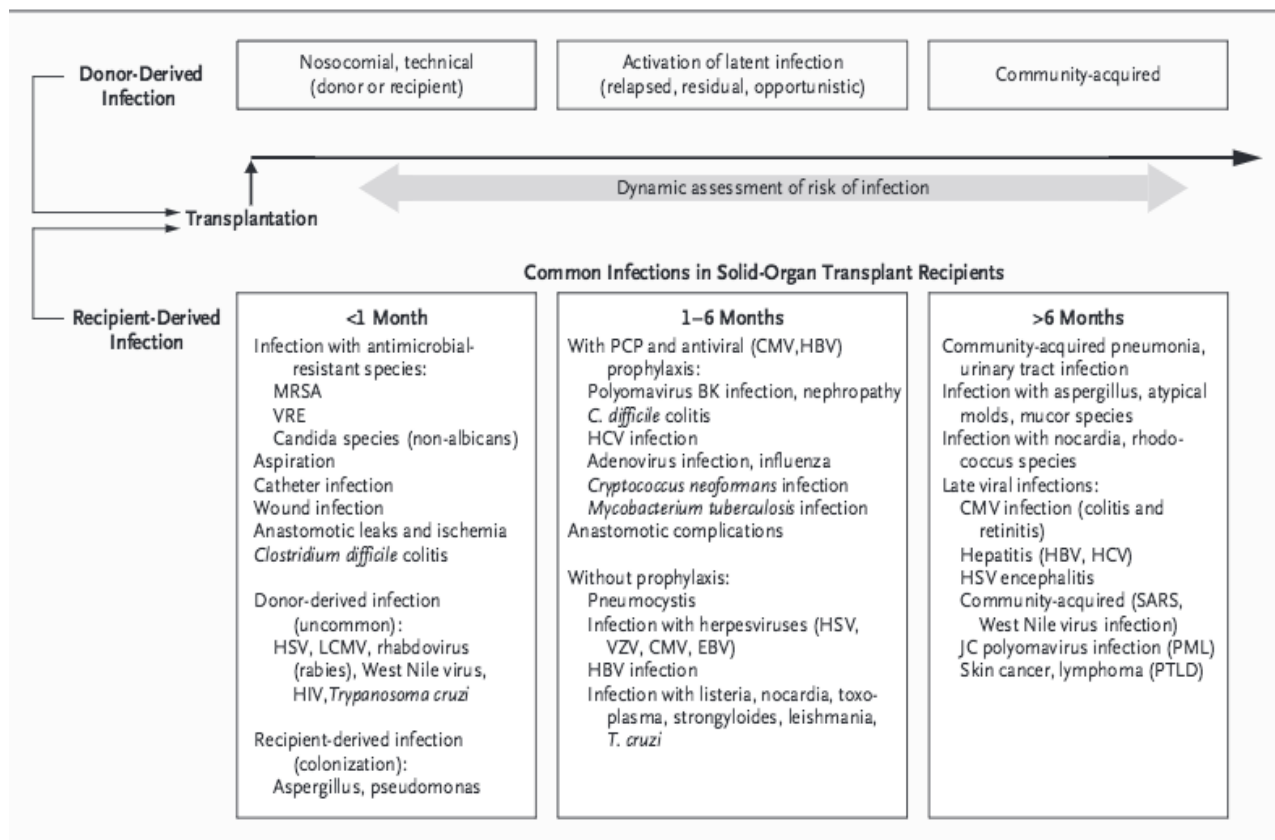
**Mrs. X's donor had received bilateral thoracostomy tubes during resuscitation in a wilderness location and there was some concern for soil contamination, but there was no noted surface lung abnormalities noted during procurement.**

**CT imaging on her readmission to hospital showed new bilateral pulmonary infiltrates and pleural effusions. She was initiated on antimicrobial therapy with vancomycin and piperacillin-tazobactam. Both pleural spaces were drained and pleural fluid sent for cultures which grew a mold identified as *Scopulariopsis brumpti*.**

*Adapted from: Shaver et al. Fatal Scopulariopsis Infection in a Lung Transplant Recipient: Lessons of Organ Procurement. Am J Trans. 2014 (14); 2893-2897*

**Question 1: How do you approach infections in a solid organ transplant recipient?**

The type of infection generally depends on how “far out” the recipient is from their date of transplant. Infections within the first month of transplant are generally donor or recipient derived (often nosocomial pathogens, e.g. Candida, MRSA) whereas reactivation of latent infections and opportunistic pathogens must be considered for those infections that present between one and six months after transplant. Infections more than six months after transplant are typically community-acquired or late viral infections. However, this timeline may be altered depending on the type of induction and maintenance immunosuppression, the baseline recipient and donor immunologic status, the development of rejection episodes requiring augmented immunosuppression, and use of fungal and *Pneumocystis jirovecii* prophylaxis. For instance, the use of anti-lymphocyte agents (like thymoglobulin) may result in prolonged leukopenia and impact latent viral infections like CMV.(2)



Borrowed from: Fishman JA. Medical Progress: Infection in Solid-Organ Transplant Recipients. NEJM. 2007; 357: 2601-14.

**Mrs. X was initiated on micafungin and voriconazole. She also underwent bronchoscopy with transbronchial biopsies, notable for A1 acute cellular rejection and organizing pneumonia, and she was taken to the operating room for debridement and sternal repair. Cultures from sternum and pleura in the OR diffusely grew *S. brumpti*.**

**Question 2: What screening tests are performed to evaluate donors for communicable infections?**

All potential donors are screened for infection with the following testing:

- Blood, sputum and urine cultures
- HIV antibody or antigen/antibody testing
- Hepatitis B surface antigen, core antibody
- Hepatitis C antibody and RNA
- SARS-CoV-2 (COVID-19) nucleic acid testing (NAT) (See Question 4 below)
- CMV, EBV, RPR
- Toxoplasma Immunobulin G

Previously, the Public Health Service (PHS)/Centers for Disease Control (CDC) would designate donors as “increased risk” based on donor history. New recommendations as of March 2021 have removed this designation, as all donors are required to be screened for HIV, HBV, and HCV. If a donor fulfills specific risk criteria (see Table 1 supplement), then recipients will be informed, but no specific consent obtained unless a donor tests positive for Hepatitis B, C or HIV (4). Donor HIV, HCV and HBV NAT must also be obtained. Recipients of these organs receive screening for HIV, HBV and HCV at 4-6 weeks post-transplant (as well as prior to transplant, which is standard of care).

Despite comprehensive infectious disease screening, recipients do often acquire donor-derived infections, which are most often treatable. Though often incomplete, information regarding donor history and circumstances of death and resuscitation should be carefully reviewed prior to procurement and implantation.

**Question 3: When should we be concerned about an infection in a lung transplant patient?**

Lung transplant patients may not present with typical findings of infection, such as fever or leukocytosis, but may present with end-organ dysfunction such as confusion, hypoxia or acute kidney injury in the setting of bacteremia, pneumonia or another infection. In addition, infection can be concomitant or mimic presentations of acute cellular and antibody-mediated rejection.

Pneumonia is the leading cause of infection in lung transplant patients. This is due to multiple factors including ongoing allograft exposure to environmental pathogens (via inhalation), impaired cough reflex and mucociliary clearance due to post-transplant airway denervation, impaired lymphatic drainage, anastomotic complications and susceptibility to donor infection transmission and potential need for prolonged ventilation peri-transplant (3)

**Question 4: How are we evaluating lung transplant donors for SARS-CoV2 (COVID-19)?**

There have been several cases since the start of the COVID-19 epidemic in 2020, where a deceased donor tested negative for COVID 19 via upper airway (nasopharyngeal swab) PCR testing and then retrospectively tested positive via lower respiratory tract samples. This resulted in a donor-derived infection in three cases, and a subsequent death in one recipient due contraction of this infection. An Organ Procurement Transplant Network (OPTN) policy change occurred in May 2021 in response to these events, now NAT COVID-19 test results from lower respiratory tract specimens are required from a potential deceased lung donor, prior to lung transplantation (OPTN Policy 1.2: Definitions, Policy 2.9: Required Deceased Donor Infectious Disease Testing).

**Question 5: What can transplant recipients do to minimize infection (beside avoiding sick contacts and taking prescribed prophylaxis)?**

- Washing hands frequently to prevent infection: before eating, after using the restroom, after touching animals, after changing a diaper, after going to a public place, before and after touching catheters or wounds
- Starting at 3-6 months after transplant patients should obtain yearly influenza vaccination, COVID-19 vaccinations, varicella vaccinations and pneumococcal vaccinations every 3-5 years. They should avoid live vaccines.
- Use of a mask in public indoor places for those who are not vaccinated against COVID-19 (recommendations continue to be in flux at this time) or as otherwise directed by their transplant program (guidelines are often institution-dependent)
- Avoid well and lake water (*Cryptosporidium* or *Giardia*), undercooked meats, unwashed fruits and vegetables, and unpasteurized dairy products (*E.coli* or *Listeria monocytogenes*)
- Avoid marijuana smoke (risk of *Aspergillus*), gardening and farming (*Sporothrix schenckii*, non-tuberculosis mycobacterium, *Aspergillus*, *Scedosporium*), cleaning cat litter box (*Toxoplasmosis*) or handle other animal waste like cleaning fish tanks (*Mycobacterium*) or animal cages. Avoid pets such as birds or reptiles during or after transplant if able.
- Travel to different locations worldwide where other highly contagious infections may be endemic; e.g. Africa, India (Tuberculosis, Malaria, etc.).

**Scenario two:**

**Mr. BZB is a 51-year-old male with a history of idiopathic pulmonary fibrosis (IPF) s/p bilateral lung transplant (CMV D+/R-) who received basiliximab induction therapy and immunosuppression with prednisone, tacrolimus, and mycophenolate mofetil. His post-transplant course was complicated by primary graft dysfunction (PGD), right phrenic nerve paresis with right hemidiaphragm paradoxical movement, and prolonged delirium requiring tracheostomy/PEG (now decannulated) who is about to be discharged after initial hospitalization for lung transplantation.**

**Question 6: What is the timing and risk of CMV infection/disease after lung transplantation? Should he be discharged with CMV prophylaxis or just trend quantitative CMV serology and treat when "positive?"**

CMV is the most prevalent opportunistic infection in lung transplant recipients. Incidence varies but is highest in lung transplant recipients and in CMV D+/R-. Without prophylaxis, incidence in lung or heart-lung is as high as 50-75%. Symptomatic disease typically occurs 30-90 days after solid organ transplantation (2,6-7). However, this timing is changing due to the increasing commonality of universal prophylaxis post-transplant. CMV can augment existing immunosuppression and can facilitate other opportunistic bacterial and fungal infections, and can also predispose recipients to acute and chronic allograft rejection.

Risk factors for CMV infection/disease:

- Serostatus of donor and recipient: Any non- CMV D-/R- (with CMV D+/R- being at especially high risk)
- Induction therapy with depleting anti-lymphocyte antibodies (like anti-thymocyte globulin or alemtuzumab)
- Acute allograft rejection requiring higher immunosuppression
- Concurrent infections
- Blood transfusions – CMV D-/R- should receive transfusion from CMV D – or leukocyte-depleted products

Prophylaxis versus preemptive treatment for CMV disease remains controversial especially as different thresholds are used to treat and there is potential for greater drug toxicity (including cytopenias) for prolonged prophylaxis. Universal prophylaxis as opposed to preemptive treatment for CMV D+/R- patients is one of the recommendations of consensus guidelines published in 2018 for the management of CMV in solid organ transplant. Given the association between CMV and subsequent risk of bronchiolitis obliterans syndrome, most centers administer universal prophylaxis for patients at high risk (all but CMV donor negative/recipient negative serologic status), and the recommended duration is between 6 to 12 months of therapy (5). Evidence also supports use of prophylaxis for up to 12 months without the development of CMV resistance. (8)

- Potential therapies:
  - Valganciclovir 900mg/day or Ganciclovir 5mg/kg/day (both need dose adjustments for CrCl<60)
- Duration
  - Minimum of 6 months is recommended in all high-risk patients
  - 12 months possible in select patients who can tolerate (8)
  - Consider prolonged prophylaxis in those with reduced peripheral absolute lymphocyte count (<610/uL) (9)
  - Restart prophylaxis if treating for ACR/AMR (5)
- Monitoring
  - <6 months: q 2 week CMV PCR
  - 6-12 months: monthly CMV PCR
  - Whole blood PCR tend to have higher quant than plasma, so use a consistent source when monitoring
- Serology-based regimens:
  - CMV D+/R-: Valganciclovir 900mg/day for 6-12 months
  - CMV D-/R+ or CMV D+/R+: Valganciclovir 900mg/day for 6-12 months
  - CMV D-/R-: Valacyclovir/Acyclovir indefinitely (Recommendations are for continued protection against varicella and herpes simplex viruses (5)

In contrast, pre-emptive treatment is treatment of those recipients with an active infection in order to prevent the development of clinically significant disease. The level (copies, logarithmic quantity (IU/mL) at which this should be initiated is often institution-specific, but recommendations indicate that viral load changes exceeding 0.5 log IU/mL are significant. (5)

**On his 6-month surveillance bronchoscopy (no pulmonary symptoms, PFTs at their peak) while on valganciclovir, CMV BAL was 674.**

**Question 7: Does this represent CMV disease? What is the clinical significance of isolation of CMV from BAL?**

CMV disease has several manifestations which include:

**Latent infection:** CMV in latent state, typically in cells of the myeloid lineage without active replication. CMV DNA is generally not detected in peripheral blood based on the available NAT assay.

**Active infection:** Evidence of asymptomatic CMV replication by antigenemia or NAT.

**Disease:** Symptomatic viremia or "CMV syndrome" requires detection of CMV with NAT with two of the following; Fever, malaise, weakness, myalgias, and/or arthralgia without end-

organ involvement, leukopenia (<3500cells/uL) or neutropenia (<1500cells/uL), thrombocytopenia (<100Kcells/uL), or elevated transaminases (10)

**Invasive disease:** Specific symptoms in a target organ and histologic findings demonstrating cytopathic effect of the virus in tissue. May or may not be evidence of viral replication in peripheral blood. This is especially true for CMV colitis or meningoencephalitis in which case isolation of CMV in gastrointestinal biopsy or CSF is needed.

Symptoms of CMV pneumonitis include low-grade fever, shortness of breath, nonproductive cough and change in pulmonary function. Due to these non-specific symptoms, many other diagnoses (infectious and non-infectious) could be the culprit. CMV PCR from BAL is very sensitive (approaches 100% negative predictive value), but a significant viral load cut off is difficult to determine. Therefore, in the absence of symptoms of pneumonitis, it may just suggest early infection or viral shedding, therefore a next step would be assessing serum CMV NAT testing. Histology (via transbronchial biopsy) with PCR or staining supportive of CMV may assist in diagnosis of CMV pneumonitis. (10)

Due to high efficacy of valganciclovir, one must consider the possibility of development of antiviral resistance if active infection develops in the setting of prophylaxis. Risk factors include CNV D+/R- status, increased immunosuppressive therapy or inadequate drug delivery. (3)

Treatment of ganciclovir-resistant CMV:

- Ganciclovir 5mg/kg BID (dose based on CrCl)
- Foscarnet 80mg/kg q24h if cr<1.75, 60mg/kg q 24h if cr 1.72-2.19, 50mg/kg q 24h if cr >2.2. Do not redose if cr >2.7

### **Scenario three:**

**Ms. C is s/p bilateral lung transplant for cystic fibrosis and has started to smoke marijuana to help her sleep at night. Bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsies were completed due to decrease in FEV1. She was found to have *Aspergillus fumigatus* in her fungal cultures**

**Question 8: What is the relevance of a positive fungal culture in a transplant patient?**

The presence of a positive fungal culture may indicate:

- = Colonization: Presence of fungus in sputum/BAL detected by culture, PCR or biomarker in the absence of symptoms, radiology and endobronchial changes
- = Invasive fungal disease (IFD): Presence of fungus (as noted above) **in the presence of symptoms, radiology and endobronchial changes OR presence of histological changes consistent with fungal invasion of tissue**

Overall, the presence of fungal colonization is high; between 20-50% in all lung transplant recipients, but it is more frequent in patients with cystic fibrosis. The most common species to colonize was *Aspergillus*, specifically *Aspergillus fumigatus*.

IFD is much less common and its frequency ranges from 3-14%, again being more common in patients with cystic fibrosis. Risk factors include fungal colonization prior to or immediately following lung transplant, PGD and the presence of airway stents. The use of BAL galactomanin may be used to identify invasive disease or to guide pre-emptive antifungal therapy, since this testing is more specific and detects growing hyphae. (12)



## **Question 9: What are the indications for fungal prophylaxis post-lung transplant?**

Similar to the treatment of CMV, the two approaches to anti-fungal therapy include **pre-emptive therapy** and **universal prophylaxis**. Pre-emptive treatment is the initiation of therapy for fungal disease diagnosed in surveillance bronchoscopy without evidence of invasive disease (often colonization), whereas universal prophylaxis is the initiation of with antifungal agents to all patients immediately post-transplant. At present there are no clear recommendations for one approach over the other.

A variety of agents have been used for universal prophylaxis and pre-emptive therapy. In the early post-transplant period, the use of inhaled amphotericin B has been proven to be safe and effective in uncontrolled studies, and voriconazole, despite its toxicities (CNS adverse effects, drug interactions, dermatitis and cancer risks), has documented effectiveness retrospectively. Voriconazole should not be continued if possible long-term due to increased risk of squamous cell carcinoma and periostitis.

In the first 30 days following transplant, *Candida* species are often encountered, whereas molds predominate in the subsequent period. Certain molds have a greater risk of invasive disease including aspergillus colonization, mucorales and scedosporium.

The optimal duration of anti-fungal prophylaxis following transplant is unclear and data suggests that the greatest risk for aspergillus is within the first 6 months of transplant, as such recommendations from the ISHLT are for 4-6 months of prophylactic therapy. Often prophylaxis is continued beyond this time if there is anticipated ongoing exposure based on environmental, travel or lifestyle exposures (e.g. farming), and can also be resumed during times of augmented immunosuppression (e.g. treatment for acute rejection). (12)

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## Supplementary Material

**Table 1: Donor Risk Criteria**

**Risk criteria (during the 30 days before organ procurement):**

Sex (i.e., any method of sexual contact, including vaginal, anal, and oral) with a person known or suspected to have HIV, HBV, or HCV infection  
Man who has had sex with another man  
Sex in exchange for money or drugs  
Sex with a person who had sex in exchange for money or drugs  
Drug injection for nonmedical reasons  
Sex with a person who injected drugs for nonmedical reasons  
Incarceration (confinement in jail, prison, or juvenile correction facility) for  $\geq 72$  consecutive hours  
Child breastfed by a mother with HIV infection  
Child born to a mother with HIV, HBV, or HCV infection  
Unknown medical or social history