Infections after lung transplantation

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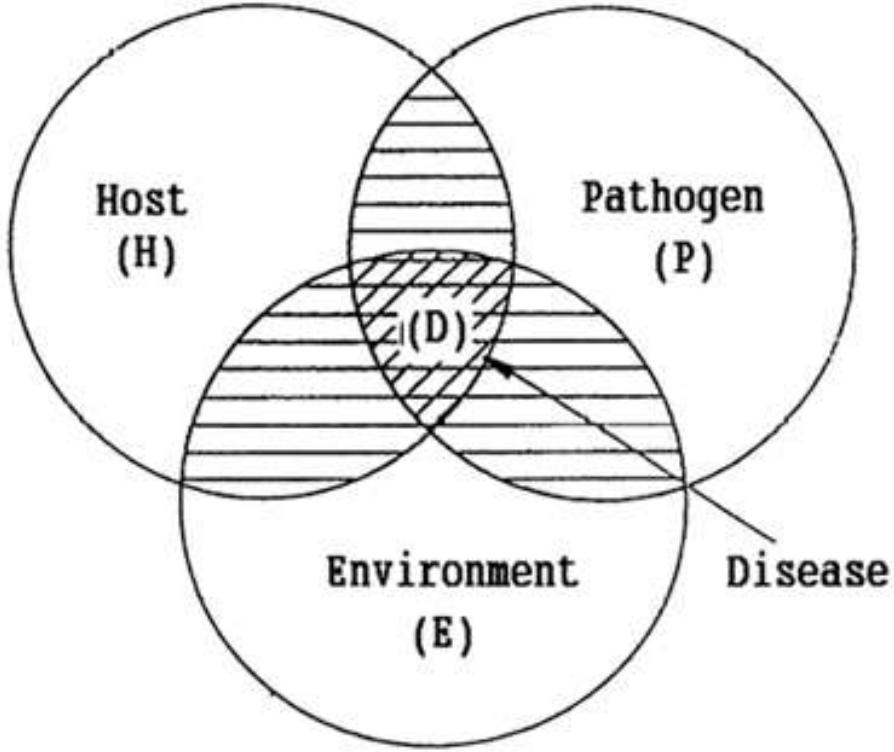
Objectives

1)

Disclosures

- Nothing to declare.
- Many immunosuppressants and antimicrobials are used in ways that are outside of the specific indications for which they have been approved by the Food and Drug Administration.



Svobodová Z. Lloyd R. Máchová J. Vykusová B. Water quality and fish health. EIFAC Technical Paper. No. 54. Rome, FAO. 1993.

Lung transplantation

- Lung transplantation is increasingly accepted as a modality for end stage lung disease.
- However, survival rates are inferior to those seen with other solid organ transplants.
- Only 50% of patients undergoing lung transplant survive to five years.

Lung transplantation

- Indications
  - Obstructive lung disease
  - Fibrosing lung disease
  - CF/bronchiectasis
  - Pulmonary hypertension
  - Cardiopulmonary syndromes (in conjunction with heart transplant)

J Heart Lung Transplant 2006; **25** :745 – 55.

Lung transplantation

- Can be single lung or double lung
- Septic indications for transplantation such as cystic fibrosis mandate double lung transplantation.

J Heart Lung Transplant 2006; **25** :745 – 55.

Lung transplantation

- HLA matching is not done in lung transplantation as it is not feasible. Accordingly, lung transplant patients are typically very aggressively immunosuppressed.
- Surveillance bronchoscopy with trans-bronchial biopsy is standard at many institutions.

J Heart Lung Transplant. 2011 Apr;30(4):426-34.

Lung allocation score

Table 9.3 Lung allocation scoring (LAS) system in the USA

LAS score determinants	Calculation of the LAS score
• Specific disease indication for lung transplant	• Waiting list survival probability during next year is calculated
• Forced vital capacity (percent predicted)	• Calculate wait-list urgency
• Pulmonary arterial systolic pressure	• Calculate post-transplant survival probability during first post-transplantation year
• Supplemental oxygen requirement (L/min)	• Calculate post-transplant survival measure
• Age	• Calculate raw allocation score
• Height and weight	• Raw allocation score is then normalized (0–100; organ offers go to candidate with highest score within specific blood group and thoracic dimension category)
• Functional status (I, II, III)	
• 6MWT distance	
• Ventilator use	
• Pulmonary capillary wedge pressure	
• Serum creatinine	
• PCO_2	

Primer on Transplantation.

Assessment of the host post-transplant

"Net state of immunosuppression"

“Net state of immunosuppression”

- A frequently quoted but nebulous concept
- Ultimately, the “net state of immunosuppression” is a subjective assessment.

Clin Infect Dis. 2001 Jul 1;33 Suppl 1:S1-4.

Liver Transpl. 2012 Oct;18(10):1245-53.

"Net state of immunosuppression"

- How does one assess the net state of immunosuppression?
  - Underlying medical conditions and their treatment prior to transplantation
  - Immunosuppression history
  - History of rejection/GVHD and treatment
  - Impairment of natural host defenses
  - Prior infectious complications and prophylaxis
    - CMV and other immunomodulatory viruses
    - Other opportunistic infections

Clin Infect Dis. 2001 Jul 1;33 Suppl 1:S1-4.

Induction immunosuppression after SOT

- The initial immunosuppression that is given to prevent acute rejection after SOT
- Protocols are highly variable and depend on institutional preference, the organ to be transplanted, the degree of HLA mismatch between donor and recipient, and the need to avoid other agents in the post-transplant period.
  - Thymoglobulin
  - Basiliximab

Transplantation. 2004;78(Suppl 2):120.

Maintenance immunosuppression after SOT

- The daily immunosuppression given to prevent organ rejection after the initial period.
- As immune tolerance to the organ develops, the goal is to taper this immunosuppression over time to the minimal required to maintain graft function.

Transplantation. 2004;78(Suppl 2):120.

Rejection

- Can be cellular or humoral
- Treatment
  - Cellular
    - Steroids
    - Thymoglobulin
    - Anti-IL-2R antibodies (basilixumab)
    - Alemtuzumab
  - Humoral
    - Plasmapheresis
    - IVIG
    - Rituxumab

Semin Immunol. 2011 Aug;23(4):224-34.

The social history

- Recent sick contacts and/or recent exposure to kids
- Hx of any recent dental procedures (cleanings? Teeth extractions? Risk for BACTEREMIA/ABSCESSES)
- Recent travels
- Lifetime foreign travel (risk for lots of things that can *reactivate*)
- Lifetime US travel (and where lived in the USA ever) (risk for endemic mycoses and other site-specific organisms like Lyme, RMSF, babesiosis, etc.)
- Exposure to farms/farm ANIMALS – *ever*? (risk for zoonoses)
- Exposure to waters (pools, oceans, lakes, hot tubs, **manicure/pedicure** baths) (risk for water bugs – nice Up to Date card on infections related to water exposure)
- Exposure to animals (household pets or unwanted creatures in the house like mice/bats) (risk for zoonoses)
- Occupation (?soil exposure with various fungi and mycobacteria)
- Hobbies such as gardening (fungi, mycobacteria, sporothrix are in soil)
- Hobbies such as hiking and drinking water on the trails (ex. risk for giardia)
- Hobbies such as hunting
- Exposure to jails (risk for TB)
- Exposure to [living, working, volunteering] homeless shelters (risk for TB)
- Known exposure to someone with known TB (risk for TB)
- Hx of skin test for TB (PPD)? When? Result?
- Raw food eater? (risk for various zoonoses and listeria and other things)
- Unpasteurized cheese/dairy (e.g., from family members across the border??) (ris for zoonoses)
- Any recent blood product transfusions? (Risk of transmitted pathogens)
- Hx of IVDU or other recreational drugs (risk for HIV, Hep C, candida, skin flora with IVDU; risk for aspergillosis pulmonary infection with marijuana; risk for various things with inhaled cocaine; etc.)
- *Brief* sexual history – prior hx of any STD? (may need to know more detailed hx prn: # partners past year, heterosexual?)

The social history

- I once saw a liver transplant patient intubated on ECMO.
  - **Animals**: The family has two *dogs*.
  - **Travel:** Prior to falling ill, he had just returned from an *overnight camping trip* in East Texas. During the trip he *shot, skinned and ate a deer*. There was *flash flooding* in the area and they camped out in the flooded out campground. Subsequently, he had gone to a cabin. There was moldy wood at the cabin, and the patient had been *chopping wood covered in mold* without wearing a mask.
  - He also *visited Belize* for 5 days in June, where he fished and swam at a resort but did not travel the countryside or eat unusual foods. He was bitten by mosquitoes and did not take malaria prophylaxis.
  - **Sick contacts**: His granddaughter, who he visits regularly, has *URI symptoms* being treated with amoxicillin. His wife had bronchitis and an oral herpes outbreak treated with antibiotics and acyclovir 2mo ago.
  - **TB exposure**: He was *incarcerated* for 7 years in the 1990s for making meth. His *wife is PPD+* but has never been treated for LTBI; his brother in law had spinal TB.

Elements unique to the lung transplantation workup

- Aggressive evaluation and treatment of sinus disease
- Aggressive evaluation and treatment of GERD
- Evaluation of colonizing bacterial, fungal, and mycobacterial pathogens

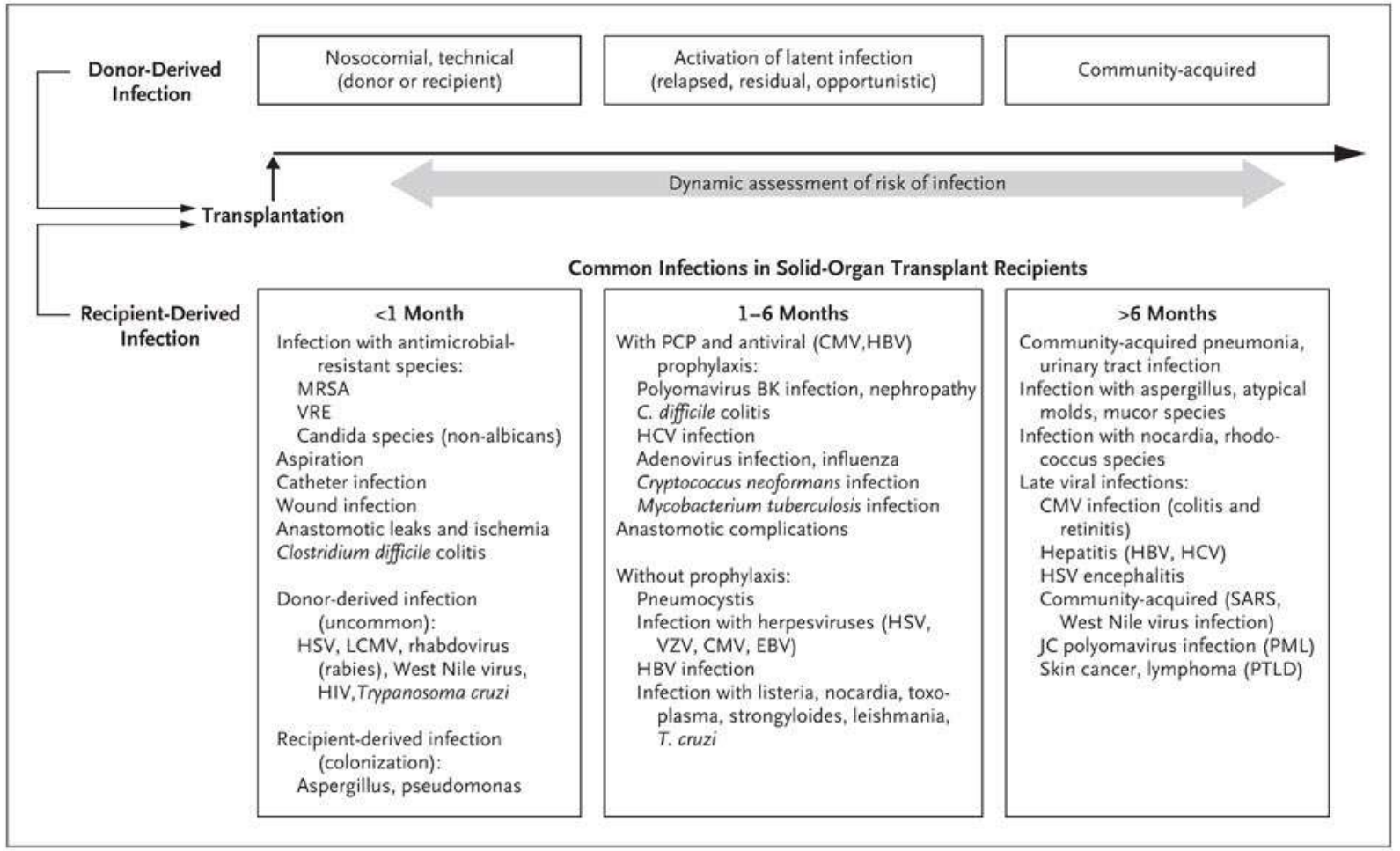
Am J Rhinol. 2008 Mar-Apr;22(2):192-6.
Curr Gastroenterol Rep. 2010 Jun;12(3):160-6

Infections after lung transplantation

- Infection is the primary cause of death after lung transplantation
  - Technical factors
  - Degree of immunosuppression

J Heart Lung Transplant. 2011 Oct;30(10):1104-22.

Infections after lung transplantation



N Engl J Med 2007;357:2601-2614

Prophylaxis

- Since donor lungs are nearly invariably colonized with pathogens at the time of transplant, donor bronchoscopy with the administration of a prolonged course of antibacterials tailored to bronchoscopic results is standard practice.
- Prophylaxis may also need to account for recipient colonization.
- Despite prophylaxis, rates of post-operative pneumonia are 10-20%.

Am J Transplant. 2006;6(1):178

Bacterial pneumonia

Table 1. Conditions predisposing for infections after lung transplantation.

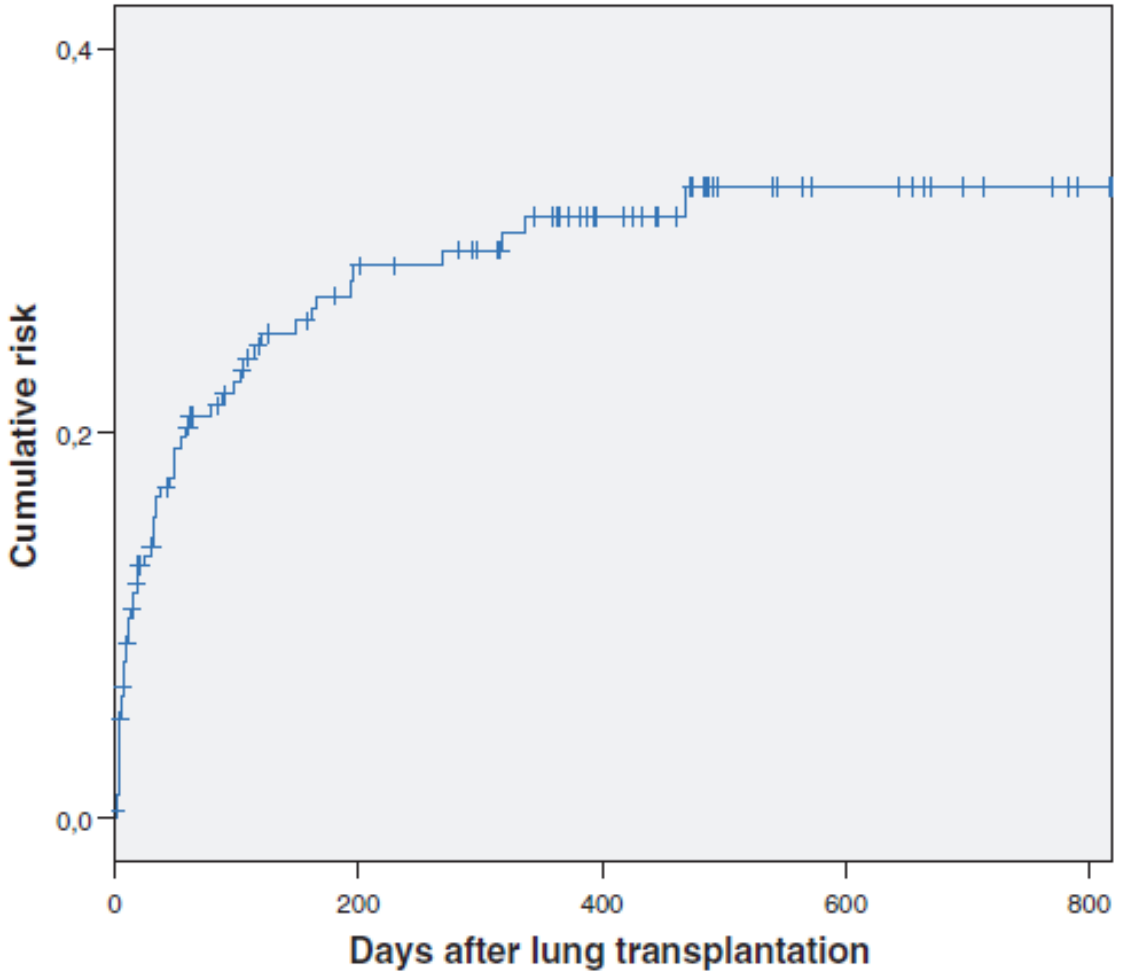
Lung allograft is continuously exposed to the external environment
Denervation of allograft:
Diminished cough reflex
Abnormal mucociliary clearance
Reactive hyperresponsiveness
Interrupted lymphatic drainage (especially during first weeks)
Anastomosis site:
May enhance colonization
Airway dehiscence and mediastinitis
Bronchial stenosis and postobstructive infection
Acute rejection episodes:
Require enhanced immunosuppression
Inflammatory response at port of entry of infections
Donor lung may transmit infections:
From prolonged mechanical ventilation
From previous inactive infections (tuberculosis, *Candida* and *Aspergillus* species, *Histoplasmosis, Coccimycosis*)
Native lung after single-lung transplantation:
Occult pretransplant infection (tuberculosis, *Aspergillus* species, *Pneumocystis carinii,* etc., especially after immunosuppression before transplantation)
Posttransplant infections in destroyed lung
Sinus infection in cystic fibrosis and ciliary dysfunction syndromes
Bronchiolitis obliterans:
Enhanced immunosuppression
Impaired clearance
Bronchiectasis

Clinical Infectious Diseases 2001; 33(Suppl 1):S58–65

Bacterial pneumonia

Table 1: Number and incidence of pneumonia episodes per 100 lung transplants, per month after transplant

Month	Number of episodes	Incidence (n° episodes per 100 lung transplant)
1	40	17
2	12	5
3	5	2
4	7	3
5	3	1,3
6	4	1,7
7	3	1,3
8	3	1,3
9	2	0,8
10	0	0
11	1	0,4
12	1	0,4
>12	4	1,7
Total	85	36



Am J Transplant. 2007 Aug;7(8):1989-96.

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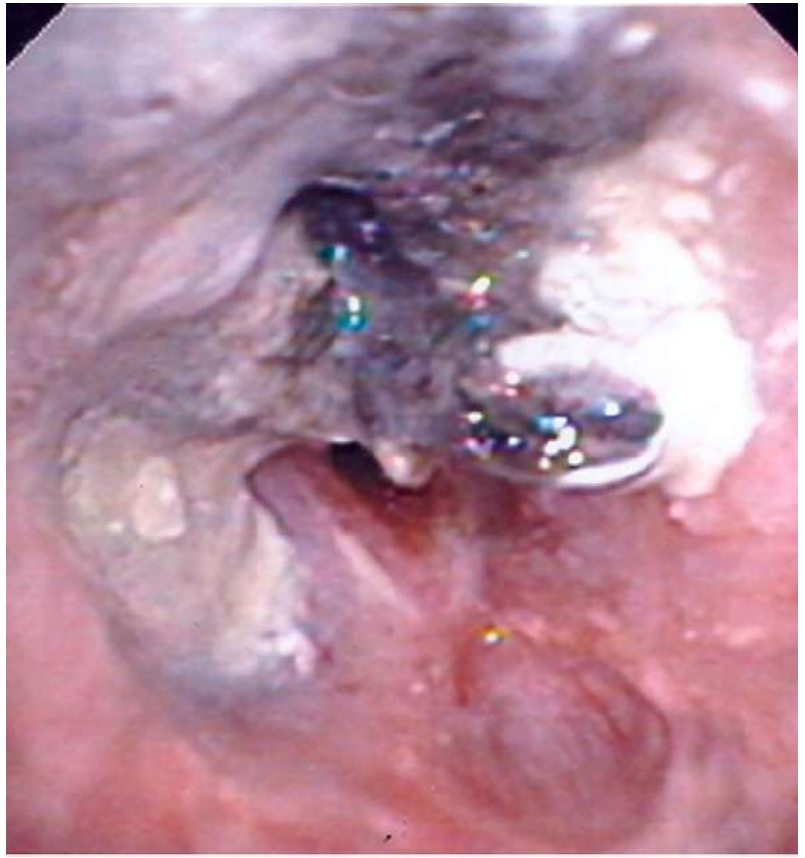
PJP

- High rates of this infection were described prior to the institution of universal prophylaxis.
- Incidence is much lower now as patients typically receive lifelong PJP prophylaxis.

Transplantation. 1992 Mar;53(3):586-9.

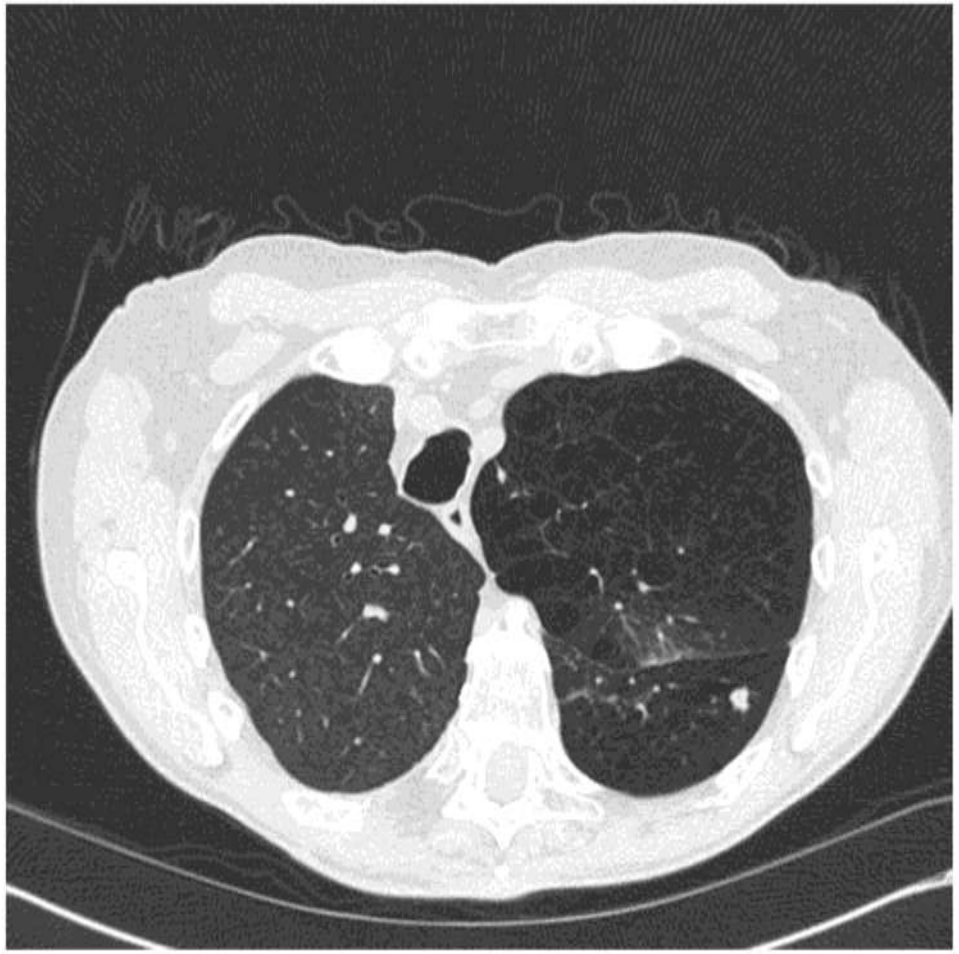
Aspergillus

- Colonization in 20-85% of patients
- Infection occurs in 3-15% of patients (frequently asymptomatically).
- A presentation unique to lung transplant patients is tracheobronchitis involving the anastomosis.



Clin Microbiol Rev. 2005;18(1):44.
Am J Transplant. 2011 Feb;11(2):361-6.
Eur J Cardiothorac Surg 1999; 16:54–8.
Proc Am Thorac Soc. 2009 Jan 15;6(1):79-93.

Aspergillus



Invasive aspergillosis typically affects the native lung.

Diagnosis is typically delayed.

Mortality is over 80% despite treatment.

Native lung pneumonectomy may be useful as a salvage measure.

J Heart Lung Transplant. 1999 Aug;18(8):810-3.
Am J Transplant. 2007 Aug;7(8):1989-96.
Clin Chest Med. 2017 Sep; 38(3): 511–520.

Aspergillus

- Prophylactic strategies: Universal prophylaxis with inhaled amphotericin and/or systemic azoles; pre-emptive therapy
- There is little evidence with which to state that one strategy is preferable to another.

Am J Transplant. 2011 Feb;11(2):361-6.
Curr Infect Dis Rep. 2013 Dec;15(6):514-25.

Aspergillus

	Arm 1	Arm 2	Arm 1	Arm 2	Arm 1	Arm 2	Both Arms	Arm 1	Arm 2
Reichenspurner, 1997 [20]&	Universal	None	AMB 5 mg tid titrated up to 20 mg tid within 5 days of surgery	N/A	Hospitalization period	N/A	1 year	3/126	12/101
Calvo, 1999 [21]	Universal	None	a. AMB -0.2 mg/kg q8h + b. Fluc 200 mg bid	N/A	Mean 42 days (30–92)	N/A	Post-operative period (?1 month)	0/52	2/13
Minari, 2002 [22]	Universal	None	a. AMB 5-10 mg bid + b. Itra 200 mg po NR[!]	N/A	a. Immediate post-transplant period + b. ?Lifelong	N/A	Arm 1 - 126 ty Arm 2 - 322 ty	4/81	16/88
Drew, 2004 [19]^	Universal	Universal	ABLC 100 mg - intubated pts, 50 mg - extubated pts, once daily x 4 days, then once weekly	AMB 50 mg - intubated pts, 25 mg - extubated pts, once daily x 4 days, then once weekly	7 weeks	7 weeks	2 months	1/ 51	1/49
Mattner, 2005 [40]	a. Universal b. Targeted*	Universal	a. Itra NR b. Vori 200 mg po bid	Itra NR	a. NR (likely post-operative period) b. 6 weeks	NR (likely post-operative period)	Peri-operative hospital stay	2/65	5/54
Husain, 2006 [24]	Universal	a. Universal b. Targeted@	Vori 6 mg/kg/dose iv x 2 then 200 mg po bid	a. Fluc 200 mg po qday b. Itra 200 mg po bid +/- AMB NR	4 months	a. 3 months b. 4-6 months	1 year	1/65	7/ 30
Lowry, 2007 [25]	? Universal	? Universal	L-AMB 5- 20 mg bid	AMB 2.5 -10 mg bid	Median 7 days (1–128)	Median 11 days (1–68)	Same as prophylaxis period	0/11∞	1/18∞
Cadena, 2009 [27]	Universal	Universal	a. AMB 10 mg bid + b. Vori 200 mg po bid	Itra 200 mg po bid	a. 2 weeks + b. 3 months	3 months	3 months	0/35	4/32
Monforte, 2010 [26]	Universal	Universal	L-AMB - 25 mg thrice weekly to 60 days, 25 mg once weekly 60-180 days, then 60 mg once every 2 weeks	AMB – 6 mg every 8 hours to day 120, then 6 mg once daily	Lifelong	Lifelong	1 year	3/104	4/49
Koo, 2012 [41]	a. Universal + b. Targeted DLT + c. Targeted$	Universal	a. AMB 25 mg bid/L-AMB 20 mg bid + b. Mica 100 mg iv qday + c. $	AMB 25 mg bid/L-AMB 20 mg bid	a. Hospitalization period + b. 7–10 days + c. 3–6 months	Hospitalization period	1 year	2/83	8/82
Tofte, 2012 [23]	Universal	None	Vori 200 mg po bid	N/A	3 months	N/A	40 months #	16/57	14/82

Curr Infect Dis Rep. 2013 Dec;15(6):514-25.

Mycobacterial infection

- Knoll *et al* examined the incidence of NTM lung infection after lung transplant.
- Sporadic isolation of NTM was common after lung transplant (22.4% of patients).
- Only two patients met criteria for pulmonary disease necessitating treatment (incidence 1.1/100 person-years; 95% CI 0.49–2.2). Four others developed surgical site infections with NTM.

Transpl Infect Dis 2012: 14: 452–460.

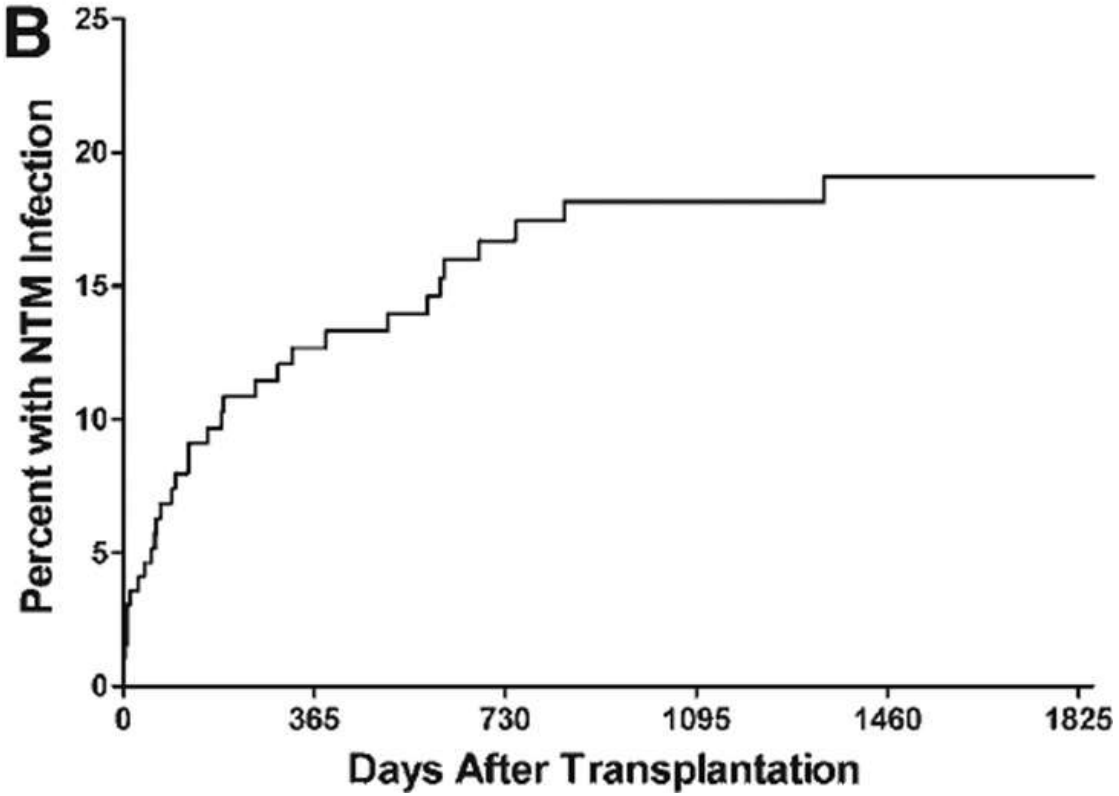
Mycobacterial infection

- Studies have conflicted as to the effect of NTM on outcomes after lung transplantation.
- One study by Chalermskulrat *et al* found that 5 of 20 colonized recipients with CF developed NTM disease post-transplant without effect on survival.

Transpl Infect Dis 2012: 14: 452–460.
Thorax. 2006 Jun;61(6):507-13.

Mycobacterial infection

- Huang *et al* at UCLA found a high rate of infection (colonization or disease) in their cohort.



J Heart Lung Transplant. 2011 Jul;30(7):790-8.

Mycobacterial infection

- In contrast with other studies, however, they found an impact on mortality and BOS.

Association of NTM and Mortality: Univariate and Multivariate Models

	Univariate models		Multivariate models[a]	
NTM variable type	HR (95% CI)	*p*	HR (95% CI)	*p*
NTM infection	2.61 (1.59–4.28)	0.001	2.18 (1.26–3.76)	0.005
NTM colonization	2.47 (1.42–4.31)	0.002	1.93 (1.03–3.62)	0.04
NTM disease	3.98 (1.69–9.37)	0.002	3.50 (1.46–8.38)	0.005

CI, confidence interval; HR, hazard ratio; NTM, non-tuberculous mycobacterium.

[a] Adjusted for single lung transplant (time-independent) and bronchiolitis obliterans syndrome (time-dependent).

J Heart Lung Transplant. 2011 Jul;30(7):790-8.

Mycobacterial infection

- Overall, the role of mycobacterial infection in outcomes after lung transplant remains an area of active investigation.

CMV pneumonitis

- Much higher risk in lung transplant patients in relation to the level of immunosuppression
- In D+/R- patients, in the absence of prophylaxis, over 90% of patients will develop CMV pneumonitis.
- CMV predisposes to rejection and to other opportunistic infections

Clinical Infectious Diseases 2001; 33(Suppl 1):S58–65

CMV prophylaxis post-transplant

- In general, options for post-transplant CMV management include pre-emptive therapy and prophylaxis.
- Standard prophylaxis is valganciclovir; some centers also utilize CMV-specific IVIG (Cytogam)

Am J Transplant. 2013;13 Suppl 4:93.

CMV prophylaxis post-transplant

- A multicenter randomized trial was published in 2010 comparing 3 months and 12 months of prophylaxis in patients after lung transplant.

Ann Intern Med. 2010;152(12):761.

CMV prophylaxis post-transplant

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Ann Intern Med. 2010;152(12):761.

CMV prophylaxis post-transplant

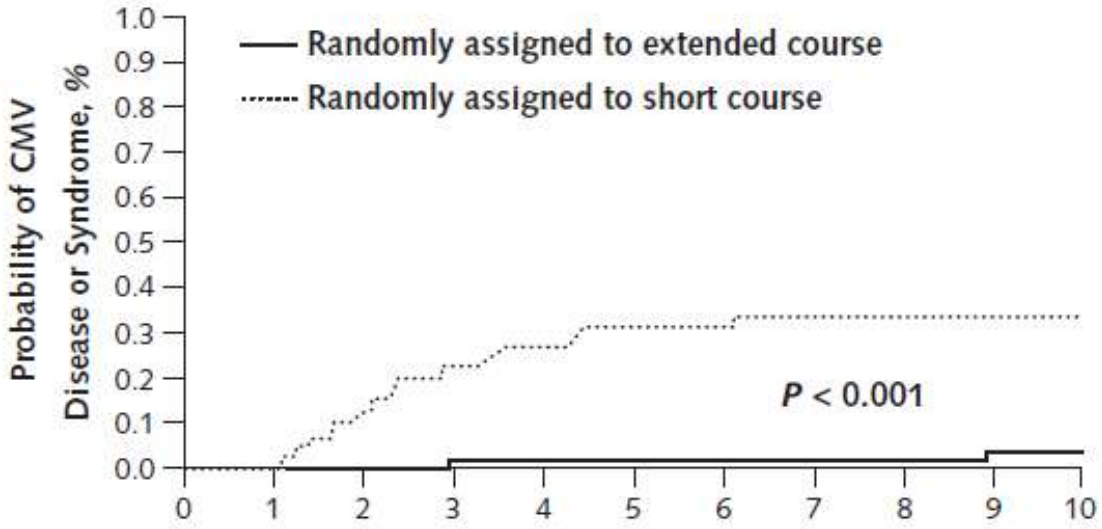
Table 2. Clinical Outcomes, by Treatment Group

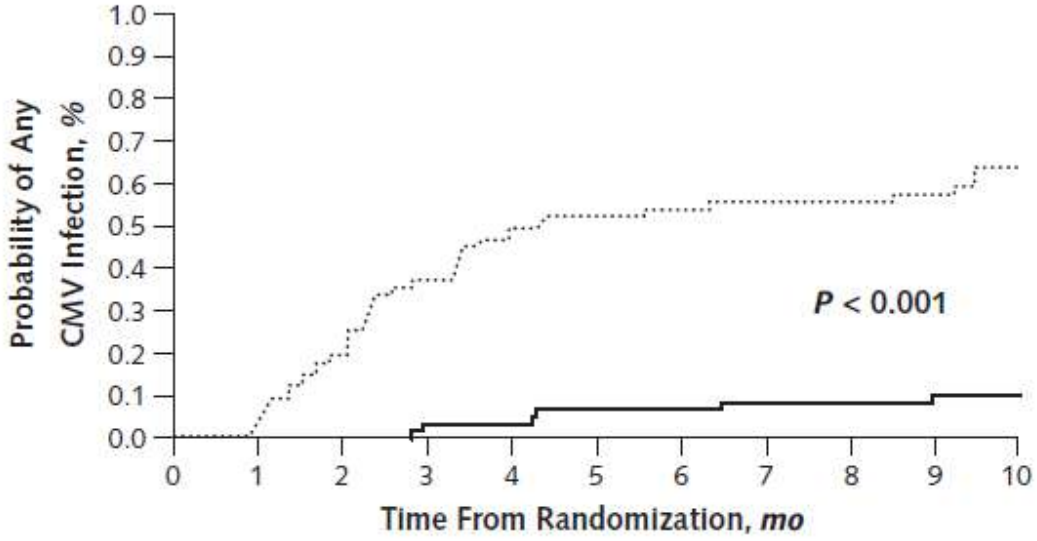
Variable	Short Course (n = 66)*	Extended Course (n = 70)*	P Value†
Rates for primary and secondary outcomes, by event			
CMV syndrome or disease	32.1 (20.1–44.1)	3.57 (0.0–8.5)	<0.001
Invasive disease	20.6 (10.1–31.0)	1.56 (0.0–4.6)	0.001
CMV syndrome	19.0 (8.9–29.2)	3.57 (0.0–8.5)	0.004
PCR at diagnosis, *copies/mL*‡	110 000 (40 000–361 569)	3200 (2700–3700)	0.009
Any CMV infection§	63.9 (49.9–77.9)	10.3 (2.5–18.2)	<0.001
Biopsy-proven acute rejection	32.7 (20.7–44.6)	21.2 (10.9–31.5)	0.09
Non-CMV infection	53.0 (39.6–66.5)	54.6 (38.9–70.9)	0.74

Ann Intern Med. 2010;152(12):761.

CMV prophylaxis post-transplant

Figure 2. **Primary study and secondary outcomes in randomized study cohort (intention-to-treat population).**





CMV = cytomegalovirus. **Top.** Probability of CMV disease or syndrome from randomization to 10 months (300 days) after randomization. **Bottom.** Probability of any CMV infection from randomization to 10 months (300 days) after randomization.

Ann Intern Med. 2010;152(12):761.

CMV prophylaxis post-transplant

	Hazard Ratio (95% CI)	*P* Value
Effect of extended-course treatment in Cox models for primary and secondary outcomes, by event‖		
CMV syndrome or disease¶	0.09 (0.021–0.39)	0.001
Any CMV infection¶	0.11 (0.047–0.29)	<0.001
Biopsy-proven acute rejection**	0.50 (0.24–1.03)	0.06
Non-CMV infection**	0.94 (0.563–1.56)	0.79
Death††	1.23 (0.274–5.476)	0.79

Ann Intern Med. 2010;152(12):761.

CMV prophylaxis post-transplant

- Based on the results of this study, guidelines strongly favor universal prophylaxis in lung transplant patients.
- Duration of prophylaxis:
  - D+/R-: Minimum 12 months
  - R+: 6-12 months

Am J Transplant. 2013;13 Suppl 4:93.

HSV pneumonitis

- Approximately 10% of patients developed HSV infections post-transplant prior to the institution of prophylaxis
- Diagnosis of HSV pneumonitis is by pathology or direct visualization of HSV vesicles during bronchoscopy
- Mortality is 20%.

Transplantation 1990; 49: 735–9.

Viral pneumonitis due to common respiratory viruses

- Viral infections are never just “a cold” in this population
- Up to 25% of infections may progress to viral pneumonitis

Transplantation. 2010 Apr 27;89(8):1028-33.

Viral pneumonitis due to common respiratory viruses

- One study applied respiratory PCRs to a cohort of patients undergoing surveillance bronchoscopy after lung transplant.

Transplantation. 2010 Apr 27;89(8):1028-33.

Viral pneumonitis due to common respiratory viruses

TABLE 2. Distribution of respiratory viruses in BAL samples in asymptomatic and symptomatic patients

	Virus present	Rhinovirus	Parainfluenza 1–4	Influenza A or B	hMPV	Coronavirus[a]	RSV-B
Asymptomatic, N=419, (%)	60 (14.3)[b]	37	12	0	4	8	2
Symptomatic, N=163, (%)	21 (12.9)	9	5	4	0	3	0
Total, N=582, (%)	81 (13.9)[b]	46	17	4	4	11	2

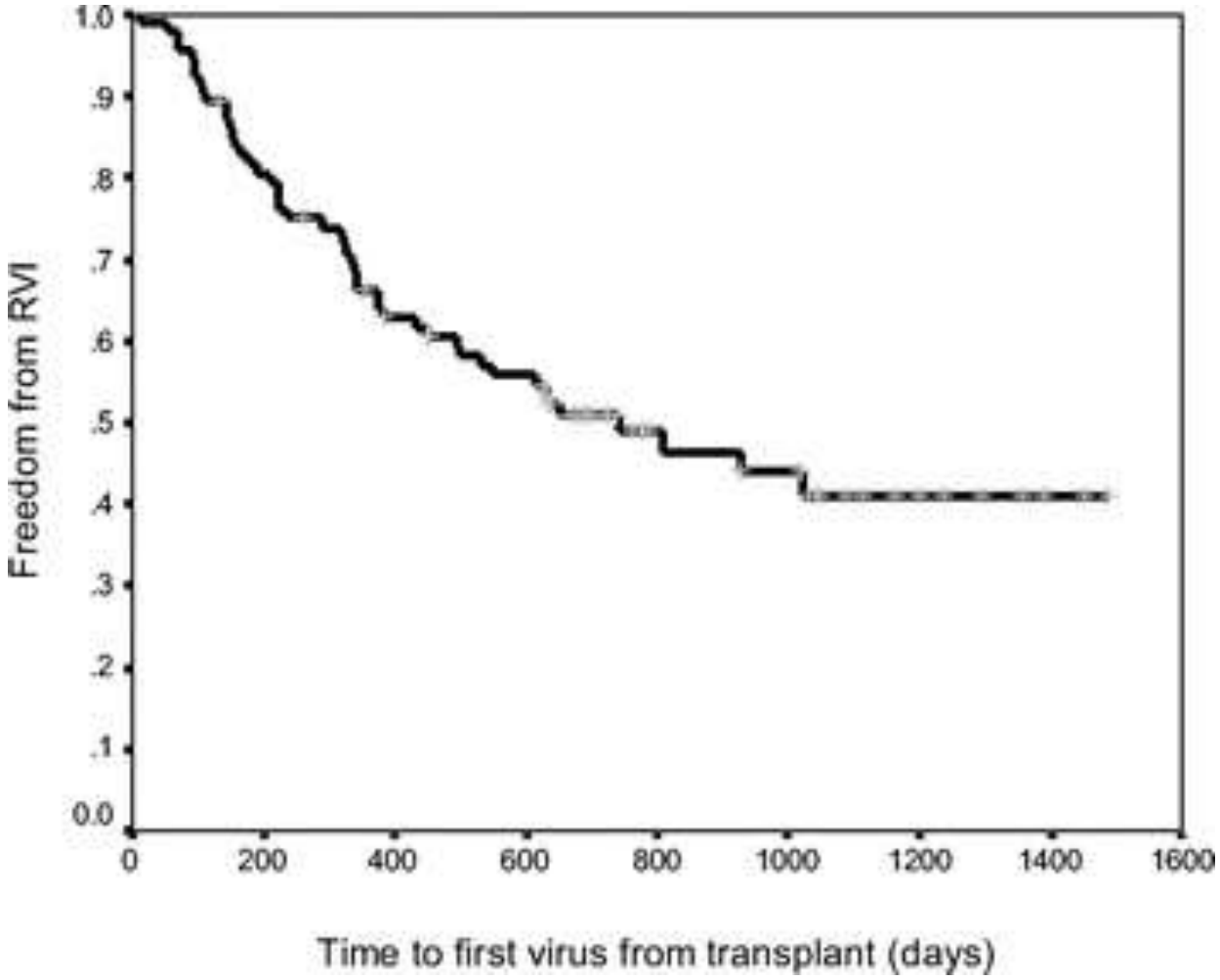
[a] Coronaviruses isolated in asymptomatic patients were 229E (n=4), OC43 (n=2), HKU1 (n=1), and NL63 (n=1); in symptomatic 229E (n=2) and NL63 (n=1).

[b] Coinfections with two viruses were present in three specimens where patients were asymptomatic. These were (i) rhinovirus or coronavirus 229E; (ii) parainfluen_a 3 or coronavirus 229E; and (iii) rhinovirus or parainfluen_a 4.

hMPV, human metapneumovirus; BAL, bronchoalveolar lavages; RSV, respiratory syncytial virus.

Transplantation. 2010 Apr 27;89(8):1028-33.

Viral pneumonitis due to common respiratory viruses



Transplantation. 2010 Apr 27;89(8):1028-33.

Viral pneumonitis due to common respiratory viruses

- Biopsy-proved grade 2 or worse rejection or decline in FEV1 of over 20% occurred in 16/48 pts with a viral respiratory infection, and 3/45 of patients without.
- The death rate was 7/16 in patients with and 2/32 of patients without a viral URI.
- A more detailed statistical analysis was not undertaken.

Transplantation. 2010 Apr 27;89(8):1028-33.

Viral pneumonitis due to common respiratory viruses

- Many centers will treat all respiratory viral infections with inhaled and/or systemic ribavirin and possibly with immune globulins or palivizumab.
- This is based on the above data on the negative effects of respiratory viruses and absolutely no efficacy data whatsoever.

Acute rejection

- Rejection and infection in this population are clinically indistinguishable. Accordingly, patients may receive empiric treatment for both pending results of bronchoscopy and transbronchial and transbronchial biopsy.

Bronchiolitis Obliterans Syndrome

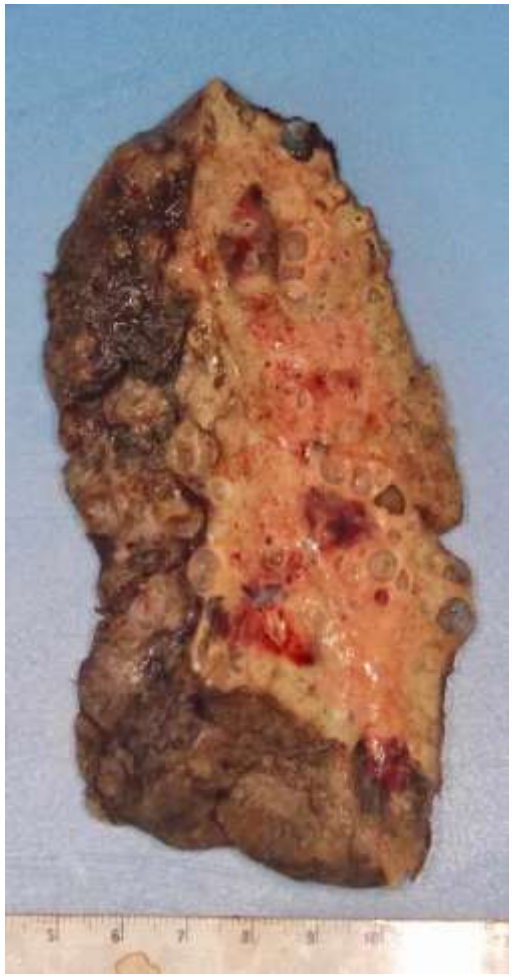
- Chronic rejection/BOS/Chronic Lung Allograft Dysfunction is the major non-infectious life-limiting long-term complication after lung transplantation
- Risk factors:
  - Acute rejection
  - Anti-HLA antibodies
  - **Pseudomonas colonization**
  - **Community-acquired respiratory viral infection**
  - **CMV pneumonitis**
  - GERD

Pulm Med. 2014; 2014: 621342
Clin Chest Med. 2011 Jun;32(2):311-26.

COVID and lung transplant

Table 1. Characteristics of Lung Transplant Recipients (continued)

Variable	Patients, No. (%)	
	COVID-19 (n = 30)	Non-COVID-19 (n = 72)
Pretransplant status		
Karnofsky Performance Status, median (IQR)[g]	30 (20-40)	50 (40-60)
Respiratory support		
Venovenous ECMO	17 (56.7)	1 (1.4)
Nasal cannula oxygen	7 (23.3)	65 (90.3)
Invasive mechanical ventilation	4 (13.3)	2 (2.8)
High-flow nasal cannula oxygen	2 (6.7)	3 (4.2)
Thrombotic events while receiving ECMO		
Deep vein thrombosis	6/17 (35.2)	0/1
Pulmonary embolism	0/17	0/1
Circuit thrombosis	0/17	0/1
Lung allocation score, median (IQR)[h]	85.8 (69.4-87.5)	46.7 (38.9-54.3)
Time on waitlist, median (IQR), d	11.5 (5.0-26)	15 (6.0-60)
COVID-19 vaccination prior to transplant	0	1 (3.3)



Northwestern Medicine

While good outcomes can be achieved by lung transplant in patients with COVID ARDS or COVID fibrosis, the perioperative and post-operative management poses a number of challenges.

JAMA. 2022 Jan 27;e220204.

COVID and lung transplant

Table 2. Intra- and Postoperative Features of Lung Transplant Recipients

Variable	Patients, No. (%) COVID-19 (n = 30)	Non-COVID-19 (n = 72)
Consent obtained from transplant recipients[a]	29 (96.7)	72 (100)
Intraoperative		
Operating time, median (IQR), h	8.5 (8-9.7)	7.4 (5.8-8.3)
Blood transfusion, median (IQR), units		
Red blood cell	6.5 (2-10)	0 (0-2)
Fresh frozen plasma	1 (0-5)	0 (0-0)
Platelet	0.5 (0-2)	0 (0-0)
Venoarterial ECMO use	29 (96.7)	45 (62.5)
Venoarterial ECMO time, median (IQR), h	3.1 (2.6-3.4)	2.5 (0-3.3)
Allograft ischemic time, median (IQR), h[b]	5.6 (5-6)	4.7 (3.9-5.5)
Postoperative		
Venovenous ECMO use	13 (30)	3 (4.1)
Venovenous ECMO duration, median (IQR), d	0 (0-4)	0 (0-0)
Acute kidney injury[c]	16 (53.3)	26 (36.1)
Dialysis	7 (23.3)	8 (11.1)
Temporary	3 (10.0)	4 (5.5)
Permanent	4 (13.3)	4 (5.5)
Primary graft dysfunction grade 1-3 within 72 h	21 (70.0)	15 (20.8)
Post-lung transplant ICU stay, median (IQR), d	18 (12-24.5)	9 (6-15)
Posttransplant ventilator use, median (IQR), d	6.5 (2-17)	2 (1-4)
Pleural drainage, d	19 (14.3-23.8)	11 (8.8-18.8)
Posttransplant hospital stay, median (IQR), d	28.5 (18.3-37.8)	16 (11-28.5)
Improvement in Karnofsky Performance Status, %[d]	84.8	11
Histological acute rejection during study period[e]	0	9 (12.5)
Creatinine level 1 mo after lung transplant, median (IQR)	0.9 (0.6-1.2)	0.9 (0.8-1.2)
Follow-up, median (IQR), d	351 (176-555)	488 (368-570)
No. of patients alive[f]	30 (100)	60 (83.3)

Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

[a] Medical power of attorney was used to obtain consent for lung transplant in 1 patient who was unable to provide consent.

[b] Allograft ischemic time is defined as time from termination of cardiac circulation in the donor to reperfusion of the allograft.

[c] Acute kidney injury is defined using the Risk, Failure, Loss of kidney function, and End-stage kidney disease classification as an increase in serum creatinine to 1.5 times baseline or higher or urine output less than 0.5 mL/kg/h for 6 hours or longer.

[d] Karnofsky Performance Status is assessed prior to and then at 30 days after lung transplant and the percentage improvement was calculated. The Karnofsky Performance Status score ranges from 0 to 100, with scores greater than 80 indicating normal; 50 to 70, unable to work and needs varying amounts of assistance; and less than 40, needs institutional or hospital care.

[e] Acute rejection was determined using bronchoscopic transbronchial biopsy and standard transplant rejection criteria on histology.

[f] As of November 15, 2021.

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COVID and lung transplant

	Covid-19 respiratory failure	Covid-19 acute respiratory distress syndrome	Covid-19 pulmonary fibrosis
	n = 183	**n = 118**	**n = 65**
Age (IQR)	52 (43 – 58)	51 (42 – 56)	56 (48 – 62)
Donor age (IQR)	33 (22 – 45)	31.5 (21 – 43)	35 (23 – 46)
Female gender (%)	38 (20.8)	25 (21.2)	13 (20)
Donor female gender (%)	70 (38.3)	41 (34.8)	29 (44.6)
Body mass index (IQR)	26.8 (24 – 30)	26.8 (24 – 30.2)	26.5 (24 – 29.4)
Patient location prior to transplant (%)			
Hospitalized in the intensive care unit	148 (80.9)	109 (92.4)	39 (60)
Hospitalized not in the intensive care unit	25 (13.7)	7 (5.9)	18 (27.7)
Not hospitalized	10 (5.5)	2 (1.7)	8 (12.3)
Lung allocation score (IQR)	87.5 (80.8 – 89.1)	88 (86.2 – 89.2)	85.3 (69.4 – 88.4)
Days on waitlist (IQR)	10 (5 – 22)	10 (5 – 20)	10 (6 – 26)
Diabetes (%)	51 (27.9)	27 (23.1)	24 (36.9)
Donor diabetes (%)	16 (8.7)	10 (8.5)	6 (9.2)
Donor hypertension (%)	45 (24.6)	33 (28)	12 (18.5)
Creatinine at offer/removal time	0.61 (0.48 – 0.84)	0.57 (0.44 – 0.77)	0.68 (0.53 – 0.9)

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Donor creatinine	0.92 (0.7 – 1.5)	0.9 (0.7 – 1.4)	1.1 (0.7 – 1.6)
History of cigarette use (%)	55 (30.1)	30 (25.4)	25 (38.5)
Donor history of tobacco use (%)	9 (4.9)	4 (3.4)	5 (7.7)
History of malignancy (%)	10 (5.5)	4 (3.4)	6 (9.2)
Donor history of malignancy (%)	4 (2.2)	4 (3.4)	0 (0)
Prior dialysis (%)	9 (4.9)	9 (7.6)	0 (0)
Pan-resistant bacterial lung infection at listing (%)	3 (1.7)	2 (1.7)	1 (1.5)
Prior cardiac surgery at time of listing (%)	4 (2.2)	0 (0)	4 (6.2)
Prior lung surgery between listing and transplant (%)	2 (1.1)	1 (0.85)	1 (1.5)
Tracheostomy (%)	72 (39.3)	55 (46.6)	17 (26.2)
On ventilator (%)	97 (53)	80 (67.8)	17 (26.2)
On inhaled nitric oxide (%)	10 (5.5)	8 (6.8)	2 (3.1)
Pre-transplant ECMO (%)	118 (64.5)	96 (81.4)	22 (33.9)

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COVID and lung transplant

	Covid-19 respiratory failure	Covid-19 acute respiratory distress syndrome	Covid-19 pulmonary fibrosis
	n = 183	n = 118	n = 65
Bilateral lung transplant (%)	171 (93.4)	117 (99.2)	54 (83.1)
Dual organ transplant (%)	7 (3.8)	6 (5.1)	1 (1.5)
30-day mortality (%)	4 (2.2)	2 (1.7)	2 (3.1)
90-day mortality (%)	6 (3.3)	4 (3.4)	2 (3.1)
3-month survival (95% CI)	95.6 (90.1 – 98.1)	95.3 (87.7 – 98.3)	96.8 (88 – 99.2)
6-month survival (95% CI)	92 (83.4 – 96.3)	93.3 (84.1 – 97.3)	89.7 (65.1 – 97.3)
Any acute rejection (%)	11 (6)	11 (9.3)	0 (0)
Primary graft dysfunction (%)	0 (0)	0 (0)	0 (0)
Dehiscence (%)	2 (1.1)	2 (1.7)	0 (0)
Stroke (%)	6 (3.3)	3 (2.5)	3 (4.6)
Ventilation > 48 hours (%)	143 (78.1)	98 (83.1)	45 (69.2)
Post-operative ECMO* (%)	8 (12.3)	3 (13.6)	5 (11.6)
New dialysis** (%)	24 (13.8)	16 (14.7)	8 (12.3)
Length of stay (days) IQR	26 (18 – 41)	33.5 (22 – 49.5)	17.5 (13 – 25)

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