Infections in Heart, Lung, and Heart-Lung Transplantation

2

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Historical Perspective

We have conceived the human heart as the main source of our deep emotions and feelings. A place where our very conscious resides as portrayed by Edgar Allan Poe in his famous *The Tell-Tale Heart* short story: "I felt that I must scream or die! And now—again!—hark! Louder! Louder! Louder! Louder!" Dr. John Gibbon Jr. used for the first time in 1953 a heart-lung respirator to keep a patient alive while performing heart surgery. Dr. Norman Shumway at Stanford developed and perfected the first surgical technique leading to heart transplantation surgery. After Dr. Christian Barnard's first orthotopic heart transplant in December 1967, and Dr. Shumway first heart transplant in the United States in January 1968, heart transplantation became a standard therapeutic option for life-threatening congestive failure and started to be performed in the hundreds over the next following years at different centers. Heart transplant surgery faced complications due in part to rejection and infection. However, the development of more selective immunosuppressive therapy and improvements in prevention, detection, and treatment of infections allowed for heart transplant surgery to increase rapidly worldwide.

Four thousand and ninety six heart (3529 adults) transplants were reported to the International Society of Heart and Lung Transplant Registry (ISHL) in 2011 [1]. The landscape of infection affecting heart transplant patients has been shaped by different factors: (A) implementation of more selective calcineurin-based immunosuppressive protocols, (B) lessened immunosuppressive induction regimens, (C) the institution of antimicrobial prophylaxis resulting in a significant decrease or delay in the emergence of major infections episodes including *P. jirovecii* (PCP), *Nocardia* spp., *Listeria spp.*, *Toxoplasma gondii*, cytomegalovirus, toxoplasmosis, cytomegalovirus (CMV), herpes simplex virus (CMV), varicella zoster virus (VZV), and invasive fungal infections, (D) introduction of novel diagnostic technology facilitating earlier recognition and treatment of infections, (E) expansion in the criteria to select donors and recipients to include various scenarios dealing with HBV, HCV, and HIV infections [2], and (F) shift toward predominantly Gram-positive bacterial infections and multiresistant bacteria in recent years [3–5].

A Stanford team lead by Dr. Bruce Reitz performed a Lung transplantation as a combined heart-lung transplant procedure in 1981 [6]. Shortly after, thoracic surgeons optimized the single- and double-lung transplant procedures. Improvement of surgical techniques, especially bronchial anastomosis and evolution of flush perfusion lung preservation, decreased the perioperative bronchial complications substantially. Similarly to heart transplantation, improvements in immunosuppressive regimens, antimicrobial prophylaxis, and graft preservation led to enhancement in survival among lung transplant recipients. In contrast to cardiac, lung transplantation has faced the challenge of infections unique to the transplant of this organ. Mold infections of the anastomotic site, host versus graft disease, and serious infections with *Mycobacterium abscessus*, *Chlamydia* spp., bronchiolitis, and *Burkholderia cepacia* complex are among infectious complications rarely observed in other transplant patients [7].

Transplantation of thoracic organs has improved the quality of life and prevented the death of thousands of

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individuals worldwide. Graft survival and life expectancy have been markedly improved in these patients due to the introduction of more optimal immunosuppression, antimicrobial prophylaxis, and diagnostic technology allowing the earlier diagnosis and treatment of infection and rejection. Finally, further control of infection is likely to result from implementation of new approaches to assess the net state of immunosuppression in these patients.

Epidemiology

Infection was recognized as a major threat to thoracic transplantation from the early inception days [8]. There are several factors predisposing thoracic transplant recipients to infections: (A) factors present before transplantation: age, presence of comorbidities (e.g., chronic kidney disease, diabetes mellitus, cancer, etc.), nutrition status, latent infections, colonization with healthcare-associated organisms, and occult community-acquired infections; (B) factors during the surgery: duration of the transplant procedure, graft injury including ischemic time, colonization or latent infection of the graft, surgical instrumentation (e.g., mechanical ventilation, invasive devices such as catheters, drains, Foley catheters, etc.), ICU stay, and need for re-interventions; and (C) factors present after transplant: degree of immunosuppression, CMV infection, and rejections (Table 2.1).

Table 2.1 Clinical features modifying infection risk in transplantation

Before transplantation
Age
Comorbidities: diabetes mellitus, chronic kidney disease, cancer, etc.
Nutrition status
Latent infections or occult community-acquired infections
Colonization with healthcare-associated organisms
During transplantation
Duration of the transplant procedure
Graft injury
Ischemic time
Anastomosis site in lung transplant
Denervation of allograft (e.g., diminished cough reflex)
Lymphatic drainage disruption
Colonization or latent infection of the graft
Surgical instrumentation (e.g., mechanical ventilation)
ICU stay
Need for re-interventions
After transplantation
Immunosuppression
CMV infection
Rejections

Heart Transplant Infections

A total of 4096 heart transplants were performed in 2011. Heart transplant recipients have an average age of 54 years and are predominantly man (76%). They have a significant history of smoking (46%) and hypertension (45%) and have cardiomyopathy (54%) followed by coronary artery disease (37%) as the leading causes of transplant [1]. The historical (pediatric and adult transplants between 1982 and 2011) 1-year, 5-year, and 10-year survival rates are 81%, 69%, and 50%, respectively. Overall median survival is 11 years, but it increases up to 13 years for those surviving the first year after transplantation. Although not associated with increased posttransplant mortality, infections before transplant can affect up to 25% of heart transplant candidates. Being bronchitis and soft tissue infections, the more commonly present [9]. Despite no major changes in the distribution of causes of death since 1994, infections remained a predominant factor of mortality during the first 3 years after transplant. It contributes with up to almost 20% of causes of death [3]. The global incidence of infections in heart transplant ranges between 30% and 60% and the associated mortality between 4% and 15% [10]. The incidence of infection measured as major infectious episodes per patient has steadily declined from 2.83 in the early 1970s to 0.81 in the early 2000s [3, 8, 11]. The most frequent type of infection is bacterial (44%), followed by viral (42%), fungal including *Pneumocystis jirovecii* (14%), and protozoa (0.6%). Unfavorable functional outcomes are observed in patients who developed infections in the first year of transplant, mainly associated with bloodstream, CMV, and lung infections [12]. Pulmonary and central nervous system (CNS) infections are independent predictors of mortality among heart transplant recipients. Reactivation of latent parasitic infections residing in extra-cardiac tissues in the host or transmitted in the transplanted heart is an important consideration. The classic example is the reactivation of *Trypanosoma cruzi*. Chagas disease is a vector-borne illness transmitted by triatomine bugs, and it is endemic in Latin America. The ethnicity or origin of either the donor or the recipient from these regions should raise the concern for possible reactivation. Chagas reactivation was documented in 38.8% of cases in a cohort of Brazilian heart transplant recipients, where Chagas cardiomyopathy was the second most common indication for transplant (34.9%) [13]. Chagas can also reactivate from the transplanted heart procured from a seropositive donor and transplanted into a seronegative recipient. Although with a substantial decreased on its prevalence in the most recent eras, toxoplasmosis is another important consideration in this setting. Similarly to Chagas, *Toxoplasma gondii*—also

with a predilection to invade the myocardium—can be transmitted by reactivation of quiescent cysts in the recipient or the transplanted heart [14].

Lung and Heart-Lung Transplant Infections

By 2011, 3640 adults received lung transplantation, the highest reported number of procedures up to that date, driven mainly by the increase of double-lung transplants. Double-lung transplant is indicated for septic lung diseases (e.g., cystic fibrosis). Around 66% of recipients were aged 45–65 years old. The most frequent indications for transplant were COPD (34%), followed by interstitial lung disease (ILD) (24%), bronchiectasis associated with cystic fibrosis (CF) (17%), and α1AT deficiency-related COPD (6%) [15]. The overall (from 1994 to 2011) 1-year, 5-year, and 10-year survival rates among lung recipients are 79%, 53%, and 31%, respectively. Overall median survival is 5.6 years. Lung transplants from CMV seronegative donors have better survival rates than from CMV seropositive donor. Thirty-day mortality was led by graft failure (24.7%) and non-CMV infections (19.6%). During the remainder of the year, non-CMV infections were the leading cause of death (35.6%). Infection is still prominent as the cause of death following the first year of transplant after bronchiolitis obliterans syndrome (BOS)/chronic lung rejection or graft failure [15]. Other infections complications historically present among the ten primary causes of death within the first year include sepsis, pneumonia, and fungal infections [16]. High lung allocation score (LAS) at the time of transplantation is associated with a lower 1-year survival and higher rates of infections among lung transplant recipients [17].

Sixty-three adult Heart-Lung transplantations were reported to the ISHL registry in 2011. Sixty-six percent of recipients were in the group range from 18 to 49 years old. Sixty-three percent of the indications were for congenital heart disease and idiopathic pulmonary arterial hypertension. Heart-lung transplant for CF was higher in Europe and other centers compared to North American. When compared to lung only transplants, short-term survival was worse, but long-term survival was better for the heart-lung transplant recipients. Their 1-year, 5-year, and 10-year survival rates were 63%, 44%, and 31%, respectively. The median survival was 3.3 years and 10 years for those surviving the first year. Similarly, they have graft failure (27%), technical complications (21.9%), and non-CMV infections (17.8%) as leading causes of death during the first 30 days posttransplant. Non-CMV infections (35.1%) were the top cause of death after 1 month and within 1 year of transplant. After the first year, BOS/late graft failure and non-CMV infections were the predominant causes of death [15].

Among other risk factors for mortality in lung transplantation are cystic fibrosis, nosocomial infections, and mechanical ventilation before transplant [18].

Infections in lung transplant recipients are predominantly bacterial (48%), viral (35%), fungal (13%), and mycobacterial (4%) [19]. In 60%, the infection site is pulmonary. Risk factors for infection vary by the type of organism. Mechanical ventilation (MV) for >5 days immediately following transplant surgery and isolation of *Staphylococcus aureus* (SA) from airway cultures in the recipient were considered risk factors for invasive SA infections in a retrospective study of patients with lung and heart-lung transplants [20]. Likewise, risk factors for the development of healthcare-associated infections with Gram-negative organisms, *Aspergillus*, *Legionella*, and MRSA (methicillin-resistant *Staphylococcus aureus*), include prolonging MV, renal failure, use of ATG (antithymocyte globulin), and recurrent rejections episodes [21]. Additionally, α-1-antitrypsin deficiency and repeat transplantation are also risk factors for nosocomial infections. *Mycobacterium tuberculosis* transmission from lung donors with latent infection has been documented in highly endemic areas [22]. Colonization with MDR organisms (*Pseudomonas aeruginosa*, *Burkholderia*, *Acinetobacter*, nontuberculous mycobacteria (NTM), and *Scedosporium*) before transplant—especially important in CF patients—can predict the development of challenging infections to treat after transplant [23].

Pretransplant Evaluation of Recipients and Donors

Pretransplant Screening of Recipients

Patients should undergo a comprehensive evaluation of potential infectious complications associated with transplantation. A detailed medical history including previous vaccinations, history of past infections, exposures (geographical, occupational, animal, etc.), travel, and foreign-born status among others should be obtained.

Clinicians shuold perform routine serologies for the detection of pathogen-specific IgG for CMV, HSV, EBV (VCA), VZV, hepatitis B (HBsAg, HBsAb, HBcAb), HIV, hepatitis C, and syphilis. Toxoplasma IgG should also be performed in heart and heart-lung transplant candidates. Additionally, we recommend to obtain UA, urine culture, CXR, and tuberculin skin test (TST), or a Quantiferon assay. In lung and heart-lung transplant candidates, sputum should be cultured for bacterial, fungal, and AFB studies.

Some centers advocate the screening of patients for colonization with MDR (multidrug resistant) bacteria such as MRSA and VRE (vancomycin resistant *Enterococci*),

which it may have an impact on the type of antibacterial prophylaxis used preoperatively or the empirical antibiotics should sepsis develop in the immediate postoperative period. In potential lung recipients, previous respiratory colonization with MDR *Pseudomonas*, especially in CF patients, should not exclude them from transplant [24]. On the other hand, if colonization with *B. cenocepacia* (genomovar III) in CF is present transplant is relatively contraindicated [25, 26].

Checking for endemic fungi such as *Coccidioides immitis* or for the parasites *Trypanosoma cruzi*, *Strongyloides stercoralis*, and *Leishmania* spp. is indicated in the presence of the appropriate risk factors [27–31].

Histoplasma capsulatum has reactivated during immunosuppressive therapy [32]. Infections after solid organ transplantation (SOT) are rare and attributable to transmission from the donor [33]. Furthermore, latent histoplasmosis can be present with negative serologies and treatment after transplant carries a good outcome. Therefore the role of screening for histoplasmosis is of questionable significance [34].

Pretransplant Screening of Donors

The type of evaluation may change if the donor is alive or deceased depending on the available time to collect the samples. Similarly to recipients, donors should undertake a comprehensive assessment including a complete history, assessment of risk factors, exposures, immunizations, and previous or current infections. Donors should be screened for HIV, hepatitis B/C, syphilis, and tuberculosis. Furthermore, we recommend to obtain serologies for CMV, EBV, HSV, VZV, and *Toxoplasma gondii*, and for HTLV-1/HTLV-2 in endemic areas. In high-risk donors, the use of nucleic acid amplification tests (NAAT) for HBV, HCV, and HIV should be considered. Additionally, blood cultures to document an occult bacteremia are recommended. In lung transplant donors, we recommend obtaining respiratory cultures through bronchoscopy to detect colonizing organisms and target them to prevent invasive infections in the donor. Culturing the media of the allograft during acquisition or processing have been advocated to reduce the risk of mycotic aneurysms among kidney transplant recipients, which may apply to other SOT [35]. Screening of donors for endemic mycosis is not well established. On the other hand, heart transplant donors should be screened for Chagas if the donor was born in Latin America [29]. Finally, it is important to highlight the increase recognition of emerging, unusual viral infections such as West Nile virus, lymphocytic choriomeningitis virus, rabies, and different human coronaviruses [34, 36]. Testing for those organisms should be done based on individual assessments. Table 2.2 describes and summarizes the diagnostic workup recommend among donors and recipients.

Table 2.2 Infectious screening during transplantation

Diagnostic workup among donors and recipients
Routine tests obtained among donors and recipients:
Viral test: HIV Elisa, hepatitis C antibody, HBV (HBsAg, HBcAb total, HBsAb), IgG antibody for CMV, HSV, EBV VCA, VZV
Bacterial: Treponemal antibody (e.g., EIAs, FTA-ABS), QFN assay or PPD
Parasite: Toxoplasmosis IgG (routinely indicated for heart transplant patients)
Other screening to consider among donors or recipients in the presence of specific risk factors:
Viral: NAAT for HIV, HCV, HBV in high-risk donors. HTLV-1/HTLV-2 in donors from endemic areas

Bacterial:
    Recipients: UA, urine culture, CXR, and sputum culture.
Optional: To consider screen for colonization with MDR organisms (MRSA or VRE)
    Donors: Blood cultures, allograft media culture, and bronchoscopy with culture from respiratory specimens in lung donors

Parasite: Ortho EIA and Abbott Prism Chagas test to screen for *Trypanosoma cruzi* in donors or recipients from Latin America. *Strongyloides stercoralis* and *Leishmania* spp. serologies should be obtained in recipients in the presence of appropriate geographic risk factors
Fungal: EIA for coccidioidal antibodies or complement fixing antibodies for cocci

Abbreviations: NAAT Nucleic acid amplification test, *CXR* chest X-ray, *MDR* multidrug resistant, *EIA* enzyme-linked immunosorbent assay

Prevention of Infections

Immunizations

Immunization should be optimized before transplantation since the recipient will have better chances to mount an adequate immune response [37]. The advisory committee on immunization practices (ACIP) [38] and the guidelines for immunizations in solid organ transplantation [39] recommend inactivated influenza vaccine annually. Tetanus, diphtheria, and acellular pertussis (Tdap) should be administered to all adults who have not previously received Tdap or have an unknown status. Varicella vaccination with two doses in patients without evidence of immunity or a single dose of zoster vaccination, inactivated polio vaccine, hepatitis A/B, HPV (three series through 26 years of age), and meningococcal and pneumococcal vaccines should be administered [38]. It is remarkably important to vaccinate all household members as well. BCG and rabies vaccines can be considered under some extenuating or exposure-related indications. See Table 2.3.

Avoidance of Exposures

Education of the patient and the family members is a cornerstone to establishing effective preventive measures. Emphasis should be enforced about hand hygiene and food handling.

Table 2.3 Immunizations recommendations during transplantation

Recommended vaccines among heart, lung, and heart-lung recipients
Annual inactivated influenza vaccine
Tdap (should be administered to all adults who have not previously received Tdap or have an unknown status)
VZV (two series) in patients without evidence of immunity
Zoster vaccine should be given in varicella-positive candidates age ≥60 years and considered in candidates aged 50–59 (>4 weeks before transplant)
Inactivated polio
Hepatitis A series
Hepatitis B series
HPV (three series through 26 years of age)
Pneumococcal: Pneumococcal conjugate 13-valent (PCV13) followed by pneumococcal polysaccharide 23 (PPSV23) vaccine 8 weeks later (If PPSV23 was received first; PCV13 should be given at least 1 year after)
Meningococcal conjugate vaccine
Under special circumstances: Rabies and BCG

Additionally, potential sources of bacteria, fungi (e.g., *Aspergillus*), and toxoplasmosis such as plants and flowers, cleaning pet's litter or cages, eating uncooked meat, acquiring new pets, construction areas, farming, barnyard activities, and smoking marihuana should be avoided. If those recreational or occupational exposures are unavoidable; appropriate gear, such gloves, must be worn. Education about possible community exposures is also important. Close contacts with persons with fevers or rash potentially infected with VZV, herpes zoster, or influenza should be circumvented as well. Patients should cook all meals thoroughly, wash all fruits and vegetables, and shun all unpasteurized products. Safe sex practices are recommended. If any foreign travel is planned, seeking evaluation in a specialized travel clinic is advisable.

Prophylaxis

Guidelines for the management of surgical antimicrobial prophylaxis list cefazolin (2 g, 3 g for patients with weight >120 Kg every 4 h) as the recommended regimen for heart, lung, and heart-lung transplantation surgery. Clindamycin (900 mg every 6 h) or vancomycin (15 mg/kg) can be substituted as alternative agents in beta-lactam allergic patients [40, 41]. This recommendation can be adjusted individually, based on local hospital surveillance data or previous knowledge of colonizing organisms (e.g., addition of aztreonam, gentamicin, or a single-quinolone dose). However, the widespread use of quinolones may increase the resurgence of antimicrobial resistance. The antibiotic should be administered within 60 min before surgical incision (within 120 min for vancomycin or quinolones) and to be continued for 24–48 h in heart transplants and 48–72 h and no longer than 7 days in lung and heart-lung transplant recipients. Recommendation to continue antibacterial prophylaxis until chest and mediastinal tubes are removed lacks sufficient evidence. Redosing will depend on the procedure duration and associated blood loss.

The recipient does not need treatment if a localized infection was present in the donor, except during meningitis where concomitant bacteremia often coexist. In meningitis and bacteremia, it is prudent to treat the recipient for 2–4 weeks [34].

Indications for antifungal prophylaxis in heart transplant recipients are not clear. A systemic review showed no benefit of antifungal therapy to prevent invasive fungal infections in transplants recipients other than liver [42]. Although a prospective cohort of heart transplant recipients showed targeted prophylaxis—an echinocandin for a median of 30 days with the presence of at least one risk factor for invasive aspergillosis (IA) (reoperation, cytomegalovirus disease, posttransplantation hemodialysis, and another patient with IA in the program 2 months before or after the procedure)—was highly effective and safe in preventing IA episodes [43], no consensus exists for universal antifungal prophylaxis in heart transplant recipients. Most centers have adopted antifungal prophylaxis including inhaled amphotericin B, oral itraconazole, or IV targeted echinocandin prophylaxis.

In lung and lung-heart transplant recipients, fungal prophylaxis should be considered, especially if pretransplantation respiratory cultures either from the donor lung or recipient airways shows *Aspergillus* or *Candida*. One approach is to use inhaled amphotericin B (50 or 100 mg in extubated or intubated patients, respectively) daily until 4 days after transplant and then weekly until hospital discharge in patients with no known colonization [44, 45]. If a mold has been isolated, voriconazole is recommended up to 4 months after transplant. Although evidence and efficacy need to be confirmed, combination antifungal prophylaxis therapies is used at some centers [46].

Pneumocystis jiroveci prophylaxis is done with trimethoprim-sulfamethoxazole (TMP-SMX) for 6 months, up to 1 year. Some centers extend the PJP prophylaxis to lifelong. TMP-SMX also confers protection against *Toxoplasma*, *Nocardia*, and *Listeria* species infections. Alternatively, dapsone, inhaled pentamidine, or atovaquone can be used in patients with a history of sulfa allergy. TMP-SMX is recommended at many centers for lifelong in toxoplasmosis seronegative recipients of seropositive cardiac donors (*Toxoplasma* D+/R−) [11].

CMV prevention is recommended to all D+/R− and R+ patients. There are two common strategies for CMV prevention: antiviral prophylaxis and preemptive therapy. Both approaches possess similar success rate and their advantages and disadvantages [47]. Guidelines recommend valganciclovir or intravenous ganciclovir as the preferred antivirals. Oral ganciclovir is an option in heart transplant patients, although it possesses a low oral bioavailability and therefore the theoretical risk of increased resistance. Often, CMV immune globulin is used as an adjunctive agent. In heart recipients, prophylaxis is recommended for 3–6 months in D+/R− and 3 months in R+. In lung and heart-lung recipients, the duration of prophylaxis is 12 months and 6–12 months in D+/R− and R+ recipients, respectively [48]. In D−/R− patients, otherwise not receiving CMV active

agents, antiviral prophylaxis against other herpes viruses, such as HSV and VZV, should be considered. Use of oral CMX001 (oral liposomal formulation of cidofovir) in hematopoietic-cell transplants reduced CMV-related events and may have a potential role in preventing CMV in other transplant settings [49]. Refer to Table 2.4 for a list of prophylaxis recommendations.

Table 2.4 Antimicrobial prophylaxis

Prophylaxis in heart, lung, and heart-lung transplant
Bacterial[a]:
Preferred: Cefazolin 2 g (3 g for patients with weight >120 Kg). Redose every 4 h for extended procedure time and significant blood loss
Alternative: Vancomycin 15 mg/kg or clindamycin, 900 mg IV
CMV prophylaxis[b]:
Valganciclovir, 900 mg PO once daily
IV ganciclovir, 5 mg/kg IV once daily
Oral ganciclovir (heart transplant), 1 gr PO three times a day
Consider adjuvant therapy with CMV immune globulin
Pneumocystis jiroveci:
TMP-SMX, one single tablet a day or one double-strength tablet three to seven times a week for 6–12 months
Alternatively, dapsone (100 mg PO daily); inhaled pentamidine (300 mg/dose monthly) or atovaquone (1500 mg PO once daily) can be used
Other: In D−/R− patients, otherwise not receiving CMV prophylaxis, consider acyclovir to prevent HSV/VZV reactivation
Prophylaxis in heart transplants
Parasitic:
Consider lifelong TMP-SMX in toxoplasmosis mismatch recipients (D+/R−)
CMV prophylaxis:
Doses as above. Duration: 3–6 months in D+/R− and 3 months in R+ recipients
Fungal (optional):
IV echinocandin daily for 30 days in the presence of IA risk factors
Prophylaxis in lung and heart-lung transplants
Bacterial:
Consider the addition of aztreonam, gentamycin, or a single-quinolone dose in the presence of previous respiratory cultures positive for Gram negatives
CMV prophylaxis[b]:
Doses as above. Duration: 12 months in D+/R− and 6–12 months in R+ recipients
Fungal:
Negative pretransplant respiratory cultures: Inhaled *amphotericin B*, 50 or 100 mg in extubated or intubated patients, respectively, daily until 4 days after transplant and then weekly until hospital discharge
Positive pretransplant respiratory cultures for *Aspergillus*: *voriconazole*, 6 mg/kg every 12 h for 2 doses; followed by maintenance dose of 4 mg/kg every 12 h, is recommended up to 4 months after transplant. Maintenance dose can be achieved with oral voriconazole 200 mg PO every 12 h

Abbreviation: IA Invasive aspergillosis

[a]The antibiotic should be administered within 60 min before surgical incision (within 120 min for vancomycin or quinolones) and to be continued for 24–48 h in heart transplants and 48–72 h and no longer than 7 days in lung and heart-lung transplant recipients

[b]Doses of valganciclovir, ganciclovir, and other antibiotics may require adjustment for renal function

Risk of Infection Posttransplantation

<1 Month

This period is characterized more commonly for nosocomial, bacterial infections. Thus, the bacterial organisms present are often MDR (e.g., VRE, MRSA). In heart transplant recipients, skin and soft tissue infections (SSTI), surgical site infection, and mediastinitis are of concern during this period. Likewise, lung and lung-heart transplant recipients may develop infections related to previous respiratory colonization (*Pseudomonas, Aspergillus*). Other significant infections include aspiration pneumonitis, healthcare- and ventilator-associated pneumonia, catheter-related bloodstream infections (CRBSI), nosocomial UTIs, and *Clostridium difficile* colitis. Donor-derived infections during this period can be present and will include HSV, lymphocytic choriomeningitis virus (LCMV), rhabdovirus (rabies), West Nile virus (WNV), and HIV. *Toxoplasma gondii* and *Trypanosoma cruzi* are also serious donor-derived infections in heart transplant recipients that can develop within the first 6 months posttransplantation [50].

1–6 Months

During this period, reactivation of latent infections usually occurs. Hence, bacterial infections such as those caused by *Nocardia asteroides*, *Listeria monocytogenes*, and *Mycobacteria tuberculosis* typically occur. Additionally, fungal infections by *Aspergillus* spp., *Cryptococcus neoformans*, and *P. jiroveci* and parasitic by *Toxoplasma gondii*, *Leishmania* spp., *Strongyloides*, and *Trypanosoma cruzi* can also be seen. Viral infections present during this period include herpesviruses (HSV, VZV, CMV, and EBV) and adenovirus.

>6 Months

Development of infections after 6 months are predominantly community-acquired pneumonia and urinary tract infections. Other diseases include *Aspergillus* and *Mucor* species, *Nocardia*, *Rhodococcus*, and late viral infections including CMV, hepatitis B and C, JC polyomavirus infection, post-transplant lymphoproliferative disorder (PTLD), HSV encephalitis, and viral community-acquired infections (e.g., coronavirus, West Nile virus, influenza).

Monitoring

Infections

It is important to recognize transplant recipients as a patient population with increased susceptibility to infections and

have a low threshold to perform diagnostic workup in the presence of any concerning signs or symptoms. Infections monitoring is also done in a structured way when preemptive therapy for CMV is in place (as opposed to universal prophylaxis). Protocols vary by the transplant center but, usually, implies a weekly CMV PCR or pp65 Ag monitoring [51]. Likewise, monitoring of cell-mediated immunity (CMI) using a Quantiferon-CMV assay may be useful predicting late-onset CMV disease once CMV prophylaxis has been stopped [52]. CMI also have been monitored for EBV using an enzyme-linked immunoSpot assay [53].

Immunoglobulin G (IgG), C3, IgG2 levels, and NK cell counts have been proposed as an attempt to identify the risk of infection in heart transplant recipients within the first year [54].

Drug-Drug Interactions

Significant drug-drug interactions exist among antimicrobial and immunosuppressive agents. Patient medication list should be reviewed carefully. CTP3A4 strong inducers such as nafcillin reduce tacrolimus serum concentrations. In contrast, azoles such as fluconazole can result in increased levels of tacrolimus or cyclosporine. For voriconazole, the dose of tacrolimus needs to be reduced by two-thirds [55] and the cyclosporine dose by 50% [56]. Rifamycins can have an opposite drug-drug interaction by decreasing the concentrations of prednisone, cyclosporine, tacrolimus, sirolimus, and mycophenolate mofetil (MMF) [57, 58]. Likewise, tacrolimus administration along with quinolones may cause QT prolongation [59].

Infections in Heart Transplantation

Infecting Microbial Agents

Bacterial

In heart transplant patients, bacterial infections have similar clinical manifestations commonly observed in other patient populations. However, clinical signs may be subtle or absent (e.g., afebrile). They are the most frequent type of infections in this setting, reaching up to 50% of all infections [3]. The most common are pulmonary infections followed by bacteremias, mediastinal, and skin infections. *Staphylococcus aureus*—predominantly methicillin-resistant—can cause SSTI, ventilator-associated pneumonia, mediastinitis, CRBSI, other forms of bacteremia, and osteomyelitis. In contrast, coagulase-negative *Staphylococcus* is more commonly associated with CRBSI. Among Gram-negative bacteria, *Pseudomonas aeruginosa* is common, usually of pulmonary origin. *Escherichia coli* is the primary causal organism of UTIs. Extended-spectrum β-lactamase (ESBL)-producing *Klebsiella pneumoniae*, *Escherichia coli*,

Klebsiella oxytoca, and *Citrobacter freundii* are also found in 2.2% of heart transplant recipients [60].

Nocardia species are well recognized as an opportunistic pathogen in this setting. Although relatively rare in heart transplant recipients (frequency <1%), *Nocardia* is only second in frequency in heart transplant after lung transplant recipients [61–63]. Pertinent-independent risk factors associated with the development of this infection in SOT include high-dose steroids, history of CMV disease, and high levels of calcineurin inhibitors [62]. With the almost universal prophylaxis with TMP-SMX, *Nocardia* infection is less common and often present late, usually after 1 year posttransplant [63]. When they occurred, they affect the lung predominantly, which is the port of entry for disseminated infections and CNS invasion. Also, it can cause skin nodules and abscesses. *Listeria monocytogenes* can also be seen in heart transplant recipients and can count for a significant proportion of the bacterial meningitis cases in this setting [64]. Additionally, myocarditis and myocardial abscesses with this organism have also been documented [65]. *Mycobacterium tuberculosis* and nontuberculous mycobacteria (NTM), although, documented to occur in heart transplantation, are rare in the United States [66, 67]. However, it is important to recognize that the development of tuberculosis (TB) can be more prevalent in some endemic regions and often present with extrapulmonary involvement [68, 69]. *Legionellosis* and *Rhodococcus equi* with mainly pulmonary manifestations (pneumonia, pulmonary infiltrates, or cavitation) are another significant infections among heart transplant recipients [70].

Fungal

Fungal infections excluding PCP represent around 4.0% of all the infections. From them, invasive mold infections (IMI) are a significant contribution to morbidity and mortality among heart transplant recipients. The incidence in this population can reach 10 per 1000 person-years, and its associated mortality is approximately 17% [71]. *Aspergillus* represents up to 65% of all IMI. Its median time of onset is about 46 days, although late presentation (>90 days) has been more recently recognized associated with receipt of sirolimus in conjunction with tacrolimus for refractory rejection or cardiac allograft vasculopathy [72]. The most common clinical presentation for aspergillosis includes fever, cough, and single or multiple pulmonary nodules [73]. Extrapulmonary manifestations include spondylodiscitis, infective endocarditis, mediastinitis, endophthalmitis, and brain and cutaneous abscesses [74–78]. Dissemination tends to affect the CNS in a good proportion of the cases. Mucormycosis is the second most frequent mold affecting heart transplant recipients. *Mucor*, along with other non-*Aspergillus* molds (e.g., *Scedosporium*, *Ochroconis gallopava*), are associated with disseminated infections, CNS involvement, and poorer outcomes [79, 80]. *Pneumocystis jiroveci* (PCP)—although with a marked reduction in inci-

dence with the introduction of universal prophylaxis—is still a significant pathogen and cases may occur late after heart transplant. Cryptococcosis, although infrequent among SOT patients, has its higher incidence in heart transplant recipients [81]. Usually, its manifestations present late and affect the lungs and the CNS predominantly. Histoplasmosis and coccidioidomycosis occurred typically in the first year after transplant. Antigenuria was the most sensitive diagnostic test in SOT for histoplasmosis [82]. Finally, *Candida* infections are an important cause of morbidity and mortality as well. Rate of colonization is higher than in the general population [83]. *Candida* most commonly causes an oral mucosa infection. Although there has been a decline of invasive infections over time, these do occur and typically in the form of bloodstream infections secondary to catheter-related infections, tracheobronchitis, or disseminated disease [84]. Additionally, other confined end-organ injuries such as endophthalmitis and esophagitis can also be seen.

Viral

CMV infection is of critical importance among SOT. In heart transplant recipients, CMV has been inconsistently associated with cardiac allograft vasculopathy [85]. Furthermore, CMV leads to upregulation of pro-inflammatory cytokines, increase procoagulant response, left ventricular dysfunction, allograft rejection, and an increase of opportunistic infections [86]. The greatest risk for developing CMV disease is CMV-negative recipients of CMV-positive organs (D+/R−), followed by D+/R+ and D−/R+. A clinical report estimated that the rate of *infections* in heart transplant ranges between 9% and 35%, and *disease* is present in around 25% of patients [87]. The clinical manifestations are not unique to heart transplant recipients and include a CMV syndrome (fevers, myalgias, arthralgias, malaise, leukopenia, and thrombocytopenia). CMV-associated end-organ injury in this setting includes most frequently pneumonitis and gastrointestinal disease [10]. Other manifestations comprise myelosuppression, hepatitis, and pancreatitis. In contrast to the high frequency observed in AIDS patients, chorioretinitis in heart transplant patients is relatively rare [87]. Guidelines on CMV diagnosis and managements are discussed in more detail in Chap. 55 and also have been published elsewhere [88]. Other herpes viruses are of important consideration as well. EBV-associated T-cell PTLDs are more frequent in heart transplant recipients (0.4%) than in other SOT patients [89]. PTLD is a significant contributor to morbidity and mortality in the pediatric heart transplant population [90]. Human T-lymphotropic virus type I (HTLV1), human herpes virus (HHV)-6, HHV-7, and HHV-8 might play a role in EBV(−) T-cell PTLDs as well. Herpes viruses can manifest, as in other hosts, as mucocutaneous lesions for HSV,

herpes zoster for VZV, infectious mononucleosis in the case of EBV, Kaposi sarcoma for HHV-8, and encephalitis for HHV-6/7. Hepatitis, colitis, pneumonitis, and gastrointestinal disease have also been attributed to dissemination with certain herpes viruses. Herpes viruses can present with disseminated skin lesions (with or without vesicle formation) and fever of unknown origin.

Adenovirus has been associated with rejection, ventricular dysfunction, coronary vasculopathy, and the need for retransplantation. The current standard treatment for adenovirus is cidofovir, but outcomes are not optimal [91].

Chronic hepatitis without an identifiable cause should prompt testing for hepatitis E virus (HEV). Chronic HEV infection leads to the rapid development of fibrosis. HEV testing should be done with RNA PCR due to a delay in the antibody response. We recommend decreased immunosuppression and ribavirin therapy for 3 months [92, 93]. Other less common manifestation that should be considered under the correct epidemiologic risk factors include HTLV-1/HTLV-2-associated myelopathy, rabies, lymphocytic choriomeningitis virus, subacute measles encephalitis, mumps (associated parotitis, orchitis, vestibular neuritis, and allograft involvement), dengue virus, orf virus, human coronavirus, and influenza [36].

Parasitic

Cardiac transplant itself is one the predictors for development of toxoplasmosis [94]. Other associated risk factors include negative serum status before transplant, diagnosis of cytomegalovirus (CMV) infection, and high-dose prednisone. Toxoplasmosis can be transmitted by the donor heart (D+/R−, especially during the first 3 months) or can reactivate from the recipient (>3 months). Most of the infections developed during the first 6 months posttransplant and are predominantly primary infections. About 22% of infected patients had a disseminated infection carrying an estimated 17% mortality. Toxoplasmosis can manifest otherwise with myocarditis, encephalitis, pneumonitis, or chorioretinitis. Diagnosis requires identification of tissue cysts surrounded by an abnormal inflammatory response, detection of *Toxoplasma* DNA in body fluids by PCR, or positive *Toxoplasma*-specific immunohistochemistry in affected organs. Posttransplant serological tests are not helpful for diagnosis and may be misleading since results may change or not regardless of the presence of toxoplasmosis [95]. The preferred treatment regimen is a combination of pyrimethamine with sulfadiazine [96].

Advanced Chagasic cardiomyopathy is a primary indication for heart transplantation in some centers [13]. *Trypanosoma cruzi*, the causal organism of Chagas disease, can be transmitted up to 75% of the time from infected heart donors (D+/R−) [97]. Additionally, Chagas disease can reactivate from the donor once immunosuppression is

in place (R+). The reactivation rate can range between 22% and 90% in recipients with chronic chagasic cardiomyopathy undergoing heart transplant [98–100]. Additional risk factors for reactivation include rejection episodes, neoplasms, and use of MMF [98]. The mean onset of symptoms is approximately 112 days [101]. Once manifested, Chagas can present with nonspecific symptoms such as fever, malaise, anorexia, hepatosplenomegaly, and lymphadenopathy. Myocarditis, pericarditis, and encephalitis are also seen. Reactivation can mimic rejection and exhibits congestive heart failure, AV block and skin manifestations such as nodules and panniculitis. Increased eosinophil count and anemia can be indirect indicators of reactivation [102]. Diagnosis is made with the visualization of circulating trypomastigotes in peripheral blood. Additionally, blood and tissue PCR can be used. Tissue amastigotes can be seen in biopsy H&E preparations (Fig. 2.1). Finally, serologies are a crucial aspect in the diagnosis especially if seroconversion have been documented. In asymptomatic individuals, when the diagnosis of Chagas has been established in the donor, monitoring should be instituted with weekly blood *T. cruzi* PCR and microscopy [29]. Preferred antitrypanosomal therapy consists on benznidazole. Nifurtimox is an alternative treatment option. Posaconazole has anti-parasitic activity but carries high failure rates [103, 104]. GI disease with *Isospora* (*Cystoisospora*) *belli*, *Cryptosporidium*, *Cyclospora*, and *Microsporidia* has been reported to affect SOT recipients. Microsporidiosis can manifest with disseminated disease: fever, keratoconjunctivitis, CNS involvement, cholangitis, cough, and thoracic/abdominal pain [94]. Other rare parasitic infections affecting heart transplants include leishmaniasis, strongyloidiasis, and free-living amoebas [94, 105].
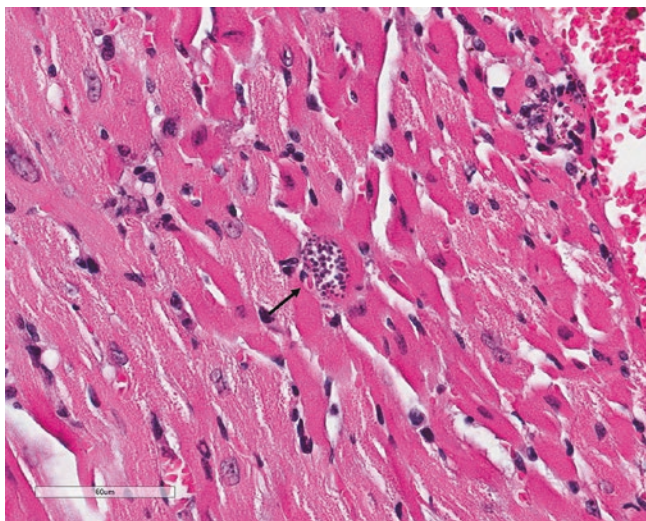

Fig. 2.1 *Trypanosoma cruzi* amastigote in heart tissue (H&E stain, 400×)

Sites and Types of Infection

Skin, Soft Tissue, and Bone

The rate of surgical site infections (SSI)—sternal wound infections—in patients receiving antimicrobial prophylaxis ranged from 5.8% to 8.8% following heart transplant procedures [41]. Heart transplantation itself is an independent risk factor for SSIs. Other risk factors include age, prophylaxis with ciprofloxacin alone, positive wire cultures, female gender, previous left ventricular assist device (VAD) placement, BMI >30 kg/m^2, previous cardiac procedures, and inotropic support for hemodynamic instability [41, 106]. Similarly to other hosts, *Staphylococcus* species are the predominant organism causing SSTIs. MRSA can reach up to 21% of the cases. Gram-positive organisms: VRE (*E. faecalis*), coagulase-negative staphylococci, and other *Enterococcus* species are other etiologic agents. Candida and selected gram negatives such as *Enterobacteriaceae*, *P. aeruginosa*, and *Stenotrophomonas maltophilia* can cause SSIs as well [107]. Sternal osteomyelitis often complicates deep SSI. Additionally, sternal wound infections by NTM and fungi such as *Aspergillus* and *Scedosporium* have been documented [108, 109]. Herpes zoster is also an important consideration and source of morbidity. Herpes zoster (HZ) is found as a complication in 19–22% of the patients with a median time of presentation ranging from 0.73 to 2.10 years [64, 110]. Close to half may develop postherpetic neuralgia. Multi-dermatome involvement, zoster ophthalmicus, and meningoencephalitis are also described. Exposure to MMF is an independent risk factor. Conversely, CMV prophylaxis reduces the risk for HZ.

Bloodstream

Bloodstream infections (BSIs) are a risk factor for mortality among heart transplant recipients. Likewise, SOT recipient status is an independent risk factor for developing bacteremia [111]. In heart transplant recipients; the rate of BSI ranged between 16% and 24%. The median onset is about 51–191 days, and the sources are in order of frequency: lower respiratory tract, urinary tract, and CRBSI. Gram-negative bacteria were more commonly isolated. They are in order of appearance *E. coli*, *P. aeruginosa*, and *K. pneumoniae*. More common Gram-positive bacteria were *S. aureus*, *S. epidermidis*, *E. faecalis*, and *L. monocytogenes*. Directly attributable mortality is 12.2%. Among the identifiable independent risk factors to develop BSI are hemodialysis, prolonged intensive care unit stay, and viral infections [112, 113]. Infective endocarditis (IE) is seen more frequently among heart transplant recipients than in the general population. With IE occurred, it most commonly involves the mitral and tricuspid valves and *Staphylococcus aureus* and *Aspergillus* are the main etiologic organisms. The main predisposing factors in this setting are believed to be the frequent use of vascular indwelling cathe-

ters and the frequency of endomyocardial biopsies [114]. *Staphylococcus aureus* bacteremia in heart transplant recipients ranges from 10% to 38% [11, 115]. The sources of SA bacteremia in SOT are CRBSI (30%), pneumonia (24%), wound (14%), endocarditis (10%), intra-abdominal infections (9%), bone and joint (7%), cardiac devices (3%), UTI (1%), and SSTI (1%) [115].

Chest

Immediately following heart transplant and during the 1st month, patients are more susceptible to develop pneumonia, most of which are healthcare or ventilator associated and therefore caused by nosocomial organisms such as MRSA, *Pseudomonas aeruginosa*, and other Gram negatives including *Acinetobacter* and ESBL-*Enterobacteriaceas*. Pneumonia is one the major contributors to mortality in the early postoperative period. Pneumonia-related mortality approaches 15% [116]. After the 1st month, interstitial pneumonia and pneumonitis can develop, and the differential includes herpesviruses (HSV, CMV, VZV) and respiratory syncytial virus (RSV), *Toxoplasma gondii* and *Pneumocystis jiroveci*. Pulmonary nodules with or without cavitation can be caused by fungi such as coccidioidomycosis, aspergillosis, mucormycosis, cryptococcosis; bacterial including actinomycosis, tuberculosis, atypical mycobacterial infections, *Nocardia*, *Rhodococcus equi*, and Gram-negative bacilli; and noninfectious causes like pulmonary infarction or lymphoproliferative disorders [117, 118]. Pulmonary nodules are seen in about 10% of the patients, and the median detection time is about 66 days. The associated symptoms are fever and cough. The most frequent etiology is *Aspergillus* followed by *Nocardia*, and *Rhodococcus*. CMV is an exceedingly rare cause of pulmonary nodules. The diagnostic approach with the higher yield is transthoracic fine needle aspiration followed by bronchoalveolar lavage and transtracheal aspiration [118]. Community-acquired pneumonia caused by *Streptococcus pneumonia*, *Legionella* spp., mycoplasma, and influenza is another source of morbidity [10].

Mediastinitis is a common complication in this setting. In patients receiving antimicrobial prophylaxis, mediastinitis develops in 3–7% of the patients [107, 119]. A CT scan is usually necessary to determine the extension of the infection. MRSA *Staphylococcus epidermidis*, Gram-negative bacteria, and *Aspergillus fumigatus* are frequently found as the causal organisms [120]. Antimicrobial therapy should be accompanied by aggressive surgical debridement [121].

Abdominal/Genitourinary

There are not distinctive abdominal-pelvic complications among heart transplant recipients. *Clostridium difficile* is a common hospital-related cause of diarrhea associated with the use of antimicrobials. Other etiology for diarrhea secondary to acute gastroenteritis can present in a protracted way in this setting. Listeria infection can present as a febrile gastroenteritis illness as well. Nontyphoid *Salmonella* infection has been described to complicate the early postoperative period in a center in Taiwan [122]. Acute cholecystitis can affect heart transplant recipients advocating to have a low threshold to use ultrasound as a screening method [123]. Acute pancreatitis with abscess formation has also been described [124]. As pointed above, hepatitis E can present with persistently abnormal liver tests.

Although less frequent than in kidney transplant recipients, urinary tract infections are an important cause of morbidity. UTIs are predisposed by Foley catheters. The organisms most commonly involved are Gram-negative bacteria, *Enterococcus*, and *Candida*. Polyomavirus nephropathy by BK virus has been described in heart transplant recipients and might be a contributor to chronic kidney disease [125].

Central Nervous System

The need for urgent transplantation and multiple transfusions are independently associated with infectious, neurologic complications. Its overall mortality can reach 12% [64]. Donor-derived meningoencephalitides affecting heart transplant recipients usually manifest within the first 30 days. These infections include West Nile virus, arenaviruses (e.g., LCMV), and rabies. WNV can manifest with a Guillain-Barré-like axonopathy with cerebrospinal fluid (CSF) pleocytosis. In addition to meningitis or encephalitis, ataxia, myelitis, optic neuritis, polyradiculitis, and seizures can also be observed [126]. WNV can be also acquired by the recipient in the community or through blood transfusions and present at a later time [127]. Other infectious forms of meningitis and encephalitis that can present after the 1st month include listeriosis, *Streptococcus pneumoniae*, *Trypanosoma cruzi*, *Toxoplasma*, HHV-6, and disseminated herpes virus infections (CMV, VZV, HSV, and EBV) [128–130]. The absence of appropriate primary prophylaxis or monitoring increases their risk. *Aspergillus* causes the majority of brain abscess. Additionally *Toxoplasma*, tuberculosis, *Listeria* spp., *Cryptococcus neoformans*, *Scedosporium* spp., and *Nocardia* can also be causative agents [129]. Concomitant pulmonary involvement is common, particularly for those whose portal of entry is the respiratory tract.

Progressive multifocal leukoencephalopathy (PML), a demyelinating disease caused by the reactivation of JC virus, has a usual median onset of 27 months. It carries a marked high case fatality rate and a median survival of 6.4 months in SOT [131]. The use of rituximab as an antirejection treatment seems to confer an increased risk for PML [132]. HTLV-1-associated myelopathy (HAM) has been described as well in SOT.

Infections in Lung and Heart-Lung Transplantation

Infecting Microbial Agents

Bacterial

Bacterial infections are the most common type of infections among lung and lung-heart transplant recipients. The anatomic site most frequently affected is the respiratory tract, usually manifested with pneumonia, sinusitis, or tracheobronchitis. Previous colonization, healthcare associated, and procedures related are the primary sources. For patients with cystic fibrosis (CF), knowledge of previous colonization results may provide some diagnostic and therapeutic advantages. *Pseudomonas aeruginosa* is a predominant colonizing pathogen in CF. However, *Acinetobacter baumannii*, *Burkholderia* species, *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, NTM, *Pandorea*, and *Ralstonia* are also observed [23]. Furthermore, pathogens that are known to cause nosocomial pneumonia during the 1st month include *Staphylococcus aureus*, *Pseudomonas aeruginosa*, other Gram negatives (*Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Escherichia coli*, *Acinetobacter* species), and anaerobes.

Gram-positive bacteria are a common source of infections making up to 40% of them [133]. The most common sites affected were the respiratory tract, followed by bacteremia, skin, wound, and catheter related. The pathogens more frequently identified are *Staphylococcus* species (77%), *Enterococcus* species (12%), *Streptococcus* species (6%), *Pneumococcus* (4%), and *Eubacterium lentum* (1%). *Staphylococcus aureus* infection can develop up to 20% of lung recipients. SA commonly causes pneumonia, followed by tracheobronchitis, bacteremia, intrathoracic infections, and SSTIs [20]. *Streptococcus pneumoniae* is community acquired and present with pneumonia, usually after 6 months posttransplant. *Pseudomonas aeruginosa* has high rates of colonization (up to 40%) and disease (30%) [134]. Other significant bacterial infections that may present after the 1st month are *Mycobacterium tuberculosis*, NTM, *Nocardia*, *Rhodococcus*, and *Legionella*. Isolation of NTM in lung transplant recipients without evidence of disease is not associated with increased mortality [135]. Nocardiosis can occur in about 2% of the lung transplant recipients. The median time of onset ranges from 14.3 to 34.1 months [136, 137]. *Nocardia asteroides*, *N. farcinica*, *N. nova*, and *N. brasiliensis* have been reported. *N. farcinica* appears to carry worse outcomes. This infection can present as a breakthrough in the presence of trimethoprim-sulfamethoxazole for *P. jiroveci* prophylaxis, although the isolates may remain susceptible. Mortality has been reported to range between 18% and 40%. The native lung is more frequently affected in single-lung transplant recipients. Nodules are the more prevalent radio-graphic finding. Extrapulmonary involvement affecting the skin and brain can be seen. Hypogammaglobulinemia and neutropenia seem to confer additional risk factors for nocardiosis in this setting [137].

Fungal

Fungal infections are frequent complications in lung and lung-heart transplant. They present in about 15–35% and carry an overall mortality close to 60% [138]. *Aspergillus* and *Candida* are the most frequent causative agents. Other important fungi include *Cryptococcus* spp., mucormycosis, endemic fungi (*Histoplasma*, *Coccidioides*, and *Blastomyces* spp.), *Scedosporium* spp., *Fusarium* spp., and dematiaceous molds. Candida infections are prominent during the 1st month after transplantation. It can be one of the most common causes of BSI in this setting [139]. Although colonization of the upper airways and gastrointestinal tract is common, *Candida* additionally can cause mucocutaneous disease, tracheobronchitis, anastomosis site infections, CRBSI, and disseminated disease. *Aspergillus* spp. lead as the cause of invasive fungal infections. Its attack rate of infection is almost ten times compared to that in other SOT patients (estimated incidence of 6% among lung transplant recipients) [140, 141]. *A. fumigatus* is the most common species, but *A. terreus*, *A. flavus*, and *A. niger* have been described as well. The main predisposing risk factors in this setting are intense immunosuppression, previous colonization with *Aspergillus* spp., airway ischemia, and BOS. Single-lung transplant possesses the greatest risk to developing an invasive *Aspergillus* infection carrying a higher mortality than double-lung and heart-lung transplant recipients. Single-lung recipients are usually older and more likely to have COPD as the indication for transplantation [140]. *Aspergillus* infections can present as tracheobronchitis, pneumonia, or disseminated disease. Extrapulmonary involvement includes sinusitis, CNS or orbits infections, and vertebral osteomyelitis. Aids in the diagnosis can include surveillance bronchoscopies (bronchoalveolar lavage stain and culture; biopsy), chest CT and serum/BAL galactomannan, beta-D-glucan, and PCR. The presence of pulmonary nodular lesions in invasive infections can carry better outcomes [142]. Voriconazole is the treatment of choice. It is important to note that immune reconstitution inflammatory syndrome (IRIS) can develop at a median of 56 days in 7% of treated lung transplant recipients [143]. In *Aspergillus* tracheobronchitis, nebulized amphotericin B and debridement of the bronchial anastomosis are important adjuvant measures to systemic antifungal therapy [144, 145]. *Pneumocystis jirovecii* pneumonia manifests from 1 to 6 months. Its incidence has been reduced dramatically with universal TMP/SMX prophylaxis. Cryptococcosis with a rate of 2% in lung transplant recipients presents with pulmonary involvement, but dissemination with meningitis can occur. Furthermore, *Cryptococcus* skin manifestations

like cellulitis and *Cryptococcus*-associated IRIS have been documented [146, 147].

Viral

Viral infections are a common cause of morbidity among lung transplant recipients. The most common viruses are (1) CMV among the herpes viruses and (2) community-acquired respiratory viruses. As in other SOT recipients, the higher risk to develop CMV infection is among D+/R−, followed by D+/R+, D−/R+, and D−/R−. This last scenario carries less than 5% of risk [48, 148]. Lung transplant recipients possess higher risk for CMV than other SOT with an estimated incidence of 30–86% [87]. The lung is considered a primary reservoir for CMV latency, and abundant lymphocytic tissue surrounds the transplanted organ. Additionally, the use of antilymphocyte antibodies to treat rejection or for immunosuppression and other herpesviruses infections are additional risk factors for CMV disease [149]. Interferon (IFN)-γ (+874T/T) polymorphism increases IFN levels and may be a predisposition for CMV disease [150]. CMV is significantly associated with BOS, which reduces survival after the first year posttransplant [151]. CMV disease is most commonly manifested by pneumonitis or viral syndrome and less frequently with gastrointestinal disease. Among lung transplant recipients, ganciclovir-resistant CMV carries an increased morbidity and mortality [152].

Infections with community-acquired respiratory viruses ranged from 7.7% to 64%. These infections are associated with increased risk to develop pneumonia, graft dysfunction manifested by lung function loss, BOS, high calcineurin inhibitor blood levels, and increase mortality [153–155]. These viruses include influenza, parainfluenza, respiratory syncytial virus (RSV), coronaviruses, human rhinovirus, adenovirus, human metapneumoviruses, and bocaviruses. The hospitalization rates are higher for influenza and parainfluenza (50% and 17%, respectively) [154]. Symptoms are usually nonspecific. Diagnosis often requires detection of viral nucleoprotein antigens in nasopharyngeal swabs or bronchoalveolar lavage (BAL) by enzyme immunoassay or fluorescent antibody or the amplification of nucleic acid by PCR. Ribavirin may possess activity against *Paramyxoviruses* (RSV, *Metapneumovirus*, and parainfluenza). Ribavirin is administered inhaled, orally, or intravenously. Oseltamivir or zanamivir is the treatment choice of influenza A or B [156]. Adamantanes (amantadine and rimantadine) are not active against influenza B, and there is a marked increase resistance among influenza A strains [156]. Similarly to other SOT recipients, DNA viruses like non-CMV herpesviruses (HSV-1,-2), VZV, HHV-6,-7,-8, and EBV are a source of significant morbidity including but not limited to CMV-negative viral syndrome, rash, pneumonitis, hepatitis, and encephalitis [157]. Lastly, polyomavirus such as BK virus (BKV), JC virus (JCV), and simian virus 40 (SV40)—although fre-

quently encountered in lung transplant recipients with an unclear causality—may cause worsening renal function or survival [158]. PTLD is also a well-recognized complication. A trend toward late PTLD presentation (>1 year) has been documented where B symptoms are more predominant as well as extra-graft involvement [159].

Parasitic

As other immunosuppressive states, certain parasitic infections can complicate lung and heart-lung transplants recipients. It is critical to elicit a detailed history and geographic risk factors to determine the risk of acquisition and the potential etiologic agent. Toxoplasmosis can result from primary infection or reactivation of previous latent infections. Toxoplasmosis can develop in patients with negative epidemiological history for cat ownership or consumption of undercooked meat. In patients with primary toxoplasmosis, nonspecific symptoms such as fever, lymphadenopathy, or organ injury may be present. Reactivation can cause encephalitis with or without space-occupying brain lesions, seizures, chorioretinitis, fever of unknown origin, pneumonitis, myocarditis, and rash. Although cases of the lung fluke, *Paragonimus westermani* have not been reported in lung transplantation, it can be a potential threat in endemic areas where this organism is endemic. Other parasites that can target the lung in immunosuppressive states include *Echinococcus*, *Schistosoma*, and *Strongyloides stercoralis* [160]. Strongyloidiasis can present as hyperinfection syndrome [161]. *Leishmania*, although infrequently seen, has been reported among lung and lung-heart recipients [30]. Free-living amoebas can affect this population as well. Amoebic granulomatous dermatitis and disseminated infection presenting with ulcerative skin lesions, respiratory failure, and seizures have been described in lung transplant recipients [162, 163]. Finally, alimentary protozoa, including *Cryptosporidium*, which present with diarrhea and may elevate tacrolimus levels [164], and microsporidia, which present with unusual manifestations like myositis or granulomatous interstitial nephritis, affects lung transplant recipients [165, 166].

Sites and Types of Infection

Skin, Soft Tissue, and Bone

The overall rate of SSIs is about 13% with a significant proportion of infections being organ or space occupying (72%), deep incisional (17%), and superficial (10%) [18, 41]. Independent risk factors to develop SSI are diabetes, female donor, prolonged ischemic time, and the number of red blood cells transfusion during the perioperative period [167]. SSIs are associated with a 35% mortality within the first year of transplantation. The most common organisms found to cause

SSI or mediastinitis are *P. aeruginosa*, *Candida* species, *S. aureus* (including MRSA), *Enterococcus*, coagulase-negative *Staphylococci*, *Burkholderia cepacia*, *E. coli*, *Proteus mirabilis*, *Serratia marcescens*, *Acinetobacter baumannii*, *Enterobacter cloacae*, and *Klebsiella* species. There is a correlation in up to 33% of the patients' SSI causative organisms with previous pathogens colonizing recipients' native lungs at the time of the transplant [167]. The median onset is 25 days after lung transplant [167]. Although rare, NTM can cause SSI infections among lung transplant recipients. The most frequently encountered are *Mycobacterium avium* complex followed by *Mycobacterium abscessus* and *Mycobacterium gordonae*. NTM SSI infections can be complicated by progressive disseminated disease or requirement of lifelong suppressive therapy [135]. Other organisms such as *Mycoplasma hominis* and *Lactobacillus* spp. have also been described. Deep infections can affect up to 5% of the patients. Sternal osteomyelitis can reach up to 6% of these deep infections. Causative organisms for sternal osteomyelitis include *Pseudomonas aeruginosa*, *Serratia marcescens*, and *Scedosporium*. Non-sternal osteomyelitis affecting the calcaneus bone has complicated a disseminated infection with *Aspergillus fumigatus* [168].

Bloodstream

Bloodstream infections (BSIs) occur with an estimated rate of 25% among lung transplant recipients. A major proportion of BSIs occur in the early posttransplant period. BSIs infections are significantly associated with worse survival [139, 169]. The most common organisms encountered are *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida* [139]. *Pseudomonas aeruginosa* BSI—predominantly present during the transplant hospitalization period and more commonly affecting CF patients—is followed in frequency by *Burkholderia cepacia* and *Candida albicans*. Conversely, *Staphylococcus aureus* was the predominant organism after transplantation discharge. In an estimated 70% of BSI, the source was pulmonary, followed in frequency by CRBSI, gastrointestinal infection, peritonitis, and UTI. A pulmonary source of bacteremia in SOT often develops into septic shock [170]. Although unusual, cases of *Aspergillus fumigatus* endocarditis have been described following lung transplantation [171]. Often patients had CF as the underlying lung disease and a median of 8 ± 6 months presentation. This complication carries a high mortality and often requires a combination of antifungal therapy with valvular replacement surgery.

Chest

Infectious complications related to the chest cavity include mediastinitis, cardiac (pericarditis and myocarditis), lung parenchyma infections (nodular infiltrates, cavitation, or pneumonia), bronchial anastomosis infections, and pleural space infections (bronchopleural fistula and empyema). Empyema followed by mediastinitis and pericarditis, in addition to surgical wound infections and sternal osteomyelitis, is the most frequent deep SSI complications affecting the chest cavity. Empyema presents in around of 3.6% of cases. It occurs during the first 6 months after transplantation (median 46 ± 39 days) carrying an estimated mortality of 28.6% [172]. Most common organisms found are *Staphylococcus* spp., *E. coli*, *Enterobacter* spp., *Klebsiella* spp., *Mycoplasma hominis*, VRE, and *Candida*. Furthermore, *Mycobacterium abscessus* was isolated as a rare causative agent of empyema as well [173]. The degree of immunosuppression, reduced renal function, previous sternotomy, and re-exploration due to bleeding are listed as potential risk factors for mediastinitis [119]. There is an increased prevalence of mediastinitis caused by Gram negatives and fungi among lung transplant recipients. Causative organisms for mediastinitis are similar to SSI and are listed above. Infectious pericarditis can be present up to 6% of the patients (isolated organisms include MSSA, *Mycoplasma hominis*, and *Scedosporium prolificans*) [167, 174, 175]. Due to their high fatal rate, fungal bronchial anastomotic infections are critical to recognize.

Pneumonia is believed to affect around 21% of lung recipients and 40% of heart-lung recipients. Nosocomial organisms cause early pneumonia as in other posttransplant settings. The donor's lung seems to be the primary source for pneumonic infections, although the recipients' upper airways or sinuses are also potential sources. Preoperative colonization with Gram-negative rods and colonized infected donor bronchus or perfusate are recognized risk factors for pneumonia. Likewise, pretransplantation colonizing microorganisms from suppurative lung disease are associated with pneumonia development posttransplant [176]. The most common causal organisms are *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Aspergillus* spp. Other pathogens include bacteria such as *B. cepacia*, *Enterobacter* species, *S. maltophilia*, *Klebsiella* species, *S. epidermidis*, and *E. coli*, and fungi such as *Fusarium* spp., *Cryptococcus neoformans*, and *Paracoccidioides brasiliensis* [176]. After the 1st month, pneumonia can present as local infiltrates, diffuse interstitial infiltrates, and nodules with or without cavitation. This type of presentation may aid in the possible causative microorganism. The list of potential pathogens is extensive and includes in addition to the already mentioned *Nocardia*, *Chlamydia pneumonia*, *Legionella*, TB, NTM, *Pneumocystis jirovecii*, *Rhodococcus*, herpesviruses (CMV, HSV, and VZV), respiratory viruses, endemic fungi (e.g., histoplasmosis), mucormycosis, and *Scedosporium* spp. [177–179].

Abdominal/Genitourinary

Similarly to other SOT, common infectious complications affecting the gastrointestinal or genitourinary tract include *Clostridium difficile* colitis and UTIs. Intra-abdominal com-

plication carries an overall increase mortality [180]. Frequent GI symptoms presenting posttransplant are diarrhea which can affect almost 30% of lung transplant recipients and abdominal pain. Abdominal pain should prompt further investigation for potential intra-abdominal causes. In the pediatric population, the possibility of PTLD should be investigated since it carries a high mortality [181]. Other described infectious intra-abdominal complications include digestive perforation (seen in 6%) [182], retroperitoneal abscesses, cholecystitis, perianal abscesses, esophagitis, pancreatitis, pancreatic abscesses, hepatitis, diverticulitis, appendicitis, CMV colitis, megacolon, and colon rupture [180, 183, 184]. In developing countries, persistently abnormal liver enzymes should prompt testing for HEV. HEV RNA should be used for screening. Oral ribavirin seems to be safe and effective in this setting [185].

Central Nervous System (CNS)

CNS symptoms developing during the 1st month following lung or heart-lung transplantation should trigger the concern for donor-derived viral infections. LCMV often is accompanied by CSF normal to low glucose, marked elevated protein, and mild pleocytosis [36]. Although with unclear benefit, ribavirin has been used. Donor-transmitted rabies is an uncommon but neurologic devastating complication that occurs within the first 30 days of transplant. Lung transplantation has been described as a potential causal mechanism [186]. Other organisms known to cause meningitis in lung transplant recipients are *Cryptococcus*, tuberculosis, WNV, and herpesviruses [187, 188]. Diagnosis of WNV in this setting requires nuclear acid amplification due to the unreliability of serologic testing. *Scedosporium apiospermum* infections often cause dissemination including CNS abscesses in addition to pulmonary involvement among lung transplant recipients [189]. It is important to differentiate from other molds, since amphotericin B is ineffective against *Scedosporium* spp. In severe cases or refractory disease without an appropriate surgical debridement, the addition of terbinafine to voriconazole may prove to be useful [190]. Other recognized organisms causing occupying brain lesions are *Fusarium*, *Nocardia*, *Aspergillus*, toxoplasmosis, *Cryptococcus neoformans*, *Listeria*, and *Cladophialophora bantiana* [191–193]. PML, a late manifestation, can be associated with intensified immunosuppression or rituximab. Cidofovir followed by mirtazapine can be considered as a form of therapy for PML.

Conclusions

Infections in heart, lung, and heart-lung transplant recipients are a complex, dynamic, and evolving process. Many factors such as demographics, timing, type of transplant, anatomy, and microbiology, among others, interplay in the development of these fatal complications. Pertinent recognition and treatment of these infections improve transplantation outcomes.

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