INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION (ISHLT) ACADEMY

Core Competency Curriculum Document (CCCD)

Core Competencies in
Diagnosis and Management of Infectious Diseases in
Cardiothoracic Transplantation and Mechanical Circulatory Support

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Introduction and Overall Goals

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D. Influenza and Other Seasonal Respiratory Viruses
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F. Other Viral Infections

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G. Management of non-VAD infections in MCS

H. Pharmacology of Anti-infective Agents in the Setting of MCS

Introduction and Overall Goals

This core competency document provides a practical and concise clinical review for medical professionals to develop understanding and management of infectious diseases in recipients of cardiothoracic transplantation (CT TX) and mechanical circulatory support (MCS). It is meant to be a guide for expert development and serves as part of the educational curriculum at the ISHLT Academy. It provides the basis for learning activities and self-directed study.

Advances in immunosuppression and MCS technology have prolonged life and required the need for new considerations in preventing and managing infectious diseases in these patients. Our core competency curriculum provides the essential background and clinical information to equip the medical professional to manage infectious disease issues in these complex patients. The curriculum covers a broad range of infections and focuses on prevention, recognition of clinical presentation, diagnosis, treatment and the impact on outcome for CT TX and MCS.

Every effort has been made to provide up to date information. Due to the multiple circumstances these disease processes are encountered, the document is a reflection of current learning objectives and priorities and does not assume completeness. Fundamental knowledge and basic application skills are emphasized. Literature resources are provided as selective references for further self-study and the text may serve as a guide for self-directed learners. The following learning objectives have been considered:

**General Learning Objectives**

This curriculum allows learners and participants of learning activities based on its objectives, to develop or improve competence and professional performance in their ability to:

1. Evaluate and minimize the risk of infection in cardiothoracic transplant and MCS recipients through prescreening evaluation.
2. Control and prevent infection in cardiothoracic transplantation and MCS.
3. Understand the pharmacology of anti-infective agents in the setting of cardiothoracic transplantation and MCS.
4. Recognize and manage bacterial, fungal, viral and parasitic infections in cardiothoracic transplant and MCS recipients.
5. Use diagnostic methodology for detection of infectious diseases in cardiothoracic transplant and MCS recipients.
6. Prepare the cardiothoracic transplant recipient for safe travel.
7. Understand the approaches to emerging infectious pathogens in cardiothoracic transplantation and MCS.

**Educational Goals**

The overarching educational goals of this curriculum are to provide a concise review of clinical knowledge topics and essential skills required to facilitate best practice in the prevention and treatment of infectious diseases in patients undergoing cardiothoracic transplantation or mechanical circulatory support.

**On behalf of the Infectious Disease Council of the ISHLT,**
Section I: Historical Overview of Infection in CT TX

A. Learning Objectives for Infections in Heart Transplantation: Historical Perspective

1) Understand the historical perspective and evolution of immunosuppression: Impact on infection related mortality and morbidity during induction phase and maintenance phase of immunosuppression in heart transplantation
2) Understand the historical perspective and evolution of infections in heart transplantation
3) Appreciate the effects of prophylactic antimicrobial agents in heart transplant on:
   a. Nosocomial Infections
   b. Bacterial and Viral Infections
   c. Fungal Infections
   d. Emergence of multidrug resistant organisms

Essential Content

1. Historical perspective of heart transplantation
   a. Early outcomes
2. Historical perspective on immunosuppressive drugs and risk of infection
   a. Induction immunosuppression
   b. Maintenance immunosuppression
3. Historical perspective on infections in heart transplantation
   a. Nosocomial infections and antimicrobial resistance
   b. Opportunistic infections
      i. Viral
      ii. Bacterial
      iii. Protozoal infections
      iv. Fungal
4. Historical perspective on donor selection

Key References


B. Learning Objectives for Infections in Lung Transplantation: Historical Perspective

1) Understand the historical perspective and evolution of immunosuppression: Impact on infection related mortality and morbidity during induction phase and maintenance phase of immunosuppression in lung transplantation
2) Understand the historical perspective and evolving patterns of infection since the advent of lung transplantation
3) Appreciate the effects of prophylactic antimicrobial agents in lung transplant on:
   a. Nosocomial Infections
   b. Bacterial and Viral Infections
   c. Fungal Infections
   d. Emergence of multidrug resistant organisms

Essential Content

1. Historical perspective of lung transplantation
   a. Early outcomes
2. Historical perspective on immunosuppressive drugs and risk of infection
   a. Induction immunosuppression
   b. Maintenance immunosuppression
3. Historical perspective on infections in lung transplantation
   a. Nosocomial infections and antimicrobial resistance
   b. Opportunistic infections
      i. Viral
      ii. Bacterial
      iii. Protozoal infections
      iv. Fungal
4. Historical perspective on donor selection

Key References


Section II: Evaluating and Minimizing Risk of Infection in CT TX

A. Learning Objectives for Pre-transplant Screening of Recipients in CT TX

1) List the screening and diagnostic tests for infection that are commonly obtained on prospective transplant recipients during the pre-transplant evaluation, and describe the significance of these tests in pre- and post-transplant management
2) Explain which vaccines should be administered to the transplant candidate during the pre-transplant evaluation and in the post-transplant period
3) Understand the rationale for the major principles of infection prevention that form part of patient counseling during the pre-transplant evaluation (e.g. with regard to food, pets, outdoor activities)
4) Understand the unique infectious disease considerations in patients with Cystic Fibrosis, particularly with regards to persistent colonization, antibiotic-resistant organisms, non-bacterial microorganisms and complications of prolonged antibiotic treatment

Essential Content

1. Screening for latent and active infection
   a. Viruses
   b. Bacteria
   c. Fungi and parasites
   d. Acute infection or fever in the candidate
2. Determination of need for vaccination
   a. Serological assays
   b. Recommended vaccine schedules
3. Patient education to prevent infection
   a. Hand hygiene
   b. Food
   c. Animal exposure
   d. Outdoor activities and travel
4. Recipient with cystic fibrosis
   a. Multi drug resistant and pan resistant gram-negative bacteria
   b. *Burkholderia cepacia* complex
   c. Methicillin-resistant *Staphylococcus aureus*
   d. Non tuberculous mycobacteria
   e. Filamentous fungi
5. Ongoing management of infectious disease issues in potential lung transplant recipients
a. Pulmonary exacerbations
b. Sinus disease
c. Clostridium difficile

Key References

1. Michaels M, Kumar D, Avery R. Chapter 4: Pre transplant screening of recipients in cardiothoracic transplant and mechanical circulatory support recipients as a bridge to transplantation. In: ISHLT Monograph Series Volume 5: Diagnosis and Management of Infectious Diseases in Cardiothoracic Transplantation and Mechanical Circulatory Support. Edited by ML. Mooney, MM. Hannan, S. Husain and JK. Kirklin. 2011

B. Learning Objectives for Pre-Transplantation Screening of Donors for CT TX: Current Standards for Infection Screening and Geographically Restricted Infections

1) Understand the current standards for infection screening evaluation of potential cardiothoracic organ donors, including the pertinent medical history and physical examination and the appropriate microbiologic, virologic, and serologic testing
2) Recognize the social, behavioral, medical, and laboratory features of donors at increased potential for human immunodeficiency virus (HIV), hepatitis B, and hepatitis C infection and the limitations of serologic testing in these donors

3) Appreciate the increasing importance of geographically restricted donor infections with pathogens such as *Mycobacterium tuberculosis*, the endemic fungi, *Trypanosoma cruzi*, *Strongyloides stercoralis*, and West Nile virus

**Essential Content**

1. Screening potential organ donors for infection
   a. Human immunodeficiency virus
   b. Hepatitis viruses
   c. Herpesviruses
   d. *Treponema pallidum*
   e. *Mycobacterium tuberculosis*
   f. Other bacterial and fungal pathogens
   g. *Toxoplasma gondii*

2. High risk donor
   a. Methods of identification
   b. Limits of serological testing

3. Geographically restricted donor infections
   a. Fungal
   b. Parasitic
   c. Viral

**Key References**


5. Lease ED, Zaas D. Complex Bacterial Infections Pre- and Posttransplant. Semin Respir Crit Care Med 2010; 31: 234–42
C. Learning Objectives for Donor-derived Infections after CT TX

1) Recognize the common and expected donor-derived infections such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis B virus (HBV), hepatitis C virus (HCV), and toxoplasmosis

2) Become familiar with the unexpected donor-derived pathogens such as *Mycobacterium tuberculosis* (TB), West Nile virus, rabies virus and other geographically restricted pathogens that can result in significant morbidity and mortality after cardiothoracic transplantation

3) Understand the timing and clinical presentations of donor-derived infections

Essential Content

1. Recognition and diagnosis of common donor derived infections
   a. CMV
   b. EBV
   c. Hepatitis B virus
   d. Hepatitis C virus
   e. Toxoplasmosis

2. Recognition and diagnosis of unexpected donor derived infections
   a. TB
   b. West Nile virus
   c. Rabies virus
   d. Geographically restricted infections

3. Timing and clinical presentation of donor-derived infections

4. Resources for reporting donor-derived infections

Key References


Section: III: Pharmacology of Anti-infectious Agents in the Setting of CT TX

A. Learning Objectives for Therapeutic Drug Monitoring (TDM)

1) Understand the use of TDM in managing infections in CT TX
2) Appreciate and anticipate the potential for drug-drug interactions with anti-infective agents with other medications in CT TX
3) Describe the factors that impact the pharmacokinetic and pharmacodynamics properties of the anti-infective drugs in CT TX
4) Understand the effects cystic fibrosis may have on drug absorption and TDM

Essential Content

1. Contributing factors of drug-drug interactions
   a. Route of administration
   b. Onset and strength of the drug interaction
   c. Pharmacodynamics
   d. Ethnicity
   e. Cystic Fibrosis
   f. Age-related pharmacokinetics
   g. Gastric acid alteration and drug absorption

2. Key Points for TDM
   a. Selection of appropriate test
   b. Test methods
   c. Turn-around time of lab tests
   d. Timing of TDM
   e. Target level
   f. Interpreting results

3. Anti-infectives and TDM
   a. Glycopeptides
      i. Vancomycin
   b. Aminoglycosides
      i. Amikacin
      ii. Gentamicin
      iii. Tobramycin
   c. Azoles
      i. Itraconazole
      ii. Voriconazole
      iii. Posaconazole
   d. Polymyxin
      i. Colistin
   e. Antiviral
      i. Ribavirin
ii. GCV
iii. ACV
f. Anti-retroviral
   i. Protease inhibitors

Key References


B. Learning Objectives for Anti-infective Drug interactions, Toxicities, and Clinical Management in CT TX for Mycobacterial Infections

1) Describe the immunosuppression dosing changes and monitoring necessary when starting Tuberculosis treatment with maintenance immunosuppression in CT TX
2) Appreciate the pharmacodynamics and pharmacokinetic interactions of anti-infective agents with immunosuppressants and select cardiac drugs
3) Appreciate the need for Q-T interval monitoring with the addition of some anti-infective therapies in CT TX

Essential Content

1. Pharmacokinetic and pharmacodynamic interactions of anti-mycobacteria drugs with immunosuppressants and selected cardiovascular drugs – dose adjustments, toxicities, and monitoring
   a. Isoniazid
   b. Rifamycin group
      i. Rifampicin (rifampin)
      ii. Rifabutin
      iii. Rifapentine
   c. Pyrazinamide
   d. Ethambutol
   e. Azithromycin
   f. Clarithromycin
g. Trimethoprim-sulfamethoxazole  

h. Ciprofloxacin/levofloxacin  
i. Imipenem-cilastin  
j. Tigecycline

Key References


C. Learning Objectives for Immunoglobulins in CT TX Infections: Prophylaxis and Treatment

1) Understand the rationale for replacement therapy with intravenous immunoglobulins (IVIg) in CT TX  
2) Describe the indications for replacement therapy with IVIg or cytomegalovirus (CMV)-specific immunoglobulin in CT TX  
3) Recognize the potential role of IVIg or CMV immunoglobulin for prophylaxis and treatment of CMV disease

Essential Content

1. In solid organ transplantation (SOT) the potential for immunoglobulin repletion for infection prevention has not yet been fully explored  
2. Incidence of hypogammaglobulinemia (HGG) is high in the first year post CT TX:  
   a. Mild to moderate HHG (IgG 400-700)  
      i. 49% Heart  
      ii. 63% Lung  
   b. Severe HHG (IgG < 400)  
      i. 21% Heart  
      ii. 22% Lung  
   c. Severe HHG has adverse effects in infection–related morbidity and early mortality  
   d. Consideration for monitoring IgG levels post CT TX to identify this high risk group for infection is evolving  
   e. Benefit in preemptive treatment with IVIG for severe HGG in the SOT group has been demonstrated in historical series  
3. The role of CMV immunoglobulin or IVIG in prevention and treatment of CMV disease in CT TX is still being explored
a. Historical studies are limited due to single-center analysis over long time periods over eras of different immunosuppression and prophylactic protocols
b. Some centers use CMV immunoglobulin for CMV prophylaxis in addition to the appropriate antiviral prophylaxis, primarily in high risk thoracic transplant recipients
c. IVlg or CMV immunoglobulin may be considered adjuvant therapy for severe CMV disease

Key References


Section IV: Bacterial Infections in CT TX

A. Learning Objectives for Epidemiology of Bacterial Infections in CT TX

1) Understand the role of pre- and post-transplant exposures in the development of bacterial infection in cardiothoracic transplant recipients
2) Describe common and uncommon causes of pneumonia after CT TX
3) Describe the post-transplant comorbidities that predispose to infections after CT TX
Essential Content

1. Potential exposures to bacterial pathogens before and after transplantation
   a. Recipient-derived infections
      i. Geographic exposures
      ii. Hospital-acquired infections
      iii. Community-acquired infections
   b. Donor-derived infections
      i. Geographic exposures
      ii. Hospital-acquired infections prior to donation

2. Co-morbid conditions that predispose to bacterial infections CT TX
   a. Surgical and mechanical factors
   b. Allograft rejection
   c. Bronchiolitis obliterans after lung transplantation
   d. Colonization (carrier state) with multidrug resistant bacteria
   e. Special considerations for recipients with cystic fibrosis

3. Causes of pneumonia in the cardiothoracic transplant recipient
   a. Common causes of bacterial pneumonia
      i. Causes of early pneumonia (including gram-negative bacilli, *Staphylococcus aureus*)
      ii. Causes of late-onset pneumonia including *Streptococcus pneumoniae*
   b. Unusual causes of bacterial pneumonia
      i. *Legionella pneumophila*
      ii. *Nocardia* spp.

Key References


B. Learning Objectives for Multidrug Resistant Gram Positive Bacteria

1) Describe the incidence, diagnosis, treatment and prevention of methicillin-resistant *Staphylococcus aureus* (MRSA) in cardiothoracic transplant recipients
2) Describe the incidence, diagnosis, treatment and prevention of vancomycin-resistant Enterococcus (VRE) in cardiothoracic transplant recipients
3) Describe the definition, epidemiology, diagnosis, treatment, and prevention of *Clostridium difficile* (CDI) infection in cardiothoracic transplant recipients
Essential Content

1. MRSA infections in cardiothoracic transplant recipients
   a. Incidence of MRSA infections after transplant
   b. Risk factors for MRSA infection
   c. Laboratory detection methods for MRSA
      i. Culture methods
      ii. Nucleic acid-based detection of MRSA
   d. Antibiotic resistance mechanisms in S. aureus
   e. Therapeutic options for MRSA infections
   f. Prevention of MRSA infections
   g. Emerging threats: vancomycin-intermediate S. aureus (VISA) and vancomycin-resistant S. aureus (VRSA)

2. VRE infections in cardiothoracic transplant recipients
   a. Incidence of VRE infections after transplant
   b. Risk factors for VRE infection and colonization
   c. Laboratory detection methods for VRE
      i. Culture methods
      ii. Nucleic acid-based detection of VRE
   d. Antibiotic resistance mechanisms in VRE
   e. Therapeutic options for VRE infections
   f. Prevention of VRE infections

3. CDI in cardiothoracic transplant recipients
   a. Incidence of CDI infections after cardiothoracic transplant
   b. Risk factors for CDI
   c. Clinical features of CDI
      i. Mild-moderate severity CDI
      ii. Severe CDI
   d. Laboratory detection methods for CDI
   e. Therapeutic options for CDI
      i. Treatment of for mild-moderate CDI
      ii. Treatment of severe and complicated CDI
      iii. Treatment of recurrent CDI
      iv. Fecal microbiota transplantation
   f. Prevention of CDI

Key References


C. Learning Objectives for Multidrug Resistant (MDR) Gram Negative Bacteria

1) **Understand the risk factors and mechanism of antibiotic resistance for multidrug-resistant (MDR) gram negative pathogens in CT TX**
2) **Describe the epidemiology of MDR Gram negative organisms in patients with cystic fibrosis**
3) **Understand the treatment of severe infections caused by MDR gram-negative organisms including *P. aeruginosa*, *B. cepacia*, *Acinetobacter*, *Stenotrophomonas maltophilia* and Extended-spectrum beta-lactamase (ESBL) producing Enterobacteriaceae and carbapenemase-producing Enterobacteriaceae (CPE)**

**Essential Content**

1. Spectrum of MDR gram negative pathogens encountered in CT TX and common mechanisms of antibiotic resistance
   a. *Pseudomonas aeruginosa*
   b. *Acinetobacter baumannii*
   c. *Burkholderia cepacia*
   d. *Stenotrophomonas maltophilia*
   e. Enterobacteriaceae
      i. Extended-spectrum B-lactamase producing bacteria
      ii. Carbapenemase producing bacteria
2. Risk factors for acquisition of MDR gram negative bacteria
3. MDR gram negative bacterial infection treatment principles
   a. Anti-infective therapeutic options
      i. Interpretation of antibiotic susceptibility testing
      ii. Antibiotic choices based on site of infection
      iii. Combination antibiotic therapy
   b. Importance of source control for successful treatment
4. Prevention of MDR gram negative bacterial colonization and infection
5. Decision making: MDR gram negative bacterial colonization and infection and transplant candidacy
   a. Management of MDR gram negative infections and colonization in cystic fibrosis patient and transplant candidacy

Key References


D. Learning Objectives for Mycobacterial Infections

1) Learn the epidemiology of the different mycobacterial infections post CT TX
2) Identify the clinical presentations associated with different mycobacterium and the impact on outcome post CT TX
3) Understand the diagnosis and treatment of the different mycobacterium
4) Understand the possible complications of treatment including drug interactions of antibiotics with immunosuppressive medication
5) Appreciate the risk of donor-derived infection in cardiothoracic transplant recipients, particularly with M.tuberculosis
Essential Content

1. *Mycobacterium tuberculosis* infections after CT TX
   a. Epidemiology of *M. tuberculosis* infections after transplantation
      i. Incidence and timing of tuberculosis infections after transplantation
      ii. Risk factors for acquisition of *M. tuberculosis*
      iii. Donor-derived infections
   b. Clinical spectrum of *M. tuberculosis* infections after transplantation
      i. Pulmonary tuberculosis
      ii. Extra-pulmonary (disseminated) tuberculosis
   c. *M. tuberculosis* general treatment principles
   d. Outcomes of tuberculosis after transplantation
   e. Prevention of tuberculosis in transplant recipients
      i. Screening for latent tuberculosis
      ii. Therapeutic options for latent *M. tuberculosis* infection

2. Non-tuberculous mycobacterial (NTM) infections after CT TX
   a. Epidemiology of NTM infections after transplantation
      i. Incidence and timing of NTM infections after transplantation
      ii. Risk factors for acquisition of NTM, especially in lung transplant candidates and recipients
      iii. Donor derived infections
   b. Most common NTM species affecting (lung) transplant recipients
      i. *M. avium* complex
      ii. *M. abscessus*
      iii. *M. haemophilum*
   c. Clinical spectrum of NTM infections
      i. Routes of NTM acquisition
      ii. Cutaneous and musculoskeletal infections
      iii. Pulmonary infections
      iv. Catheter-associated infections
      v. Disseminated NTM infections
   d. General treatment principles for NTM infections
   e. Outcomes of NTM infections after CT TX

3. Diagnosis of mycobacterial infections after CT TX
   a. Appropriate specimens for laboratory testing
   b. Laboratory methods for diagnosis of mycobacteria
      i. Traditional microbiological/culture methods for detection
      ii. Nucleic acid based detection and identification of mycobacteria
      iii. Histopathology
      iv. Antimicrobial susceptibility testing

4. Pharmacologic considerations during treatment of mycobacterial infections after transplantation
   a. Drug toxicity
b. Potential drug interactions between antimycobacterial and immunosuppressive agents

5. Prevention of NTM infections

Key References


E. Learning Objectives for Nocardia Infection

1) Understand the risk factors, clinical presentation, and potential complications related to infection with Nocardia species in cardiothoracic transplant recipients
2) Understand the various techniques employed in diagnosing Nocardia infections
3) Understand the importance of speciation and susceptibility testing of Nocardia species, and appreciate the strategies necessary for treating Nocardia infections in cardiothoracic transplant recipients

Essential Content

1. Epidemiology of Nocardia infections in CT TX
   a. Ecological niche of Nocardia spp.
b. Incidence of nocardiosis after transplantation

c. Risk factors for nocardiosis after transplantation
   i. Environmental exposures
   ii. Immunosuppression and impairment of cell-mediated immunity
   iii. Additional predisposing factors

d. Spectrum of clinical presentations of nocardiosis
   i. Sites of primary infection including lung and skin
   ii. Disseminated infection including central nervous system disease

e. Outcomes of *Nocardia* infections after transplantation

2. Modalities for diagnosis of nocardiosis
   a. Microbiology
      i. Appropriate specimens for laboratory testing
      ii. Morphologic and growth characteristics of *Nocardia* spp.
      iii. Importance of polymerase chain-based species identification
      iv. Importance of antimicrobial susceptibility testing
   b. Radiographic imaging of nocardiosis
      i. Plain radiography
      ii. CT imaging
      iii. MR imaging

3. Treatment of *Nocardia* infections
   a. Principles of antimicrobial therapy
      i. Induction (initial) therapy
      ii. Maintenance therapy
   b. Monitoring response to therapy
      i. Clinical parameters
      ii. Radiographic response
   c. Determining duration of therapy
      i. Pulmonary nocardiosis
      ii. CNS nocardiosis

4. Prevention of nocardiosis after CT TX
   a. Safe living strategies after transplantation
      i. Precautions for outdoor activities
      ii. Avoidance of outdoor activities during periods of intense immunosuppression
   b. Efficacy of anti-infective prophylaxis
      i. Primary prevention (with *Pneumocystis* prophylaxis regimens)
      ii. Secondary prevention

**Key References**


Section V: Fungal Infections in CT TX

A. Learning objectives for Yeast Infection

1) Understand the differences in incidence, epidemiology, timing and clinical presentation of yeast infections in the cardiothoracic transplant recipient
2) Appreciate the role of molecular and serologic tests in diagnosis
3) Appreciate the risk of emergent yeast species resistant to azoles
4) Understand the risk of immune-reconstitution inflammatory syndrome (IRIS) associated with yeast infections in transplant recipients

Essential Content

1. Epidemiology in CT TX. Incidence/prevalence of yeast infections. Special considerations according to different scenarios
   a. Lung recipients
   b. Heart
2. Most frequent yeast
   a. Candida albicans and non albicans species
   b. Emergent yeast species resistant to azoles
   c. Other yeast
   d. Cryptococcosis
   e.
3. Risk Factors with special consideration to the different scenarios of lung or heart transplantation
   a. Early period
   b. Late period post-transplant/surgery
4. Clinical presentations with special consideration to the different scenarios of lung or heart transplantation
   a. Colonization, organ infection, bloodstream infections
   b. Candida in respiratory cultures
   c. Candida in urinary cultures
5. Diagnosis
   a. Microbiological tests
6. Prophylaxis with special consideration to the different scenarios of lung or heart transplantation
   a. Universal prophylaxis
   b. Targeted prophylaxis
7. Treatment
   a. MIC different antifungal drugs, usual susceptibility patterns for yeasts
   b. Recommended therapy
   c. Combination therapy and step down phase
8. Immune Reconstitution Inflammatory Syndrome
   a. Epidemiology
   b. Frequent Scenarios
   c. Inflammatory response
   d. Treatment

Key References

8. Husain S et al 2014 ISHLT Fungal guidelines for MCS and CT TX
B. Learning Objectives for Mold Infection

1) Understand and appreciate the differences in the incidence, epidemiology, timing and clinical presentation of mold infections in the lung transplant and heart transplant recipient in the early and late post-transplant periods

2) Recognize the risk factors for these different scenarios in order to plan a reasonable prophylaxis

3) Understand the role of non-microbiological tests in blood and bronchial alveolar lavage (BAL) for diagnosis of mold infection

4) Appreciate the different approaches available to treat severe mold infections including prophylaxis, treatment, and new immunomodulatory strategies

Essential Content

1. Epidemiology in CT TX: incidence/prevalence of molds infection with special consideration to the different scenarios
   a. Lung recipients
   b. Heart recipients

2. Most frequent molds
   a. Aspergillus
   b. Non – Aspergillus molds. Scedosporium, Fusarium, zygomycetous fungi
   c. Breakthrough infections

3. Risk Factors with special consideration to the different scenarios of lung or heart transplantation
   a. Early period post-surgery
   b. Late period post-surgery

4. Clinical presentations with special consideration to the different scenarios of lung or heart transplantation
   a. Colonization
   b. Airway disease
   c. Invasive pulmonary disease
   d. Disseminated disease
   e. Surgical wound infections

5. Diagnosis
   a. European Organization for Research and Treatment of Cancer and Mycoses Study Group (EORTC/MSG) and ISHLT criteria
   b. Microbiological tests including fungal smear and culture
   c. Non culture diagnostic methods
      i. Galactomannan
      ii. Beta-D-glucan
      iii. Polymerase chain reaction (PCR)

6. Radiological methods
a. CT Scan
b. Positron-emission tomography with 18-fluoro-2-deoxyglucose (PET)

7. Prophylaxis
   a. Lung Transplant
      i. Targeted versus universal prophylaxis
      ii. Antifungal drugs used for prophylaxis, role of azoles and nebulized amphotericin
   b. Heart transplant

8. Treatment
   a. Antifungal drugs
   b. Usual susceptibility patterns for molds
   c. Amphotericin B, azoles, echinocandins
   d. Interactions/ side effects
   e. Therapeutic drug monitoring
   f. Recommended treatment for molds
   g. Special situations
      i. Combination therapy and step down phase
      ii. Surgery
      iii. Sanctuary infections
      iv. Local instillation of antifungal drugs

Key References

9. Husain S et al 2014 ISHLT Fungal guidelines for MCS and CT TX

C. Learning Objectives for Endemic Mycoses Infection

1) Understand the epidemiology, pathogenesis, clinical presentation, treatment and prevention of the most prevalent endemic mycoses infections in CT TX, including histoplasmosis, blastomycosis, and coccidiodomycosis
2) Recognize the risk factors for these endemic mycosis in the donor or transplant recipient in order to plan a reasonable prophylaxis for the cardiothoracic transplant recipient
3) Understand the role of microbiological and non-microbiological testing in blood and BAL in the diagnosis of active or previous or latent infection with the endemic mycosis infections in the cardiothoracic transplant recipient

Essential Content

1. Introduction
   a. Description
   b. Geographical distribution
   c. Endemic fungal donor derived infections
2. Histoplasmosis
   a. Epidemiology and pathogenesis
   b. Prevention
   c. Clinical presentation
   d. Diagnosis: fungal stain, culture, antigen detection and serologic test
   e. Treatment
   f. Prevention
3. Blastomycosis
   a. Epidemiology and pathogenesis
   b. Prevention
   c. Clinical presentation
   d. Diagnosis: fungal stain, culture, antigen detection and serologic test
   e. Treatment
   f. Prevention
4. Coccidiodomycosis
   a. Epidemiology and pathogenesis
   b. Prevention
c. Clinical presentation
d. Diagnosis: fungal stain, culture, antigen detection and serologic test
e. Treatment
f. Prevention

Key References

7. Husain S et al. 2014 ISHLT Fungal guidelines for MCS and CT TX

Section VI: Viral Infections in CT TX

A. Learning Objectives for Cytomegalovirus (CMV)

1) Understand CMV epidemiology and clinical biology
   a. Understand donor and recipient’s serology and associated risk
   b. Basic knowledge of the interplay between CMV and host immune system
2) Recognize CMV infection (primary vs. reactivation) and CMV disease
   a. Understand the different assays for CMV monitoring
   b. Recognize the possible clinical presentations of CMV disease
   c. Awareness of direct and indirect effects of CMV infection
3) Plan prevention, treatment and monitoring strategies for CMV infection
   a. Awareness of the pros/cons of prophylaxis vs. pre-emptive strategies and ability to customize strategy according to Centre’s and patient’s features
   b. Knowledge of the anti-CMV drugs available, their indications and mode of use, including the interaction of CMV with immunosuppressive strategies
   c. Recognize CMV drug resistance and plan alternative strategies
Essential Content

1. CMV
   a. Definitions
      i. CMV infection
      ii. CMV syndrome
      iii. CMV disease
   b. Epidemiology
      i. Heart: Adult & pediatric
      ii. Lung: Adult & pediatric
   c. Risks for CMV
      i. Donor/recipient serostatus
      ii. Immunosuppression & augmentation of immunosuppression
      iii. Induction therapy
   d. Indirect effects of CMV
      i. Immunomodulatory effects of virus
      ii. Associated infections (fungal, bacterial)
      iii. Coronary artery vasculopathy (heart)
      iv. Acute/chronic rejection (lung)

2. CMV infection and disease
   a. Monitoring assays
      i. Viral presence: antigenemia, PCR, international standards
      ii. Immunologic responses
         1. ELISPOT, IFN-gamma assays
   b. Clinical presentation

3. Prevention
   a. Definitions of prevention strategies
      i. Prophylaxis
      ii. Pre-emptive therapy
      iii. Hybrid/sequential therapy
   b. Comparison of risk/benefits of prevention strategies
   c. Interplay between monitoring capacity and prevention strategy choice
   d. Prophylaxis vs. pre-emptive therapy – current data
      i. Heart
      ii. Lung

4. Treatment
   a. Antivirals
      i. Ganciclovir/Valganciclovir
      ii. Foscarnet
      iii. Cidofovir (including new formulations)
      iv. Products in the pipeline
   b. Adjunctive therapy
      i. Immunoglobulins (CMVIG, IVIG)
      ii. Emerging therapy including viral-specific T-cell infusions
5. Resistance
   a. Mechanisms
   b. Timing
   c. Risks for resistance
   d. Assays to detect resistance
   e. High-level/Low-level resistance mutations
   f. Treatment alternatives

Key References

B. Learning Objectives for Epstein-Barr Virus (EBV)

1) Understand the relationship between EBV and post-transplant lymphoproliferative disorder (PTLD), and appreciate the risk for developing PTLD in cardiothoracic transplant recipients
2) Understand the clinical presentation, diagnostic strategies, and appropriate management for EBV infections in cardiothoracic transplant recipients
3) Understand the role of immunoprophylaxis, chemoprophylaxis, and pre-emptive strategies for preventing EBV infections in cardiothoracic transplant recipients

Essential Content

1. Epstein Barr Virus
   a. Lytic and latent phases
   b. Definition of syndrome including clinical presentation
   c. Risk for infection
      i. Primary vs reactivation including definitions
      ii. Donor/recipient serostatus
      iii. Impact of CMV prevention on EBV
   d. Diagnosis
      i. Molecular assays including international standards
      ii. Serology
   e. Interventions
      i. Decreased immunosuppression
      ii. Controversy over antiviral administration

2. Post-transplant lymphoproliferative Disease
   a. Presentation
      i. Introduction of EBV-related vs non-EBV related PTLD
   b. EBV-related PTLD Risk factors
      i. Age
      ii. Donor/recipient serostatus
      iii. Primary vs reactivation infection
      iv. Role of EBV monitoring and prediction of PTLD
   c. Diagnosis
      i. Tissue diagnosis and classification system
   d. Treatment strategies
      i. Immunosuppression reduction
      ii. Rituximab
         1. Pre-emptive rituximab included
      iii. Chemotherapy

Key References
C. Learning Objectives for Other Herpes Virus Infections

1) **Understand the epidemiology, presentation, timing, diagnosis and therapy for herpes simplex (HSV) and varicella-zoster (VZV) in the cardiothoracic transplant recipient**
2) **Plan appropriate prevention strategies including vaccination, immunoglobulin use and antiviral therapy for HSV and VZV in cardiothoracic transplant candidates and recipients**
3) **Appreciate the clinical presentations associated with human herpes viruses (HHV) 6, 7 and 8 in cardiothoracic transplant recipients including the risk of donor derived infection with HHV 8**

**Essential Content**

1. HSV
   a. Epidemiology and changes since introduction of routine prophylaxis
   b. Presentation and timing
   c. Primary vs reactivation
   d. Diagnostic techniques
      i. Serology, direct fluorescent antibody (DFA), culture, PCR
   e. Treatment
      i. Antiviral therapy
   f. Recurrence prevention
      i. Suppressive antivirals

2. VZV
   a. Epidemiology
   b. Presentation and timing
      i. Primary disease
      ii. Disseminated disease
      iii. Reactivation (zoster)
         1. Single vs multiple dermatome involvement
         iv. Unusual presentations in immunocompromised hosts
   c. Diagnostic techniques
      i. Serology, DFA, culture, PCR
d. Treatment
   i. Antiviral therapy

e. Prevention
   i. Pre-transplant vaccination
   ii. Response to exposures in seronegative patients
      1. Monitoring
      2. Immunoglobulin infusions
      3. Antiviral prophylaxis
   iii. Infection control measures

3. HHV-6 and HHV-7
   f. Associated syndromes reported
   g. Diagnostics
      i. Serology including avidity testing
      ii. PCR
   h. Controversy regarding viral presence and disease association

4. HHV-8
   i. Epidemiology
      i. Geographical risk
      ii. Demographic risk
   j. Kaposi sarcoma

Key References


D. Learning Objectives for Influenza and Other Seasonal Respiratory Viruses

1) Know the clinical presentation, incidence, diagnosis, treatment and prevention of common, community acquired respiratory viruses (CARV) including influenza, parainfluenza, respiratory syncytial virus, human metapneumovirus, coronavirus/rhinovirus, and adenovirus in the cardiothoracic transplant population
2) Discuss what is known about the possible association of CARV and development of rejection and bronchiolitis obliterans syndrome (BOS) in lung transplant recipients
3) Understand the unique considerations for cardiothoracic transplant centers during an influenza epidemic or pandemic period

Essential Content

1. CARV – virus specific information
   a. Influenza
      i. Epidemiology & Seasonality
      ii. Presentation
         1. Pulmonary
         2. Non-pulmonary
      iii. Diagnostics
         1. Rapid antigen testing – false-negative rates
         2. Molecular diagnostics
      iv. Treatment
         1. Antivirals including emerging antivirals
         2. Treatment of resistant virus
      v. Prevention strategies
         1. Vaccination of patient and close contacts (“circle of protection”)
         2. Prophylactic use of antivirals
            a. For exposure
            b. Seasonally
      3. Donor considerations
   b. Parainfluenza
      i. Epidemiology and community infection patterns
      ii. Emerging antiviral therapy
   c. Respiratory Syncytial Virus (RSV)
      i. Epidemiology
      ii. Presentation
      iii. Treatment strategies in lung transplantation
         1. Antivirals, steroids, immunoglobulin combinations
         2. Palivizumab
   d. Human metapneumovirus
      i. Epidemiology
      ii. Diagnostics (culture negative)
   e. Rhinovirus
      i. Epidemiology
      ii. Persistence
   f. Adenovirus
      i. Epidemiology
      ii. Presentation
         1. Pulmonary
         2. Non-pulmonary
      iii. Treatment
1. Antivirals
2. Adenovirus-specific T-cell infusions (investigative)

2. CARV and Associated Outcomes
   a. CARV and acute rejection
   b. CARV and BOS
      i. Virus-specific data

Key References


E. Learning Objectives for Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV)

1) Understand the lessons learned from liver and kidney transplantation in HIV infected patients
2) Understand the potential drug interactions between HIV antiretrovirals and immunosuppressants
3) Recognize the challenges of current HCV treatment modalities in transplant recipients and gaps in knowledge to guide the management of HCV in thoracic transplant candidates and recipients

Essential Content

1. HIV
   a. Experience in liver/kidney
      i. Outcomes
      ii. Monitoring
      iii. Drug interactions
      iv. Teamwork/multidisciplinary team use
   b. Strategies in cardiothoracic transplantation
      i. Current data on outcomes
ii. Pre-transplant assessment, criteria for listing and monitoring
   1. Potential for changing regimen pre-transplant to decrease post-transplant drug-drug interactions

iii. Post-transplant planning
   1. Drug interaction and HIV monitoring
   2. Involvement of HIV-focused team-members
   3. Risk for rejection
   4. Long-term outcome monitoring

2. HCV
   a. Epidemiology
      i. Geographic and demographic risk
      ii. Current outcomes
      iii. Diagnosis and monitoring
         1. Reactivation of disease
      iv. Treatment
         1. Pre-transplant
         2. Post-transplant

Key References

4. 2014 Lung Listing Criteria Consensus Document
5. 2014 Heart Listing Criteria Consensus Document

F. Learning Objectives for Other Viral Infections

1) Know the clinical manifestations, diagnosis, prevention, and treatment of less prevalent viruses including Human T cell lymphotrophic virus types 1 and 2 (HTLV 1-2), Parvovirus B19, JC polyomavirus, West Nile virus, Rabies, and Lymphocytic choriomeningitis virus (LCMV)

Essential Content

1. HTLV 1-2
a. Epidemiology & Geographic distribution
b. Presentation and associated diseases
c. Diagnosis
d. Treatment

2. Parvovirus
   a. Pre-transplant association with cardiac disease
   b. Post-transplant
      i. Presentation
         1. Initial presentation
         2. Persistence of infection in immunocompromised hosts
         Diagnosis
      ii. Treatment
      iii. Isolation practices

3. JC virus
   a. Epidemiology
   b. PML presentation
      i. Association with rituximab
   c. Diagnostics

4. West Nile virus
   a. Donor-derived infection reports
   b. Presentation/Clinical syndrome
   c. Diagnosis
   d. Treatment
   e. Prevention strategies

5. Rabies
   a. Epidemiology
   b. Donor-derived infection reports
   c. Presentation/ Clinical syndrome
   Diagnosis
   d. Post-exposure prophylaxis

6. LCMV
   a. Donor-derived infection reports
   b. Presentation and diagnosis

Key References


Section VII: Parasitic Infections in CT TX

A. Learning Objectives for Toxoplasmosis and Strongyloidiasis

1) Understand the transmission, prophylaxis and treatment of toxoplasmosis (Toxoplasma gondii) and how it affects heart transplantation in particular
2) Understand the life cycle of Strongyloides stercoralis and how it impacts latent infection
3) Know the epidemiology, clinical manifestations (primary, chronic and hyper infection syndrome), diagnosis, prevention, and treatment of Strongyloides infection

Essential Content

1. Toxoplasma gondii lifecycle
   a. Growth from oocyst, to tachyzoite, to bradyzoite (within cysts)
   b. Cat is target host
2. Toxoplasma transmission
   a. Contact with cysts in meat or soil
   b. Oocysts in cat feces
   c. Via organ or blood transmission
   d. Seronegative heart transplant recipients are at increased risk for symptomatic infection when receiving hearts from seropositive donors
   e. Maternal-fetal
3. Prevention of toxoplasmosis
   a. Screening of donor or recipient for heart transplant or in high prevalence areas by antibody testing, PCR testing if concern for active infection
   b. Trimethoprim sulfamethoxazole daily or thrice weekly is preferred therapy
   c. Dapsone plus pyrimethamine has been used in HIV infected patients, atovaquone is also likely to be effective
   d. The optimal length of prophylaxis is unknown
   e. Avoid contact with undercooked meat or animal feces
4. Clinical presentation of toxoplasmosis
   a. Often presents in first 3 months post transplant or after stop of prophylaxis
   b. Fever, pancytopenia, lymphadenopathy, hepatosplenomegaly can be seen
   c. Often with characteristic ring-enhancing lesions with CNS disease
4. Myocarditis, meningitis, brain abscess, chorioretinitis, pneumonitis, disseminated disease

5. Treatment of toxoplasmosis
   a. Pyrimethamine and sulfadizine is preferred regimen
   b. Pyrimethamine and clindamycin if sulfa allergic
   c. Chronic suppression therapy after induction is recommended

6. *Strongyloides stercoralis* lifecycle
   a. Can complete its lifecycle in the human host or the environment
   b. Endemic to the tropics and subtropics as well as southern and eastern Europe, the United Kingdom, and the southeastern United States
   c. Filariform larvae enter through the skin then pass through blood to lung, then the gastrointestinal system
   d. Sexual and asexual reproduction, perpetuating the infection
   e. Immunosuppression accelerates larval development, leading to auto-reinfection and the development of a large parasitic burden

7. Strongyloidiasis clinical syndromes
   a. Primary
      i. Purpuric rash, pneumonitis, or asymptomatic
      ii. Eosinophilia
   b. Chronic
      i. Abdominal pain, possible nausea, vomiting, diarrhea
      ii. Sometimes eosinophilia
   c. Hyper infection
      i. Respiratory symptoms, can progress to acute respiratory distress syndrome (ARDS) and respiratory failure
      ii. Gastrointestinal symptoms can cause ileus and bleeding
      iii. Eosinophilia frequently absent
      iv. Can cause bacteremia due to Gram negative enteric organisms as larvae migrate from gastrointestinal tract to blood
   d. Disseminated infection
      i. Larvae travel through the venous system throughout the body
      ii. Can cause meningitis, cholecystitis, liver abscess, pancreatitis

8. Strongyloidiasis diagnosis
   a. Serology testing
   b. Stool ova and parasite exam or wet mount of respiratory specimen
   c. Duodenal biopsy

9. Strongyloidiasis prevention
   a. Screening of patients from endemic regions or with unexplained eosinophilia

10. Strongyloidiasis treatment
    a. Ivermectin x 2 days for uncomplicated intestinal disease, alternately albendazole
    b. Ivermectin for prolonged course for hyperinfection or disseminated disease, consider reduction in immunosuppression
    c. Broad spectrum antibiotics if suspect secondary bacterial infection
Key References

2. Schwartz BS, Mawhorter SD, and the AST Infectious Diseases Community of Practice; Parasitic Infections in Solid Organ Transplantation; Am J of Transplantation, 2013; 13 (Supple 4): S280-303

B. Learning Objectives for Chagas Disease

1) Understand the role of Chagas Disease in heart failure
2) Know the clinical presentation, diagnosis, treatment, and prevention of Chagas Disease in heart transplant recipients

Essential Content

1. Trypanosoma cruzi lifecycle and epidemiology
   a. Acquired through vector-borne transmission via triatomine insects
   b. Trypomastigotes disseminate via lymphatics and bloodstream, can infect multiple cell types
   c. Natural infection occurs in the North and Central America from the southern United States to Argentina and Chile
   d. Post-transplant disease may be due to transmission via infected organ or reactivation of chronic infection
2. Pathophysiology of Chagas disease
   a. After insect-borne transmission an antibody response limits parasite replication but does not clear infection
   b. In chronic infection multifocal mononuclear inflammatory infiltrates occur with low-grade tissue parasite infestation, but low or undetectable parasitemia
   c. Organ injury may be inflammatory, vascular, or due to direct parasite injury, or some combination of these
3. Chagas Clinical syndromes
   a. Heart disease
      i. Myocarditis in acute disease
      ii. Arrhythmias including sinus bradycardia, AV block, RBBB, NSVT, atrial fibrillation
      iii. Heart failure progressing to global cardiac dilatation and diffuse hypokinesis
b. Gastrointestinal disease
   i. Esophageal motility disorder
   ii. Megacolon

c. Central Nervous System disease
   i. Meningoencephalitis
   ii. Brain abscess

d. Skin disease has been reported in transplant recipients

4. Chagas diagnosis
   a. Antibody detection
   b. Microscopy of peripheral blood smear or buffy coat preparation
   c. PCR of whole blood or tissue

5. Chagas prevention
   a. Screening of potential donors and recipients born in Mexico, Central America, and South America
   b. Hearts from known infected donors should not be transplanted
   c. If transplantation of organ from infected donor occurs, recipients should be monitored by PCR and buffy coat microscopy

6. Chagas treatment
   a. Nifurtimox and benznidazole have efficacy against *T. cruzi*; however both can cause significant side effects. In the United States it can be obtained from the CDC Drug Service, Acute or reactivated Chagas disease should be treated immediately
   b. There is no data that prior treatment or post-transplant prophylaxis decreases reactivation of chronic disease

Key References

Section VIII: Diagnostic Methods for Detection of Infectious Diseases in CT TX

A. Learning Objectives for Diagnostic Radiology for Infections in CT TX

1) Understand the role of imaging in CT TX
2) Understand the sensitivity and specificity of imaging in central nervous system (CNS) infection
3) Understand the utilization of C.T. imaging of the chest in diagnosing infections in cardiothoracic transplant recipients

Essential Content

1. Imaging in CNS infections for the cardiothoracic transplant recipient
   a. Role of the non-contrast brain CT scan: to rule out intra-cerebral hemorrhage, space-occupying lesions, cerebral vascular accident (CVA), and cerebral edema
   b. Importance of considering intra-cerebral hemorrhage particularly in an anti-coagulated patient, with rapid imaging and neurosurgical consultation
   c. Risks and benefits of the use of intravenous contrast in CT scanning and gadolinium in MRI scanning, particularly in patients with renal dysfunction
   d. Role of the brain CT scan with intravenous contrast: enhancing lesions may indicate brain abscesses (bacterial, fungal, parasitic including toxoplasmosis), septic emboli related to bloodstream infection or endocarditis, malignancy including PTLD
   e. Role of the MRI scan: better delineation of focal lesions such as brain abscess, CVA, masses and characteristic changes of progressive multifocal leukoencephalopathy (PML) and posterior reversible encephalopathy (PRES)
   f. Radiographic characteristics of bacterial brain abscesses, septic emboli, nocardial infections
   g. Radiographic characteristics of fungal brain lesions
   h. Radiographic characteristics of cerebral tuberculosis and non-tuberculous mycobacterial infections
   i. Radiographic characteristics of viral encephalitis (HSV, CMV, HHV-6 etc)
   j. Radiographic characteristics of PTLD in the CNS
   k. Radiographic characteristics of JC-virus associated PML
   l. Radiographic characteristics of PRES related to calcineurin inhibitors or sirolimus
   m. Radiographic characteristics of more unusual conditions (echinococcosis, cysticercosis)
   n. Radiographic imaging of the sinuses and orbits: distinguishing acute from chronic sinusitis, air-fluid levels, bony involvement, cavernous sinus involvement.
2. Role of CT imaging of the chest in diagnosis of infections in cardiothoracic transplant recipients
   a. Sternal wound infections and mediastinitis post-transplant
   b. Other surgical infectious complications including empyema, infected hydropneumothorax, bronchopleural fistula
   c. Pulmonary infiltrates (bacterial, viral, fungal, parasitic, and non-infectious causes)
   d. Characteristics of imaging of the lung parenchyma that help to distinguish possible underlying causes: focal vs. multifocal vs. diffuse infiltrates, lobar pattern, air bronchograms, nodules, cavitations, halo sign; hilar and mediastinal adenopathy.
   e. Importance of comparison with pre-transplant chest CT imaging if available (e.g. old scarring, pre-existing nodules)
   f. Radiographic characteristics of Pneumocystis jiroveci pneumonia
   g. Radiographic characteristics of CMV pneumonitis
   h. Radiographic characteristics of PTLD in the thorax
   i. Radiographic characteristics of lower respiratory tract infection due to community respiratory viruses
   j. Radiographic characteristics of nocardial infection
   k. Radiographic characteristics of fungal infection
   l. Radiographic characteristics of tuberculosis and nontuberculous mycobacterial infection
   m. Noninfectious causes of radiographic pulmonary abnormalities: e.g. pulmonary edema, malignancy, sirolimus-associated interstitial pneumonitis
   n. Unusual radiographic manifestations in the differential diagnosis: e.g. diffuse infiltrates in the setting of overwhelming fungal infection, nodular presentation of Pneumocystis
   o. Importance of considering infection with more than one pathogen, or simultaneous infectious and noninfectious processes
   p. Role of CT guidance for aspiration and biopsy of suspicious nodules or masses for microbiologic testing and pathology/cytopathology

Key References

1. Lawler L, Kinsella A, O'Shea D; Chapter 29: Diagnostic Radiology for Infectious Diseases in the Cardiothoracic Transplant and Mechanical Support Recipient in ISHLT Monograph Series 5: Diagnosis and Management of Infectious Diseases in Cardiothoracic Transplantation and Mechanical Circulatory Support, Edited by M Mooney, M Hannan, S Hannan, J Kirklin 2011
B. Learning Objectives for Diagnostic Microbiology for Infections in CT TX

1) Understand the diagnostic options in microbiology for diagnosing bacterial, mycobacterial, viral, fungal and parasitic infections in cardiothoracic transplant recipients

2) Understand the use of serologic and polymerase chain reaction (PCR) testing for donor and recipient screening

3) Understand the use of PCR testing in the diagnosis of endogenous viral reactivation infections in the post-transplant period in the cardiothoracic transplant recipient

4) Appreciate the importance and methods of surveillance for CMV in the post cardiothoracic transplant period

5) Understand the role of microbiology in identifying multidrug resistant bacteria and viruses

6) Appreciate the limitations of fungal susceptibility testing

Essential Content

1. Diagnostic options in microbiology for bacterial, mycobacterial, viral, fungal, and parasitic infections in cardiothoracic transplant recipients
   a. Standard blood cultures: at least 2 sets of cultures taken over 24 hours, including at least 1 peripheral and 1 central if a central venous catheter (CVC) is present; including both aerobic and anaerobic bottles, and at least 10 ml for adults and 1 ml/kg for pediatric patients (up to 10 ml) per bottle
   b. Standard urine cultures (clean-catch if possible, or straight-catheterized) should be accompanied by urinalysis to detect pyuria
   c. Urine fungal cultures may be helpful for organisms such as C. glabrata
   d. Limitations of urine cultures in patients with indwelling bladder catheters
   e. Expectorated sputum for Gram stain and routine bacterial culture (or sometimes fungal stain and culture, AFB stain and culture in particular circumstances)
   f. Induced sputum for Pneumocystis
   g. “Immunocompromised Panel” performed on bronchoalveolar lavage (BAL) fluid should include gram stain and bacterial culture, Legionella culture, fungal stain and culture, AFB stain and culture, BAL galactomannan, CMV testing (e.g. PCR or shell-vial culture), respiratory virus testing (e.g. multiplex PCR panel), Pneumocystis stain, cytology, and may include other tests per center preference
   h. Transbronchial biopsy specimen should be obtained in addition to BAL fluid wherever possible, and the above tests performed for microbiology in addition to histopathology (see below)
   i. Discussion of utility of BAL galactomannan, serum galactomannan, blood beta-d-glucan assay, blood serologies for Histoplasma, Blastomyces, Coccidioides, blood cryptococcal antigen, urine Histoplasma antigen
j. Discussion of respiratory viral testing; nasopharyngeal versus BAL, testing modalities (rapid influenza test lower sensitivity, DFA versus PCR, different multiplex tests available)

k. Importance of detection of respiratory viruses particularly in lung transplant recipients due to potential later effects on allograft function

l. Discussion of utility of urine Legionella antigen (only L. pneumophila type 1) and urine pneumococcal antigen testing

m. Stool samples: C. difficile toxin PCR, stool culture for enteric pathogens, detection for Shiga-like toxin, stool microscopic ova and parasites examination, stool EIA for Giardia and Cryptosporidium, stain for Microsporidia, PCR for norovirus, PCR or antigen testing for rotavirus, AFB culture.

n. Nasal S. aureus PCR and sometimes throat or groin swabs for S. aureus PCR surveillance monitoring for infection control and/or decolonization purposes. Stool may be sent for VRE surveillance monitoring

o. Testing on CSF for suspected CNS infection should include cell count and differential, protein, glucose, Gram stain and culture, cryptococcal antigen, fungal stain and culture, AFB stain and culture, syphilis testing e.g. CSF VDRL, cytology, and may include PCR’s for HSV, VZV, CMV, EBV, HHV-6 and 7, JC virus, West Nile virus, Toxoplasma. If epidemiology suggests, can include CSF beta-d-glucan, serology for lymphocytic choriomeningitis virus, regional and seasonal encephalitis viruses as well as other organisms

p. PCR monitoring for T. cruzi for patients at risk for reactivation or donor-derived transmission for Chagas disease, per current guidelines

2. Serologic and PCR testing for screening of donor and recipient
   a. Primary reasons for serologic testing include: risk stratification and post-transplant prevention protocols (e.g. donor/recipient CMV IgG serostatus, donor anti-HBc positivity); in some cases restriction of donor to a subset of recipients (e.g. donor HCV to HCV D+/R+); or occasionally disqualification of the donor (HIV, although that is changing)

b. Changes in the era in which nucleic acid-based test (NAT) testing has become available in the deceased-donor time frame

c. Utility of viral NAT testing: reliability of serologic testing vis-à-vis the window period for HIV, HBV, HCV. The debate and changing environment regarding NAT testing of donors for HIV, HBV, HCV (shortening the window period). Concerns re: false positives and disqualifying donors

d. The most recent proposals of NAT testing of all deceased donors for HCV, no NAT testing for HBV, and NAT testing for HIV for CDC high-risk donors

e. Recipient should be monitored with surveillance molecular testing for HIV, HBV, HCV if high-risk donor is used

f. Current limitations of donor testing due to the nature of the assays: e.g. latent TB infection

g. Regional and exposure-based additions to standard serology panel for donor and recipient: Trypanosoma cruzi, Strongyloides, etc.

3. Use of PCR testing for reactivation of endogenous viral infections post-transplant
a. Monitoring of quantitative EBV PCR for transplant recipients at high risk for PTLD (especially EBV D+/R-) has been shown particularly in pediatric liver recipients to predict PTLD risk and to guide intervention such as reduction of immunosuppression

b. Monitoring of BKV virus PCR in urine or blood for combined thoracic and renal transplant recipients (who are at risk for BKV allograft nephropathy) should be performed, since BKV monitoring in renal transplant recipients is now standard

c. Other PCR testing on blood that may be sent “for cause” in compatible clinical situations, but usually not protocol monitoring in solid organ transplant recipients: includes PCR’s for adenovirus, JC virus, West Nile virus, parvovirus, human herpesvirus 6.

d. Reactivation of HSV and VZV may be in classic localized or disseminated cutaneous forms or occasionally visceral forms with/without rash (hepatitis, pneumonitis, meningoencephalitis.) Diagnosis of cutaneous HSV and VZV relies on skin scraping for Tzanck prep, DFA, viral culture

e. Reactivation of HHV-8 can occasionally occur although histopathology is most helpful in diagnosis of Kaposi’s sarcoma

f. For PCR testing on CSF for suspected meningoencephalitis, see 1q. above.

4. Assays for the detection and surveillance of CMV in the post-transplant patient

a. Serology (IgG) most useful for risk stratification at time of transplant. IgM does not have sufficient sensitivity for diagnosis of active infection

b. Historical perspective: CMV tissue culture, shell-vial culture, pp65 antigenemia assay – still sometimes used, but largely replaced by molecular testing for diagnosis of active viremia

c. Molecular era: quantitative CMV PCR, other molecular assays. Advantages: quantitation, stability when mailed into central lab

d. Inter-laboratory variation should decrease with introduction of International Units and the first FDA-approved quantitative CMV PCR in 2013

e. Pre-emptive therapy: importance of frequency of monitoring and prompt action particularly for high-risk patients

f. Correlation of height of viral load with likelihood of symptomatic CMV (including CMV syndrome, tissue-invasive CMV) while lower viral loads are often associated with asymptomatic viremia

g. Exceptions to the above: occasionally biopsy-proven tissue-invasive CMV (especially in the GI tract) with low or undetectable blood viral load

5. Role of the microbiology laboratory in detection of antimicrobial-resistant bacteria and viruses

a. Detection of and surveillance of MRSA (e.g. nasal PCR) and VRE (stool)

b. Standard panels of antimicrobials for susceptibility testing for gram-negative isolates

c. Rise of carbapenemase-producing Enterobacteriaceae and multi drug resistant (MDR) Pseudomonas, Stenotrophomonas, Achromobacter, Burkholderia
d. Additional susceptibilities which may be requested individually, that might not be on standard panels (fosfomycin for urine isolates, colistin for Pseudomonas, tigecycline for some gram-negative rods but not Pseudomonas or Proteus, ceftaroline for MRSA)

e. Importance of susceptibility panels of previous isolates from the same patient, for formulation of empiric therapy in the febrile or septic patient

f. Antiviral resistance in CMV: UL97 and UL54 mutation genotyping for CMV (most commonly seen in multiply-treated D+/R- recipients)

g. Antiviral resistance in HSV: detection of acyclovir-resistant HSV (uncommon in SOT but seen more often after HSCT)

h. Antiviral resistance in influenza: Follow CDC guidelines each influenza season for antiviral management and for incidence of resistance to oseltamivir and other antivirals. Resistance testing for influenza

6. Understanding the limitations of antifungal susceptibility testing

a. Most important for Candida spp. particularly non-albicans

b. C. krusei is intrinsically fluconazole-resistant; C. glabrata is frequently fluconazole-resistant; even when “SDD” (susceptible, dose-dependent), therapy with fluconazole may fail. Other non-albicans Candida spp. such as C. parapsilosis and C. kefyr are on the rise and susceptibilities may be unpredictable

c. Candida spp. susceptibility testing generally includes fluconazole and an echinocandin but amphotericin, flucytosine, and other agents may be requested

d. Refer to currently changing national and international guidelines with regards to azole and echinocandin susceptibility breakpoints for Candida spp. Also consult latest candidemia guidelines for updates to recommendations

e. Susceptibility testing for mold isolates is more difficult and harder to interpret, and generally performed only by a few highly specialized laboratories. MIC breakpoints are not clearly defined

Key References


3. Husain S et al  2014 ISHLT  Fungal guidelines for MCS and CT TX

C. Learning Objectives for Diagnostic Pathology for Infections in CT TX
1) Appreciate that the appropriate multidisciplinary diagnostic strategy for diagnosing bacterial/ viral/ parasitical/ fungal infection in cardiothoracic transplant recipients includes the clinical pathologist

2) Understand that classic tissue reactions to pathogens may be lacking in the cardiothoracic transplant recipient and a broad differential diagnosis needs to be considered when the pathologist is interpreting tissue reaction patterns in this patient population

3) Appreciate the usefulness of BAL and trans-bronchial biopsy specimens for the cytologic and pathologic evaluation of a pulmonary infection with a variety of methods of staining to identify specific pathogens, like fungal, mycobacterial, viral and atypical bacteria

**Essential Content**

1. Multidisciplinary strategies for diagnosing infection, including the clinical pathologist
   a. The clinical pathologist is a key member of the team; the histopathologic findings and microbiologic findings are often complementary, and together can guide clinicians to a diagnostic and therapeutic strategy
   b. Cultures are all too frequently no growth due to prior antibiotic therapy, in which case histopathology as well as molecular testing assume even greater importance
   c. In addition to tissue patterns of host response and inflammation, which can provide clues to the nature of the pathogen, visualization of morphology of pathogens in tissue may be diagnostic (i.e. characteristic appearance of certain fungi such as zygomycetes that can be difficult to grow in culture)

2. Classic tissue patterns may be absent in severely immunocompromised transplant recipients.
   a. Both the pathologist and the clinician should be aware that the absence of classic reactions to pathogens such as granulomatous inflammation does not rule out certain infections (e.g. mycobacterial) as immune responses may be altered in this population
   b. Neutropenic transplant recipients (due to viral infection or medications) will have an even more impaired inflammatory response to infection
   c. Broad differential diagnosis should be considered, using histopathologic responses as clues, but not as rigid criteria for ruling out pathogens
   d. Immunostaining or in situ hybridization or other molecular testing performed on tissue can give additional pathogen-specific information (CMV, EBV, adenovirus, HSV, etc.)

3. The importance of BAL and trans-bronchial biopsy specimens for cytologic and pathologic examination
   a. Cytology on BAL fluid and histopathology on the transbronchial biopsy
   b. Cytology may reveal evidence of malignancy (including lung cancer or PTLD), alveolar hemorrhage (hemosiderin-laden macrophages) diagnostic clues to
pathogens (eosinophilia may indicate fungal or parasitic infection; lymphocytosis or atypical lymphocytes in some viral infections); or occasionally cells with direct pathogen visualization, e.g. viral inclusions or intracytoplasmic parasites such as *Histoplasma capsulatum*.

c. Transbronchial biopsy adds information to the BAL fluid: special stains (GMS, AFB, PAS, etc). Histopathology may reveal pathologic patterns such as PTLD, fungal hyphal tissue invasion, viral inclusions such as CMV or adenovirus.

d. #2d above applies to transbronchial biopsy specimens, in terms of immunostaining and molecular diagnostic assays on tissue. Immunostaining is particularly helpful for CMV pneumonitis, as occasional cases do not show characteristic viral inclusions on histopathology but are positive by immunostain for CMV.

e. Importance of the transbronchial biopsy in assessing rejection since infection and rejection can coexist, and modulation of immunosuppression is dependent on these results.

**Key References**


**Section IX: Other Areas of Concern in CT TX**

**A. Learning Objectives for CT TX and Travel**

1) Understand the increased travel-related risks posed to the immunocompromised cardiothoracic transplant recipient

2) Identify and understand strategies to minimize travel-related risks

3) Manage illness during travel, including patient education and preparation, travel restrictions, recommended (or contraindicated) immunizations, prophylactic medications, communication with transplant center and other resources available while abroad
4) **Understand the risks associated with donor travel and transplant tourism**

**Essential Content**

1. Timing of travel post-transplant
2. Routine vaccines
3. Preparation prior to travel based on geography
   a. Review of travel resources including Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO)
   b. Travel vaccines
   c. Malaria prophylaxis
   d. Gastroenteritis management
   e. High altitude
4. Travel-related educational information
   a. Clean food and water
   b. Insect avoidance measures
   c. Minimizing sun exposure
   d. Obtaining optimal medical care away from home
   e. Reducing risk of blood-born and sexually transmitted infections
5. Illness abroad
   a. Plan for medical care and emergency contacts if needed
6. Transplant tourism
   a. Risk of infection
   b. Post-transplant screening for infections after return to home country
      i. Blood-borne pathogens
      ii. Endemic pathogens depending on geography
7. Donor travel
   a. History of travel not always known
   b. Donor derived infections in recipient based on geography of travel of donor

**Key References**


**B. Learning Objectives for Approaches to Emerging Infectious Pathogens**
1) Recognize the vulnerability of cardiothoracic organ recipients to pathogens such as antimicrobial-resistant bacteria, viruses, and fungi

2) Recognize that the clinical presentation and pathogen behavior may be altered in the cardiothoracic transplant recipient

3) Become familiar with the resources available to the cardiothoracic transplant specialist for identifying and managing infections caused by emerging pathogens

Essential Content

1. Risk of emerging infections
   a. Pertinent history from transplant donor at time of cardiothoracic transplantation
      i. Unexplained symptoms at time of death such as encephalitis
      ii. Geographic location of donor at death
      iii. Epidemiologic exposures of donor: occupation, hobbies, pets, travel history
      iv. High-risk activities: multiple sexual partners, men who have sex with men (MSM), intravenous drug use (IVDU)
      v. Pertinent donor culture and microbiological data at time of death
   b. Pertinent history from mechanical circulatory support at time of transplant surgery
      i. Relevant culture data from patient
      ii. Local epidemiological data from hospital
      iii. Indwelling devices at time of surgery (ex, central lines)
      iv. Antimicrobial exposures prior to surgery
      v. Cause of heart failure such as acute and unexplained or chronic disease
   c. Unique presentation of emerging infections in the transplant recipient relative to “normal” host
      i. More symptomatic after exposure to particular organism
      ii. Increased severity or chronicity of disease after exposure to particular pathogen
      iii. Multiple potential routes of infection (healthcare exposures, antibiotic exposures/prophylaxis, mucosal breakdown with immunosuppression)
      iv. Contagious for prolonged period of time (prolonged viral shedding,) may lead to increased mutations and novel pathogens

2. Emerging infections in transplant recipients
   a. Lymphocytic choriomeningitis virus
   b. Rabies
   c. *Strongyloides stercoralis*
   d. *Trypanosoma cruzi*
   e. West Nile Virus
   f. Multi-drug resistant organisms
      i. Inducible-beta lactamases
ii. ESBL-positive gram negative rods
iii. KPC-positive gram negative rods
iv. MRSA/VRSA/VISA and VRE

3. Approach to diagnosis
   a. Advantages and disadvantages of different diagnostic tools
   b. Pitfalls in diagnosing infection in the immunocompromised patient
      i. Serological data – lower yield for detection of acute disease in transplant recipient; only useful for detecting prior exposure
      ii. Molecular data (PCR) – higher yield in transplant recipient for acute disease, especially when obtained from source of infection (ex, CSF, pleural fluid)
   c. Diagnostic Strategies:
      i. Cultures
         1. Type: Aerobic/anaerobic, Fungal, AFB, Viral
         2. Source: blood, bronchoscopy, CSF, bone marrow, body fluids
      ii. Serological Data
         1. Atypical bacteria (Legionella, Chlamydia)
         2. Fungal pathogens (Endemic mycoses, Invasive fungi)
         3. Viral pathogens
         4. Parasites
      iii. Molecular Data
         1. Viral pathogens
   iv. Cytology/Pathology
   v. Imaging

Resources for the Transplant Specialist (webpages, organizations)


Key References

General

2. Humar A, Stosor V. Chapter 33: Approaches to Emerging Infectious Pathogens in Cardiothoracic Transplantation and Mechanical Circulatory Support. In: ISHLT Monograph
Lymphocytic choriomeningitis


Rabies


**Strongyloides stercoralis**


Trypanosoma cruzi


West Nile Virus


**Multi-drug resistant organisms**


**Section X: Infection in the Setting of Mechanical Circulatory Support (MCS)**

**A. Learning Objectives for Historical Overview**

1) Appreciate the change in the types of devices over the past 2 decades
2) Learn about new and upcoming devices
3) Discuss the change in the patient population in whom these devices are implanted and change in indications
4) Know the prevalence and incidence of infections in MCS recipients over time

**Essential Content**
1. INTERMACS registry updates and clinical trials which show changes over time
   a. Device size
   b. Device type- pulsatile vs. continuous flow
   c. Driveline size
   d. Intra-corporeal
   e. Magnetic
2. New devices
   a. Intra-pericardial placement
   b. Trans-cutaneous energy transfer
3. Change in patient population and indications
4. Change in incidence of infections and sepsis over time
5. Discuss limitations in studies as well as lack of standardized definitions for infections

Key References


B. Learning Objectives for Evaluating and Minimizing Risk of Infection in MCS

1) Learn how to optimize patient selection for MCS via ideal screening for latent/unrecognized infections in candidates for MCS, both destination therapy (DT) and bridge to transplant (BTT)
2) Learn how to manage microbial colonization prior to MCS placement
3) Know the management of nosocomial infections prior to MCS implantation (pneumonia, catheter-related bacteremia, UTI, Clostridium difficile infection)
4) Recognize risk factors associated with device infection

Essential Content

1. Screening for latent/unrecognized infections
   a. latent TB; hepatitis A, B and C; HIV; syphilis, endemic fungal infections (in appropriate geographic areas – Coccioidiodes, histoplasmosis); parasitic infections (in appropriate geographic areas – T. cruzi, S. stercoralis), +/- viral infections (mainly in BTT – CMV, EBV)
2. Screening and treatment of MRSA colonization
3. Infection control practices for VRE, multi-drug resistant gram negative rods, *C. difficile*
4. Appropriate diagnosis and treatment of infections prior to MCS implantation
   a. Dental abscesses, pneumonia, catheter-related bacteremia, UTI, *C. difficile* infection, *Candida* species colonization, as well as potential timing of MCS implantation when such an infection is present
5. Review various risk factors associated with device infections
   a. Obesity, use of TPN, renal failure, multiple lines

Key References


C. Learning Objectives for Prevention of Infections in MCS

1) **Recognize the importance of appropriate peri-operative surgical prophylaxis for MCS implantation**
2) **Understand that driveline care is critical to preventing driveline infections**
3) **Understand relevant vaccination strategies in the MCS recipient, especially if BTT.**

Essential Content

1. Recent guidelines on perioperative antibiotic prophylaxis
2. Modification of antimicrobials based on recent culture data/ colonization as well as allergies
3. Use of various driveline dressing change protocols and need for device stabilization to decrease DL infections
4. Importance of patient education and training re: device care to decrease infections
5. Immunization guidelines pediatric and adult
   a. For destination MCS
   b. For immunocompromised host for bridge to transplant MCS

Key References


D. Learning Objectives for Diagnosis of Infections in MCS

1) To be aware of the recent standardized document for ventricular assist device (VAD) infection definitions
2) How to best utilize microbiological techniques in making a diagnosis of VAD-specific and related infections
3) Identify appropriate radiological tests used to make a diagnosis of VAD-specific and related infections

Essential Content

1. ISHLT guidelines for defining VAD-specific, related and unrelated infections in MCS recipients
2. Discuss biofilm nature of device infections and how that plays into yield of microbiological investigations
3. Utility and yield for blood, exit site, pocket and device cultures in making a diagnosis of VAD-specific and related infections

Key References


3. Baron et al. A Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2013 Recommendations by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM). Clinical Infectious Diseases; 2013; 1 -100


E. Learning Objectives for Management of VAD-specific Infections

1) Learn how to manage pump and/or cannula infections (both bacterial and fungal)
2) Learn how to manage pocket infections (both bacterial and fungal)
3) Learn how to manage percutaneous driveline infections (both bacterial and fungal)

Essential Content

1. Epidemiology
   a. Bacteria
   b. Fungal
2. Medical/ surgical management
   a. Bacteria
   b. Fungal
3. Recent consensus recommendations from ISHLT regarding fungal infections in MCS

Key References


F. Learning Objectives for Management of VAD-related infections

1) Learn how to treat infective endocarditis in the MCS recipient (both bacterial and fungal)
2) Learn how to treat bloodstream infections in the MCS recipient and understand the risk of device infection in such cases (both bacterial and fungal)

3) Learn how to treat mediastinitis associated with MCS placement (both bacterial and fungal)

Essential Content

1. Treatment of infective endocarditis in the MCS recipient
   a. Medical treatment
   b. Surgical treatment
   c. Bacteria
   d. Fungal

2. Treatment of bloodstream infections in the MCS recipient
   a. Catheter-related bacteremia
   b. Non-catheter related bacteremia
   c. Candidemia

3. Treatment of mediastinitis
   a. Bacterial
   b. Fungal

Key References


G. Learning Objectives for Management of non-VAD infections in MCS

1) Know the appropriate methods of diagnosis of infections after MCS implantation both nosocomial and community acquired

2) Know the treatment of infections after MCS implantation both nosocomial and community acquired

Essential Content

1. Pneumonia (including ventilator-associated pneumonia)
2. Catheter-associated urinary tract infection
3. *Clostridium difficile* infection
4. Abdominal infections (cholecystitis)
5. Sacral decubitus ulcers
Key References


H. Learning Objectives for Pharmacology of Anti-infectious Agents in the Setting of MCS

1) Understand the use of therapeutic drug monitoring in managing infections mechanical circulatory support (MCS) recipients
2) Appreciate and anticipate the potential for drug-drug interactions with anti-infective agents with other medications in MCS
3) Describe the factors that impact the pharmacokinetic and pharmacodynamics properties of the anti-infective drugs in the MCS

Essential Content

1. Contributing factors of drug-Drug interactions of anti-infectives and anticoagulants
   a. Route of administration
   b. Onset and strength of the drug interaction
   c. Pharmacodynamics
   d. Gastric acid alteration and drug absorption
   e. Age
2. Key Points for Therapeutic Drug Monitoring
   a. Selection of appropriate test
   b. Test methods
   c. Turn-around time of lab tests
   d. Timing of TDM

Key References