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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ISHLT ID in CT TX and MCS CCC: LIST OF CONTENTS

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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

1. Gomez C, Tan SH, Gould K, Valantine H, Montoya J. Chapter 1: Infections in Heart Transplantation: Historical Perspective. 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
2. Christie JD, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult lung and heart-lung transplant report- 2010. J Heart Lung Transplant 2010; 29(10): 1104-18

3. Smart F, Naftel DC, Costanzo M, et al. Risk factors for early, cumulative and fatal infections after heart transplantation: a multi-institutional study. J Heart Lung Transplant 1996; 15:329-41
4. Haddad F, Deuse T, Pham M, et al. Changing trends in infectious disease in heart transplantation. J Heart Lung Transplant 2010;29:306-15
5. Felker GM, Milano CA, Yager JE, et al. Outcomes with an alternate list strategy for heart transplantation. J Heart Lung Transplant 2005;24:1781-6

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

1. Westall G, Snell G, Keshavjee S, Strueber M. Infections in lung transplantation: historical perspective. 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

2. Christie JD, Edwards LB, Kucheryavaya AY, et al. The Registry of the ISHLT; twenty-seventh official adult lung and heart-lung transplant report- 2010. J Heart Lung Transplant 2010;29(10): 1104-1118

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**

<u>Essential Content</u>

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
2. Danziger-Isakov L, Kumar D. Vaccination in solid organ transplantation. Am J Transplant 2013; 13 (Suppl 4): S311-17
3. Fisher SA, Lu K. Screening of donor and recipient solid organ transplantation. Am J Transplant 2013; 13 (Suppl 4): S9-21
4. Kotton CN, Kumar D, Caliendo AM et al. Updated international consensus guidelines on the management of cytomegalovirus in solid organ transplantation. Transplantation 2013 Aug 27;96(4): 333-360.
5. Snydman DR, Limaye AP, Potena L, Zamora MR. Update and review: state-of-the-art management of cytomegalovirus infection and disease following thoracic organ transplantation. Transplant Proc 2011; 43 (3 Suppl): S1- S17
6. Avery, RK, Michael, MG. Strategies for safe living after solid organ transplantation. Am J Transplant 2013; 13: 304-310
7. Judge EP, Foweraker JE, Lorda JL. Chapter 5: Pre-lung Transplant Infectious Disease Considerations for Patients with Cystic Fibrosis. 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
8. Braun AT, Merlo CA. Cystic fibrosis lung transplantation. Curr Opin Pulm Med. 2011 Nov;17(6):467-72
9. Alexander BD, Petzold EW, Reller LB, Palmer SM, Davis RD, Woods CW, Lipuma JJ. Survival after lung transplantation of cystic fibrosis patients infected with Burkholderia cepacia complex. Am J Transplant. 2008 May;8(5):1025-30
10. Littlewood J et al. The Burkholderia cepacia complex. Suggestions for prevention and Infection Control. In: Report of the UK Cystic Fibrosis Trust Infection Control Group, September 2004

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

1. Len O, Stosor V. Chapter 7: Pre-Transplantation Screening of Donors for Cardiothoracic Transplantation: Current Standards for Infections Screening and Geographically Restricted Infections. 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
2. Fischer SA, Lu K; AST Infectious Diseases Community of Practice. Screening of donor and recipient in solid organ transplantation. Am J Transplant 2013; 13(Suppl 4):S9-21
3. Martín-Dávila P, Fortún J, López-Vélez R, Norman F, Montes de Oca M, Zamarrón P, González MI, Moreno A, Pumarola T, Garrido G, Candela A, Moreno S. Transmission of tropical and geographically restricted infections during solid organ transplantation. Clin Microbiol Rev 2008; 21:60-96
4. Guidance for recognizing central nervous system infections in potential deceased organ donors: what to consider during donor evaluation and organ offers. http://optn.transplant.hrsa.gov/ContentDocuments/Guidance_DTAC_CNS_Infections_07-2012.pdf
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

1. Ison MG. Chapter 8: Donor-Derived Infections After Cardiothoracic 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
2. Ison MG, Grossi PA; AST Infectious Diseases Community of Practice. Donor-derived infections in solid organ transplantation. Am J Transplant 2013; 13(Suppl 4):S22-30
3. Kaul DR. Donor-derived infection: epidemiology and outcomes. Curr Infect Dis Rep 2012; 14:676-682.
4. Morris MI, Day JS, Blumberg E, et al. Diagnosis and management of tuberculosis in transplant donors: a donor-derived infections consensus conference report. Am J Transplant 2012; 12 (9): 2288-2300
5. Chin-Hong PV, Schwartz BS, Bern C, et al. Screening and treatment of chagas disease in organ transplant recipients in the United States: recommendations from the chagas in transplant working group. Am J Transplant 2011; 11 (4): 672-680

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

1. Uber PA, Billaud EM. Chapter 10: Therapeutic Drug Monitoring in Cardiothoracic Transplant. 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
2. Girnita DM, Webber SA, Ferrell R, et al. Disparate distribution of 16 candidate single nucleotide polymorphisms among racial and ethnic groups of pediatric heart transplant patients. Transplantation 2006; 82:1774-1780
3. Knoop C, Thiry P, Saint-Marcoux F, et al. Tacrolimus pharmacokinetic and dose monitoring after lung transplant for cystic fibrosis and other conditions. Am J Transplant 2005 Jun; 5(6):1477-1482
4. Trofe-Clark J, Lemonovich TL. Interactions between anti-infective agents and immunosuppressants in solid organ transplantation. Am J Transplant 2013; 13: 318- 326

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

1. Daley CL, Uber PA. Chapter 11: Antiinfective Drug Interactions, Toxicities, and Clinical Management in Cardiothoracic Transplantation for Mycobacterial Infections. 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
2. Owens RC Jr, Nolin TD. Antimicrobial-associated QT interval prolongation: pointes of interest. Clin Infect Dis 2006; 43(12):1603-1611

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. IVIg or CMV immunoglobulin may be considered adjuvant therapy for severe CMV disease

Key References

1. Carbone J, Mawhorter S, Yamani M, Avery R. Chapter 12: Immunoglobulins in Cardiothoracic Transplant Infections: Prophylaxis And Treatment. 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
2. Florescu DF, Kalil AC, Qiu F, et al What is the impact of Hypogammaglobulinemia on the Rate of Infections and Survival in Solid Organ Transplantation? A Meta-Analysis. Am J Transplant 2013; 13: 2601-2610
3. Avery RK, Blumberg EA. Hypogammaglobulinemia: Time to Reevaluate? Am J Transplant 2013; 13: 2517-2518
4. Mawhorter S, Yamani MH. Hypogammaglobulinemia and infection risk in solid organ transplant recipients. Curr Opin Organ Transplant 2008;13(6):581-585
5. Yamani MH, Avery R, Mawhorter SD, et al. The impact of CytoGam on cardiac transplant recipients with moderate hypogammaglobulinemia: a randomized single-center study. J Heart Lung Transplant 2005;24(11):1766-1769
6. Kotton C, Kumar D and the Transplantation Society International CMV Consensus Group. Updated International Consensus Guidelines on the Management of Cytomegalovirus in Solid-Organ Transplantation. Transplantation 2013;96(4):333-360
7. Cunningham ED, Jules-Elysee K, Brochstein JA et al. Cytomegalovirus pneumonia after bone marrow transplantation successfully treated with the combination of ganciclovir and high-dose intravenous immune globulin. Ann InternMed 1988; 109(10): 777-782

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

1. Martin SI, Samuals, J. Chapter 13: Epidemiology of Bacterial Infections in Cardiothoracic 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
2. Fishman JA, Greenwald MA, Grossi PA. Transmission of Infection With Human Allografts: Essential Considerations in Donor Screening. Clin Infect Dis 2012; 55: 720–7

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

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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 carbenenemase-producing Enterobacteriaceae (CPE)**

<u>Essential Content</u>

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

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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

1. Morales P, Santos M, Hadjiliadis D, Aris R. Chapter 16: Mycobacterial Infections in Cardiothoracic 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
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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 nocardiasis 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 nocardisis 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

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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

    b. Non culture diagnostic methods
        i. Role of serologic tests
        ii. Role of molecular 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

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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**

<u>Essential Content</u>

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 instillations of antifungal drugs

Key References

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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**

<u>Essential Content</u>

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

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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

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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**

<u>Essential Content</u>

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

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2. Allen U, Preiksaitis J, AST Infectious Diseases Community of Practice. Epstein-Barr virus and posttransplant lymphoproliferative disorder in solid organ transplantation. Am J Transplant 2013;13 (Suppl 4): S107-120
3. Dharmidharka VR, Lamb KE, Gregg JA, Meier-Kriesche HU. Associations between EBV serostatus and organ transplant type in PTLD Risk: an analysis of the SRTR National Registry Data in the United States. Am J Transplant 2012;12:978-83

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**

<u>Essential Content</u>

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

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2. Pergam SA, Limaye AP; AST Infectious Diseases Community of Practice. Varicella Zoster Virus in solid organ transplantation. Am J Transplant 2013;13 (Suppl 4):S138-146
3. Le J, Gantt S; AST Infectious Diseases Community of Practice. Human Herpesvirus 6, 7 and 8 in solid organ transplantation. Am J Transplant 2013;13 (Suppl 4):128-37.
4. Wilck MB, Zuckerman RA. Herpes simplex virus in solid organ transplantation. Am J Transplant 2013; 13: 121-127

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

1. Ramaprasad C, Zamora MR, Hopkins PM et al Influenza and Other Seasonal Respiratory Viruses in Cardiothoracic 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
2. Vu DL, Bridevaux PO, Aubert JD, Soccal PM, Kaiser L. Respiratory viruses in lung transplant recipients: a critical review and pooled analysis of clinical studies. Am J Transplant 2011,11:1071-1078
3. Lopez-Medrano F, Aguado JM, Lizasoain M, Folgueira D, Juan RS, Diaz-Pedroche C, et al. Clinical implications of respiratory virus infections in solid organ transplant recipients: a prospective study. Transplantation 2007,84:851-856
4. Danziger-Isakov L, Husain S, Mooney ML et al. The novel2009 H1N1 influenza virus pandemic: unique considerations for programs in cardiothoracic transplantation. J Heart Lung Transplant 2009 Dec; 28 (12): 1341-1347

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

1. Grossi PA and Blumberg EA. Chapter 25: Human Immunodeficiency Syndrome and Hepatitis C Virus in Cardiothoracic Transplantation and MCS. 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
2. Blumberg EA and Rogers CC; AST Infectious Diseases Community of Practice. Solid Organ Transplantation in the HIV-Infected Patient. Am J Transplant. 2013 March;13:S169-178
3. Huprikar S. Chapter 24: Management Algorithm for Transplantation in Patients with Human Immunodeficiency Virus. In: The AST Handbook of Transplant Infections. Edited by D Kumar and A Humar. 2011
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 lymphotropic 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

<u>Key References</u>

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2. Kaul DR and Davis JA; AST Infectious Diseases Community of Practice. Human T Cell Lymphotropic Virus in Solid Organ Transplantation. Am J Transplant. 2013 March;13:355-360

3. Eid AJ and Chen SF; AST Infectious Diseases Community of Practice. Human Parvovirus B19 in Solid Organ Transplantation. Am J Transplant. 2013 March; Vol 9 Suppl 4:S201-5
4. Martín-Dávila P, Fortún J, López-Vélez R, Norman F, Montes de Oca M, Zamarrón P, González MI, Moreno A, Pumarola T, Garrido G, Candela A, Moreno S. Transmission of tropical and geographically restricted infections during solid organ transplantation. Clin Microbiol Rev 2008; 21:60-96

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

    d. 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. <u>Strongyloidiasis prevention</u>
    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

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1. Martin S: Chapter 27: Toxoplasmosis and Strongyloides in Cardiothoracic Transplantation 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
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
3. Coster LO. Parasitic Infections in Solid Organ Transplant Recipients; Inf Dis Clin NA, 2013; 27 (2): 395-427
4. Roxby A, Gottlieb G, Limaye A: Strongyloides in Transplant Patients, Clin Inf Dis; 2009 Nov 49: 1411-1423

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

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2. Ribeiro AL, Nunes MP, Teixeira MM, Rocha MO. Diagnosis and management of Chagas disease and cardiomyopathy. Nat Rev Cardiol. 2012 ;9:576-589
3. Bern C. Chagas disease in the immunosuppressed host. Curr Opin Infect Dis. 2012 ;25:450-7
4. Pinazo MJ, Miranda B, Rodríguez-Villar C, Altclas J, Brunet Serra M, García-Otero EC, de Almeida EA, de la Mata García M, Gascon J, García Rodríguez M, Manito N, Moreno Camacho A, Oppenheimer F, Puente S, Riarte A, Salas Coronas J, Salavert Lletí M, Sanz GF, Torrico F, Torrús Tendero D, Ussetti P, Shikanai-Yasuda MA. Recommendations for management of Chagas disease in organ and hematopoietic tissue transplantation programs in nonendemic areas. Transplant Rev (Orlando). 2011 ;25:91-101
5. Chin-Hong PV, Schwartz BS, Bern C, et al. Screening and treatment of Chagas disease in organ transplant recipients in the United States: recommendations from the Chagas in transplant working group. Am J Transplant 2011; 11 (4): 672-680

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 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

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2. Borhani A, et al: Imaging of Posttransplant Lymphoproliferative Disorder after Solid Organ Transplantation, Radiographics 2009 July-Aug 94: 981-1000
3. Bargehr J, Flors L, Leiva-Salinas C et al. Nocardiosis in solid-organ transplant recipients: Spectrum of image findings. Clin Radiol 2013 May; 68 (5):e266-271

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**

<u>Essential Content</u>

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

<u>Key References</u>

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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. Ctology 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

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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

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2. CDC Travelers' Health website. http://wwwnc.cdc.gov/travel/ Access last reviewed 3/7/14.
3. World Health Organization International Travel and Health webpage. http://www.who.int/ith/en/ Access last reviewed 3/7/14.

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)

1. World Health Organization. http://www.who.int/en/ Access last reviewed 3/18/14.
2. Centers for Disease Control and Prevention. http://www.cdc.gov/ Access last reviewed 3/18/14.
3. Infectious Diseases Society of America Practice Guidelines. http://www.idsociety.org/IDSA_Practice_Guidelines/ Access last reviewed 3/18/14.
4. United Network for Organ Sharing (UNOS) http://www.unos.org/ Access last reviewed 3/18/14.

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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

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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 – *Cocciodiodes*, 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

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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

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1. Feldman et al. The 2013 International Society for Heart and Lung Transplantation Guidelines for Mechanical Circulatory Support: Executive Summary. J Heart Lung Transplant. 2013 Feb;32(2):157-87
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3. Rubin et al. 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host. Clin Infect Dis. Feb 2014
4. Pickering LK, et al 2009 IDSA clinical Practice Guideline for Immunization Programs for infants, Adolescents and Adults. CID 2009; 49(6): 817-840

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
4. Role of CT, US, trans-esophageal echocardiogram, and radionuclide imaging for VAD-specific and related infections.

Key References

1. Hannan et al. Working formulation for the standardization of definitions of infections in patients using ventricular assist devices. J Heart Lung Transplant. 2011 Apr;30(4):375-84.
2. Lawler et al. Diagnostic Radiology for Infectious Diseases in the Cardiothoracic Transplant and Mechanical Circulatory Support Recipient. 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.
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
4. Padera RF. Infection in Ventricular Assist Devices: the role of biofilm. Cardiovasc Pathol 2006; 15 (5):264-270

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

1. Husain et al. 2014 ISHLT Guidelines for the Management of Fungal Infections in MCS and CT Organ Transplant Recipients: Executive Summary.
2. Holman et al. Chapter 9: Prevention and control of infection in the ventricular assist device recipient. 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

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

1. Husain et al. 2014 ISHLT Guidelines for the Management of Fungal Infections in MCS and CT Organ Transplant Recipients: Executive Summary.
2. Holman et al. Chapter 9: Prevention and control of infection in the ventricular assist device recipient. 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

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

1. Mermel et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009; 49:1 - 45
2. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005; 171: 388-416
3. Cohen et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control and Hosp Epidemiol; 2010; 31 : 431-455
4. Solomkin JS et al. Diagnosis and Management of Complicated Intra-abdominal Infection in Adult and children: Guidelines by the Surgical Infection Society and IDSA. CID 2010; 50 (2): 133-164
5. Yokoe et al. A compendium of strategies to prevent healthcare-associated infections in acute care hospitals. Infect Control Hosp Epidemiol 2008; 29 Suppl 1; S 12-21

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

1. Uber PA, Billaud EM. Chapter 10: Therapeutic Drug Monitoring in Cardiothoracic Transplant. 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
2. Ghaswalla PK et al. Warfarin-antibiotic interactions in older adults of an outpatient anticoagulation clinic. Am J Geriatr Pharmacother. 2012; 10(6):352-360