

INTERNATIONAL SOCIETY FOR HEART AND LUNG
TRANSPLANTATION
(ISHLT)

**THORACIC TRANSPLANT PHARMACY
PROFESSIONALS
CORE COMPETENCY CURRICULUM
(ISHLT PHARMACY AND PHARMACOLOGY CCC)**

FIRST EDITION

THE EDUCATIONAL WORKFORCE OF THE
ISHLT SCIENTIFIC COUNCIL ON PHARMACY AND
PHARMACOLOGY

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ISHLT Pharmacy and Pharmacology CCC

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Minimum Experience Recommendation
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9. Goals of therapy

Minimum Experience Recommendation

Suggested References and Resources

INTRODUCTION

Section Lead: Robert Page, PharmD

Co-Authors: Patricia Uber, PharmD

Over the past four decades, there has existed a world-wide trend for the practice of pharmacy to move away from its original focus on medication distribution and towards a more inclusive focus on patient care. The role of the pharmacist has evolved from a compounder and supplier of medications to that of a provider of information regarding complex pharmacotherapy and ultimately a more direct role in patient care. This has inevitably evolved into an educational mandate for professionals in this field. In order to meet the dynamic demands of an ever growing health care system, pharmacy education and training has drastically changed. The International Society for Heart and Lung Transplantation (ISHLT) has provided an educational forum for multiple disciplines committed to patient care in end-stage heart and lung disease and transplantation. The purpose of this document is to provide a guideline for independent revision and the development of learning activities according to generic learning needs and common practice gaps in the field.

In the United States, the baccalaureate degree in pharmacy has been replaced with a clinically intensive entry level Doctor of Pharmacy (Pharm.D.) degree. Portugal, Hungary, Italy, the Netherlands, Spain, Republic of Ireland, and the UK, offer a more clinically-based Masters Degree in Pharmacy (MPharm) for pharmacy graduates. Post MPharm and baccalaureate, Pharm.D degree programs can now be found in Canada, France, the United Kingdom(UK) and the Czech Republic. World-wide, residency programs or advanced internships are available to provide pharmacists with advanced patient care experiences within the various subspecialties of medicine. (Table 1)

As the pharmacy profession has expanded in depth and breadth of clinical knowledge, so have the documented improvements in health outcomes associated with the provision of pharmaceutical care by pharmacists in both the inpatient and outpatient setting and across multiple disease states. In Europe, the United States, and Canada, the addition of a pharmacist to a multidisciplinary team has been associated with reductions in mortality and hospitalizations, minimization of adverse drug reactions, enhanced medication adherence, as well as improved management of chronic disease states such as hypertension, hyperlipidemia, heart failure, diabetes, and transplantation.

In many countries, pharmacists with expertise in transplantation have been included as an essential member of a multidisciplinary team dedicated to the provision of medication therapy management and education for transplant recipients. In the United States, the perception and role of the pharmacist was further justified in 2004 when the United Network of Organ Sharing bylaws and the Centers for Medicare and Medicaid accreditation standards were amended to include a pharmacist or someone with expertise in pharmacology as a necessary member of the transplant team.

As variations exist world-wide in the education, expertise, and clinical practice of thoracic pharmacy practitioners, the purpose of this compendium of core competencies is designed to provide a concise synopsis of clinical knowledge and associated essential professional skills to facilitate the mastery of pharmacotherapy involved in the care of patients receiving a heart or lung transplant. This compendium cannot replace organized professional development and internationally recognized certification. The contents focused on organ-specific and population-specific competencies. The key learning objectives are outlined and extensive referencing may

assist individual self-directed study. This is intended to augment competency in various aspects of thoracic transplantation.

The Educational Workforce of Pharmacy and Pharmacology Council of International Society for Heart and Lung Transplant (ISHLT) hopes that this compendium will serve as a useful tool for thoracic pharmacy practitioners world-wide to enhance their current practice, review their standards of care, and develop and implement protocols for the management of this patient population. Comments and feedback as well as suggestions for further refinements of this document would be appreciated.

On behalf of the Pharmacy and Pharmacology Council of ISHLT

The Core Competency Workforce

Table 1. Pharmacist Training and Education—By Country

| Requirement | US | UK | France | Germany | Australia | Canada | Republic of Ireland | Singapore |
|---------------------------------------------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------|------------------------------------------------------|----------------------|---------------------------------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------|
| Previous undergraduate degree required? | No, but generally 2-3 years of pre-pharmacy undergraduate coursework | No | No | No | No | No | No | No |
| Years of pharmacy school | 3-4 | 4 | 6-9 | 4 | 4 (Bachelors); 2 (Master's) | 5 (Bachelors); 7 (PharmD) | 4 | 4 |
| Degree Title | PharmD | MPharm , Optional MSc PhD or PharmD | PharmD | Bachelor of Pharmacy | Bachelor of Pharmacy; Master of Pharmacy | Bachelor of Science in Pharmacy (BSc Pharm); PharmD | MPharm | Bachelor of Science in Pharmacy (BSc Pharm) |
| Clinical/residency training | Clinical training during study; optional post-graduate residencies and fellowships | 1 year post-graduate for licensing. 2 year post-graduate diploma. | 18 months to 4 years during study, depending on path | 1 year during study | 1 year post-graduate | 16 weeks during study; 4 months post-graduate; optional 1 year residency | 1 year post graduate for licensing. 2 year post graduate Diploma, or 3 year MSc | 12 weeks during study; 1 year post-graduate |
| Specialty training | Optional | Optional-Speciality expertise recognised with Faculty membership | Optional (by exam, extended program) | N/A | N/A | Optional | Optional | Optional |
| Licensing/certification/registration | National exam | National exam | National exams | National exams | National exams | National exams | National exam | National exams |
| Re-licensure Requirements | Requirements vary by state | Process under development | N/A | N/A | Annual | Annual | Process under development | Every two years |
| Continuing education required for renewal? | Generally required, varies by state | Yes | Policy in development | Voluntary | Yes | Yes | Yes | Yes |
| Prescribing authority | Limited; state dependent | Yes | No (except emergency contraception) | No | Limited | Limited to full; province dependent | no | No |

N/A: Not applicable, US: United States, UK: United Kingdom, PharmD: Doctor of Pharmacy, MPharm: Master of Pharmacy

Chapter 1

ADULT ORGAN SPECIFIC COMPETENCIES- HEART

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1.1 HEART FAILURE

Heart Failure is a clinical syndrome characterized by systemic perfusion inadequate to meet the body's metabolic demands as a result of impaired cardiac pump function. Acute decompensated heart failure can result from various causes presenting as pulmonary or systemic congestion secondary to elevated ventricular pressures with or without reduced cardiac output. The goals of therapy include improving patient morbidity, mortality, symptoms and quality of life.

Learning Objectives

1. Understand neurohormonal activation in heart failure and the consequences of low cardiac output on end-organ function.
2. Interpret invasive cardiac parameters, laboratory studies, hemodynamic studies, and imaging in order to provide evidence-based pharmacotherapeutic recommendations.
3. Develop patient specific monitoring plans assessing the efficacy and toxicities of pharmacotherapy.
4. Provide medication education regarding drug therapies utilized in patients with heart failure.
5. Apply advanced knowledge of pharmacokinetic and pharmacodynamic properties of drug therapy.

Topic Outline

1. Neurohormonal pathways
 - a. Renin Angiotensin Aldosterone System
 - b. Adrenergic Nervous System
2. Heart Failure Classification
 - a. Heart failure with Reduced Ejection Fraction
 - b. Heart failure with Preserved Ejection Fraction
3. Cardiorenal Syndrome
4. Hepatic Congestion
5. Diagnosis and monitoring
 - a. Invasive Parameters
 - i. Cardiac Output/Cardiac Index
 - ii. Central Venous Pressure
 - iii. Mean Arterial Pressure
 - iv. Pulmonary Capillary Wedge Pressure
 - b. Laboratory Studies
 - i. Electrolytes
 - ii. Creatinine Clearance
 - iii. B-type Natriuretic Peptide
 - iv. Complete Blood Count
 - v. Liver Function Tests

- c. Cardiac Imaging/Investigations
 - i. Electrocardiogram
 - ii. Echocardiogram
 - iii. Right and Left Heart Catheterization
 - iv. Cardiac Computed Tomography
 - v. Cardiac Magnetic Resonance Imaging
- d. Other
 - i. Chest X-ray
- e. Clinical Status
 - i. Stages of Heart Failure
 - ii. New York Heart Association Functional Classifications
 - iii. Seattle Heart Failure Model
- f. Heart Failure specific pharmacotherapy (see Table 2)
 - i. Patient adherence
- g. Goals of therapy
 - i. Morbidity
 - ii. Mortality
 - iii. Symptom Control

TABLE 2. HEART FAILURE PHARMACOTHERAPY

| | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Diuretics Loop – bumetanide, furosemide, torsemide, ethacrynic acid</p> <p>Thiazide – chlorothiazide, hydrochlorothiazide, metolazone,</p> <p>Vasodilators Nitroglycerin, nitroprusside</p> <p>Natriuretic Peptides Nesiritide</p> <p>Calcium Sensistizers Levosimendan</p> <p>Inotropes Dobutamine, dopamine, milrinone</p> | <p>Digitalis Glycosides Digoxin</p> <p>Beta-blocker Bisoprolol, carvedilol, metoprolol succinate, nebivolol</p> <p>ACEI/ARB Lisinopril, enalapril, captopril Candesartan, valsartan</p> <p>Mineralocorticoid/aldosterone antagonist Spironolactone, eplerenone</p> <p>Sinus node inhibitor Ivabradine</p> <p>Neprilysin Inhibitor Sacubitril/Valsartan</p> |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker

Minimum Experience Recommendation for Management of Heart Failure

1. Participate in the evaluation and care of 5 or more heart transplant candidates for a minimum of 3 months from the time of referral to the time of listing and/or transplantation.
2. Participate in the evaluation and care of 3 or more heart transplant candidates undergoing urgent in-hospital evaluation for heart transplantation.

Selected Hyperlinks for Heart Failure

- Acute Heart Failure: diagnosing and managing acute heart failure in adults. NICE Guidelines 2014 <http://www.nice.org.uk/guidance/cg187/evidence/cg187-acute-heart-failure-full-guideline3>

Suggested References for Heart Failure

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Hasselblad V, Gattis Stough W, Shah MR, et al. Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. *Eur J Heart Fail* 2007;9:1064-9.

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1.2 MECHANICAL CIRCULATORY ASSIST DEVICES

Mechanical circulatory assist devices (MCADs) consisting of ventricular assist devices (VADs) and total artificial hearts (TAHs) have become important treatment options for patients largely because of limited donor heart availability. The ongoing advancement of MCADs has implications to pharmacotherapy, and therefore, competency and advanced knowledge of devices, complications and therapies used in this area is prudent for clinical pharmacists.

Learning Objectives

1. Understand the indications for insertion of a MCAD.
2. Understand VAD parameters and implications for drug therapy.
3. Interpret coagulation and platelet function studies.
4. Understand the management of MCAD related complications
5. Develop patient specific monitoring plans assessing the efficacy and toxicities of pharmacotherapy.
6. Provide medication education regarding drug therapies utilized to this patient group.
7. Apply advanced knowledge of pharmacokinetic and pharmacodynamic properties of drug therapy.

Topic Outline

1. Patient Selection
 - a. NYHA Classification
 - b. INTERMACS profile
 - c. Comorbidities
 - i. Valvular heart disease
 - ii. Arrhythmias
 - iii. Vascular disease
 - iv. Pulmonary hypertension
 - v. Coagulation/hematologic disorders
 - d. Destination therapy versus bridge to transplantation
2. Devices
 - a. Type
 - i. Axial
 - ii. Centrifugal
 - iii. Pulsatile
 - b. Parameters
 - i. Mean Arterial Pressure
 - ii. Flow
 - iii. Pulsatility
 - iv. Power
 - v. Speed
3. Thromboprophylaxis
 - a. Peri-operative
 - b. Post-operative
 - i. Anticoagulation management
 1. Unfractionated heparin
 2. Direct thrombin inhibitor
 3. Low molecular weight heparin
 4. Warfarin
 5. Aspirin
 6. Dipyridamole
 - ii. Coagulation evaluation
 1. Activated Partial Thromboplastin Time /Prothrombin Time/International Normalized Ratio
 2. Fibrinogen
 3. Platelets
 4. Thromboelastography /Thromboelastometry
 5. Lactate Dehydrogenase
 6. Plasma Free Hemoglobin
 - c. Hemorrhagic/thrombotic complications
 - i. INTERMACS definition

- ii. Pharmacologic/blood product management for complications
 - 1. Hemorrhage
 - a. Packed Red Blood Cells
 - b. Platelets
 - c. Fibrinogen
 - d. Cryoprecipitate
 - e. Factor VII
 - f. Prothrombin complex concentrates
 - g. Protamine
 - h. Desmopressin Acetate
 - i. Antifibrinolytics
 - j. Vitamin K
 - 2. Thombosis
 - a. Alteplase
 - b. Glycoprotein IIb/IIIa inhibitors
- 4. Hypertension
 - a. Pharmacotherapy
 - i. Beta-blockers
 - ii. ACEI/ARBs
 - iii. Other Blood Pressure lowering therapy
 - iv. Mean Arterial Pressure goals
- 5. Right ventricular dysfunction
 - a. Pharmacotherapy
 - i. Diuretics
 - ii. Inotropes
 - iii. Pulmonary vasodilators
 - iv. Phosphodiesterase-5 inhibitors
 - b. Mechanical support
- 6. Arrhythmia management
 - a. Atrial versus Ventricular
 - b. Pharmacotherapy
 - i. Rate
 - ii. Rhythm
 - c. Device/Surgical management
- 7. Bleeding
 - a. INTERMACS definition
 - b. Pharmacotherapy
 - i. Modifications to antithrombotic therapy
 - ii. Therapies to manage ulceration
 - iii. Therapies to manage arteriovenous malformations
 - c. Surgical intervention
- 8. Infections
 - a. Pre- and peri-operative antimicrobials
 - b. Sternal and drive-line wound care
 - c. Sternal wound infection
 - d. Drive-line infection
 - e. Pocket infection
 - f. Endocarditis
 - g. Device infections
- 9. Goals of therapy
 - a. Morbidity
 - b. Mortality
 - c. Symptom Control
 - d. Patient adherence

Minimum Experience Recommendation for MCADS

1. Participate in evaluation of 10 patients with MCADs prior to transplantation.
2. Treat and/or modify the regimen of 10 patients with MCADs.

Selected Hyperlinks for MCADS

- INTERMACS <http://www.uab.edu/medicine/intermacs/>
- INTERMACS profiles of advanced heart failure: the current picture.. http://ac.els-cdn.com/S1053249809001910/1-s2.0-S1053249809001910-main.pdf?_tid=884d3ce6-1c27-11e5-b32d-00000aab0f27&acdnat=1435339362_b40bd2d226277b4ff279d0e97925cd07
- The 2013 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support: Executive summary. <http://dx.doi.org/10.1016/j.healun.2012.09.013>
- International Society for Heart and Lung Transplantation. A 2010 working formulation for the standardization of definitions of infections in patients using ventricular assist devices (VADs). <http://www.ishlt.org/contentdocument/VAD.pdf.2010>.
- Focus on thrombosis and ventricular assist devices. [http://www.jhltonline.org/issue/S1053-2498\(13\)X0013-0](http://www.jhltonline.org/issue/S1053-2498(13)X0013-0)

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1.3 MANAGEMENT OF THE SENSITIZED PATIENT (Refer to Chapter 5)

1.4 MONITORING AND SELECTION OF IMMUNOSUPPRESSION (Refer to Chapter 5)

1.5 SURVEILLANCE OF HEART FUNCTION

Thoracic pharmacists play an important role by interpreting and helping alter immunosuppressive therapy based on surveillance of heart function. Thoracic pharmacists deemed competent in the management of thoracic transplant recipients must be knowledgeable in the area of heart function surveillance including; histopathologic testing, gene expression testing (GEP), clinical imaging, and clinical assessment of graft function.

Learning Objectives

1. Understand the diagnosis algorithm of acute cellular and antibody mediated rejection.
2. Demonstrate knowledge in the application of various immunofluorescence staining techniques and histocompatibility tests.
3. Understand the ISHLT grading schema for acute cellular rejection.
4. Interpret GEP results with the understanding of how GEP is influenced by immunosuppressive regimens and patient specific factors.
5. Understand new or emerging data surrounding novel approaches to immunosuppression monitoring and surveillance of graft function, including GEP and cell free DNA.
6. Demonstrate knowledge of clinical imaging modalities that determine graft function.
7. Assemble clinical, laboratory, pathology, and histocompatibility data and apply knowledge of graft imaging techniques to adjust immunosuppression pharmacotherapy to optimize graft function and patient survival.

Topic Outline

1. Diagnosis of acute cellular rejection and antibody mediated rejection
 - a. Biopsy grading
 - i. 1990 ISHLT Nomenclature
 - ii. 2005 ISHLT Nomenclature Update
 - iii. 2013 Working group definitions of Antibody Mediated Rejection (AMR)
 1. Histopathologic findings
 2. Immunopathologic findings
 - a. C3d, C4d, CD68
 - b. Donor specific antibodies
 - c. Non-Human Leukocyte Antigen (HLA) antibodies
 3. Pathologic findings
 - b. Assessment of graft function
 - i. Advantages and disadvantages of commonly used non-invasive imaging techniques
 1. Echocardiography
 2. Multi Gated Acquisition Scan
 3. Cardiac Magnetic Resonance Imaging
 4. Angiography
 - ii. Advantages and disadvantages of right heart catheterization
2. Minimally invasive assessment of rejection
 - a. Gene Expression Profiling
 - i. Key Trials
 1. IMAGE
 2. E-IMAGE
 3. CARGO
 4. CARGO II
 - b. Cell-free DNA

Minimum Experience Recommendation for Surveillance of Heart Function

1. Participate in evaluation of heart function surveillance in 15 transplant recipients.
2. Participate in the interpretation and treatment of endomyocardial biopsies or Gene Expression Profiling in 15 transplant recipients.

Selected Hyperlinks for Surveillance of Heart Function

- The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. J Heart Lung Transplant 2010;29:914-956 DOI: <http://dx.doi.org/10.1016/j.healun.2010.05.034>
- Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. <http://www.jhltonline.org/article/S1053-2498%2805%2900203-2/pdf>

Suggested references for Surveillance of Heart Function

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Cooper LT, Baughman KL, Feldman AM, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. J Am Coll Cardiol 2007;50:1914-31.

Deng MC, Eisen HJ, Mehra MR, et al. Noninvasive discrimination of rejection in cardiac allograft recipients using gene expression profiling. Am J Transplant 2006;6:150-60.

Horenstein MS, Idriss SF, Hamilton RM, et al. Efficacy of signalaveraged electrocardiography in the young orthotopic heart transplant patient to detect allograft rejection. Pediatr Cardiol 2006;27:589-93.

Kemkes BM, Schutz A, Engelhardt M, Brandl U, Breuer M. Noninvasive methods of rejection diagnosis after heart transplantation. J Heart Lung Transplant 1992;11:S221-31.

Keslar K, Rodriguez ER, Tan CD, Starling RC, Heeger PS. Complement gene expression in human cardiac allograft biopsies as a correlate of histologic grade of injury. Transplantation 2008;86:1319-21.

Pham MX, Teuteberg JJ, Kfoury AG, et al. Gene-expression profiling for rejection surveillance after cardiac transplantation. N Engl J Med 2010;362:1890-900

Rosenthal DN, Chin C, Nishimura K, et al. Identifying cardiac transplant rejection in children: diagnostic utility of echocardiography, right heart catheterization and endomyocardial biopsy data. J Heart Lung Transplant 2004;23:323-9.

Schweiger M, Wasler A, Prenner G, et al. The prognostic validity of the ventricular evoked response (VER) signals in cardiac transplantation. J Heart Lung Transplant 2005;24:1730-5.

Stehlik J, Starling RC, Movsesian MA, et al. Utility of long-term surveillance endomyocardial biopsy: a multi-institutional analysis. J Heart Lung Transplant 2006;25:1402-9.

1.6 PREVENTION AND MANAGEMENT OF HEART TRANSPLANT POST-OPERATIVE COMPLICATIONS

Minimizing complications in transplantation is paramount to maintaining graft patency and prolonging recipient survival. These complications can result from opportunistic infection in the immunocompromised host, rejection of the allograft, organ dysfunction, metabolic disorders, and malignancy.

1.6.1 Infectious Complications

Learning Objectives

1. Identify common opportunistic pathogens (viral, fungal, and bacterial) and appropriate prophylaxis strategies for thoracic transplant recipients.
2. Understand diagnostic techniques for opportunistic infections in thoracic transplant, specifically interpretation of serologic assays for viral and fungal pathogens.
3. Develop patient specific pharmacotherapy, and corresponding monitoring plans, for opportunistic infections
4. Apply appropriate immunization principles, both pre- and post-transplant, to minimize risk associated with common communicable disease.

Topic Outline

1. Overview and Timeline of Infections following Heart Transplant
2. Diagnosis, prophylaxis and management/treatment of opportunistic infections
 - a. Viral
 - i. Risk stratification based on donor and recipient serologic assessments
 - ii. Cytomegalovirus (CMV)
 - iii. Herpes Simplex Virus (HSV)
 - iv. Epstein-Barr Virus (EBV)
 - v. Human Herpesvirus-6 (HHV-6)
 - vi. Polyoma virus
 - b. Fungal
 - i. Candida spp. infections
 - ii. Aspergillus spp. infections
 - iii. Cryptococcus spp. infections
 - iv. Pneumocystis jiroveci infections(PJP)
 - c. Bacterial
 - i. Nosocomial infections in the immunocompromised host
 - ii. Nocardia spp. infections
 - d. Parasitic
 - i. Toxoplasmosis gondii
3. Immunization Schedules
 - a. Pre-transplant
 - b. Post-transplant
4. Factors for consideration in anti-infective regimen
 - a. Infection status prior to transplant
 - b. Infection risk of the donor
 - c. Institutional antibiotic resistance pattern
 - d. Associated surgical or other complications
 - e. Open chest/re-exploration
 - f. Pre- or post-operative MCS
 - g. Prolonged mechanical ventilation
 - h. Acute kidney injury/renal replacement therapy
 - i. Potential opportunistic infections secondary to immunosuppressive state
 - j. Emergence of resistance with prolonged or multiple courses of antibiotic therapy

Minimum Experience Recommendation for Infectious Complications

1. Participate in evaluation of the risk for infections in 15 transplant recipients.

2. Treat 15 patients with post heart transplant infections, adjust medicines for the infections, whether or not it is medication related, for target levels, adverse effects, and drug interactions

Selected Hyperlinks for Infection after Heart Transplantation

- The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. J Heart Lung Transplant 2010; 29: 914-56.
<http://www.jhltonline.org/article/S1053-2498%2810%2900358-X/pdf>
- A 2010 working formulation for the standardization of definitions of infections in cardiothoracic transplant recipients. J Heart Lung Transplant 2011; 34: 361-374.
<http://www.jhltonline.org/article/S1053-2498%2811%2900731-5/pdf>

Suggested references for Infection after Heart Transplantation

Gupta S, Mitchell JD, Markham DW, et al. High incidence of cytomegalovirus disease in D+/R- heart transplant recipients shortly after completion of 3 months of valganciclovir therapy. J Heart Lung Transplant 2008; 27: 536-539.

Humar A, Snyderman D. Cytomegalovirus in solid organ transplant recipients. Am J Transplant 2009; 9: S78-S86.

Kotton C, Kumar D, Caliendo AM, et al. Updated international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. Transplantation 2013; 96: 333-360.

1.6.2 Rejection Management

Learning objectives

1. Understand current diagnostic criteria and grading scale for rejection.
2. Develop a patient specific treatment plan based on type and severity of rejection.
3. Develop a pharmacotherapy treatment plan for infectious prophylaxis during rejection treatment and for maintenance immunosuppression after rejection treated.

Topic Outline

1. Treatment of Acute Cellular Rejection
 - a. Risk factors
 - b. Definition
 - c. Treatment options
 - i. Steroid pulse with or without taper
 - ii. Antithymocyte globulin
 - iii. Alemtuzumab
 - iii. Modifications to maintenance immunosuppression
 - iv. Others
 - d. Outcomes
2. Antibody mediated rejection
 - a. Risk factors
 - b. Definition
 - c. Antibody interpretation
 - d. Treatment options
 - i. Steroids
 - ii. Antithymocyte globulin
 - iii. Proteasome inhibitors
 - iv. Anti CD-20
 - v. Complement inhibitors
 - vi. Intravenous Immunoglobulin

- vii. Non-pharmacologic therapies with effects on drug therapy
 - 1. Plasmapheresis
 - 2. Photopheresis
 - 3. Immunoabsorption
- viii. Novel therapies
- e. Modification of maintenance immunosuppression
- f. Outcomes

Minimum Experience Recommendation for Management of Rejection

1. Participate in evaluation of the rejection in 15 transplant recipients.
2. Treat 15 patients with post heart transplant rejection, adjust other medicines for the therapy of choice, for target levels, adverse effects, and drug interactions

Selected Hyperlinks for Management of Rejection

- The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. J Heart Lung Transplant 2010; 29: 914-56.
<http://www.jhltonline.org/article/S1053-2498%2810%2900358-X/pdf>

Suggested References for Management of Rejection

Berry GJ, Angelini A, Burke MM, et al. The ISHLT working formulation for pathologic diagnosis of antibody-mediated rejection in heart transplantation: evolution and current status (2005-2011). J Heart Lung Transplant 2011; 30: 601-11.

Berry GJ, Burke MM, Andersen C, et al. The 2013 International Society for Heart and Lung Transplantation working formulation for the standardization of nomenclature in the pathologic diagnosis of antibody-mediated rejection in heart transplantation. J Heart Lung Transplant 2013; 32(12): 1147-1162

Kobashigawa JA, Kiyosaki KK, Patel JK, et al. Benefit of immune monitoring in heart transplant patients using ATP production in activated lymphocytes. J Heart Lung Transplant 2010; 29: 504-8.

Pham MX, Teuteberg JJ, Kfoury AG, et al., Gene-expression profiling for rejection surveillance after cardiac transplantation. N Engl J Med 2010; 362: 1890-900.

Stewart S, Winters GL, Fishbein MC, Tazelaar HD, et al. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. J Heart Lung Transplant 2005; 24: 1710-20.

1.6.3 Nephrotoxicity

Learning Objectives

1. Understand pathophysiology and treatment of common nephrotoxicities after heart transplant.
2. Describe risk factors associated with developing renal dysfunction after transplantation.

Topic Outline

1. Drug-related Nephrotoxicity
 - a. Calcineurin inhibitor induced nephrotoxicity
 - b. Hemolytic Uremic Syndrome
 - c. Acute tubular necrosis
 - d. Electrolyte abnormalities
2. Disease-related Nephrotoxicity
 - a. Diabetic nephropathy

- b. Thrombotic Thrombocytopenia Purpura
 - c. Proteinuria
 - d. Renal Tubular Acidosis
3. Iatrogenic Causes
- a. Dehydration
 - b. Contrast-induced nephropathy

Minimum Experience Recommendation for Nephrotoxicities

1. Participate in evaluation of nephrotoxicities in 15 transplant recipients.
2. Treat 15 patients with nephrotoxicities, adjust medicines, whether or not it is medication related, for target levels, adverse effects, and drug interactions

Selected Hyperlinks for nephrotoxicity

- Kidney disease: <https://www.kidney.org/kidneydisease>

Suggested References for nephrotoxicity

Gonzalez-Vilchez F, Vazquez de Prada JA. Chronic renal insufficiency in heart transplant recipients: risk factors and management options. *Drugs* 2014; 74(13): 1481-1494.

Lechance K, White M, Carrier M, et al. Long-term evolution, secular trends, and risk factors for renal dysfunction following cardiac transplantation. *Transpl Int.* 2014; 27(8): 824-837.

Zuckermann A, Eisen H, See Tai S, et al. Sirolimus conversion after heart transplant: risk factors for acute rejection and predictors of renal function response. *Am J Transplant* 2014; 14(9): 2048-2054.

1.6.4 Prevention and Management of Long Term Complications

Learning Objectives

1. Identify long-term complications of transplant immunosuppression.
2. Design pharmacotherapeutic regimens and monitoring plans that prevent, treat, or mitigate long-term complications of immunosuppression.
3. Recognize modifiable risk factors early in post-transplant care, and recommend changes to reduce the incidence or severity of long-term complications in heart transplant patients.

Topic Outline

1. Endocrine
 - a. New onset diabetes mellitus after transplantation
 - b. Metabolic diseases (metabolic syndrome)
 - c. Hyperparathyroidism
 - d. Osteoporosis/bone disease
 - e. Gout
 - f. Pancreatitis
2. Renal
 - a. Anemia management
 - b. Electrolyte management
 - c. Osteopenia/osteoporosis
3. Cardiovascular
 - a. Cardiovascular risk management
 - b. Heart failure
 - c. Coronary artery disease
 - i. Hyperlipidemia

1. HMG-CoA Reductase Inhibitors
 - a. Lipid lowering effects
 - b. Pleotropic effects
- d. Hemodynamic conditions
- e. Hypertension
- f. Orthostatic hypotension
4. Post-transplant infection considerations
 - a. Dental procedure prophylaxis
 - b. HSV and Herpes Zoster
 - i. Infectious exposure management
 - ii. Measles
 - iii. Varicella (chicken pox)
 - c. Surgical site infection prophylaxis
 - d. Sepsis
 - e. Tuberculosis
5. Malignancy
 - a. Malignancy surveillance
 - b. Kaposi's Sarcoma
 - c. Lymphoma
 - d. Post-transplant lymphoproliferative disease (PTLD)
 - e. Risk of new malignancy or recurrent malignancy
 - f. Skin cancer
 - g. Modulation of immunosuppression in the face of malignancy
6. Chronic Rejection/Cardiac Allograft Vasculopathy
 - a. Risk factors
 - i. Multiple rejection episodes
 - ii. CMV disease
 - b. Utilization of mammalian target of rapamycin (mTOR) inhibitors/antiproliferatives
 - c. Lipid control
 - d. Antiplatelet therapy
 - e. Coronary interventions in transplant recipients

Minimum Experience Recommendation for Prevention And Management of Long Term Complications

1. Participate in evaluation of the risk for complications in 15 transplant recipients.
2. Treat 15 patients with post heart transplant complications, adjust medicines for the complication, whether or not it is medication related, for target levels, adverse effects, and drug interactions

Selected Hyperlinks for Long Term Complications

- Cancer overview: <http://www.cancer.gov/>
- Transplant Specific Cancer: <http://www.transplantliving.org/after-the-transplant/cancer/types/>
- Diabetes information: <http://www.diabetes.org>
- Transplant infection: http://www.cdc.gov/transplantsafety/transplant_overview.html

Suggested References for Long Term Complications

Allen U, Preiksaitis J. Epstein-Barr virus and posttransplant lymphoproliferative disorder in solid organ transplant recipients. *Am J Transplant* 2009; 9: S87-S96.

Arora S, Gullestad L. The challenge of allograft vasculopathy in cardiac transplantation. *Curr Opin Organ Transplant*. 2014; 19(5): 508-514.

Choquet S, Varnous S, Deback C. Adapted treatment of Epstein-Barr virus infection to prevent posttransplant lymphoproliferative disorder after heart transplantation. *Am J Transplant* 2014; 14:857-866.

Lane JT, Dagogo-Jack S. Approach to the patient with new-onset diabetes after transplant (NODAT). *J Clin Endocrinol Metab*. 2011; 96(11): 3289-3297.

Kittleson MM, Kobashigawa JA. Long-term care of the heart transplant recipient. *Curr Opin Organ Transplant*. 2014; 19(5): 515-524.

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Chapter 2

ADULT ORGAN SPECIFIC COMPETENCIES – LUNG

Section Lead: Christopher Ensor, PharmD, BCPS-CV

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2.1 MANAGEMENT OF CONDITIONS LEADING TO TRANSPLANTATION

Learning Objectives

1. Understand the overall, and in particular, the medical management of antecedent disorders leading to transplantation.
2. Delineate how to alter and optimise the lung transplant candidate's medications prior to surgery, including medications for concomitant conditions as well as for the antecedent lung disorder leading to transplant
3. Devise individualised patient specific perioperative medication plans for complex patients where necessary.
4. Develop a patient-specific monitoring plan assessing the efficacy and toxicities of therapy.
5. Identify gaps in the patient's understanding of their pre-transplant medication regimen, the importance of medication adherence, and provide education regarding their drug therapy.
6. Apply advanced knowledge of the pharmacology, pharmacokinetic and pharmacodynamic properties of drug therapy.

Topics Outline

1. Antecedent conditions
 - a. Including but not limited to: cystic fibrosis (CF), bronchiectasis, alpha-1 antitrypsin deficiency, interstitial lung diseases, chronic obstructive pulmonary disease, pulmonary arterial hypertension, dermatomyositis, scleroderma, mixed-connective tissue disorders, rheumatoid arthritis, selected immunodeficiencies, alveolar proteinosis, acute lung injury from epidemic viruses, bronchioloalveolar carcinoma, lymphangiomyomatosis.
2. Medication Optimisation
 - a. Lung associated medications (see Table 3).
 - b. Concomitant conditions, eg diabetes, nutrition, osteoporosis, cardiac
 - c. Medication alterations for emergent surgery
3. Perioperative medication plans
 - a. Nontuberculous Mycobacteria
 - b. Anticoagulants
4. Patient Education
 - a. Barriers to adherence; intentional and non-intentional
 - b. Addictions

Table 3. Drug Therapy for Selected Antecedent Disorders Prior to Lung Transplantation

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Cystic Fibrosis</p> <p>CFTR potentiators (ivacaftor) and correctors (lumacaftor)</p> <p>Anti-inflammatory antimicrobials: azithromycin</p> <p>Mast-cell stabilizers: montelukast</p> <p>Airway clearance: dornase alfa, n- acetylcysteine, hypertonic saline</p> <p>Insulin, vitamin supplementation, pancreatic enzyme supplementation</p> <p>Nebulized antimicrobials</p> | <p>Interstitial lung diseases</p> <p>Corticosteroids: prednisone Thalidomide Pirfenidone Tyrosine kinase inhibitors: nintedanib</p> <p>Alpha-1 Antitrypsin Replacement Prolastin-C, Aralast NP, Zemaira, Glassia</p> |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

CFTR: cystic fibrosis transmembrane conductance regulator

Minimum Experience Recommendation for Management of Conditions Leading to Transplantation

1. Participate in the evaluation and care of 5 or more lung transplant candidates for a minimum of 3 months from the time of referral to the time of listing and/or transplantation.
2. Participate in the evaluation and care of 3 or more lung transplant candidates undergoing urgent in-hospital evaluation for lung transplantation.

Suggested Hyperlinks for Management of Conditions Leading to Transplantation

- International Guidelines for the Selection of Lung Transplant Candidates: 2006 Update - A Consensus Report from the ISHLT Pulmonary Scientific Council: <http://www.jhltonline.org/article/PIIS1053249806002518/fulltext>
- International Guidelines for the Selection of Lung Transplant Candidates. The International Society for Heart and Lung Transplantation, the American Thoracic Society, the American Society of Transplant Physicians, the European Respiratory Society: <http://ajrccm.atsjournals.org/cgi/content/full/158/1/335>

Suggested References for Management of Conditions Leading to Transplantation

American Thoracic Society/European Respiratory Society Statement: Standards for the Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency. *Am J Respir Crit Care Med* 2003;168: 818-900.

Constantiner M, Cukor D. Barriers to Immunosuppressive Medication Adherence in High-Risk Adult Renal Transplant Recipients. *Dial Transplant* 2011;40:60–66.

Griffith DE. An Official ATS/IDSA Statement: Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases. *Am J Respir Crit Care Med* 2007;175:367–416.

Hadjiiladis D. Special considerations for patients with cystic fibrosis undergoing lung transplantation. *Chest*. 2007 Apr;131(4):1224-31.

Hugon A. Influence of intention to adhere, beliefs and satisfaction about medicines on adherence in solid organ transplant recipients. *Transplantation*. 2014;98:222-8.

Kelly E, Greene CM, Carroll TP, McElvaney NG, O'Neill SJ. Alpha-1 antitrypsin deficiency. *Respir Med* 2010;104:763-72.

Modrykamien A, Stoller JK. Alpha-1 antitrypsin (AAT) deficiency – what are the treatment options? *Expert Opin Pharmacother* 2009;10:2653-61.

Myers JL. NSIP, UIP, and the ABCs of idiopathic interstitial pneumonias. *Eur Respir J* 1998;12:1003-4.

Raghu G. An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management. *Am J Respir Crit Care Med* 2011;183:788–824.

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Shuhaiber JH, Kim JB, Hur K, Gibbons RD. Survival of primary and repeat lung transplantation in the united states. *Ann Thorac Surg* 2009;87:261-6.

Todd A . Update in Lung Transplantation 2013. *Am J Respir Crit Care Med* 2014;190:19-24.

2.2 MANAGEMENT OF PULMONARY HYPERTENSION

Learning Objectives

1. Describe the World Health Organization (WHO) clinical classification of PH (Pulmonary Hypertension) in order to distinguish treatment recommendations based on the underlying etiology.
2. Describe the pharmacology and usual dosing regimens, including in-class differences, for medications used to manage patients with PH.
3. Outline treatment options for patients with PAH (Pulmonary Arterial Hypertension) based on WHO functional capacity.
4. Describe PAH treatment product administration, including parenteral and inhaled device choice.
5. Recognize PAH medication procurement and regulatory requirements for monitoring.
6. Design a patient-specific regimen and monitoring plan for evaluation of effectiveness and safety in patients with PAH.
7. Evaluate PAH medications for the presence of common drug interactions and adverse events.
8. Determine appropriate management strategies for patients with PAH in the setting of perioperative care and critical illness.

Topics outline

1. Classification
 - a. WHO Groups 1 through 5
2. Pharmacotherapy for PAH (see Table 4)
 - a. Background therapy
 - b. Prostacyclins
 - c. Oral PAH-specific therapies
 - i. Endothelin, Nitric Oxide pathways
3. Treatment algorithm
 - a. Vasoreactivity testing for select patients
 - b. Risk assessment
4. Special Considerations
 - a. Perioperative care
 - b. Intensive care unit management

Table 4: Drug Therapies for Treatment of PAH

Phosphodiesterase (PDE) type-5 inhibitors

Sildenafil, Tadalafil

Soluble guanylate cyclase stimulators

Riociguat

Nitric Oxide

Endothelin receptor antagonists

Bosentan, Ambrisentan, Macitentan

Prostacyclins

Oral - Treprostinil, Beraprost

Inhaled - Iloprost, Treprostinil

Subcutaneous - Treprostinil

Intravenous - Epoprostenol, Treprostinil, Iloprost

Inotropes

Beta-agonists – Dobutamine, Dopamine

PDE-3 inhibitors – Milrinone

Calcium sensitizers - Levosimendan

Calcium channel blockers

Diltiazem, nifedipine

Minimum Experience Recommendation for the Management of Pulmonary Hypertension

1. Participate in evaluation of 10 patients with pulmonary hypertension.
2. Treat and/or modify the regimen of 10 patients with pulmonary hypertension.

Suggested References for the Management of Pulmonary Hypertension

Galie N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension. *J Am Coll Cardiol* 2013;62:D60-72.

Hoepfer MM, Granton J. Intensive care unit management of patients with severe pulmonary hypertension and right heart failure. *Am J Respir Crit Care Med* 2011;184:1114-24.

Kim NH, Delcroix M, Jenkins DP, et al. Chronic thromboembolic pulmonary hypertension. *J Am Coll Cardiol* 2013;62:D92-9.

Le Pavec J, Girgis RE, Lechtzin N, et al. Systemic sclerosis-related pulmonary hypertension associated with interstitial lung disease. *Arth Rheum* 2011;63:2456-64.

McLaughlin VV, Shah SJ, Souza R, et al. Management of pulmonary arterial hypertension. *J Am Coll Cardiol* 2015;65:1976-97.

Meyer S, McLaughlin VV, Seyfarth HJ, et al. Outcomes of noncardiac, nonobstetric surgery in patients with PAH: an international prospective survey. *Eur Respir J* 2013;41:1302-07.

Savarese G, Paolillo S, Costanzo P, et al. Do changes of 6-minute walk distance predict clinical events with pulmonary arterial hypertension? *J Am Coll Cardiol* 2012;60:1192-1202.

Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2013;62:D34-41.

Taichman DB, Ornelas J, Chung L, et al. Pharmacologic therapy for pulmonary arterial hypertension in adults. *Chest* 2014;146:449-75.

2.3 MANAGEMENT OF THE SENSITIZED PATIENT (Refer to Chapter 5)

2.4 MONITORING AND SELECTION OF IMMUNOSUPPRESSION (Refer to Chapter 5)

2.5 PREVENTION AND MANAGEMENT OF LONG TERM COMPLICATIONS

Learning Objectives

1. Know the risk factors that threaten the graft and compromise patient survival and quality of life, according to the ISHLT Registry data.
2. Understand complex therapeutic regimens, including drug toxicities, drug monitoring, drug interactions (with drugs, food, dietary supplements) and drug administration.
3. Counsel and educate patients and caregivers during the pre- and peri-transplantation period in order to prevent long-term complications and improve adherence.
4. Recognize opportunities for expanding pharmaceutical care into the ambulatory or clinic setting in order to assess drug therapy and the associated monitoring in conjunction with other health professionals.

Topics Outline

1. Graft and Patient Survival and quality of life
 - a. Bronchiolitis obliterans syndrome
 - b. Infection
 - c. Cardiovascular- lipids, hypertension
 - d. Malignancy
 - e. Endocrine- diabetes and CF related diabetes
 - f. Graft Failure
 - g. Renal Dysfunction
 - h. Osteoporosis
 - i. Haematological
 - j. Gastroesophageal reflux
2. Complex therapeutic regimens
 - a. Drug-drug interactions
 - b. Drug-food interactions
 - c. Drug-comorbidity interactions
 - d. Medication alterations due to swallowing difficulties
3. Education of patients and caregivers
 - a. Barriers to adherence
4. Clinic Setting
 - a. Medication optimisation and rationalisation
 - b. Planning pregnancy
 - c. Co-morbidity/iatrogenic illness recognition

Minimum Experience Recommendation for Prevention And Management of Long Term Complications

1. Participate in evaluation of the risk for complications in 15 transplant recipients.
2. Treat 15 patients with post lung transplant complications, adjust medicines for the complication, whether or not it is medication related, for target levels, adverse effects, and drug interactions

Suggested Hyperlinks for Prevention And Management of Long Term Complications

- An international ISHLT/ATS/ERS clinical practice guideline: diagnosis and management of bronchiolitis obliterans syndrome

https://www.isHLT.org/ContentDocuments/AN_INTERNATIONAL_ISHLT-ATRS_CLINICAL_PRACTICE_GUIDELINE_DIAGNOSIS_AND_MANAGEMENT_OF_BRONCHIOLITIS_OBLITERANS_SYNDROME.pdf

- 2014 ISHLT slide set- adult lung transplantation
<https://www.isHLT.org/registries/slides.asp?slides=heartLungRegistry>
- Phrenic nerve dysfunction after heart-lung and lung transplantation. *J Heart Lung Transplant* 2004; 23:105. <http://www.jhltonline.org/article/S1053-2498%2801%2900676-3/pdf>

Suggested Readings for Prevention And Management of Long Term Complications:

Arora S, Gude E, Sigurdardottir V, et al. Improvement in renal function after everolimus introduction and calcineurin inhibitor reduction in maintenance thoracic transplant recipients: the significance of baseline glomerular filtration rate. *J Heart Lung Transplant* 2012;31:259-65.

Chhajed PN, Dickenmann M, Bubendorf L, Mayr M, Steiger J, Tamm M. Patterns of pulmonary complications associated with sirolimus. *Respiration* 2006;73:367–374.

Chisholm MA, Mulloy LL, Jagadeesan M, DiPiro JT. Impact of clinical pharmacy services on renal transplant patients' compliance with immunosuppressive medications. *Clin Transplant* 2001;15:330-6.

Chisholm MA, Mulloy LL, Jagadeesan M, Martin BC, DiPiro JT. Effect of clinical pharmacy services on the blood pressure of African-American renal transplant patients. *Ethn Dis* 2002;12:392-7.

Chisholm-Burns MA, Pinsky B, Parker G, Johnson P, Arcona S, Buzinec P, Chakravarti P, Good M, Cooper M. Factors related to immunosuppressant medication adherence in renal transplant recipients. *Clin Transplant*. 2012;26(5):706-13.

Davis RD Jr, Lau CL, Eubanks S, et al. Improved lung allograft function after fundoplication in patients with gastroesophageal reflux disease undergoing lung transplantation. *J Thorac Cardiovasc Surg* 2003;125:533–542.

Gilljam M, Chaparro C, Tullis E, Chan C, Keshavjee S, Hutcheon M. GI complications after lung transplantation in patients with cystic fibrosis. *Chest* 2003;123:37–41.

Grimm JC, Lui C, Kilic A, Valero V, Sciortino CM, Whitman GJ, Shah AS. A risk score to predict acute renal failure in adult patients after lung transplantation. *Ann Thorac Surg*. 2015 Jan;99(1):251-7.

Hackman KL, Bailey MJ, Snell GI, Bach LA *Am J Transplant*. 2014;14(2):438-45. Diabetes is a major risk factor for mortality after lung transplantation.

Harrison JJ, Wang J, Cervenka J, Jackson L, Munyal D, Hamandi B, Chernenko S, Dorosz J, Chaparro C, Singer LG. Pilot study of a pharmaceutical care intervention in an outpatient lung transplant clinic. *Clin Transplant*. 2012;26(2):149-57.

Kremer BE. Post-transplant lymphoproliferative disorder after lung transplantation: a review of 35 cases *J Heart Lung Transplant*. 2012 Mar;31(3):296-304

Kulak CA, Borba VZ, Kulak J Jr, Custódio MR. Osteoporosis after transplantation. *Curr Osteoporos Rep*. 2012;10(1):48-55.

Ollech JE, Kramer MR, Peled N, et al. Post-transplant diabetes mellitus in lung transplant recipients: incidence and risk factors. *Eur J Cardiothorac Surg* 2008;33:844–848.

Snell GI, Levvey BJ, Chin W, et al. Sirolimus allows renal recovery in lung and heart transplant recipients with chronic renal impairment. *J Heart Lung Transplant* 2002;21:540-6.

Stemer G, Lemmens-Gruber R. Clinical pharmacy services and solid organ transplantation: a literature review. *Pharm World Sci* 2010;32:7-18.

Swanson MA, Palmeri D, Vossler ED, Bartus SA, Hull D, Schweizer RT. Noncompliance in organ transplant recipients. *Pharmacotherapy* 1991;11:173S-4S.

Vos R, Vanaudenaerde BM, Verleden SE, et al. A randomised controlled trial of azithromycin to prevent chronic rejection after lung transplantation. *Eur Respir J* 2011;37:164-72.

Weinstein RS. Clinical practice. Glucocorticoid-induced bone disease. *N Engl J Med*. 2011

Jul 7;365(1):62-70.

Zamora MR, Lyu DM Medical Complications of Lung Transplantation. Proceedings of the American Thoracic Society, 2009 ;6: 101-107.

2.6 PREVENTION AND TREATMENT OF OPPORTUNISTIC INFECTIONS

Learning Objectives

1. Recognize causative factors, their contribution to loss of allograft function and development of Bronchiolitis Obliterans Syndromes and? to understand the risks confronting lung transplant recipients.
2. Develop an extensive knowledge of prophylaxis against opportunistic infections and treatment of associated infections.
3. Have an up to date knowledge regarding immunization schedules
4. Recognize the clinical impact and management strategies for each of the different pathogens
5. Ensure appropriate antibiotic prophylaxis.
6. Understand the impact of T cell depleting antibody induction therapies
7. Collaborate with other health professionals in optimizing appropriate selection of drug therapy for patients.

Topics Outline

1. Opportunistic infections
 - a. Bacteria
 - b. Fungus
 - c. Virus
 - d. Parasites
2. Infectious locations
 - a. Pneumonia
 - b. Bacteremia
 - c. Empyema
 - d. Skin and skin structure
 - e. Deep tissue
 - f. Central Nervous System
 - g. Urine
3. Infectious prophylaxis
 - a. Fungus
 - b. Virus
 - c. Opportunistic infections
 - d. Donor derived infections
4. Infectious treatment
 - a. Bacteria
 - b. Fungus
 - c. Virus
 - d. Parasites
5. Agent selection and dosing factors
 - a. Age
 - b. Site penetration
 - c. Allergies
 - d. Target susceptibility
 - e. Combination regimens
 - f. Dosing principles
 - i. Absorption

- ii. Distribution
- iii. Metabolism
- iv. Elimination
- g. Special populations
- h. Delayed gastric emptying
- i. Impaired transit
- j. Esophageal dysmotility
- k. Roux-En-Y gastric bypass

Minimum Experience Recommendation for Prevention and Treatment of Opportunistic Infections

1. Treat 15 patients after transplantation with the site specific prophylactic regimen, adjust medicines for target levels, adverse effects, and drug interactions.
2. Treat 15 patients with post lung transplant opportunistic infections, adjust medicines for target levels, adverse effects, and drug interactions

Suggested Readings for Prevention and Treatment of Opportunistic Infections

- Aaron SD**, Ferris W, Henry DA, Speert DP, MacDonald NE. Multiple combination bactericidal antibiotic testing for patients with cystic fibrosis infected with *Burkholderia cepacia*. *Am J Respir Crit Care Med* 2000;161:1206-12.
- Arthurs SK**, Eid AJ, Deziel PJ, et al. The impact of invasive fungal diseases on survival after lung transplantation 2010; 24: 341-348.
- Alexander BD**, Petzold EW, Reller LB, et al. Survival after lung transplantation of cystic fibrosis patients infected with *Burkholderia cepacia* complex. *Am J Transplant* 2008; 8:1025.
- Bonde P**, Patel N, Borja M, et al. Impact of donor Lung Organisms on post-lung transplant pneumonia. *J Heart Lung Transplant* 2006; 25: 99-105.
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- Chernenko SM**, Humar A, Hutcheon M, et al. Mycobacterium abscessus infections in lung transplant recipients: the international experience. *J Heart Lung Transplant* 2006;25:1447-55.
- Drew WL**. Cytomegalovirus resistance testing: pitfalls and problems for the clinician. *Clin Infect Dis* 2010;50:733-6.
- Fishman JA**. Prevention of infection caused by pneumocystis carinii in transplant recipients. *Clin Infect Dis* 2001; 33:1397.
- Hibberd PL**, Rubin RH. Approach to immunization in the immunosuppressed host. *Infect Dis Clin North Am* 1990; 4:123.
- Hopkins P**, McNeil K, Kermeen F, et al. Human metapneumovirus in lung transplant recipients and comparison to respiratory syncytial virus. *Am J Respir Crit Care Med* 2008;178:876-81.
- Husain S**, Paterson DL, Studer S, et al. Voriconazole prophylaxis in lung transplant recipients. *Am J Transplant* 2006;6:3008-16.
- Husain S**, Singh N. Bronchiolitis obliterans and lung transplantation: evidence for an infectious etiology. *Semin Resp Infect* 2002; 17:310.
- Ison MG**. Adenovirus infections in transplant recipients. *Clin Infect Dis* 2006;43:331-9.
- Kaiser L**, Aubert JD, Pache JC, et al. Chronic rhinoviral infection in lung transplant recipients. *Am J Respir Crit Care Med* 2006;174:1392-9.
- Kotton CN**, Kumar D, Caliendo AM, et al. International consensus guidelines on the management of cytomegalovirus in solid organ transplantation. *Transplantation* 2010;89:779-95.
- Lease E**, Zaas D. Complex bacterial infections pre- and posttransplant. *Seminars in Resp and Critical Care Medicine* 2010; 31: 234-242.

Liu V, Dhillon GS, Weill D. A multi-drug regimen for respiratory syncytial virus and parainfluenza virus infections in adult lung and heart-lung transplant recipients. *Transpl Infect Dis* 2010;12:38-44.

Mitsiani D, Nguyen MH, Kwak EJ, et al. Cytomegalovirus disease among donor-positive/recipient-negative lung transplant recipients in the era of valganciclovir prophylaxis. *J Heart Lung Transplant* 2010;29:1014-20.

Neoh CF, Snell GI, Kotsimbos T, et al. Antifungal prophylaxis in lung transplantation – A world-wide survey. *Am J Transplant* 2011;11:361-6.

Palmer SM, Limaye AP, Banks M, et al. Extended valganciclovir prophylaxis to prevent cytomegalovirus after lung transplantation: A randomized, controlled trial. *Ann Intern Med* 2010;152:761-9.

Reichenspurner H, Gamberg P, Nitschke M, et al. Significant reduction in the number of fungal infections after lung-, heart-lung, and heart transplantation using aerosolized amphotericin B prophylaxis. *Transplant Proc* 1997;29:627-8.

Remund KF, Best M, Egan JJ. Infections relevant to lung transplantation. *Proc Am Thorac Soc* 2009;6:94-100.

Shah PD, Mcdyer JF. Viral infections in lung transplant recipients. *Seminars in Resp and Critical Care Medicine* 2010; 31: 243-254.

Speich R, van der Bij W. Epidemiology and management of infections after lung transplantation. *Clin Infect Dis* 2001;33:S58-65.

Soave R. Prophylaxis strategies for solid-organ transplantation. *Clin Infect Dis* 2001;33:S26-31.

Stelzmueller I, Lass-Floerl C, Geltner C, et al. Zygomycosis and other rare filamentous fungal infections in solid organ transplant recipients. *Transplant Int* 2008;21:534-46.

Vu DL, Bridevaux PO, Aubert JD, Soccac PM, Kaiser L. Respiratory viruses in lung transplant recipients: A critical review and pooled analysis of clinical studies. *Am J Transplant* 2011;11:1071-8.

Weinberg A, Lyu DM, Li S, Marquesen J, Zamora MR. Incidence and morbidity of human metapneumovirus and other community-acquired respiratory viruses in lung transplant recipients. *Transplant Infect Dis* 2010;12:330-5.

Chapter 3

PEDIATRIC ORGAN SPECIFIC COMPETENCIES- HEART

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Co-Authors: Jennifer Eshelman, PharmD

3.1 PEDIATRIC HEART FAILURE

In pediatric patients with advanced heart failure, extenuating issues such as the spectrum of age, unrepaired or repaired structural/congenital heart disease, and the role of genetic mutations increase the complexity in the management of this patient population.

Pharmacokinetic and pharmacodynamics differences including drug disposition, metabolism, and therapeutic effect may be substantially influenced by level of maturity of end organ systems. Other anatomic and physiologic factors that exist in patients with congenital heart disease and genetic abnormalities may also influence outcomes with pharmacotherapy compared to other types of heart disease in pediatric patients. Thoracic pharmacists providing care for such a broad spectrum of pediatric heart failure patients must be able to meet the following objectives:

Learning Objectives

1. Describe the anatomy, physiology, and pathophysiology of patients with repaired and unrepaired congenital heart disease, myocarditis, and all forms of cardiomyopathy.
2. Summarize the impact of genetic mutations on the development of pediatric heart disease, associated end organ anomalies, and outcomes.
3. Discuss the effect of patient age, as well as anatomic and physiologic differences on pharmacokinetic and pharmacodynamics principles, in pediatric patients with heart failure and congenital heart disease.
4. Describe the secondary effects from cardiac disease in pediatric patients and the impact it can have on the management of heart failure.
5. Apply the pharmacokinetic and pharmacodynamics principles of drug therapy combined with knowledge of anatomic, physiologic, and pathophysiologic features of pediatric acute decompensated heart failure to design pharmacotherapeutic regimens that maximize efficacy and minimize toxicity.

Topic Outline

1. Anatomy and Physiology
 - a. Repaired and Unrepaired Congenital Heart Disease
 - i. Single Ventricle Physiology
 1. Hypoplastic Left Heart Syndrome
 2. Tricuspid Atresia
 3. Double Inlet Left Ventricle
 4. Unbalanced Atrioventricular Septal Defect
 - ii. Aortic stenosis
 - iii. Ebstein's Anomaly
 - iv. Transposition of the Great Arteries
 - v. Congenitally Corrected Transposition of the Great Arteries
 - vi. Tetralogy of Fallot
 - vii. Truncus Arteriosus
 - viii. Pulmonary Atresia with Intact Ventricular Septum
 - ix. Anomalous Left Coronary Artery from the Pulmonary Artery

- b. Myocarditis
- c. Cardiomyopathy
 - i. Dilated
 - ii. Hypertrophic
 - iii. Restrictive
 - iv. Non-compaction
 - v. Arrhythmogenic ventricular
- 2. Genetic Mutations and Associated Non-Cardiac Anomalies
 - a. Cardiomyopathy linked genetic mutations
 - i. Barth Syndrome
 - ii. Dannon Syndrome
 - iii. Duchenne Muscular Dystrophy
 - iv. Becker Muscular Dystrophy
 - v. Noonan Syndrome
 - b. Congenital heart disease linked genetic mutations
 - i. Trisomy 21
 - ii. 22q11 deletion
 - iii. Heterotaxy Syndrome
 - c. Non-cardiac anomalies associated with the genetic mutations listed above
 - i. Renal
 - ii. Neurologic
 - iii. Vascular
 - iv. Respiratory/Airway
 - v. Gastrointestinal
 - vi. Hematologic
 - vii. Immunologic
 - viii. Musculoskeletal
- 3. Pharmacokinetics and pharmacodynamics throughout development in pediatrics and pediatric heart failure
 - a. Pharmacokinetic principles for neonates, infants, children, adolescents, and adults including adult congenital heart disease patients
 - i. Medication Absorption
 - 1. Gastric pH
 - 2. Gastric motility
 - 3. Transporter maturity
 - 4. Intestinal surface area
 - 5. Perfusion to site of absorption
 - ii. Volume of distribution
 - 1. Body composition
 - 2. Plasma protein binding
 - 3. Membrane permeability
 - iii. Metabolism
 - 1. Phase I metabolism
 - 2. Phase II metabolism
 - iv. Elimination
 - 1. Renal clearance
 - b. Specific PK/PD changes in pediatric heart failure and acute illness
 - i. Medication Absorption
 - 1. Perfusion to site of absorption
 - 2. Gastric motility
 - 3. Use of enteral feeding tubes for administration
 - ii. Volume of Distribution
 - 1. Rapid changes in body composition with fluid overload and diuretic therapy
 - 2. Decrease plasma proteins

- iii. Metabolism and Elimination
 1. End-organ dysfunction
 2. Drug-Drug Interactions
4. Secondary effects of congenital heart disease and comorbidities in pediatric heart failure
 - a. Hypertension
 - b. Pulmonary edema
 - c. Dysrhythmia
 - d. Thrombosis
 - e. Acute kidney injury and chronic kidney disease
 - f. Elevated pulmonary pressures/pulmonary hypertension
 - g. Growth failure
 - h. Depression and anxiety
 - i. Necrotizing enterocolitis
 - j. Diaphragmatic or vocal cord palsy/paralysis
 - k. Cirrhosis
 - l. Chylothorax
 - m. Plastic Bronchitis
 - n. Protein Losing Enteropathy
5. Pharmacologic agents used to manage pediatric heart failure and congenital heart disease
 - a. For each class of medications the pharmacist must know the mechanism of action, role in pediatric heart failure (if any), adverse effects, dosing, monitoring, potential drug-drug or drug-disease interactions, and pharmacokinetic/pharmacodynamic differences by age of the child (refer to Chapter 1)

Minimum Experience Recommendation for Management of Pediatric Heart Failure

1. Participate in the evaluation and care of 25 or more patients with pediatric heart failure

Suggested Hyperlinks for Pediatric Heart Failure

- The International Society for Heart and Lung Transplantation Guidelines for the management of pediatric heart failure: Executive summary
<http://dx.doi.org/10.1016/j.healun.2014.06.002>

Suggested References for Pediatric Heart Failure

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3.2 PEDIATRIC MECHANICAL CIRCULATORY SUPPORT

Mechanical circulatory support (MCS) is considered the standard treatment in patients with circulatory failure refractory to medical therapy. Extracorporeal membrane oxygenation (ECMO) continues to be the primary means of MCS for acute decompensated heart failure refractory to medical management in pediatric patients as a bridge to recovery or transplant. More recently, MCS with VADs have been introduced as an alternative for cardiac support in pediatric patients. These devices possess potential advantages and disadvantages in providing MCS to this population, but continue to be limited by the balanced risk between hemorrhage and thrombosis. In adult patients with end-stage left sided heart failure, implantable left ventricular assist devices (ex: Heartmate II®, Heartware HVAD®) are also used as destination therapy in patients who are not candidates for cardiac transplantation. Although not indicated for destination therapy in pediatric patients, use has been described as a longer term bridge to transplant. With the use of ECMO, and the continued evolution of

VAD technology in this population, it is imperative that the thoracic pharmacist be competent in the following:

Learning Objectives

1. Understand indications for ECMO or VAD, as well as the advantages and disadvantages of each in pediatric patients requiring MCS for advanced heart failure.
2. Describe hemorrhagic and thrombotic risk of MCS and pharmacologic management of each complication.
3. Understand infection risks associated with the placement of MCS devices, monitoring strategies, limitations to monitoring depending on device type, and appropriate antibiotic selection.
4. Utilize understanding of pharmacokinetic and pharmacodynamic variations in patients on MCS, or those weaning from MCS, to design medication regimens and monitoring strategies that address adjunctive cardiovascular therapies.
5. In pediatric patients receiving implantable left ventricular assist devices (ex: Heartmate II®, Heartware HVAD®), address long term issues associated with these devices (See Adult Core Competencies on MCS).

Topic Outline

1. Device Selection
 - a. Support devices
 - i. ECMO
 - ii. Berlin Heart EXCOR ®
 - iii. Centrimag®
 - iv. PediMag®
 - v. Heartmate II ®
 - vi. Heartware HVAD®
 - b. Support/Implant Considerations
 - i. Cardiac versus cardiopulmonary support
 - ii. Left ventricular, right ventricular, or biventricular support
 - iii. Patient size/device limitations
 - iv. Anatomical considerations (ex: single versus biventricular physiology)
 - v. Duration of support
2. Risk Management of Hemorrhagic and Thrombotic Complications (See Chapter 1, Section 1.2)
 - a. Device Type
 - b. Timing from device placement
 - i. Intra-operative/acute post-operative bleeding
 - ii. Long Term
 - c. Surgical bleeding vs coagulopathy
 - i. Coagulation evaluation
 - d. Bleeding Site
 - e. Anticoagulation factors
 - i. Anticoagulant
 - ii. Anticoagulation goal and monitoring tests
 - f. Other management considerations
 - i. Invasive procedures or surgical intervention for hemorrhage/thrombosis
 - ii. Other invasive procedures (ex: endoscopy, embolectomy),
 - iii. Revision/replacement/removal of mechanical assist device
 - g. Pharmacologic/blood product management for hemorrhagic/thrombotic complications
 - i. Hemorrhage

- ii. Thombosis
- 3. Infection Risks, Antibiotic Selection and Monitoring strategies (Refer to Chapter 1, Section 1.2)
 - a. Device Type
 - b. Timing from device placement
 - c. Associated surgical or other complications/factors
 - i. Bleeding or thrombotic complications
 - 1. Open chest/chest re-exploration
 - 2. Device revision/placement
 - ii. Prolonged mechanical ventilation
 - iii. Acute kidney injury/renal replacement therapy
 - iv. Malnutrition and immunocompromised
 - v. Emergence of antimicrobial resistance and opportunistic infections
 - vi. Other
 - d. Antibiotic Selection
 - i. Knowledge of antibiotic classes, properties, pharmacokinetics, pharmacodynamics, and resistance patterns
 - ii. Account for age related differences and above associated factors in proper designing of regimens
 - e. Monitoring
 - i. Device related effects and changes on various pharmacokinetic and pharmacodynamics features
 - 1. Volume of distribution
 - 2. Binding characteristics to the device
 - 3. Changes in elimination secondary to device characteristics or use of other associated therapies (ex: renal replacement therapies)
 - 4. Device effects on various monitoring parameters
- 4. Other Therapeutic Considerations in Pediatric Patients on MCS
 - a. Device Type
 - b. Indication
 - i. Bridge to recovery
 - ii. Bridge to transplant
 - iii. Bridge to durable mechanical support
 - c. Pharmacokinetic and pharmacodynamics effects based on age and genetics
 - d. End-organ function and need for additional support (eg. Continuous Renal Replacement Therapy)
 - e. Duration of support
 - f. Cardiovascular medications (Refer to Chapter 1, Section 1.1)
 - g. Other pharmacologic needs on MCS
 - i. Central Nervous System
 - 1. Pain, Sedation, Skeletal muscle relaxants
 - ii. Monitoring for propofol related infusion syndrome (PRIS)
 - iii. Gastrointestinal
 - 1. Parenteral vs enteral nutrition
 - 2. Stress ulcer prophylaxis
 - iv. Renal
 - 1. Fluid and electrolyte management
 - v. Endocrine
 - 1. Glycemic control
 - 2. Adrenal insufficiency management
 - 3. Other endocrine disorders
- 5. Long term complications associated with MCS devices (Refer to Chapter 1 Section 1.2)

Minimum Experience Recommendation for Management of Pediatric MCS

1. Participate in the evaluation and care of 5 or more pediatric patients supported with MCS devices

Suggested References for Pediatric MCS

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3.3 MANAGEMENT OF THE SENSITIZED PATIENT (Refer to Chapter 5)

3.4 MONITORING AND SELECTION OF IMMUNOSUPPRESSION (Refer to Chapter 5)

3.5 PREVENTION AND MANAGEMENT OF INTRA-OPERATIVE AND POST-OPERATIVE COMPLICATIONS

Recipient intra-operative and post-operative management of a pediatric heart transplant patient is largely dependent on the patient's age, pre-operative diagnosis and associated risk factors. Surgical bleeding, acute graft failure, infection, end-organ dysfunction, and rejection are all sources of increased mortality post-transplant, but pediatric patients with complex congenital heart disease appear to be at the greatest risk for these complications. Other factors including age, and transplant compatibility (eg: ABO incompatible, highly sensitized patient) will also directly affect therapeutic decisions including post-operative immunosuppressive regimens, with associated immunosuppressive therapies, and proper drug dosing.

Learning Objectives

1. Understand risk factors for increased intra-operative and post-operative bleeding and coagulation management.
2. Understand risk factors for the development of primary graft dysfunction post-transplantation in this population.
3. Understand the post-operative hemodynamic management of a pediatric heart transplant patient including pharmacokinetic and pharmacodynamics principles of inotropic and vasoactive agents as well as therapies associated with use of MCS in patients with primary graft dysfunction refractory to medical management.
4. Recognize and discuss other management issues required in the acute post-transplant period including nutritional support, antimicrobial prophylaxis including surgical site, Pneumocystis jiroveci pneumonia (PJP), CMV, and antifungal prophylaxis.

Topics Outline

1. Risk Factors for Intra-Operative and Post-Operative Bleeding and Management Strategies
 - a. Associated Risks
 - b. Re-operation or repeat sternotomy
 - c. Pre-operative or post-operative coagulopathy or use of anticoagulation
 - d. Pre-operative or post-operative MCS
 - e. Prolonged time on cardiopulmonary bypass
 - f. Inadequate surgical hemostasis
 - g. Other
 - h. Management
 - i. Evaluation and reversal of coagulopathy or anticoagulation
 1. Coagulation evaluation (Refer to Chapter 1, Section 1.2)
 2. Coagulopathy or anticoagulation reversal (Refer to Chapter 1, Section 1.2)
2. Risk Factors For Development of Primary Graft Dysfunction
 - a. Congenital Heart Disease
 - b. Pre-transplant MCS and/or mechanical ventilation
 - c. Allosensitization
 - d. Prolonged donor ischemic time

- e. Donor-recipient size mismatch
- f. Poor donor heart quality
- g. Other
- 3. Post-operative Hemodynamic Management Considerations
 - a. Allograft function intra-operatively and immediately post-operatively
 - i. Primary graft dysfunction or graft failure
 - 1. Right ventricular dysfunction/failure with or without PAH
 - 2. Left ventricular dysfunction/failure
 - 3. Biventricular dysfunction/failure
 - 4. Cardiopulmonary failure
 - b. Mechanical circulatory support
 - i. Device type
 - ii. Support/implant considerations
 - 1. Cardiac vs cardiopulmonary support
 - 2. Left ventricular vs right ventricular vs biventricular support
 - 3. Patient size/device limitations
 - 4. Duration of support
 - c. Coagulopathy with product resuscitation
 - i. Hemodynamic changes with volume shifts
 - ii. Hemodynamic adjustments to minimize bleeding
 - d. End-organ function
 - i. Prolonged mechanical ventilation
 - ii. Renal replacement therapy
 - iii. Hepatic dysfunction
 - e. Pharmacokinetic and pharmacodynamics effects based on age, end organ dysfunction, and genetic issues
 - i. Alteration in pediatric absorption, distribution, metabolism, and elimination
- 4. Cardiovascular medications (Refer to Chapter 1, Section 1.1)
- 5. Other Management Issues in the Care of a Post-Operative Pediatric Heart Transplant patient
 - a. Central Nervous System
 - i. Pain, Sedation, Skeletal muscle relaxants
 - a. Monitoring for propofol related infusion syndrome (PRIS)
 - b. Gastrointestinal
 - i. Critical assessment of baseline nutritional status
 - 1. Age effect on nutrition needs
 - 2. Effect of disease state
 - a. Protein losing enteropathy post Fontan
 - b. Prolonged heart failure with failure to thrive
 - c. Other
 - ii. Parenteral vs enteral nutrition
 - iii. Stress ulcer prophylaxis
 - c. Renal
 - i. Fluid and electrolyte management accounting for age and disease state
 - d. Endocrine
 - i. Glycemic control
 - ii. Other endocrine disorders
 - e. Post-operative antimicrobial therapy/prophylaxis (Refer to Chapter 1, Section 1.61)
 - i. Antibiotic selection
 - 1. Account for age related differences and dosage forms/medications used in pediatrics

Minimum Experience Recommendation for Intra-Operative and Post-Operative Complications

1. Participate in evaluation of the risk for complications in 5 transplant recipients.
2. Treat 5 patients with post pediatric heart transplant complications, adjust medicines for the complication, whether or not it is medication related, for target levels, adverse effects, and drug interactions

Suggested References for Intra-Operative and Post-Operative Complications

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3.6 PREVENTION AND MANAGEMENT OF PEDIATRIC LONG TERM COMPLICATIONS

The goal of post-operative and long term immunosuppressive therapy in pediatric heart transplant patients is to balance prevention of acute rejection and graft loss, while minimizing adverse events and long term complications associated with their therapeutic regimens. Competencies for adult heart transplant pharmacists which review surveillance of heart function and the prevention and management of post-operative complications are also required by pediatric heart transplant pharmacists (See Adult Core Competencies on Surveillance of Heart Function and Prevention and Management of Post - Operative Complications). However, pediatric patients possess some unique factors that also must be taken into account when planning therapeutic strategies for short and long term care.

Patient age at transplantation, history of congenital heart disease, and allosensitization, are all complicating factors in achieving this immunosuppressive balance. As previously discussed, the therapeutic effect of medications may be substantially influenced by level of maturity of end organ systems and the immune system which will continue to change as the patient grows and matures. Pediatric patients will require the initiation of individualized therapy with immunosuppressive agents based on their developmental differences in pharmacokinetics and pharmacodynamics, which will need to be continually refined over time as the child develops.

Learning Objectives

1. Describe the side effect profiles of immunosuppressive medications and strategies to limit or manage these adverse effects in pediatric patients
2. Understand the methods and limitations of rejection monitoring in pediatric patients
3. Describe the differences in presentation and treatment of infections and infectious manifestations between pediatric and adult patients
4. Understand the influence of immunosuppression and age on immunization effectiveness, schedule modifications, and contraindications in pediatric heart transplant recipients
5. Summarize the types of secondary malignancies seen in the pediatric population and how they differ from those seen in adults including risk factors and surveillance strategies.
6. Differentiate the presentation and treatment of transplant cardiac allograft vasculopathy in pediatrics and adult patients
7. Understand the potential for re-transplantation in pediatric patients and factors that contribute to patient eligibility and therapeutic management.
8. Recognize the influence of pediatric transplantation and age at time of transplantation on quality of life and long term outcomes

Topic Outline

1. Immunosuppression Selection in Pediatric Patients (Refer to Chapter 5)
2. Rejection Monitoring and Limitations to Monitoring in Pediatrics
 - a. Hemodynamics
 - b. Echochardiography
 - c. Cardiac catheterization
 - d. Endomyocardial biopsies
 - e. Non-invasive laboratory monitoring
3. Rejection Management (Refer to chapter 1, Section 1.62)
4. Presentation, Prevention, and Treatment of Infection
 - a. Timing of infection
 - b. Potential Sources of Infection
 - c. Infections with unique considerations or presentation in pediatric transplant patients
 - i. Prevention and exposure management
 1. Ebstein Barr Virus
 2. HSV
 3. Respiratory Syncytial Virus
 4. Varicella Zoster
5. Immunizations
 - a. Standard immunization schedule
 - b. Catch-up schedule
 - c. Timing of vaccinations around transplant
 - d. Live vaccines
 - e. Monitoring of vaccine titers

6. Malignancy
 - a. Common types post-transplant (Refer to Chapter 1, Section 1.6.4)
 - b. Risk factors
 - c. Surveillance monitoring
7. Cardiac Allograft Vasculopathy(Refer to Chapter 1, Section 1.6.4)
 - a. Presentation and monitoring in pediatrics
 - b. Limitations to coronary interventions and revascularization in pediatric patients
 - c. Prevention and treatment
8. Retransplantation
 - a. Eligibility
 - b. Multi-organ transplantation
 - c. Risk factors
9. Quality of Life and Long-Term Follow Up
 - a. Growth
 - b. Developmental milestones
 - c. Psychosocial function
 - d. Medication compliance
 - e. Transition to adult care
 - f. Family planning

Minimum Experience Recommendation for Pediatric Long Term Complications

1. Participate in evaluation of the risk for complications in 5 transplant recipients.
2. Treat 5 patients with post pediatric heart transplant complications, adjust medicines for the complication, whether or not it is medication related, for target levels, adverse effects, and drug interactions

Suggested Hyperlinks for Pediatric Long Term Complications

- [Centers for Disease Control and Prevention – Birth-18 Years & “Catch-Up” Immunization Schedules](#)
- [International Society of Heart and Lung Transplantation Guidelines for the Care of Heart Transplant Recipients](#)
- [The Registry of the International Society for Heart and Lung Transplantation: Seventeenth Official Pediatric Heart Transplantation Report—2014; Focus Theme: Retransplantation](#)
- [International Society for Heart and Lung Transplantation Working Formulation of a Standardized Nomenclature for Cardiac Allograft Vasculopathy—2010](#)

Suggested References for Pediatric Long Term Complications

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Chapter 4

PEDIATRIC ORGAN SPECIFIC COMPETENCIES- LUNG

Section Lead: Katrina Ford, BSc, BPharm, MSc

The vast majority of pediatric lung transplants are performed at small centers, where fewer than 4 transplants are done each year. This activity is probably insufficient to support the need for a full time specialist pediatric lung transplant pharmacist at these centers, and consideration should be given to linking this role with the pediatric cardiac transplant pharmacist, or the pediatric respiratory pharmacist so that the pharmaceutical care needs of this small but complex group are met.

4.1 MANAGEMENT OF CONDITIONS LEADING TO PEDIATRIC LUNG TRANSPLANTATION (Refer to Chapter 2, Section 2.1)

Learning Objectives

1. Understand the pathophysiology of cystic fibrosis and its drug management in pediatric patients.
2. Understand the pathophysiology of pulmonary artery hypertension and its drug management in pediatric patients.
3. Understand the basic pathophysiology of pulmonary vascular disease, congenital heart disease and chronic lung disease.
4. List the indications for lung transplantation in pediatric patients
5. Understand the developmental and physiological changes through infancy and childhood as they relate to pharmacodynamics and pharmacokinetics and choice of formulation

Topic Outline

1. Cystic Fibrosis
 - a. Pathophysiology and disease related impact on pharmacokinetics
 - b. Drug therapy: dose, pharmacokinetics, administration, drug-drug interactions and adverse effects as they relate to pediatrics (Refer to Chapter 2, Table 3)
2. Pulmonary Artery Hypertension
 - a. Pathophysiology
 - b. Drug therapy: dose, pharmacokinetics, administration, drug-drug interactions and adverse effects as they relate to pediatrics (Refer to Chapter 2, Section 2.1)
3. Pulmonary Vascular Disease, Congenital Heart Disease and Chronic Lung Disease (Refer to Chapter 2 Section 2.1 and Chapter 3 Section 3.1)
 - a. Basic pathophysiology
 - b. Drug therapy: dose, pharmacokinetics, administration, drug-drug interactions and adverse effects as they relate to pediatrics
4. Age-related effects on pharmacokinetics (Refer to Chapter 3, Section 3.1)
5. Age-related considerations for choice of formulation and route of administration
 - a. Nebulised
 - b. Parenteral
 - c. Oral and gastric tube

Minimum Experience Recommendation for Prevention And Management of Conditions Leading to Transplant

1. Participate in evaluation of 5 transplant candidates.
2. Participate in the treatment and management of 5 transplant candidates for a minimum of 3 months prior to transplantation.

Selected Hyperlinks related to Conditions Leading to Pediatric Lung Transplantation

- Pediatric Lung Transplant Statistics: ISHLT Registries
<http://www.isHLT.org/registries/slides.asp?slides=heartLungRegistry>

Suggested References for Conditions Leading to Pediatric Lung Transplantation

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4.2 MANAGEMENT OF PULMONARY HYPERTENSION (Refer to Chapter 2 Section 2.2)

4.3 MANAGEMENT OF THE SENSITIZED PATIENT (Refer to Chapter 5)

4.4 MONITORING AND SELECTION OF IMMUNOSUPPRESSION (Refer to Chapter 5)

4.5 PREVENTION AND MANAGEMENT OF LONG TERM COMPLICATIONS

Learning Objectives

1. Discuss the risk factors that threaten the graft and compromise patient survival and quality of life, according to the ISHLT Registry data
2. Knowledge of the side effect profiles of all immunosuppressants as they relate to pediatrics, and strategies for monitoring and minimising side effects
3. Discuss the use of antibiotics, antivirals and antifungals in long term therapy taking into consideration clinical risk, pill burden, route of administration, fluid status, drug interactions, adverse effects and compliance issues in the pediatric patient

4. Knowledge of drug-drug interactions between immunosuppressants and anti-infective agents, and strategies for monitoring therapeutic efficacy
5. Understand the influence of immunosuppression and age on immunization effectiveness, schedule modifications, and contraindications in pediatric heart transplant recipients

Topic Outline

1. Fluid status in children and implications for administration of intravenous infusions
2. End organ function and implications for pediatric pharmacokinetics (Refer to Chapter 3 Section 3.1)
 - a. Lung function
 - b. Renal function
 - c. Liver function
 - d. Gut function
3. Management of Infection (Refer to Chapter 2, Section 2.5)
 - a. Bacterial Pneumonia: Prophylaxis and Treatment
 - b. Fungal Infection: Prophylaxis and Treatment
 - c. CMV Infection: Prophylaxis and Treatment
 - d. Utility of Inhaled Agents in the Post-Operative Period
4. Patient compliance and pill burden
5. Implications for treatment success and quality of life

Minimum Experience Recommendation for Prevention and Management of Long Term Complications

1. Participate in evaluation of the risk for complications in 5 transplant recipients.
2. Treat 5 patients with post pediatric lung transplant complications, adjust medicines for the complication, whether or not it is medication related, for target levels, adverse effects, and drug interactions

Selected Hyperlinks related to Prevention And Management of Long Term Complications

- Generic Drug Immunosuppression in Thoracic Transplantation: An ISHLT Educational Advisory: https://www.isHLT.org/ContentDocuments/JHLT_July2009_Generic_Concensus_Statement.pdf
- International Society for Heart and Lung Transplantation. [The registry of the International Society for Heart and Lung Transplantation: seventeenth official pediatric lung and heart-lung transplantation report--2014; focus theme: retransplantation.](#)

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4.6 PREVENTION AND TREATMENT OF OPPORTUNISTIC INFECTIONS (Refer to Chapter 2 Section 2.6)

Chapter 5

Immunosuppression Competencies- All Organs

Section Lead: Michael Shullo, PharmD

Co-Authors: All

5.1 MONITORING AND SELECTION OF IMMUNOSUPPRESSION

Thoracic pharmacists deemed competent in the management of thoracic transplant recipients must be experts in immunosuppression to appropriately recommend patient specific therapy and monitoring plans. This requires an in-depth understanding of human immunology and the pharmacokinetic/pharmacodynamic properties, adverse effects, interactions of all immunosuppressive therapies, and an extensive knowledge of the evidence that exists in the literature for these therapies.

Pharmacists who manage pediatric patients undergoing thoracic transplantation require additional knowledge of extenuating issues such as age, comorbidities, and congenital heart disease history. Pharmacokinetic and pharmacodynamic issues such as drug disposition, metabolism, and therapeutic effect may be substantially influenced by level of maturity of end organ systems and will continue to change as the patient grows and matures. This includes changes in the immune system itself, which like other organ systems evolves over time, and may have a direct effect on immunosuppressive strategies. Congenital heart disease carries an increased risk for mortality in patients undergoing transplantation and may be related to surgical risk associated with prior operations and presensitization to HLA antigens associated with blood products and/or allograft material exposure.

Learning Objectives

1. Understand how immunosuppressive therapies affect recipient immune function
2. Understand the pharmacokinetics and pharmacodynamics of immunosuppressive medications
3. Understand infectious risk and how to modify immunosuppressive therapy in this setting
4. Understand the role of therapeutic drug monitoring for immunosuppressive agents
5. Develop patient specific monitoring plans assessing the efficacy and toxicities of pharmacotherapy
6. Provide medication education regarding drug therapies utilized to this patient group
7. Discuss the development of a general immunosuppressant strategies
8. Understand educational needs of medical and nursing staff medication education needs.
9. Understand cost effectiveness and suitability for generic substitution.
10. Discuss the available formulations, supply, and reimbursement of immunosuppressive agents.

Topic Outline

1. Immunology
 - a. Innate versus adaptive immunity
 - b. Cells of the immune system
 - i. T cells

- ii. B cells
 - iii. Plasma cells
 - iv. NK Cells
- c. Immune system development and function
 - i. T and B Cell immunity
 - 1. Neonate
 - 2. Infant
 - 3. Child
 - 4. Adolescent
 - 5. Adult
 - 6. ABO incompatible transplantation
 - d. Thymectomy effects following congenital heart disease and surgical repair
 - e. Response to foreign antigen
 - f. Assessment of immunologic risk
- 2. Immunosuppressive agents (Table 5)
 - a. Immunosuppressant action and the immune cascade
 - b. Induction
 - c. Maintenance agents
 - d. Agents for the treatment of Rejection
 - i. Pharmacodynamics and Pharmacodynamics
 - ii. Therapeutic drug monitoring (Table 6)
 - iii. Age related differences
 - iv. Renal replacement therapy
 - v. Plasmapheresis
 - vi. Ventricular Assist Devices
 - vii. Extracorporeal membrane oxygenation
 - e. Adverse events
 - f. Drug preparation, administration, and storage challenges
 - i. Storage
 - ii. Administration through enteral feeding tubes
 - iii. Medication adherence to plastic
 - iv. Oral liquid palatability
 - v. Vascular access requirements and challenges
 - vi. Pre-medication and emergency medication requirements for infusions
- 3. Polypharmacy and drug-drug interactions
- 4. Goals of therapy
 - a. Morbidity
 - b. Mortality
 - c. Symptom Control
 - d. Patient adherence
- 5. Appropriate drug selection and dosing
 - a. Comorbid conditions
 - b. Pregnancy
 - c. Malignancy
 - d. Deteriorating renal function
 - e. Deteriorating respiratory function
 - f. Increasing time since transplant
 - g. Toxicities and adverse effects of medications
 - h. New drug interactions
- 6. Dialogue with and provide education to patients to establish adherence with prescribed regimens
- 7. Management of rejection
 - a. Acute cellular rejection
 - b. Antibody mediated rejection
 - c. Prevention of opportunistic infections with rejection treatment

TABLE 5. CURRENT IMMUNOSUPPRESSANTS

| | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Antibody Preparations Monoclonal <ul style="list-style-type: none"> • Basiliximab • Alemtuzumab Polyclonal <ul style="list-style-type: none"> • Antithymocyte globulin Anti-CD20 – <ul style="list-style-type: none"> • Rituximab Proteasomal inhibitors Bortezomib Carfilzomib | Calcineurin Inhibitors Cyclosporine, Tacrolimus Proliferation Signal Inhibitors Everolimus Sirolimus Antimetabolites Azathioprine Mycophenolate mofetil Mycophenolic acid Corticosteroids Methylprednisolone Prednisolone Prednisone Dexamethasone |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

TABLE 6. THERAPEUTIC DRUG MONITORING

| Medication | Therapeutic Drug Monitoring Target |
|-----------------------|-------------------------------------------|
| Cyclosporine | Trough and C ₂ |
| Tacrolimus | Trough |
| Everolimus | Trough |
| Sirolimus | Trough |
| Mycophenolate mofetil | Trough and AUC |
| Mycophenolic acid | AUC |

C₂: cyclosporine 2 hour post dose level; AUC: area under the curve

Minimum Experience Recommendation for Monitoring and Selection of Post-Transplant Immunosuppression

1. Participate in evaluation of the immunologic work up of 15 transplant recipients.
2. Treat 15 patients with immunosuppression post transplant, adjust doses for target levels, adverse effects, and drug interactions

Suggested Hyperlinks for Monitoring and Selection of Immunosuppression

- [International Society of Heart and Lung Transplantation Consensus Statement: Generic Drug Immunosuppression in Thoracic Transplantation](#)
- The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. J Heart Lung Transplant 2010;29:914-956 DOI: <http://dx.doi.org/10.1016/j.healun.2010.05.034>

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5.2 MANAGEMENT OF THE SENSITIZED PATIENT

Thoracic pharmacists must have extensive knowledge in immunology, immunosuppressive agents, pharmacokinetic and pharmacodynamics of medications, especially in the setting of extracorporeal therapy. This knowledge is necessary to appropriately design, implement, and monitor therapeutic plans to ensure sensitized recipients achieve prolonged, stable allograft function.

Allosensitivity is particularly problematic for pharmacists involved in pediatric heart transplantation. Congenital heart disease carries an increased risk for mortality in patients undergoing transplantation and may be related to surgical risk associated with prior operations and presensitization to HLA antigens associated with blood products and/or allograft material exposure. In addition, pharmacists who manage pediatric patients undergoing thoracic transplantation require additional knowledge of ABO incompatible transplants in young children due to the immaturity of their immune system and lack of early production of antibodies against blood group antigens.

Learning Objectives

1. Describe the role of allosensitization in patients and its effect on donor availability and long-term outcomes
2. Understand the factors that contribute to patient allosensitization
3. Describe the immunologic mechanisms that lead to allosensitization
4. Interpret the immunologic tests utilized in the pre and post transplantation
5. Describe the therapies aimed at reducing allosensitization, understanding the benefits and risks and applying advanced knowledge of pharmacokinetic and pharmacodynamic properties of each modality
6. Create a patient specific desensitization regimen and associated monitoring plan for efficacy and toxicity (infections, etc.).
7. Provide medication education regarding drug therapies utilized to this patient group

Topic Outline

1. B cell immunology
 - a. Naïve cell maturation to plasma cell
 - b. Plasma cell-based antibody production
2. Allograft physiology and antibody binding
3. Immunogenetics
 - a. ABO Blood System
 - b. Major Histocompatibility Complex I and II
4. Methods used to detect anti-HLA antibodies
 - a. Plasma monitoring
 - i. Enzyme-Linked Immunosorbent assay
 - ii. Anti-human Globulin Augmented Complement-Dependent Cytotoxicity
 - iii. Luminex platform (L)
 - iv. Single antigen bead solid phase assays (SAB)
 - v. Flow cytometry
 - vi. Complement fixation L-SAB
5. Screening Strategies
 - a. Prospective crossmatch
 - b. Retrospective crossmatch
 - c. Virtual crossmatch
 - d. Panel reactive antibody

6. Non-HLA Antigens
7. Desensitization regimens (Table 7)
 - a. Antibody removal: plasma exchange, immunoadsorption
 - b. T-cell help depression: corticosteroids
 - c. B-cell differentiation inhibitors
 - d. Plasma cell depletion
 - e. Immunomodulation (immune globulins)
 - f. Conventional immunosuppression
 - g. Novel therapies
8. Effects of mechanical means of antibody removal such as total plasma exchange on drug therapy
9. Goals of therapy
 - a. Morbidity
 - b. Mortality
 - c. Patient adherence

Table 7. THERAPIES FOR PREOPERATIVE ANTIBODY DEPLETION.

| Drug-based Therapies | Antibody-based Therapies |
|-----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cyclophosphamide Mycophenolate | Total intravenous immunoglobulin Cytomegalovirus hyperimmune globulin Anti-CD20: rituximab Anti-CD52: alemtuzumab Proteasome inhibitors: bortezomib, carfilzomib B-cell activating factor inhibitors: belimumab C5-convertase inhibitor: eculizumab |

Minimum Experience Recommendation for Management of the Sensitized Transplant Candidate:

1. Participate in the evaluation and care of 3 or more heart or lung transplant candidates with an elevated Calculated Panel Reactive Antibody of > 25% from the time of patient referral to the time of transplantation incorporating desensitization procedures as appropriate.

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