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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**Minimum Experience Recommendation**  
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**Minimum Experience Recommendation**  
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Minimum Experience Recommendation
Suggested References and Resources

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Minimum Experience Recommendation
Suggested References and Resources

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Minimum Experience Recommendation
Suggested References and Resources

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Minimum Experience Recommendation
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Minimum Experience Recommendation
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Minimum Experience Recommendation
Suggested References and Resources

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Minimum Experience Recommendation
Suggested References and Resources

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Minimum Experience Recommendation
Suggested References and Resources

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4. Other Therapeutic Considerations in Pediatric Patients on MCS
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Minimum Experience Recommendation
Suggested References and Resources

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Minimum Experience Recommendation
Suggested References and Resources

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7. Management of rejection

Minimum Experience Recommendation
Suggested References and Resources

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5. Screening Strategies
6. Non-HLA Antigens
7. Desensitization regimens
8. Effects of mechanical means of antibody removal such as total plasma exchange on drug therapy
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
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<td>1 year post-graduate</td>
<td>16 weeks during study; 4 months post-graduate; optional 1 year residency</td>
<td>1 year post-graduate for licensing; 2 year post graduate Diploma, or 3 year MSc</td>
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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

Section Lead: Michael Shullo, PharmD

Co-Authors: Adam Cochrane, PharmD, BCPS
Rochelle Gellately, PharmD
Edward Horn, PharmD

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.
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

<table>
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<tr>
<th>Diuretics</th>
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<td>Thiazide – chlorothiazide, hydrochlorothiazide, metolazone,</td>
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**Vasodilators**
- Nitroglycerin, nitroprusside

**Natriuretic Peptides**
- Nesiritide

**Calcium Sensitizers**
- Levosimendan

**Inotropes**
- Dobutamine, dopamine, milrinone

**ACEI/ARB**
- Lisinopril, enalapril, captopril
- Candesartan, valsartan

**Mineralocorticoid/aldosterone antagonist**
- Spironolactone, eplerenone

**Sinus node inhibitor**
- Ivabradine

**Neprilysin Inhibitor**
- Sacubitril/Valsartan

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

**Suggested References for Heart Failure**


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. Thrombosis
      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]
- Focus on thrombosis and ventricular assist devices. [http://www.jhltonline.org/issue/S1053-2498(13)X0013-0]

Suggested References for MCADS


Najjar SS, Slaughter MS, Pagani FD et al.: An analysis of pump thrombus events in patients in the HeartWare ADVANCE bridge to transplant and continued access protocol trial. J Heart Lung Transplant 2014;33:23-34.


Slaughter MS, Pagani FD, McGee EC et al.: HeartWare ventricular assist system for bridge to transplant: Combined results of the bridge to transplant and continued access


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 medicated 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

Suggested references for Surveillance of Heart Function


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


Suggested references for Infection after Heart Transplantation


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. Proteosome 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. Immunoadsorption
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**

**Suggested References for Management of Rejection**

### 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](https://www.kidney.org/kidneydisease)

**Suggested References for nephrotoxicity**


### 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**
- Diabetes information: [http://www.diabetes.org](http://www.diabetes.org)

**Suggested References for Long Term Complications**


Chapter 2

ADULT ORGAN SPECIFIC COMPETENCIES – LUNG

Section Lead: Christopher Ensor, PharmD, BCPS-CV

Co-Authors: Patricia Ging, BPharm, MPSI, MSc
            James C. Coons, PharmD, BCPS-CV

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, lymphangioleiomyomatosis.
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

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

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. 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](http://ajrccm.atsjournals.org/cgi/content/full/158/1/335)

**Suggested References for Management of Conditions Leading to Transplantation**


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


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
Suggested Readings for Prevention And Management of Long Term Complications:


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 Syndrome 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


Chapter 3

**PEDIATRIC ORGAN SPECIFIC COMPETENCIES - HEART**

Section Lead: Walter Uber PharmD

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
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. Thrombosis

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
      a. Monitoring for propofol related infusion syndrome (PRIS)
      ii. Gastrointestinal
         1. Parenteral vs enteral nutrition
         2. Stress ulcer prophylaxis
      iii. Renal
         1. Fluid and electrolyte management
      iv. 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


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**


### 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. Echocardiography
   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
Brady MT, Byington CL, Davies HD et al. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial


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


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


Suggested References for Management of Long Term Complications


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**

<table>
<thead>
<tr>
<th>Antibody Preparations</th>
<th>Calcineurin Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal</td>
<td>Cyclosporine, Tacrolimus</td>
</tr>
<tr>
<td>• Basiliximab</td>
<td>Proliferation Signal Inhibitors</td>
</tr>
<tr>
<td>• Alemtuzumab</td>
<td>Everolimus, Sirolimus</td>
</tr>
<tr>
<td>Polyclonal</td>
<td>Anti-CD20 –</td>
</tr>
<tr>
<td>• Antithymocyte globulin</td>
<td>Antimetabolites</td>
</tr>
<tr>
<td>• Rituximab</td>
<td>Azathioprine</td>
</tr>
<tr>
<td><strong>Proteasomal inhibitors</strong></td>
<td>Mycophenolate mofetil</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Mycophenolic acid</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td><strong>Corticosteroids</strong></td>
</tr>
<tr>
<td>Complement inhibitors –</td>
<td>Methylprednisolone</td>
</tr>
<tr>
<td>Eculizumab</td>
<td>Prednisolone</td>
</tr>
<tr>
<td>Co-stimulation blocker</td>
<td>Prednisone</td>
</tr>
<tr>
<td>Belatacept.</td>
<td>Dexamethasone</td>
</tr>
</tbody>
</table>

**TABLE 6. THERAPEUTIC DRUG MONITORING**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Therapeutic Drug Monitoring Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
<td>Trough and C₂</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Trough</td>
</tr>
<tr>
<td>Everolimus</td>
<td>Trough</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Trough</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Trough and AUC</td>
</tr>
<tr>
<td>Mycophenolic acid</td>
<td>AUC</td>
</tr>
</tbody>
</table>

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

**Selected References for Monitoring and Selection of Immunosuppression**


Kirk AD. Induction immunosuppression. Transplantation 2006;82:593-602

Knight SR. Morris PJ. Does the evidence support the use of mycophenolate mofetil therapeutic drug monitoring in clinical practice? (A systematic review). Transplantation 2008;85:1675–1685


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.

<table>
<thead>
<tr>
<th>Drug-based Therapies</th>
<th>Antibody-based Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>Total intravenous immunoglobulin</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>Cytomegalovirus hyperimmune globulin</td>
</tr>
<tr>
<td></td>
<td>Anti-CD20: rituximab</td>
</tr>
<tr>
<td></td>
<td>Anti-CD52: alemtuzumab</td>
</tr>
<tr>
<td></td>
<td>Proteasome inhibitors: bortezomib, carfilzomib</td>
</tr>
<tr>
<td></td>
<td>B-cell activating factor inhibitors: belimumab</td>
</tr>
<tr>
<td></td>
<td>C5-convertase inhibitor: eculizumab</td>
</tr>
</tbody>
</table>

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.

Suggested References for Management of the Sensitized Transplant Candidate:

Girnita AL, McCurry KR, Iacono AT, et al. HLA-specific antibodies are associated with high-grade and persistent-recurring lung allograft acute rejection. J Heart Lung Transplant


Tambur AR, Pamboukian SV, Costanzo MR, et al. The presence of HLA-directed antibodies after heart transplantation is associated with poor allograft outcome. Transplantation 2005;80:1019–1025

Vaidya S. Clinical importance of anti-human leukocyte antigen-specific antibody concentration in performing calculated panel reactive antibody and virtual crossmatches. Transplantation 2008;85:1046–1050