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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INTRODUCTION

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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 COMPTENCIES- 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

Diuretics Loop – bumetanide, furosemide, torsemide, ethacrynic acid Thiazide – chlorothiazide, hydrochlorothiazide, metolazone, **Vasodilators** Nitroglycerin, nitroprusside **Natriuretic Peptides** Nesiritide **Calcium Sensistizers** Levosimendan **Inotropes** Dobutamine, dopamine, milrinone	**Digitalis Glycosides** Digoxin **Beta-blocker** Bisoprolol, carvedilol, metoprolol succinate, nebivolol **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

- 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

Abraham WT, Adams KF, Fonarow GC, et al. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). J Am Coll Card 2005;46:57-64.

Basaraba JE, Barry AR. Pharmacotherapy of Heart Failure with Preserved Ejection Fraction. Pharmacotherapy 2015; 35:351-360.

Cohn JN, Franciosa JA, Francis GS, et al. Effect of short-term infusion of sodium nitroprusside on mortality rate in acute myocardial infarction complicated by left ventricular failure: results of a Veterans Administration cooperative study. N Engl J Med 1982;306:1129 –35.

Coons JC, McGraw M, Murali S. Pharmacotherapy for Acute Heart Failure Syndromes. Am J Health Syst Pharm. 2011;68(1):21-35.

Costanzo MR, Guglin ME, Saltzberg MT et al. Ultrafiltration versus intravenous diuretics for patient hospitalized for acute decompensated heart failure. J Am Coll Cardiol 2007;49:675-83.

Cotter G, Cotter OM, Kaluski E. Hemodynamic monitoring in acute heart failure. Crit Care Med 2008;36:S40-3.

Cotter G, Felker GM, Adams KF, Milo-Cotter O, O'Connor CM. The pathophysiology of acute heart failure - is it all about fluid accumulation? Am Heart J 2008;155:9-18.

Cuffe MS, Califf RM, Adams KF Jr., et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA 2002;287:1541-7.

De Luca L, Fonarow GC, Mebazaa A, et al. Early pharmacological treatment of acute heart failure syndromes: a systematic review of clinical trials. Acute Card Care 2007;9:10-21.

Elkayam U, Janmohamed M, Habib M, Hatamizadeh P. Vasodilators in the management of acute heart failure. Crit Care Med 2008;36:S95-105.

Felker GM, Benza RL, Chandler AB, et al. Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. J Am Coll Cardiol 2003;41:997-1003.

Felker GM, Lee KL, Bull DA, et al. Diuretic Strategies in Patients with Acute Decompensated Heart Failure. New Eng J Med 2011;364:797-805.

Gattis WA, O'Connor CM, Gallup DS, Hasselblad V, Gheorghiade M. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial. J Am Coll Cardiol 2004;43:1534-41.

Gheorghiade M, Gattis Stough W, Adams KF Jr., Jaffe AS, Hasselblad V, O'Connor CM. The Pilot Randomized Study of Nesiritide Versus Dobutamine in Heart Failure (PRESERVD-HF). Am J Cardiol 2005;96:18G-25G.

Gheorghiade M, Pang PS. Acute Heart Failure Syndromes. J Am Coll Cardiol 2009;53:557-73.

Gheorghiade M, van Veldhuisen DJ, Colucci WS. Contemporary use of digoxin in the management of cardiovascular disorders. Circulation 2006;113:2556-64.

Giglioi C, Landi D, Cecchi E et al. Effects of Ultrafiltration vs. Diuretics on clinical, biohumoral and haemodynamic variables in patients with decompensated heart failure: the ULTRADISCO study. Eur J Heart Fail 2011;13:337-46.

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.

Hershberger RE, Nauman D, Walker TL, Dutton D, Burgess D. Care processes and clinical outcomes of continuous outpatient support with inotropes (COSI) in patients with refractory endstage heart failure. J Card Fail 2003;9:180-7.

Krell MJ, Kline EM, Bates ER, et al. Intermittent, ambulatory dobutamine infusions in patients with severe congestive heart failure. Am Heart J 1986;112:787-91.

Levy P, Compton S, Welch R, et al. Treatment of severe decompensated heart failure with high-dose intravenous nitroglycerin: a feasibility and outcome analysis. Ann Emerg Med 2007;50:144 –52.
Lindenfeld J, Albert NM, Boehmer JP et al. Executive summary: HFSA 2010 comprehensive heart failure practice guideline. J Card Fail 2010;16:475-539.
Mann DL, Bristow MR. Mechanisms and Models in Heart Failure: The Biomechanical Model and Beyond. Circulation 2005;111:2837-2849.
McMurray JJV, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. Eur Heart J 2012;33:1787-847.
McMurray JJV, Packer M, Desai AS, et al. Angiotensin-Neprilyin Inhibition versus Enalapril in Heart Failure. N Engl J Med 2014; 371:993-1004.
Mebazaa A, Nieminen MS, Packer M, et al. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE randomized trial. JAMA 2007;297:1883-91.
Mullens W, Abrahams Z, Francis GS, et al. Sodium nitroprusside for advanced low-output heart failure. J Am Coll Cardiol 2008;52:200-7.
O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med 2011;365:32-43.
Packer M. REVIVE II: multicenter placebo-controlled trial of levosimendan on clinical status in acutely decompensated heart failure. Circulation 2005;112:3362-4.
Petersen JW, Felker GM. Inotropes in the management of acute heart failure. Crit Care Med 2008;36:S106-11.
Publication Committee for the VMAC Investigators (Vasodilatation in the Management of Acute CHF). Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. JAMA 2002;288:577.
Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. JAMA 2005;293:1900-5.
Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. Circulation 2005;111:1487-91.
Sarraf M, Masoumi A, Schrier RW. Cardiorenal Syndrome in Acute Decompensated Heart Failure. Clin J Am Soc Nephrol 2009;2013-26.
Sarraf M, Schrier RW. Cardiorenal Syndrome in Acute Heart Failure Syndromes. Int J Neph 2011; doi:10.4061/2011/293938.
Swedberg K, Komajda M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomized placebo-controlled study. Lancet 2010;376:875-885.
Van der Meer P, Groenveld HF, Januzzi JL, Van Veldhuisen DJ. Erythropoietin treatment in patients with chronic heart failure: a meta-analysis. Heart 2009; 95: 1309-1314.
Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure. Circulation 2013;e240-e327.
Zile MR, Bennett TD, St John Sutton M, et al. Transition from Chronic Compensated to Acute Decompensated Heart Failure: Pathophysiological Insights Obtained From Continuous Monitoring of Intracardiac Pressures. Circulation 2008;118:1433-41.

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

Suggested References for MCADS

Acharya MN, Som R, Tsui S. What is the optimum antibiotic prophylaxis in patients undergoing implantation of a left ventricular assist device? Interact Cardiovasc Thorac Surg 2012;14:209-14.

Aggarwal A. Incidence and Management of Gastrointestinal Bleeding With Continuous Flow Assist Devices. Ann Thoracic Surg 2012;93:1534-40

Almadi M, Gahli PM, Constantin J, et al. Recurrent obscure gastrointestinal bleeding: Dilemmas and success with pharmacological therapies. Case series and review. Can J Gastroenterol 2009; 23: 625–631.

Al-Quthami AH, Jumean M, Kocoil R, et al. Eptifibatide for the treatment of HeartMate II Left Ventricular Assist Device Thrombosis Circ Heart Failure 2012;5:e68-70.

Andersen M, Videbaek R, Boesgaard S, Sander K, Hansen PB, Gustafsson F. Incidence of ventricular arrhythmias in patients on long-term support with a continuous-flow assist device (HeartMate II). J Heart Lung Transplant 2009;28:733-5.

Badiye A, Hernandez GA, Chaparro S. Argatroban as novel therapy for suspected thrombosis in patients with continuous-flow left ventricle assist device and hemolysis. ASAIO J 2014;60:361-5.

Bedi M, Kormos R, Winowich S, McNamara DM, Mathier MA, Murali S. Ventricular arrhythmias during left ventricular assist device support. Am J Cardiol 2007;99:1151-3.

Bellumkonda L, Subrahmanyan L, Jacoby D, et al. Left ventricular assist devices pump thrombosis: is there a role for glycoprotein IIb/IIIa inhibitors? ASAI0 J 2014;60:134-6.

Benken ST, Tillman N, Dajani S, et al. A retrospective evaluation of fondaparinux for confirmed or suspected heparin-induced thrombocytopenia in left-ventricular-assist device patients. J Cardiothorac Surg 2014, 9:55

Birks EJ, George RS, Hedger M, et al. Reversal of severe heart failure with a continuous-flow left ventricular assist device and pharmacological therapy: a prospective study. Circulation 2011;123:381-90.

Birks EJ, Tansley PD, Hardy J, et al. Left ventricular assist device and drug therapy for the reversal of heart failure. N Engl J Med 2006;355:1873-84.

Blich M, Fruchter O, Edelstein S, et al. Somatostatin therapy ameliorated chronic and refractory gastrointestinal bleeding caused by diffuse angiodysplasia in a patient on anticoagulation therapy. Scand J Gastroenterol 2003; 38: 801-803.

Blitz A. Pump thrombosis – A riddle wrapped in a mystery inside an enigma. Ann Cardiothorac Surg 2014;3:450-71

Boyle AJ, Ascheim DD, Russo MJ, et al. Clinical outcomes for continuous-flow left ventricular assist device patients stratified by pre-operative INTERMACS classification. J Heart Lung Transplant 2011;30:402-7.
Boyle AJ, Jorde UP, Sun B, et al.: Pre-operative risk factors of bleeding and stroke during left ventricular assist device support: an analysis of more than 900 HeartMate II outpatients. J Am Coll Cardiol 2014;63:880-8
Boyle AJ, Russell SD, Teuteberg JJ, et al. Low thromboembolism and pump thrombosis with the HeartMate II left ventricular assist device: analysis of outpatient anticoagulation. J Heart Lung Transplant 2009;28:881-7.
Brouwers C, Denollet J, de Jonge N, Caliskan K, Kealy J, Pedersen SS. Patient-reported outcomes in left ventricular assist device therapy: a systematic review and recommendations for clinical research and practice. Circ Heart Fail 2011; 4: 714-723.
Califano S, Pagani FD, Malani PN. Left Ventricular Assist Device - Associated Infections. Infect Dis Clin N Am 2012;26:77-87.
Cesario DA, Saxon LA, Cao MK, Bowdish M, Cunningham M. Ventricular tachycardia in the era of ventricular assist devices. J Cardiovasc Electrophysiol 2011;22:359-63.
Chinn R, Dembitsky W, Eaton L, et al. Multicenter experience: prevention and management of left ventricular assist device infections. ASAIO J 2005;51:461-70.
Copeland JG, Arabia FA, Tsau PH, Nolan PE, et al. Total artificial hearts. Bridge to transplantation. Cardiol Clin 2003; 21: 105-117.
Copeland JG, Smith RG, Arabia FA, Nolan PE, Sethi GK, et al. Cardiac replacement with a total artificial heart as a bridge to transplantation. N Engl J Med 2004; 351: 859-867.
Crouch MA, Kasirajan V, Cahoon W, et al. Successful use and dosing of bivalirudin after temporary total artificial heart implantation: a case series. Pharmacotherapy 2008;28:1413-20.
Crow S, Chen D, Milano C, et al. Acquired von Willebrand syndrome in continuous-flow ventricular assist device recipients. Ann Thorac Surg 2010;90:1263-9.
Crow S, John R, Boyle A, et al. Gastrointestinal bleeding rates in recipients of nonpulsatile and pulsatile left ventricular assist devices. J Thorac Cardiovasc Surg 2009;137:208-15.
Delgado R 3rd, Frazier OH, Myers TJ, et al. Direct thrombolytic therapy for intraventricular thrombosis in patients with the Jarvik 2000 left ventricular assist device. J Heart Lung Transplant 2005;24:231-3.
Demirozu ZT, Radovancevic R, Hochman LF, et al. Arteriovenous malformation and gastrointestinal bleeding in patients with the HeartMate II left ventricular assist device. J Heart Lung Transplant 2011;30:849-53.
Ensor CR, Paciullo CA, Cahoon WD Jr, et al. Pharmacotherapy for mechanical circulatory support: a comprehensive review. Ann Pharmacother 2011;45:60-77.
Favaloro EJ. The utility of the PFA-100 in the identification of von Willebrand disease: a concise review. Semin Thromb Hemost 2006; 32: 537-545.
Geisen U, Heilmann C, Beyersdorf F, et al. Non-surgical bleeding in patients with ventricular assist devices could be explained by acquired von Willebrand disease. Eur J Cardiothorac Surg 2008;33:679-84.
Goldstein DJ, John R, Salerno C, et al. Algorithm for the diagnosis and management of suspected pump thrombosis. J Heart Lung Transplant 2013;32:667-70
Hill NS, Roberts KR, Preston IR. Postoperative Pulmonary Hypertension: Etiology and Treatment of a Dangerous Complication. Respir Care 2009;54:958-68.
Hirri HM, Green PJ, Lindsay J. Von Willebrand's disease and angiodysplasia treated with thalidomide. Hemophilia 2006; 12: 285–286.
Holman WL, Rayburn BK, McGiffin DC, et al. Infection in ventricular assist devices: prevention and treatment. Ann Thorac Surg 2003;75:S48-57.
Holman WL, Skinner JL, Waites KB, Benza RL, McGiffin DC, Kirklin JK. Infection during circulatory support with ventricular assist devices. Ann Thorac Surg 1999;68:711-6.
Jennings DL, Chamber RM, Schillig JM. The pharmacotherapy of the HeartMate II, a continuous flow left ventricular assist device, in patient with advanced heart failure: integration of disease, device and drug. Ann Pharmacother 2010;44:1647-50.

John R, Kamdar F, Liao K, et al. Low thromboembolic risk for patients with the Heartmate II left ventricular assist device. J Thorac Cardiovasc Surg 2008;136:1318-23.
John R, Panch S, Hrabe J, et al. Activation of endothelial and coagulation systems in left ventricular assist device recipients. Ann Thorac Surg 2009; 88: 1171-1179.
Kamouh A, Eckman JR. Successful treatment of early thrombosis of HeartWare left ventricular assist device with intraventricular thrombolytics. Ann Thorac Surg 2012;94:281-3.
Kasirajan V, Smedira NG, Perl, et al. Cerebral embolism associated with left ventricular assist device support and successful therapy with intraarterial urokinase. Ann Thorac Surg 1999;67:1148-50.
Kiernan MS, Pham DT, DeNofrio D, Kapur NK. Management of HeartWare left ventricular assist device thrombosis using intracavitary thrombolytics. J Thorac Cardiovasc Surg 2011;142:712-4.
Klovaite J, Gustafsson F, Mortensen SA, Sander K, Nielsen LB. Severely impaired von Willebrand factor-dependent platelet aggregation in patients with a continuous-flow left ventricular assist device (HeartMate II). J Am Coll Cardiol 2009;53:2162-7.
Lietz K, Long JW, Kfoury AG, et al. Outcomes of left ventricular assist device implantation as destination therapy in the post- REMATCH era: implications for patient selection. Circulation 2007;116:497-505.
Meyer AL, Malehsa D, Bara C, et al. Acquired von Willebrand syndrome in patients with an axial flow left ventricular assist device. Circ Heart Fail 2010;3:675-81.
Miller LW, Pagani FD, Russell SD, et al. Use of a continuous-flow device in patients awaiting heart transplantation. N Engl J Med 2007;357:885-96.
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.
Pagani FD, Miller LW, Russell SD, et al. Extended mechanical circulatory support with a continuous-flow rotary left ventricular assist device. J Am Coll Cardiol 2009;54:312-21.
Pappalardo F, Scandroglio AM, Potapov E, et al. Argatroban anticoagulation for heparin induced thrombocytopenia in patients with ventricular assist devices. Minerva Anestesiol 2012;78:330-5.
Pieri M, Agracheva N, Di Prima AL, et al. Primary anticoagulation with bivalirudin for patients with implantable ventricular assist devices. Artif Organs 2014;38:342-6.
Refaat M, Chemaly E, Lebeche D, Gwathmey JK, Hajjar RJ. Ventricular arrhythmias after left ventricular assist device implantation. Pacing Clin Electrophysiol 2008;31:1246-52.
Rommel JJ, O'Neill TJ, Lishmanov A, et al. The Role of Heart Failure Pharmacotherapy After Left Ventricular Assist Device Support. Heart Fail Clinics 2014; 10:653-660.
Rothenburger M, Wilhelm MJ, Hammel D, et al. Treatment of thrombus formation associated with the MicroMed DeBakey VAD using recombinant tissue plasminogen activator. Circulation 2002;106:I189-92.
Samuels LE, Kohout J, Casanova-Ghosh E, et al. Argatroban as a primary or secondary postoperative anticoagulant in patients implanted with ventricular assist devices. Ann Thorac Surg 2008; 85:1651-5.
Sarsam SH. Bivalirudin for treatment of aortic valve thrombosis after left ventricular assist device implantation. ASAIO J 2013; 59:448-9.
Schettle SD, Pruthi RK, Pereira. Continuous-flow left ventricular assist devices and gastrointestinal bleeding: Potential role of danazole. J Heart Lung Transplant 2014;33:549-550
Schlendorf K, Patel CB, Gehrig T, et al. Thrombolytic therapy for thrombosis of continuous flow ventricular assist devices. J Cardiac Fail 2014;20:91e97.
Slaughter MS, Naka Y, John R, et al. Post-operative heparin may not be required for transitioning patients with a HeartMate II left ventricular assist system to long-term warfarin therapy. J Heart Lung Transplant 2010;29:616-24.
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

protocol. *J Heart Lung Transplant* J Heart Lung Transplant 2013;32:675–683.
Slaughter MS, Pagani FD, Rogers JG, et al. Clinical management of continuous-flow left ventricular assist devices in advanced heart failure. J Heart Lung Transplant 2010;29:S1-39.
Slaughter MS, Rogers JG, Milano CA, Russell SD, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 2009; 361: 2241-2251.
Steinlechner B, Dworschak M, Birkenberg B, et al. Platelet dysfunction in outpatients with left ventricular assist devices. Ann Thorac Surg 2009;87:131-7.
Stern DR, Kazam J, Edwards P, Maybaum S, Bello RA, D'Alessandro DA, Goldstein DJ. Increased Incidence of Gastrointestinal Bleeding Following Implantation of the HeartMate II LVAD. J Card Surg 2010;25:352-6.
Stevenson LW, Miller LW, Desvigne-Nickens P, et al. Left ventricular assist device as destination for patients undergoing intravenous inotropic therapy: a subset analysis from REMATCH (Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure). Circulation 2004;110:975-81.
Strueber M, O'Driscoll G, Jansz P, Khaghani A, Levy WC, Wieselthaler GM. Multicenter evaluation of an intrapericardial left ventricular assist system. J Am Coll Cardiol 2011; 57: 1375–1382.
Suarez J, Patel CB, Felker GM, Becker R, Hernandez AF, Rogers JG. Mechanisms of bleeding and approach to patients with axial-flow left ventricular assist devices. Circ Heart Fail 2011; 4: 779-784.
Tarzia V, Dal Lin C, Bottio T, Benvenuti S, et al. Occult gastrointestinal bleeding in patients with a left ventricular assist device axial flow pump: Diagnostic tools and therapeutic algorithm. J Thorac Cardiovasc Surg 143(4): e28-31.
Tedford RJ, Hemnes AR, Russell SD, et al. PDE5A inhibitor treatment of persistent pulmonary hypertension after mechanical circulatory support. Circ Heart Fail 2008;1:213-9.
Tellor BR, Smith JR, Prasad SM, et al. The use of eptifibatide for suspected pump thrombus or thrombosis in patients with left ventricular assist devices. J Heart Lung Transplant 2014;33:94-101.
Thomas MD, Wood C, Lovett M, Dembo L, O'Driscoll G. Successful treatment of rotary pump thrombus with the glycoprotein IIb/IIIa inhibitor tirofiban. J Heart Lung Transplant 2008;27:925-7.
Uriel N, Pak SW, Jorde UP, Jude B et al. Acquired von Willebrand Syndrome After Continuous-Flow Mechanical Device Support Contributes to a High Prevalence of Bleeding During Long-Term Support and at the Time of Transplantation. J Am Coll Cardiol 2010; 56:1207-13.
Vrtovec B, Radovancevic R, Delgado RM, et al. Significance of anaemia in patients with advanced heart failure receiving long-term mechanical circulatory support. Eur J Heart Fail 2009; 11: 1000-1004.
Warkentin TE, Moore JC, Morgan DG. Aortic stenosis and bleeding gastrointestinal angiodysplasia: is acquired von Willebrand's disease the link? Lancet 1992;340:35-7.
Ziv O, Dizon J, Thosani A, Naka Y, Magnano AR, Garan H. Effects of left ventricular assist device therapy on ventricular arrhythmias. J Am Coll Cardiol 2005;45:1428-34.

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 immunofluoresence 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
- 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

Butler CR, Thompson R, Haykowsky M, Toma M, Paterson I. Cardiovascular magnetic resonance in the diagnosis of acute heart transplant rejection: a review. J Cardiovasc Magn Reson 2009;11:7

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

<u>Minimum Experience Recommendation for Infectious Complications</u>

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 Transplant2011; 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, Snydman 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. 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

- 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 inhbitor 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 nephrorotoxicity

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 allograf 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 Edndocrinal 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.
Kittleson MM, Kobashigawa JA. Statins in heart transplantation. Clin Transplant. 2013: 135-143.
Potena L, Grigioni F, Ortolani P, et al. Safety and efficacy of early aggressive versus cholesterol-driven lipid-lowering strategies in heart transplantation: a pilot, randomized, intravascular ultrasound study. J Heart Lung Transplant. 2011; 30(12): 1305-1311.
Stein E, Ebeling P, Shane E. Post-transplantation osteoporosis. Endocrinol Metab Clin North Am. 2007; 36(4): 937-963.
Wilson W, Taubert KA, Gewitz M, et al. Prevention of infectious endocarditis Guidelines from the American Heart Association. Circulation 1997; 116: 1736-1754.

Chapter 2

ADULT ORGAN SPECIFIC COMPTENCIES – LUNG

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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, lymphangioleiomyomatosis.
2. Medication Optimisation
    a. Lung associated medications (see Table 3).
    b. Concommitant 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

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

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.
Hadjiliadis 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.
Randall L. Rosenblatt Lung Transplantation in Cystic Fibrosis. Respir Care. 2009;54:777-86.
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.
Hoeper 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 interations
    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-ATS-ERS_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, Cervenko 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.
Campos S, Caramori M, Teixeira R, et al. Bacterial and fungal pneumonias after lung transplantation. Transplantation Proceedings 2008; 40:822-824.
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 pneumocystic 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 filamentus fungal infections in solid organ transplant recipients. Transplant Int 2008;21:534-46.
Vu DL, Bridevaux PO, Aubert JD, Soccal PM, Kaiser L. Respiratory viruses in lung transplant recipients: A critical review and pooled analysis of clinical studies. Am J Transplant 2011;11:1071-8.
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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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

Altamira LA, Redington AN (2011) Right ventricular failure in congenital heart disease. In: Shaddy RE (ed) Heart Failure in Congenital Heart Disease. Springer-Verlag, London.
Benson DW. Genetic origins of pediatric heart disease. Pediatr Cardiol 2010;31:422-29.
Berger S, Dubin AM, Arrhythmogenic forms of heart failure in children. Heart Failure Clin 2010;6:471-81.
Booker PD.Pharmacological support for children with myocardial dysfunction. Paediatr Anaesth 2002;12:5-25.
Colan SD. Hypertrophic cardiomyopathy in childhood. Heart Failure Clin 2010;6:433-44.
Deal BJ, Jacobs ML. Management of the failing Fontan circulation. Heart 2012;98:1098-1104.
Kaltman JR, Andropoulos DB, Checchia PA, et al. Report of the Pediatric Heart Network and National Heart, Lung, and Blood Institute Working Group on the Perioperative Management of Congenital Heart Disease. Circulation 2010;121:2766-72.
Hoffman TM,Wernovsky G, Atz AM, et al. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. Circulation 2003;107(7):996-1002.

Hsu DT, Lamour JM. Changing Indications for Pediatric Heart Transplantation: Complex Congenital Heart Disease. 2015;131:91-99.
Hsu DT, Zak V, Mahony L, et al. Enalapril in infants with single ventricle, results of a multicenter randomized trial. Circulation 2010;122:333-40.
Huang M, Zhang X, Chen S, et al. The effect of carvedilol treatment on chronic heart failure in pediatric patients with dilated cardiomyopathy: a prospective, randomized-controlled study. Pediatr Cardiol 2013;34(3):680-5.
Jefferies JL, Hoffman TM, Nelson DP. Heart failure treatment in the intensive care unit in children. Heart Failure Clin 2010;6:531-58.
Kearns GL, Abdel-Rahman, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology-drug disposition, action, and therapy in infants and children. N Engl J Med 2003;349:1157-67.
Kantor PF, Redington AN. Pathophysiology and management of heart failure in repaired congenital heart disease. Heart failure Clin 2010;6:497-506.
Kuhl U, Schulthiess HP. Myocarditis in children. Heart Failure Clin 2010;6:483-96
Denfield SW, Webber SA. Restrictive cardiomyopathy in childhood. Heart Failure Clin 2010;6:445-52.
Lin KY, Shaddy RE (2011) Chronic heart failure in children with congenital heart disease. In: Shaddy RE (ed) Heart Failure in Congenital Heart Disease. Springer-Verlag, London.
Medar SS, Hsu DT, Lamour JM, Aydin SI. Acute Kidney Injury in Pediatric Acute Decompensated Heart Failure. Pediart Crit Care Med 2015; [E-pub ahead of date]
O'Connor MJ, Rosenthal DN, Shaddy RE. Outpatient management of pediatric heart failure. Heart Failure Clin 2010;6:515-29.
Pierpont ME, Basson CT, Benson DW, et al. Genetic basis for congenital heart defects: current knowledge. A scientific statement from the American Heart Association Congenital Cardiac Defects Committee, Council on Cardiovascular Disease in the Young. Circulation 2007;115:3015-38
Price JF (2011) Unique aspects of heart failure in the neonate. In: Shaddy RE (ed) Heart Failure in Congenital Heart Disease. Springer-Verlag, London.
Shaddy RE, Boucek MM, Hsu DT, et al. Carvedilol for children and adolescents with heart failure: a randomized controlled trial. JAMA 2007;298(10):1171-9.
Tayman C, Rayyan M, Allegaert K. Neonatal Pharmacology: Extensive Interindividual Variability Despite Limited Size. J Pediatr Pharmacol Ther 2011;16:170-184.
Vatta M, Ackerman MJ. Genetics of heart failure and sudden death. Heart Failure Clin 2010;6:507-14.
Towbin JA. Left ventricular noncompaction: a new form of heart failure. Heart Failure Clin 2010;6:453-69.
Wilkinson JD, Landy DC, Colan SD, et al. The pediatric cardiomyopathy registry and heart failure: key results from the first 15 years. Heart Failure Clin 2010;6:401-13.

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
        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

Almond CS, Morales DL, Blackstone EH, et al. Berlin heart EXCOR pediatric ventricular assist device for bridge to heart transplantation in US children. Circulation 2013;127:1702-11.
Annich G, Adachi I. Anticoagulation for pediatric mechanical circulatory support. Pediatr Crit Care Med 2013;14:S37-S42.
Baird CW, Zurakowski D, Robinson B, et al. Anticoagulation and pediatric extracorporeal membrane oxygenation: impact of activated clotting time and heparin dose on survival. Ann Thorac Surg 2007;83:912-20.
Brown KL, Ichord R, Marino BS, Thiagarajan RR. Outcomes following extracorporeal membrane oxygenation in children with cardiac disease. Pediatr Crit Care Med 2013;14:S73-S83.
Butt W, Heard M, Peek GJ. Clinical management of the extracorporeal membrane oxygenation circuit. Pediatr Crit Care Med 2013;14:S13-S19.
Cooper DS, Pretre R. Clinical management of pediatric ventricular assist devices. Pediatr Crit Care Med 2013;14:S27-S36.
d'Udekem Y, Shime N, Lou S, MacLaren G. Recurrent or prolonged mechanical circulatory support: bridge to recovery or road to nowhere? Pediatr Crit Care Med 2013;14:S69-S72.
Dalton HJ, Dodge-Khatami A, MacLaren G. Pediatric mechanical circulatory support: future directions. Pediatr Crit Care Med 2013;14:S94-S95.
Dodge-Khatami A, Checchia PA. Partial mechanical circulatory support in children. Pediatric Crit Care Med 2013;14:S62-S68.
Jaquiss RDB, Bronicki RA. An overview of mechanical circulatory support in children. Pediatr Crit Care Med 2013;14:S3-S6.
Jefferies JL, Morales DL. Mechanical circulatory support in children: bridge to transplant versus recovery. Curr Heart Fail Rep 2012;9:236-43.
Kaufmann CR, Dwyer KM, Crews JD, et al. Usefulness of thrombelastography in assessment of trauma patient coagulation. J Trauma 1997;42:716-22.
Luddington RJ. Thrombelastography/thromboelastometry. Clin Lab Haem 2005;27:81-90.
Lequier L, Horton SB, McMullan DM, Bartlett RH. Extracorporeal membrane oxygenation circuitry. Pediatr Crit Care Med 2013;14:S7-S12.
MacLaren G, Dodge-Khatami A, Dalton HJ, et al. Joint statement on mechanical circulatory support in children: a consensus review from the Pediatric Cardiac Intensive Care Society and Extracorporeal Life Support Organization. Pediatr Crit Care Med 2013;14:S1-S2.
Nankiervis CA, Preston TJ, Dysart KC, et al. Assessing heparin dosing in neonates on venoarterial extracorporeal membrane oxygenation. ASAIO Journal 2007;53:111-14.
Ravishankar C, Dominguez TE, Rosenthal TM, Gaynor JW (2011) Mechanical circulatory support in the patient with congenital heart disease. In: Shaddy RE (ed) Heart Failure in Congenital Heart Disease. Springer-Verlag, London
Sivarajan VB, Almodovar MC, Rodefeld MD, Laussen PC. Pediatric extracorporeal life support in specialized situations. Pediatr Crit Care Med 2013;14:S51-S61.
Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 2009;361:2241-51.
Stiller B, Adachi I, Fraser Jr CD. Pediatric ventricular assist devices. Pediatr Crit Care Med 2013;14:S20-S26.
Vandiver JW, Vondracek TG. Antifactor Xa levels versus activated partial thromboplastin time for monitoring unfractionated heparin. Pharmacotherapy 2012;32:546-58.
VanderPluym C, Urschel S, Buchholz H. Advanced therapies for congenital heart disease: ventricular assist devices and heart transplantation. Canadian Journal of Cardiology

2013;29:796-802.

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, Section1.61)
        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

Auerbach SR, Richmond, ME, Chen JM, et al. Multiple risk factors before pediatric cardiac transplantation are associated with increased graft loss. Pediatr Cardiol 2012;33(1):49-54.
Costanzo MR, et al. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. J Heart Lung Transplant 2010;29:914-56.
Daftari B, Alejos JC, Perens G. Initial experience with Sildenafil, Bosentan, and Nitric Oxide for pediatric cardiomyopathy patients with elevated pulmonary vascular resistance before and after orthotopic heart transplantation.[published online ahead of print March 10, 2010] J Transplant 2010.
Dionigi B, Razzouk AJ, Hasaniya NW, Chinnock RE, Bailey LL. Late outcomes of pediatric heart transplantation are independent of pre-transplant diagnosis and prior cardiac surgical intervention. J Heart Lung Transplant 2008; 27(10):1090-5.
Huang J, Trinkaus K, Huddleston CB, Mendeloff EN, Spray TL, Canter CE. Risk factors for primary graft failure after pediatric cardiac transplantation: importance of recipient and donor characteristics. J Heart Lung Transplant 2004;23(6):716-22.
Hoskote A, Carter C, Rees P, Elliott M, Burch M, Brown K. Acute right ventricular failure after pediatric cardiac transplant: Predictors and long-term outcome in current era of transplantation medicine. J Thorac Cardiovasc Surg 2010;139:146-53.
Joffe AR,Quiñonez LG, Robertson CM, et al. Outcomes after heart transplantation in children under six years of age. Ann Thorac Surg 2011;92(1):174-82.
Karamlou T,Diggs BS, Wlke K, et al. Impact of single-ventricle physiology on death after heart transplantation in adults with congenital heart disease. Ann Thorac Surg 2012;94(4):1281-8.
Kaufman BD, Chuai S, Dobbels F, Shaddy RE. Wasting or obesity at time of transplant does not predict pediatric heart outcomes: Analysis of ISHLT Pediatric Heart Transplant Registry. J Heart Lung Transplant 2009;28:1273-8.
Mahle WT, Tresler MA, Edens RE, et al. Allosensitization and outcomes in pediatric heart transplantation. J Heart Lung Transplant 2011;30:1221-7.
Murtuza B, Fenton M, Burch M, et al. Pediatric heart transplantation for congenital and restrictive cardiomyopathy. Ann Thorac Surg 2013;95(5):1675-84.
Murtuza B, Dedieu N, Vazquez A, et al. Results of orthotopic heart transplantation for failed palliation of hypoplastic left heart. Eur J Cardiothorac Surg. 2013 Mar;43(3):597-603.
Pietra BA, Kantor PF, Bartlett HL, et al. Early predictors of survival to and after heart transplantation in children with dilated cardiomyopathy. Circulation 2012;126(9):1079-86.
Uzark K, Griffin L, Rodriguez R, et al. Quality of life in pediatric heart transplant recipients: a comparison with children with and without heart disease. J Heart Lung Transplant 2012;31(6):571-8.

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

Abuali MM, Arnon R, Posada R. An update on immunizations before and after transplantation in the pediatric solid organ transplant recipient. Pediatr Transplant 2011;15:770-7.
Behnke-Hall K, Bauer J, Thul J, et al. Renal function in children with heart transplantation after switching to CNI-free immunosuppression with everolimus. Pediatr Transplant 2011;15:784-9.
Berry GJ, Burke MM, Anderson 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;32:1147-1162.
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

virus infection. Pediatrics 2014;134:e620-638.
Chinnock R, Webber SA, Dipchand AL, Brown RN, George JF, Pediatric Heart Transplant Study Investigators. A 16-Year multi-institutional study of the role of age and EBV status on PTLD incidence among pediatric heart transplant recipients. Am J Transplant 2012 Nov;12:3061-8.
Danzinger-Isakov L, Kumar D. Guidelines for vaccination of solid organ transplant candidates and recipients. Am J Transplant 2009;9(Suppl 4):S258-62.
Everitt MD, Pahl E, Schechtman KB, et al. Rejection with hemodynamic compromise in the current era of pediatric heart transplantation: a multi-center study. J Heart Lung Transplant 2011;30:282-8.
Everitt MD, Hammond MEH, Snow GL, et al. Biopsy-diagnosed antibody-mediated rejection based on the proposed International Society for Heart and Lung Transplantation working formulation is associated with adverse cardiovascular outcomes after pediatric heart transplant. J Heart Lung Transplant 2012;31:686-93.
Hollander SA, Chen S, Luikart H et al. Quality of life and metrics of achievement in long-term adult survivors of pediatric heart transplant. Pediatr Transplant 2015;19:76-81.
Kobashigawa J, Crespo-Leiro MG, Ensminger SM, et al. Report from consensus conference on antibody-mediated rejection in heart transplantation. J Heart Lung Transplant 2011;30:252-69.
Oliva M, Singh TP, Gauvreau K, VanderPluym CJ, Bastardi HJ, Almond CS. Impact of medication non-adherence on survival after pediatric heart transplantation in the USA. J Heart Lung Transplant 2013;32:881-888.
Schumacher KR, Almond C, Singh TP, et al. Predicting Graft Loss by 1 Year in Pediatric Heart Transplantation Candidates: An Analysis of the Pediatric Heart Transplant Study Database. Circulation 2015;131:890-898.
Xie HG. Personalized immunosuppressive therapy in pediatric heart transplantation: progress, pitfalls and promises. Pharmaco Ther 2010;126:146-58.

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. Cyctic 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

Adler FR, Aurora P, Barker DH, et al. Lung transplantation for cystic fibrosis**.** Proc Am Thorac Soc 2009; 6:619-33.
Aurora P, Gassas A, Ehtisham S et al. The effect of prelung transplant clinical status on post-transplant survival of children with cystic fibrosis. Eur Respir J 2000;16:1061-4.
Chmiel JF, Aksamit TR, Chotirmall SH et al. Antibiotic management of lung infections in cystic fibrosis. I. The microbiome, methicillin-resistant Staphylococcus aureus, gram-negative bacteria, and multiple infections. Ann Am Thorac Soc. 2014 Sep;11(7):1120-9.
Chmiel JF, Aksamit TR, Chotirmall SH et al. Antibiotic management of lung infections in cystic fibrosis. II. Nontuberculous mycobacteria, anaerobic bacteria, and fungi. Ann Am Thorac Soc. 2014 Oct;11(8):1298-306.
Ivy DD, Abman SH, Barst RJ at el. Pediatric pulmonary hypertension. J Am Coll Cardiol. 2013 Dec 24;62(25 Suppl):D117-26
Kearns GL, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology--drug disposition, action, and therapy in infants and children.N Engl J Med 2003; 349:1157-67.
Lammers AE, Burch M, Benden C, et al. Lung transplantation in children with idiopathic pulmonary arterial hypertension. Pediatr Pulmonol 2010; 45(3):263-9
Mogayzel PJ Jr, Naureckas ET, Robinson KA et al. Pulmonary Clinical Practice Guidelines Committee. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2013 Apr 1;187(7):680-9.
Redfern J, Webb K. Benefits of a dedicated cystic fibrosis pharmacist. Journal of the Royal Society of Medicine 2004; 97: 2-8
Vorhies EE, Ivy DD. Drug treatment of pulmonary hypertension in children. Paediatr Drugs. 2014 Feb;16(1):43-65.
Zijlstra WM, Ploegstra MJ, Berger RM. Current and advancing treatments for pulmonary arterial hypertension in childhood. Expert Rev Respir Med. 2014 Oct;8(5):615-28.

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.

Suggested References for Management of Long Term Complications.

Benden C, Danziger-Isakov L, Faro A. New developments in treatment after lung transplantation. Curr Pharm Des. 2012;18(5):737-46.
Benden C, Kansra S, Ridout DA, et al. Chronic kidney disease in children following lung and heart-lung transplantation. Pediatr Transplant 2009;13:104-10.
Benden C, Aurora P, Curry J, et al. High prevalence of gastroesophageal reflux in children after lung transplantation. Pediatr Pulmonol 2005;40:68-71.
Danziger-Isakov LA, Worley S, Michaels MG, et al. The risk, prevention, and outcome of cytomegalovirus after pediatric lung transplantation.Transplantation. 2009; 87:1541-8.
Danziger-Isakov LA, Worley S, Arrigain S, et al. Increased mortality after pulmonary fungal infection within the first year after pediatric lung transplantation. J Heart Lung Transplant 2008;27:655-61.

Gruber S, Eiwegger T, Nachbaur E et al. Lung transplantation in children and young adults: a 20-year single-centre experience. Eur Respir J. 2012 Aug;40(2):462-9.
Liu M, Worley S, Arrigain S, et al. Respiratory viral infections within one year after pediatric lung transplant. Transpl Infect Dis 2009;11:304-12.
Robinson PD, Harris KA, Aurora P et al. Paediatric lung transplant outcomes vary with Mycobacterium abscessus complex species. Eur Respir J. 2013 May;41(5):1230-2.
Snell GI, Paraskeva M, Westall GP. Managing bronchiolitis obliterans syndrome (BOS) and chronic lung allograft dysfunction (CLAD) in children: what does the future hold? Paediatr Drugs. 2013 Aug;15(4):281-9..

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 • Basiliximab • Alemtuzumab Polyclonal • Antithymocyte globulin Anti-CD20 – • Rituximab **Proteasomal inhibitors** Bortezomib Carfilzomib **Complement inhibitors** – Eculizumab **Co-stimulation blocker** Belatacept.	**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

C_2: 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

Alloway RR, Dupuis R, Gabardi S, et al. American Society of Transplantation Transplant Pharmacy Community of Practice and the American College of Clinical Pharmacy Immunology/Transplantation Practice and Research Network. Am J Transplant. 2011 Aug;11(8):1576-83.

Anora 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.
Asante-Korang A, Amankwah E, Lopez-Cepero M, et al. Outcomes in highly sensitized pediatric heart transplant patients using current management strategies. J Heart Lung Transplant 2015;34:175-181.
Asante-Korang A, Jacobs JP, Ringewald J, et al. Management of children undergoing cardiac transplantation with high panel reactive antibodies. Cardiol Young 2011;21(Suppl.2): 124-132.
Bai JPF, Lesko LJ, Burckart GJ. Understanding the genetic basis for adverse drug effects: the calcineurin inhibitors. Pharmacotherapy 2010;30:195-209.
Baran DA, Zucker MJ, Arroyo LH, et al. Randomized trial of tacrolimus monotherapy: tacrolimus in combination, tacrolimus alone compared (the TICTAC trial). J Heart Lung Transplant 2007;26:992–997
Barnard JB, Thekkudan J, Richardson S, et al. Cyclosporine profiling with C2 and C0 monitoring improves outcomes after heart transplantation. J Heart Lung Transplant 2006;25:564–568
Barr ML, Sanchez JA, Seche LA, et al. Anti-CD3 monoclonal antibody induction therapy(Immunological equivalency with triple-drug therapy in heart transplantation). Circulation 1990;82:IV291–IV294
Belperio JA, Weight SS, Fishbein MC, Lynch JP. Chronic lung allograft rejection, mechanisms and therapy. Proc Am Thorac Soc 2009;6:108-121.
Beniaminovitz A, Itescu S, Lietz K, et al. Prevention of rejection in cardiac transplantation by blockade of the interleukin-2 receptor with a monoclonal antibody. N Engl J Med 2000;342: 613–619
Bhama JK, Shulman J, Bermudez CA, et al. Heart transplantation for adults with congenital heart disease: results in the modern era. J Heart Lung Transplant 2013;32:499-504.
Bhorade S, Ahya VN, Baz MA, et al. Comparison of sirolimus with azathioprine in a tacrolimus-based immunosuppressive regimen in lung transplantation. Am J Respir Crit Care Med 2011;183:379-87.
Bhorade SM, Stern E. Immunosuppression for lung transplantation. Proc Am Thorac Soc 2009;6:47-53.
Bonnefoy-Berard N, Revillard JP. Mechanisms of immunosuppression induced by antithymocyte globulins and OKT3. J Heart Lung Transplant 1996;15:435-442.
Brandhorst G, Tenderich G, Zittermann A, et al. Everolimus exposure in cardiac transplant recipients is influenced by concomitant calcineurin inhibitor. Ther Drug Monit 2008;30:113–116
Cantarovich M, Giannetti N, Barkun, J, et al. Antithymocyte globulin induction allows a prolonged delay in the initiation of cyclosporine in heart transplant patients with postoperative renal dysfunction. Transplantation 2004;78:779–781
Cantarovich M, Ross H, Arizon JM, et al. Benefit of Neoral C2 monitoring in de novo cardiac transplant recipients receiving basiliximab induction. Transplantation 2008;85:992–999
Carlsen J, Johansen M, Boesgaard S, et al. Induction therapy after cardiac transplantation: a comparison of anti-thymocyte globulin and daclizumab in the prevention of acute rejection. J Heart Lung Trans- plant 2005;24:296-302.
Carrier M, Leblanc MH, Perrault LP, et al. Basiliximab and rabbit anti-thymocyte globulin for prophylaxis of acute rejection after heart transplantation: a non-inferiority trial. J Heart Lung Transplant 2007; 26:258-63.
Chin C, Chen G, Sequeria F, et al. Clinical usefulness of a noval C1q assay to detect immunoglobulin G antibodies capable of fixing complement in sensitized pediatric heart transplant patients. J Heart Lung Transplant 2011;30:158-63.
Clatworthy MR. Targeting B cells and antibody in transplantation. Am J Transplant 2011;11:1359-67.

Costanzo MR, et al. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. J Heart Lung Transplant 2010;29:914-56.
Delgado DH, Miriuka SG, Cusimano RJ, et al. Use of basiliximab and cyclosporine in heart transplant patients with pre-operative renal dysfunction. J Heart Lung Transplant 2005;24:166–169
Delves PJ, Roitt IM. The immune system. First of two parts. N Engl J Med. 2000 Jul 6;343(1):37-49.
Delves PJ, Roitt IM. The immune system. Second of two parts. N Engl J Med. 2000 Jul 13;343(2):108-17
Dipchand AI,Pietra B, McCrindle BW, Rosebrook-Bicknell HL, Boucek MM. Mycophenolic acid levels in pediatric heart transplant recipients receiving mycophenolate mofetil. J Heart Lung Transplant 2001;20(10):1035-43.
Eisen HJ, Tuzcu EM, Dorent R, et al. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. N Engl J 2003;349:847–858
Enderby CY, Habib P, Patel PC, et al. Belatacept Maintenance in a Heart Transplant Recipient. Transplant 2014;98:e74-e75.
Ensor CR, Trofe-Clark J, Gabardi S, McDevitt-Potter LM, Shullo MA. Generic maintenance immunosuppression in solid organ transplant recipients. Pharmacotherapy 2011;31:1111-29.
Estenne M, Maurer JR, Boehler A, et al. Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. J Heart Lung Transplant 2002; 21:297-310
Feingold B, Park SY, Comer DM, Moore CG, Webber SA, Bryce CL. Outcomes after listing with a requirement for a prospective crossmatch in pediatric transplantation. J Heart Lung Transplant 2013;32:56-62.
Feingold B, Webber SA, Bryce Cl, et. al. Comparison of listing strategies of allosensitized heart transplant candidates requiring transplant at high urgency: a decision model analysis. Am J Transplant 2015;15:427-435.
Ford KA,Cale CM, Rees PG, Elliot MJ, Burch M. Initial data on basiliximab in critically ill children undergoing heart transplantation. J Heart Lung Transplant 2005;24(9):1284-8.
Gajarski RJ, Crowley DC, Zamberlan MC, Lake KD. Lack of Correlation between MMF dose and MPA level in pediatric and young adult cardiac transplant patients: Does the MPA level matter? Am J Transplant 2004;4(9)1495-1500.
Gijsen V,Mital S, van Schaik RH, et al. Age and CYP3A4 genotype affect tacrolimus dosing requirements after transplant in pediatric heart recipients. J Heart Lung Transplant 2011;30:1352-9.
Glanville AR, Aboyoun CL, Morton JM, Plit M, Malouf MA. Cyclosporine C2 target levels and acute cellular rejection after lung transplantation. J Heart Lung Transplant 2006;25:928-34.
Goland S, Czer LS, Coleman B, et al. Induction therapy with thymoglobulin after heart transplantation: impact of therapy duration on lymphocyte depletion and recovery, rejection, and cytomegalovirus infection rates. J Heart Lung Transplant 2008;27:1115–1121
Gonzalez-Vilchez F, de Prada JA, Exposito V, et al. Avoidance of calcineurin inhibitors with use of proliferation signal inhibitors in de novo heart transplantation with renal failure. J Heart Lung Trans- plant 2008;27:1135-41.
Grimm M, Rinaldi M, Yonan NA, et al. Superior prevention of acute rejection by tacrolimus vs. cyclosporine in heart transplant recipients—a large European trial. Am J Transplant 2006;6:1387–1397
Groetzner J, Meiser B, Landwehr P, et al. Mycophenolate mofetil and sirolimus as calcineurin inhibitor-free immunosuppression for late cardiac-transplant recipients with chronic renal failure. Transplantation 2004;77:568-74
Gullestad L, Iverson M, Mortenson SA, et al. Everolimus with reduced calcineurin inhibitor in thoracic transplant recipients with renal dysfunction: A multicenter, randomized trial. Transplantation 2010;89:864-72.

Halloran PF, Gourishankar S. Principles and overview of immunosuppression. in: D.J. Norman, N.J. Laurel (Eds.) Primer on transplantation. American Society of Transplantation, Mt Laurel, NJ; 2001:87–98
Henderson HT, Canter CE, Mahle WT, et al. ABO-incompatible heart transplantation: analysis of the pediatric heart transplant study (PHTS) database. J Heart Lung Transplant 2012;31:173-9.
Hershberger RE, Starling RC, Eisen, HJ, et al. Daclizumab to prevent rejection after cardiac transplantation. N Engl J Med 2005;352:2705–2713
Irving C, Gennery A, Kirk R. Pushing the boundaries: the current status of ABO-incompatible cardiac transplantation. J Heart Lung Transplant 2012;31:791-6.
Keogh A., Richardson M, Ruygrok P, et al. Sirolimus in de novo heart transplant recipients reduces acute rejection and prevents coronary artery disease at 2 years: a randomized clinical trial. Circulation 2004;110:2694–2700
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
Knoop C, Vervier I, Thiry P, et al. Cyclosporine pharmacokinetics and dose monitoring after lung transplantation: comparison between cystic fibrosis and other conditions. Transplantation 2003;76:683-8.
Kobashigawa J, Miller L, Renlund D, et al. A randomized active-controlled trial of mycophenolate mofetil in heart transplant recipients(Mycophenolate Mofetil Investigators). Transplantation 1998;66:507-15.
Kobashigawa JA, Miller LW, Russell SD, et al. Tacrolimus with mycophenolate mofetil (MMF) or sirolimus vs. cyclosporine with MMF in cardiac transplant patients: 1-year report. Am J Transplant 2006;6:1377–1386
Krasinskas AM, Kreisel D, Acker MA, et al. CD3 monitoring of antithymocyte globulin therapy in thoracic organ transplantation. Transplantation 2002;73:1339–1341
Kumbala D, Zhang R. Essential concept of transplant immunology for clinical practice. World J Transplant 2013;3:113-118.
Lee JC, Christie JD. Primary graft dysfunction. Proc Am Thorac Soc 2009;6:39-46.
Lehmkuhl H, Livi U, Arizon J, et al. Results of a 12-month, multicenter, randomized trial of everolimus with reduced-exposure cyclosporine versus mycophenolate mofetil and standard-exposure cyclosporine in de novo cardiac transplantation recipients. J Heart Lung 2008;27:S65
Lindenfeld J, Miller GG, Shakar SF, et al. Drug therapy in the heart transplant recipient: part II: immunosuppressive drugs. Circulation 2004;110: 3858–3865
Macdonald PS, Mundy J, Keogh AM, et al. A prospective randomized study of prophylactic OKT3 versus equine antithymocyte globulin after heart transplantation—increased morbidity with OKT3. Transplantation 1993;55:110–116
Mancini D, Pinney S, Burkhoff D, et al. Use of rapamycin slows progression of cardiac transplantation vasculopathy. Circulation 2003;108:48–53
Marshall CD, Richmond ME, Singh RK, et al. A Comparison of Traditional versus Contemporary Immunosuppressive Regimens in Pediatric Heart Recipients. J Pediatr 2013;163(1):132-6.
Mattei MF, Redonnet M, Gandjbakhch I, et al. Lower risk of infectious deaths in cardiac transplant patients receiving basiliximab versus anti-thymocyte globulin as induction therapy. J Heart Lung Transplant 2007;26:693-9.
Mehra MR, Zucker, MJ, Wagoner L, et al. A multicenter, prospective, randomized, double-blind trial of basiliximab in heart transplantation. J Heart Lung Transplant 2005;24:1297–1304
Meiser B, Reichart B, Adamidis I, Uberfuhr P, Kaczmarek I. First experience with de novo calcineurin-inhibitor-free immunosuppression following cardiac transplantation. Am J Transplant 2005;5:827- 31.

Monchaud C, Marquet P. Pharmacokinetic optimization of immunosuppressive therapy in thoracic transplantation: part I. Clin Pharmacokinet. 2009;48(7):419-62.
Monchaud C, Marquet P. Pharmacokinetic optimization of immunosuppressive therapy in thoracic transplantation: part II. Clin Pharmacokinet. 2009;48(8):489-516.
O'Connor MJ, Lind C, Tang X, et al. Persistence of anti-human leukocyte antibodies in congenital heart disease late after surgery using allografts and whole blood. J Heart Lung Transplant 2013;32:390-97.
Pham SM, Jimenez J. Bednar BM, et al. Campath-1H in clinical heart transplantation. J Heart Lung Transplant 2006;25:S228.
Raichlin E, Khalpey Z, Kremers W, et al. Replacement of calcineurin-inhibitors with sirolimus as primary immunosuppression in stable cardiac transplant recipients. Transplantation 2007;84:467-474.
Robinson BV, Boyle GJ, Miller SA, et al. Optimal dosing of intravenous tacrolimus following pediatric heart transplantation. J Heart Lung Transplant 1999;18:786-791.
Segovia J, Rodriguez-Lambert JL, Crespo-Leiro MG, et al. A randomized multicenter comparison of basiliximab and muromonab (OKT3) in heart transplantation: SIMCOR study. Transplantation 2006;81:1542-8.
Shyu S, Dew AM, Pilewski JM, et al. Five-year outcomes with alemtuzumab induction after lung transplantation. J Heart Lung Transplant 2011;30:743-54.
Snell GI, Valentine VG, Vitulo P, et al. Everolimus versus azathioprine in maintenance lung transplant recipients: an international, randomized, double-blind clinical trial. Am J Transplant 2006;6:169-77.
Stenton SB, Partovi N, Ensom MH. Sirolimus: the evidence for clinical pharmacokinetic monitoring. Clin Pharmacokinet 2005;44:769–786
Stewart S, Fishbein MC, Snell GI, et al. Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. J Heart Lung Transplant 2007;26:1229-42.
Taylor DO, Barr ML, Radovancevic B, et al. A randomized, multicenter comparison of tacrolimus and cyclosporine immunosuppressive regimens in cardiac transplantation: decreased hyperlipidemia and hypertension with tacrolimus. J Heart Lung Transplant 1999;18:336-34.
Teuteberg J, Shullo M, Zomak R, et al. Alemtuzumab induction facilitates corticosteroid-free maintenance immunosuppression inhuman cardiac transplantation. J Heart Lung Transplant 2008;27:S201–S202
Teuteberg J, Shullo M, Zomak R, et al. Aggressive steroid weaning after cardiac transplantation is possible without the additional risk of significant rejection. Clin Transplant 2008;22:730–737
Treede H, Glanville AR, Klepetko W, et al. Tacrolimus and cyclosporine have differential effects on the risk of development of bronchiolitis obliterans syndrome: Results of a prospective, randomized international trial in lung transplantation. J Heart Lung Transplant 2012;31:797-804.
Urschel S, Larsen IM, Kirk R, et al. ABO-incompatible heart transplantation in early childhood: an international multicenter study of clinical experiences and limits. J Heart Lung Transplant 2013;32:285-92.
Verleden GM, Vanaudenaerde BM, Dupont LJ, Van Raemdonck DE. Azithromycin Reduces Airway Neutrophilia and Interleukin-8 in Patients with Bronchiolitis Obliterans Syndrome. Am J Respir Crit Care Med 2006; 174:566–570
West LJ, Pollock-Barziv SM, Dipchand AI, et al. ABO-incompatible heart transplantation in infants. N Engl J Med 2001;344:793-800.
Zuckermann A, Wang S-S, Epailly E, et al. Everolimus immunosuppression in de novo heart transplant recipients: What does the evidence tell us now? Transplant Rev 2013;27:76-84
Zuckermann AO, Grimm M, Czerny M, et al. Improved long-term results with thymoglobuline induction therapy after cardiac transplantation: a comparison of two different rabbit-antithymocyte globulines. Transplantation 2000;69:1890–1898

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.

Suggested References for Management of the Sensitized Transplant Candidate*:*

Berry G, Burke M, Anderson C, et al. Pathology of pulmonary antibody-mediated rejection: 2012 update from the pathology council of the ISHLT. J Heart Lung Transplant 2013;32:14-21.

Betkowski AS, Graff R, Chen JJ, et al. Panel-reactive antibody screening practices prior to heart transplantation. J Heart Lung Transplant 2002;21:644–650

Bharat A, Saini D, Steward N, et al. Antibodies to self-antigens predispose to primary lung allograft dysfunction and chronic rejection. Ann Thorac Surg 2010;90:1094-101.

Christie JD, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: 29th Adult Lung and Heart-Lung Transplant Report-2012. J Heart Lung Transplant 2012;31:1072-86.

Clatworthy MR. Targeting B cells and antibody in transplantation. Am J Transplant 2011;11:1359-67.

Girnita AL, Duquesnoy R, Yousem SA, et al. HLA-specific antibodies are risk factors for lymphocytic bronchiolitis and chronic lung allograft dysfunction. Am J Transplant 2005;5:131-8.

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

2004;23:1135-41.
Hachem RR, Yusen RD, Meyers BF, et al. Anti-human leukocyte antigen antibodies and preemptive antibody-directed therapy after lung transplantation. J Heart Lung Transplant 2010;29:973-80.
Jordan SC, Toyoda M, Kahwaji J, Vo AA. Clinical aspects of intravenous immunoglobulin use in solid organ transplant recipients. Am J Transplant 2011;11:196-202.
Kobashigawa J, Crespo-Leiro MG, Ensminger SM, et al. Report from a consensus conference on antibody-mediated rejection in heart transplantation. J Heart Lung Transplant 2011;30:252-69.
Kobashigawa J, Mehra M, West L, et al. Report from a consensus conference on the sensitized patient awaiting heart transplantation. J Heart Lung Transplant 2009;28:213–225
Liu C, Wetter L, Pang S, Phelan DL, Mohanakumar T, Morris GP. Cutoff values and data handling for solid-phase testing for antibodies to HLA: effects on listing unacceptable antigens for thoracic organ transplantation. Human Imm 2012;73:597-604.
Margo CM, Harman AP, Klinger D, et al. Use of C4d as a diagnostic adjunct in lung allograft biopsies. Am J Transplant 2003;3:1143-54.
Martinu T, Chen DF, Palmer SM. Acute rejection and hormonal sensitization in lung transplant recipients. Proc Am Thorac Soc 2009;6:54-65.
Montgomery RA, Hardy MA, Jordan SC, et al. Consensus opinion from the antibody working group on the diagnosis, reporting, and risk assessment for antibody-mediated rejection and desensitization protocols. Transplantation 2004;78:181-5.
Morrell MR, Patterson A, Trulock EP, Hachem RR. Acute antibody-mediated rejection after lung transplantation. J Heart Lung Transplant 2009;28:96-100.
Pajaro OE, George JF. On solid-phase antibody assays. J Heart Lung Transplant 2010;29:1207-9.
Patel J, Everly M, Chang D, et al. Reduction in alloantibodies via proteasome inhibition in cardiac transplantation. J Heart Lung Transplant 2011;30:1320-6.
Pisani BA, Mullen GM, Malinowska K, et al. Plasmapheresis with intravenous immunoglobulin G is effective in patients with elevated panel reactive antibody prior to cardiac transplantation. J Heart Lung Transplant 1999;18:701–706
Shah AS, Nwakanma L, Simpkins CS, Williams J, Chang DC, Conte JV. Pretransplant panel reactive antibodies in human lung transplantation: An analysis of over 10000 patients. Ann Thorac Surg 2008;85:1919-24.
Takemoto SK, Zeevi A, Feng S, et al. National conference to assess antibody-mediated rejection in solid organ transplantation. Am J Transplant 2004;4:1033-41.
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
Yousem SA, Zeevi A. The histopathology of lung allograft dysfunction associated with the development of donor-specific HLA alloantibodies. Am J Surg Pathol 2012;36:987-92.