BANNER UNIVERSITY MEDICAL CENTER LIVER TRANSPLANT HANDBOOK

Version 1.0

July 1st, 2017

Introduction

This compilation serves as a primer on issues surrounding diagnosis and management of patients immediately prior to and after liver transplantation. When applicable, evidenced-based algorithms and protocols have been created to guide management of common issues after liver transplant and with end stage liver disease. Contents of this document do not represent inflexible standards of care and DO NOT replace the need for standard communication among providers on the transplant team. References in support of suggested algorithms are placed at the conclusion of each topic section and original source articles will be available in the institute building's shared y: drive Computer→Groups→(\\BHS) Y:→BGSMC→GS_Trans→"Transplant Protocol Articles"

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Primer on Immunosuppression after Liver Transplantation

Background: The immunosuppression (IS) used in the immediate postoperative phase, usually referred to as IS induction is not discussed in detail here. Choice of IS during this early period can be highly variable depending upon a number of inpatient variables after surgery.

List of Common Agents/Rationale:

Steroids [Prednisone]
Corticosteroids exert their immunosuppressive effect by blocking T-cell derived and antigen-presenting cell-derived cytokine expression. This includes IL-1, IL-2, IL-3, and IL-6. Corticosteroids continue to be used in reversing acute rejection and in maintenance therapy. Dosing varies widely but initially after surgery can be summarized as follows: a bolus dose of methylprednisolone just prior to surgery, i.e., 500 to 1,000 mg, followed by rapid taper over next few weeks to minimal dose, i.e., 25-50 mg/day. In the vast majority of cases, attempt is made to wean corticosteroids off within the first few weeks post LT.

Basiliximab
Basiliximab, a monoclonal interleukin-2 receptor antibody, is employed as an induction agent to delay initiation of tacrolimus in those with perioperative kidney dysfunction. Basiliximab is given as 20 mg intravenous doses, starting on postoperative day (POD) 1 and repeated on POD 5. Patients may be given concomitant steroids and cell cept. Timing of tacrolimus initiation after basiliximab induction is variable and determined by the inpatient team.

Cyclosporine (CyA) [Gengraf, neoral]
CyA causes suppression of cell-mediated immunity via inhibition of T-cell activation. Nephrotoxicity is a major side effect of CyA therapy. This can be both an acute and a long-term complication, inducing a post-OLT rate of renal failure up to 20%. Common metabolic abnormalities include: hyperkalemia, hypomagnesemia, hyperlipidemia, and hyperglycemia. Hypertension, gingival hyperplasia and hirsutism are also a common occurrence. Many patients have neurological manifestations ranging from mild tremor and peripheral neuropathy to psychoses, hallucinations, motor weakness, and seizures.

CyA initial dosage ranges from 10 to 15 mg/kg/day divided into 2 doses. Adjustment of the oral dose is based on trough level measurement, usually within 24 hours of starting CyA. Target trough levels vary widely.

Commonly used dose-targeted ranges in liver transplantation: 250-350 ng/mL during weeks 1-2, 200-300 ng/mL during weeks 3-4, 150-250 ng/mL during weeks 5-24, and 100-200 ng/mL during weeks 25-52.

More recently, dose adjustment based on blood concentration at 2 hours after dose has been shown to more closely correlate total exposure vs. C0 monitoring (trough). One

example of this would be target blood concentration levels of 850 to 1400 ng/mL at 2 hours after dose from 0 to 3 months post-transplant.

Tacrolimus (Prograf) [TAC or FK]
FK is 100 times more potent than CyA and exerts its action by binding to FK binding protein (FKBP12). This complex then inhibits calcineurin, which is responsible for transcription of IL-2, IL-3,IL-4, IL-8, and various chemotactic factors. TAC absorption occurs in the duodenum and jejunum. Unlike CyA, TAC absorption is not influenced by presence of bile, which is advantageous in cholestatic patients or those with biliary diversion or ileus.

Food reduces bioavailability, and TAC should be taken on an empty stomach. Metabolism occurs in the liver via the cytochrome P450-3A. Coadministration of medications that inhibit or induce cytochrome P450 may significantly affect blood levels of TAC. Side effects are similar to CyA: nephrotoxicity, neurotoxicity, post-transplant diabetes mellitus, and hyperkalemia.

Initial dose guidelines for TAC range from 0.1 to 0.15 mg/kg/day orally. Dosages are modulated based on trough levels. Factors affecting adjustments are disease state, renal function, patient age, and other concomitant medications. Therapeutic goals for TAC early after surgery would be around 10 ng/mL

Mycophenolate mofetil (MMF, CellCept)
Mycophenolate mofetil (MMF, CellCept) and mycophenolic acid (MPA, Myfortic) are antimetabolites. MPA is a delayed-release product in contrast to MMF, which is immediately released. Both formulations inhibit de novo purine nucleotide synthesis via abrogation of the inosine monophosphate dehydrogenase and the production of guanosine nucleotides. This leads to a blockage of DNA replication in T and B lymphocytes.

Studies have shown a large variation in MMF pharmacokinetics in liver transplantation related to fluctuations in serum albumin concentrations, and as such, we don't routinely follow levels. Liver dysfunction impairs MPA conjugation and prolongs MPA half-life. Furthermore, TAC has been shown to augment the bioavailability of MPA, resulting in higher exposure to MPA. Adverse effects (nausea, gastritis abdominal pain, diarrhea, and neutropenia) requiring dose reduction or withdrawal is high.

Initial dosage ranges from 2-3g daily for MMF and 720 to 1,440 mg daily for MPA, divided into 2 doses.

Sirolimus (Rapamune)
Sirolimus (Rapamune, RAP) is a macrocyclic triene antibiotic (structurally related to TAC) with immunosuppressive, antitumor, and antifungal properties. RAP binds to the immunophilin FKBP12 and blocks the response of T- and B-cell activation by cytokines, which prevents cell-cycle progression and proliferation; in contrast, TAC and CyA inhibit the production of cytokines. Although not FDA approved for liver transplant, sirolimus can be utilized for renal protection and potentially in recipients with recurrence of HCC. Early

usage has been associated with the development of hepatic artery thrombosis. Dosing can range from 0.5 mg daily to 2.0 mg daily depending on time from transplant.

Everolimus
Everolimus' primary mechanism of action is mediated via blockade of interleukin-2 and interleukin-15 induction of proliferation of T and B cells. Everolimus, the hydroxyethyl derivative of RAP, is more hydrophilic and therefore has greater oral absorption.

Everolimus is FDA approved for liver transplantation. Dosing is typically 0.5–1.0mg BID. Its half-life is shorter (24 h) compared with RAP (64 h), and oral dosing is adjusted to target a blood level between 3 and 12 ng/ml. Metabolism occurs via the hepatic cytochrome P450 system and therefore levels must be monitored carefully for patients with hepatic dysfunction or if coadministered with drugs altering P450 metabolism.

Thymoglobulin
Polyclonal preparations are directed at multiple different epitopes on the T cell (CD2, CD3, CD4, CD8, CD28, and the T-cell receptor) as well as CD16 found on natural killer cells and macrophages. These antibodies cause depletion of T cells by apoptosis, antibody mediated cytolysis and internalization of the cell surface receptors. The biologic effects of the depleting antibodies are profound and are long lasting. Side effects can include a "first-dose effect" (cytokine release syndrome) and is related to the myriad of cytokines released by these lymphocytes upon their demise. The symptoms typically include fever, chills, tachycardia, gastrointestinal disturbances, bronchospasm, and fluctuations of blood pressure, which all can be ameliorated by pretreatment with corticosteroids, diphenhydramine, and acetaminophen.

Dosing ranges from 1.5 to 5mg/kg as a single infusion usually over 4 to 6 hours for 3-5 days, depending on the indication. See section on acute cellular rejection.

In the first 3 months following the transplant, the risk of allograft dysfunction secondary to rejection is higher, compared to other times after transplant. During this period the IS doses are adjusted according to liver chemistry tests and drug level.

The reminder of this protocol addresses management of IS after the initial 3 months.

I) Rational for IS dose adjustment:

After the first year post-transplant the most common causes of mortality are malignancy, cardiovascular disease, infection and renal failure. These are associated with IS medications and therefore de-escalation or minimization of IS is a highly effective way to promote medium and long term survival following liver transplant.

II) When and who can have the IS minimized:

The best time to start the minimization of the IS regimen is after the first 3 months if liver chemistry tests have remained normal for the previous 4 weeks.

All patients are potential candidates for IS minimization protocol, with the exception of three groups:
A) Patients who had a biopsy proven episode of steroid resistance rejection.
B) Patients transplanted for immune –mediated diseases who had a previous transplant
C) Those who had an episode of Antibody Mediated Rejection (AMR)

With the exception of the patients above, any patients who are still on steroids by month 3, should be weaned off. Even patients who were transplanted because of immune mediated diseases (AIH, PBC and PSC) may tolerate d/c of steroids. The process is accomplished by decreasing the dose of steroids slowly to a minimum, then stopping it. If d/c of steroids becomes difficult to attain, consideration should be given to using Azathioprine or Mycophenolate Mofetil (MMF) in order to allow complete steroid withdrawal.

III) Different IS protocols:

A) CNI monotherapy:
1) If opting for monotherapy with Tacrolimus, at 3 months the trough level should be of 7-10 ng/ml. If opting for Cyclosporine (CsA) monotherapy, at 3 months the trough level should be 150-200 ng/ml.
2) After the first 3 months the CNI doses can be decreased slowly, monitoring laboratory tests, for a goal of Tacrolimus through level not higher than 5 & CsA levels no higher than 100 ng/ml
3) By 5 years, levels are less relevant and levels less than 3ng/ml would be acceptable, if good graft function.

B) Dual therapy:
1) Most patients who still need dual therapy at 3 months are those who have immune mediated diseases, neurologic dysfunction, or those with kidney disease.
2) If monotherapy is not an option, after the first 3 months the Tacrolimus trough should be no higher than 8 ng/ml if combined with MMF, and 3-5ng/ml if combined with Everolimus.
3) If later on the patient's clinical condition allows to follow the minimization strategy, then consider withdrawal of the second agent for a goal of monotherapy at 1 year. If using Tacrolimus the level should be around 5 ng/ml, for Everolimus the range should be 3-8 ng/ml and if using MMF 1 gram every 12 hrs.
4) After 1 year, if patient on dual therapy, lower levels are acceptable, provided the graft function is normal.
5) Complete withdrawal should be limited to clinical trials with the exception of patients with PTLD or other malignancy, particularly while on chemotherapy.

IV) Exceptions:

A) Azathioprine may be an alternative to MMF in patients with immune mediated disease or inflammatory bowel disease.

B) In some particular circumstances i.e. Posterior Reversible Encephalopathy Syndrome (PRES) or other neurologic complications, the switch to everolimus monotherapy may be done earlier. Careful monitoring of laboratory tests is necessary to identify rejection

C) For patients at higher risk to have renal insufficiency, some strategies to minimize the risk of renal related CNI toxicity have been evaluated in clinical trials. The renal protection strategies can, and many times do start with the choice of best regimen for IS induction.

V) Technical remark:

Even though Sirolimus (RAP) is not approved in the US for use in liver transplant recipients, many Transplant Centers use Rapamune, particularly in renal protection protocols and patients with cancer.

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Acute Cellular and Chronic Ductopenic Rejection

Background: Acute cellular rejection following liver transplantation has decreased in incidence but still affects up to 15-30% of recipients. It is most common within the first 3 months following transplant but can occur at any time. The consequences of acute cellular rejection are variable. Whereas it can predispose to steroid-resistant rejection and graft loss, most episodes do not have long-term adverse effects and are treated with increasing doses of immunosuppression or enforcement of medication compliance.

Chronic ductopenic rejection results in fibrosis and disappearance of bile ducts (ductopenia) and this may develop in recipients with uncontrolled acute rejection episodes—resulting in cholestatic jaundice.

Both forms of rejection are, until late stages, asymptomatic, and diagnosis is made through investigation of abnormal liver tests and can be confirmed on the basis of histology (liver biopsy). For both cellular rejection and ductopenic rejection, the Banff criteria (Rejection Activity Index [RAI]) has been adopted to define nature and severity. On biopsy, cellular rejection is characterized by the triad of: inflammatory bile duct damage, subendothelial inflammation of the portal, central, or perivenular veins, and a predominantly lymphocytic portal inflammatory infiltrate with neutrophils and eosinophils. The focus of inflammation may be portal, central, or both, but the central component is more prominent and frequently occurs as pure centrilobular necroinflammation (isolated central perivenulitis).

Liver tests in patients with late-onset cellular rejection show nonspecific abnormalities with a rise in serum bilirubin and aminotransferases. Late acute rejection differs from early acute cellular rejection by having fewer classic histological features.

Acute Cellular Rejection Protocol

Abnormal lab testing on 2 consecutive occasions and review of clinical history by covering physician should prompt:

1) **Allograft biopsy**

    a) **If allograft biopsy read as Mild ACR [RAI ≤ 4/9]**

        a. Then increase maintenance immunosuppression to ensure target levels
            i. e.g. tacrolimus increase for levels to 12-15 ng/dL
            ii. initiate/increase mycofenolate mofetil
        b. Recheck labs at 1 week
            i. If improvement, follow
            ii. If NO improvement, treat as moderate ACR

    b) **If biopsy read as Mod ACR [RAI 5-6/9] and Severe [RAI ≥ 7/9]**

        a. Admission to hospital for administration for parenteral steroid therapy
            i. Initiate solumedrol 1 gram IV day (maximum 3 days)
                1. Labs Improving:
                    a. Transition to PO Prednisone Taper
                        i. 40mg PO for 10 days
                        ii. 30mg PO for 10 days
                        iii. 20mg PO for 10 days
                        iv. 10mg PO for 10days
                        v. 5mg PO for 10 days
                        vi. Discontinue

                2. Labs not improving
                    a. Re-biopsy at 7-10 days
                    b. See Thymoglobulin

Thymoglobulin Protocol

Rarely, allograft function and liver enzymes will not improve despite administration of high dose IV steroid. In these cases, the scenario is labeled “steroid-resistant rejection.” The surgeon or hepatologist may order administration of thymoglobulin (a polyclonal lymphocyte preparation) in an effort to control rejection.

1) **Admission to the hospital. Thymoglobulin is only to be administered in inpatient setting with appropriate monitoring**

2) **Prior to initiation, previously discontinued or ongoing opportunistic infection prophylaxis to be reviewed:**
    a. Resume or continue Bactrim SS daily or DS TIW
    b. Resume of continue Diflcuan 100mg PO daily
    c. Initiate or change CMV prophylaxis from valcyte to IV ganciclovir
        i. Resume valcyte at renal appropriate dosing on discharge for minimum 3 months after administration

3) **Initial dose is given 1.5 mg/kg IV (dose not to exceed 100mg) on day 1 [12 hour infusion]**
    a. Premedication: Methylprednisone 250mg IV (prednisone 20mg 1 hour prior to subsequent doses)
    b. Benadryl 50mg IV and Tylenol 650 mg PO 30 minutes prior to every dose
    c. Daily reassessment as to need for ongoing thymoglobulin doses, not to exceed 5 days total

4) **Ongoing maintenance immunosuppression targets:**
    a. Goal Tacrolimus levels < 6.0 ng/dl
    b. Mycophenolate mofetil no >500mg PO BID

Antibody Mediated Rejection Protocol

Antibody-mediated rejection (AMR) is a rare cause of allograft injury and loss after ABO-compatible liver transplantation that can be confused with or overlap with acute cellular rejection. Humoral alloreactivity mediated by antibodies against donor human leukocyte antigen (HLA) molecules, acting in concert with cellular mechanisms, may play a role in the development of ductopenia. Proposed features of AMR in liver transplants include donor-specific HLA alloantibodies in serum, microvascular endothelial cell injury on biopsy, and linear C4d positivity in liver sinusoids, in the absence of other causes of liver injury.

1) **Allograft biopsy. Expert pathologic consultation for appropriate staining and consensus of AMR.**

2) **Upon pathologic confirmation:**
    a. **Admission to the hospital**
    b. **Plasmapheresis/IVIG**
        i. Consult Nephrology/Hematology for plasmapheresis:
        ii. Plasmapheresis every other day for a total of 5 therapies.
            1. Order sucrose-free IVIG 100mg/kg IV following first 4 sessions of plasmapheresis (rounded to nearest 5g)
            2. Administer dose over 2 hours
            3. Order sucrose-free IVIG 2g/kg IV following 5th session of plasmapheresis (max dose = 140g, rounded to nearest 5g)
            4. Dose may be split into 2 doses of 1mg/kg IV (max 70g) to be infused on separate days
               Begin infusion at 50 ml/hr and double rate every 30 min as tolerated to a max infusion rate of 250 ml/hr
            5. IVIG should be given AFTER plasmapheresis, but prior to Thymoglobulin (if prescribed) Pre-medicate with acetaminophen 650mg and diphenhydramine 50mg if patient did not receive with plasmapheresis.
            6. Repeat DSA titers prior to the 5th session of plasmapheresis, and again 30 days after administering 2g/kg dose of IVIG.
    c. **High Dose IVIG for Antibody Mediated Rejection**
            1. Order sucrose-free IVIG 2g/kg IV (max dose = 140g, rounded to nearest 5g)
            2. Dose may be split into 2 doses of 1mg/kg IV (max 70g) to be infused on sep days
            3. Begin infusion at 50ml/hr and double rate every 30 min as tolerated to a max infusion rate of 250ml/hr. Pre-medicate with acetaminophen 650mg and diphenhydramine 50mg
            4. Repeat DSA titers 30 days after administration.

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Infection Prophylaxis After Liver Transplantation

Background: Opportunistic infections are a leading cause of morbidity and mortality after orthotopic liver transplantation. Immunosuppression renders the recipient susceptible to *de novo* infection with bacteria, viruses and fungi post-transplantation as well to reactivation of pre-existing, latent disease. Pathogens are also transmissible via the donor organ. The time from transplantation and degree of immunosuppression guide the differential diagnosis of potential infectious agent. Typical systemic signs and symptoms of infection (i.e. fever) are often absent or blunted after transplant and high index of suspicion is needed. Invasive procedures are often required to procure tissue for culture and guide antimicrobial therapy. Antimicrobial prophylaxis reduces the incidence of opportunistic infections and is routinely employed in the care of patients after liver transplant.

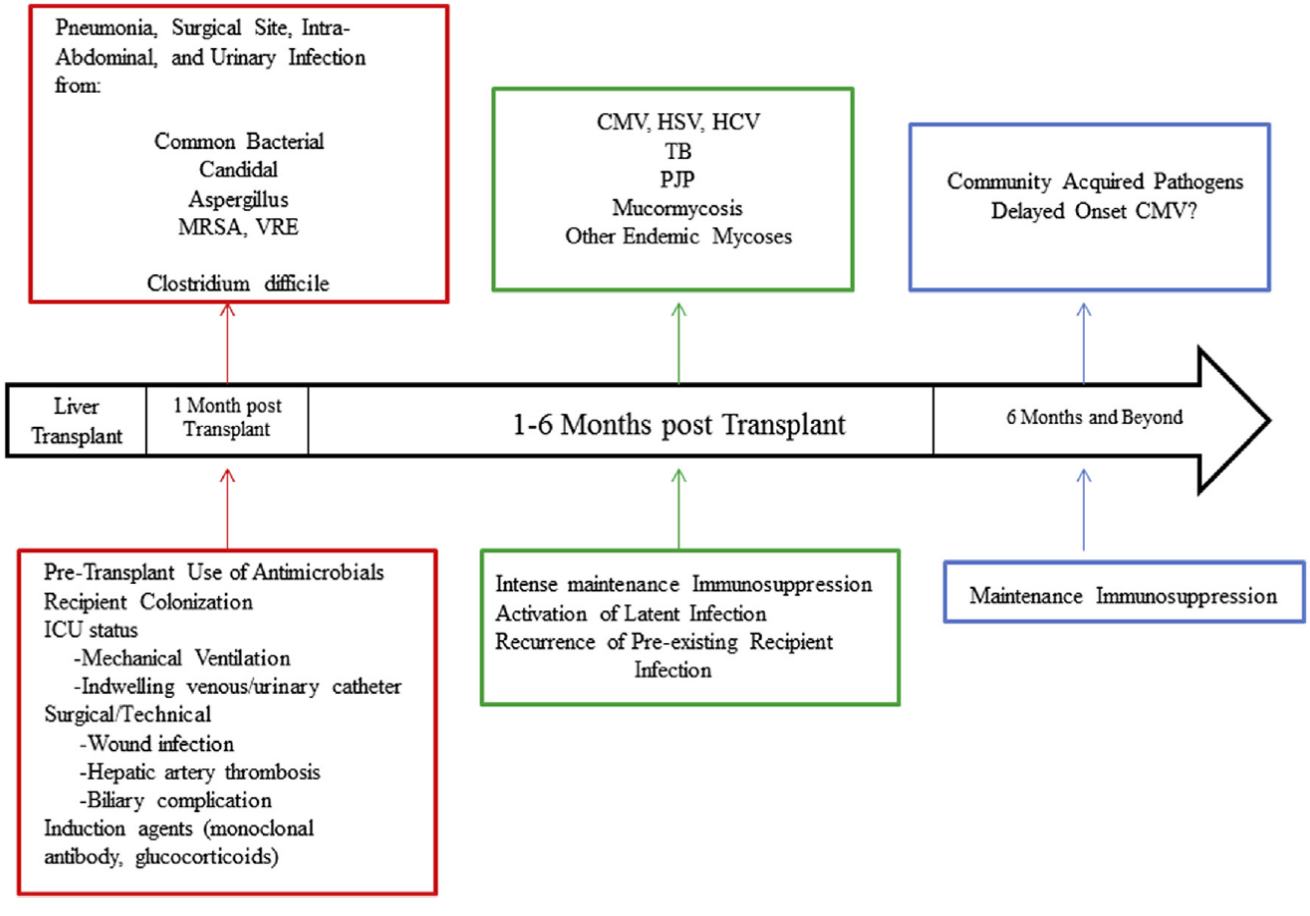

Table 1. Summary of Risk Factors for Infection and Potential Agents
Summary of potential infectious agents (above arrow) and risk factors for infection (below arrow). Risk of infection if correlated to the degree of immunosuppression (high doses early predispose to greater risk).

Pneumocystis jiroveci

Pneumocystis jiroveci is a well-established opportunistic pathogen whose incidence is recognized in both immunodeficient states (human immunodeficiency virus) and in immunosuppressed patients after solid organ transplant. Patient with pneumocystis infection may present with fever, shortness of breath, and nonproductive cough. Classically, bilateral interstitial infiltrates are seen in chest X-ray.

Patients should be prophylaxed with trimethoprim-sulfamethoxazole unless a strong contraindication (intolerance, allergy) is identified. Alternative treatments include aerosolized pentamidine , dapsone (in patients who are not deficient in glucose-6-phosphate dehydrogenase), atovaquone, and clindamycin-primaquine.

Recommended PJP Prophylaxis

- Bactrim (TMP-SMX) single strength (SS) one tablet po daily <or> Bactrim (TMP-SMX) double strength (DS) Mon, Weds, Fri for 6 months in recipients with no sulfa allergy
- In Recipients with Sulfa allergy:
  - Dapsone 100mg po daily (commonly used)
  - Inhaled Pentamidine weekly
  - Atovaquone 1500mg orally daily
- Consider extension of PJP prophylaxis to one year in simultaneous liver/kidney recipients or in liver recipients receiving multiple therapies for acute cellular rejection

Cytomegalovirus:

Cytomegalovirus (CMV) is a member of the human herpesvirus (HHV) group and is a common cause of morbidity after liver transplant. Cytomegalovirus 'CMV infection' is defined as isolation of the CMV virus or detection of viral proteins or DNA in any body fluid or tissue specimen. The minimum conditions for determination of 'CMV disease' are fever (>38 degrees C, for at least 2 days within a 4-day period), neutropenia or thrombocytopenia, and the detection of CMV in blood. End-organ disease, e.g., pneumonia, retinitis, nephritis, or central nervous disease is common and requires detection of CMV in tissue examination. In liver transplantation, a common end-organ disease is CMV hepatitis.

The risk of acquiring CMV infection or disease after transplantation can be stratified by the serologic status of the donor and the recipient. The highest risk of developing CMV infection occurs in the seronegative recipient (R) of an organ from a seropositive donor (D) (referred to as D+/R-). CMV infection will eventually develop in most recipients in this category and a high percentage of them will become symptomatic. Endogenous CMV can be reactivated in seropositive recipients, or they can sometimes become superinfected with an exogenous *de novo* virus from the donor organ (D+/R+). Seronegative recipients who receive an organ from a seronegative donor (D-/R-) are considered at low risk, although

CMV infection can still develop (unscreened blood transfusion). Other risk factors for CMV infection include use of high-dose prednisone or calcineurin inhibitor.

Recommended CMV Prophylaxis

- **High Risk Recipients (CMV D+/R-):** Valgancylovir dosed according to GFR [CrCl >60 900mg qd; 40-59 450mg qd; 25-39 450mg q48hrs; 10-24 450mg BIW; <10/HD use IV ganciclovir (0.625mg/kg after HD] for **6 months**
- **Intermediate Risk Recipients (CMV D+/R+, D-/R+):** Valgancylovir dosed according to GFR [CrCl >60 900mg qd; 40-59 450mg qd; 25-39 450mg q48hrs; 10-24 450mg BIW; <10/HD use IV ganciclovir (0.625mg/kg after HD] for **3 months**
- **Low Risk Recipients (CMV D-/R-):** No antiviral prophylaxis needed; CMV DNA PCR check as needed for: fever, compatible symptoms, or leukopenia

Other Considerations:
For low risk recipients not on valcyte consider HSV prophylaxis with acyclovir 200mg capsule two capsule bid x 4 weeks. If CrCl <30, 200mg bid x 4 weeks.

Recipients with CMV viremia and associated symptoms should be admitted to the hospital for initation of treatment with IV gancyclovir—usually in consult with ID

Coccidiomycoses (Valley Fever)

Coccidiomycosis is an infection caused by Coccidioides species, which are endemic for the Southwestern United States including Arizona. Inhalation of spores may be common and result in subclinical presentations in immunocompetent hosts. Post transplantation, *de novo* or reactivated infection can occur with systemic immunosuppression as well.

Recommended Coccidiomycoses Prophylaxis

- Prior cocci exposure: Lifelong prophylaxis with Fluconozole 100mg po daily, adjust to Renal function
- No prior exposure: Fluconozole 100mg po daily for 6 months, adjust to renal function

Other Considerations:

Consider extension of fluconazole to 1 year in recipients with simultaneous liver/kidney transplant or undergoing treatment for acute cellular rejection

Hepatitis B Core Antibody Positive Donors

Use of organs from donors testing positive for hepatitis B virus (HBV) safely expand the donor pool. Transmission risk is highest with liver donors and significantly lower with non-liver (kidney and thoracic) donors.

Antiviral prophylaxis significantly reduces the rate of transmission to liver recipients from isolated HBV core antibody positive (anti-HBc+) donors. Organs from anti-HBc+ donors should be considered for all adult transplant candidates after an individualized assessment of the risks and benefits and appropriate patient consent.

Indefinite antiviral prophylaxis is recommended in liver recipients with no immunity or vaccine immunity but not in liver recipients with natural immunity. Although no longer the treatment of choice in patients with chronic HBV, lamivudine remains a cost-effective and highly tolerable choice for prophylaxis in this setting.

Recipients Receiving Hep B core Ab positive Allograft:

With previous immunity (i.e. detectable sAb): no hepatitis B immunoglobulin or antiviral is needed

With no documented immunity (i.e. undetectable sAb prior to transplant):

- HBIG IV 10,000U in anhepatic phase then 10,000U daily x 5 days.
- Initiation of nucleos(t)ide analog e.g. lamivudine 100mg daily
- Hep Bs Ag, Hep Bs Ab, Hep Be Ag, Hep Be Ab, HBV DNA Quant will be check every 3 months x 1 yr then every 6 months with AFP.

Hepatitis C Positive Allografts

Use of organs from donors with reactive Hep C Ab may safely expand donor pool. With advent of highly effective and tolerable direct acting antiviral therapy, HCV recurrence can be successfully treated in most cases with no long-term damage to the allograft.

Organs from anti-HCV reactive donors should be considered (even in HCV negative recipients) after an individualized assessment of the risks and benefits and appropriate patient consent including: risk of transmission of HCV with likely development of viremia, possibility of severe HCV recurrence-Fibrosing Cholestatic Hepatitis, and need for additional antiviral therapy post transplant,

Recipients Receiving Hepatitis C Allografts

- Assessment of HCV RNA, HCV genotype, HAV Ab, Hep sAb, sAg, cAb, HIV, CBC, CMP, PT/INR, urine drug screen at 3 months
- Initiation of antiviral therapy within the 1st year from transplant surgery based on clinical course (see section on recurrent disease)

Summary of Opportunistic Infection Prophylaxis after Liver Transplantation

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- No prior exposure: Fluconozole 100mg po daily for 6 month, adjust to Renal function
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References:

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Vascular Complications after Liver Transplant

Hepatic artery stenosis/thrombosis

Angiographic evidence of greater than 50% reduction in caliber of the lumen of hepatic artery is defined as hepatic artery stenosis (HAS). Hepatic artery stenosis (HAS) after liver transplantation (LT) usually has no specific symptoms and manifests as graft dysfunction. Untreated stenosis may progress to hepatic artery thrombosis (HAT) in >50% of patients, leading to ischemic biliary complications and eventual graft loss.

HAT has 30%-50% risk of graft loss and an overall mortality of 50%. Of those 50%, nearly a third die even after a re-LT. Incidence of HAS ranges from 5% to 15%, but true incidence is difficult to assess because most stenoses are discovered at the stage of thrombosis and different definitions of HAS are used in the medical literature. **By Doppler ultrasound, presence of low resistive index of less than 0.5 with increase in focal peak velocity are suggestive HAS.**

Traditional surgical options include resection of the stenotic segment with re-anastomosis, aortic conduit graft, interposition vein or artery graft, or vein patch angioplasty. Endovascular treatment (IR therapy) by percutaneous transluminal angioplasty stenting (PTA) has been developed as the primary treatment of hepatic arterial complications including HAS **except in those with very early thrombosis or stenosis (<7 days from LT) which are treated by surgical revascularization.**

PTA ensures good arterial patency and improves graft and patient survival in patients with HAS. At present, there are no generally accepted management guidelines for HAS by an endovascular approach especially in patients with established biliary ischemia.

Portal vein stenosis/thrombosis

Portal vein stricture can present shortly after LT by increased production of ascites and liver allograft dysfunction. Ultrasonography and CT angiography are usually diagnostic. Treatment is by surgical intervention in early post LT period and by percutaneous transhepatic dilatation or stenting of the stricture later after LT. If left untreated, it can progress to complete thrombosis of the vein or severe graft dysfunction and hemodynamic instability secondary to massive production of ascites. It could happen as a result of technical errors such as kinking or redundancy of the vein, poor mesenteric flow secondary to open collateral venous system (steal syndrome), or major anastomotic stricture or twist.

Treatment is immediate surgical revascularization of the graft by thrombectomy and correction of the technical problem, ligation of large collaterals in the portal venous system, bypass grafting via the superior mesenteric vein. Otherwise, re-transplantation may be the only therapeutic option.

Hepatic outflow obstruction
Complications associated with vena cava stenosis include a 2.5% to 6% incidence of venous outflow obstruction (iatrogenic Budd-Chiari syndrome), caused by either rotation of the liver graft or anastomotic stricture. Stenosis of the suprahepatic cava anastomosis can present with hepatic outflow obstruction in the form of liver allograft dysfunction, ascites formation, and impairment of the renal function.

Diagnosis can be made by cavagram and measurements of the venous pressure gradients proximal and distal to the anastomosis. Treatment options are by angioplasty, stent placement or surgical correction of the strictured area. Anastomosis between the infrahepatic donor cava to the recipient cava in patients with piggy-back technique can decompress the liver in patients with outflow obstruction secondary to anastomotic narrowing between the suprahepatic donor cava and confluence of the hepatic vein in the recipient. When all these measures fail, re-transplantation may be the only option.

SUMMARY AND SUGGESTED ALGORITHM FOR VASCULAR COMPLICATIONS

1) The following clinical scenarios may prompt evaluation for vascular complications
    a. Abnormal imaging (for other indication) showing vascular stenosis
    b. Non-anastomotic stricture(s)/bile leak
    c. New onset ascites after liver transplant
    d. Unexplained rise in cholestatic markers: ALP, GGT, Tbil

2) Order abdominal ultrasound complete with doppler to evaluate hepatic inflow (venous/arterial) and outflow

3) Presentation of Results at Multidisciplinary radiology conference for review of resistive indices/flow

4) Based on 3); consideration of CT Angiography or direct IR consult

5) If IR intervention performed (i.e. thrombectomy, PTCA)
    a) Follow IR procedural report recommendations for follow up imaging
    b) For those with stent placement
        a. Plavix for minimum of 3 months; if unable to take Plavix then ASA 325mg daily for 3 months

References

1) Muthukumarassamy R, Sameh A, Oriana C et. al. Intention-to-Treat Analysis of Percutaneous Endovascular Treatment of Hepatic Artery Stenosis After Orthotopic Liver Transplantation *Liver Transpl* 2016 22(7):923-33.
2) Duffy JP, Hong JC, Farmer DG, Ghobrial RM, Yersiz H, Hiatt JR, Busuttil RW. Vascular complications of orthotopic liver transplantation: experience in more than 4,200 patients. *J Am Coll Surg* 2009 208:896-903.
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Biliary Complications after Liver Transplant

Background: Biliary complications occur in 5-15% of patients after deceased donor liver transplant (DDLT). The most common complication is biliary stricture, followed by bile leak, and sphincter of oddi dysfunction (SOD).

Biliary strictures are classified as anastomotic or non-anastomotic. The majority of biliary strictures occur within the first year of transplant, but can occur several years after transplant. Anastomotic strictures (AS) are defined as segmental or focal narrowing around the biliary anastomosis. They generally occur as a result of fibrotic healing related to local ischemia at the end of donor and recipient bile duct. Early bile leaks are also a risk factor for an anastomotic stricture. Non anastomotic strictures (NAS) are defined as 1 or more focal areas of narrowing of the bile ducts proximal to the biliary anastomosis. They are more often related to ischemia, hepatic artery thrombosis (HAT), chronic ductopenic rejection, immunologic events such as ABO incompatibility, and PSC prior to transplant. Bile leaks generally occur in the post-operative period at the biliary anastomosis, cystic duct remnant, or accessory right hepatic duct. SOD can occur from denervation of the common bile duct and development of a hypertonic sphincter.

The goal of this guideline is to ensure proper diagnosis and uniform management of biliary complications after transplant, specifically stricture management to ensure long term patency.

Diagnosis

Clinical signs and symptoms of a biliary complication include: jaundice, fever, right upper quadrant pain, and pruritus but this not required. Liver function tests (LFTs) will show a cholestatic pattern of elevated alkaline phosphatase, GGT, direct bilirubin levels, and variable elevation in transaminase levels. Imaging is an important first step. **US with doppler should be consider in any post-transplant patient with elevated LFTs to rule out hepatic artery stenosis or thrombosis.**

The sensitivity of ultrasound in detecting bile duct obstruction in liver transplant is low. Dilation of donor duct is not required in the setting of post-transplant obstruction. **MRCP is the imaging modality of choice for detection of post-transplant biliary strictures prior to ERCP or percutaneous cholangiography (PTC)**. MRCP has a high sensitivity and overall accuracy in diagnosis of post-transplant biliary complications. Bile leaks generally manifest in the post-operative period with bilious output from surgical drains or intra-abdominal fluid collections. Hepatobiliary scans can be considered in indeterminate cases of bile leak. SOD should be suspected when there is evidence of biliary ductal obstruction and diffuse dilation of the biliary system without filling defects.

Treatment Algorithms for Biliary Complications

The initial intervention of choice when a biliary complication has been diagnosed or suspected is ERCP. The management of strictures is based on progressive dilation and stenting every 2-3 months. **All patients should receive a dose of IV antibiotics pre-procedure, generally Cipro 400mg IV x 1.** The **endoscopic end point** is disappearance of the stricture by occlusion cholangiography without significant indentation, and/or easy passage of 9mm balloon through the anastomosis. Additionally, contrast should empty from the biliary system under fluoroscopy.

Bile leaks

1. ERCP. If leak is confirmed then sphincterotomy and placement of stent. If the leak is from the biliary anastomosis, then placement of 7Fr stent across the anastomosis. No biliary dilation if < 1 month post-operative, due to risk of rupture at the anastomosis. If biliary dilation is needed to place a stent, start with 4mm. There is high rate of subsequent anastomotic stricture in the setting of a bile leak. Repeat ERCP in 6-8 weeks at which time dilation and further stenting may be required for stricture management.

Anastomotic stricture

1. ERCP with sphincterotomy. Initial biliary dilation of 4 to 6mm, with placement of 1-2 plastic stents. Repeat ERCP in 3 months with goal of progressive biliary dilation and increase number or size of stents. Patient may require stenting for 6 to 12 months. Long term patency rates of 75-90%. There is limited experience with fully covered SEMS in this setting and should be reserved for refractory strictures.

Non Anastomotic strictures (NAS)

These strictures are generally more challenging because of multiple strictures, secondary stones, and biliary casts. Patient require more interventions. Strictures in the smaller secondary and tertiary bile ducts may not be amenable to endoscopic treatment. The goal should be restoring bile flow through the larger bile ducts. Long term patency rates are 50-70%.

1. ERCP with sphincterotomy. Dilation of intrahepatic NAS generally begins with a 4mm dilation. Larger bile ducts can be treated more aggressively, and stent placement should be done with the goal of progressive biliary dilation. Repeat ERCP in 2 months to prevent stent occlusion and secondary cholangitis from biliary sludge that may develop from untreated strictures. Consider management by Interventional GI service.

SOD

1. Suspected SOD should be treated by ERCP with sphincterotomy

Special considerations

1. Patients with Roux en Y biliary enteric anastomosis require balloon assisted ERCP and should be done by Interventional GI service.
2. Discussion with Transplant Surgery for surgical revision is appropriate for refractory strictures after 12 months of endoscopic therapy.

References:

1) Villa NA and Harrison ME. Management of Biliary Strictures after Liver Transplantation. *Gastroenterol* Hepatol (NY) 2015 11(5):316-28
2) Macias Gomez C. Endoscopic management of biliary complications after liver transplantation: An evidence based review. *World J Gastrointest Endosc* 2015 7(6):606-16

Recurrent Disease Management After Liver Transplantation

Background: Liver transplantation is curative for many forms of end-stage liver disease; however, the original etiology often can and does recur after liver transplantation. This is a brief overview of prevention and management of recurrent disease after liver transplant.

Alcohol

The risk of recidivism after liver transplant is not fully known but no doubt occurs in our patients and programs across the country. Ongoing assessment and evaluation in post-transplant clinic and identification of resources to maintain structured sobriety are encouraged.

Hepatitis B Recipient Protocol

Those with established HBV cirrhosis receiving transplant should undergo the following to prevent reinfection of the new liver:

- HBIG IV 10,000U in anhepatic phase then 10,000U daily x 5 days.
- Antiviral therapy:
    - Whatever nucleos(t) analog on prior to transplant should be resumed with attention to renal function (exception for Vemlidy/tenofovir alafenamide)
    - Patients on Truvada (emtricitabine/tenofovir disoproxi)l may be switched to Viread/tenofovir disoproxil and dose per renal function.
    - Labs (HBV DNA Quant) will be checked post-transplant and again prior to discharge
    - Hep Bs Ag, Hep Bs Ab, Hep Be Ag, Hep Be Ab, HBV DNA Quant will be check every 3 months x 1 yr then every 6 months with AFP.
        - Maintenance sAb level >500 1st yr; >100 year 2 to 5; >50 year 5-8; >25 year 8 or greater.

Hepatitis C

Hepatitis C likely re-infects the new allograft as soon as it is reperfused in the recipient who has active viremia at the time of transplant. Clinically, the ability of the virus to reestablish in the liver and generate inflammation (manifested by increased ALT and AST) may take 6-8 weeks. In general, patients should be offered therapy with direct acting antiviral against HCV as soon as hepatologist feels they can commence therapy.

Guidelines for DAA based therapy for HCV recurrence are consistently evolving and may be referenced at www.hcvguidelines.org.

Recent AASLD/IDSA recommended regimens are on the following pages; however, options are often limited by recipient insurance coverage:

Recommended Regimens for Treatment-naïve and -Experienced Patients with HCV Genotype 1 or 4 Infection in the Allograft, Including Those with Compensated Cirrhosis

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with weight-based ribavirin for 12 weeks is a Recommended regimen for patients with HCV genotype 1 or 4 infection in the allograft, including those with **compensated cirrhosis**.

Recommended Regimens for Treatment-naïve Patients with HCV Genotype 1 or 4 Infection in the Allograft and with Compensated Liver Disease, Who Are Ribavirin Ineligible

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 24 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 1 or 4 infection in the allograft and with compensated liver disease, who are ribavirin ineligible.

Recommended Regimen for Treatment-naïve and -Experienced Liver Transplant Recipients with Decompensated Cirrhosis (Child Turcotte Pugh [CTP] Class B or C) Who Have HCV Genotype 1 or 4 Infection in the Allograft

- Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated) for 12 weeks is a Recommended regimen for liver-transplant recipients with **decompensated cirrhosis (CTP class B or C)** who have HCV genotype 1 or 4 infection in the allograft.

Recommended Regimens for Treatment-naïve and -Experienced Patients with HCV Genotype 2 Infection in the Allograft, Including Those with Compensated Cirrhosis

- Daily daclatasvir (60 mg) plus sofosbuvir (400 mg), with low initial dose of ribavirin (600 mg, increased as tolerated) for 12 weeks is a Recommended regimen for patients with HCV genotype 2 infection in the allograft, including those with **compensated cirrhosis**.

- Daily sofosbuvir (400 mg) and weight-based ribavirin for 24 weeks is a Recommended regimen for patients with HCV genotype 2 infection in the allograft, including those with **compensated cirrhosis**.

Recommended Regimen for Treatment-naïve and -Experienced Patients with HCV Genotype 2 Infection in the Allograft, Including Those with Compensated Cirrhosis, Who Are Ribavirin Ineligible

- Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) for 24 weeks is a Recommended regimen for patients with HCV genotype 2 infection in the allograft, including those with with **compensated cirrhosis**, who are ribavirin ineligible.

Recommended Regimen for Treatment-naïve and -Experienced Liver-Transplant Recipients with <u>Decompensated Cirrhosis (Child Turcotte Pugh [CTP] Class B or C)</u> Who Have HCV Genotype 2 Infection in the Allograft

- Daily sofosbuvir (400 mg) and ribavirin (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated to weight-based dose) for 24 weeks is a Recommended regimen for liver-transplant recipients with **<u>decompensated cirrhosis (CTP class B or C)</u>** who have HCV genotype 2 infection in the allograft.

Recommended Regimen for Treatment-naïve and -Experienced Patients with HCV Genotype 3 Infection in the Allograft, Including Those with <u>Compensated Cirrhosis</u>

- Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increased as tolerated) for 12 weeks is a Recommended regimen for patients with HCV genotype 3 infection in the allograft, including those with **<u>compensated cirrhosis</u>**.

Recommended Regimen for Treatment-naïve and -Experienced Patients with HCV Genotype 3 Infection in the Allograft, Including Those with <u>Compensated Cirrhosis</u>, Who Are Ribavirin Ineligible

- Daily daclatasvir (60 mg) plus sofosbuvir (400 mg) for 24 weeks is a Recommended regimen for patients with HCV genotype 3 infection in the allograft, including those with **<u>compensated cirrhosis</u>**, who are ribavirin ineligible.

Primary Sclerosing Cholangitis

Recipients undergoing liver transplant for ESLD secondary to PBC often receive hepaticojejunostomy to remove native duct tissue. Recurrence can occur in native duct left behind after surgery.

- Possibility of recurrence should be entertained when elevations of ALP, GGT, or Tbil are noted. Screening test would be MRCP to evaluated hepaticjejunostomy and potentially followed by ERCP by interventional endoscopy.
- Recipients with concomitant inflammatory bowel disease (Crohn's Disease/Ulcerative Colitis) will need frequent colonoscopy, q1-2 years depending on characteristics—consult with hepatologist

Primary Biliary Cholangitis

Recipients undergoing transplant for PBC may experience recurrence of the disease as manifested by similar symptoms and elevations of ALP and Tbil. Diagnosis can be made with allograft biopsy and imaging to exclude extrahepatic ductal obstruction (usually MRCP). Treatment for PBC recurrence is weight based ursodiol.

Autoimmune hepatitis

Recipients undergoing transplant for AIH may experience recurrence as manifested by similar symptoms as prior to transplant an elevation of ALT/AST. Diagnosis is made by allograft biopsy. Treatment generally involves upward titration of immunosuppression regimen and or addition of prednisone

NASH

Recipients undergoing transplant for NASH may experience disease recurrence, often asymptomatic. Suspicion is raised by rapid weight gain and the development or uncontrolled conditions of the metabolic syndrome: diabetes mellitus, hypertension, and hyperlipidemia. Diagnosis is made by allograft biopsy. Treatment involves controlling elements of metabolic syndrome, diet, and weight loss.

Inherited Metabolic Disease

Liver transplant is considered curative of Hereditary Hemochromatosis, Alpha 1 antritrypsin deficiency, and Wilson's Disease. Iron loading can reoccur after liver transplant based upon molecular defect; however, rarely to the point where the allograft would be compromised.

References:

1) Pena Polanco NA, Levy C, Martin E. Cholestatic Liver Diseases After Liver Transplant. *Clin Liver Dis*. 2017 May;21(2):403-420
2) Kim H, Lee K, Lee KW et al. Histologically proven non-alcoholic fatty liver disease and clinically related factors in recipients after liver transplantation. *Clin Transplant*. 2014 May;28(5):521-9. doi: 10.1111*/ctr.12343*
3) *www.hcvguidelines.org*; Accessed June 2017
4) Watt KD. Keys to long-term care of the liver transplant recipient. *Nat Rev Gastroenterol Hepatol*. 2015 Nov;12(11):639-48.

HCC Surveillance after Liver Transplant

Among liver transplant recipients with HCC, approximately 5-10% experience tumor recurrence following transplantation with risk highest in the first 5 years. Routine surveillance of the allograft is necessary to identify and promptly treat any recurrence. Risk factors for recurrence include: lymphovascular invasion on explant, high AFP at HCC diagnosis prior to transplant (>400ng/dL); short wait times (<6months) and long wait times (>18 months).

Algorithm for Identification and Surveillance of Liver Allografts for HCC

1) **All liver transplant explant pathology will be reviewed by pathologist with standard synoptic microscopic description of:**
    a. Tumor number
    b. Differentiation; grade/stage when applicable
    c. Presence/absence of lymphovascular invasion
    d. Extrahepatic lymph node involvement
    e. Residual active tumor (if IR therapy used en route to transplant)

2) **Those transplanted with known HCC or with HCC identified on explant (incidental HCC) will enter one of 2 pathways for allograft surveillance**

    2a) Recipients with any ONE of the following: lymphovascular invasion, poorly differentiated HCC, wait time < 6months or >18 months, or AFP >400 at diagnosis will receive:

    TRIPHASIC ABDOMINAL CT AND NON CONTRAST CHEST CT at **6 month intervals** for the first 5 years post transplant

    2b) Recipients with none of the above will receive:

    TRIPHASIC ABDOMINAL CT AND NON CONTRAST CHEST CT at **1 year intervals** for the first 5 years post transplant

References:

1) Mehta N, Heimbach J, Lee D et. al. Wait Time of < 6 and > 18 Months Predicts Hepatocellular Carcinoma Recurrence after Liver Transplantation: Proposing a Wait Time "Sweet Spot". *Transplantation*. 2017 Mar 28. EPUB
2) Castroagudín JF, Molina-Pérez E, Ferreiro-Iglesias R, et. al. Late recurrence of hepatocellular carcinoma after liver transplantation: is an active surveillance for recurrence needed? *Transplant Proc* 2012 44(6):1565-7.
3) Yanik EL, Chinnakotla, S, Gustafson, MS et. al. Effects of maintenance immunosuppression with sirolimus after liver transplant for hepatocellular carcinoma. *Liver Transpl* 2016 22: 627–634.

Post Transplant Metabolic Syndrome

Background: Metabolic syndrome represents a constellation of findings: obesity, impaired fasting glucose, hypertension and hyperlipidemia—their development and association with cardiovascular disease significantly influences patient morbidity and mortality well beyond the perioperative period and dominate long-term outcomes. Metabolic syndrome is uncommon in patients before transplant (though this is changing with increased prevalence of nonalcoholic steatohepatitis [NASH] related cirrhosis), but increases dramatically after liver transplant, with 44% to 58% of patients affected.

Hypertension

Hypertension develops in 60% to 70% of patients after OLT. Increased prevalence is related to immunosuppressant medications, in particular calcineurin inhibitors (CNIs) by causing renal afferent vasoconstriction and chronic sympathetic over-activity; along with corticosteroids through mineralocorticoid effects. The effects of chronic kidney disease and denervation relating to surgery itself also contribute to development of hypertension.

The diagnosis of hypertension in OLT recipients is based on the recommendations of the Seventh Report of the Joint National Commission on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, for the general population.

Target blood pressure of lower than 140/90 mm Hg is appropriate for most patients without other major cardiovascular risks; target should be lower than 130/80 mm Hg in patients with diabetes, CKD, and/or a history of cardiovascular disease.

Lifestyle modifications including: weight loss, physical activity, and dietary sodium restriction, are advised for all patients.

Dihydropyridine calcium channel blockers (eg, amlodipine, nifedipine), which cause vasodilation of renal afferent arterioles, are preferred first-line agents. The usual starting dose of amlodipine is 2.5 to 5.0 mg daily, and of nifedipine is 30 to 60 mg daily. Common adverse effects: headache, flushing, palpitations, and peripheral edema.

Nondihydropyridine agents such as diltiazem or verapamil should generally be avoided as they increase the level of cyclosporine or tacrolimus.

After the early posttransplant period, angiotensin-converting enzyme inhibitors (ACEi's) and angiotensin receptor blockers (ARBs) have a nephroprotective effect (especially in diabetic patients with proteinuria), and may also have an antifibrotic effect in patients at high risk for post-OLT hepatic fibrosis. Lisinopril (starting dose 10 mg daily) and enalapril (starting dose 5 mg daily) are commonly used ACEi's. Adverse effects include: hypotension, cough, and rarely angioedema. In patients who develop cough due to ACEi's, losartan (starting dose 25 mg daily) and valsartan (starting dose 80 mg daily) are preferred ARBs. Close monitoring for hyperkalemia is recommended for both ACEi's and ARBs when used in association with either cyclosporine or prograf.

Beta –Blockers may be used as adjunctive treatment; however, carvedilol (coreg) can increase the level of CNIs by inhibiting the P-glycoprotein pathway. In addition, nonselective Beta-blockers may reduce splanchnic pressure affecting portal inflow, which should be avoided in the early post-transplant setting. Thiazide or loop diuretics must be used with close follow-up owing to the risk for hyperuricemia and the potential for electrolyte abnormality and renal dysfunction.

Antisympathetic antihypertensives such as clonidine and doxazosin may be used as second- or third-line agents for poorly controlled hypertension. Up to 30% of patients require 2 or more antihypertensives to achieve blood pressure goals.

Diabetes

The prevalence of type 2 diabetes mellitus increases from 15% before OLT to 30% to 40% after transplant. Almost 80% of new-onset diabetes after transplant (NODAT) cases develop within the first month posttransplant, 12% after the first year of follow-up. In the long term, 20% to 40% of OLT recipients remain diabetic.

Risk factors for post-OLT diabetes include pretransplant diabetes, obesity, hepatitis C infection, corticosteroids (by inducing insulin resistance, increasing gluconeogenesis, decreasing peripheral insulin utilization), CNIs (through pancreatic beta-cell toxicity and inducing insulin resistance, commonly thought tacrolimus more so than cyclosporine, but this is controversial), and mammalian target of rapamycin (mTOR) inhibitor use (by inducing insulin resistance, increasing gluconeogenesis, and decreasing peripheral insulin utilization).

Both pre- and post-OLT diabetes are risk factors associated with higher mortality and morbidity in OLT recipients. Post-OLT diabetes not only is associated with the usual microvascular and macrovascular complications but also has a significant impact on liver allograft survival, particularly in patients with hepatitis C. The 5-year likelihood of advanced fibrosis is increased in patients with diabetes when compared with patients who have normal insulin sensitivity. Post-OLT diabetes has also been associated with late-onset hepatic artery thrombosis, acute and chronic rejection, and development of recurrent or de novo NASH of the allograft.

Per International Consensus Guidelines for NODAT, weekly fasting plasma glucose screening is recommended for the first month after OLT, followed by screening at 3, 6, and 12 months and annually thereafter. Hemoglobin A1c may not be accurate in the early posttransplant period owing to anemia and high red blood cell turnover.

Management is similar to that for the general population. Lifestyle and dietary modifications should be recommended for all individuals.

Insulin is often required in the perioperative and postoperative period during high-dose corticosteroid use, but most recipients can gradually be transitioned to oral agents.

Most older,established oral hypoglycemic agents including: metformin, sulfonylureas, and thiazolidinediones, can be used safely in the OLT population. Thiazolidinediones may have the additional benefit of improved liver biochemistry and histology in patients with NASH. More data is needed. Newer agents such as the DPP4 inhibitor sitagliptin (Januvia) and the SGLT-2 inhibitor canaglifozin (Invokana) require more data in the post LT setting but we are seeing increased use.

Dyslipidemia

Dyslipidemia is unusual in patients with cirrhosis, which usually results in marked decline in cholesterol levels due to impaired hepatic synthesis. After OLT, 45% to 69% of patients develop dyslipidemia, which is a risk factor for cardiovascular morbidity and mortality over the long-term.

Cyclosporine increases low-density lipoprotein and total cholesterol more than does tacrolimus. Sirolimus and everolimus are strongly associated with dyslipidemia, even more so than cyclosporine, because it affects the insulin signaling pathway by increasing adipose tissue lipase activity and decreasing lipoprotein lipase.

Based on this increased risk of dyslipidemia, monitoring of fasting lipid panel at 4 to 6 months after transplant and annually thereafter is recommended. Liver transplant is considered a coronary heart disease risk equivalent and is considered high risk based on the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.

Therapeutic lifestyle measures are recommended for all patients, although dietary modification alone is often inadequate, making pharmacotherapy necessary.

3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are first-line therapy for elevated cholesterol and triglyceride levels and are safe, well tolerated, and effective in LT recipients. Calcineurin inhibitors as well as statins are metabolized by the CYP3A4 pathway, leading to a potentially increased risk of statin-related myopathy or toxicity; thus, careful clinical and laboratory follow-up is required on initiation.

Pravastatin and fluvastatin are not metabolized by the CYP3A4 metabolic pathway and thus are preferred. Statin medications should be initiated at low doses and gradually titrated to desired management goals as tolerated. For example, pravastatin, 10 to 20 mg daily, or atorvastatin, 20 to 40 mg daily, can be initiated.

Fibric acid derivatives (eg, fenofibrate, gemfibrozil) are generally well tolerated but when used in combination with statins are associated with an increased risk of myotoxicity.

Hypertriglyceridemia, with normal cholesterol levels, is frequently noted in LT patients. Omega-3 fatty acids (fish oil), at a starting dose of 1000 mg twice daily and gradually titrated to a 4000-mg daily dose, may be used for managing isolated hypertriglyceridemia. Fish oil may have other benefits, such as anti-inflammatory and/or antiproliferative properties and might improve hepatic steatosis. Fish oil may increase the low-density lipoprotein level, so a follow-up lipid panel should be performed.

Post Transplant Metabolic Syndrome Summary and Protocol Recommendations

1. **Hypertension**
    a. **Target blood pressure <140/90 [<130/80 in those with preexisting DM, renal disease of CAD] on 2 successive post-transplant clinic visits**
        i. Nutrition Consult for enforcement of therapeutic lifestyle measures
        ii. Review current immunosuppression regimen identifying targets for reduction
        iii. Identification of primary care physician [or referral to internal medicine clinic] for consideration of pharmacotherapy
            1. Preferred agents
                a. Amlodipine (Norvasc) 5mg PO daily
                b. ACE-inhibitor or angiotensin receptor blocker

2. **Diabetes**
    a. **Weekly Fasting Glucose the 1st month after OLT; followed by fasting plasma glucose at 3, 6, 9 and 1 year; annually thereafter**
    b. **Any above FPG>100 should be confirmed as fasting and repeated the following week, if again above 100:**
        i. Nutrition Consult for discussion of therapeutic lifestyle measures
        ii. Review current immunosuppression regimen identifying targets for reduction
        iii. Identification of primary care physician [or referral to internal medicine clinic or endocrine clinic] for consideration of pharmacotherapy
            1. Preferred agents
                a. **Long-term treatment of DM is not anticipated in the post-transplant clinic. With the safety of multiple agents established primary care/endocrine partners should be empowered to manage**.

3. **Hyperlipidemia**
    a. **Fasting lipid profile will be checked and documented at 6 months post transplant and then yearly at anniversary visits**
    b. **Hyperlipidemia e.g. LDL >130 with no risk factors; >100 with risk factors [DM, htn, NAFLD], or >70 with established preexisting heart disease**
        i. Nutrition Consult for discussion of therapeutic lifestyle measures
        ii. Review current immunosuppression regimen identifying targets for reduction
        iii. Identification of primary care physician [or referral to internal medicine clinic or cardiologist] for consideration of pharmacotherapy
            1. Preferred Agents
                a. Statins: Ideally pravastatin, fluvastatin begun at low levels and titrated to goal
                b. Fish oil for isolated increase in triglycerides

References:

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3) Heller JC, Prochazka AV, Everson GT et. al. Long-term management after liver transplantation: primary care physician versus hepatologist. Liver Transpl. 2009 15(10): 1330-1335.

Health Maintenance after Liver Transplantation

Malignancy Screening in Transplant Recipients

The incidence of malignancy is increased in liver transplant recipients. Both skin cancer and non-skin malignancies are more common in liver transplant recipients than in the general population, with skin cancers being the most common malignancies seen. The probability of developing any non-skin malignancy varies according to underlying etiology of liver disease: highest in patients with primary sclerosing cholangitis (22 percent at 10 years) and alcohol-related liver disease (18 percent at 10 years), and about 10 percent for all other liver disease/indications for transplant.

SUGGESTED HEALTH MAINTENANCE ITEMS FOR ANNUAL REVIEW

- Physical and full body dermatologic examination.
- Dental examination.
- Mammography in women: Per general guidelines
- Annual Pap smear
- Prostate-specific antigen (PSA) in men: Per general guidelines
- Recommendations for Smoking cessation, high sun protection factor (SPF) sunblock.
- In current or ex-smokers can consider: Annual CT chest/CXR. Can consider evaluation by ENT surgeon for oro-pharyngeal cancers. No surveillance recommended for non-smokers
- Colonoscopy
    - Hx of PSC: Colonoscopy at 1 year and every 5 years
    - IBD: Annual colonoscopy
    - No h/o PSC +/- IBD: Routine surveillance per American Gastroenterological Association guidelines

Immunization in Liver Transplant Recipients

All inactivated vaccines should be given 3-6 months post-transplant if not previously vaccinated. Live viruses should be avoided and ideally, the best time to give live virus immuniziations is PRIOR to transplant

- **Hepatitis A**:
  - Hepatitis A vaccine is indicated for all pediatric solid organ transplant candidates and recipients ≥12 months of age and is particularly important for liver transplant candidates and recipients.
  - Monitoring titers is indicated only for individuals with an ongoing risk of exposure, such as planned travel to a high-risk area.
  - Solid organ transplant candidates in whom both the hepatitis A and B vaccines are indicated can receive the combined hepatitis A–hepatitis B vaccine

- **Hepatitis B:**
  - Anti-hepatitis B surface antigen (anti-HBs)-negative solid organ transplant candidates should receive the hepatitis B vaccine series
  - Those receiving hemodialysis who are ≥20 years of age should receive the high-dose (40 mcg) vaccine series
  - If a titer ≥10 milli-international units/mL is not attained following vaccination, a second three-dose series should be given. An alternative to this is to give only one additional dose of the vaccine and then recheck anti-HBs titers.
  - Solid organ transplant candidates in whom both the hepatitis A and B vaccines are indicated can receive the combined hepatitis A–hepatitis B vaccine

- **Influenza:**
  - Centers for Medicare and Medicaid Services have recommended that all patients, including transplant recipients, be immunized prior to discharge from the hospital. Revaccination of such patients three to six months following transplantation can be considered if there is still influenza activity. The intranasal live attenuated influenza vaccine (LAIV) is contraindicated in transplant recipients
  - Routine seasonal administration of an inactivated influenza vaccine is recommended for all transplant recipients every year, including during the first year after transplantation.

- **Tdap:**
  - Following transplantation, Tdap should be administered to adults who have not previously received it. Adacel or Boostrix are available for vaccination.
  - In adults aged 65 years and older, Boostrix should be used when possible.
  - Adacel has only been approved for individuals between the ages of 11 and 64 years.

- **Pneumococcus:**
  - For patients who have not previously received either PCV13 or PPSV23, a single dose of
  - PCV13 should be given, followed by a dose of PPSV23 at least eight weeks later
  - For patients who have previously received one or more doses of PPSV23, a single dose of PCV13 should be given one or more years after the last PPSV23 dose was received.
  - For patients who require additional doses of PPSV23, the first such dose should be given no sooner than eight weeks after PCV13 and at least five years after the most recent dose of PPSV23

- **Meningococcus:**
  - Meningococcal conjugate vaccine for all solid organ transplant candidates and recipients who have an indication, especially with Splenectomy.
  - Use Meningococcal conjugate vaccine (rather than the meningococcal polysaccharide vaccine) even in solid organ transplant candidates and recipients over 55 years of age.
  - Available formulations in the United States include Menactra and Menveo

- **Varicella:**
  - Varicella vaccine post-Transplant in contraindicated
  - Postexposure prophylaxis is indicated, VariZIG should be offered as soon as possible, but it may be given for up to 10 days following exposure. For high-risk patients who have additional exposures to varicella-zoster virus ≥3 weeks after initial VariZIG administration, another dose of VariZIG should be considered.
  - Patients who were unable to receive immunoprophylaxis within 10 days following exposure. Either oral acyclovir or valacyclovir can be used for postexposure prophylaxis, valacyclovir (1 g orally three times daily) is preferred given its superior bioavailability.
  - Admission for IV Acyclovir if the patient has signs of infection

- **Zoster:**
  - Zoster vaccine is contraindicated in Transplant recipients

- **Haemophilus influenzae**:
  - NO recommendations for routine vaccination
  - Should be considered if the patient underwent Splenectomy

- **Poliovirus**:
  - Adults in the developed world do not need routine polio immunization.
  - The small number of transplant candidates and recipients at risk of exposure to polio (by travel or work) should receive a primary series of the inactivated poliovirus vaccine (IPV) if there is no documentation of vaccination status. Only

one lifetime booster with IPV is recommended for vaccinated adults at continued risk of exposure

References:

1) Kim Y and Kim S. Vaccination strategies in patients with solid organ transplant:evidences and future perspectives. *Clin Exp Vaccine Res*. 2016 5(2):125-31
2) Miyairi I, Funaki T, Saitoh A. Immunization practices in solid organ transplant recipients.*Vaccine* 2016 34(16):1958-64.

End Stage Liver Disease and Associated Complications Introduction

The development of cirrhosis, the final common result of diverse insults to the liver, significantly affects both quality and quantity of life for patients referred to the liver disease center. In general terms, the development of cirrhosis has consequences in 2 major areas: 1) Hepatic function and 2) Development of portal hypertension.

Components of hepatic function are largely reflected in lab tests and partially addressed by the MELD (Model for End Stage Liver Disease) score. The two blood tests that best characterize a patient's *liver function* are the serum albumin and the prothrombin time/international normalized ratio (PT/INR). Albumin, the major oncotic protein circulating in blood, is synthesized by the liver; and with advancing stages of liver disease the serum albumin lowers. The liver is also the site of synthesis/processing of clotting factors and with advancing liver disease, production is altered and PT/INR generally rises. While albumin is included in older scoring systems (Child's Class) it is not incorporated into the MELD score; however, severe hypoalbuminemia has been correlated with poor outcomes in liver transplant recipients. Another component of the MELD score is the serum bilirubin, which reflects the liver's ability to synthesize, process, and excrete bile. Serum bilirubin will rise in advanced liver disease; however, it is important to rule out extrahepatic obstruction (bile duct blockage) when this occurs. The serum bilirubin is incorporated into the MELD score—though it's "weight" in the calculation is not as high as other components. Another component of the MELD score is the serum creatinine which is reflective of kidney function. Kidney function is highly variable in patients with end-stage liver disease and cirrhosis. The final component of the MELD score is the serum sodium, generally included when native (older system) MELD score is greater than 11. Serum sodium (see below) is a surrogate for degree of illness in many chronic disease states including end stage liver disease and congestive heart failure.

Independent of deficits in liver function, **patients with cirrhosis also struggle with the development of portal hypertension**. As healthy liver is replaced by scar tissue, a number of changes occur: the once smooth vascular channels of the liver are distorted and do not allow for low resistance passage of blood from the lower extremities back to the heart (as it would in healthy livers). In addition, certain chemicals (key player is nitric oxide) decrease in the liver which in turn increases resistance to flow in the liver. Nitric oxide increases outside the liver in the veins (portal, SMV etc.) leading to it which compounds the problem. As a consequence of these changes, blood flow to the kidney is compromised and a patient's body feels as though it is constantly "underfilled" or dehydrated. In an effort to maintain blood volume, hormones in the body are elaborated that promote reabsorption of sodium; this leads to volume overload (water follows the absorption of salt in the body).

The consequences of portal hypertension are multiple and often dominate quality of life discussion during clinic visits. This includes the development and management of ascites, bleeding from and surveillance of varices; and identification/treatment of hepatic encephalopathy. When one of the aforementioned occurs (complication of portal

hypertension) the hepatologist may refer to this as a “decompensating event” or the beginning of decompensation.

It is important to understand that patients referred to the advanced liver disease clinic may have very little insight into their disease process and what we offer for management. Unfortunately, use of MELD by non-transplant physicians is commonplace given its widespread availability for calculation on both the internet and phone apps. Indeed, calculated MELD scores have been correlated and validated to predict survival at 3 months; however, remember these numbers reflect *chances without specialized advanced liver disease care or possibility of liver transplantation*.

Elements of the Initial Hepatology Consult in a Patient Referred for Liver Transplant

1)History and physical examination; often liver focused, identifying potential etiologies for the development of liver disease

2) General social history with attention to the use of alcohol or illicit substance, last usage, criminal record, engagement in structured sobriety; identification of care givers should transplant be necessary

3) Basic introduction to the MELD score as global assessment of hepatic function and its role in organ prioritization

4) Review/screen for complications of portal hypertension

- a) History of GI bleeding/screening for varices
- b) History of ascites, diuretic usage, need for paracentesis
- c) Screening for hepatic encephalopathy and treatment regimen

5) Review and discussion of enrollment in hepatocellular cancer screening

- a) Review of previous liver imaging

6) General discussion of/screening for necessary lifestyle modifications

- a) Discussion of low salt diet intake/education on nutrition labeling
- b) Review of need for structured sobriety/counseling in those with alcohol and illicit drug use
- c) Review of ability to drive automobile or operate heavy machinery in those with hepatic encephalopathy

General Guidelines for Hepatology Management Prior to or En Route to Liver Transplant Evaluation

- **Chronic Liver Disease Workup**

    - Hep A Ab total, Hep B sAg, Hep B sAb, Hep B cAb Total,HCV Ab, ANA, Anti-Smooth muscle, Anti-Mitochondrial Ab, ceruloplasmin, A1AT level, Serum Ferritin
        - Patients with reactive Hep B sAb AND Hep B cAb reactive likely represent a scenario where someone has come into contact with hepatitis B and has generated immunity. This is in contrast to patients who have simply been immunized to hepatitis B (these patients only have reactive Hep sAb and NOT Hep B cAb reactive)
            - Full Hep B serolgies including eAg, eAb, and HBV DNA should be checked in instance of suspected natural immunization
        - All cirrhotics who do not have reactive Hep A Ab nor Hep B sAb should be immunized to both HAV and HBV by primary care physician office or instructed to obtain at Banner family pharmacy

- **Architectural Assessment**
    - Ultrasound or cross sectional imaging (triphasic CT scan or MRI with eovist) confirming architectural changes consistent with cirrhosis, screen for focal hepatic lesions, and suitability for inflow/outflow (patency/size of portal vein)

- **Variceal Screening**
    - Upper endoscopic screen/surveillance for esophageal varices
    - Upper endoscopy is always deferred to referring gastroenterologist if patient is being seen by one; however, if patient is not being seen they should be referred to Drs. Patel, Ramos, Mehta, Fallon, or Seetharam

- **Ascites Management**
    - Low salt diet education, diuretic usage, spontaneous bacterial peritonitis (SBP) prophylaxis, paracentesis schedule, review of suitability/need for TIPS

- **Encephalopathy Management**
    - Lactulose usage, rifaximin prior authorization

The remainder of this handbook addresses specific complications of end stage liver disease and their management. In addition, specific components of the transplant evaluation are addressed and their performance may occur prior to formal candidate evaluation or as part that process.

Ascites

Background: Ascites is the most common complication in patients with cirrhosis, and approximately 60% of patients with cirrhosis will develop ascites within 10 years after initial diagnosis. Ascites is also the most common complication of cirrhosis leading to hospital admission. Ascites may become refractory over time as portal hypertension worsens, which significantly shortens survival.

Refractory ascites occurs in 5% to 10% of cirrhotic ascites patients and portends a poor prognosis. The definition of refractory ascites is (1) lack of response to high-dose diuretics (400mg of spironolactone and 160mg of furosemide/day) while remaining compliant with a low-sodium diet or (2) frequent ascites recurrence shortly after therapeutic paracentesis. Patients with recurrent side effects from diuretic therapy, including symptomatic hyponatremia, renal insufficiency, or hepatic encephalopathy, are also considered to have refractory ascites.

Spontaneous bacterial peritonitis (SBP) is a common and frequently fatal bacterial infection of ascites that occurs in 10-30% of patients. Ascitic fluid should be tested for SBP on every paracentesis. SBP may present with NO symptoms and does not necessarily cause abdominal pain.This guideline will cover evidence based and practical approaches uncomplicated ascites, refractory ascites, and SBP.

- **Management of uncomplicated ascites**

1. Diagnostic abdominal paracentesis should be performed and ascitic fluid should be obtained in patients with clinically apparent new-onset ascites.
2. Initial ascitic fluid should be sent for cell count, differential, albumin, protein, and culture.
3. First line treatment is dietary sodium restriction to 2000 mg daily, and oral diuretics.
4. The usual diuretic regimen consists of spironolactone beginning at 100mg daily, and furosemide beginning at 40mg daily.
5. Diuretic dose can be increased every 3 to 5 days to a maximum dose of spironolactone 400mg daily and furosemide 160mg daily.
6. There is no limit to daily weight loss in patients with significant edema. Once edema has resolved, 0.5 kg, is a reasonable daily goal for weight loss.
7. Kidney function and potassium should be monitored while patients are on diuretics.
8. NSAIDs, ACE inhibitors, and ARB medications should be discontinued due to risk of acute kidney injury.
9. Uncontrolled or recurrent encephalopathy, serum sodium less than 120 mmol/L despite fluid restriction, or serum creatinine greater than 2.0 mg/dL should lead to cessation of diuretics.

- **Management of refractory ascites**

1. Dietary sodium restriction, 2000mg daily.
2. If intolerant to diuretics because of side effects, then diuretics should be stopped.
3. Serial paracentesis with goal to minimize frequency of procedures to every 2 weeks.
4. Albumin replacement for removal of > 5L ascites. Replacement protocols generally call for 6-8 g/L removed. Ascitic fluid tested on each paracentesis for SBP.
5. Consideration of discontinuation of beta blocker.
6. Consideration of initiation of midodrine 7.5 to 10 mg PO TID to increase mean arterial pressure, urine volume, serum sodium, and possibly survival. May convert patient from diuretic resistant back to diuretics sensitive.
7. Consideration for TIPS and liver transplantation evaluation

- **Spontaneous Bacterial Peritonitis**

1. Diagnosis - Polymorphonuclear (PMN) count, which is the result of multiplying the total ascitic fluid white blood cell count by the neutrophil count > 250. The ascitic fluid culture does not need to be positive.
2. Patients with SBP should be hospitalized to receive IV antibiotics and IV albumin.
3. The mainstay for secondary prevention of SBP is antibiotic therapy. Patients should receive either Ciprofloxacin 500mg PO daily, Bactrim DS PO daily, or Norfloxacin 400mg PO daily
4. Other considerations including discontinuation of PPI, correction of Vit D deficiency, and discontinuation of beta blocker based on risk/benefit ratio.

References

1) Runyon B. Management of the patient with ascites due to cirrhosis. AASLD Practice Guideline. 2012.
2) Dever JB and Sheikh MY. Review article: spontaneous bacterial peritonitis – bacteriology, diagnosis, treatment, risk factors and prevention. *Aliment Pharmacol Ther*. 2015 41(11):1116-3
3) Sola et al. Management of uninfected and infected ascites in cirrhosis. *Liver Int*. 2016. Liver Int. 2016 Jan;36 Suppl 1:109-15

Esophageal Varices in Cirrhosis, treatment and need for and frequency of Upper Endoscopy (EGD)

Background: Development of esophageal and gastric varices is common in the natural history of cirrhosis. Variceal bleeding is a lethal consequence of portal hypertension and missed opportunities for screening and surveillance lead to significant morbidity and mortality in waitlisted patients. Upper endoscopy is generally a 5-10 minute procedure performed while the patient is under conscious sedation (midazolam and fentanyl) or monitored anesthesia care (propofol). Upper endoscopic surveillance (last EGD, timing of next, need for pharmacologic prophylaxis) will be addressed in most hepatology notes. Variceal screening/surveillance should be deferred to referring gastroenterologists but can be easily performed by all GI trained hepatologists in the program if needed. The following is an adaptation of AASLD guidelines for screening/surveillance intervals for varices:

SUGGESTED VARICEAL SCREENING/SURVEILLANCE INTERVALS

I) Patients with compensated cirrhosis without varices on screening EGD:

- Patients with compensated cirrhosis (CC) **without varices** on screening endoscopy should have endoscopy repeated **every 2 years** (with ongoing liver injury or associated conditions, such as obesity and alcohol use) or **every 3 years** (if liver injury is quiescent, e.g., after viral elimination, alcohol abstinence).

II) Patients with compensated cirrhosis and small varices on screening EGD:

- Patients with CC with **small varices** on screening endoscopy should have endoscopy repeated **every year** (with ongoing liver injury) or **every 2 years** (if liver injury is quiescent, e.g., after viral elimination, alcohol abstinence).

III) Patients with compensated cirrhosis w/o varices or with small varices who decompensate:

- Patients with CC without varices or with small varices who develop decompensation should have a repeat endoscopy when this occurs.
- Drugs that act on portal flow, such as NSBBs, will be mostly ineffective in this stage, given that the hyperdynamic circulatory state is not fully developed.
- There is no evidence at present to recommend the use of NSBBs in preventing formation of varices.

IV) Patients with cirrhosis and medium or large size varices on EGD and who never bled:

- Either traditional NSBBs (propranolol, nadolol), carvedilol, or EVL is recommended for the prevention of first VH (primary prophylaxis) in patients with medium or large varices (Table3 for doses and schedules). Choice of treatment should be based on patient preference and characteristics. **Patients on NSBBs or carvedilol for primary prophylaxis do not require monitoring with serial EGD**. Combination therapy NSBB plus EVL is not recommended for primary bleed prophylaxis TIPS placement is not recommended in the prevention of first VH.

TABLE 3. Management of Patients With Moderate/Large Varices That Have Not Bled

Therapy	Recommended Dose	Therapy Goals	Maintenance/Follow-up
Propranolol	• 20-40 mg orally *twice* a day • Adjust every 2-3 days until treatment goal is achieved • Maximal daily dose: ○ 320 mg/day in patients without ascites ○ 160 mg/day in patients with ascites	• Resting heart rate of 55-60 beats per minute • Systolic blood pressure should not decrease <90 mm Hg	• At every outpatient visit make sure that heart rate is on target • Continue indefinitely • No need for follow-up EGD
Nadolol	• 20-40 mg orally *once* a day • Adjust every 2-3 days until treatment goal is achieved • Maximal daily dose: ○ 160 mg/day in patients without ascites ○ 80 mg/day in patients with ascites	• Resting heart rate of 55-60 beats per minute • Systolic blood pressure should not decrease <90 mm Hg	• At every outpatient visit make sure that heart rate is on target • Continue indefinitely • No need for follow-up EGD
Carvedilol	• Start with 6.25 mg *once* a day • After 3 days increase to 6.5 mg twice-daily • Maximal dose: 12.5 mg/day (except in patients with persistent arterial hypertension)	• Systolic arterial blood pressure should not decrease <90 mm Hg	• Continue indefinitely • No need for follow-up EGD
EVL	• Every 2-8 weeks until the eradication of varices	• Variceal eradication (no further ligation possible)	• First EGD performed 3-6 months after eradication and every 6-12 months thereafter

Any of these four therapies can be used, but current data do not support the use of combination therapy.

V) Patients with cirrhosis and esophageal varices who have recovered from first bleeding episode:

- Combination of NSBB+EVL is first-line therapy in the prevention of rebleeding (Table 5 for recommended doses and schedules).
- Patients who have a TIPS placed successfully during the acute episode do not require NSBBs or EVL.
- TIPS is the recommended rescue therapy in patients who experience recurrent hemorrhage despite combination therapy NSBB+EVL.

TABLE 5. Treatments for the Prevention of Recurrent Esophageal Variceal Hemorrhage

Therapy	Recommended Dose	Therapy Goals	Maintenance/Follow-up
Propranolol	• 20-40 mg orally *twice* a day • Adjust every 2-3 days until treatment goal is achieved • Maximal daily dose: ○ 320 mg/day in patients without ascites ○ 160 mg/day in patients with ascites	• Resting heart rate of 55-60 beats per minute • Systolic blood pressure should not decrease <90 mm Hg	• At every outpatient visit make sure that heart rate is on target • Continue indefinitely
Nadolol	• 20-40 mg orally *once* a day • Adjust every 2-3 days until treatment goal is achieved • Maximal daily dose: ○ 160 mg/day in patients without ascites ○ 80 mg/day in patients with ascites	• Resting heart rate of 55-60 beats per minute • Systolic blood pressure should not decrease <90 mm Hg	• At every outpatient visit make sure that heart rate is on target • Continue indefinitely
EVL	• Every 1-4 weeks until the eradication of varices	• Variceal eradication (no further ligation possible)	• First EGD performed 3-6 months after eradication and every 6-12 months thereafter

The combination of either propranolol or nadolol *plus* EVL is recommended. Carvedilol is not recommended in this setting.

VI) Patients with cirrhosis and gastric varices who never bled:

- For prevention of first VH from GOV2 or IGV1, NSBBs can be used, although the data are not as strong as for EV.
- Prevention of first bleeding from GOV1 varices may follow the recommendations for EV.
- Neither TIPS nor BRTO are recommended to prevent first hemorrhage in patients with fundal varices that have not bled.

Reference:

1) AASLD Gudielines on Variceal Bleeding www.aasld.org; accessed June 2017

Hepatic Encephalopathy

Background: Hepatic encephalopathy (HE) is a spectrum of neurocognitive manifestations often seen in patients with liver injury or rarely in patients with portosystemic shunting without liver injury. It can be divided into minimal (covert) hepatic encephalopathy and overt hepatic encephalopathy, depending on severity.

Patients with hepatic encephalopathy have compromised clinical outcomes, decreased quality of life, and increased healthcare utilization, often resulting in a heavy financial and personal burden on caregivers. The diagnosis remains largely clinical, with the exclusion of possible other causes for the altered mental status.

The pathogenesis of HE is likely multifactorial and complex. Ammonia and dysregulation of the urea cycle is often implicated in the pathogenesis of HE. Nitrogenous compounds excreted by gut bacteria are transported to the liver via the portal circulation where it, along with endogenous nitrogen, enter the urea cycle. The end process is the generation of urea which is subsequently excreted through urine. In advanced liver disease, damaged hepatocytes and the development of portosystemic shunts results in ammonia bypassing the liver and accumulating in the systemic circulation. Ammonia then crosses the blood-brain battier and is metabolized by astrocytes to synthesize glutamine from glutamate via glutamine synthetase. Glutamine increases the osmotic pressure within the astrocyte resulting in morphologic malformations similar to those seen in Alzheimer's disease.

Hepatic Encephalopathy Protocol

1. **Identifying Hepatic Encephalopathy**
    a. Assess orientation to person, place and time.
    b. Inquire about previous circumstances/interactions
    c. Seek family/caregiver assessment and impression of behavior

2. **Identify Potential Precipitant**
    a. Assess recent labs for change renal function, MELD
    b. Evaluate for history of infection
    c. Review if any luminal GI tract bleed history or symptoms
    d. Review last imaging with respect to portal vein and HCC
    e. Inquire re: recent TIPS
    f. Inquire about HE management adherence

3. **Treatment Recommendations**
    a. Lactulose titrated to 3-5 soft BMs
    b. One hospital admission, without precipitant from 2, should prompt prior authorization for xifaxin 550mg PO BID

4. **Prevention Strategies and Management Points**
    a. **Venous blood ammonia levels are NOT reflective of the degree of mental status** impairment nor are serial levels predictive of overt episodes; they should not be ordered by program

b. **Dietary protein DOES NOT reliably make HE worse**. In fact, maintaining adequate protein intake is essential in preventing muscle wasting
    i. Optimal daily energy intake should be 35 to 40kcal/kg of ideal body weight with daily protein intake of 1.2 to 1.5 g/kg ideal body weight and fiber intake of 25 to 45 g daily. Meals should be small and evenly distributed during the day with a late night snack of complex carbohydrates to minimize protein utilization overnight.
c. In general, those with a documented diagnosis of hepatic encephalopathy should not be operating a motor vehicle or employed in an occupation involving utilization of heavy machinery
d. Hospital admissions: If encountering a patient/family member where overt HE is a concern, advise for immediate administration of lactulose if PO intake is feasible. If not, advise for/activate emergency services. Patients should be instructed to obtain care at the closest emergency room setting. Transfer to BUMCP if warranted can be arranged once stabilized.

References:

1) 1)Suraweera D, Sundaram V, Saab S. Evaluation and Management of Hepatic Encephalopathy: Current Status and Future Directions. *Gut and Liver*, 2016, 10:4 509-519
2) Stepanova M, Mishra A, Venkatesan C, Younossi ZM. In-hospital mortality and economic burden associated with hepatic encephalopathy in the United States from 2005 to 2009. *Clin Gastroenterol Hepatol* 2012;10:1034-1041
3) Bajaj JS. Review article: the modern management of hepatic encephalopathy. *Aliment Pharmacol Ther* 2010 31:537-547.

HCC Screening in the Cirrhotic Patient/Screening Protocol in Waitlist Active Patients

Background: The presence of cirrhosis represents a key risk factor for the development of HCC. The prevalence of cirrhosis among patients with HCC has been estimated to be 85%-95% and HCC incidence rate among patients with cirrhosis has estimated at 2%-4% per year As such, patients with cirrhosis constitute a high-risk group for efforts at prevention and early detection. The fact that patients with HCC have underlying liver disease significantly impacts the management and therapeutic options.

In patients with cirrhosis and suspected HCC, diagnostic imaging is used to noninvasively verify the presence of HCC (diagnosis) and determine its extent (radiological staging). The goals are to: measure tumor burden, guide management, and help prioritize patients for liver transplantation.

Unlike most other malignancies, the diagnosis of HCC can be established noninvasively, and treatment may be initiated based on imaging alone, without confirmatory biopsy. The rationale is that in patients with cirrhosis, the pretest probability of HCC is sufficiently high, and pretest probability of lesions that may mimic HCC at imaging is sufficiently low such that a lesion meeting HCC imaging criteria (LIRADs) can be assumed reliably and confidently to be HCC.

Although there is strong consensus that the imaging diagnosis of HCC requires multiphasic imaging, there is not agreement about which diagnostic imaging test to use. Commonly used methods in clinical practice include multiphasic CT with extracellular agents, multiphasic MRI with extracellular agents (gadolinium-based compounds that stay in the extracellular space and permit characterization of blood flow), and multiphasic MRI with gadoxetate disodium (a specific gadolinium-based compound that accumulates in hepatocytes and permits characterization of hepatocellular “function” in addition to blood flow).

Candidacy for transplant is determined by either **Milan/T2 criteria** [one lesion smaller than 5 cm; up to 3 lesions smaller than 3 cm; and no extrahepatic disease] or **UCSF criteria** [ingle tumor ≤6.5cm or up to three tumors, the largest ≤4.5 cm and total tumor diameter ≤8 cm without gross vascular invasion]. It is important to rememeber that Milan/T2 has lower limits as well; and patients will not qualify for exception if a solitary lesion is treated before its size was demonstrated to be 2cm or greater. In addition, recent changes by UNOS call for tumor patients to be listed and remain at their native (biologic or blood) MELD score for a period of 6 months prior to obtaining MELD exception points.

PROTOCOL FOR HCC SCREENING/SURVEILLANCE IN NON TRASPLANTED PATIENTS

1. HCC screening in cirrhotic patient **without known HCC** undergoing evaluation or waitlist active
    a. Ultrasound +/- AFP q 6 months
    b. Consider alternating in cross-sectional imaging (CT or MRI) at 6 month intervals

2. HCC surveillance in cirrhotic patient **WITH known HCC** undergoing evaluation or waitlist active and **undergoing locoregional downstaging/bridging therapy**
    a. Multiphasic CT or MRI performed 4-6 weeks after IR session
        i. If no residual, anticipate repeat in imaging in 3 months
        ii. If residual
            1. Presentation in multidisciplinary conference to determine course of action
    b. Non Contrast CT of the CHEST q 6 months
    c. Annual bone scan
    d. AFP measurement IR treatment, imaging follow up, and with surveillance imaging

- Ordered imaging must meet minimum technical and imaging protocol requirements per UNOS guidelines and interpreted by a radiologist at a Transplant Center with AFP

References:

1) Kulik LM, Chokechanachaisakul A. Evaluation and management of hepatocellular carcinoma. *Clin Liver Dis*. 2015 19(1):23-43
2) Bruix J, Reig M, Sherman M. Evidence-Based Diagnosis, Staging, and Treatment of Patients With Hepatocellular Carcinoma. *Gastroenterology*. 2016 150(4):835-53.
3) Dulku G, Dhillon R, Goodwin M et. al. The role of imaging in the surveillance and diagnosis of hepatocellular cancer. *J Med Imaging Radiat Oncol*. 2017 61(2):171-179.

Cardiovascular Evaluation

Background: The goal of cardiac evaluation pre transplant is to assess perioperative risk and exclude concomitant cardiac disorders that would preclude good long-term outcome. Although the typical hemodynamic state of cirrhosis results in a low prevalence of systemic hypertension and impaired hepatic production of lipids may reduce serum cholesterol levels, coronary artery disease (CAD) is at least as frequent in LT candidates as in the general population and is influenced by typical cardiovascular risk factors.

Noninvasive testing with echocardiography/bubble study is indicated for all adult LT candidates to assess systolic function (ejection fraction), screen for the presence of patent foramen ovale, assess for valvular disorders and estimate pulmonary arterial systolic pressure (PASP). Aortic valve replacement has been performed simultaneously with LT; however, current medical therapy may sufficiently improve ventricular function to permit safe LT. Unsuspected pulmonary hypertension as discussed subsequently may be initially detected by echocardiography during the LT evaluation (see pulmonary workup section).

Patients with advanced liver disease may be unable to achieve the target heart rate during a standard exercise test. Patients should undergo pharmacological stress with adenosine (or acceptable stress agent) combined with nuclear imaging for assessment of at risk myocardium.

Abnormal non-invasive testing or patient risk factors may prompt consideration of cardiac catheteriziation. Cardiac catheterization in a patient with cirrhosis is more likely to result in vascular complications such as bleeding compared to controls without liver disease. In addition, many decompensated patients with cirrhosis have tenuous renal function, increasing the risk of contrast-induced nephropathy. If significant coronary artery stenosis (>70% stenosis) is detected, revascularization may be attempted prior to LT, although rigorous proof of benefit in asymptomatic recipients is lacking. Bare metal stents are favored to avoid the need for dual antiplatelet therapy (clopidogrel plus aspirin rather than the latter alone), although the requirement for antiplatelet agents to prevent stent occlusion may delay candidacy for liver transplant.

Cardiac surgery carries an increased risk in patients with cirrhosis, especially with more decompensated disease. Recent data demonstrates superior outcomes in patients who have undergone cardiac stenting with single vessel disease compared to outcomes for patients with prior CABG for multivessel disease.

Cardiovascular Workup Protocol for Liver Transplant Candidates

- **As part of standard transplant evaluation, all candidates will undergo transthoracic echocardiography with bubble study and adenosine/nuclear stress testing**

- **Echocardiography** results will be reviewed with attention to the following with **abnormal results** prompting **formal cardiac consultation**:
    1) Systolic ejection fraction<55%
    2) Presence of patent foramen ovale (PFO)
    3) Valvular Function (moderate, severe stenosis or regurgitation)
    4) Estimated Pulmonary Arterial Systolic Pressure (>40mmHg)

- **Nuclear Stress Testing results will be reviewed with attention to areas of myocardium with evidence of previous infarction or potentially at risk. All abnormal stress testing will be followed up by referral to cardiology for left heart catheterization.**

- **In the event of normal nuclear stress testing, the evaluating hepatologist or transplant committee may recommend left heart catheterization for further risk stratification for liver transplant. This recommendation will be based on traditional cardiac risk factors:**

    - Age>45 for male, >55 for female
    - Hypercholesterolemia
    - Diabetes Mellitus
    - Hypertension
    - Tobacco Use
    - Family history of premature CAD (male<55; female <65)
    - Personal history of CAD (previous stent, CABG)

- Candidates with **3 or more of the above risk factors** will likely be expected to undergo **formal cardiac consultation and left heart catherization** for further risk stratification regardless of non-invasive testing

References:

1) Adapted from AASLD guidelines; www.aasld.org; accessed June 2017
2) Raval Z, Harinstein ME, Skaro AI, et. al. Cardiovascular risk assessment of the liver transplant candidate. *J Am Coll Cardiol*. 2011 58(3):223-31.
3) Martinez-Palli G, Cárdenas A. et. al. Pre operative cardio pulmonary assessment of the liver transplant candidate. *Ann Hepatol*. 2011 10(4):421-33.

Pulmonary Workup Protocol for Liver Transplant Candidates

Background: Screening for lung complications is a critical component of liver transplant evaluation. An estimated 50–70% of patients with cirrhosis undergoing evaluation for liver transplantation complain of shortness of breath. The differential diagnosis of dyspnea in chronic liver disease is broad and there are a number of causes to consider. The most common causes of these abnormalities are intrinsic cardiopulmonary disorders independent of liver disease (i.e., chronic obstructive pulmonary disease, interstitial lung disease, and congestive heart failure).

Symptoms may result from general complications of cirrhosis such as: deconditioning, sarcopenia, the presence of tense ascites, and/or hepatic hydrothorax. Certain liver diseases may be associated with specific pulmonary abnormalities such as panacinar emphysema in α_1-antitrypsin.

Two distinct pulmonary vascular complications of liver disease, the hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH) are important causes of lung dysfunction. HPS results from vasodilatation leading to impaired gas exchange; while POPH results when vasoconstriction/remodeling increases pulmonary vascular resistance and elevates mean pulmonary artery pressure. Transthoracic Doppler echocardiography with bubble study may screen for both disorders.

At present, liver transplantation is the only established therapy for HPS; however, survival benefit is unclear in subjects with severe gas exchange impairment. POPH, when moderate or severe, is a contraindication to transplant but can be considered in those mild elevation of PA pressure controlled with medical therapy. Screening for both disorders is critical as their occurrence influences candidacy for liver transplant and survival.

Suggested Pulmonary Workup for Liver Transplant Candidates

- **As part of standard transplant evaluation, potential recipients will undergo: chest x-ray, pulmonary function testing, room air arterial blood gas, and transthoracic echocardiogram with bubble study**

- Pulmonary function tests will be reviewed with attention to FVC, FEV1, FEV1/FVC ratio and DLCO. Abnormalities in any of the aforementioned may trigger formal pulmonary consultation.

- Transthoracic echocardiogram will be reviewed for presence of delayed shunt (>3 cardiac cycles) and for estimation of PA systolic pressure.

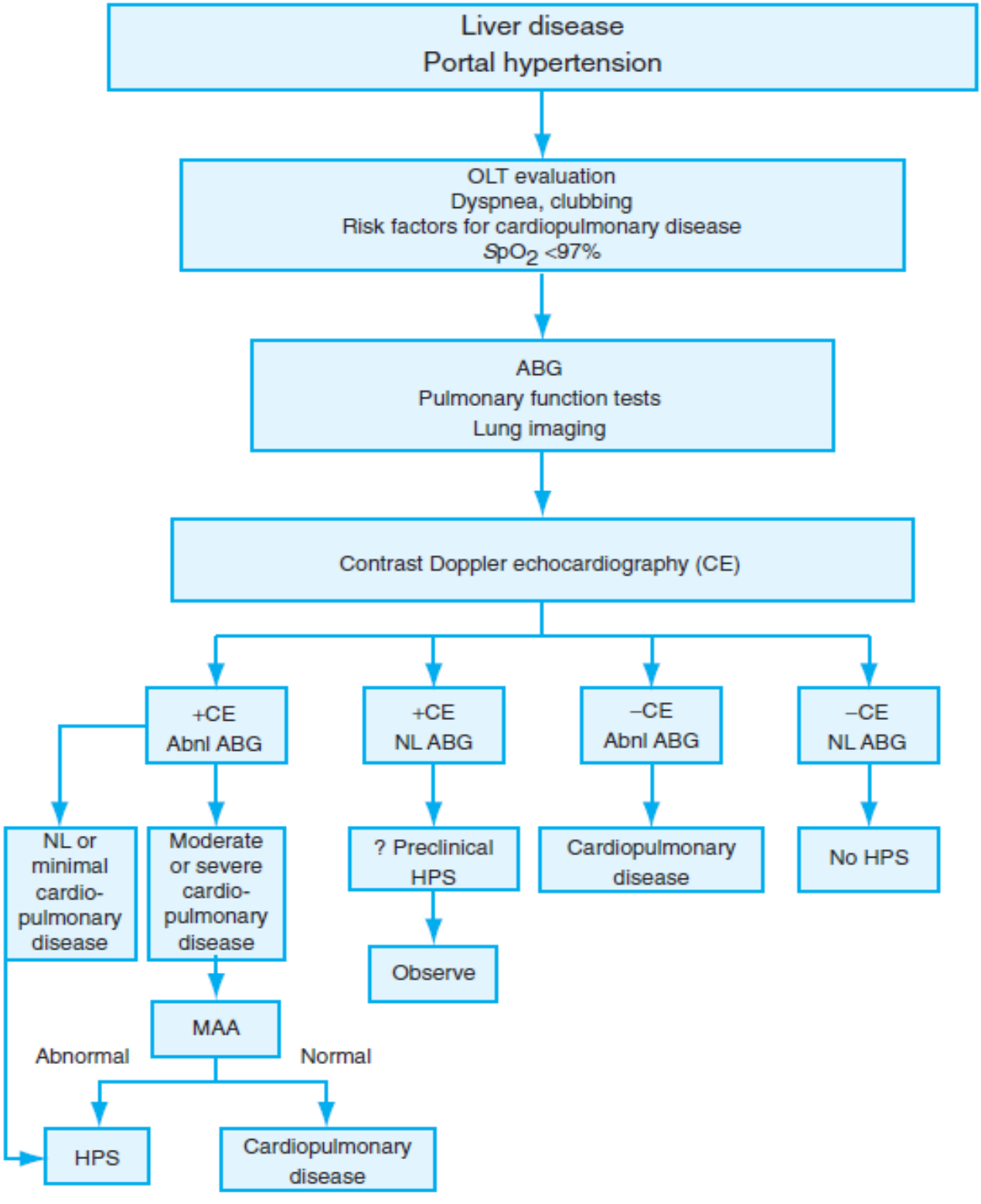
    - **Presence of delayed shunt** raises concern for **hepatopulmonary syndrome** mandating **room air ABG q 3 months** for monitoring of Pa02 to assess severity and possible MELD exception (Pa02<60mmHg)

    - **Estimated PASP > 40mmHg** on Echo should trigger either cardiology or pulmonary consultation for **right heart catherization** to confirm POPH and distinguish from pulmonary venous hypertension

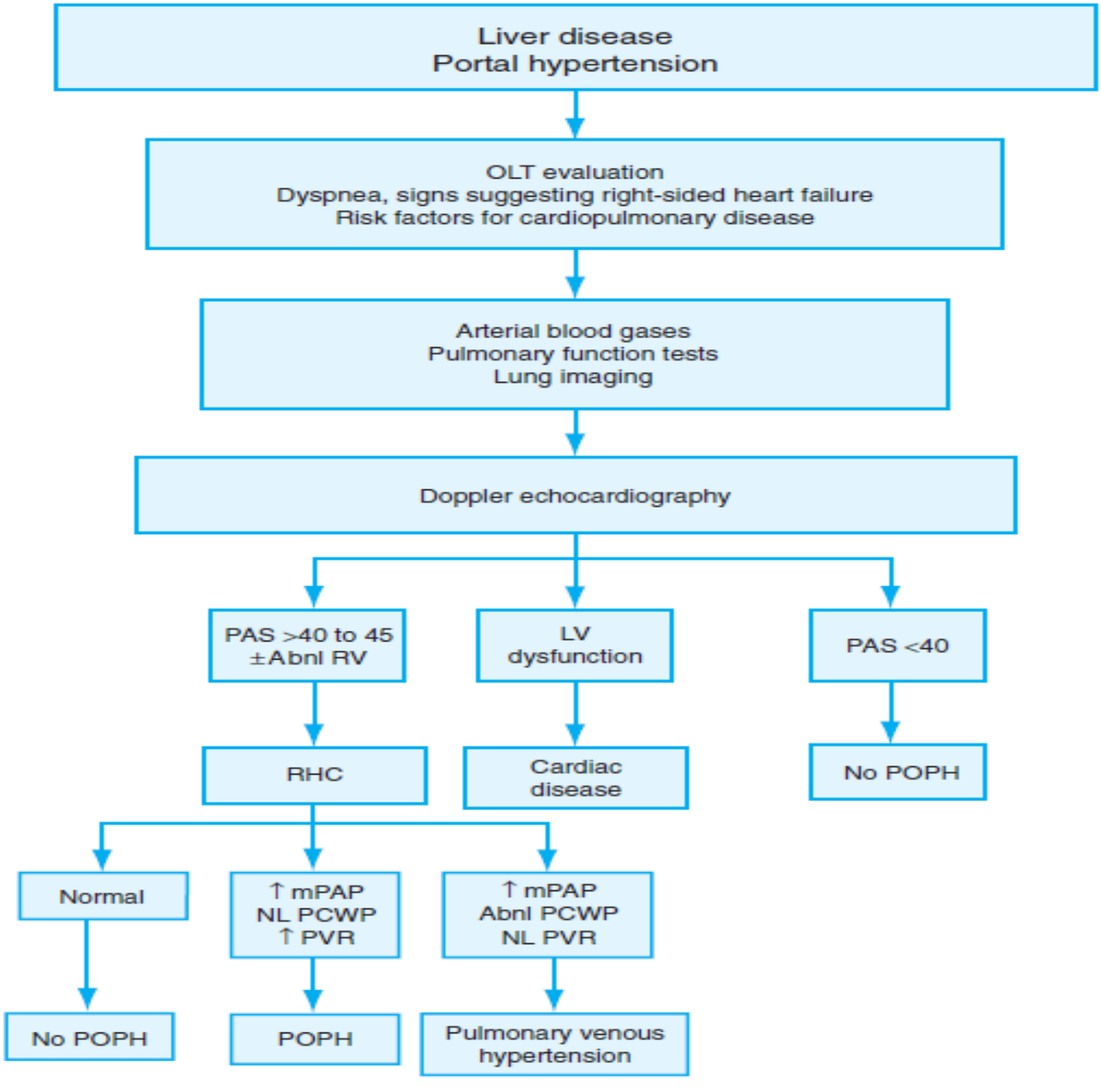
        - Right heart catheterization should be done to confirm hemodynamics consistent with diagnosis of POPH: mPAP >25 mm Hg, PVR > 3 wood units (240 dynes/s per cm−5) and PAWP < 15 mm Hg
        - Severity of POPHcan be described in terms of mPAP (assuming increased PVR) as follows: mild 25 ≤ mPAP < 35); moderate (35 ≤ mPAP <45) and severe 45 ≤ mPAP)
        - Moderate and severe cases or POPH should have ongoing pulmonary assessment for vasodilatory therapy to determine whether mPAP can be lowered into acceptable ranges to qualify for liver transplant

- **Summary of the diagnostic algorithms for the 2 classic liver-lung syndromes are summarize on the following 2 pages.**

Diagnostic Algorithm for Hepatopulmonary Syndrome



Diagnostic Algorithm for Portopulmonary Hypertension



Coccidiomycoses

Coccidiomycoses (Valley fever) is endemic to the state of Arizona and may cause pulmonary symtpoms in either immunocompetent or immunocompromised hosts. Routine serologic testing will be performed in all transplant candidates.

- Reactive serologic testing will prompt infection disease consultation for risk stratification
- Indeterminate testing should be repeated in 3-4 weeks
- Regardless of negative testing, transplant recipients will receive 6 months of diflucan prophylaxis (see opportunistic infection section)

References:

1) Adaptation from AASLD Guidelines; www.aasld.org; accessed June 2017
2) Krowka MJ, Fallon MB, Kawut SM, et. al. International Liver Transplant Society Practice Guidelines: Diagnosis and Manageme nt ofHepatopulmonary Syndrome and Portopulmonary Hypertension. *Transplantation.* 2016 100(7):1440-52.
3) Fritz JS, Fallon MB, Kawut SM et. al. Pulmonary vascular complications of liver disease. *Am J Respir Crit Care Med*. 2013187(2):133-43
4) Kahn A, Carey EJ, Blair JE. Universal fungal prophylaxis and risk of coccidioidomycosis in liver transplant recipients living in an endemic area. *Liver Transpl*. 2015 21(3):353-6
5) Figures reproduced from Fallon et. al. Schiff's Disease of the Liver, Wiley

Evaluation of Renal Function and Need for Simultaneous Kidney Transplant

Background: Recognition of renal dysfunction in patients with cirrhosis has a dramatic effect on prognosis, with substantial increase in mortality. In a recent meta-analysis, risk of death increased 7-fold in patients with renal dysfunction; with 50% of patients with cirrhosis dying within a month of the onset of renal dysfunction.

The differential diagnosis of renal failure in patients with cirrhosis is broad and includes intercurrent sepsis, hypovolemia, parenchymal renal disease, and hepatorenal syndrome (HRS).

Working groups have proposed the following definitions of renal dysfunction complicating liver disease:

Acute kidney injury that includes all causes of acute deterioration of renal function with an increase in serum creatinine of >50% from baseline, or a rise in serum creatinine of >0.3 mg/dL) in <48 hours.

Chronic renal disease is defined as an estimated glomerular filtration rate (GFR) of <60 mL/min calculated using the Modification of Diet in Renal Disease (MDRD) formula.

Evaluation of renal dysfunction in patients with decompensated cirrhosis should include an accurate calculation of the true glomerular filtration rate (GFR) and determination of the precise etiology as it impacts prognosis both with and without LT. In a recent study of 463 patients with cirrhosis and renal dysfunction, survival was significantly worse in patients with HRS versus those without HRS. Since the introduction of MELD for organ allocation the number of simultaneous liver kidney (SLK) transplants continues to rise.

Because of concerns surrounding the increased use of renal grafts in LT recipients, a panel of experts convened to evaluate and recommend the most appropriate indications for SLK. **SLK was sanctioned for (1) endstage renal disease (acute HRS etiology excluded) with cirrhosis; (2) liver failure with chronic kidney disease (CKD) and GFR <30 mL/min, (3) acute kidney injury or HRS with creatinine >2.0 mg/dL and dialysis for >8 weeks; or (4) liver failure with CKD and renal biopsy demonstrating >30% glomerulosclerosis or >30% fibrosis.** These recommendations continue to evolve with increasing experience of SLK.

Suggested Evaluation of Candidates with Acute and Chronic Renal Dysfunction

- **ESLD Candidates with acute kidney injury**
  - Review of current medications and discontinuation of nephrotoxic agents (e.g. NSAIDs, ace-inhibitor)
  - Review of current medications and need for renal dosing
  - Discontinuation of diuretic therapy
  - Trial of volume expansion with albumin or normal saline
  - Determination of spot urine sodium (<15 consistent with pre-renal causes or developing hepatorenal syndrome)

- In those with persistent sodium avidity despite adequate volume expansion, initiation of "triple therapy" with daily albumin, midodrine 10mg TID, and octreotide subcutaneously

- Review of transplant candidacy and discussion with nephrology regarding appropriateness of hemodialysis initiation as a bridge to liver transplant

- **ESLD Candidates with chronic kidney injury**
  - ESLD candidates should be considered for simultaneous liver/kidney transplant if **one of the following criteria are met**:

1) endstage renal disease (acute HRS etiology excluded) with cirrhosis
2) liver failure with chronic kidney disease (CKD) and GFR <30 mL/min
3) acute kidney injury or HRS with creatinine >2.0 mg/dL and dialysis for >12 weeks
4) liver failure with CKD and renal biopsy demonstrating >30% glomerulosclerosis or >30% fibrosis.

References:

1) Wong F, O'Leary JG, Reddy KR, et. al. Acute Kidney Injury in Cirrhosis: Baseline Serum Creatinine Predicts Patient Outcomes. *Am J Gastroenterol*. 2017. EPUB
2) Nadim MK, Sung RS, Davis CL, et. al. Simultaneous liver-kidney transplantation summit: current state and future directions. *Am J Transplant*. 2012 12(11):2901-8
3) Parajuli S, Foley D, Djamali A, et. al. Renal Function and Transplantation in Liver Disease. *Transplantation*. 2015 99(9):1756-64.
4) Levitsky J, Baker T, Ahya SN, et. al. Outcomes and native renal recovery following simultaneous liver-kidney transplantation. *Am J Transplant*. 2012 12(11):2949-57
5) AASLD Guidelines, www.aasld.org; accessed June 2017

Nutritional Assessment

Background: Assessment and counseling by a dietician is an integral part of the evaluation process, including correcting misconceptions about restriction of protein and addressing the possible need for enteral or even parental feeding prior to liver transplant.

- Candidates undergoing liver transplant evaluation experience a variety of issues including effects of a catabolic chronic illness (liver inflammation/cirrhosis from diverse causes) often accompanied by reduced appetite (generalized cachexia, mass effect on stomach from ascites).

- The specific etiology of liver disease can also lead to additional nutritional deficiencies such as fat-soluble vitamin (A, D, E, and K) malabsorption in cholestatic liver disease (PBC or PSC).

- Malnutrition leads to poorer outcomes following LT with a BMI<18.5 identified by UNOS data as a key predictor. Importantly, severity of muscle wasting (sarcopenia) can be masked by ascites and obesity.

- With the increasing prominence of NAFLD as an indication for LT many candidates have features of the metabolic syndrome resulting in the development of posttransplant diabetes mellitus. Pre-LT diabetes is managed with insulin and oral hypoglycemics, although the latter should be used with caution because of the risk of hypoglycemia. Hyperlipidemia, if present, should be managed as in the general population.

- Herbal supplement history should be reviewed as frequently as necessary for evaluation of component and source. Their use is generally discouraged as formulation/manufacturing is not regulated by the Food and Drug Administration and usage may precipitate drug induced liver injury.

References:

1) Adapted from AASLD Guidelines; www.aasld.org; accessed June 2017
2) Bambha KM, Dodge JL, Gralla J et. al. Impact of body mass index on posttransplant outcomes reexamined. Liver Transpl. 2016 22(2):261-2
3) Abbas N, Makker J, Abbas H et. al. Perioperative Care of Patients With Liver Cirrhosis: A Review. Health Serv Insights. 2017 24; EPUB

Social Work Evaluation

Background: Social workers and/or mental health professionals typically provide psychosocial evaluation with input from psychiatrists or other specialty physicians (e.g., addiction medicine). Components of the psychosocial evaluation that are relevant to transplant outcomes include:

1) evidence of compliance with medical direction

2) adequate support from able caregivers especially in the perioperative period

3) absence of active psychiatric disorders with the potential to impact compliance or include behaviors harmful to health (e.g., alcohol, tobacco, or illicit drug use).

- While the effect of nonsubstance abuse-related psychiatric disorders on transplant outcomes have not been fully determined, research suggests that depressive symptoms particularly in the early postoperative period are associated with poorer outcomes after LT. However, there is **no psychiatric disorder that is an absolute contraindication to transplantation and even the most psychiatrically complex patient, for example, with a psychotic disorder or mental retardation, with proper evaluation and preparation, as well as adequate social support, can have successful long-term outcomes**.

- In addition to addressing psychiatric and substance abuse issues, the evaluation process should also include an assessment of the patient's social support network. As the care of a transplant patient involves frequent office visits and tests, two caregivers (primary and backup) need to be identified to undertake transport and other logistical tasks, especially in patients with history of encephalopathy who should not be left alone to drive. It is also necessary to ensure that a potential recipient will have adequate posttransplant medication coverage.

- Tobacco Consumption Cigarette smoking is implicated in a number of adverse outcomes in LT recipients including cardiovascular mortality and an increased incidence of hepatic artery thrombosis, oropharyngeal and other neoplasms following LT are also linked to cigarette smoking and can result in significant potentially avoidable long-term mortality.. There are compelling reasons to prohibit all tobacco use in LT candidates, and indeed some programs make cigarette cessation a condition for listing for LT and require negative serial nicotine screens for documenting tobacco cessation.

- Marijuana Consumption: Prescription marijuana use is available in the state of Arizona and cirrhosis (as well as hepatitis C) are examples of qualifying conditions. Candidates with legal prescription usage are not penalized for usage; however recommendations may be made based on individual candidate circumstances. All

efforts will be made to counsel regarding the risks of inhalation of marijuana smoke pre and post transplant and discussion of alternatives: oils and/or edible.

- Aforementioned social and psychiatric issues are complex with need for longitudinal multidisciplinary assessment. These issues, influence on transplant candidacy, and progress will be discussed during transplant selection committee at intial candidate presentation and subsequent re-presentations to the committee.

References:

1) Volk ML, Goodrich N, Lai J et. al. Decision support for organ offers in liver transplantation. *Liver Transpl*. 2015 21(6):784-91
2) Volk ML, Biggins SW, Huang MA et. al. Decision making in liver transplant selection committees: a multicenter study. *Ann Intern Med*. 2011 155(8):503-8.
3) Bramstedt KA, Chalfant A, Wright C. Emergency consults in the setting of transplant medicine: dilemmas for social workers and bioethicists. *Prog Transplant*. 2007;17(1):36-9

Waitlist Mechanics

- Candidates presented and accepted for listing will be notified by coordinator via telephone within 48 hours and via letter per UNOS suggested time frame

- Waitlist active status includes routine updates to the MELD score. Frequency of updates may be individualized for each candidate and may depend on inpatient/outpatient clinical status

    - Meld Updates Frequency
        i. MELD <20 monthly update
        ii. MELD>20-30 bimonthly
        iii. MELD>30 weekly

- Committee contingencies for waitlist active status will be formulated at the time of transplant committee and listing decision for each patient. In certain circumstances, the committee decision may be to proceed with formal listing while reserving the right to inactivate status if following criteria have not been met:

    - Non compliance with remaining evaluation testing
    - Non compliance with routine health maintenance screening
    - Relapse of alcohol or illicit drug use by patient report
    - Non compliance with random alcohol and drug screening
    - Change in/loss of caregiver status
    - Insurance change with loss of transplant benefits

- All waitlist active candidates should carry in their wallet/purse and identification card specifying
    - Waitlist active status at BUMCP
    - Name of transplant coordinator
    - Name of primary hepatologist
    - Phone number to Banner University Advanced Liver disease and transplant center

- Liver transplant candidates with MELD scores >20 or at the top half of the list should have address and phone number verified on a monthly basis in the event of organ offers

- Patients with hepatocellular cancer and receiving locoregional therapy will be encouraged to have all therapy and imaging performed by the BUMCP departments of radiology and interventional radiology

- Informed consent for surgery and discussion of DCD and extended criteria donors will occur as part of the evaluation process and consistently readdressed by primary hepatologist during subsequent clinic visits

- Waitlist active candidates are encouraged to seek inpatient medical care at BUMCP whenever feasible and safe. Waitlist active candidates or their caregivers are encouraged to call and notify their transplant coordinator in the event they are hospitalized outside BUMCP. In the event of this situation, the contacted coordinator will:

    - Email the covering inpatient hepatologist (ccing the primary/evaluating hepatologist in the event they are not on inpatient service) summarizing briefly the medical events of the situation and current MELD

    - By default, the program's expectation is that the great majority of waitlist active patients outside of BUMCP will be accepted for any medical condition/situation (hepatology or non hepatology) for transfer to BUMCP

- In the event that waitlist active patients, hospitalized in BUMCP, experience a change in status which renders immediate candidacy in question:

    - Covering inpatient hepatologist will notify on call coordinator and surgeon through appropriate means of communication

    - Covering inpatient hepatologist will notify on call coordinator and surgeon when status can be reactivated

- Inpatient evaluations will be subject to multidiscipilinary review. In the event of urgent listing for fulminant hepatic failure or for a candidate with ESLD whose candidacy requires prompt review:

    - A phone conference or "virtual committee" via email will be initiated by the on call coordinator with summary of evaluation and relevant testing in SBAR format

    - Evaluating hepatologist is expected to be primary responder to initial email to address questions from participants