Hospital Medicine Liver and Liver Transplant Manual

Contributors

Hepatology

Helen Te, MD

Sonali Paul, MD

Anjana Pillai, MD

Hospital Medicine

Nicole Bendin, MD

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Important Numbers and Cross Coverage

Hospital Medicine

- L service attending (p6111)
- L service NP/PA (p6116)
- T service attending, liver overflow (p7215)
- Nicole Bendin, transplant service liaison (p5876)
- Brenda Garrett, case management (p4078)
- Casey Connor, social work (p4005)
- Ashley Loethen, transplant pharmacist (p9420)

Hepatology

- Liver fellow (p2453): Notify for all unexpected admissions (if not already done by ED). Do not need to contact for expected admissions (should already have a documented note with plan in the chart). Cross cover should page for any urgent questions/updates including GI bleed and ICU transfer.
- Service attendings: Andrew Aronsohn, Michael R. Charlton, Sonali Paul, Anjana Pillai, K. Gautham Reddy, Helen S. Te
- Lisa Potter, liver/lung transplant pharmacist (p4962)
- GI endoscopy on call (p9894): Urgent overnight endoscopy coverage.

Transplant Surgery

- Transplant Surgery resident (p8767)
- Service attendings: Talia Baker, Diego di Sabado, John Fung, Dympna Kelly, J. Michael Millis

Consultants

- Immunocompromised ID (p7322): Cover all ID related consults for transplant patients.
- Interventional Radiology: Scheduling x68318, MD x41513, after hours RROC (p 7046)
- Cardiology (for liver transplant candidate evaluation): Page cardiology consult fellow (p3547), will be staffed by attending Dr. Amit Patel.

VIBES: A Systematic Approach to Cirrhosis Management

Volume (ascites, edema, hepatic hydrothorax, hepatorenal syndrome)
- Current diuretics
- Sodium restriction, fluid restriction if indicated by serum sodium
- Need for large volume paracentesis, thoracentesis for hepatic hydrothorax, TIPS
- Address HRS if applicable

Infection (SBP, other infections)
- Prior history of SBP (primary or secondary) or indication for long-term SBP prophylaxis
- Current treatment if SBP on diagnostic paracentesis
- Empiric treatment with ceftriaxone if GI bleeding (prevents all types of infections, not just SBP)
- Consider full infectious evaluation (blood cultures, diagnostic tap, UA, CXR) if signs/symptoms of infection (fever, leukocytosis, SIRS), AKI, or encephalopathy

Bleeding (esophageal/gastric varices, coagulopathy)
- Prior history/source of bleeding, therapies, current prophylaxis (beta blocker)
- Current severity, medical therapy, empiric antibiotics (ceftriaxone) in active bleed

Encephalopathy
- Prior history, treatment, precipitant
- Current severity, trend, therapy (lactulose/rifaximin/zinc) and titrate to 2-3 bowel movements

Screening (more outpatient management)
- Avoid NSAIDS, sleep aids, minimize/avoid opiates/benzos
- Vaccinations: Hep A, B, influenza, pneumovax
- HCC screening: imaging and AFP every 6 months
- Variceal screening

Volume Management in Cirrhotics

Ascites

Pathogenesis

- Due to portal hypertension – hepatic venous pressure gradient (HVPG) > 5 mmHg/hypoalbuminemia
- Most common complication; 15% 1 yr mortality; 44% 5 year mortality
- 60% cirrhotics will develop ascites in 10 years; 50% mortality at 5 years *(Hepatology 2009; 29:2087)*

Evaluation (*Hepatology 2009; 29:2087; JAMA 2008; 299:1166)*

- **Physical exam**
- **RUQ ultrasound for new ascites:** rule out portal vein thrombosis (PV included on abd US limited)
- **Diagnostic paracentesis:** perform in all patients with new onset ascites and cirrhotic with existing ascites with indication (concern for infection, encephalopathy, AKI). If known cirrhotic and prior taps, likely only need cell count/diff, C&S. Use Procedure team order set 3194.
    - **Body Fluid Cell Count and Differential**
    - **Fluid Culture & Stain**
    - **Fluid Albumin:** Serum Ascites Albumin Gradient (SAAG) = Serum Albumin - Fluid Albumin ≥ 1.1 indicative of portal hypertension
    - **Fluid Protein**
        - > 2.5 indicates cardiac ascites
        - < 1.5 and meets other liver parameters, merits primary SBP ppx
    - **Cytology**: usually low yield, need large volume to improve yield
    - **Glucose, LDH:** glc < 50 and LDH > upper limit serum nl suggest secondary peritonitis

	(+) Ascites culture	(-) Ascites culture
PMN ≥250/µL	Spontaneous Bacterial Peritonitis (SBP) (Secondary Peritonitis → polymicrobial)	Culture Negative Neutrocytic Ascites (CNNA)
PMN <250/µL	Non-neutrocytic bacterascites (NNBA)	Normal
CNNA has similar presentation and prognosis as SBP → if PMN ≥250/µL, treat for suspected SBP without waiting for (+) culture results		
Hemorrhagic ascites: RBC >50,000/mm^3, often due to traumatic tap → correct PMN count by subtracting 1 PMN for every 250 RBCs		

SAAG ≥1.1 g/dL	SAAG <1.1 g/dL
Etiology related to portal hypertension	**Etiology not related to portal hypertension**
• Cirrhosis (ascites fluid total protein [AFTP] <2.5 g/dL) • CHF (AFTP typically >2.5 g/dL), includes TR and congestion • Acute hepatitis • Massive liver metastases • Hepatocellular carcinoma • Budd-Chiari syndrome • Portal vein thrombosis • Schistosomiasis	• Spontaneous or secondary bacterial peritonitis ○ ↑LDH, ↓glucose, ascitic CEA > 5 ng/mL, ascitic ALP >240 U/L → can help detect gut perforation • TB peritonitis • Peritoneal carcinomatosis (liver or ovarian cancer) • Pancreatobiliary • Chylous • Hypoalbuminemia – malnutrition, nephrotic syndrome
SAAG (serum-ascites albumin gradient) differentiates portal hypertensive vs. non-portal hypertensive ascites 96.7% of the time	
AFTP (ascites fluid total protein) is useful adjunct in discrimination of high SAAG ascites[8]	

Management

1. **Sodium restriction:** 2 g/day
2. **Fluid restriction:** 1.5 L only if Na < 125
3. **Diuresis:** furosemide and spironolactone (40/100 mg ratio, max 160/400 mg) if Cr and Na allows
   - Urine Na/K > 1 suggests >2 g daily urine Na excretion
     - With weight loss = sensitive and adherent to regimen
     - Without weight loss = non compliance with 2 g sodium diet
   - Urine Na/K < 1= resistance or inadequate dosing
   - Often use midodrine to increase systolic blood pressures if hypotensive; helps with renal perfusion
4. **Large volume paracentesis (LVP):** some patients with refractory ascites may need serial LVP. Also consider if ascites tense and concern for intra-abdominal HTN (bladder pressure >15)→ AKI or if ascites interferes with respiration or oral intake.
   - If concerned about SBP, only do diagnostic (LVP can precipitate renal failure).
   - If tenuous kidney function, do not remove > 4 liters. Consider giving albumin even if less than 4L removed.
   - If > 4L removed, give 6-8 g/Lof 25% albumin, see table below. Reduces mortality (OR 0.64); *(Hepatology 2012; 55:1172-1181).*

Volume Removed (L)	Albumin Dose g (mL)
≤ 3 L	Do Not Admin.
4 L	25 g (100 mL)
5-6 L	37.5 g (150 mL)
7-8 L	50 g (200 mL)
9-10 L	62.5 g (250 mL)
11-12 L	75 g (300 mL)
13-14 L	87.5 g (350 mL)
15-16 L	100 g (400 mL)

Hepatic Hydrothorax

Pathogenesis

- Transudative pleural effusion caused by fluid shifts across diaphragm, R > bilateral > L when there is a diaphragmatic defect
- Associated with ascites but negative pleural pressure can cause abdominal ascites into chest

Evaluation

- CXR
- Consider CT after thoracentesis (if not done prior) to evaluate for other etiologies
- Thoracentesis: transudative by Light's criteria with exclusion of other causes
- Can develop spontaneous bacterial empyema (SBE), even in the absence of SBP. Diagnostic criteria:
    - Positive pleural fluid culture and PMN >250 **OR** negative pleural fluid culture and PMN >500
    - No evidence of pneumonia on a chest imaging study

Management

1. Same as ascites (diuresis, fluid/Na restriction), therapeutic thoracentesis if needed, TIPS if refractory
2. Chest tube, pleural drains, pleurodesis NOT recommended unless palliative purpose

Spontaneous Bacterial Peritonitis (SBP)

Pathogenesis

- Often gut bacterial translocation, other sources UTI, respiratory tract, bacteremia
- Usually monomicrobial (spontaneous): GNR 70% (*E. coli, Klebsiella)*, GPC 25% (*S pneumoniae*), anaerobes 5%
- Differentiate from secondary bacterial peritonitis, often polymicrobial → may have surgically treatable intra-abdominal source (i.e. perforated viscus like peptic ulcer, abscess)

Evaluation

- Variable presentation (encephalopathy, fever, pain, AKI) → low threshold to do diagnostic tap; 25% asymptomatic
- **Diagnostic paracentesis (approx. 50 cc):** Ideally done prior to antibiotics, but should not delay treatment if procedure cannot safely be performed.
    - <1% risk of bleeding; not correlated to INR or platelet count *(Hepatology 2004; 40:484).* Despite this, procedure team may not perform without controlled parameters. Consider TEG Transfusion Evaluation (see coagulopathy section) if correction is desired.
    - Send cell count, fluid C&S. Ascites total WBC x % PMN in diff = absolute PMNs. ≥ 250 diagnostic for SBP.
    - Need to confirm specimen gets to lab (RN can call transport to do this) and follow up counts/sign out to cross cover.
- **Non-neutrocytic bacteracites** (nl cell counts but positive culture)**:** repeat tap prior to abx. If asymptomatic, can wait for repeat culture without abx, if acting infected, treat while waiting for cultures. If repeat cx still positive, treat as SBP.

Management

1. **Ceftriaxone:** 2gm IV q24hrs x 5 days. If cephalosporin allergy, cipro 400 IV BID – but use other antibiotics if patient is already using cipro as prophylaxis.
2. **Albumin:** 25% 1.5mg/kg at time of diagnosis; 1gm/kg on day 3; increases survival *(NEJM 1999; 341:403).* Questionable utility in ESRD patients.
3. If high suspicion, start antibiotics and albumin immediately post para (do not need to wait for labs).
4. Stop beta blockers, HTN meds in setting of possible SBP/concern for infection.
5. Consider repeat paracentesis in 48 hours to document improvement/clearance (decrease PMNs by 25%) if no clinical response.

Prophylaxis

- **Primary:** Ascites total protein ≤ 1.5 **AND**
    - Na ≤ 130, Cr ≥ 1.2, BUN ≥ 35 **OR** Child-Pugh ≥ 9 with bilirubin ≥ 3. *(Am J Gastro 2009; 4:993).*
- **Secondary:** History of SBP.
- **Antibiotic choice:** First line cipro 500 mg PO daily, second line Bactrim 1 DS tab daily (adjust both for renal function).

Diagnostic Paracentesis Checklist

- ✓ Consent on chart, including blood consent
- ✓ Appropriate blood/coagulopathy parameters or corrected per TEG
- ✓ Ultrasound in 9W workroom
- ✓ Drapes, masks, gown (if desired), chlorhexadine skin prep
- ✓ Anesthetic: 22-25 gauge needle, 10 mL syringe, 1% lidocaine (no epi) 5-10 mL – order in advance from pharmacy
- ✓ Collection: 18-21 gauge needle (higher gauge if higher risk)
- ✓ Tubes: lavender top (cell count, diff), gold top (albumin, total protein), black top/urine cup (gram stain), aerobic and anaerobic culture bottle (at least 10cc/bottle)

Post-Paracentesis Hemoperitoneum

Pathogenesis

- Usual source: inferior epigastric arteries

Evaluation

- **Presentation:** bloody tap, tachycardia, hypotension, abd pain. New significant anemia can incidentally be found on lab draws. Ddx includes intestinal perforation, other sources of bleed.
- **Labs:** Stat CBC, TEG 6S, type and screen if not done within 3 days.
- **Imaging:** CTA abd/pelvis if labs and clinical picture consistent with bleed. If AKI/CKD, discuss with IR prior to ordering.

Management

1. **NPO**: pending workup in case of IR procedure.
2. **Resuscitation:** volume, blood, and correction of coagulopathy.
3. **IR consult**: for embolization (if bleed does not tamponade itself).
4. **Consider ICU** evaluation depending on hemodynamics and degree of acute blood loss anemia.

Hepatic Encephalopathy (HE) in Chronic Liver Disease

Pathogenesis

- Liver is unable to detoxify NH_3 and other substances (GABA-like) that can cause mental status changes, rarely cerebral edema

Evaluation

Identify underlying cause/precipitant

- **Medication non-compliance:** history, lactulose titration at home (goal 2-3 BM/day), constipation
- **Infection**: blood and urine cultures, CXR, diagnostic paracentesis if ascites
- **Azotemia:** overdiuresis/hypovolemia, based on exam, renal function; consider holding diuretics
- **Electrolyte abnormalities**: Na, K, Phos in particular
- **Medications**: opiates, benzos, sleep aids
- **GI bleeding**: signs/symptoms (melena, hematemesis)
- **Portal vein thrombosis**: RUQ ultrasound
- **New or worsening HCC burden**: imaging
- **Alternative causes of altered mental status:** consider head CT especially if coagulopathic to r/o ICH. Consider neuro consult if exam/clinical course not improving or c/w HE.

Diagnosis

- Clinical/exam as venous ammonia (NH_3) levels have poor sensitivity. **Serum ammonia levels DO NOT correlate with HE severity**. Normal ammonia does have good negative predictive value.
- West-Haven Criteria (see chart below)
    - Covert: grade 0 including minimal hepatic encephalopathy (MHE) - I
    - Overt: stage II-IV. Asterixis appears consistently at grade II

Grade	LOC	Behavior	Neuro Exam
0	normal	normal	normal → if nl exam but abnormalities in sleep, memory, attention, concentration consider MHE
I	mild lack of awareness	short attention span, euphoria, anxiety, altered sleep	detectable asterixis
II	lethargic, apathetic	disorientation for time, inappropriate, personality changes	obvious asterixis
III	somnolent but arousable	grossly disoriented, bizarre behavior, responds to stimuli	hyperreflexia, clonus
IV	coma	no response to even painful stimuli	decerebrate posturing

Management

1. Low threshold for ICU/intubation if concerns for poor mental status/airway protection
2. Aspiration precautions
3. Identify/treat precipitants
4. Trend exam, not ammonia - no clinical utility in monitoring daily ammonia levels (unless patient is comatose and progress cannot be ascertained clinically)
5. Medication approach
    - **Lactulose:** (acidifies colon so that $NH_3 \rightarrow NH_4^+$)
        - 20 g PO/NG, adjust frequency of dosing. Increase frequency early (especially with high grade HE) to q2-3 if needed until has large BM, then titrate frequency to 2-3 BM/day or 500 cc stool/day if rectal tube.
        - If already on home lactulose, increase home dose by 50%.
        - If unable to take PO, place Dobhoff for dosing, add lactulose enemas q6.
    - **Rifaximin:** 550 mg PO BID (decreases gut bacteria = $\downarrow NH_3$ production) *(NEJM 2010; 362:1071)* Often needs prior auth if new med.
    - **Zinc:** *UofCism*: Check zinc level and replete if low; zinc 220mg daily to BID *(Therap Adv Gastroenterol 2016; 9(5):684-91)*
    - **Polyethylene glycol:** Can also use PEG (4L), more rapid HE resolution than lactulose, but may be difficult for patient with encephalopathy to drink/tolerate volume.
6. If refractory encephalopathy despite treatment, consider oral branched chain amino acids, evaluate spontaneous portosystemic shunts and embolization, dialysis.

Hepatorenal Syndrome (HRS)

Pathogenesis

- Increased production of cytokines/vasodilation in portal HTN → arterial vasodilation in splanchnic circulation → activation of SNS, ADH, RAAS → renal vasoconstriction/decreased renal perfusion
- Precipitants: infection (SBP >other), GI bleed, fluid shift post LVP, EtOH hepatitis

Evaluation/Diagnosis

- Stop diuretics, non-selective beta blockers, stop/avoid nephrotoxins
- Volume challenge: 1gm/kg/day 25% albumin (max 100 g daily) x 48 hours
- Urine studies: UA (generally bland), urine Na, Cr (Una < 10 or FeNa < 1% consistent with HRS)
- Renal ultrasound
- Renal consult: need to exclude other causes including drugs, ATN, dehydration, GI bleed, infection.
- **HRS-AKI:** former HRS-1.
    1. Cirrhosis, acute liver failure, acute on chronic liver failure
    2. Increase in serum Cr ≥0.3 mg/dl within 48 h or ≥50% from baseline and /or UOP ≤0.5 ml/kg BW ≥6 h with Foley
    3. No response/partial response of serum creatinine after ≥48 h of diuretic withdrawal and volume expansion with albumin
    4. Absence of hypovolemic shock or infection that requires pressors
    5. No current or recent use of nephrotoxic drugs
    6. Absence of parenchymal disease (no proteinuria > 500 mg/day or hematuria >50 RBC/HPF)
- **HRS-NAKI:** former HRS-2. Patient with cirrhosis and CKD, with GFR <60 ml/min per 1.73 m2 for >3 months (HRS-CKD) when other causes have been excluded or renal dysfunction that does not meet AKI criteria, lasts for less than 90 days *(Journal of Hepatology 2019; 71(4) 811-822).*

Management

Goal to increase renal perfusion by splachnic vasoconstriction, reduces mortality *(Hepatology 2010; 51:576-584).*

1. Combination therapy (HRS cocktail)
    a. **Midodrine:** start 5-10 mg PO TID; titrate up to 15 mg TID
    b. **Octreotide:** 200 mcg SC TID vs gtt at 50 mcg/hr
    c. **Albumin:** 25%, 25 g TID
2. Adjust medication dosing with changing GFR
3. Consider ICU transfer for norepinephrine/vasopressin trial (increase MAP by 10-15 mmHg, or goal >65). Consider early, especially in transplant candidates.
4. Daily assessment for any urgent indications for HD. If considering HD, discussions with renal team (prior to patient/family) about appropriateness of HD and overall GOC, especially if patient not a transplant candidate.

Pulmonary Complications of Cirrhosis

Hepatopulmonary Syndrome

- Intrapulmonary shunting through vasodilation/AVMs, possibly related to circulating NO
- Shunting tends to occur at lung bases → platypnea (dyspnea when upright, relived when supine), orthodeoxia (upright hypoxemia, PaO_2 decreased by 4mm Hg)
- High mortality (75% at 5 years), oxygen can help, start transplant work up
- Presentation: decreased DLCO, room air blood $PaO_2 < 70$ mmHg, pulmonary vascular dilation, clubbing, cyanosis
- Diagnosis: TTE with late bubbles (3-6 cardiac cycles after RA)
- Garlic supplement 1500 mg BID (Can J Gastroenterol 210;24(3):183-8)

Portopulmonary Hypertension

- Rare cause of secondary pulmonary hypertension (mPAP > 25mmHg, PCWP < 15 mmHg) in setting of portal hypertension
- Presentation: dyspnea on exertion, exertional hypoxemia
- Diagnosis: TTE and right heart cath
- Not a contraindication for transplant unless mPAP > 35 mmHg on medical therapy

Variceal Bleeding

Pathogenesis

- 1/3 of all deaths related to cirrhosis
- Portal HTN leads to portosystemic collaterals→ variceal wall tension (higher HVPG)→ rupture
- Risk factors include size of varices, decompensated cirrhosis, red wale sign on EGD

Presentation

- Hematemesis (bright red blood and coffee ground), melena, BRBPR (if brisk upper bleed or rectal varices)
- Acute blood loss anemia - may not reflect in initial labs depending on timing of presentation
- Tachycardia (early, could be masked by BB), hypotension → look at vitals trend
- Encephalopathy

Evaluation/Initial stabilization

1. **NPO**
2. **Labs:** CBC, T&S, TEG Transfusion Evaluation, coags
3. **Access/Resuscitate**: 2 large-bore (at least 18 gauge) IVs, volume replacement if hypotensive
4. **Notify:** Hepatology for urgent EGD, consider ICU, intubation
5. **Transfuse:** to hemoglobin of 8 (do not over transfuse, can worsen bleed)
6. **Reverse coagulopathy:** see next section

Treatment

1. **Octreotide:** 50 mcg IV bolus, then 50 mcg/hr drip x 5 days
2. **Pantoprazole:** 80 mg IV bolus followed by 40 mg IV BID vs gtt 8 mg/hr
3. **SBP prophylaxis:** Ceftriaxone 1 g daily for any patient with cirrhosis and GI bleed; decreases risk of all infections *(Gastro 2006; 131;1049; Hepatology 2004; 39:746)*
4. **Urgent EGD:** often done in ICU bedside. Hepatology during the day, GI endoscopy team at night.
5. **TIPS:** if refractory hemorrhage or gastric varices
6. **Prophylaxis:** propranolol, nadolol or carvedilol (larger BP drop)
    a. **Primary:** in those with moderate to large varices or red wale sign
    b. **Secondary:** for all patients after first variceal bleed
    c. Stop non-selective beta blocker in setting of renal failure, infection, refractory ascites.

Coagulopathy Management

Pathogenesis

- Advanced cirrhosis and acute liver failure characterized by decreased synthesis of **both** procoagulants and anticoagulants → prolonged prothrombin time, INR
- **PTT inaccurate measure of true hemostatic condition** in significant liver dysfunction

Evaluation

- Goal to avoid unnecessary transfusion of blood products in liver patients especially in setting of fluid overload/hypoalbuminemia → predisposes to third-spacing of fluids
- **Thromboelastogram (TEG):** rapid global hemostasis assessment that measures the viscoelastic changes that occur during the hemostatic process. Order TEG for:
    - Cirrhotic or acute liver failure patients who have prolonged prothrombin time (INR >1.5) or thrombocytopenia (platelet <100K) **and need invasive procedures.** *(Hepatology 2016; 63:566-573)*
    - Cirrhotic or acute liver failure patients who have prolonged prothrombin time or thrombocytopenia and **are actively bleeding**.
- TEG is NOT a measure of the liver's synthetic function and should not be used in place of PT/INR to trend liver function
- TEG labs available 24/7 with short turnaround time
    - **TEG Transfusion Evaluation** plus fibrinogen and platelets– most patients, replaces TEG6S
    - TEG 2 if patient on heparin
    - TEG1 may be ordered by other services so chart included for interpretation
    - Order T&S if not already done in preparation for blood products

Treatment

1. **Vitamin K**:10 mg subq/IV daily x3 (concomitant vitamin K deficiency common, especially in jaundiced patients, EtOH use)
2. To reverse coagulopathy in **active bleed:**
    a. **FFP, cryo, platelets:** per TEG chart
    b. **DDAVP:** for symptomatic thrombocytopenia with renal dysfunction, give 0.3 mcg/kg up to maximum of 30 mcg IV over 20 minutes; if to be given for a procedure, infuse immediately prior to procedure. Check serum Na 3-4 hours post administration of DDAVP.
    c. **Protamine:** use as in standard patient if bleed on heparin product

TEG Transfusion Evaluation interpretation for non-heparinized patients

Components	Definition	UCM Normal Values for Transfusion Evaluation (TEG 6S)	Cut-Off Values for correction	Problem with	Management
Kaolin R time	Time to start forming clot	4.6 – 8.8 min	>10 min	Coagulation factors	• R time 10-14 min – give 2 units FFP • R time >14 min – give 4 units FFP

Citrated Rapid TEG (CRT) Maximum amplitude (MA)	Highest vertical amplitude of the TEG	50.4-68.5 mm	<45 mm	Platelets and/or fibrinogen	• If **no active hemorrhage**, correlate with platelet count
					• If **active hemorrhage** or platelet count is not available:
					  • If CRT MA <45 mm and FFMA is >=12 mm – give 1 unit platelet and repeat platelet count to determine need for additional platelets.
					  • If CRT MA <45 mm and FMA <12 mm – see FFMA box below.
					• Consider DDAVP (0.3 mcg/kg up to 30 mcg IV total) for platelet dysfunction in renal insufficiency.

Functional fibrinogen maximal amplitude (FFMA)*	Measures the fibrinogen that actually contributes to the clot strength after blocking the platelet contribution	13.3 – 25.0 mm	<12 mm	Fibrinogen	• If **no active hemorrhage** and fibrinogen <100 mg/dl
					  • Give 1 pool of cryoprecipitate for patients <=70 kg, then recheck fibrinogen level
					  • Give 2 pools of cryoprecipitate for patients >70 kg, no need to recheck fibrinogen level
					• If **no active hemorrhage** and fibrinogen ≥100 mg/dl, no need for cryoprecipitate repletion
					• If **active hemorrhage** and FFMA <12 mm, give 1 pool cryoprecipitate and measure plasma fibrinogen level as soon as able.

Kaolin Lysis at 30 min (LY30)	Percentage of amplitude reduction 30 min after maximum amplitude	0.0 – 3.2%	>6%	Excess fibrinolysis	Give tranexamic acid 10-20 mg/kg IV bolus or aminocaproic acid 100 mg/kg IV bolus up to maximum dose of 5 g IV

*FFMA is reflected on the TEG curve as CFF (citrated functional fibrinogen)

TEG 1 interpretation for non-heparinized patients

Components	Definition	UCM Normal Values for TEG 5000 (TEG 1)	Cut-Off Values for correction	Problem with	Management
Kaolin R time	Time to start forming clot	4 - 8 min	>10 min	Coagulation factors	• R time 10-14 min – give 2 units FFP • R time >14 min – give 4 units FFP
Kaolin With Citrated Plasma (CK) Maximum amplitude (MA)	Highest vertical amplitude of the TEG	57 – 74 mm	<50 mm	Platelets and/or fibrinogen	• If **no active hemorrhage**, correlate with platelet count. • If **active hemorrhage** or platelet count is not available: • If plasma fibrinogen level is >100 mg/dL and CK MA <50 mm – give 1 unit platelet and repeat platelet count to determine need for additional platelets • Consider DDAVP (0.3 mcg/kg up to 30 mcg IV total) for platelet dysfunction in renal insufficiency
Kaolin Lysis at 30 min (LY30)	Percentage of amplitude reduction 30 min after maximum amplitude	0.0 - 5.0%	>6%	Excess fibrinolysis	• Give tranexamic acid 10-20 mg/kg IV bolus or aminocaproic acid 100 mg/kg IV bolus up to maximum dose of 5 g IV

Medications to Avoid in Cirrhotics

- **Tylenol:** Ok up to 2g daily in short term! Watch total daily dose with combo meds.
- **Opiates:** Avoid due to sedation/encephalopathy. If necessary, use lowest dose with longer intervals. Tramadol if no seizure history. Hydromorphone first line opiate if concomitant renal failure. Try alternatives, local options (lidocaine patch up to 3 at once), neuropathic options like gabapentin (starting dose 300 mg daily).
- **NSAIDs:** Avoid due to increased risk of bleeding, impaired renal function, worsened ascites/edema.
- **Benzodiazepines:** Avoid due to sedation/encephalopathy, especially long acting (chlordiazepoxide). If needed for withdrawal, use short acting (lorazapam). If patient using at home, do not stop abruptly as can precipitate withdrawal.
- **Sleeping aids/sedatives:** Avoid unless home med or has been discussed with day team. Consider melatonin, low dose antidepressants with sedative side effects.
- **Heparin prophylaxis:** Hold if concern for active bleed, if platelets 30 or less (do not use cutoff of 50 for holding as patients prothrombotic).
- **ACE/ARBs:** Avoid in patients with ascites.

Immunosuppression in Liver Transplantation

Background

- If technical expertise is the foundation of a successful liver transplantation, immunosuppression is the backbone for graft and patient survival.
- Optimal level of immunosuppression is delicate balance between maintaining a healthy graft and minimizing adverse effects from medications.

Classifications

1. **Induction agents**
    a. Methylprednisolone/prednisone, IL-2 inhibitor (basiliximab), antithymocyte globulin
2. **Maintenance agents**
    a. **Core**: calcineurin inhibitors (cyclosporine, tacrolimus)
    b. **Adjunct:** anti-metabolite agents (azathioprine, mycophenolate mofetil, mycophenolate sodium), mTOR inhibitors (everolimus, sirolimus)

Maintenance Regimen

- Typically consist of core agent alone (i.e. tacrolimus) or combination of core agent + adjunct agent (e.g., calcineurin inhibitor and MMF, calcineurin inhibitor and mTOR inhibitor)
- **Choice of immunosuppression is tailored to an individual patient** based on multiple factors, including age, indication for transplant, co-morbidities (e.g., renal insufficiency, diabetes, neurologic diseases), adverse drug effects experienced by patient, presence of simultaneous heart or kidney transplant.
- Level of immunosuppression to be maintained is also **dependent any history of graft rejection and the time interval from liver transplantation**, with patients who are farther out typically requiring less immunosuppression.
    - Target trough drug levels are individualized for each patient using a combination of all these factors, so review of previous drug levels maintained specifically for the patient is the best way to determine the level to be targeted.

Monitoring/Adjustments

- Measure trough levels for cyclosporine, tacrolimus, everolimus and sirolimus 1 hour before the dose. Usually dosed 0600/1800.
    - Order 0400 labs as often drawn late. Tacro levels can be added on to lavender top (CBC).
    - Check actual timing of lab draw and dose to confirm true trough before any adjustment.
    - New balanced state is achieved 48 hours after a change in dose for the calcineurin inhibitors and approximately 5 days after a change in dose for mTOR inhibitors.

- Do NOT need drawn daily if no concerns for toxicity and not adjusting dose.
- *UofCism:* Although mycophenolic acid levels can be measured, our liver transplant program prefers to give flat doses of MMF/mycophenolic acid.

- Consider holding if concern for drug toxicity (i.e. AKI or concern for tac toxicity) or severe systemic infection. Do NOT hold immunosuppression without discussing with liver fellow/transplant pharmacy.
- **Immune Function Assay (Immunknow®):** another method of measuring degree of immunosuppression, used in conjunction with drug levels. Measures amount of ATP released from T-lymphocytes in response to stimulation with phytohemagglutinin, representing responsiveness of T-lymphocytes, which in turn reflects the degree of immunosuppression.

Maintenance Immunosuppressive Agents

Classification	Drugs	Trough Levels Monitoring	Common Adverse Effects
Corticosteroids	Methylprednisolone Prednisone	No	DM, HTN, dyslipidemia, weight gain, bone disease, psychiatric symptoms
Calcineurin inhibitors	Cyclosporine Tacrolimus	Yes	DM, HTN, dyslipidemia, **renal insufficiency, hyperkalemia,** hypomagnesemia, neurologic symptoms
Antimetabolites	Azathioprine Mycophenolate	MPA levels not being monitored by our program	**Leukopenia**, GI symptoms (mycophenolate), pancreatitis (azathioprine) Teratogenicity (mycophenolate)
mTOR inhibitors	Everolimus Sirolimus	Yes	Bone marrow suppression, proteinuria (no effect on creatinine), hypertriglyceridemia, edema, HTN, poor wound healing, pulmonary fibrosis (rare)

References

- *Lucey MR, Terrault N, Ojo L, et al. Long-Term Management of the Successful Adult Liver Transplant: 2012 Practice Guideline by AASLD and the AST. Accessed at https://www.aasld.org/sites/default/files/guideline_documents/managementadultltenhanced.pdf on May 28, 2019.*
- *Moini M, Shcilsky ML, Tichy EM. Review on immunosuppression in liver transplantation. W J Hepatology 2015;7:1355-1368*

Radiologic Imaging of the Liver

1. **Ultrasound abdomen limited** (includes portal vein doppler)
    a. Demonstrates hepatic parenchyma, gallbladder morphology and contents, bile duct size, portal vein patency and direction of flow
    b. Easy to obtain, no radiation
    c. Images only part of the liver at a time
    d. Limited characterization of liver lesions except for cysts
    e. Does not detect biliary strictures or partial obstruction that have not produced biliary dilation
    f. Liver contour evaluation has a sensitivity of 13-88% and specificity of 78-95% for cirrhosis
    g. Low penetrance of ultrasonic waves in patients with fatty liver or cirrhosis
    h. Best modality to evaluate gallbladder

2. **Ultrasound with dopplers** (usually ordered for transplanted liver)
    a. Ultrasound plus evaluation of the hepatic artery and hepatic vein flow

3. **CT scan with IV contrast** (no oral contrast needed if liver is the only area of interest)
    a. Provides more parenchymal details than US
    b. Triple phase contrast protocol allows for better sensitivity in detecting vascular liver lesions (e.g., hepatocellular carcinoma) and better characterization of liver lesions in general
    c. Allows better delineation of vasculature, lymph nodes
    d. Radiation exposure, potentially nephrotoxic IV contrast

4. **MRI scan with IV contrast**
    a. Provides more parenchymal details than US and CT scan
    b. Multiple sequences allows for better characterization of liver lesions that are not well characterized on CT scan
    c. No radiation exposure, nonnephrotoxic IV contrast
    d. UCM uses doltarem for contrast, which has no known reports of nephrogenic systemic fibrosis, consider risk discussion with patients whose GFR <30 cc/min
    e. Use in patients with ESRD requires intensified daily dialysis for the next 3 days
    f. Presence of metal surgical clips or TIPS stent produces artifacts
    g. Presence of ascites degrades image quality
    h. Requires patients to hold breaths longer than CT and tolerate enclosed space
    i. Higher cost than CT

5. **MR Cholangiopancreatography - MRCP** (without IV contrast if only looking for biliary evaluation, with contrast if eval for liver per above)
    a. Provides detailed evaluation of the biliary tree to detect biliary strictures (even in the absence of biliary dilation on US), bile duct stones, or biliary tumors
    b. Provides a "map" for endoscopist when doing ERCP
    c. Does not visualize ampullary region well

6. **HIDA scan**
    a. Evaluates the patency of cystic duct and contractility of the gallbladder
    b. Inaccurate in patients with hyperbilirubinemia (due to delayed excretion of tracer from the liver itself)
    c. Can detect bile leaks

7. **Vibration-controlled Transient Elastography (Fibroscan®)**
    a. Ultrasound based test that measures fat content of the liver (qualitatively) and elasticity of the liver, which corresponds to degree of fibrosis
    b. Only tests one point of the liver
    c. Inaccurate in passive congestion of the liver, severe inflammation (acute hepatitis), postprandial hyperemia (3 hours fasting required), severely obese individuals

8. **MR Elastography**
    a. Measures fat content of the liver (quantitatively) and elasticity of the liver, which corresponds to degree of fibrosis
    b. Measurements are taken at four random points of the liver
    c. Produces an elastography map of the entire liver (similar to a heat map)
    d. Inaccurate in passive congestion of the liver, severe inflammation (acute hepatitis), high hepatic iron burden

References

- *O'Neill EK, Cogley JR, Miller FH. The ins and outs of liver imaging. Clin Liver Dis 2015:19:99-121*
- *Tapper E and Lok AS. Use of liver imaging and liver biopsy in clinical practice. NEJM 2017;377:756-768*