Banner University Medical Center

Liver Handbook

Ma Ai Thanda Han, MD

Michael Fallon, MD

Moises Ilan Nevah Rubin, MD

Rohit Nathan, MD

Mark Wong, MD

Karn Wijarnpreecha, MD

Transplant Hepatologists at Banner University Medical Center Phoenix

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"

Table Of Contents

Section 1: Cirrhosis and Portal Hypertension

Cirrhosis is a heterogenous disease with different prognostic stages. They are classified as compensated cirrhosis, decompensated cirrhosis. The decompensated cirrhosis can be further decompensated and finally multi-organ failure and death.

Stages of Cirrhosis[10,13-15]

Compensated Cirrhosis is defined by the absence of present or past complications of cirrhosis. It can be divided into 2 stages, based on the presence or absence of clinically significant portal hypertension CSPH. Patients with CSPH are at risk of decompensation. The goal of therapy in compensated cirrhosis is to prevent decompensation or complication by doing primary prophylaxis.

Decompensated Cirrhosis

Events that define decompensation in a compensated patient are

1. presence of overt ascites or pleural effusion with serum ascites albumin gradient >1.1 g/dl,
2. overt hepatic encephalopathy (West Haven Grade ≥II),
3. Variceal bleeding.

Decompensated Cirrhosis patient should be considered for liver transplantation.

There are insufficient data available to be considered decompensation regarding a minimal amount of ascites only detected in imaging procedures, minimal hepatic encephalopathy, and occult bleeding from portal hypertensive gastropathy.

There are also limited data to suggest that jaundice alone in non-cholestatic etiologies should be considered true first decompensation or reflection of superimposed liver injury or acute on chronic liver failure (ACLF)

The goal of therapy in decompensated cirrhosis is to prevent further decompensation, multi-organ failure, and finally death.

Other relevant liver- related events in compensated cirrhosis are the development of superimposed liver injury, or ACLF, and hepatocellular carcinoma (HCC).

Further Decompensation is defined if any of the following

1. Development of a 2nd portal hypertension driven decompensating even (ascites, variceal hemorrhage or hepatic encephalopathy) and/or jaundice

2. Development of recurrent variceal bleeding, recurrent ascites (required ≥3 large-volume paracentesis within 1 year), recurrent encephalopathy, development of SBP and /or HRS-AKI
3. In patients presenting with bleeding alone, development of ascites, encephalopathy or jaundice after recovery from bleeding but not if these events occur around the time of bleeding

Figure 1 summarized the spectrum of different stages of cirrhosis with their clinical presentation and correlation with HVPG measurement

Diagnosis of Portal Hypertension

There are invasive and non-invasive technique to diagnose portal hypertension

1. **Invasive Technique – Hepatic Venous Pressure Gradient (HVPG) via Trans jugular Portal Pressure Measurement approach (Gold Standard)**

HVPG is a surrogate marker for portal hypertension. It is the subtraction of free hepatic venous pressure from wedge hepatic venous pressure

HVPG =Wedge Hepatic venous Pressure (WHVP) – Free Hepatic Venous Pressure (FHVP)

Degree of Portal Hypertension	**Defined by HVPG**
Mild Portal hypertension	HVPG >5 <10 mmHg
Clinically significant portal hypertension (CSPH)	HVPG ≥10 mmHg
High risk of variceal hemorrhage	HVPG ≥12 mmHg

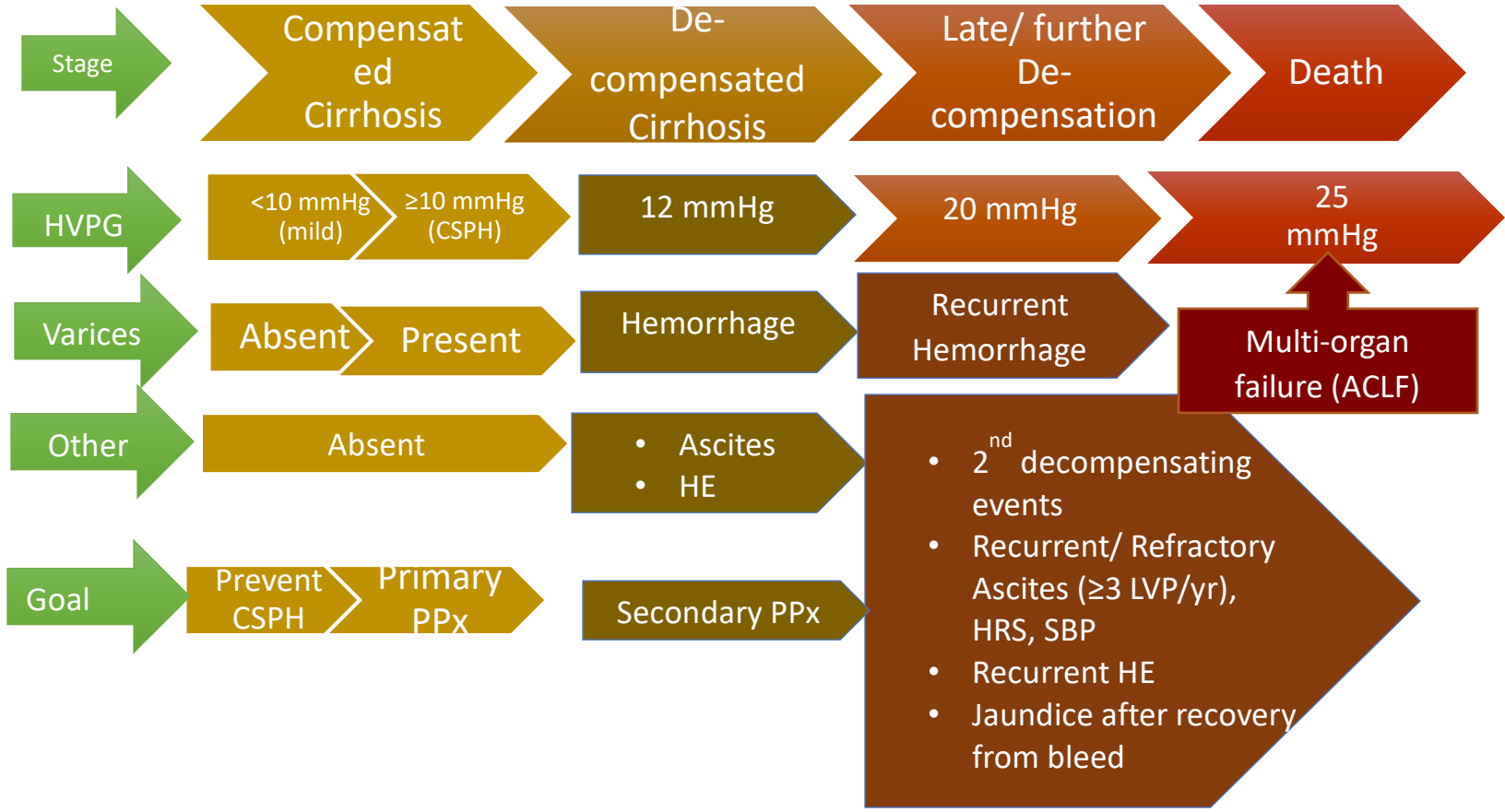
- Hepatic venous-to venous communications may result in underestimation of WHVP and must be reported
- WHVP-FHVP gradient has superior clinical prognostic value than WHVP-Right Atrial pressure gradient
- Right atrial pressure can be measured to rule out a post-hepatic component of portal hypertension
- If free hepatic venous pressure >2 mmHg above IVC, injection of small amount of contrast medium is recommended to rule out presence of hepatic venous outflow obstruction
- Deep sedation during liver hemodynamic measurement may cause inaccurate HVPG value

- If light sedation is required, low dose midazolam (0.02 mg/kg) dose not modify the HVPG measurement and is acceptable.
- In patients with primary biliary cholangitis (PBC), HVPG may underestimate the prevalence & severity of portal hypertension as there is an additional pre-sinusoidal component of portal hypertension
- In patients with NASH cirrhosis, clinical signs of portal hypertension can also be present in small portion of patients with HVPG < 10 mmHg
- Chronic liver disease patients with signs of portal hypertension (esophageal/gastric varices, portosystemic collateral) but have HVPG <10 mmHg, Porto-sinusoidal vascular disorder (PSVD) must be ruled-out

Surgical Risks and HVPG

- In patients with cirrhosis undergoing liver resection for HCC, HVPG ≥ 10 mmHg or Clinical signs of portal hypertension is associated with higher risk of decompensation & mortality
- In patients with cirrhosis undergoing non-hepatic abdominal surgery, HVPG ≥ 16 mmHg is associated with increased risk of short-term mortality after surgery

Figure 1. The spectrum of different stages of cirrhosis with their clinical presentation and correlation with HVPG measurement



2. Non-invasive Tools for compensated advanced Chronic Liver Disease (cACLD)

- cACLD has been proposed to reflect the continuum of severe fibrosis and cirrhosis in patients with ongoing chronic liver disease
- The use of elastography in clinical practice has enabled for the early identification of patients with untreated/active chronic liver disease at risk of having CSPH and consequently, at risk of decompensation and liver related death
- There are liver stiffness (LSM) (Fig.2) and Spleen stiffness (SSM) (Fig 3) parameters to identify CSPH

Figure 2. noninvasive tools for cACLD and portal hypertension – Liver stiffness

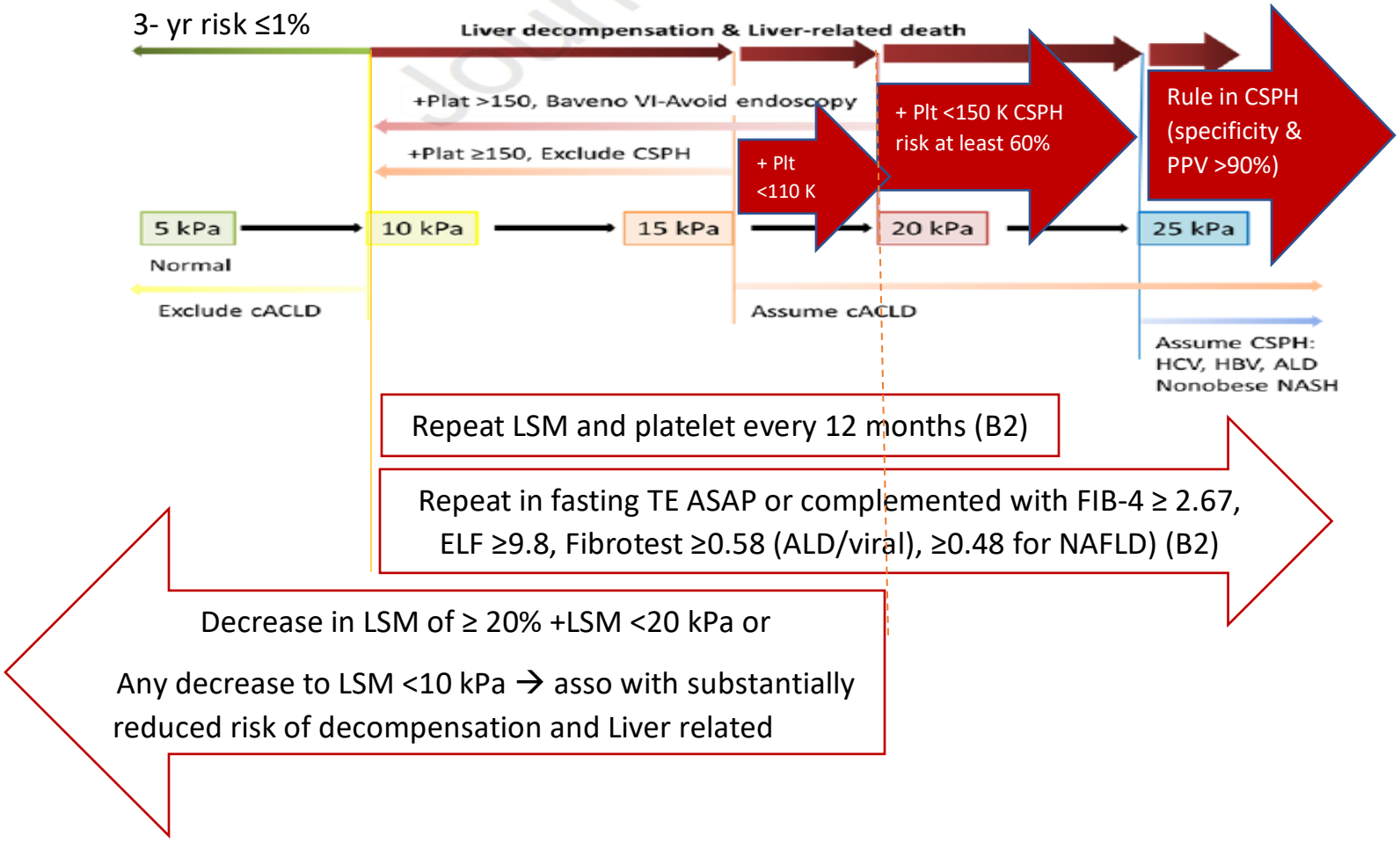


Figure 3. Noninvasive tool for cACLD and portal hypertension – Spleen stiffness

Spleen stiffness (SSM) (untreated HCV, HBV) <21 kPa → rule out CSPH [B2]

Validation -Using 100 Hz specific TE probe, as well as point shear wave and 2 D shear wave elastography is needed

Spleen stiffness (SSM) (untreated HCV, HBV) >50 kPa → rule in CSPH [B2]

Patients not candidate for NSBBB & in patients with LSM ≥ 20 kPa or Plt count ≤ 150 x 10^9 → SSM <40 kPa (low probability of high risk varices)→ can avoid EGD (C2)

Precipitation Factor for Decompensation in Compensated Cirrhosis with CSPH

- Bacterial infections in compensated patients with CSPH [B1]
- Superimposed liver damage
  - acute alcoholic hepatitis, acute viral hepatitis (HEV, HAV), HBV flares or drug induced [A1]
- Hepatocellular carcinoma (HCC) [B1]
- Major surgery [B1]

Should consider NSBBs (propranolol, nadolol or carvedilol) [B1]

<u>Carvedilol is preferred NSBB in compensated cirrhosis</u> [A1]

→ as more effective at reducing HVPG [A1]
→ Greater benefit in preventing decompensation
→ Towards better tolerance than traditional NSBBs

No indication to use NSBBs in patients without CSPH [A1]

Screening & Primary Prophylaxis of Varices

Pt characteristic	Screening Interval	Primary Prophylaxis
Cirrhosis	At time of Dx	**Risk for Varices→ virus, alcohol, non-obese NASH (BMI<30kg/m2)** Liver stiffness (TE) + Platelet ≥25kPa → CSPH (specificity & PPV >90%) [B1] 20-25 kPa + Plt <150 → CSPH (at least 60%) [B2] 15-20 kPa + PLT <110 → CSPH (at least 60%) [B2] <15 kPa +Plt ≥ 150 → rule out CSPH (sensitivity & NPV 90%) [B2]
Compensated Cirrhosis, No Varices	2 yr (ongoing injury) 3 yr (quiescent) at time of decompensate	
Compensated Cirrhosis with Varices	1 yr (ongoing injury) 2 yr (quiescent) at time of decompensate	**Carvedilol>>>NSBB¥** (small varices - start NSBB if high risk feature#)
DeCompensated Cirrhosis, +/-Small Varices	Yearly	Carvedilol or NSBB if small varices without high risk#
Medium/Large Varices or Child C	Yearly	Carvedilol or NSBB>>> EVL Carvedilol ¥>>> NSBB in compensated cirrhosis

- no EGD after Beta blocker in compensated COL if patient is effectively beta blockage
- Pts with ascites who are not on NSBB or carvedilol should undergo screening EGD

*EVL= Endoscopic Variceal Band Ligation

¥Carvedilol >>>NSBBB in compensated cirrhosis since it is more effective in reducing HVPG and tendency towards greater benefit to prevent decompensation and shown an improvement in survival

¥Compensated patients with high-risk varices who have contraindications or intolerance to NSBB→ Endoscopic band ligation to prevent 1st variceal bleeding

High risk varices –red spot sign, medium or large varices (≥5 mm), or Child-Pugh Class or Small varices in Child-Pugh C

- cACLD on NSBB without evident CSPH (LSM<25kPa) in compensated cirrhosis after removal/suppression of primary etiology →should consider for repeat EGD after 1-2 year. If negative varices→ Consider to discontinue NSBB [C2]
- In recompensated cirrhosis→ NSBB should not be discontinued unless CSPH resolve
- LSM<20 kPa + >150 (HCV SVR & HBV with viral suppression)→ avoid EGD
- HCV s/p SVR (without other co-factors such as DM, obesity) with LSM <12 kPa+Plt >150→ can be discharged from EGD surveillance, but needs to continue HCC surveillance
- Compensated cirrhosis not candidate for NSBB & LSM TE ≥20 kPa or Plt ≤ 150 → should undergo EGD

Therapy for Primary Prophylaxis/ Moderate or Large Esophageal varices that Have Not Bled

Therapy	Dose	Goal	Maintainace/follow up
Carvedilol	**Carvedilol¥** • Start with 6.25 mg daily • After 3 days, increase to 6.25 mg bid • Max 12.5 mg/day (except in patients with persistent arterial hypertension)	• SBP not <90 mmHg	• Every OPD visit – make sure HR is on target except carvedilol • Indefinitely • No need for FU EGD
Propranolol	Propranolol • 20-40 mg bid • Adjust every 2-3 D • Max 320 mg/d without ascites • Max 160 mg/d with ascites	• Resting HR 55-60/min • SBP not <90 mmHg	
Nadolol	Nadolol • 20-40 mg bid • Adjust every 2-3 D • Max 160 mg/d without ascites • Max 80 mg/d with ascites		
EVL	• Every 2-8 weeks until eradication of varices	• Variceal eradication (no further ligation possible)	• 1st EGD in 3-6 months after eradication & every 6-12 months

Acute Variceal Bleeding (AVB)

Should do Abdominal image (preferred contrast CT/MRI) to exclude splanchnic vein thrombosis and HCC and to map portosystemic collateral (Baveno VII)

A, B, C (volume resuscitation with Crystalloids or colloids)

- Intubate before EGD- pts with AMS & those actively vomiting blood
- Extubate as quick as possible after EGD (Baveno VII)

Vasoconstrictor

Octreotide IV 50 ug bolus f/b infusion 50 ug/hr) at time of admission x 2-5 days

EGD Variceal Ligation (EVL)

<12 hours after admission

Erythromycin - consider prior EGD (250 mg IV 30-120 min prior)

Antibiotic

IV Ceftriaxone 1 g/day or Norfloxacin PO 400 mg bid x 5-7Ds or until discharge

Blood Transfusion

GOAL Hb 7-8

Oral nutrition -start ASAP as malnutrition increase the risk of adverse outcomes (Baveno VII)

Control

5-Day failure (uncontrol/further bleeding within 5 Days

Bridge- self expandable metal stents (SEMS)>> Balloon tamponade (SEMS-as efficacious as Balloon & safer)

Secondary Prophylaxis (below)

Non High Risk Patients

EVL + NSBB

High Risk patients (EV, GOV1, GOV2)

(Child C with score <14, or Child B >7 with active bleeding at initial EGD, or HVPG>20 mmHg) [A1]

Early Pre-emptive TIPS* with PTEF covered stents within 72 hr, ideally 24 hr[10-12]

- After stabilizing & hemostatic tx with vasoactive drugs +EVL
- ACLF, HE & hyperbilirubinemia at admission should not be considered as contraindication

Transjugular Intrahepatic Portosystemic Shunt (TIPS) - PTFE covered TIPS

Treatment of Choice for Rescue Therapy

Reduction in HVPG[£]

1. <12 mmHg (prefer 10-12 mmHg) (small diameter 6-8 mm TIPS)
2. >20% from baseline

PTFE= polytetrafluoroethylene

TIPS may be futile

- Child ≥14 cirrhosis, or
- MELD >30 and lactate >12 mmol/l unless liver transplantation is shortly envisioned

Decision to perform TIPS- case by case basis

* **Current structure of our program may not be able to perform early pre-emptive TIPS**

- PPIs, when started before endoscopy, should be stopped immediately after the procedure unless there is a strict indication to continue them
- Hemostatic powder cannot be recommended as first-line endoscopic therapy for AVB.
- TIPS – Treatment of Choice if rebleed despite NSBB or carvedilol and EVL
- If patient who cannot get/tolerate EVL or carvedilol/NSBBB→ any of therapy can be alone and TIPS should be considered in patients with recurrent ascites
- If patient remains intolerant to NSBB, EVL is recommended

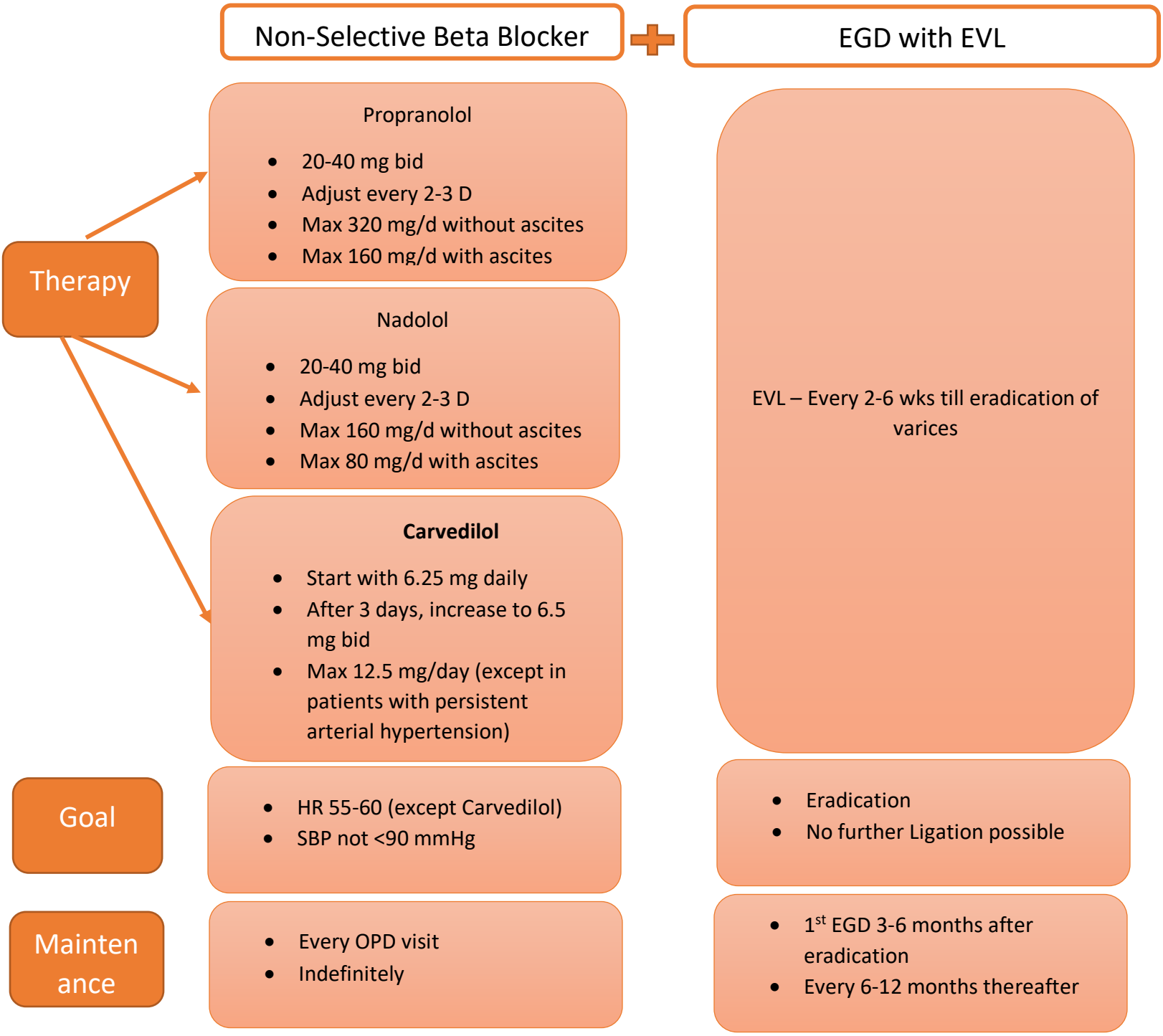
Coagulation & AVB

- Conventional coagulation tests (PT/INR, APTT) – not accurately reflect hemostatic status
- Platelet count & fibrinogen levels – no evidence of correlation with risk of failure to control bleeding or re-bleeding
- Focus on lower portal pressure rather than correcting coagulation abnormalizes
- FFP is not recommend as it will not correct coagulopathy and may lead to volume overload & worsening of portal HTN
- Platelet or fibrinogen transfusion decision- considered on case-by-case basis
- Patients with AVB on anticoagulants→ temporarily discontinued till hemorrhage is under control
- Length of discontinuation of anticoagulants should be individualized based on strength of indication for anticoagulation
- In patients with Cirrhosis and PVT, AVB management should be performed according to the guidelines for patients without PVT, when possible

Hepatic Encephalopathy & AVB

- Prevent hepatic encephalopathy in AVB- lactulose oral or enema should be used (rapid removal of blood from GI tract)
- Bout of hepatic encephalopathy in AVB – treated with lactulose oral or enema

Prevention of Recurrent Bleeding (Secondary Prophylaxis) – 1st line therapy



NSBBs should be temporarily held

(NSBB - reinitiated or re-titrated) once resolved)

Hypotension (SBP<90 mmIg or MAP <65 mmHg)

or

AKI (Acute Kidney Injury) or Sepsis or SBP

Refractory Ascites & SBP

Avoid high dose NSBB

(not >160 mg of propranolol or >80 mg of nadolol --> worse outcomes)

Gastric Varices who never bleed

Prevention of bleeding from

GOV1 → Same as EV

GOV 2 or IGV 1 → NSBBS can be used

Neither TIPS or BRTO prevent 1st hemorrhage

GOV 1= EV extending below the cardia into the lesser curvature and are the most common (75% of GV).

GOV type 2 (GOV2) = those extending into the fundus.

IGV 1= Isolated GV type 1 are in the fundus

IGV 2= Isolated GV type 2are located elsewhere in the stomach

Acute Gastric Variceal Bleeding

GOV1 Bleeding → either EVL or Cyanoacrylate glue injection

GOV2 (extend beyond cardia) or IGV1 or ectopic Bleeding → Cyanoacrylate glue
TIPS or BRTO/BATO
consider TIPS+embolization[$]

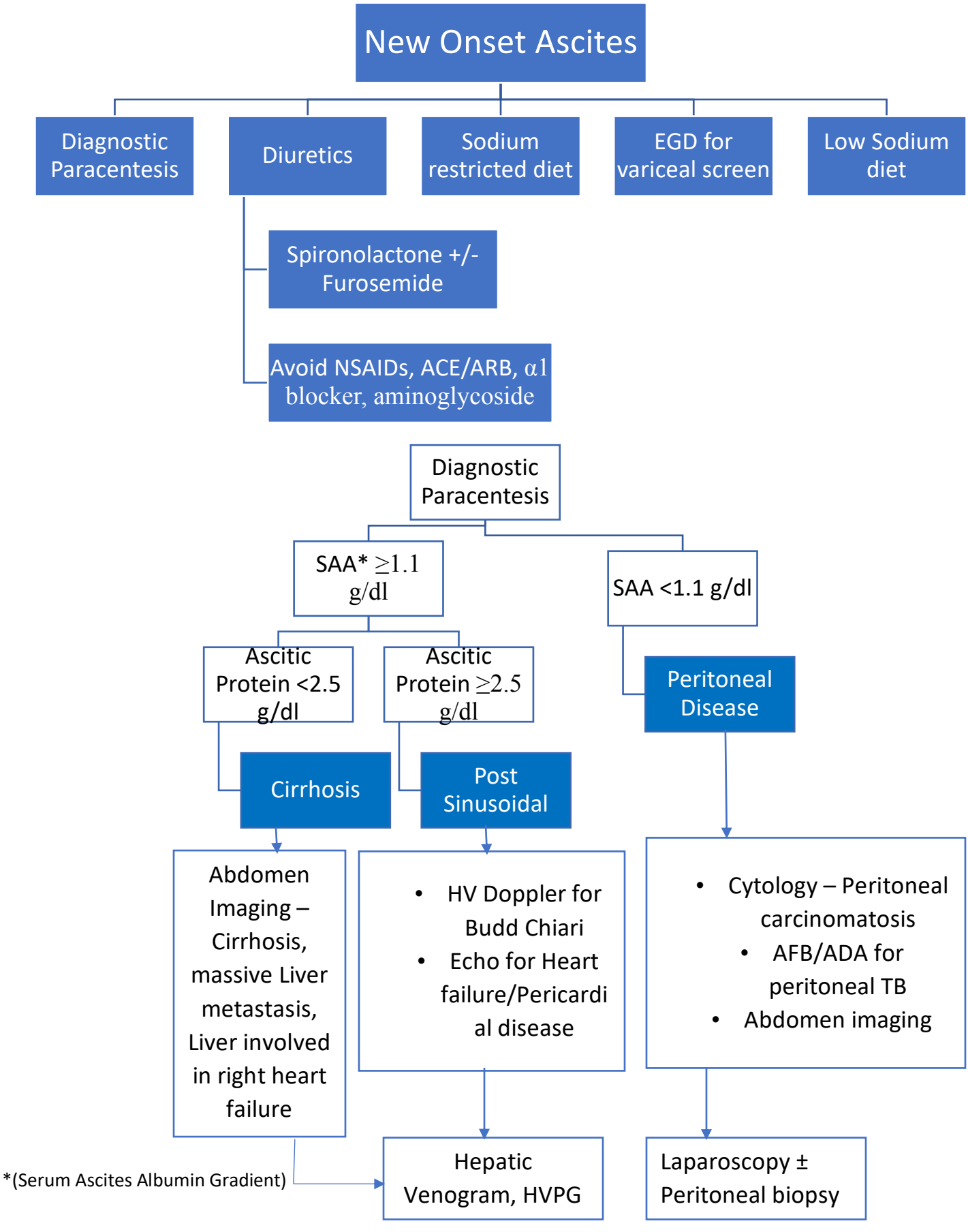
\+ NSBB once stabilize

[$]TIPS may be combined with embolization in gastric or ectopic varices bleeding to control bleeding or to reduce the risk of recurrent, particularly in cases when, despite a decrease in portosystemic pressure gradient, portal flow remains diverted to collaterals

Portal Hypertensive Gastropathy (PHG) & Intestinopathy

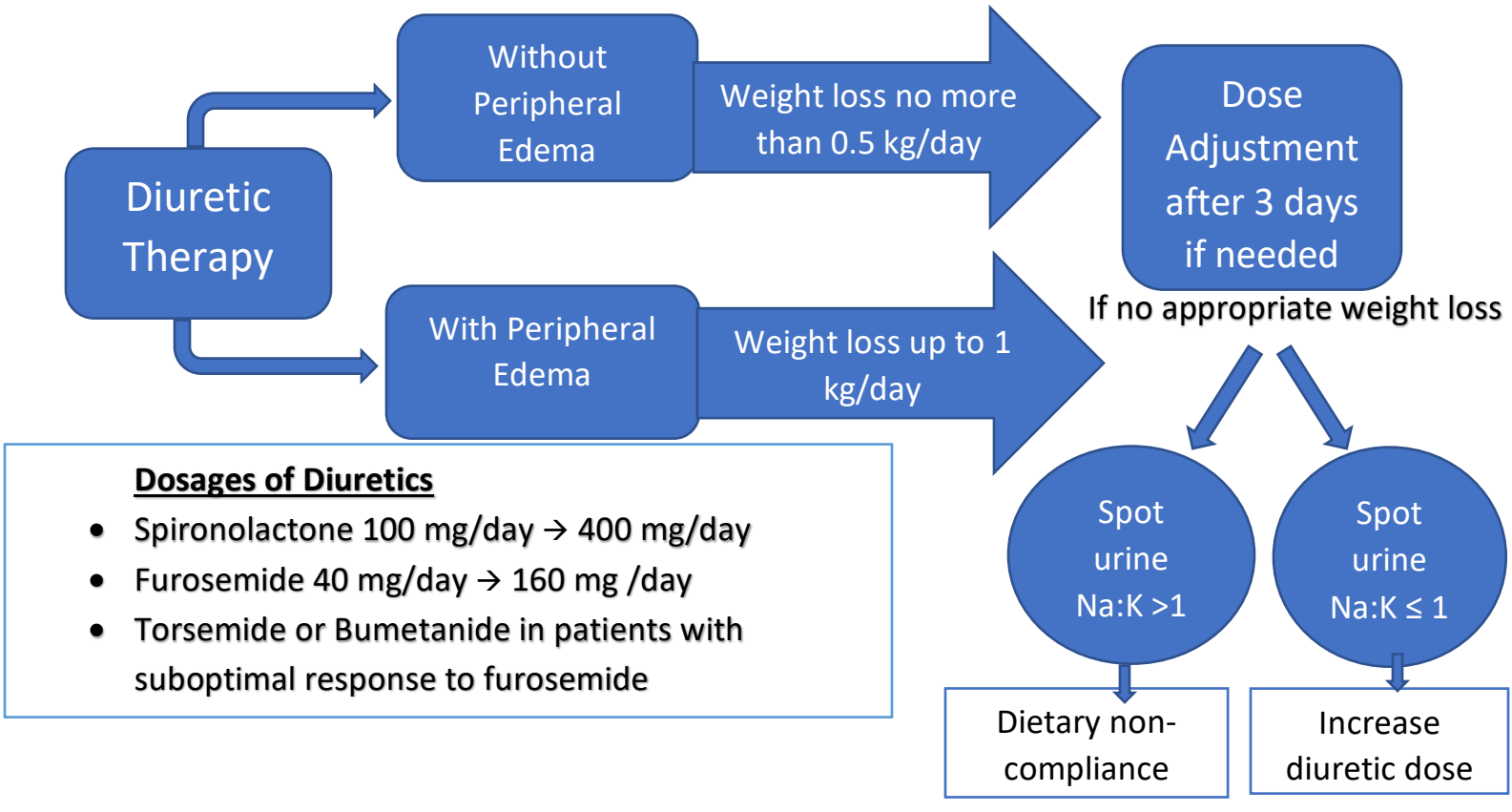
Chronic Hemorrhage from PHG	-Endoscopic (APC, RFA or band ligation for PHGand GAVE) ?hemospray PHG (may be) -NSBBs & Iron +/- blood
Transfusion dependent PHG with failed/intolerable NSBBs	Covered TIPS if no contraindication
Acute Hemorrhage from PHG	may be Octreotide gtt

Ascites


New Onset Ascites
Diagnostic Paracentesis
Diuretics
Sodium restricted diet
EGD for variceal screen
Low Sodium diet
Spironolactone +/- Furosemide
Avoid NSAIDs, ACE/ARB, α1 blocker, aminoglycoside
Diagnostic Paracentesis
SAA* ≥1.1 g/dl
SAA <1.1 g/dl
Ascitic Protein <2.5 g/dl
Ascitic Protein ≥2.5 g/dl
Peritoneal Disease
Cirrhosis
Post Sinusoidal
Abdomen Imaging – Cirrhosis, massive Liver metastasis, Liver involved in right heart failure
• HV Doppler for Budd Chiari
• Echo for Heart failure/Pericardial disease
• Cytology – Peritoneal carcinomatosis
• AFB/ADA for peritoneal TB
• Abdomen imaging
Hepatic Venogram, HVPG
Laparoscopy ± Peritoneal biopsy
*(Serum Ascites Albumin Gradient)

Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (large or gross)

• Only detected by USG
• Responsive ascites
	• Moderate symmetric distension
	• **Recurrent Ascites**
	  • (at least 3 times within 1 year despite diet & diuretic)
		• Marked distension
		• **Refractory Ascites**
		  • **Diuretic Resistant** (Persistent despite max dose of diuretic)
		  • **Diuretic Intractable** (SE preclude use of max ascites)



Dosages of Diuretics

- Spironolactone 100 mg/day → 400 mg/day
- Furosemide 40 mg/day → 160 mg /day
- Torsemide or Bumetanide in patients with suboptimal response to furosemide

Dosage Conversion

- Conversion: Spironolactone 100 mg → 50 mg Eplerenone →10 mg amiloride
- Conversion: Furosemide 40 mg PO→Furosemide 20 mg IV→ torsemide 20 mg po → Bumetanide 1 mg po/IV

Monitor Electrolytes – Hypo K and Hypo Mg

Muscle Cramps- consider electrolytes imbalance

MgO

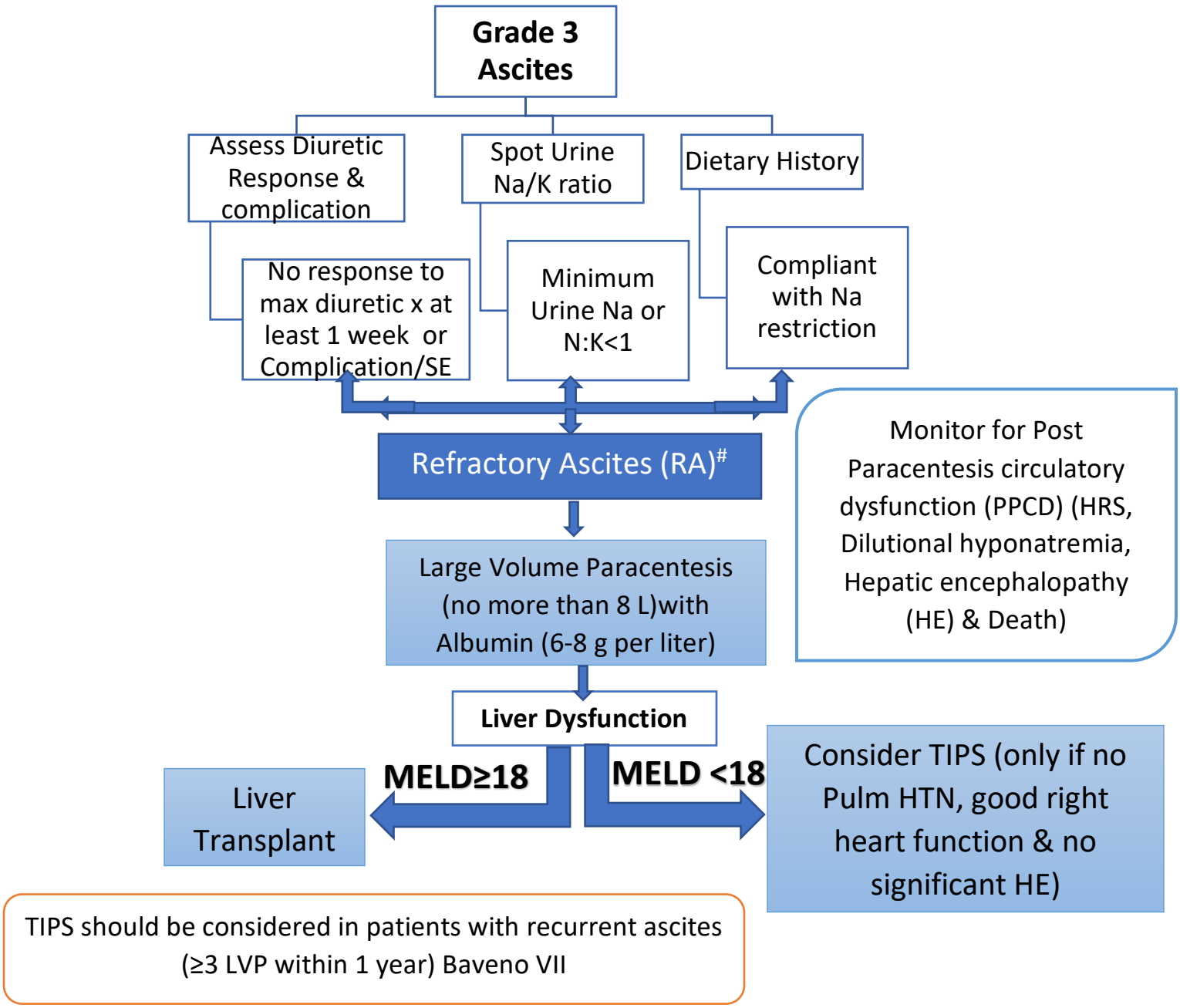
L-Carnitine 500 mg tid

Tonic water with quinin 8 ounces bid (check QT) with Lemon juice

Consider Baclofen 10 mg/day (can increase weekly by 10 mg/day up to 30 mg/day) & albumin (20-40 g/wk)

Quinidine 400 mg/day x 4 weeks (toxicity: diarrhea), Orphenadrine, methocarbamol

- Beta blocker – is not contraindicated in Refractory Ascites
- Caution/Hold-in patients with hypotension (mean arterial pressure <65mmHg), hyponatremia or AKI till it is resolved
- Reinitiate &/or re-titrate the dose once the issues resolve
- Avoid high dose NSBB (not>160 mg of propranolol or >80 mg of nadolol) in RA & SBP→ worse outcomes)



#Even though Baveno & AASLD recommends the consideration of TIPS in patients > 3LVP/year, **our program recommend to consider TIPS in anyone who is having > 6 paracentesis within a year.**

TIPS Recommendation

For TIPS insertion for refractory ascites

Both Baveno VII[10] and ATLA[17] (North American practice-based recommendation based on Advancing Liver Therapeutic Approaches Consensus recommend the following:

- use ePTFE covered controlled expansion stent –start at 8 mm diameter
- Reassess in 4-6 wks for clinical response
- If no response, → consider expansion of TIPS (8→10mm)
- Monitor TIPS with doppler ultrasound 3 months later, then every 6 months for TIPS patency and function
- Elective TIPS for ascites and/or variceal hemorrhage, embolization of spontaneous portosystemic shunt (SPSS) >6 mm may be considered to reduce the risk of post TIPS hepatic encephalopathy (ALTA)

Portal Pressure Gradient (PPG) Measurement in TIPS

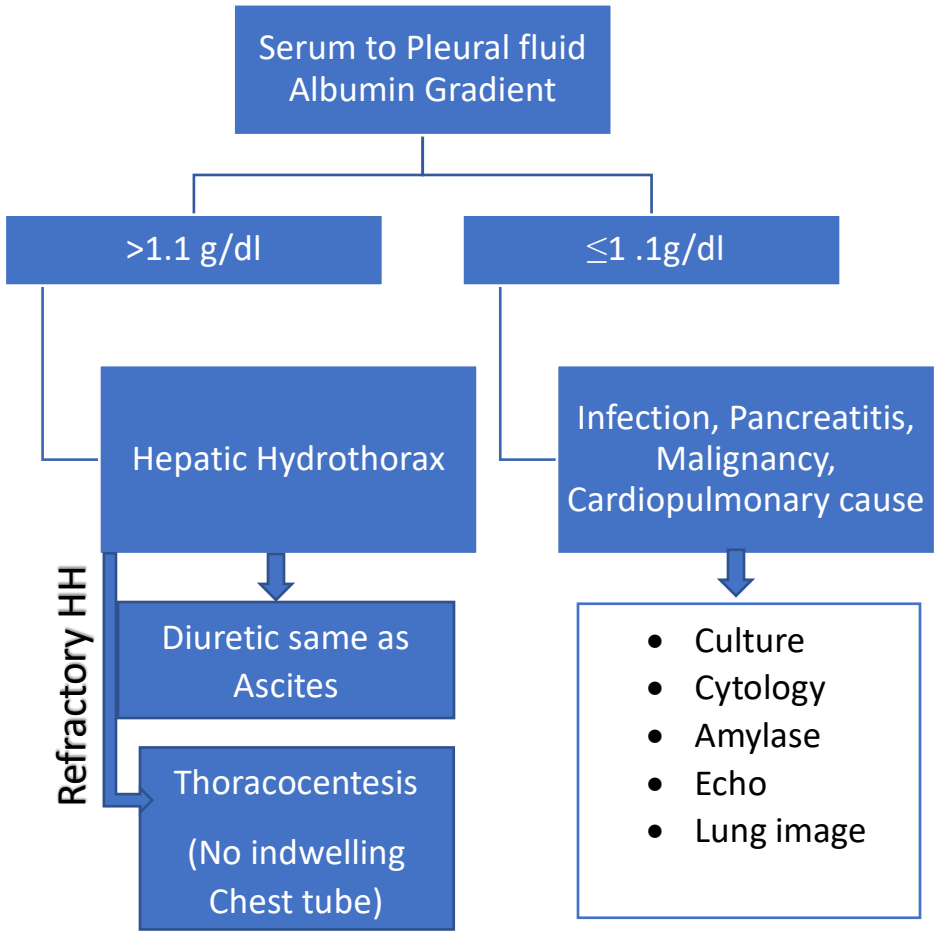
- Portal Pressure Gradient (PPG) – should be measured before & after TIPS insertion
- Anatomic locations for post-TIPS PPG measurement- should include main PV and IVC
- Immediate post TIPS PPG – influenced by general anesthesia, use of vasoactive agents or hemodynamic stability, therefore immediate post TIPS PPG may not represent long – term PPG
- PPG measurements in hemodynamically stable, non-sedated patients better reflect post TIPS PPG value
- PPG re-measurement is indicated if there is clinical or doppler ultrasonographic suspicion of TIPS dysfunction
- Monitor TIPS function → 3 months after TIPS insertion, then every 6 months with doppler ultrasound
- PPG < 12 mmHg → prevent ascites and bleeding
- PPG >10 mmHg → increase the risk of hepatic encephalopathy and liver failure

ALTA guidance for TIPS in non-transplant surgery with portal hypertension[17]

- Insufficient evidence to recommend preoperative TIPS prevent bleeding or need for blood transfusion during or after procedure

- Patient without clinically significant ascites →Insufficient evidence to recommend preoperative TIPS to prevent complications of ascites
- Patient with clinically significant ascites→ multidisciplinary approach (hepatology & HB surgery) to individualize management
- No evidence that pre-operative TIPS has an impact on post op mortality

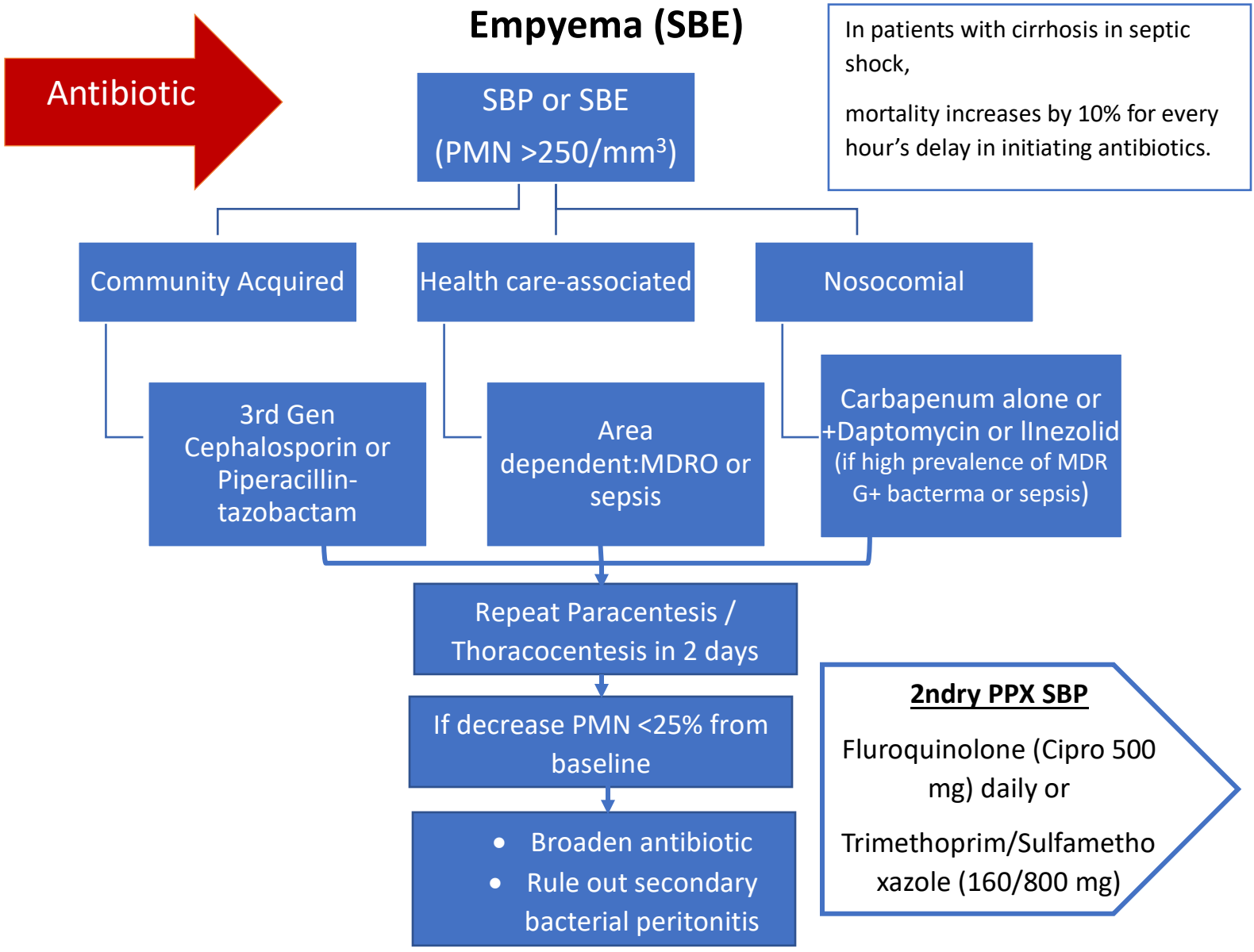
Hepatic Hydrothorax



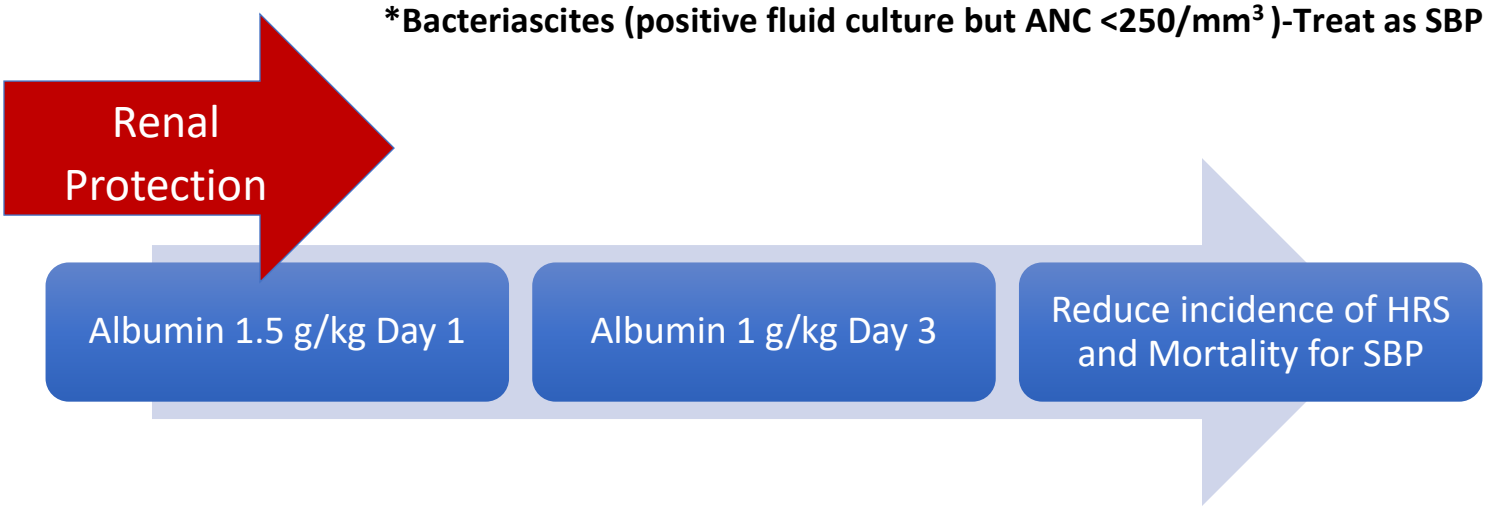
Transplant Criteria for HH (MELD exception-nonstandard)

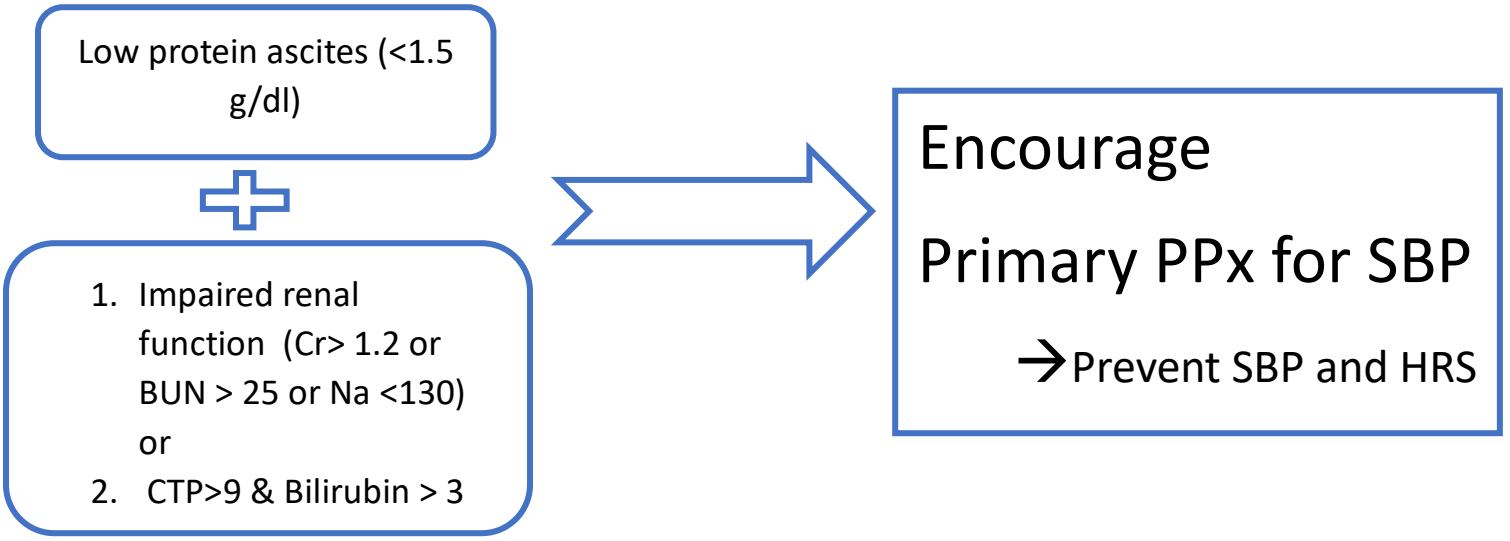
1. At least 1 thoracocentesis weekly x last 4 weeks (report date & volume of each)
2. Transudative pleural fluid (Pleural albumin-serum album gradient ≥1.1 g/dl and by cell count
3. No evidence of Heart failure (objective evidence)
4. Pleural fluid culture negative x 2 separate occasions
5. Pleural fluid cytology- benign on 2 perpetrate occasions
6. Contraindication to TIPS – specify

Spontaneous Bacterial Peritonitis (SBP) & Spontaneous Bacterial Empyema (SBE)



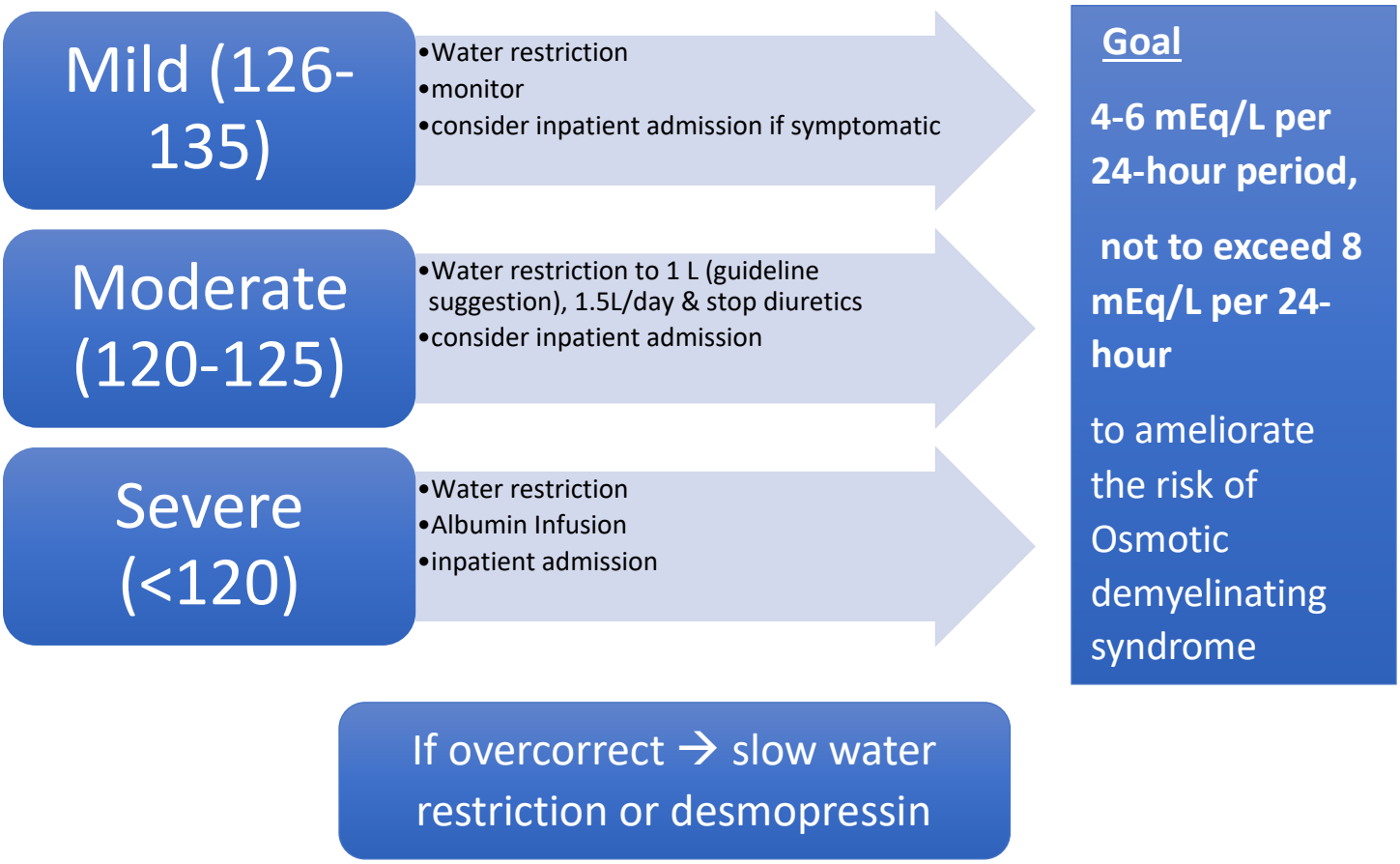
***Bacteriascites (positive fluid culture but ANC <250/mm³)-Treat as SBP**




Low protein ascites (<1.5 g/dl)
1. Impaired renal function (Cr> 1.2 or BUN > 25 or Na <130) or
2. CTP>9 & Bilirubin > 3
Encourage
Primary PPx for SBP
→Prevent SBP and HRS

Hyponatremia

Hyponatremia is associated with risk for developing hepatic encephalopathy (OR 3.4), hepatorenal syndrome (OR 3.5), SBP (OR 2.4), in-hospital and waitlist mortality



- **hypertonic saline – reserve for short term symptomatic severe or imminent LTx**

Renal Problem in Cirrhosis of Liver

Prevention of Acute Kidney Injury (AKI)[18,19]

SBP (sponetaneous Bacterial Peritonitis)	• Antibiotic • Albumin 1.5g/kg D1 & 1g/kg D3
LVP (large volume Paracentesis >4 liters)	• 8 g of albumin per liter

Albumin infusion should be strongly considered for paracentesis of a smaller volume if there is

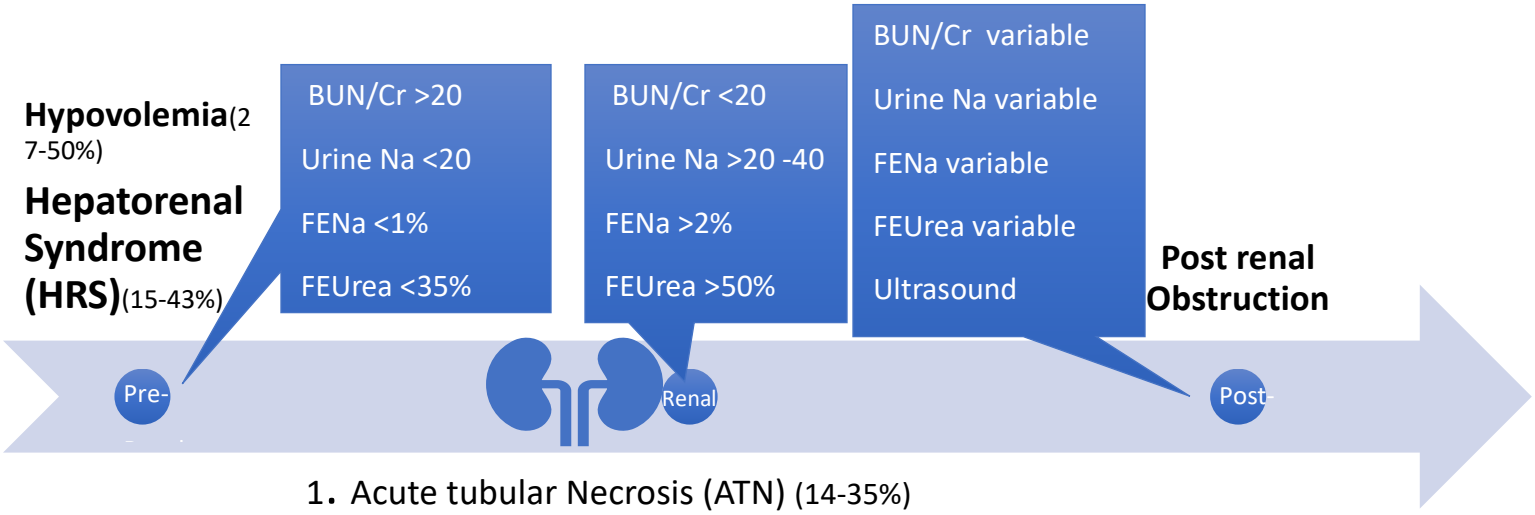
1. Hemodynamic instability (SBP <90 mmHg),
2. hyponatremia (serum sodium <130 mmol/L), and/or
3. the presence of AKI

Definition of AKI (International Club of Ascites ICA Consensus Recommendations 2015)[20]

- Increase in sCr ≥ 0.3 mg/dl (≥26.5 umol/l) within 48 hours or
- ≥ 50% increase in serum creatinine that is known or presumed to have occurred within the preceding 7 days

AKI Stage	Description
Stage 1	Increase creatinine ≥0.3 mg/dl up to 2-fold of baseline
Stage 2	Increase creatinine between 2-fold and 3-fold of baseline
Stage 3	Increase in creatinine >3-fold of baseline or creatinine >4 mg/dl (353.6 µmol/L) with an acute increase ≥0.3 mg/dl or initiation of renal replacement therapy

Etiology of AKI



1. Acute tubular Necrosis (ATN) (14-35%)

   - Septic Shock, Hypovolemic Shock, HRS Progress to ATN

2. Nephrotoxic drugs
3. Bile cast nephropathy (Hyperbilirubinemia)
4. Glomerulonephritis (GN)

   (Alcohol cirrhosis → IgA,

   HBV/HCV cirrhosis→ membranous or membranoproliferative GN)

- More likely to have CKD post LT if ATN present in pre LT
- ATN (non HRS AKI) impacts post LT mortality

Definition of HRS-AKI

- Cirrhosis with ascites
- No response after 2 consecutive days of diuretic withdrawal + Plasma volume expansion with albumin (1 g/kg/day)
- Absence of shock
- No current or recent use of Nephrotoxic drug (NSAIDs, Aminoglycosides or iodinated contrast media)
- No signs of structural kidney injury
  - Proteinuria (>500 mg/day)
  - Microhematuria (>50 RBC per high power field) &/or
  - Abnormal renal ultrasound

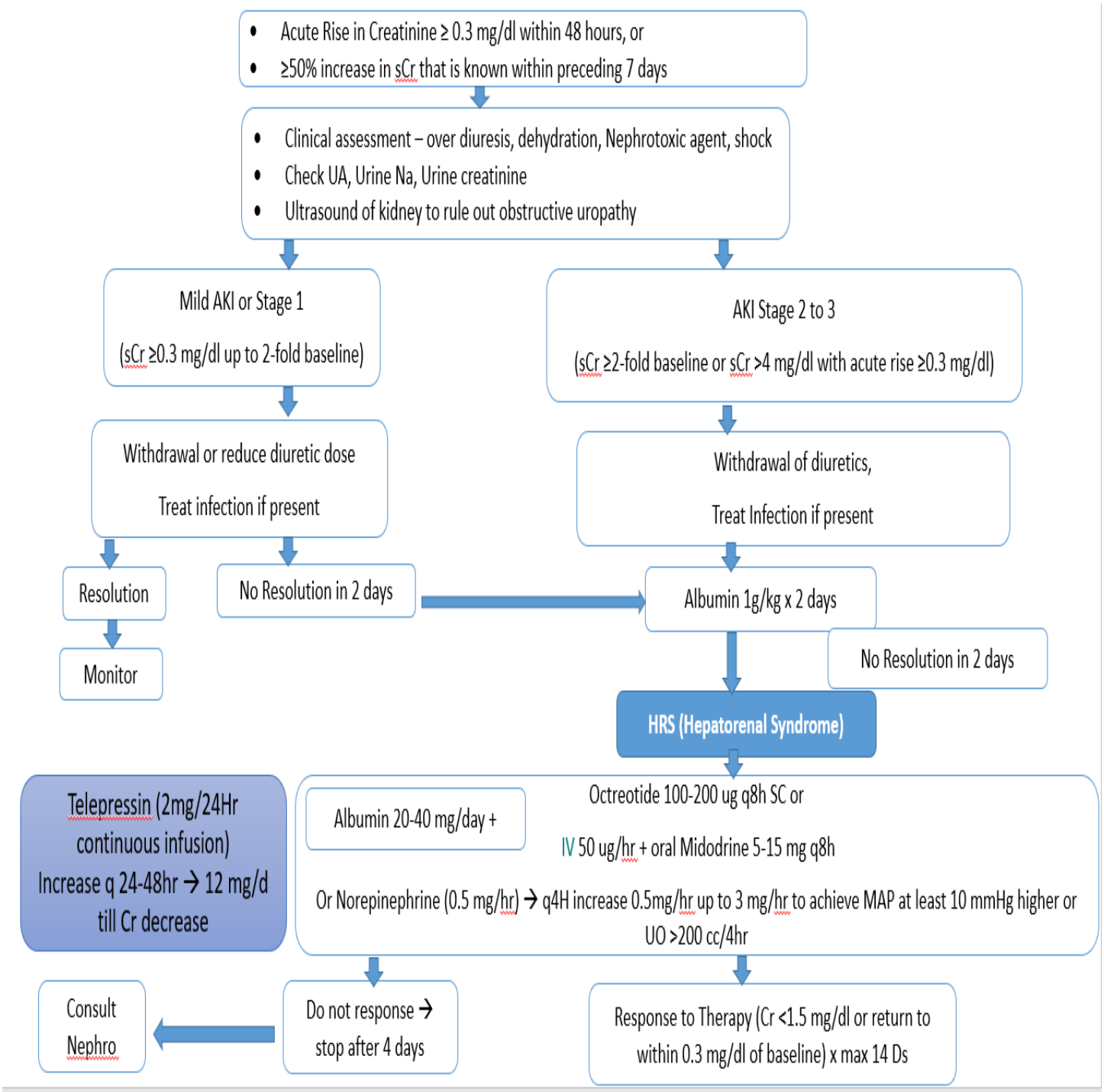
Neutrophil Gelatinase-Associated Lipocalin (NGAL)

To differentiate between **ATN vs others**

ELISA → 365 ng/ml

Particle-enhance turbidimetry → 220 ug/g

Algorithm for Management of AKI



Simultaneous Liver & Kidney Transplant Criteria (UNOS Policy: 9)

Diagnosis to qualify	Subsequent document
CKD (chronic Kidney Disease) Calculated GFR≤60 ml/min for >90 consecutive days	**Must have One of following:** 1. Initiated regularly schedule RRT 2. GFR ≤ 30 m/min at time of registration for K wait list or after registration
Sustained AKI (acute kidney injury)	**Must have One or Combination of Both, for at least 6 weeks** 1. On dialysis at lease once a week every 7 days 2. Calculated Cr Cl or GFR <25ml/min every 7 days
Metabolic Disease	1. Hyperoxaluria 2. Atypical Hemolytic Uremic Syndrome (mutation in factor H or factor I) 3. Familial non-neuropathic systemic amyloidosis 4. Methylmalonic aciduria

Safety Net: Any patient who is registered on kidney waitlist between 60 & 356 days after LT and is ether on chronic hemodialysis or has an eGFR <20 m/min will qualify for increased priority

Role of Albumin Infusion 25%

SBP [A1]	1.5 g/kg D1 & 1g/kg D3	
High Volume Paracentesis (> 4-5 liters) [A1]	8 g of albumin per liter removed	
Acute Kidney Injury (AKI) Stage 2-3 [C1]	1 g/kg for 2 days	
Hepto-renal syndrome (HRS) [B1]	1g/kg on Day 1 f/b 20 – 40 g/day	Vasoconstrictors (Tellipressin 2mg/24 hr (1st choice) or Norepinephrine (0.5 mg/hr) or Octreotide 100 -200 ug q8h or 50 ug/hr + oral Midodrine 5-15 mg q8h

Long term albumin may reduce the complications of cirrhosis and improve transplant free survival in uncomplicated ascites, but it needs further data to validate. No recommendation is given at Baveno VII

Role of Statin & Aspirin

Should be encouraged to use in cirrhosis with approved indication for statin [B1]

- Decrease portal pressure
- Improve overall survival

Child- Pugh B & C cirrhosis

- Low dose (simvastatin at max 20 mg/dl) [A1]
- Followed closely for muscle and Liver toxicity [A1]
- Child Pugh C – benefit of statin not been proven yet, should be more restrictive [D1]

Use of Aspirin should not be discouraged if there is an approved indication

- Reduce risk of HCC, Liver related complications & death [B2]

Role of Anticoagulation

Should not be discouraged if there is an approved indication [B1]

- May reduce liver-related outcomes in pts with & without PVT
- May improve overall survival

Direct- Acting Oral Anticoagulation (DOACs) [B2]

- Safe & effective in prevention of CV events in Child-Pugh A/B cirrhosis [B2]
- Caution on Child Pugh B as well as pts with Cr Cl <30 ml/min [B2]
- Not recommend in Child-Pugh C cirrhosis outside study protocols [B2]

Hepatic Encephalopathy

Factors associated with Hepatic Encephalopathy[21]

1. Liver Failure/ Hepatic dysfunction
2. Portosystemic Shunting (SPSS or TIPS)
3. Malunion, Sarcopenia, Frailty
4. Electrolyte imbalance (HypoNa, HyperK), Renal Failure
5. Precipitation events _ GI bleed, constipation, Infection, dehydration
6. Drugs – Benzodiazepines, Opioids
7. Microbiota dysbiosis – Bacterial Translocation

AASLD Recommendations[22] - Treatment	Level of Evidence
Identify and treat precipitating factors for HE (GI bleed, Infection, Electrolyte's imbalance, Volume depletion, Constipation, Medication misuse, Alcohol withdrawal)	GRADE II-2, A, 1
Lactulose is the first choice for treatment of episodic HE	GRADE II-1, B, 1
Rifaximin is an effective add-on therapy to lactulose for prevention of HE recurrence	GRADE I, A, 1
Oral BCAAs can be used as an alternative or additional agent to treat patients nonresponsive to conventional therapy	GRADE I, B, 2
IV LOLA (L-Ornithine L-aspartate) can be used as an alternative or additional agent to treat patients nonresponsive to conventional therapy	GRADE I, B, 2
Neomycin is an alternative choice for treatment of OHE	GRADE II-1, B, 2
Metronidazole is an alternative choice for treatment of OHE	GRADE II-3, B, 2

*Lactitol can be used as alternative for lactulose if patient is intolerance to lactulose

AASLD Recommendations – Prevention	Level of Evidence
Lactulose is recommended for prevention of recurrent episodes of HE after the initial episode	GRADE II-1, A, 1
Rifaximin as an add-on to lactulose is recommended for prevention of recurrent episodes of HE after the second episode	GRADE I, A, 1
Routine Prophylactic Therapy (lactulose or rifaximin) is not recommended for the prevention of post-TIPS HE	GRADE III, B, 1

AASLD Recommendations – Covert HE	Level of Evidence
Treatment of MHE and CHE is not routinely recommended apart from a case-by-case basis	GRADE II-2, B, 1

Polyethylene glycol

- Meta-analysis suggests there is a faster resolution of hepatic encephalopathy compared with lactulose[23]
- 4 liters dose

Rifaximin

- Secondary prophylaxis of hepatic encephalopathy
- considered for prophylaxis of overt HE in patients with previous overt HE who is undergoing elective TIPS
- Not indicated in primary or secondary SBP prophylaxis

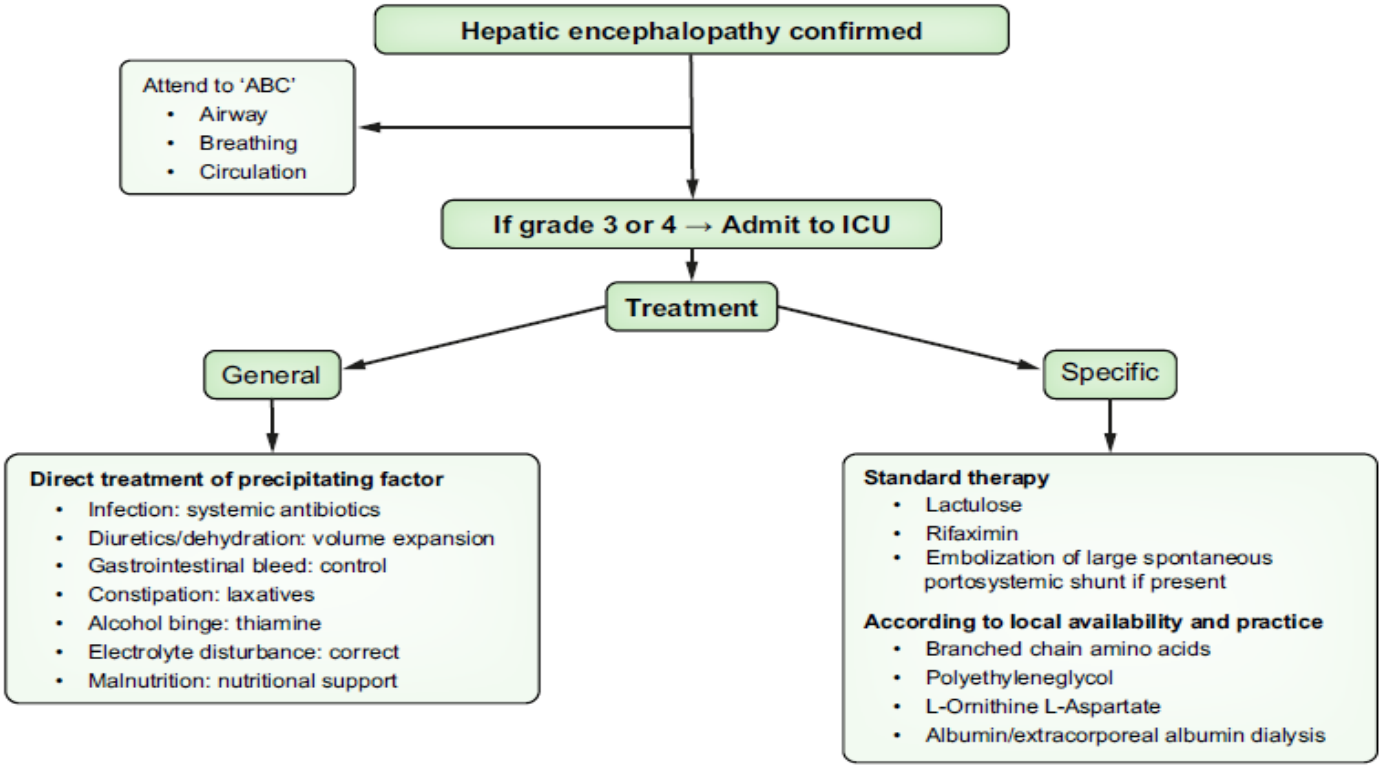
Refractory Hepatic Encephalopathy

Large SPSS shunt >6 mm – shunt embolization be considered especially patients with MELD <11

Patients who develop ascites/ varices after shunt embolization, small caliber TIPS creation could be considered

Consider TIPS diameter reduction in persistent or refractory HE post-TIPS

Algorithm of Treatment for Hepatic Encephalopathy[21]



Further Decompensation

Prevention of Further Decompensations

Decompensated cirrhosis	should be considered for Liver transplantation
Variceal Bleeding	NSBB/Carvedilol + EVL to prevent recurrent bleeding
Recurrent ascties (irrespective of varices or variceal hemorrage)	covered TIPS should be considered

Early treatment of risk fators & Triggers

Early detection of SBP

Removal/Suppression of primary Etiology

HCV –SVR

HBV- suppression in the absence of HDV coinfection

Alcohol – long term abstinence from alcohol

Role of Infection in Decompensated Cirrhosis

Bacterial infections are common in patients with decompensated cirrhosis and may cause further decompensation.[A.1]

All patients hospitalized with decompensation, bacterial infections should be ruled out.

The minimal work-up for infections should include diagnostic paracentesis, chest X-ray, cultures of blood, ascites and urine, and skin examination. [A.1]

Patients with bacterial infections should be promptly treated with antibiotics.

The **empirical antibiotic** treatment should be tailored to local epidemiology, risk factors for multidrug-resistant bacteria and severity of infection.[A.1]

If no response to antibiotics is observed, consider viral and fungal infections. [C.1]

Role of Sarcopenia and Frailty in Further Decompensation

Frailty, malnutrition, and sarcopenia have an impact on survival in patients with decompensated cirrhosis.

They should be evaluated with available standardized tools. [B.1]

All patients with decompensated cirrhosis should receive nutrition consultation and be advised regarding the benefits of regular exercise. [B.1]

While sarcopenia improves in some patients after TIPS, preprocedural sarcopenia has also been associated with poor outcomes (e.g., encephalopathy, slower resolution of ascites) and a higher mortality.

Therefore, sarcopenia by itself should not be an indication for TIPS. [C.2]

Management of ACLD after Removal/Suppression of the Primary Etiology Factor

Removal/Suppression of the primary etiology factor include

1. HCV - Sustained virological response (SVR)
2. HBV – suppression in the absence of HCV co infection
3. Alcohol related liver disease – long term abstinence from alcohol
4. Other ALDs- definition and impact is less well established

Overweight/obesity, diabetes and alcohol consumption are important contributors to liver disease progression even after removal/suppression of the primary etiology factor

Leads to potentially meaningful decreases in HVPG in most patients

Substantially reduces the risk of hepatic decompensation

Absence/resolution of CSPH following removal/suppression of the primary aetiological factor prevents hepatic decompensation

In the absence of co-factors, patients with HCV-induced cACLD who achieve SVR and show consistent posttreatment improvements with LSM values of <12 kPa + PLT >150x109/L can be discharged from portal hypertensionsurveillance (LSM and endoscopy)

In these patients, HCC surveillance should continue until further data is available.

Baveno VI criteria (i.e., LSM <20 kPa and PLT >150x109/L) can be used to rule out high-risk varices in patients with HCV- and HBV-induced cACLD who achieved SVR and viral suppression, respectively

cACLD on NSBB therapy with no evident CSPH (LSM <25 kPa) after removal/suppression of the primary etiological factor, should be considered for repeat endoscopy, preferably after 1–2 years.

In the absence of varices, NSBB therapy can be discontinued. (C2)

Re-Compensation

Definition of Re-compensation is based on expert consensus and requires meeting all the following criteria:

1. Removal/suppression/cure of the primary etiology of cirrhosis
2. Resolution of sign and symptoms without medications
    a. Resolution of ascites (off diuretic)
    b. Resolution of encephalopathy (off lactulose/rifaximin)
    c. Absence of recurrent variceal hemorrhage (for at least 12 months)
3. Stable improvement of liver function tests (albumin, INR, bilirubin)

NSBBs should not be discontinued unless CSPH resolves because CSPH may persist despite re-compensation

Following are not evidence of re-compensation

1. Resolution of ascites while on diuretics or after TIPS
2. Lack of recurrent variceal hemorrhage while on NSBBs+EVL or carvedilol +EVL or after TIPS
    a. Without removal/suppression/cure of primary etiologic factor
    b. Without improvement in liver synthetic function

Section 2: Portal Vein Thrombosis (PVT)

Portal Vein thrombosis is a serious condition encountered mainly in cirrhotic patients but also in non-cirrhotic population, leading to worsening of portal hypertension, hepatic decompensation and/or mesenteric ischemia. This Chapter will cover PVT in both cirrhotic and non-cirrhotic patients.

New standardized nomenclature for PVT has been recently described and published in 2020 AASLD guidance and Baveno VII consensus.[9] [10]

Descriptor	Definition
Time Course	
Recent	PVT presumed to be present for <6 months
Chronic	PVT present or persistent for >6 months
Percent Occlusion of Main PV	
Completely Occlusive	No persistent lumen (100% occlusive)
Partially Occlusive	Clot obstructing >50% of original vessel lumen
Minimally Occlusive	Clot obstructing <50% of original vessel lumen
Cavernous Transformation	Gross Porto portal collaterals without original PV seen
Response to Treatment or Interval Change	
Progressive	Thrombus increases in size or progress to more complete occlusion
Stable	No appreciable change in size or occlusion
Regressive	Thrombus decreases in size or degree of occlusion

Portal Vein Thrombosis in Cirrhosis

Investigations for Hyper coagulopathy & Who to refer to Hem/Onc Specialist

Portal Vein Thrombosis (PVT) in Cirrhosis

Presence of High-Risk Criteria:

1. Family History of unprovoked thrombosis in a family member <45 YO
2. Personal history of DVT/PE
3. Absence of known high risk factors such as hormone replacement therapy/OC pills, smoking, obesity, recent long travel (>12hrs), recent major abdominal surgery/trauma, or significant intra-abdominal inflammation, recent sick & hospitalized)

Hyper coagulable Work up:

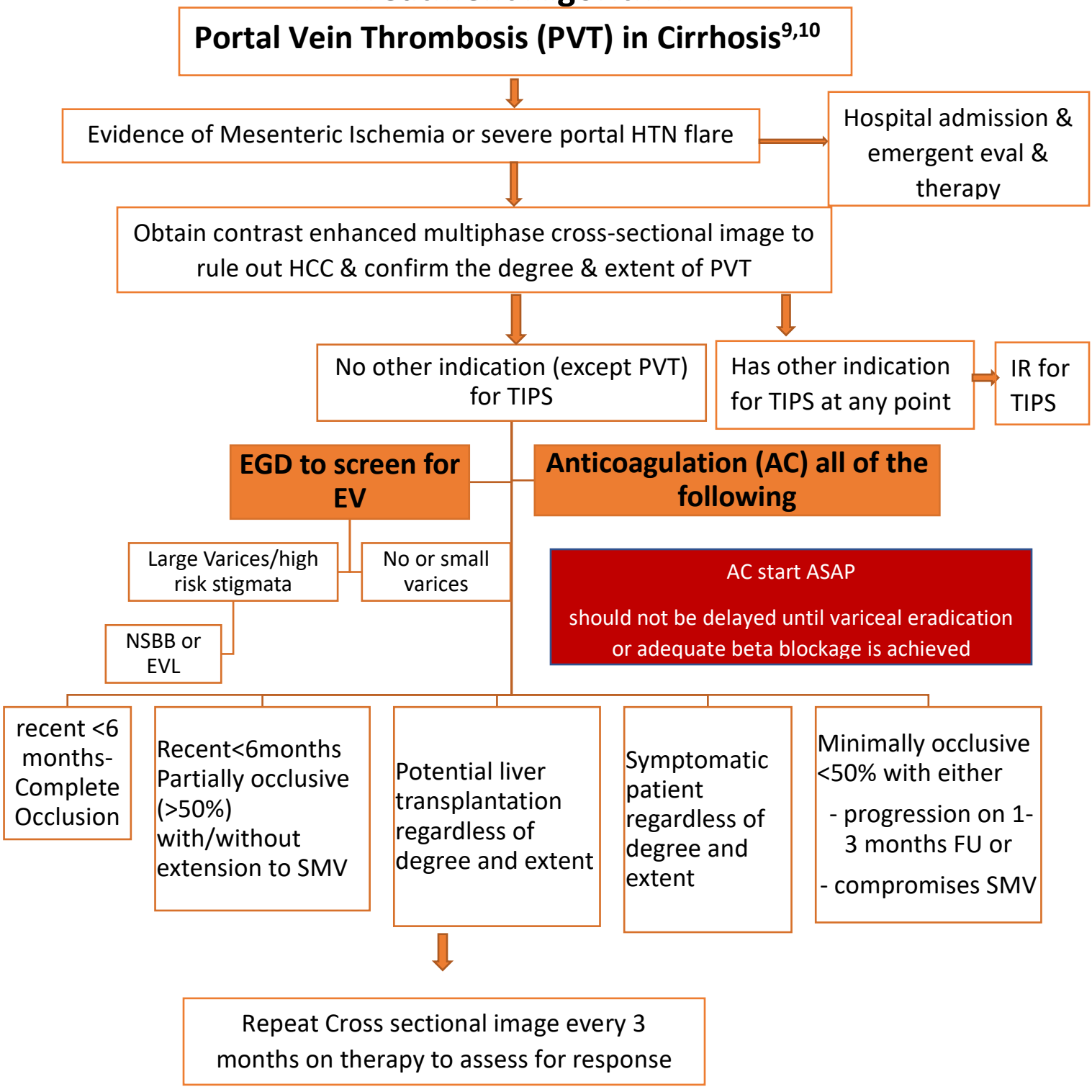
1. Prothrombin G20210 gene mutation
2. Factor V Leiden mutation
3. Factor VIII activity
4. JAK2 V617F mutation
5. Testing for Antiphospholipid syndrome (Beta-2 glycoprotein I antibodies, Cardiolipin antibodies & lupus anticoagulant)
6. If patient has IDA & Hemolysis → testing for PNH (PNH FLA flow cytometry)
7. Protein C, Protein S and Antithrombin III – only when
    a. 2-3 weeks after resolution of acute thrombotic episodes and Off anticoagulation
    b. 2-3 weeks after holding/stopping Warfarin/Coumadin
    c. 48 hours after holding/stopping DOAC
    d. 2-3 weeks after liver transplantation

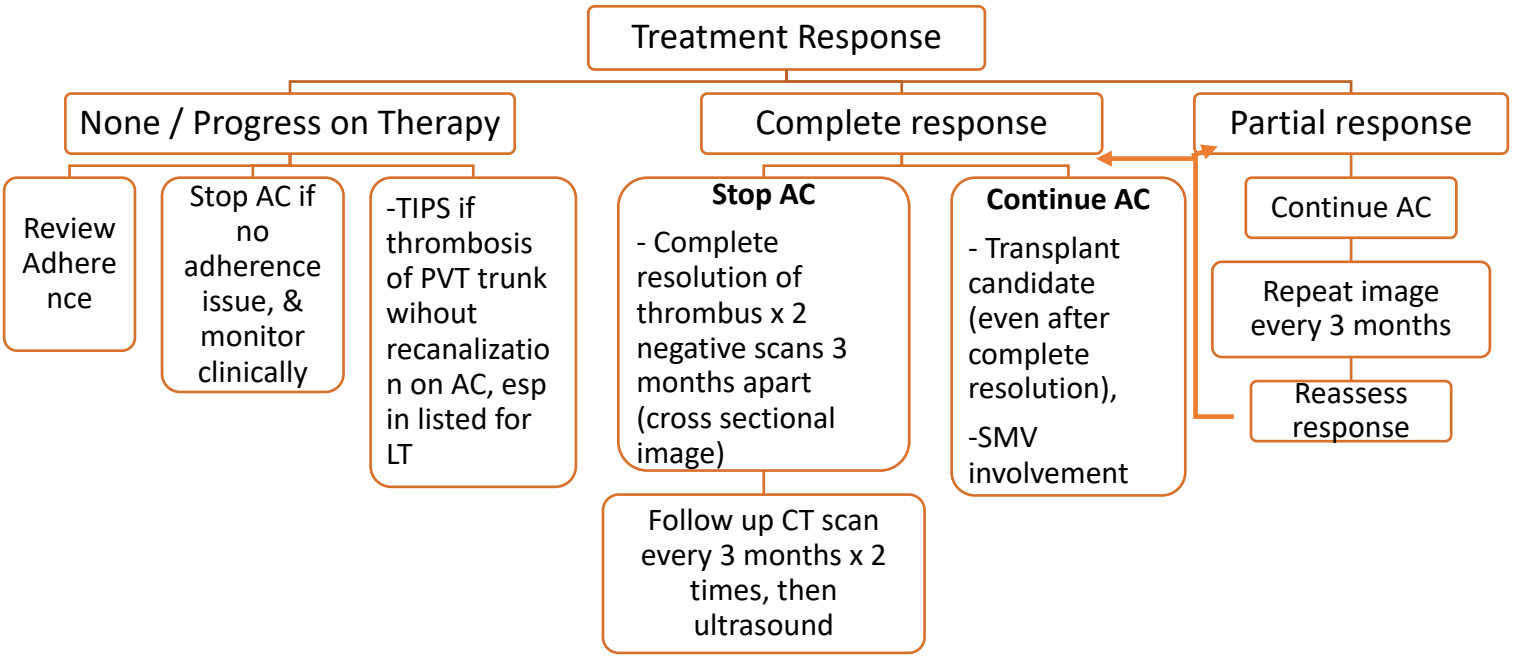
Refer to Hem/Onc Specialist if patient meet high risk criteria

Post Liver Transplant:

1. Continue anticoagulation & to follow Hem/Onc if positive Hyper coagulable work up
2. Repeat Protein C, Protein S, antithrombin tests 2-3 weeks after liver transplant if pre-LT deficient in Protein C & S and antithrombin
3. Stop anticoagulation if there is negative hypercoagulable work up

Treatment Algorithm




Treatment Response
None / Progress on Therapy
Complete response
Partial response
Review Adherence
Stop AC if no adherence issue, & monitor clinically
-TIPS if thrombosis of PVT trunk wihout recanalization on AC, esp in listed for LT
Stop AC
- Complete resolution of thrombus x 2 negative scans 3 months apart (cross sectional image)
Follow up CT scan every 3 months x 2 times, then ultrasound
Continue AC
- Transplant candidate (even after complete resolution),
-SMV involvement
Continue AC
Repeat image every 3 months
Reassess response

Type of Therapy

Initial: LMWH (preferred) or heparin continuous infusion, followed by one of the following:

Preferred anticoagulant: warfarin (goal INR 2-3, or 0.5 higher than baseline for patient with prolonged INR)

- Loading doses not recommended
- Slow up-titration of warfarin recommended to achieve target INR
- Pharmacist available to dose/monitor via collaborative practice agreement

Low Molecular Weight Heparin (Enoxaparin; preferred use as outpatient for bridging, or sole therapy without warfarin)

- CrCl ≥ 30 ml/min: enoxparin 1mg/kg SC q12h
  - *There is an increased bleeding risk with CrCl 30-50 ml/min. In this population, consider checking Anti-Xa level 4-6 hours after dose is administered. (Should not check this earlier than with third dose).*
- CrCl < 30 ml/min: enoxaparin 1mg/kg SC q24h
- Dialysis patients: avoid use

DOACs (Direct- Acting Oral Anticoagulants)

- Preferred DOAC is apixaban 5 mg PO BID
- Alternative DOAC is rivaroxaban 20 mg PO daily
  - Renal adjustments exist for rivaroxaban and should be considered prior to initiation of therapy
- Loading doses of DOACs should not be utilized
- All DOACs should be reviewed for drug interactions prior to prescribing (See Appendix A)
- DOAC safety by degree of hepatic impairment:
  - Safe in Child-Pugh A cirrhosis
  - Caution in Child-Pugh B cirrhosis
  - Contraindicated in Child-Pugh C cirrhosis

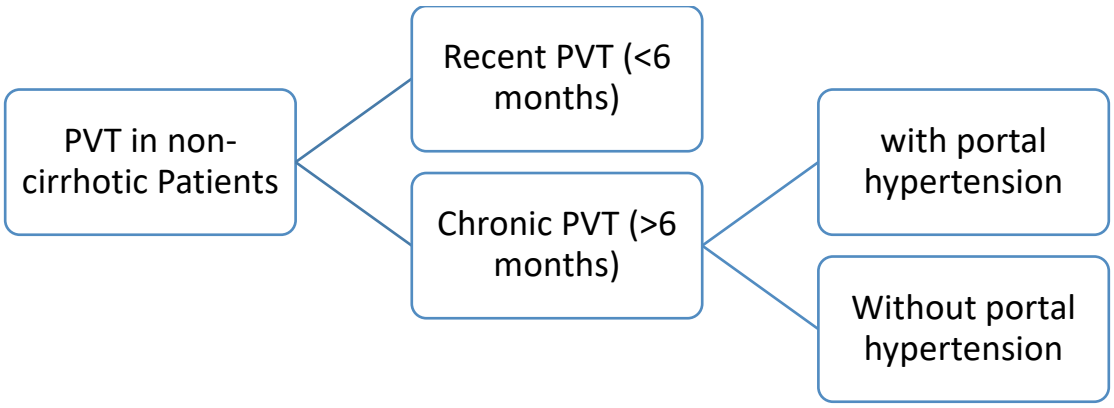
TIPS

- Multidisplinary approach to discuss about TIPS espicially PV trunk without recanalization on AC
- Recurrent bleeding &/or refractory ascites not manageable medically or endoscopicaly
- If consider LT, multidisplinary reveiw to consider revasularization

- Patients with low platelet count (e.g., <50 K) are at higher risk of PVT but also of bleeding complications on anticoagulation, so Baveno VII said these patients should be assessed on a case-by-case basis.
- After discussion with hematologist, our program consensus is
    - **Patients with Platelet <30K → half the dose of anticoagulation** (e.g., Apixaban 2.5 mg bid, Rivaroxaban 5 mg daily)
    - **Patients with Platelet <20K → absolute contraindication for anticoagulation**

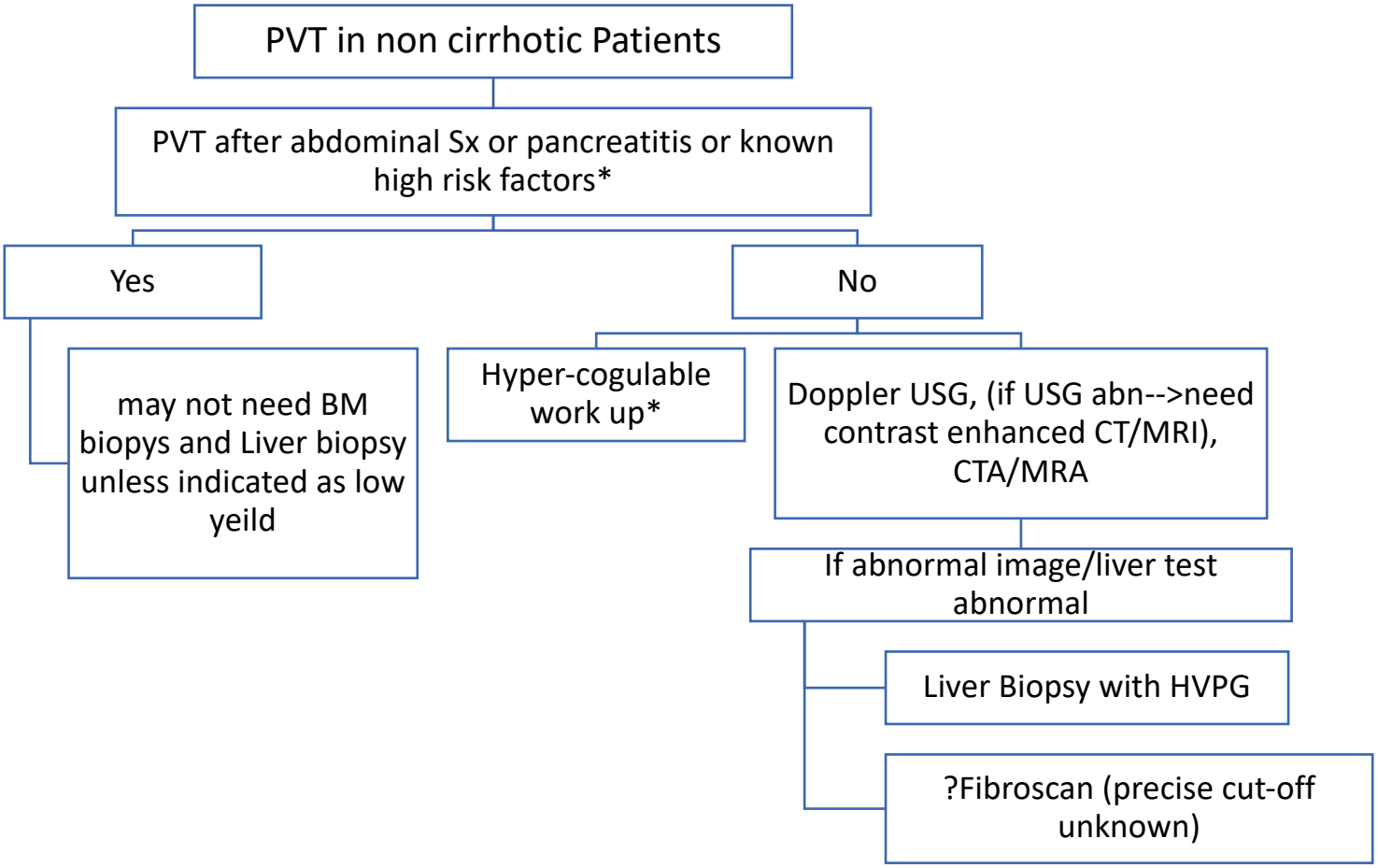
Portal Vein Thrombosis in Non-Cirrhotic patients

Classification:



Investigations:

Need imaging to distinguish PVT from extravascular compression of venous lumen by a neighboring space occupying formation. Cirrhosis and/or Malignancy should be ruled out and other underlying liver disease (e.g., PSVD or other chronic liver disease) should be investigated.



*Work up for prothrombotic factors and systemic disease similar to PVT in cirrhosis and refer to Hematologist

Myeloproliferative neoplasia (MPN) should be searched by testing V617F JAK2 mutation in peripheral blood. If negative→ bone marrow (BM) biopsy should be discussed with hematologist. BM biopsy should be considered particularly in patients without major risk factors for thrombosis

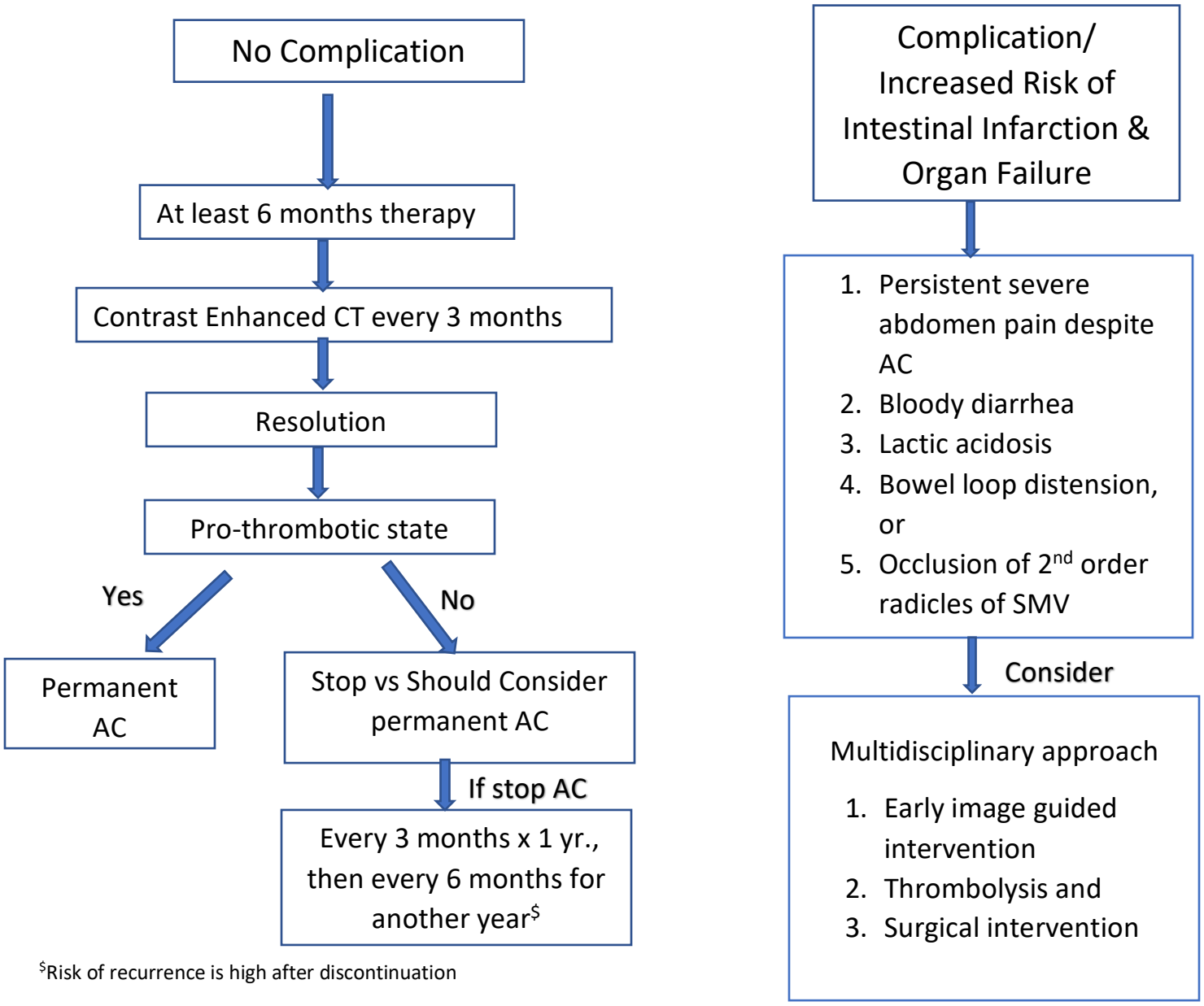
PSVD (Porto-sinusoidal vascular disorder) is a broad clinic-pathological entity encompassing non cirrhotic portal fibrosis, idiopathic portal hypertension or non-cirrhotic intrahepatic portal hypertension, and various overlapping histological patterns including nodular regenerative hyperplasia, obliterative portal venopathy, hepatoportal sclerosis, incomplete septal cirrhosis.

Treatment of PVT in non-cirrhotic patients

Heparin gtt/ LMW Heparin folllowed by either	Coumadin (goal INR 2-3, or 0.5 higher than baseline for patients with prologned INR), or
	DOAC[£] in absence of Triple positive anti-phospholipid syndrome

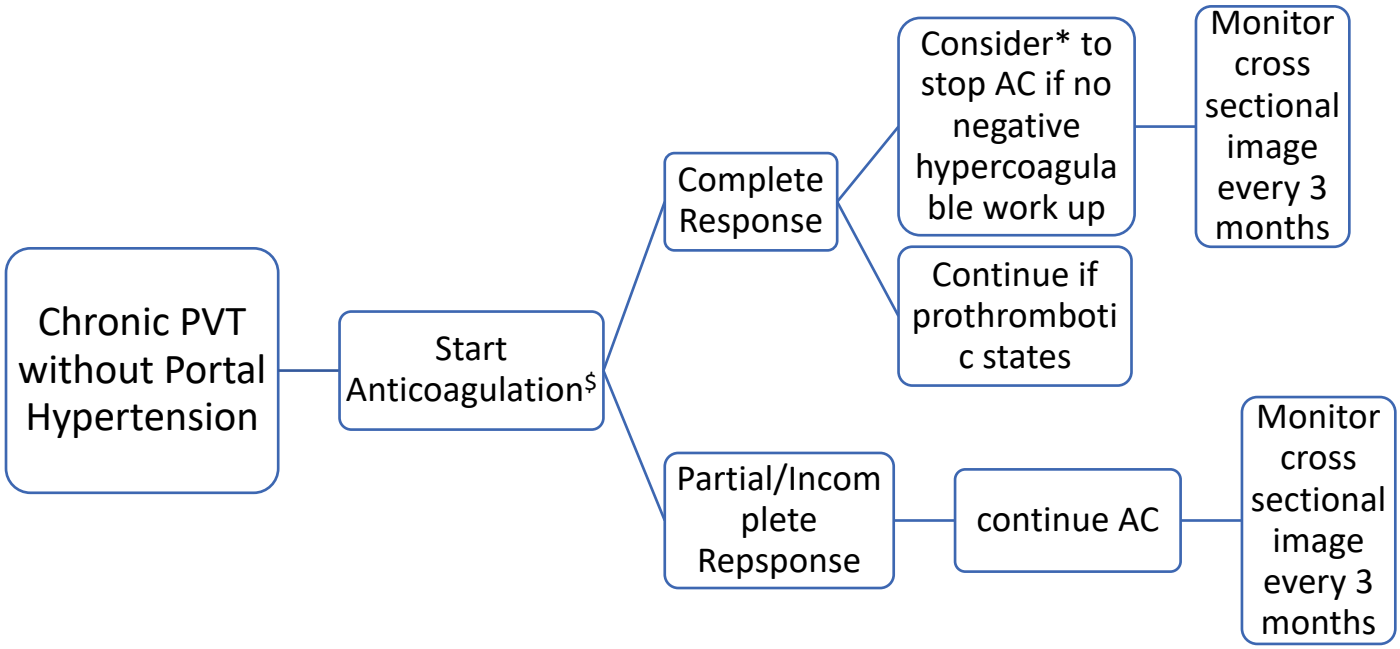
[£] Caution of DOACs – liver function impaired (~Child Class B). Contraindication of DOACs in Child C

A. Treatment Algorithm for Recent PVT (<6 months) in non-cirrhotic patients



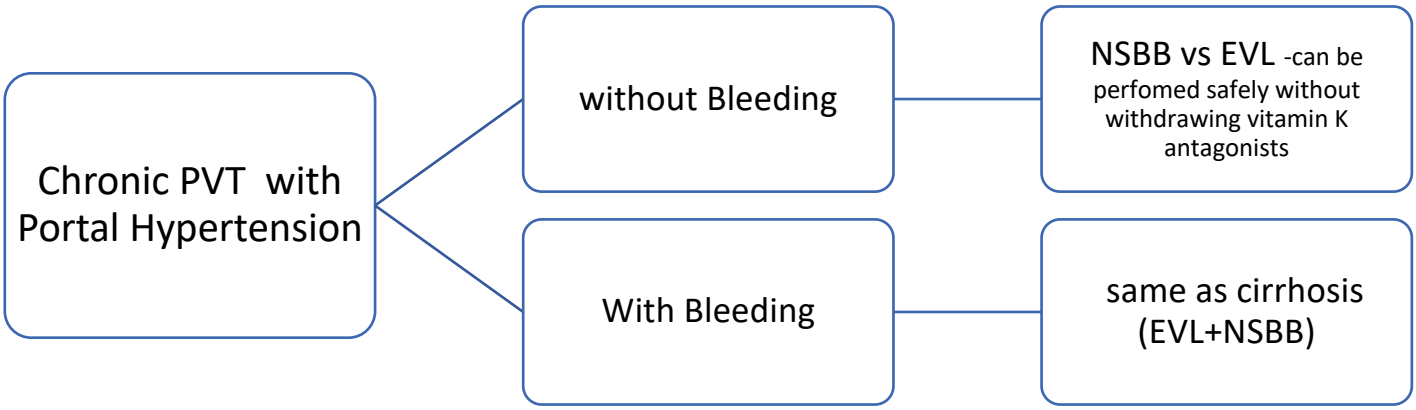
$Risk of recurrence is high after discontinuation

B. Treatment Algorithm for Chronic PVT (>6 months) in non-cirrhotic patients

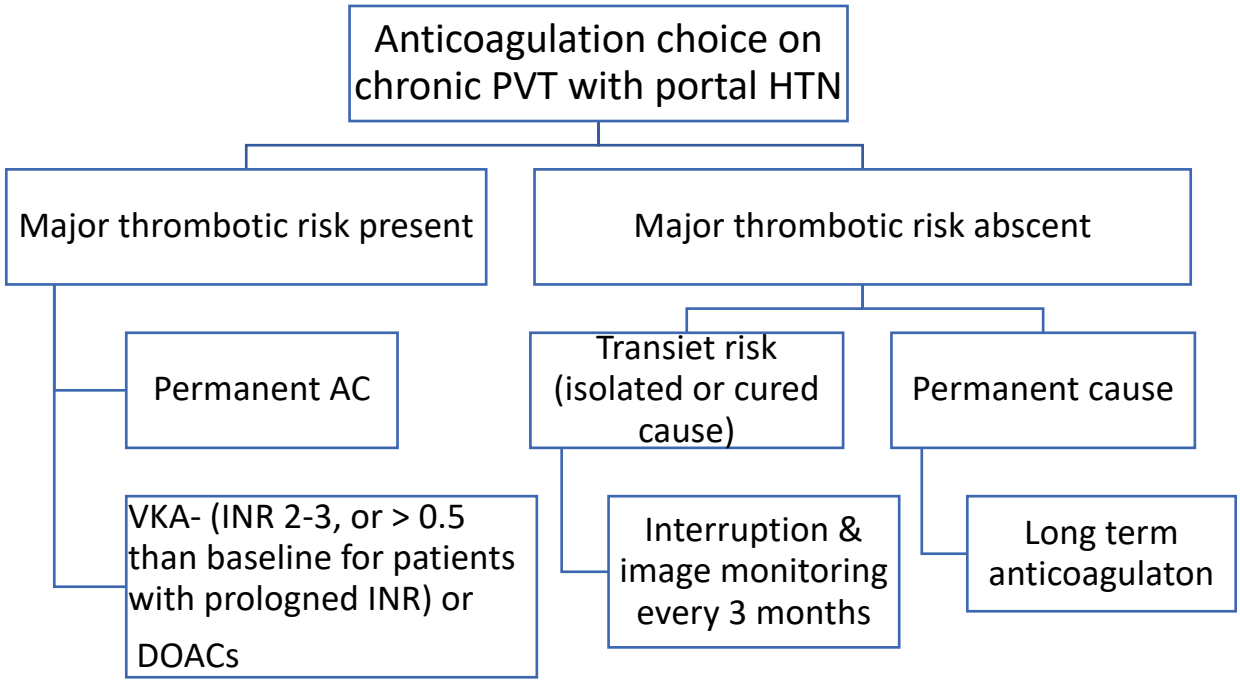


$ Past PVT or cavernoma not yet receiving anticoagulation→ AC should be started after adequate PTH bleeding PPx in pts with high-risk varices

*Consider to continue even if without prothrombotic states as risks of recurrent is high



- All patients with thrombosis (not recanalized)- should be screened for varices within 6 months of acute episode
- If no Varices on 1st EGD → EGD repeat at 12 months & 2 years there after
- Insufficient data of Beta blocker or EVL preferred for primary prophylaxis of Portal HTN related bleeding in pts with past PVT or cavernoma



- Patient with refractory complications of PVT or cavernoma→ consider percutaneous recanalization of PV or other vascular interventional procedures

Appendix:

A. Noteworthy drug interactions with DOACs

CYP 3A4 inducers (reduce DOAC exposure)	CYP 3A4 inhibitors (increase DOAC exposure)
• Carbamazepine • Phenytoin • Primidone • Rifabutin, rifampin • St. John's Wort	• Azole antifungals (recommend maximum dose of fluconazole 200mg daily and avoid concurrent use with itraconazole, posaconazole, and voriconazole) • Clarithromycin • Diltiazem • Erythromycin

Section 3: Liver Transplant Evaluation

Cardiac Evaluation[24,25]

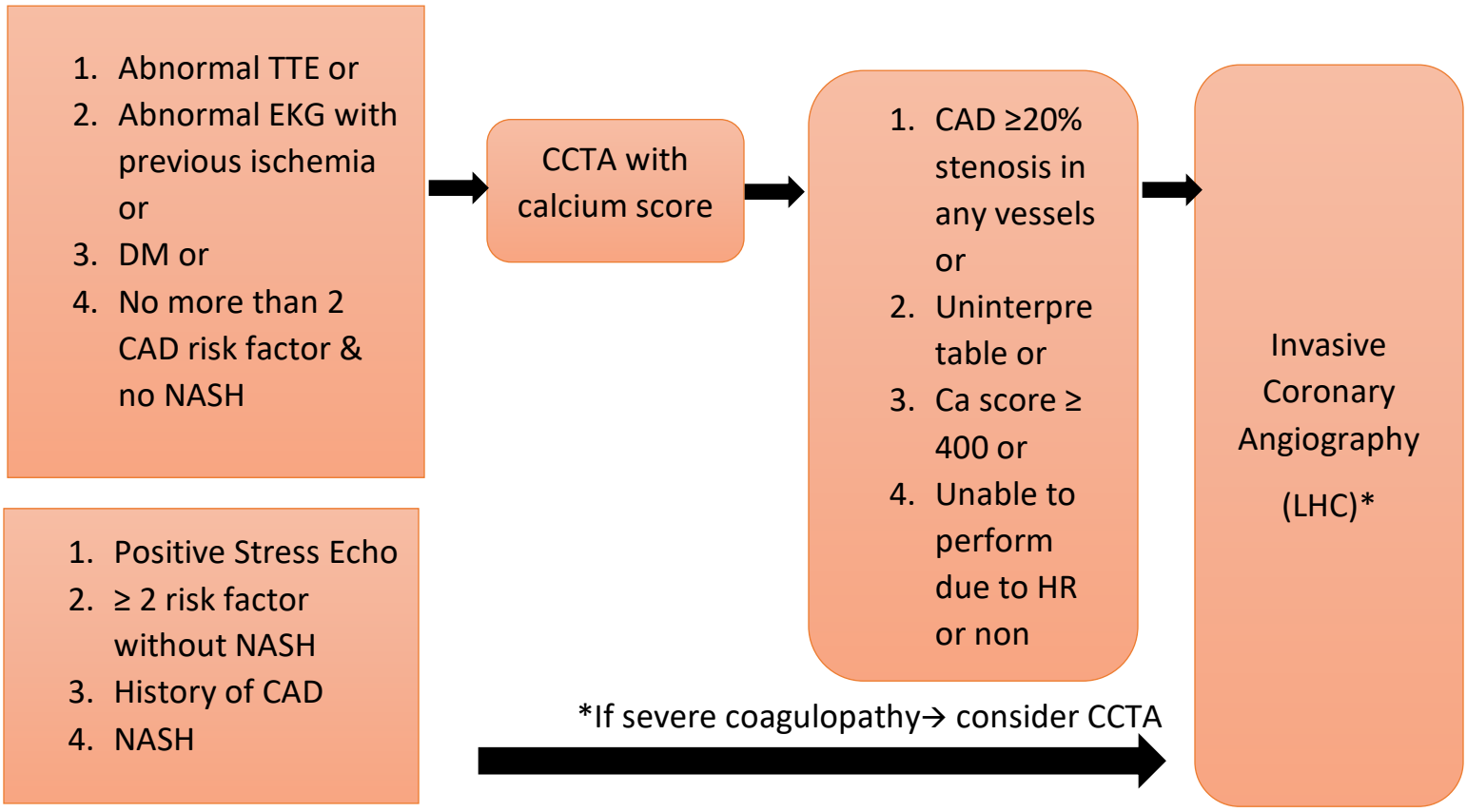
The goal of pre-liver transplant cardiac evaluation is to assess peri-operative risk and exclude concomitant cardiac disorders that would preclude good long-term outcome.

All the candidates will undergo transthoracic echocardiography with bubble study, EKG and stress echo or nuclear medicine stress testing as part of standard transplant evaluation.

If the patients unable to achieve the target heart rate during a standard exercise test, the patients should undergo pharmacological stress with adenosine (or acceptable stress agent) or nuclear imaging for assessment of at risk myocardium.

Echo with bubble study (TTE)	EKG	Stress Echo or NM stress test (≥40 yr or unable to achieve ≥4 METS)
• Assess RV & LV func • R/o HPS • R/o Pul HTN (RVSP>35 mmHg)	• prolong QTc • arrythmia	• R/o Ischemia

Algorithm of Cardiac Evaluation



CAD Risk factors[16]

1. Hyperlipidemia/dyslipidemia (LDL-C 160-189 mg/dl, non HDL-C 190-219 mg/dl)
2. Metabolic syndrome (any 3 of the following: increased WC: >102 cm in male, >88 cm in female; elevated TG ≥150 mg/dl; HTN, DM/ fasting glucose ≥110 mg/dl; & Low HDL<40 in male, <50 in female)
3. Hypertension/Hx of HTN
4. LV Hypertrophy
5. Family History of premature CAD (Male <55, Female <65)
6. Active or past tobacco use
7. CKD (eGFR15-59 ml/min/1.73m^2)
8. History of premature menopause (<40 YO) and hx of preg associated conditions that

Pulmonary Evaluation

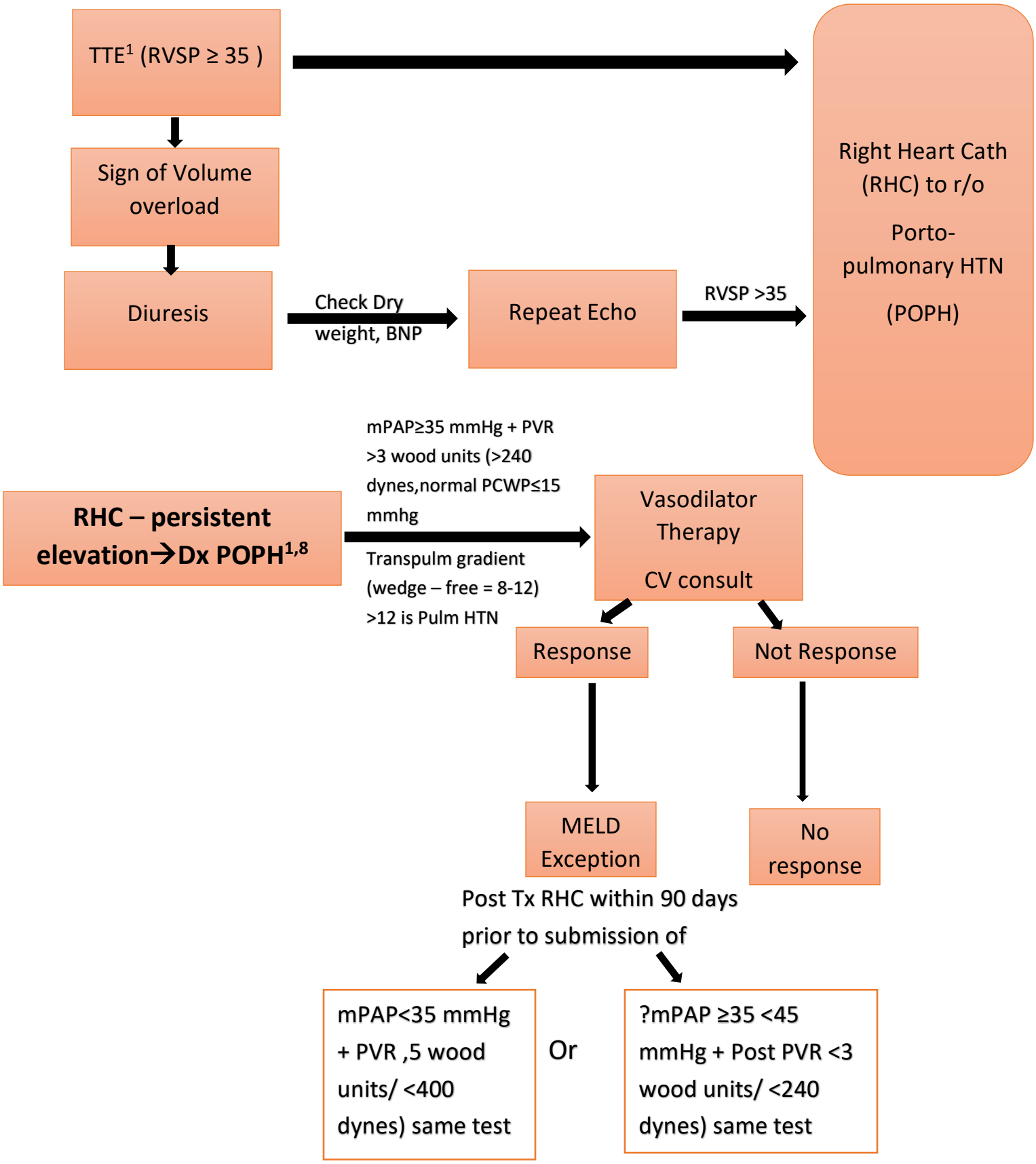
Screening for Pulmonary complications is a critical component of liver transplant evaluation. An estimated 50–70% of patients with cirrhosis undergoing evaluation for liver transplantation complain of shortness of breath. The differential diagnosis of dyspnea in chronic liver disease is broad and there are several 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).

Two distinct pulmonary vascular complications of liver disease, the hepatopulmonary syndrome (HPS) and porto-pulmonary 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.

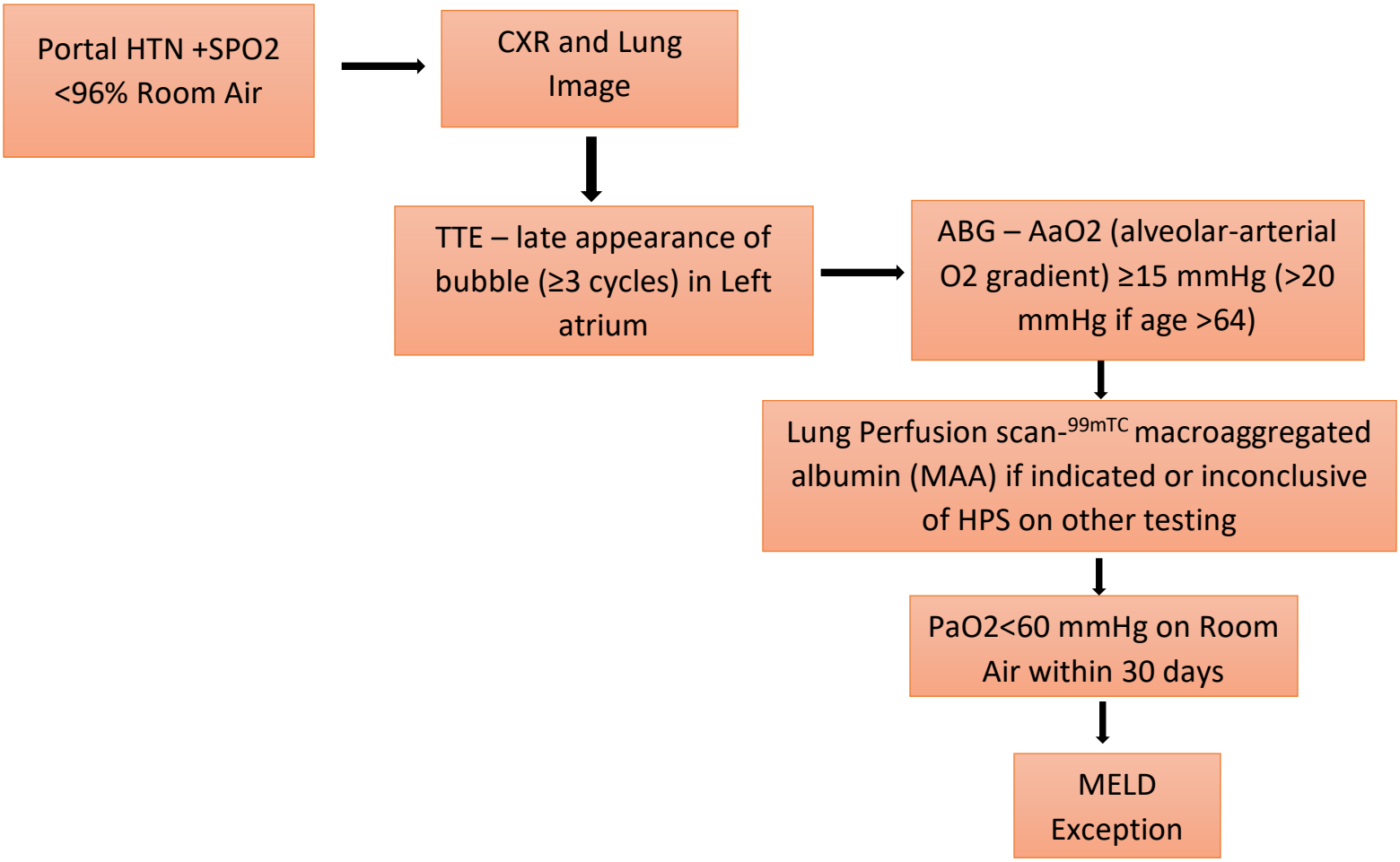
As part of standard transplant evaluation, the patients will undergo chest XR, pulmonary function testing, room air arterial blood gas and transthoracic echocardiogram with bubble study.

Chest XR	Pulmonary Function test	ABG	Transthoracic echo with bubble study
	• FVC, FEV1, FEV1/FVC • DLCO • Any abnormalities → pulmonary consultation		• check for pulmonary hypertension (RVSP) • extra-cardiac shunt (HPS)

Algorithm for Porto-Pulmonary Hypertension



Algorithm for Hepatopulmonary Syndrome



(Policy: 9 Allocation of Livers and Liver-Intestines Effective date 10/7/2021)

https://optn.transplant.hrsa.gov/media/eavh5bf3/optn_policies.pdf

Section 4: Post Liver Transplant Malignancy Screening and Surveillance

HCC Post Liver Transplant Surveillance[26,27]

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 HCC surveillance

Variable	Retreat Points
AFP at Liver Transplant, ng/ml	
0-20	0
21-99	1
100-999	*1*
≥1000	3
Microvascular Invasion	2
Largest viable tumor diameter + number	
0	0
1-4.9	1
5-9.9	2
≥10	3

Retreat Score	Surveillance Strategy
0	No Surveillance
1-3	Every 6 months for 2 years
4	Every 6 months for 5 years
5+	Every 3 months for 2 years, then every 6 months for 5 years

Colon cancer Surveillance in Post liver transplant patients who has previous history of colon cancer[2,28]

Post liver transplant patients who a history of colon cancer before the liver transplant should undergo more frequent colonoscopy for colon cancer surveillance.

Stage	Surveillance Endoscopy	Surveillance Additional duration
Low Risk- Stage 1 (T1 or T2 N0M0)	• Colonoscopy at 1 year and 3, then every 5 years lifelong. • If advanced polys (>1cm size, villous history or high-grade dysplasia present) detected→yearly	Consider CT Abdomen & Pelvis scan every 6 months and CEA every 3-6 months
Intermediate Risk Stage II (T3 or T4 N0M0) Stage III (any TN +M0)		CT Abdomen & Pelvis every 6 months and CEA every 3 months
High Risk Stage IV (Any T N with M+)		CT abdomen & Pelvis every 3 months CEA every 3 months

Post Liver Transplant Malignant Screening[2,29,30]

Post liver transplant recipient have higher overall risk of developing de novo malignancies than the general population. The identifiable risk factors for de novo malignancies include immunosuppression, the patient's age, a history of alcohol associated liver disease or nonalcoholic fatty liver disease or primary sclerosing cholangitis, smoking and viral infection with oncogenic potential. Studies showed that de novo malignancies are major cause of mortality and morbidity after liver transplantation.

Patient education including smoking cessation and application of sun cream/ avoidance of excess sun, and regular clinical follow up remain the standard of care.

Summary of de novo malignancies screening

Category	Population at risk	Strategy	Frequency
Skin	All	Dermatology exam, sun screen	annual
Colon	All	Colonoscopy	Gen- every 5 years PSC/IBD- annually
Lung	Ex/Smokers	CT chest or CXR	As per screening guideline
GU	Female	Pelvic exam, PAP	As per screening guideline
Breast	Female (≥40yr)	Mammography	As per screening guideline
Prostate	Male (≥40 yr)	PSA	As per screening guideline
Lymphoma	Donor EBV+/Recipient EBV-	EBV DNA level	High index of suspicion

Section 5: Post-Transplant Metabolic Management

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. Cardiovascular mortality is the most common cause of death in the post liver transplant patients.

Cardiovascular risk burden in the post liver transplant patients include hypertension, hyperlipidemia, diabetes mellitus and chronic kidney disease. [31]

Hypertension

Hypertension is defined by the blood pressure above 140/90 mmHg for non-high-risk population. For the patients who has diabetes mellitus, chronic kidney disease, proteinuria and/ or cardiovascular disease, hypertension is defined by the blood pressure above 130/80 mmHg.

All-cause mortality and major cardiovascular events improved with good blood pressure controlled compared to whom are not well blood pressure controlled. [31]

Management algorithm for hypertension is described below.

Algorithm in Management of Hypertension

Hypertension[2-7]

- **BP>140/90 mmHg**
- **If Proteinuria, DM, CKD &/or CV→>130/80 mmHg**

Life-Style Modification: Low Na diet (<2g/day), Exercise, Smoking cessation, Alcohol abstinence, OSA treatment

1st line

General	DM, CKD, Significant Proteinuria>1g/day, Hx of Heart failure	Active CAD
CCA ACEI/ARB	ACEI/ARB**	Beta Blocker

Unresponsive

Add ACEI/ARB >> Betablocker, Diuretics?

Others- Hydralazine, Clonidine

refractory

Nephrology consultation

Intolerable

Change to Carvedilol/ Beta blocker, or Nifedipine

**** ACEI and Diuretics→ need monitor creatinine and potassium**

Minimize CNI

Consider switch CSA to Tac, taper steroids, Avoid combination of mTORI & CNI

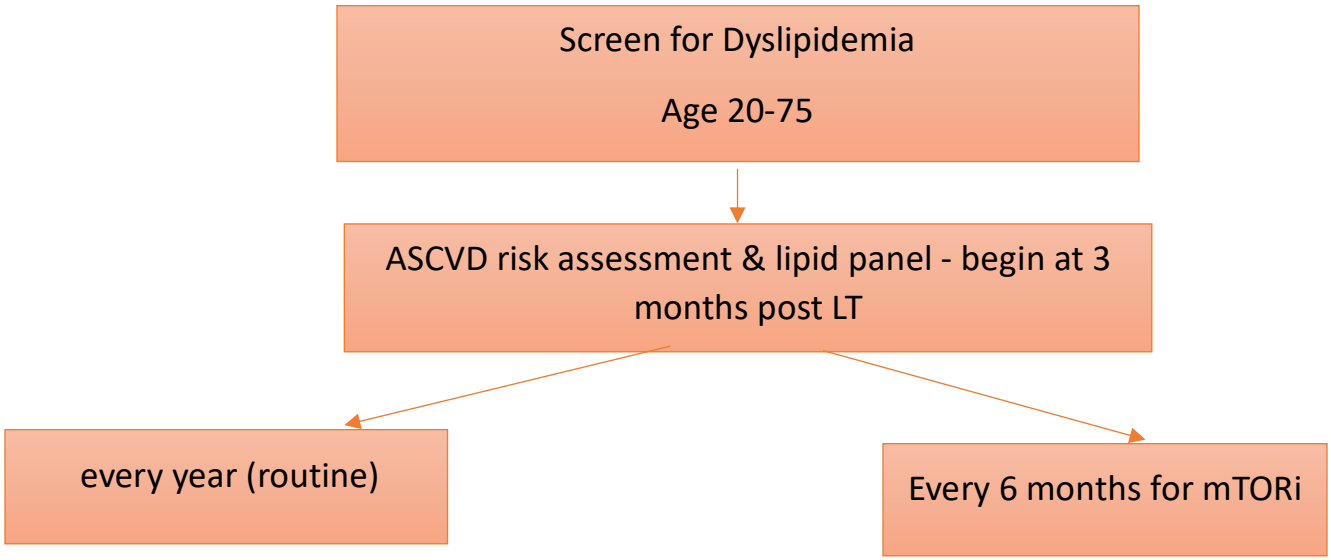
Dyslipidemia[32]

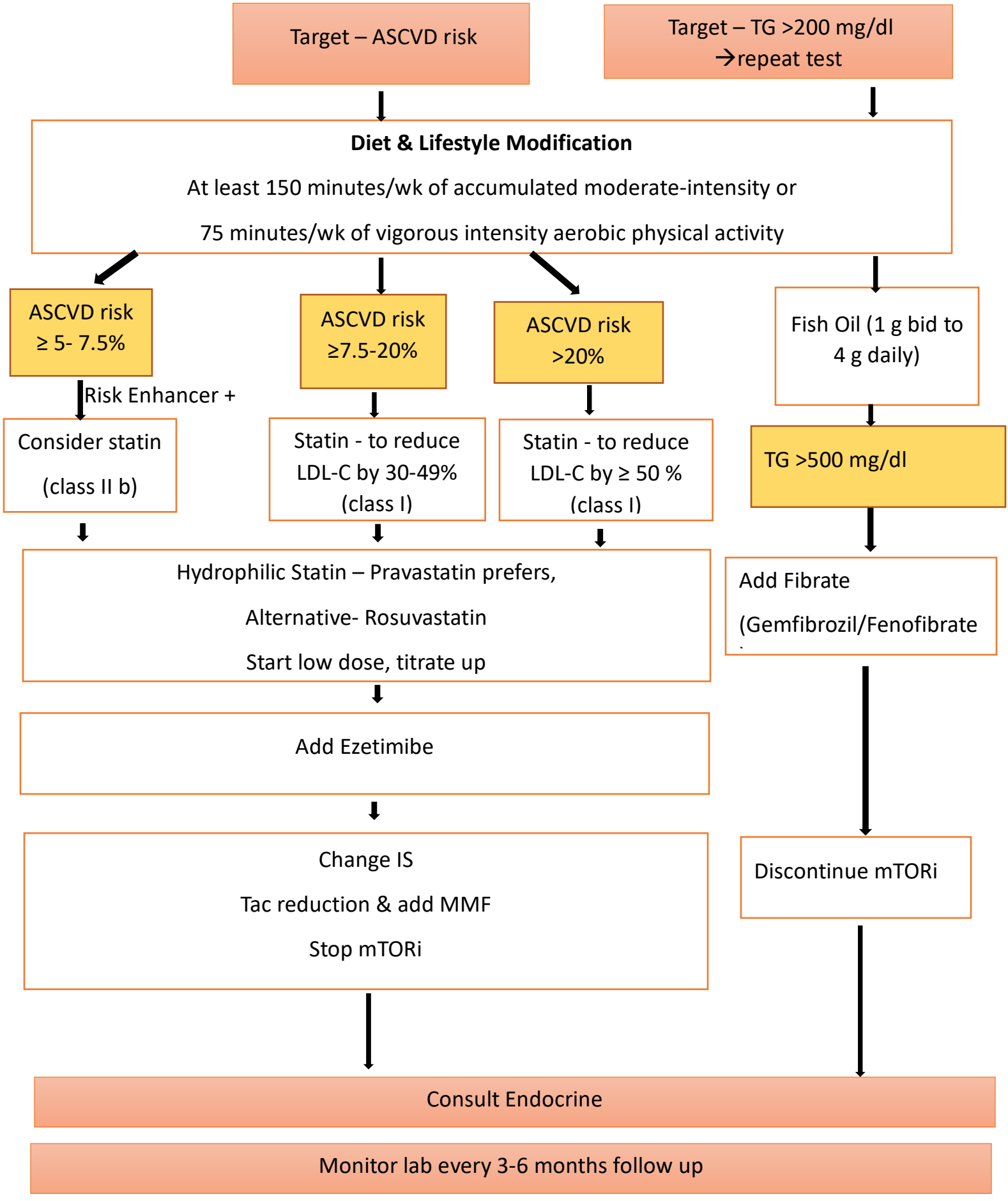
The prevalence of dysplidemia was 32.5%, 46.8% and 55.3% at 1, 3 and 5 years respectively. The median time to develop dyslipidemia from liver transplantation was 1.5 years. Unfortunately, statin was underutilized as only 45% of patients with known CAD were on statin therapy. [33]

The choice of statin is also important due to its interaction with immunosupprsents. Calcineurim inhibitor (CNI) potentiate toxicity of statins by lowering their metabolism through CYP 450 system. Interaction occurs more commonly with cyclosporin than tacrolimus.

Pravastatin is not metablized by cytochrome P450 system. Thus, it is a preferred medicine in post liver transplant patients. Alternative choice of statin is Rosuvastatin which has a minimal cytochrome P450 metabolism.[7,34]

Management algorithm for dyslipidemia is described below. [6,35]




Target – ASCVD risk
Target – TG >200 mg/dl
→repeat test
Diet & Lifestyle Modification
At least 150 minutes/wk of accumulated moderate-intensity or
75 minutes/wk of vigorous intensity aerobic physical activity
ASCVD risk
≥ 5- 7.5%
Risk Enhancer +
Consider statin
(class II b)
ASCVD risk
≥7.5-20%
Statin - to reduce
LDL-C by 30-49%
(class I)
ASCVD risk
>20%
Statin - to reduce
LDL-C by ≥ 50 %
(class I)
Fish Oil (1 g bid to
4 g daily)
TG >500 mg/dl
Add Fibrate
(Gemfibrozil/Fenofibrate
Hydrophilic Statin – Pravastatin prefers,
Alternative- Rosuvastatin
Start low dose, titrate up
Add Ezetimibe
Change IS
Tac reduction & add MMF
Stop mTORi
Discontinue mTORi
Consult Endocrine
Monitor lab every 3-6 months follow up

Risk Enhancer
Family Hx of Premature ASCVD (male, age <55 yr, Female, age <65 yr
Primary Hypercholesterolemia (LDL- C 160-189 mg/dl; non HDL-C 190-219 mg/dl)*
Metabolic Syndrome
CKD (eGFR 15-59 ml/min/1.73 m^2 with or without albumin; not HD or Kidney transplant
Chronic inflammatory condition: Psoriasis, RA, Lupus or HIV/AIDS
Hx of premature menopause (<age 40 yr) & Hx of pregnancy associated conditions that increase later ASCVD risk such as Preeclampsia
High risk Race/Ethnicity (e.g. South Asian Ancestry)
Lipid/ biomarker associated with Increased ASCVD risk (Persistently elevated TG ≥ 175 mg/dl*, non fasting) (Elevated high-sensitivity CRP (≥2 mg/dl) (Elevated Lipoprotein (a) ≥ 50 mg/dl or ≥125 nmol/l) Elevated apoB (≥130mg/dl) ABI (<0.9)

*** Optimally, 3 determinations**

Diabetes Mellitus/Hyperglycemia[2-7,36,37,38]

The prevalence of type 2 diabetes mellitus increases from 22% before OLT to 30% to 35% after transplant. Risk factors for post-OLT diabetes include pretransplant diabetes, obesity, nonalcoholic fatty liver, 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.

There are 2 types of post-transplant hyperglycemia or diabetes mellitus.

Post Transplant DM (PTDM)

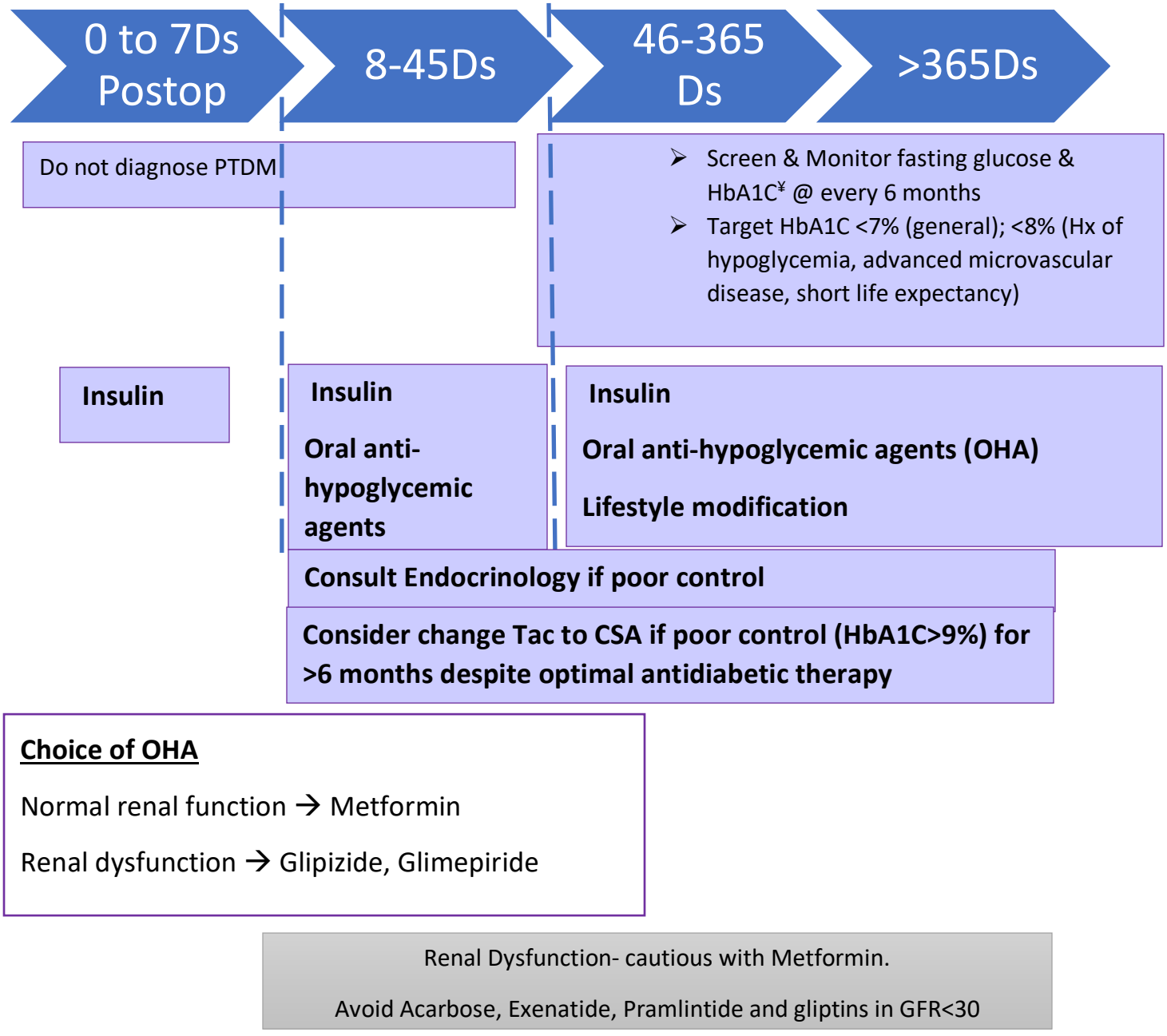
- Symptoms +
- Persistent Random glucose ≥200 mg/dl or Fasting Glucose ≥ 126 mg/dl or 2 hrs post prandial ≥ 200 mg/dl or HbA1C ≥6.5%*

Transplant Associated Hyperglycemia (TAH)

- Not reaching diagnostic threadshold for PTDM

***Anemia, History of recent blood transfusion, Renal failure may affect value**

Algorithm of Management of Hyperglycemia



Choice of OHA

Normal renal function → Metformin

Renal dysfunction → Glipizide, Glimepiride

Renal Dysfunction- cautious with Metformin.

Avoid Acarbose, Exenatide, Pramlintide and gliptins in GFR<30

¥ Anemia, History of recent blood transfusion, Renal failure may affect value

TABLE 3.

Considerations in treatment of diabetes mellitus post-LT

Drug	Available evidence in transplant patients	Considerations
Metformin	Safe in kidney transplant	Preferred with normal renal function due to decreased weight gain. Caution in AKI/CKI (lactic acidosis). Hold for significant infection. Consider in pre-DM.
Sulfonylureas	Efficacy not proven. Small study kidney transplant. No ΔCSA kinetics	More hypoglycemia with AKI/CKI DDI with CSA. Glipizide or glimepiride preferred in renal dysfunction.
Thiazoledinediones	Safe and effective in small studies KTx	Weight gain, CHF, bone loss Efficacy in pre-LT NASH, CVD protection
Repaglinide	Safe, effective, no DDI c CNI, sm study KTx c PTDM	Risk of hypoglycemia with ↓ GFR vs. sulfonylureas
DPP4 inhibitors	Vildagliptin safe, effective kidney transplant RCT Sitagliptin:(CCS and retrospective data)	Dose reduce all but linagliptin with ↓GFR
GLP-1 agonists	Liraglutide: 5 kidney transplant patients treated, no effect on IS Exenatide: no data	Nausea, impacts gastric emptying, gut motility. No if GFR < 40 mL/min
SGLT-2 inhibitors	No data	Volume depletion, increased risk of GU infection, DKA. **Avoid.**
α-glucosidase inhibitors	No data	Avoid with low GFR

Per 2019 ACC/AHA guideline:[35]

For adults with T2DM and additional ASCVD risk factors who require glucose-lowering therapy despite initial lifestyle modification and metformin, it may be reasonable to initiate a sodium-glucose cotransporter 2 (SGLT-2) inhibitor or a glucagon-like peptide-1 receptor (GLP-1R) agonist to improve glycemic control and reduce cardiovascular risk.

However, there is no good enough data on liver transplant recipients yet.

Renal Dysfunction[2-7,39]

There is increase in cumulative incidence of chronic renal failure requiring hemodialysis or renal transplantation in non-renal organ transplant developed over the years. The rest factor for chronic renal failure or CKD includes low pretransplant GFR <60ml/min, hemodialysis prior to transplant, calcineurin inhibitor, pre-transplant chronic hepatitis C, pre-transplant hypertension, and pre-transplant diabetes mellitus.

Definition of Renal Dysfunction

Acute Renal Injury

- Increase in baseline sCr of ≥ 0.3 mg/dl within 48 hr
- Increase sCr ≥ 50% from baseline occurred within the prior 7 days or within 3 months can be used as baseline

Chronic Kidney Disease

- eGFR < 60 ml/ml/1.73 m2 for > 3months
- CKD-EPI creatinine & MDRD-4 equation- most accurate

Prevention of Chronic Renal Disease after Liver Transplantation

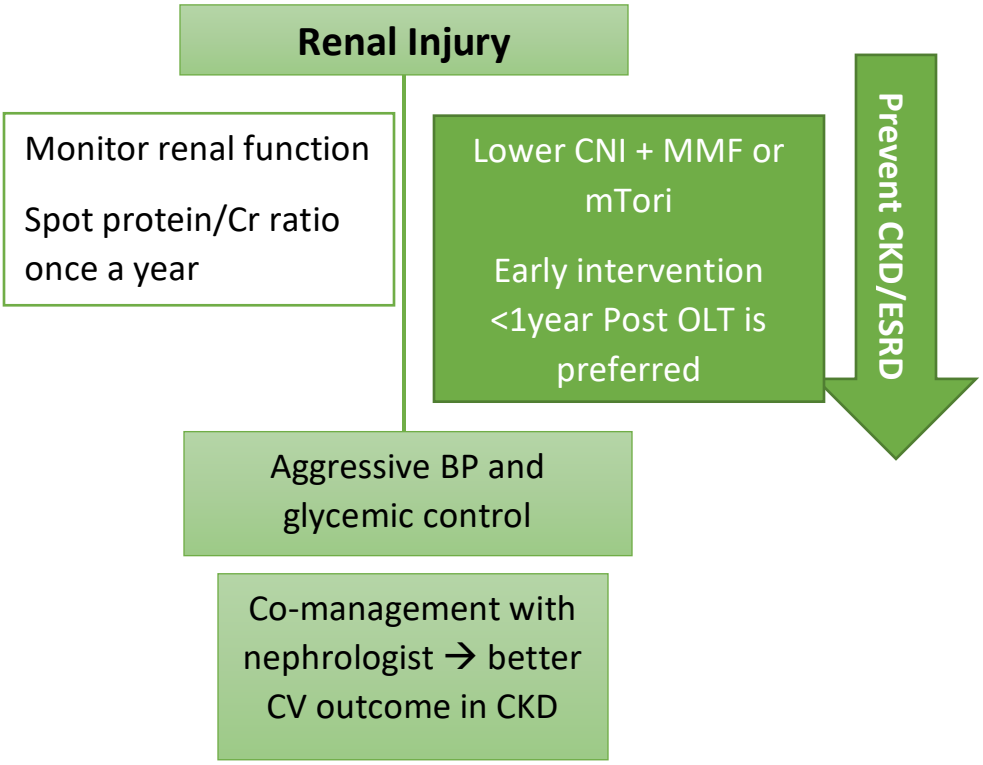
Prevention of AKI after Liver Transplant

- Avoid Nephrotoxic Medications
- Minimize Radiocontrast Contrast Exposure
- CNI sparing Protocol in immediate post LT in selected patients

Control Comorbidities & Risk Factors for CKD

- Glucose
- Blood Pressure
- Modulate Immunosuppression

Algorithm to Prevent Renal Injury Post Transplantation

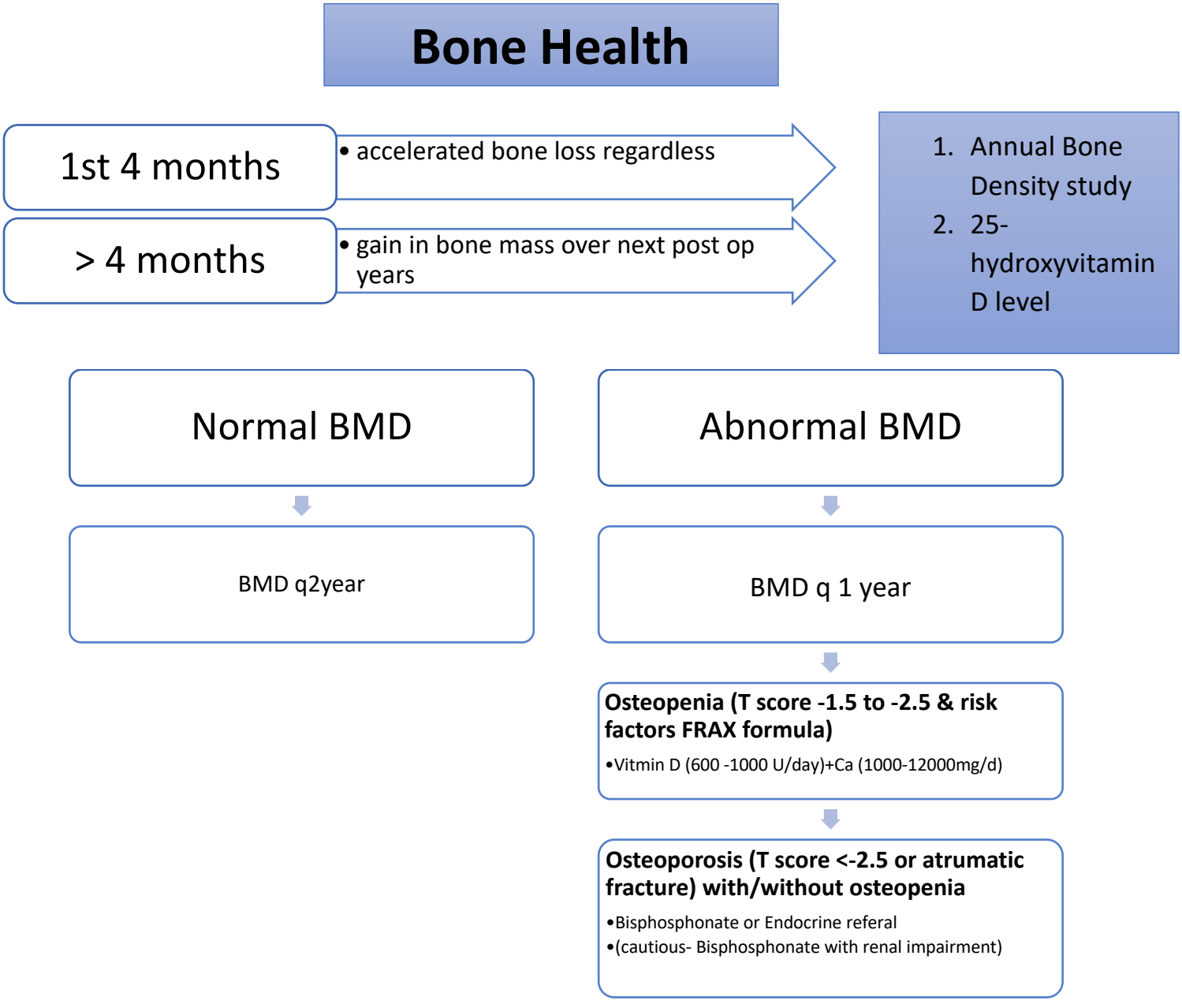


Imunosuppression will follow BUMCP Liver Transplant induction immunosuppression protocol

Bone Health[2-7]

Bone loss and fracturing of bone are complication of bone after liver transplantation. There is intial phase of accelated bone loss regardless of pre-trnsplant bone mineral density (BMD) in the first 4 post operative months, mostly due to the effects of corticosteoids and possibly CNIs. After 4 months post operative peroid, there is gradual gain in bone mass and bone metabolism in the patients with normal allograft function.

We summarize and outline the evlauation of bone metabolism in post transplatn peroid.



References

1. Raevens S, Colle I, Reyntjens K, et al. Echocardiography for the detection of portopulmonary hypertension in liver transplant candidates: an analysis of cutoff values. *Liver Transpl*. Jun 2013;19(6):602-10. doi:10.1002/lt.23649
2. Lucey MR, Terrault N, Ojo L, et al. Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Liver Transpl*. Jan 2013;19(1):3-26. doi:10.1002/lt.23566
3. Singh S, Watt KD. Long-term medical management of the liver transplant recipient: what the primary care physician needs to know. *Mayo Clin Proc*. Aug 2012;87(8):779-90. doi:10.1016/j.mayocp.2012.02.021
4. Watt KD, Pedersen RA, Kremers WK, Heimbach JK, Charlton MR. Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. *Am J Transplant*. Jun 2010;10(6):1420-7. doi:10.1111/j.1600-6143.2010.03126.x
5. Heller JC, Prochazka AV, Everson GT, Forman LM. Long-term management after liver transplantation: primary care physician versus hepatologist. *Liver Transpl*. Oct 2009;15(10):1330-5. doi:10.1002/lt.21786
6. Charlton M, Levitsky J, Aqel B, et al. International Liver Transplantation Society Consensus Statement on Immunosuppression in Liver Transplant Recipients. *Transplantation*. 05 2018;102(5):727-743. doi:10.1097/TP.0000000000002147
7. Campbell PT, VanWagner LB. Mind the Gap: Statin Underutilization and Impact on Mortality in Liver Transplant Recipients. *Liver Transpl*. Oct 2019;25(10):1477-1479. doi:10.1002/lt.25627
8. Krowka MJ, Fallon MB, Kawut SM, et al. International Liver Transplant Society Practice Guidelines: Diagnosis and Management of Hepatopulmonary Syndrome and Portopulmonary Hypertension. *Transplantation*. Jul 2016;100(7):1440-52. doi:10.1097/tp.0000000000001229
9. Northup PG, Garcia-Pagan JC, Garcia-Tsao G, et al. Vascular Liver Disorders, Portal Vein Thrombosis, and Procedural Bleeding in Patients With Liver Disease: 2020 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology*. Jan 2021;73(1):366-413. doi:10.1002/hep.31646
10. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C. Baveno VII - Renewing consensus in portal hypertension. *J Hepatol*. Dec 30 2021;doi:10.1016/j.jhep.2021.12.022
11. García-Pagán JC, Caca K, Bureau C, et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. *N Engl J Med*. Jun 24 2010;362(25):2370-9. doi:10.1056/NEJMoa0910102
12. Garcia-Pagán JC, Di Pascoli M, Caca K, et al. Use of early-TIPS for high-risk variceal bleeding: results of a post-RCT surveillance study. *J Hepatol*. Jan 2013;58(1):45-50. doi:10.1016/j.jhep.2012.08.020
13. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. *Hepatology*. Jan 2017;65(1):310-335. doi:10.1002/hep.28906
14. Biggins SW, Angeli P, Garcia-Tsao G, et al. Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology*. Aug 2021;74(2):1014-1048. doi:10.1002/hep.31884
15. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol*. Aug 2018;69(2):406-460. doi:10.1016/j.jhep.2018.03.024
16. Lloyd-Jones Donald M, Braun Lynne T, Ndumele Chiadi E, et al. Use of Risk Assessment Tools to Guide Decision-Making in the Primary Prevention of Atherosclerotic Cardiovascular Disease. *Journal of the American College of Cardiology*. 2019/06/25 2019;73(24):3153-3167. doi:10.1016/j.jacc.2018.11.005
17. Boike JR, Thornburg BG, Asrani SK, et al. North American Practice-Based Recommendations for Transjugular Intrahepatic Portosystemic Shunts in Portal Hypertension. *Clin Gastroenterol Hepatol*. Jul 15 2021;doi:10.1016/j.cgh.2021.07.018
18. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med*. Aug 5 1999;341(6):403-9. doi:10.1056/nejm199908053410603
19. Peltekian KM, Wong F, Liu PP, Logan AG, Sherman M, Blendis LM. Cardiovascular, renal, and neurohumoral responses to single large-volume paracentesis in patients with cirrhosis and diuretic-resistant ascites. *Am J Gastroenterol*. Mar 1997;92(3):394-9.

20. Angeli P, Ginès P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *J Hepatol*. Apr 2015;62(4):968-74. doi:10.1016/j.jhep.2014.12.029
21. Rose CF, Amodio P, Bajaj JS, et al. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. *J Hepatol*. Dec 2020;73(6):1526-1547. doi:10.1016/j.jhep.2020.07.013
22. Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology*. Aug 2014;60(2):715-35. doi:10.1002/hep.27210
23. Hoilat GJ, Ayas MF, Hoilat JN, et al. Polyethylene glycol versus lactulose in the treatment of hepatic encephalopathy: a systematic review and meta-analysis. *BMJ Open Gastroenterol*. May 2021;8(1)doi:10.1136/bmjgast-2021-000648
24. Barman PM, Chadha RM, VanWagner LB. Cardiac Risk Assessment in Liver Transplant Candidates: A Survey of National Practice Patterns. *Liver Transpl*. Sep 18 2021;doi:10.1002/lt.26307
25. De Gasperi A, Spagnolin G, Ornaghi M, Petrò L, Biancofiore G. Preoperative cardiac assessment in liver transplant candidates. *Best Pract Res Clin Anaesthesiol*. Mar 2020;34(1):51-68. doi:10.1016/j.bpa.2020.02.002
26. Mehta N, Dodge JL, Roberts JP, Yao FY. Validation of the prognostic power of the RETREAT score for hepatocellular carcinoma recurrence using the UNOS database. *Am J Transplant*. May 2018;18(5):1206-1213. doi:10.1111/ajt.14549
27. Verna EC, Patel YA, Aggarwal A, et al. Liver transplantation for hepatocellular carcinoma: Management after the transplant. *Am J Transplant*. Feb 2020;20(2):333-347. doi:10.1111/ajt.15697
28. Salcedo M, Vinaixa C, Javle M, Trapero-Marugán M, Bustamante J, Line PD. Evaluation and Management of Liver Transplant Candidates With Prior Nonhepatic Cancer: Guidelines From the ILTS/SETH Consensus Conference. *Transplantation*. Jan 1 2022;106(1):e3-e11. doi:10.1097/tp.0000000000003997
29. Herrero JI. Screening of de novo tumors after liver transplantation. *J Gastroenterol Hepatol*. Jun 2012;27(6):1011-6. doi:10.1111/j.1440-1746.2011.06981.x
30. Chandok N, Watt KD. Burden of de novo malignancy in the liver transplant recipient. *Liver Transpl*. Nov 2012;18(11):1277-89. doi:10.1002/lt.23531
31. VanWagner LB, Holl JL, Montag S, et al. Blood pressure control according to clinical practice guidelines is associated with decreased mortality and cardiovascular events among liver transplant recipients. *Am J Transplant*. Mar 2020;20(3):797-807. doi:10.1111/ajt.15706
32. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. Sep 10 2019;140(11):e563-e595. doi:10.1161/cir.0000000000000677
33. Patel SS, Rodriguez VA, Siddiqui MB, et al. The Impact of Coronary Artery Disease and Statins on Survival After Liver Transplantation. *Liver Transpl*. Oct 2019;25(10):1514-1523. doi:10.1002/lt.25613
34. Lemahieu WP, Hermann M, Asberg A, et al. Combined therapy with atorvastatin and calcineurin inhibitors: no interactions with tacrolimus. *Am J Transplant*. Sep 2005;5(9):2236-43. doi:10.1111/j.1600-6143.2005.01005.x
35. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. Sep 10 2019;140(11):e596-e646. doi:10.1161/cir.0000000000000678
36. Campbell PT, Kosirog M, Aghaulor B, et al. Comanagement With Nephrologist Care Is Associated With Fewer Cardiovascular Events Among Liver Transplant Recipients With Chronic Kidney Disease. *Transplant Direct*. Oct 2021;7(10):e766. doi:10.1097/txd.0000000000001220
37. Sharif A, Hecking M, de Vries AP, et al. Proceedings from an international consensus meeting on posttransplantation diabetes mellitus: recommendations and future directions. *Am J Transplant*. Sep 2014;14(9):1992-2000. doi:10.1111/ajt.12850
38. Buse JB, Wexler DJ, Tsapas A, et al. 2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. Feb 2020;43(2):487-493. doi:10.2337/dci19-0066

39. Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med*. Sep 4 2003;349(10):931-40. doi:10.1056/NEJMoa021744