Acute and Acute-on-Chronic Liver Failure: Not Just the Liver!

A 2020 Guideline Review

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Objectives

- Review the physiologic manifestations of liver failure on cardiovascular, hematologic, and endocrine systems
- Discuss resuscitation options for hemodynamic stabilization
- Assess bleeding and thrombosis risk for anticoagulation
- Consider options for nutrition support therapy
- Address drug induced liver failure phenotypes

Definitions

Acute-on-Chronic Liver Failure (ACLF)

- Syndrome characterized by acute decompensation of cirrhosis, organ dysfunction, and high short-term mortality

Acute Liver Failure (ALF)

- Occurrence of encephalopathy and hepatic synthetic dysfunction within 26 weeks of the first symptoms of liver disease in a patient without evidence of chronic liver disease

Nanchal R, et al. Crit Care Med. 2020;48(3):415-419.

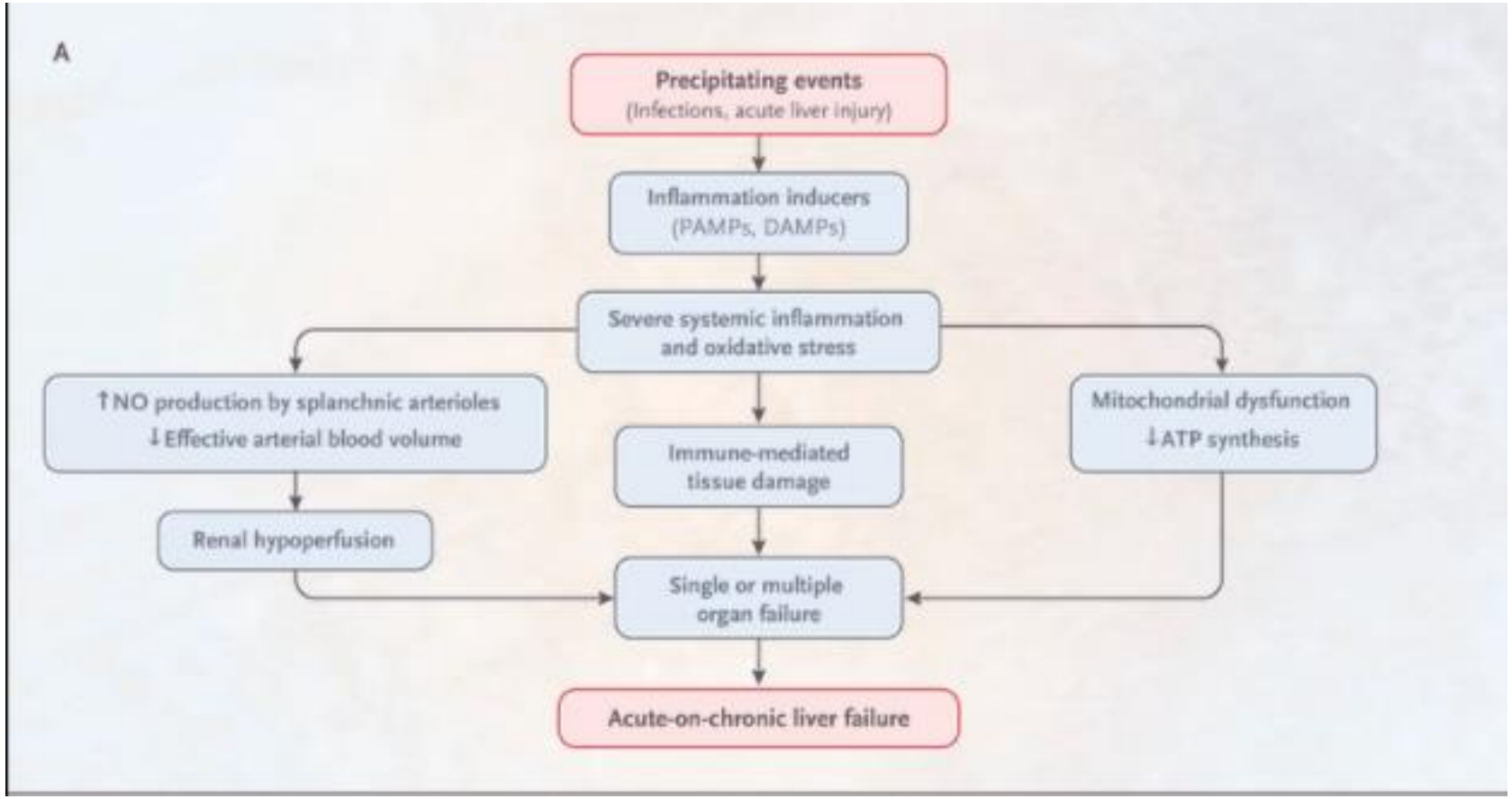
Acute-on-Chronic Liver Failure

- Syndrome associated with high risk of short-term death
  - Occurs in context of intense systemic inflammation
  - Close temporal relationship with proinflammatory precipitating events
  - Associated with single or multiple-organ failure

- Differing definitions:
  - European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) Consortium
  - North American Consortium for the Study of End-Stage Liver Disease
  - Asian Pacific Association for the Study of the Liver

N Engl J Med 2020;382:2137-45

Pathophysiology – ACLF

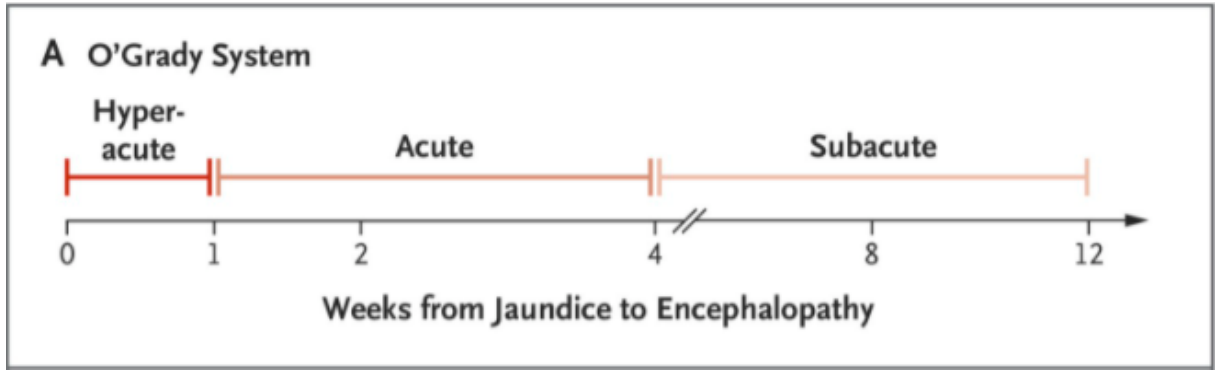


N Engl J Med 2020;382:2137-45

Acute Liver Failure

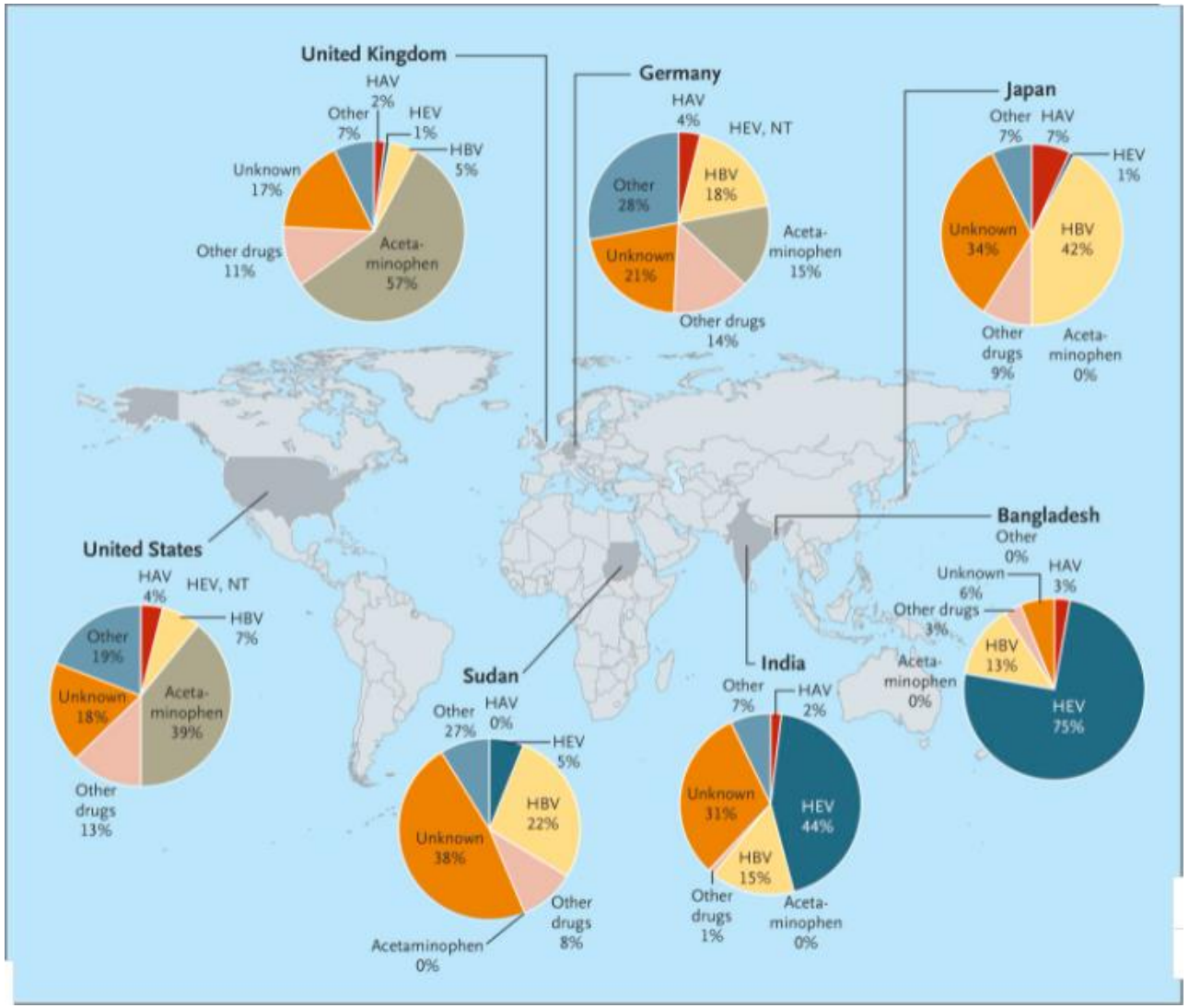
- Originally termed “fulminant hepatic failure” (1970s)
  - A severe liver injury, potentially reversible in nature and with onset of hepatic encephalopathy within 8 weeks of the first symptoms in the absence of pre-existing liver disease

- Varying definitions with interval between symptom onset and development of encephalopathy



N Engl J Med 2013;369:2525-34

Epidemiology – ALF



N Engl J Med 2013;369:2525-34

Etiology of Liver Failure

Chronic Liver Failure

- Alcohol abuse
- Hepatitis B or C
- Non-alcoholic fatty liver disease

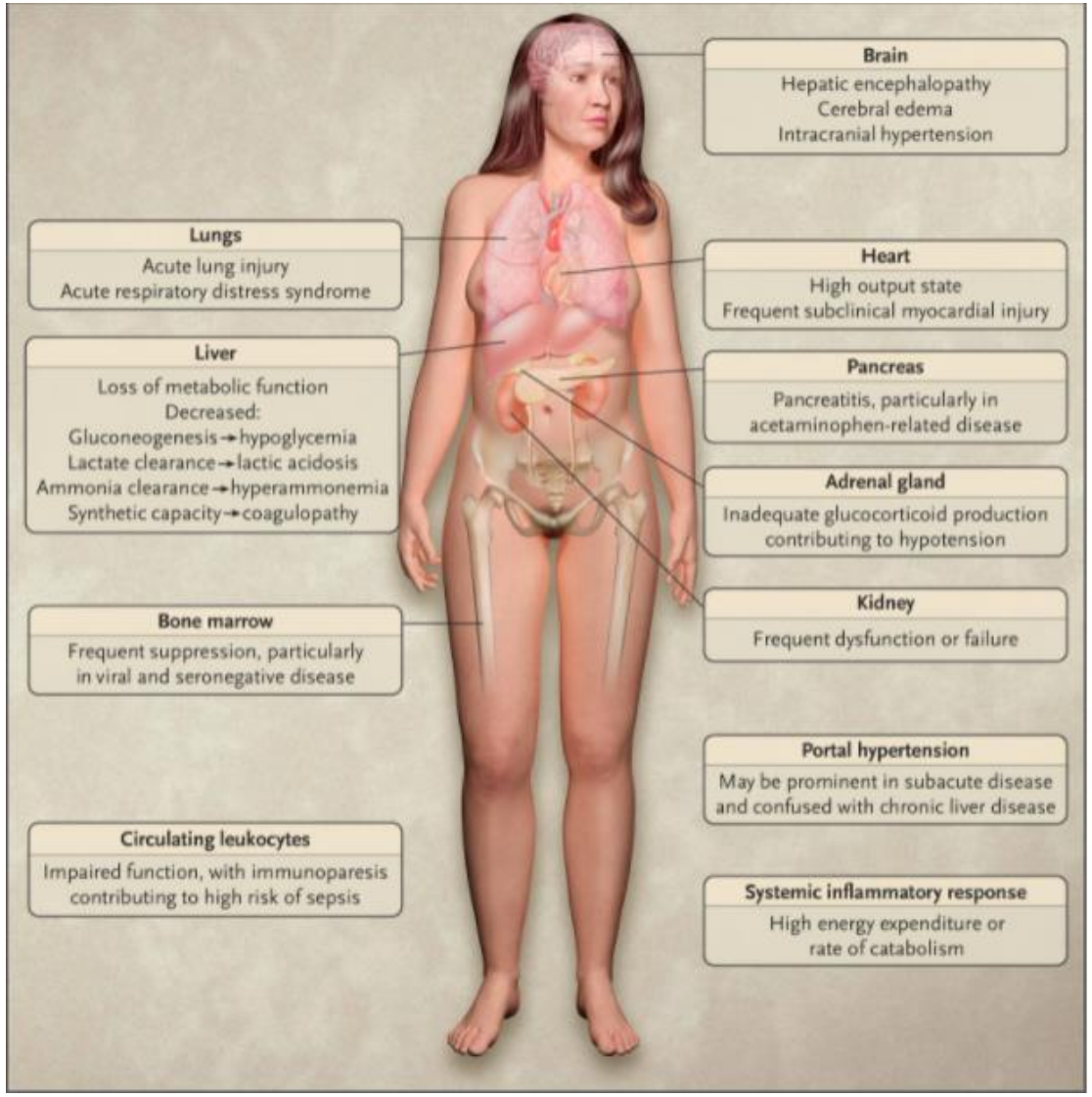
Acute Liver Failure

- Viral
  - Hepatitis B & E
- Drug-Induced Liver Injury (DILI)
  - Acetaminophen toxicity
- Hepatic ischemia
- Autoimmune diseases
- Wilson’s disease
- Indeterminate causes

N Engl J Med 2020;382:2137-45

N Engl J Med 2013;369:2525-34

Clinical Features of Liver Failure



N Engl J Med 2013;369:2525-34

Cardiovascular

	Recommendation	Strength	Quality
3	We suggesting using albumin for resuscitation over other fluids, especially when serum albumin is low (<3 mg/dL).	Conditional	Low
4	We suggest targeting a mean arterial pressure of 65 mmHg with concomitant assessment of perfusion.	Conditional	Moderate
7	We recommend using norepinephrine as a fist-line vasopressor in patients who remain hypotensive despite fluid resuscitation, or those with profound hypotension and tissue hypoperfusion even if fluid resuscitation is on-going.	Strong	Moderate
8	We suggest adding low-dose vasopressin to norepinephrine in patients who remain hypotensive despite fluid resuscitation to increase blood pressure.	Conditional	Low
26	We suggest using stress-dose glucocorticoids in the treatment of septic shock.	Conditional	Low

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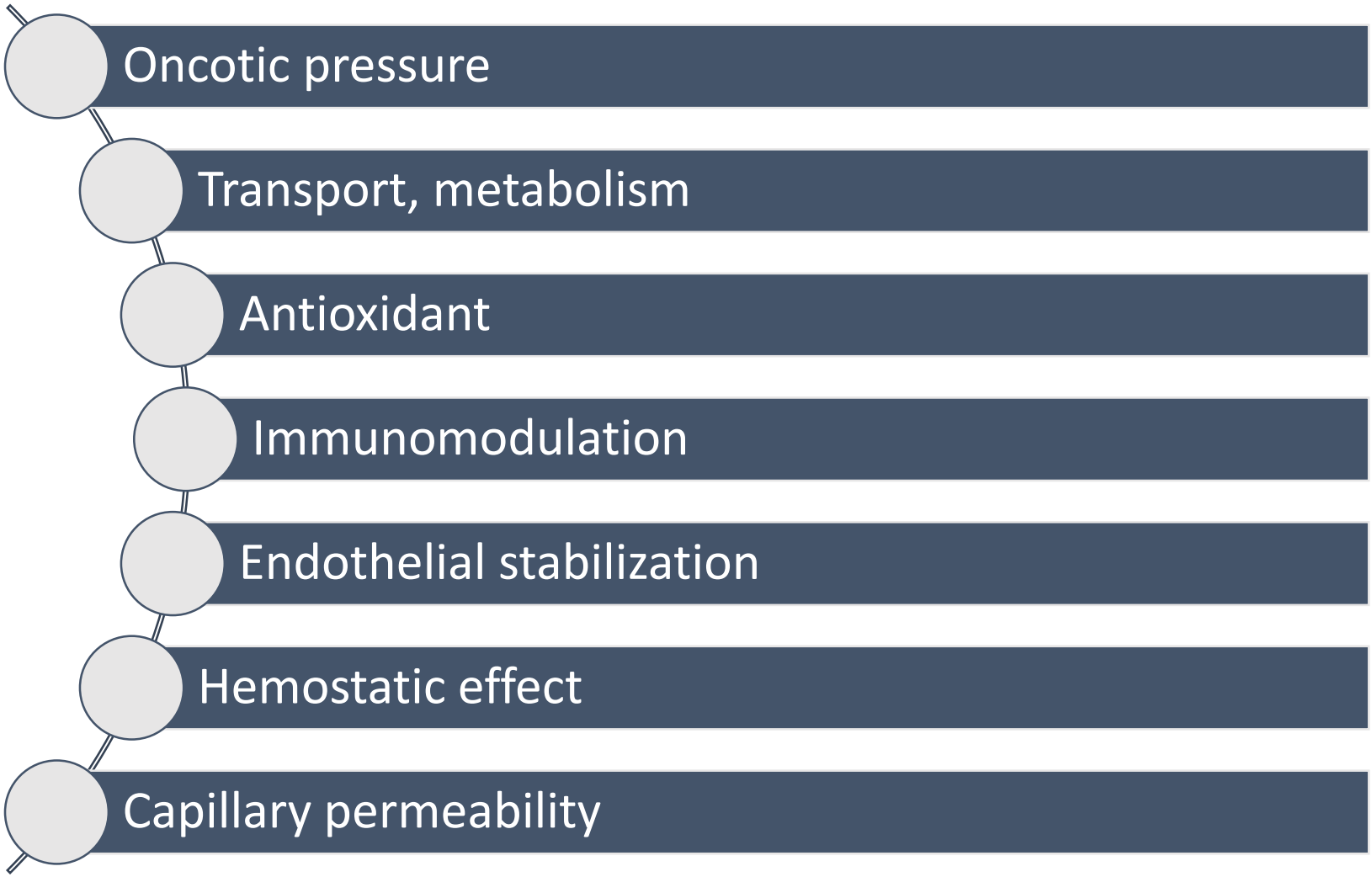
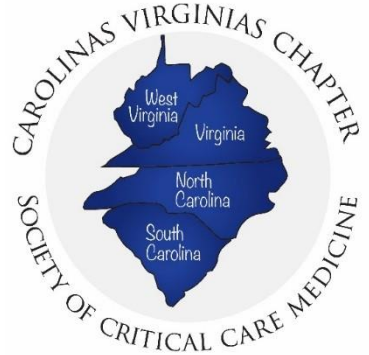
Albumin Functions



Hepatology 2013; 58:1836-1846

“The pathophysiologic rationale suggest that albumin could be considered”



Large Volume Paracentesis

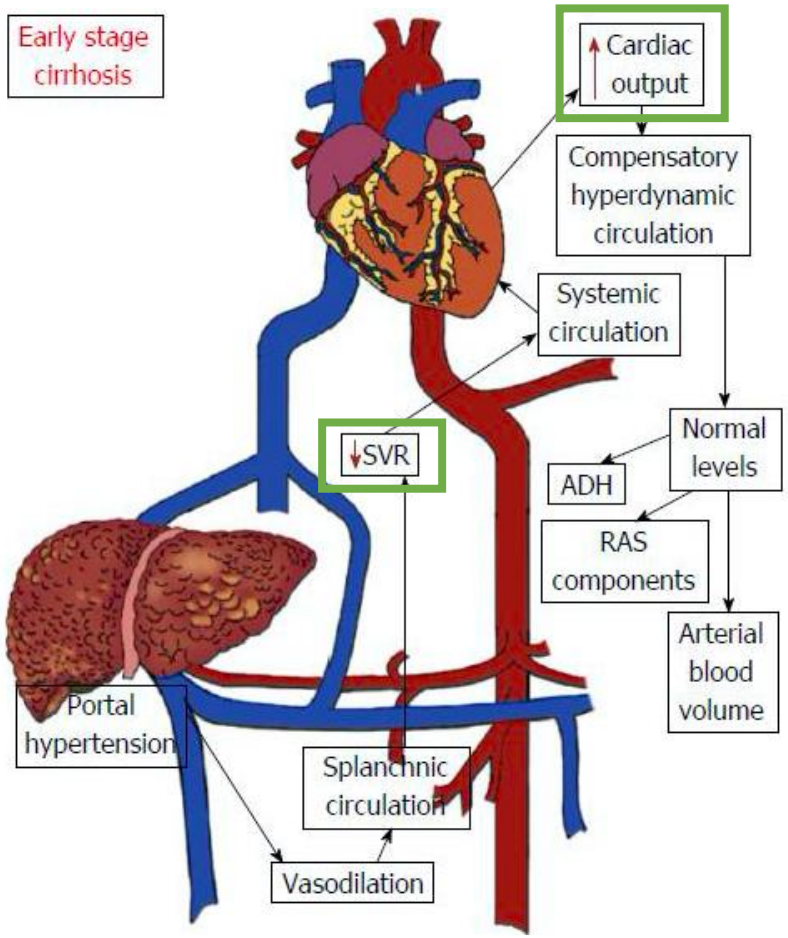
- Paracentesis-induced circulatory dysfunction ↓ 61%
- Death ↓36%
- Improved hemodynamics

Sepsis / Septic Shock

- Meta-analysis: no benefit compared with crystalloids
- ALBIOS: ↓ mortality with septic shock at enrollment
- Indirect data for liver failure

Hepatology 2012;55:1172-1181
Ann Intern Med 2014; 161:347-355
N Engl J Med 2014;370:1412-1421

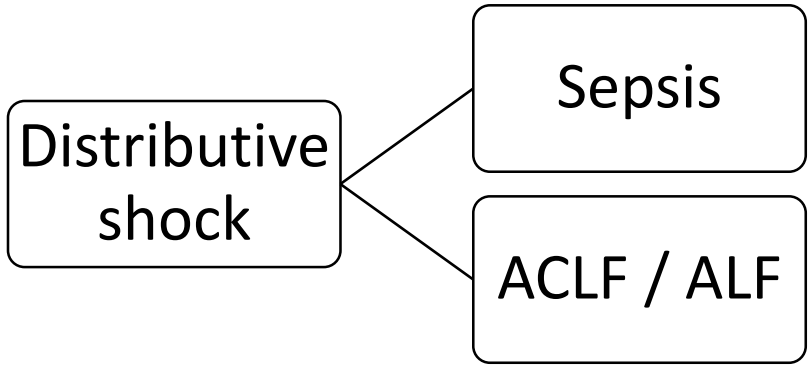
Perfusion + MAP



- Maintain MAP ≥65
  - Surviving Sepsis Guidelines
  - Strong recommendation, moderate quality evidence
- Individual perfusion assessment
  - Hyperdynamic vasodilatory state
- Suggest arterial catheters to monitor or invasive hemodynamic monitoring in specific patients

Crit Care Med 2017; 45:486-552
Crit Care Med 2020;48(3):415-419.

Vasopressors: Norepinephrine 1st



Norepinephrine vs Dopamine

- Lower mortality (NE)
- Lower risk of arrhythmias (NE)

Norepinephrine vs Epinephrine

- No difference in mortality
- Increased splenic vasoconstriction with epi?

Vasopressin

- No studies comparing with vasoactive agents as first-line

Plos One 2015;10:e0129305
JAMA 2018;319:1889-1900

Vasopressors: Vasopressin 2nd

Vasopressin + Catecholamine Vasopressors vs Catecholamines Alone		
Reduced 28 day mortality: (RR 0.89, CI 0.82-0.97) Low bias trials: no difference (RR 0.96, CI 0.84-1.11)	Liver disease (3 trials, 292 patients): Reduced mortality (RR 0.76, CI0.62-0.94) Significant bias	Digital ischemia: RR 2.38 (CI 1.37-4.12) Liver disease & Digital ischemia: RR 3 (CI 1.05-8.55)

JAMA 2018;319(19):1889-1900
Crit Care Med 2017; 45:486-552

Glucocorticoids

- Relative adrenal insufficiency is common in acutely ill patients with cirrhosis
- Meta-analysis (36 RCTs, 9,389 patients)
  - Shock reversal
  - Lower SOFA scores
  - Increased hypernatremia, Increased hyperglycemia
- Critical illness-Related Corticosteroid Insufficiency and Surviving Sepsis Guidelines
- Single-center RCT cirrhosis and septic shock (75 patients)
  - No mortality or shock reversal
  - Higher rate of shock relapse and GI bleed
  - Stopped for futility

Crit Care Med 2018;46:1411-1420
Crit Care Med 2017;45:2078-2088
Crit Care Med 2017; 45:486-552
CMAJ 2010;182:1971-1977

Hematology

Recommendation		Strength	Quality
11	We suggest using LMWH or vitamin K antagonists, over conservative management, in patients with portal venous thrombosis or pulmonary embolus.	Conditional	Very low
12	We suggest using LMWH, over pneumatic compression stockings for VTE prophylaxis in hospitalized patients with ACLF.	Conditional	Low
13	We recommend viscoelastic testing (TEG/ROTEM) over measuring INR, platelet, fibrinogen, in critically ill patients undergoing procedures.	Strong	Moderate

Nanchal R, et al. Crit Care Med. 2020;48(3):415-419.

Hematologic Changes in Liver Disease

↓ procoagulant proteins	↓ anticoagulant proteins	↑ procoagulant protein	Thrombocytopenia Functional platelet defects	↑ platelet adhesive protein	Changes in fibrinogen
↓Prothrombin ↓Factor V ↓Factor VII ↓Factor IX ↓Factor X	↓Antithrombin ↓Protein C ↓Protein S	↑Factor VIII	↓ Platelets	↑ von Willebrand factor	--Fibrinogen
↓Hepatic production	↓Hepatic production	Extra-hepatic synthesis Up-regulation of alternate production pathways ↓Clearance	↓thrombopoietin production ↑platelet consumption Congestive splenomegaly	↑ production ↓ hepatic clearance	↑fibrinolysis in ALF ↑↑fibrinolysis in advanced liver disease Normal in stable chronic disease

Crit Care Med 2016; 44:1927-33
N Engl J Med 2011;365:147-56

Bleeding vs Thrombosis: A Balance

Pro-hemostatic Drivers
-High von Willebrand factor
-Low anticoagulant factors
(antithrombin, protein C)
-High procoagulant factors
(factor VIII)
-Low plasminogen

Anti-hemostatic Drivers
-Low platelet count
-Low pro-coagulant factors
(fibrinogen, Factors II, V, VII, IX, X, XI)
-High tPA

N Engl J Med 2011;365:147-156
Crit Care Med 2016;44:1927-1933

Bleeding vs Thrombosis

DVT/PE	Portal-Vein Thrombosis	Bleeding
• OR 1.23 cirrhosis compared with no cirrhosis • 3% in hospitalized patients	• 1% compensated cirrhosis • 8-25% liver transplant candidates	• 11% (spontaneous + post-procedural bleeding) • 3.3% paracentesis • 2% thoracentesis

Crit Care Med 2020;48:e173-e191
Clin Gastroenterol Hepatol 2010;8:800-5
Thromb J 2011;9:1

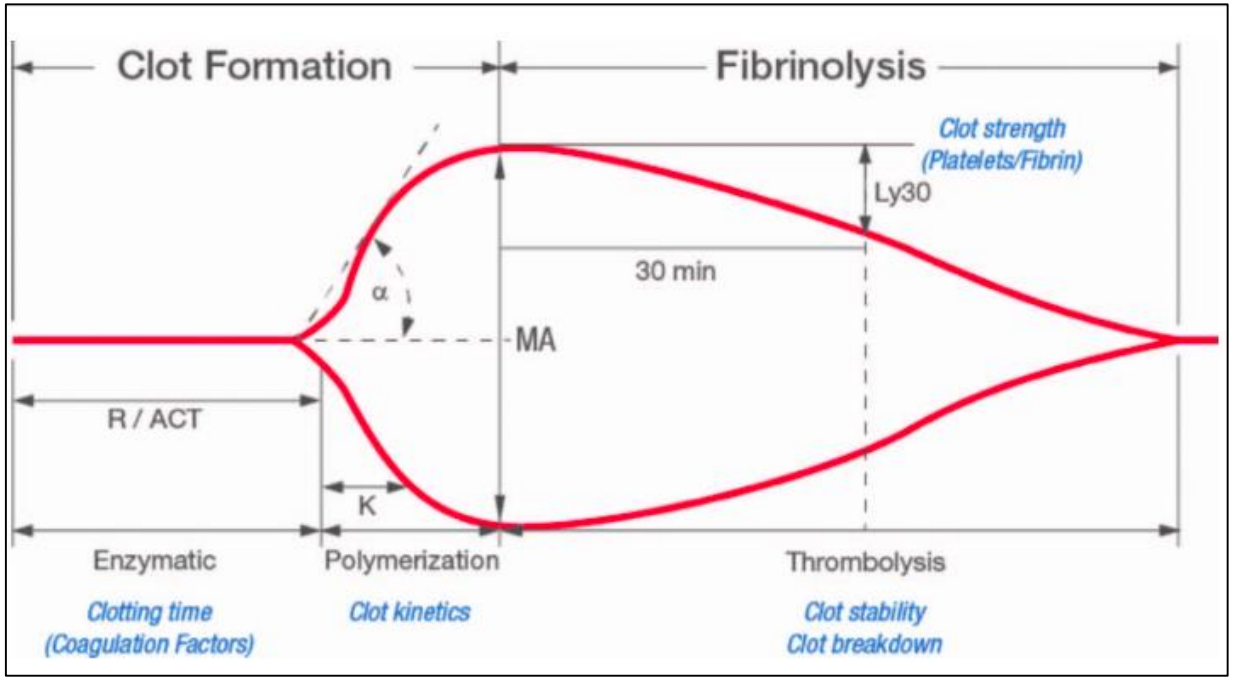
Assessing Bleeding and Thrombosis Risk

- PT/INR, aPTT
  - Developed to monitor anticoagulation
  - Only measures procoagulant factors
- Bleeding does not correlate with platelet count or INR

- Thrombin generation

- Viscoelastic testing: TEG & ROTEM
  - Functional evaluation

Principles of TEG/ROTEM



Thromboelastogram (TEG)			
Components	**Definition**	**Normal Values**	**Problem with...**
R Time	Time to start forming clot	5-10 minutes	Coagulation factors
K Time	Time until clot reached a fixed strength	1-3 minutes	Fibrinogen
Alpha angle	Speed of fibrin accumulation	53-72 degrees	Fibrinogen
Maximum amplitude (MA)	Highest vertical amplitude of the TEG	50-70 mm	Platelets
Lysis at 30 minutes (LY30)	Percentage of amplitude reduction 30 minutes after maximum amplitude	0-8%	Excess fibrinolysis

Thrombelastography-Guided Blood Product Use Before Invasive Procedures in Cirrhosis with Severe Coagulopathy: A RCT

Severe coagulopathy = INR >1.8 and/or platelet count <50 x 10^9/L	
Standard of care (n=30) All patients received FFP and/or PLT per hospital guidelines	TEG transfusion strategy (n=30) FFP if R time >40 min and/or PLT if MA <30 mm
Results Blood products received: 30 SOC vs 5 TEG (100% vs 16.7%; P<0.0001) Post-procedure bleeding: 1 SOC vs 0 TEG (3.3% vs 0%, NS) 90-day mortality: (23.3% vs 26.6%, NS)	
Conclusion TEG-guided transfusion strategy leads to significantly lower use of blood products compared to SOC without increase in bleeding complications	

Hepatology 2016;63:566-573

Treatment of thrombosis

- LMWH or Vitamin K antagonist over no anticoagulation

- Four observational studies
  - Anticoagulation vs no treatment for portal venous thrombosis
  - Greater rates of complete or partial recanalization with anticoagulation
  - No difference in risk of major bleeding

Nanchal R, et al. Crit Care Med. 2020;48(3):415-419.

Thrombosis Prophylaxis

- LMWH over Pneumatic compression stockings in ACLF
  - Insufficient evidence for ALF
- Majority of data for LMWH but can consider unfractionated heparin

LMWH vs no treatment	• Open-label, RCT • N=70 • Lower risk of PVT (8.8% LMWH vs 27.7% control) • No Increase mortality or bleeding
Pharmacologic vs Mechanical prophylaxis	• Observational • N=203 chronic liver disease • No difference in mortality • No difference in bleeding

Nanchal R, et al. Crit Care Med. 2020;48(3):415-419.

Nutrition

Recommendation		Strength	Quality
27	We suggest against using a low protein goal but rather targeting protein goals comparable to critically ills patient without liver failure (1.2-2 protein/kg dry or ideal body weight per day).	Conditional	Very low
28	We suggest not using branch chain amino acids in critically ill patients hospitalized with ALF or ACLF who are tolerating enteral medications.	Conditional	Very low
29	We suggest enteral nutrition over parenteral nutrition in patients without contraindication for enteral feeding.	Conditional	Low

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Liver Cirrhosis and Malnutrition

Decreased energy and protein intake			
Ascites	Salt restriction	Loss of smell, Loss of appetite	Portal hypertension

Malabsorption and Altered Metabolism			
Fat: Deconjugation of bile acids	Protein: Increase catabolism Decreased synthesis	Carbohydrate: Decreased glucose production	Trace elements, Vitamins: Fat malabsorption Diuretic use Inadequate intake

Malnutrition 5-92% → Knowledge gaps, Malnutrition diagnosis → Doubled rate of hospitalization & mortality

Traub et al. Nutrients. 2021;13,540

Protein Goals

SCCM & ASPEN Nutrition Guidelines (2016)

- Avoid restricting protein
- Use the same recommendations as other critically ill patients

International Protein Summit (2017)

- Protein should not be restricted
- Determine protein goals similar to any other critically ill patient in the ICU
- Dry weight should be used

Hepatic Failure	
Protein / Amino Acids (g/kg/day)	1.2-2 (based on dry weight)
Total Energy (Kcal/kg/day)	20-30

JPEN. 2016;40(2):159-211
Nutr Clin Pract. 2017;32(suppl 1):142S-151S

Branched Chain Amino Acids

SCCM & ASPEN Nutrition Guidelines (2016)

- There is no evidence of further benefit of branched-chain amino acid formulations on coma grade in the ICU patient with encephalopathy who is already receiving first-line therapy with luminal acting antibiotics and lactulose.

International Protein Summit (2017)

- Data supporting supplementation of BCAA in patients with decompensated cirrhosis and hepatic encephalopathy in the ICU are lacking, and thus their use is not recommended in the critical care or hospital settings.

Enteral (EN) over Parenteral (PN) Nutrition

SCCM/APSEN

- We suggest that EN be used preferentially when providing nutrition therapy in ICU patients with acute and/or chronic liver disease

ESICM

- Suggest early enteral nutrition (<48h) unless uncontrolled shock, hypoxemia, hypercapnia or acidosis

Compared to Early PN:

- No difference in mortality (RR 0.95; 95% CI 0.76-1.19)
- Reduced risk of infections (RR 0.55; 95% CI0.35-0.86)

JPEN 2016;40(2):159-211
Intensive Care Med 2017; 43:380–398

Pharmacology

Recommendation		Strength	Quality
30	We recommend screening patients for drug-induced causes of liver failure. Drugs that are proven or highly suspected to be the cause of ALF or ACLF should be discontinued.	Best practice statement	Best practice statement
31	We recommend adjusting the doses of medications that undergo hepatic metabolism based on the patient's residual hepatic function and using the best available literature. When available, a clinical pharmacist should be consulted.	Best practice statement	Best practice statement

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Drug-Induced Liver Injury

- Exclusion of other causes

- Most frequent cause of ALF in Western countries
  - >50% of ALF d/t DILI
  - 3-5% of hospital admissions for jaundice

- LiverTox (NIH sponsored):
  - >1200 agents associated with liver injury
  - 447 prescriptions drugs with at least 1 case report of liver injury
  - 20% of cases d/t herbal and dietary supplements (2013-2014)

N Engl J Med 2019;381:264-73
Hepatology 2017;65:363-73

Drug-Induced Liver Injury

	Direct	Idiosyncratic	Indirect
Frequency	Common	Rare	Intermediate
Dose-related	Yes	No	No
Predictable	Yes	No	Partially
Latency	Typically Rapid (days)	Variable (days to years)	Delayed (months)
Phenotypes	• Serum enzyme elevation • Acute hepatic necrosis • Sinusoidal obstruction • Nodular regeneration • Acute fatty liver	• Acute hepatocellular hepatitis • Chronic hepatitis • Mixed or cholestatic hepatitis • Bland cholestasis	• Acute hepatitis • Immune-mediated hepatitis • Fatty liver • Chronic hepatitis
Most common agents	• High dose acetaminophen • Niacin • Aspirin • Cocaine • IV amiodarone • IV methotrexate	• Amoxicillin-clavulanate • Cephalosporins • Isoniazid • Nitrofurantoin • Minocycline • Fluoroquinolones • Macrolide antibiotics	• Antineoplastic agents • Glucocorticoids • Monoclonal antibodies • Protein kinase inhibitors

N Engl J Med 2019;381:264-73

Direct Hepatotoxicity

	Serum Enzyme Elevation
Onset	
Signs & Symptoms Histology	• Elevated ALT or Alk Phos • No Hyperbilirubinemia • Minimal or nor symptoms
Treatment / Recovery	• Resolve with withdrawal • Adaptation
Offending Agent	

N Engl J Med 2019;381:264-73

Idiosyncratic Hepatotoxicity

	Acute Hepatocellular Hepatitis
Epidemiology	• Most Common • 11-15% of ALF • 10% mortality
Signs & Symptoms, Histology	• High ALT • Modest Alk Phos • Hy's law: jaundice with hepatocellular injury
Treatment	
Offending Agent	• Isoniazid • Nitrofurantoin • Diclofenac

N Engl J Med 2019;381:264-73

Indirect Hepatotoxicity

- New category
- May encompass a whole class of medications
- Results from medication actions rather than from inherent hepatotoxic effects or immunogenicity
- Examples:
  - Antipsycotics → weight gain → fatty liver
  - Anticancer agents → reactivation of hepatitis B → acute hepatitis
  - Monoclonal antibodies → immunomodulators → mixed hepatitis

N Engl J Med 2019;381:264-73

Hepatic Dose Adjustments

Endogenous Changes	Decrease 1st pass metabolism
	Altered CYP450 functions
	Impaired renal function
Predicting Hepatic Function	No simple endogenous markers
Child-Pugh Score	Assesses severity of liver function
	Does not quantitate ability of liver to metabolize drug

Eur J Clin Pharmacol. 2008; 64:1147-61

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