North Carolina Society of Gastroenterology 2024 Annual Meeting

The Tipping Point: Understanding the Point of No Return in Chronic Liver Disease and Future Considerations for ACLF

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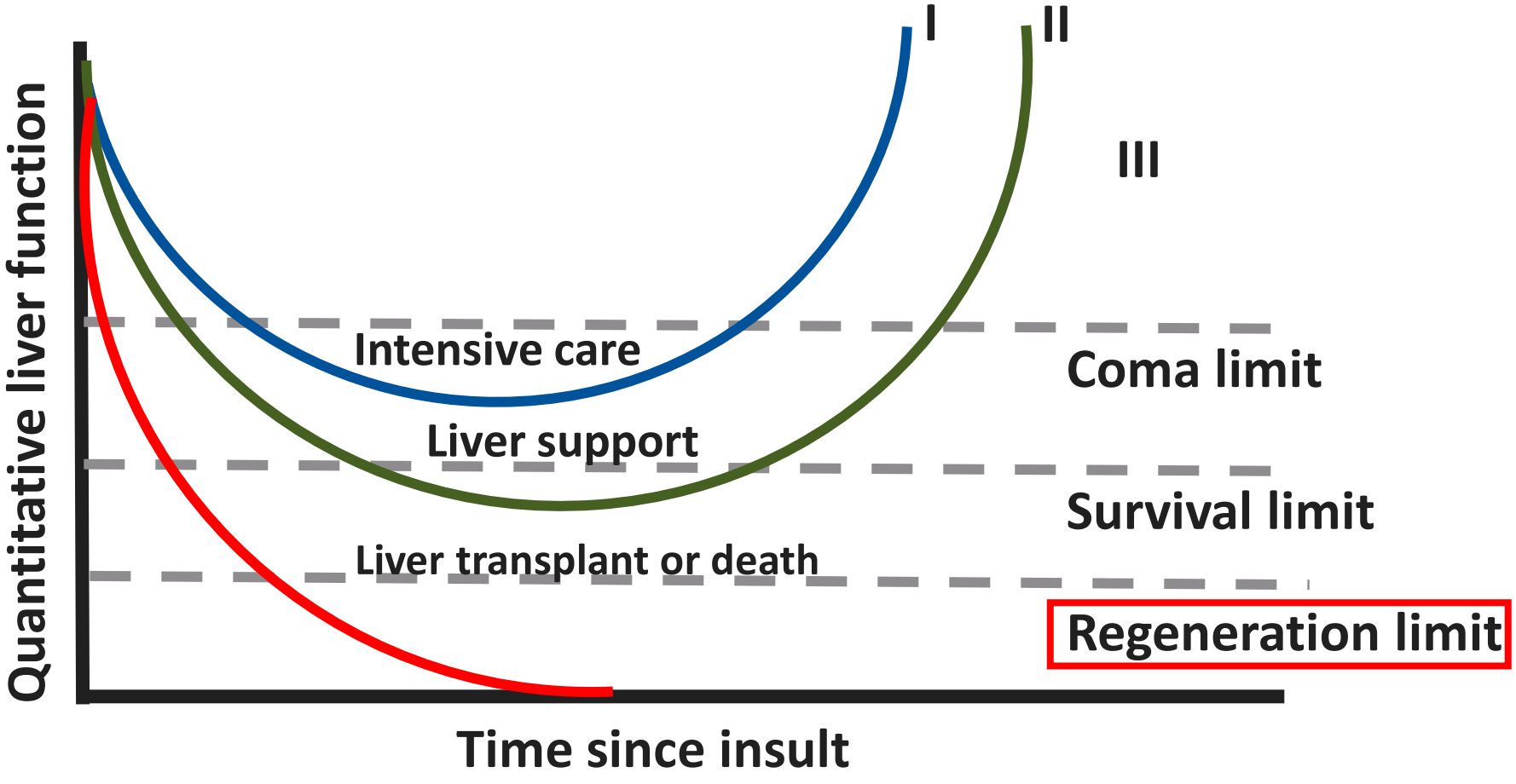
Joint Providership

ASGE
American Society for Gastrointestinal Endoscopy

Disclosures:

None relevant to this topic

ACLF Concept: The "Critical Hepatic Mass" Hypothesis



Ranek & Tygstrup 1971

Original Description of ACLF

Liver 2002: 22(Suppl. 2): 5–13
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Liver
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The pathophysiological basis of acute-on-chronic liver failure

Sen S, Williams R, Jalan R. The pathophysiological basis of acute-on-chronic liver failure.
Liver 2002: 22(Suppl. 2): 5–13. © Blackwell Munksgaard, 2002

Abstract: The vast majority of patients that are referred to a specialist hepatological centre suffer from acute deterioration of their chronic liver disease. Yet, this entity of acute-on-chronic liver failure remains poorly defined. With the emergence of newer liver support strategies, it has become necessary to define this entity, its pathophysiology and the short and long-term prognosis. This review focuses upon how a precipitant such as an episode of gastrointestinal bleeding or sepsis may start a cascade of events that culminate in end-organ dysfunction and liver failure. We briefly review the pathophysiological basis of the therapeutic modalities that are available. Our current strategy for the management of liver failure involves supportive therapy for the end-organs with the hope that the liver function would recover if sufficient time for such a recovery is allowed. Because liver failure, whether of the acute or acute-on-chronic variety, is potentially reversible, the stage is set for the application of newer liver support strategies to enhance the recovery process.

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Key words: acute-on-chronic liver failure – review

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ACLF: Objectives

- Required elements for defining a disease
- Why current definitions confuse us
- Suggested definition of ACLF
- Proposed pathophysiology
- Targets of treatment
- Take home messages

Defining ACLF: General Requirements to Characterize a Disease

- Distinct:
  - Not acute liver failure (ALF), but has ALF element
  - Not chronic liver disease, rapidly progressive
  - Not compensated cirrhosis
  - Not traditional decompensated cirrhosis
  - Usually triggered by a precipitating event
  - Associated with organ failures with **high** short-term mortality
- Unique pathophysiology
  - Pathway has to be defined
- Diagnostic signs/symptoms/test: ???
- Management change: Need for liver support

Defining ACLF is important

- Should trigger management changes
- Identify entry point for studies
- ACLF like Acute on Chronic Heart Failure or Acute on Chronic Renal Failure should reflect some degree of **reversibility** or hepatic decline from **baseline**.
  - Liver support may allow return of function

- Most patients defined as ACLF in US and Europe probably have accelerated chronic liver failure, NOT acute-on-chronic liver failure

ACLF: Definitions and Proposed Pathophysiology

- Required elements for defining a disease
- **Why current definitions confuse us**
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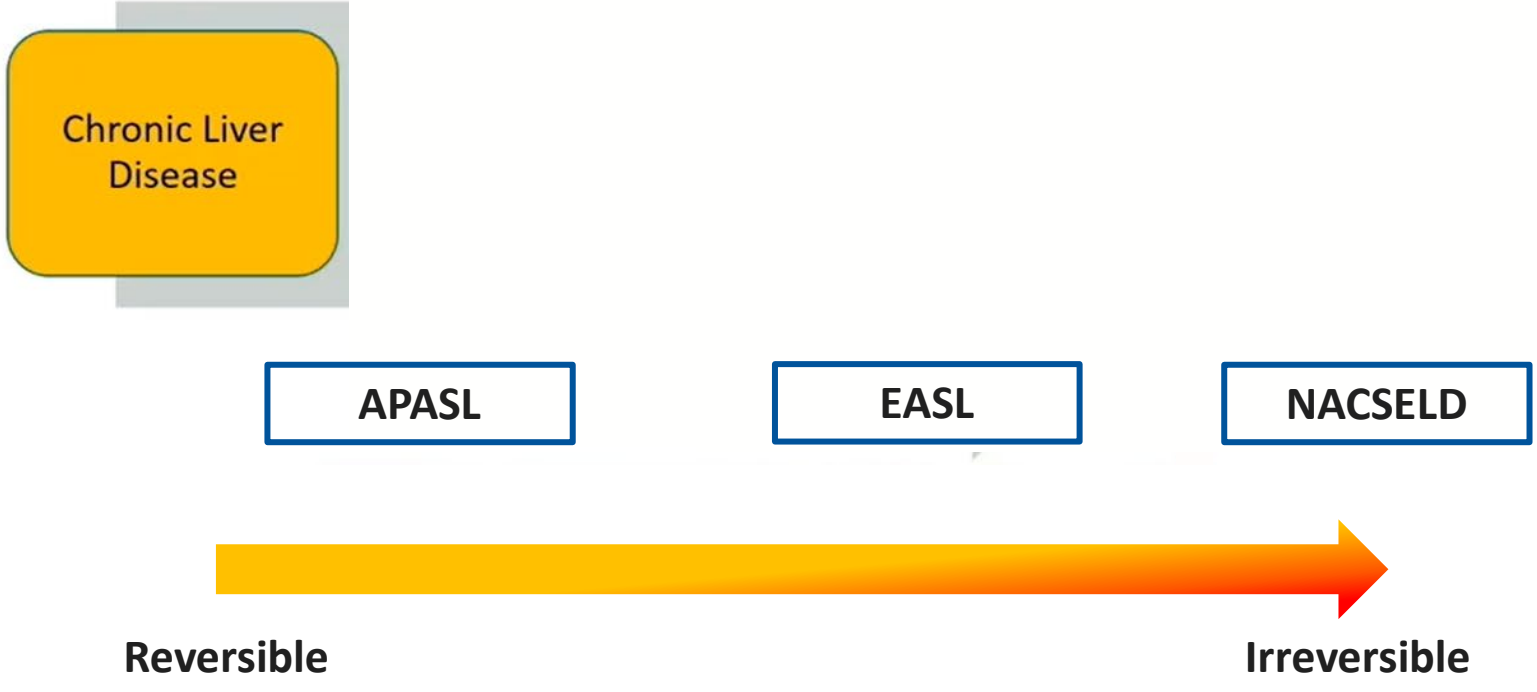
ACLF: Current definitions mark different points in time



	North American Consortium for the Study of End-Stage Liver Disease (NACSELD)	European Association for the Study of the Liver Chronic Liver Failure Consortium (EASL)	Asian Pacific Association for the Study of the Liver ACLF Consortium (APASL)
Patients included	Acutely decompensated cirrhosis with or without prior decompensation	Acutely decompensated cirrhosis with or without prior decompensation	Cirrhosis or other chronic liver disease without previous decompensation
Definition	NACSELD-ACLF Presence of two or more organ failures	CLIF-C score ACLF Grade 1: • Single kidney failure, circulatory, respiratory or liver failure, cerebral failure + cr 1.5-1.9 mg/dL ACLF Grade 2: two organ failures ACLF Grade 3: three or more organ failures	"Acute hepatic insult" in a patient with underlying chronic liver disease presenting with jaundice (serum bilirubin 5 mg/dL) and coagulopathy (INR 1.5) and resulting in the development of ascites and/or encephalopathy within a 4-wk time frame
Organ failures	1. Circulatory: MAP < 60 mm Hg 2. Respiratory: Mechanical ventilation 3. Renal: Dialysis 4. Cerebral: Grade III or IV hepatic encephalopathy	1. Circulatory: use of vasopressors 2. Respiratory: PaO2/FiO2 ≤ 200 or SpO2/FiO2 ≤ 214 3. Renal: Creatinine ≥ 2 mg/dL or RRT 4. Cerebral: Grade III or IV hepatic encephalopathy 5. Liver: Total bilirubin ≥ 12 mg/dL 6. INR ≥ 2.5	Liver failure only. Extrahepatic organ failures are considered consequences of ACLF
Triggers	Primary infection	Intrahepatic and extrahepatic including infection, gastrointestinal bleeding, alcohol	Only intrahepatic such as HBV reactivation, alcohol, etc.
Strengths	• Simple and easy to use at the bedside • Carries significant prognostic value	• Allows for ***specific*** definition of ACLF • Recognize significance of early renal dysfunction • Carries significant prognostic value	• Includes patients with chronic liver disease but who do not have cirrhosis • Allows for earlier identification of ACLF

Concern:

- By including organ failure in definition of ACLF could promote a passive, reactive approach to management

Confusion:

- NACSELD criteria outperforms EASL-CLIF in predicting **7-day mortality**

- EASL-CLIF outperforms predicting **90-day mortality**

Potential use:

- EASL-CLIF used to **prioritize** patients **for transplantation**

- NACSELD used to **exclude** patients **from transplantation**

Cao Z. Am J Gastro. 2020
Wong F. Liver Transpl. 2021

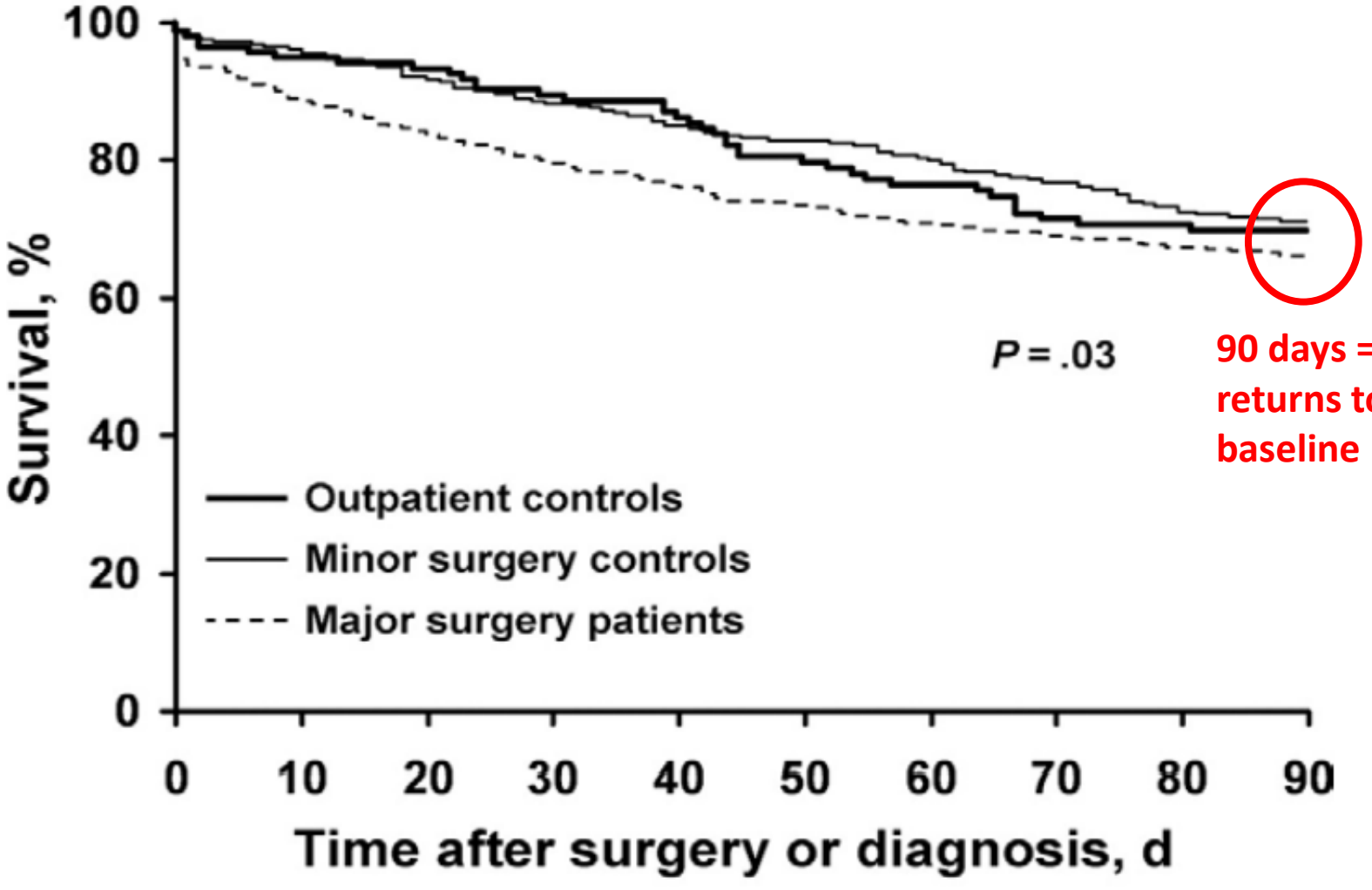
Simplified Definition of ACLF

- ACLF is a ***potentially reversible condition***
- **Underlying** chronic liver disease or compensated cirrhosis
- Usually associated with a **precipitating event**
- High risk of **3-month mortality** in the absence of treatment of precipitating event; liver support; or liver transplantation
- Challenging to define: inconsistently described across various global populations

Goal: Underlying liver disease with multiorgan failure and higher rate of short term mortality

Bajaj JS. Hepatology. 2018

Best model for ACLF is surgery: why 3 months?



Teh S. Gastroenterology 2007

ACLF: Definitions and Proposed Pathophysiology

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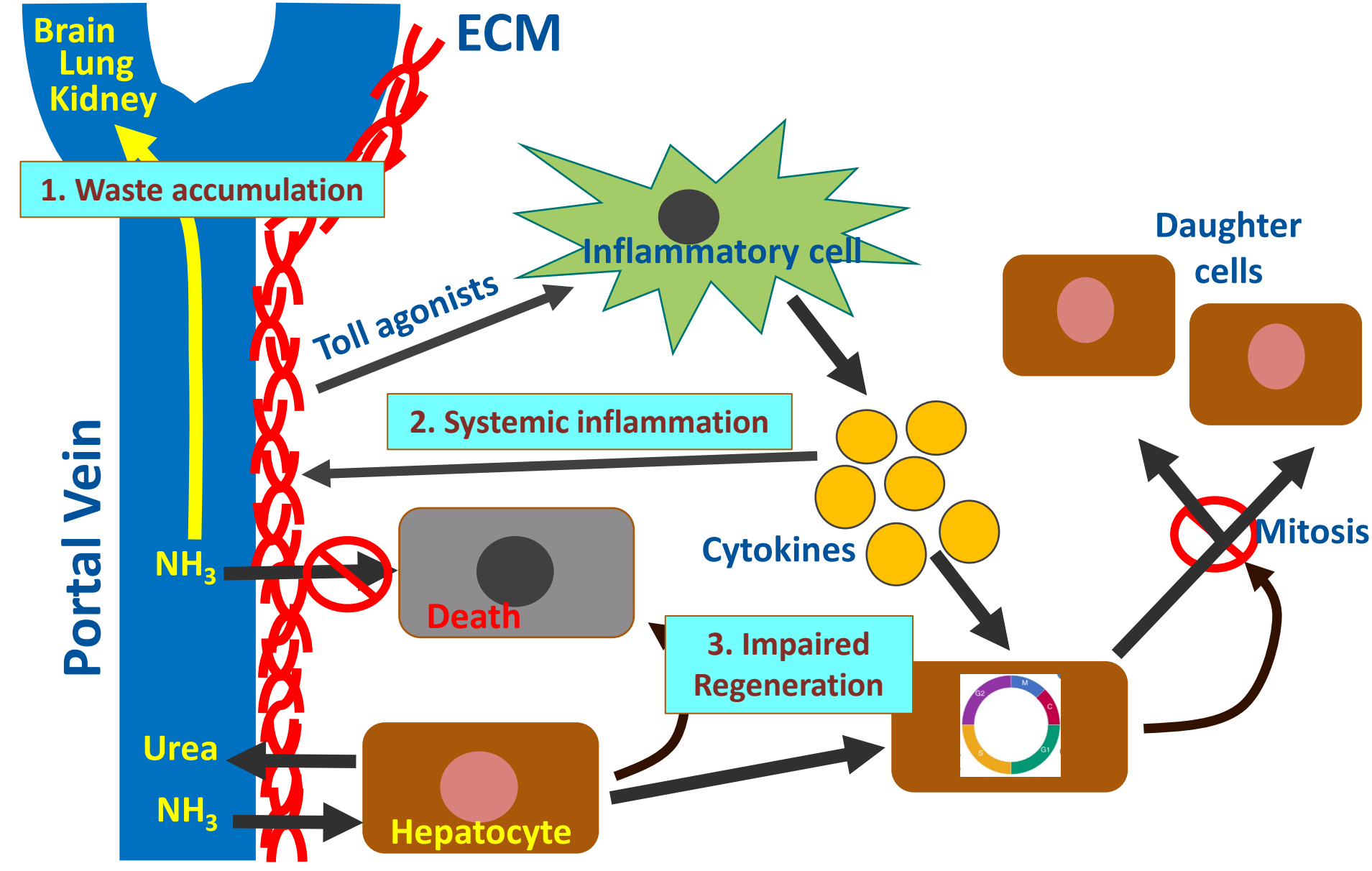
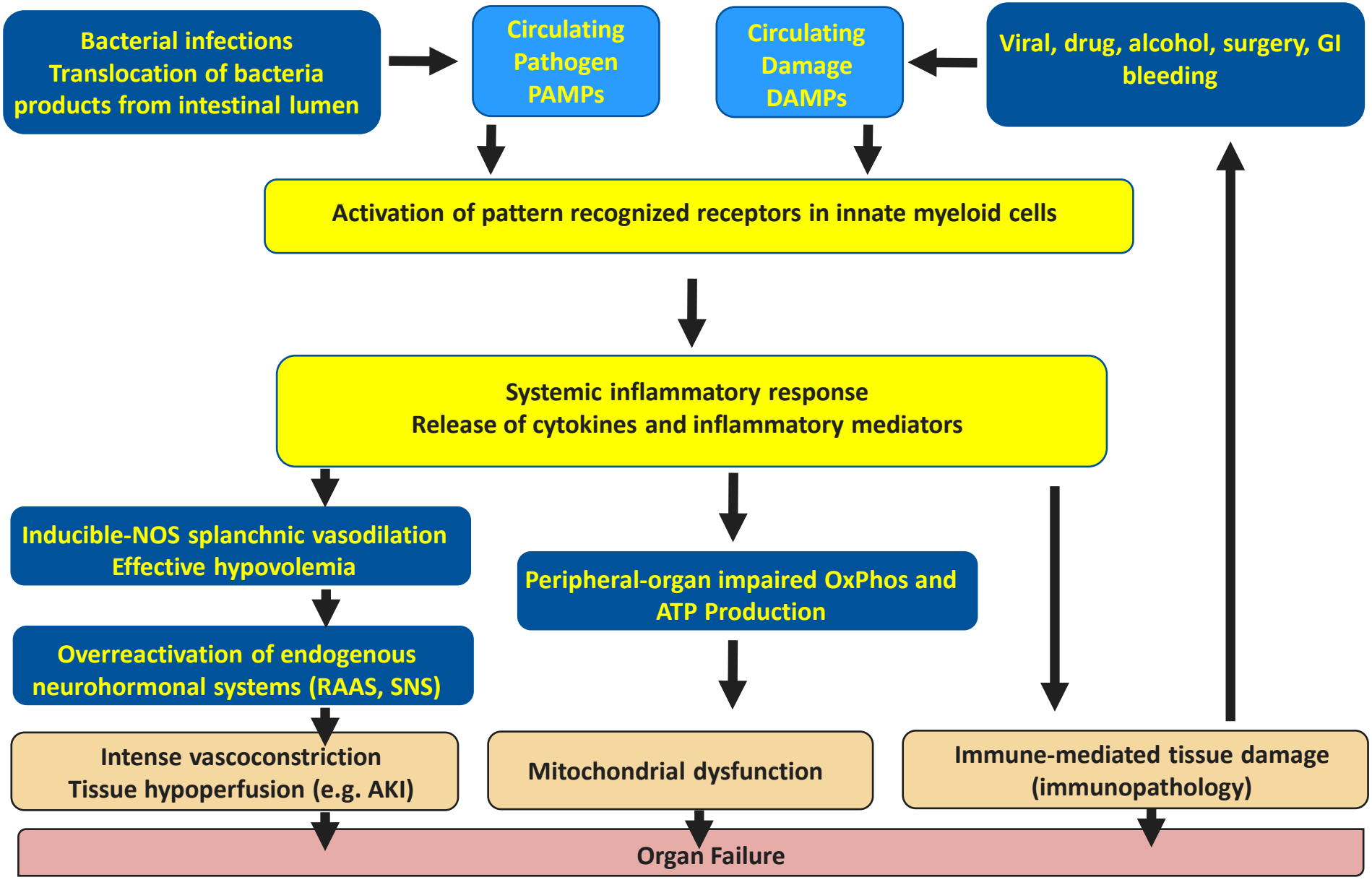
ACLF: Proposed Pathophysiology

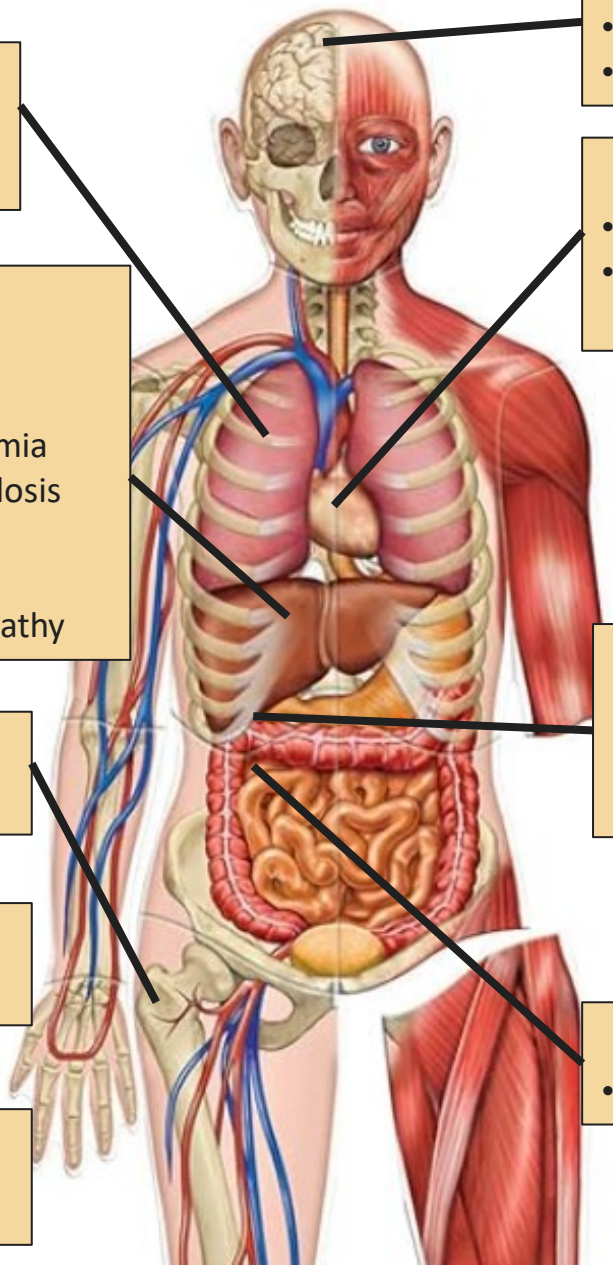


ACLF: Systemic Inflammatory Response Syndrome

Zaccherini G. Jhep Reports. 2020



Organ Dysfunction in ACLF



Brain
- Hepatic encephalopathy
- Cerebral edema

Heart
- High output state
- Subclinical myocardial injury and cardiomyocyte suppression

Lungs
- Acute lung injury
- Acute respiratory distress syndrome

Liver
- Loss of metabolic function
- **Decreased**:
  - Gluconeogenesis → hypoglycemia
  - Lactate clearance → Lactic acidosis
  - Ammonia Clearance → Hyperammonemia
  - Synthetic capacity → Coagulopathy

Adrenal gland
- Inadequate glucocorticoid production contributing to hypotension

Bone marrow
- Suppression

Sepsis
- Immunoparesis → High risk sepsis

Renal failure
- Acute kidney injury

Systemic inflammatory response

Zaccherini G. Jhep Reports. 2020

ACLF: Definitions and Proposed Pathophysiology

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- **Targets of treatment**
- Take home messages

Targets for treatment

Infections

- Complete work-up at diagnosis of ACLF to rule out infections
- High-dose broad spectrum antibiotics (tailored to local epidemiology) at ACLF diagnosis
- Daily reassesment of antibiotic therapy

- Do not delay the administration of antibiotics to the obtention of cultures
- Empirical antifungal therapy only if risk factors for invasive fungal infections

Kidney

- Assessment of AKI severity using modified KDIGO criteria from the International Club of Ascites
- 20% albumin (1 g/kg for 48 hr) in patients with AKI stage 2-3
- In type-1 hepatorenal syndrome: 20% albumin (1 g/kg for 48 hr and then 20-40 g/day) + terlipressin (2 mg/24 hr) or norepinephrine (0.5 mg/hr, when terlipressin is not available)
- RRT - define goal: bridging to LT

- Avoid nephrotoxic drugs (NSAID)
- Avoid early initiation of RRT

Lungs

- Endotracheal intubation for patients with West Heaven grade III or IV hepatic encephalopathy
- Lung protective ventilation strategy
- Prone positioning feasible
- Paracentesis in case of tense ascites

Hemodynamics

- Early goal-directed therapy within the first 6 hours
- Maintain mean arterial pressure >65 mmHg
- Fluid challenges until no further hemodynamic response
- Prefer crystalloids and 5% albumin as resuscitation fluid
- Strong indications of albumin: spontaneous bacterial peritonitis, large volume parascentesis, AKI (see kidney)
- Norepinephrine as first line vasopressor; epinephrine or terlipressin when additional agent needed
- Intravenous hydrocortisone if refractory shock (norepinephrine >0.5 mg/kg.min)

- Avoid starches formulations
- Limit saline solutions in patients with ascites or anasarca

Coagulation

- Fibrinogen and/or patelets in patients with severe hypofibrinogenemia (<1g/L) and/or thrombocytopenia (<20,000 x10^9/L) undergoing invasive procedures
- Prophylaxis for deep-vein thrombosis in patients without severe coagulopathy

- Avoid correction of INR alterations with fresh frozen plasma in the absence of bleeding

Nervous central system

- Treatment of the underlying cause
- Lactulose and enemas for hepatic encephalopathy
- Use sedation protocols, targeting specific endpoints
- Use short-acting sedative agents

- Avoid deep sedation, avoid benzodiazepines
- Avoid neuromuscular in patients without ARDS

Gastro-intestinal

- Consider stress-ulcer prophylaxis
- Administer early oral or enteral feedings, as tolerated, after ACLF diagnosis (goal: 10-15 kcal/kg/day by day 4)

Transplant for ACLF: Ultimate treatment

- Transplant free mortality is high
  - **Grade 1: 23%**
  - **Grade 2: 32%**
  - **Grade 3: 75%**

- Contrary: liver has regenerative capacity and ACLF is dynamic
  - Resolution possible:
    - **Grade 1: 55%**
    - **Grade 2: 35%**
    - **Grade 3: 15%**

- Several scores have been developed to predict transplant-free survival

- **Long term survival post LT difficult to predict due to both recipient and donor factors**

Moreau R. Gastro. 2013
Gustot T. Hepatology. 2015
Zhou Z. Can J Gastro Hep. 2022
Linecker M. J Hepatol. 2018

Post LT Survival: recipient factors

- Greater than or equal to 4 organ failures
- CLIF-C score greater than 64 at day 3 to 7
- Respiratory failure
- Mechanical ventilation
- MELD Na greater than 30 with advanced hepatic encephalopathy (HE)
- High lactate levels
- Development of HE, increase in creatinine levels and white cell counts in 7 days
- Active GI bleed, controlled sepsis for less than 24 hours, high vasopressor support (3mg/h), and/or P/F ratio less than 150
- Active drug abuse, infections with MDROs or invasive fungal infection, high cardiac risk
- Clinical frailty score greater than or equal to 7 (living with severe frailty)
- Futility risk score greater than 8

Multiple references

Donor factors

- High quality graft
  - Donor health
  - Cause of death: cardiac death = more complications
  - Shorter cold ischemia time
  - Size match
- Donor age <60
- Low macrosteatosis (<15%)
- Low donor risk index – predictive tool developed for liver donors
- Living donation setting, graft-to-recipient weight ratio of 0.8 to 1

Singal AK. Liver Int. 2022
Toshima T. Clin Transplant. 2022

Liver transplant for Patients with ACLF

Prognosticate based on # organ failures

ACLF

Indicators or futility
- Respiratory failure/mechanical ventilation (P/F ≤200)
- Noradrenaline ≥1ug/kg/m or need for 2+ vasopressors
- Multiple comorbidities
- Poor performance status (frailty)
- Psychosocial issues/active drug use
- Pre-LT lactate ≥5 mmol/L
- CLIF-C score >64
- ≥4 organ failures
- Futility risk score >8

Early listing / Optimization

Regular assessment

Golden Window
- Minimal vasopressor support
- No mechanical ventilation
- Clinically stable/improvement
- No/controlled infection
- Suitable organ available

<30 days from listing

Coordinate with palliative care

Liver transplantation

Post LT
- Regular physiotherapy
- Adequate nutrition
- Prevention of skin and soft tissue infections
- Lower CNI trough levels
- Renal sparing IS
- Broad spectrum antibiotics

- Evaluate for biliary and vascular complications (higher complication rate in ACLF)
- Renal replacement therapy
- Surveillance cultures to identify infection early

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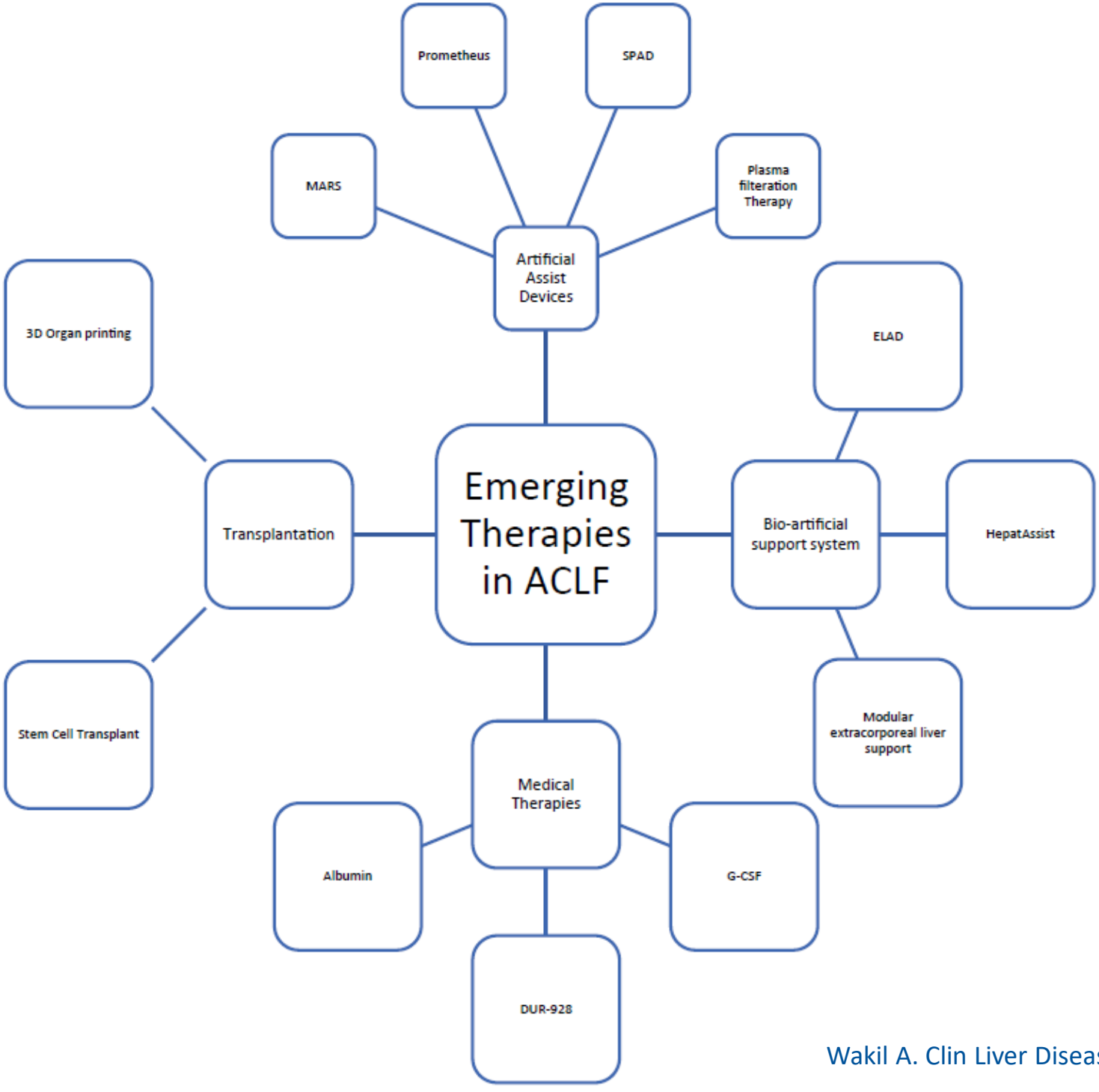
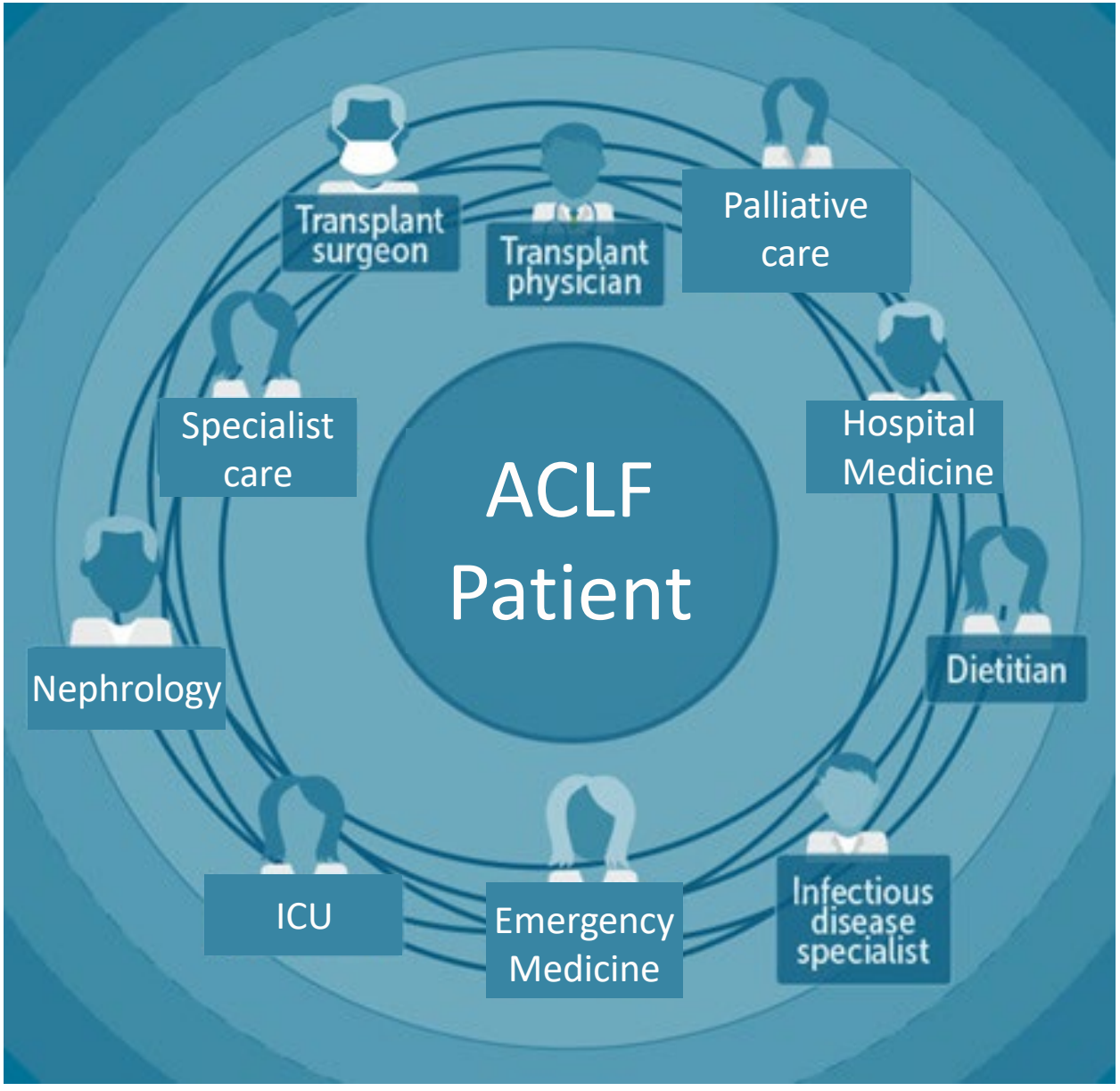


Wakil A. Clin Liver Disease. 2023

Great multidisciplinary coordination



ACLF: Definitions and Proposed Pathophysiology

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ACLF: Definitions and Proposed Pathophysiology

- ACLF term should be restricted to patients with chronic liver disease or compensated cirrhosis: reversibility is a requirement
- Optimal definition requires better understanding of pathophysiology
- Definitions as they currently stand reflect prognosis rather than define the disease
  - **Prognostic** markers should be separate from **diagnostic** markers
  - Further understand the role of systemic inflammation in ACLF
- Standard management required for international studies if consensus definitions are to be developed
- Identifying appropriate donor:recipient pairs is critical in management of ACLF with liver transplant
  - Liver transplant remains only curative therapy for ACLF

CME Question

A CLIF-C score greater than 64 at day 7 is associated with a good prognosis in a patients with alcohol induced cirrhosis admitted for spontaneous bacterial peritonitis (SBP)?

a. True

b. False

CME Question

A CLIF-C score greater than 64 at day 7 is associated with a good prognosis in a patients with alcohol induced cirrhosis admitted for spontaneous bacterial peritonitis (SBP)?

a. True

b. False

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