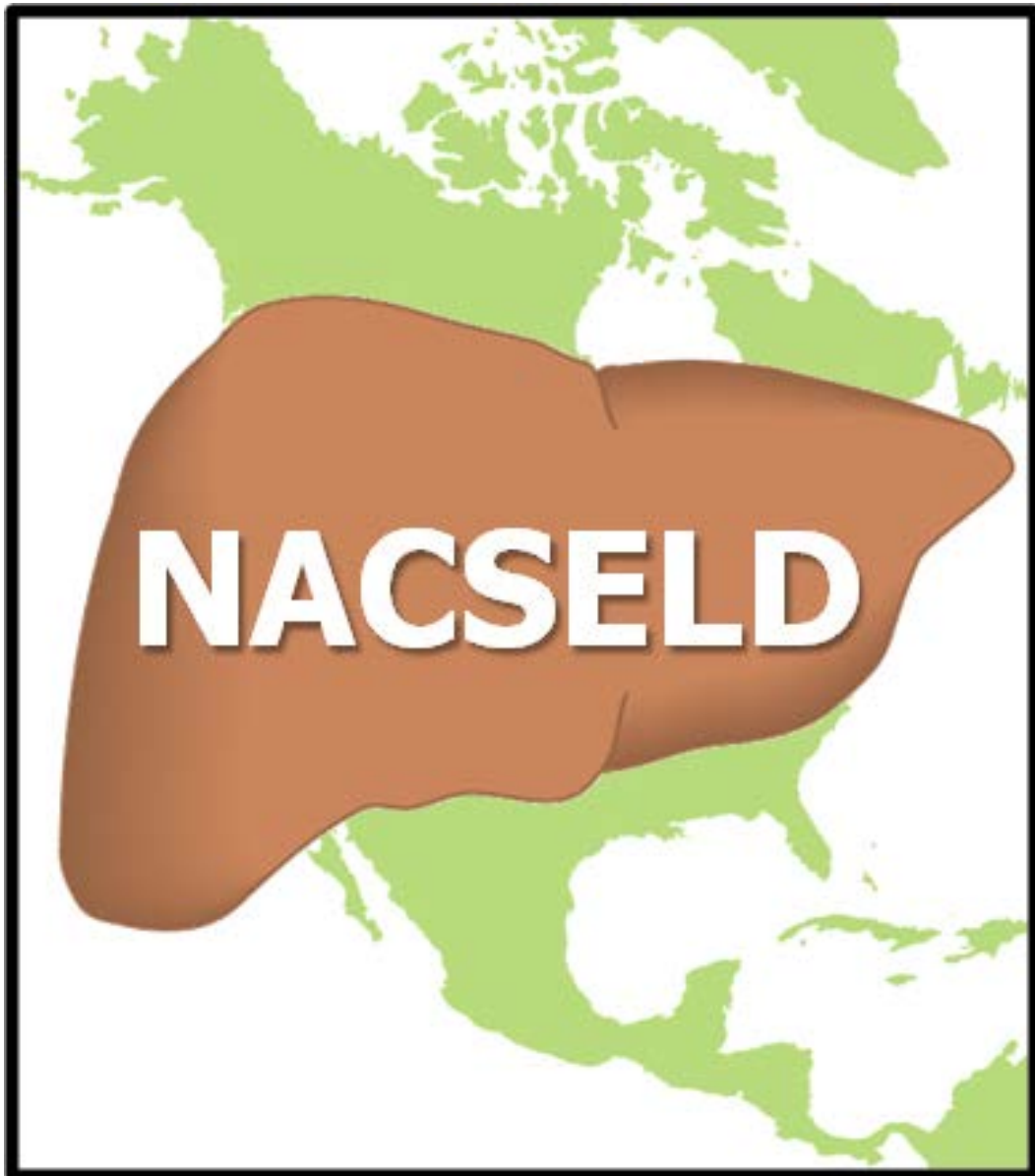# Acute-on-Chronic Liver Failure

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Dr. Jacqueline O'Leary began her pursuit of research as an undergraduate at Stanford University investigating drug development, continued at UCSF where she received an MD with thesis for work in cellular and molecular biology. Following her internal medicine residency at UT Southwestern, Dr. O'Leary did a GI fellowship and Transplant Hepatology fellowship at Massachusetts General Hospital. Her post-doctoral research there at Harvard focused on basic science immunology. Afterward, she completed a Master's in Public Health from the Harvard School of Public Health in Clinical Effectiveness. These accomplishments make her uniquely poised to translate research findings into clinical care. She has focused her clinical research on antibody-mediated rejection in liver transplantation and acute-on-chronic liver failure (ACLF) and is currently the Chief of Hepatology at the Dallas VA Medical Center.

Purpose and Overview: The purpose of this lecture will be to define ACLF, describe the expected outcome after development, and educate the audience on how to decrease its incidence.

Educational Objectives:
1) Define ACLF
2) Describe the prognosis of a patient with ACLF
3) Describe why patients with cirrhosis are at risk for ACLF
4) Delineate ways to prevent ACLF

What is ACLF?

Acute-on-Chronic liver failure (ACLF) is different from Acute Liver Failure (ALF) and acute decompensation (AD).

ALF is clearly defined as the new onset within 8 weeks of the first symptom of:
1) Hepatic encephalopathy
2) Coagulopathy (INR ≥1.5)
3) Jaundice (serum bilirubin ≥2 mg/dL)

In a patient _without_ underlying liver disease (exception Wilson disease).

AD is the new onset of ascites, hepatic encephalopathy, hepatorenal syndrome or variceal hemorrhage in a patient with underlying cirrhosis. Many times these symptoms are present in patients with ACLF, but AD only requires one of the aforementioned events, does not require an organ failure, and may or may not require hospital admission.

Consensus has been reached that ACLF is defined and graded by the type and number of hepatic and extrahepatic organ failures and only occurs in patients _with_ underlying liver disease. Although numerous nuanced definitions are current being used world-wide[1], 3 definitions are the most widely utilized.

The Asian Pacific Association for the Study of the Liver (APASL) was the first group to define ACLF using the criteria below[2]:
1) A patient with underlying liver disease (cirrhosis is not required)
2) A hepatic insult that results in jaundice (serum bilirubin ≥5 mg/dL) and coagulopathy (INR ≥1.5)
3) Complicated within 4 weeks by:
   a. Ascites and/or
   b. Hepatic encephalopathy

APASL's definition reflected the patient population most commonly seen in Asia; specifically acute insults that occurred in patients with underlying Hepatitis B, such as HBV reactivation or HAV, HDV or HEV superinfection in a patient with chronic HBV.

Next, the European Association for the Study of the Liver (EASL) formed the Chronic Liver Failure (CLIF) consortium who created the EASL-CLIF definition of ACLF[3]. Compensated or decompensated cirrhosis was required to meet the criteria for this definition, and the prognosis was dependent of the development of up to 6 organ failures:

1) Liver failure if serum bilirubin is ≥12.0 mg/dL

2) Renal failure if serum creatinine is ≥2.0 mg/dL or the patient requires dialysis

3) Cerebral failure if the Westhaven grade of hepatic encephalopathy is 3 or 4

4) <u>Coagulation failure</u> if the INR is ≥2.5 or the platelets are ≤ 20x10^9/L

5) <u>Circulatory failure</u> if dopamine, dobutamine, epinephrine, norepinephrine, or terlipressin are used.

6) <u>Respiratory failure</u> if the PaO/FiO$_2$ ratio is ≤100 OR SpO$_2$/FiO$_2$ ratio is ≤214.

However to make a diagnosis of ACLF the following criteria below were utilized[3]. Unlike APASL, ACLF was also graded depending on how many organ failures are present.
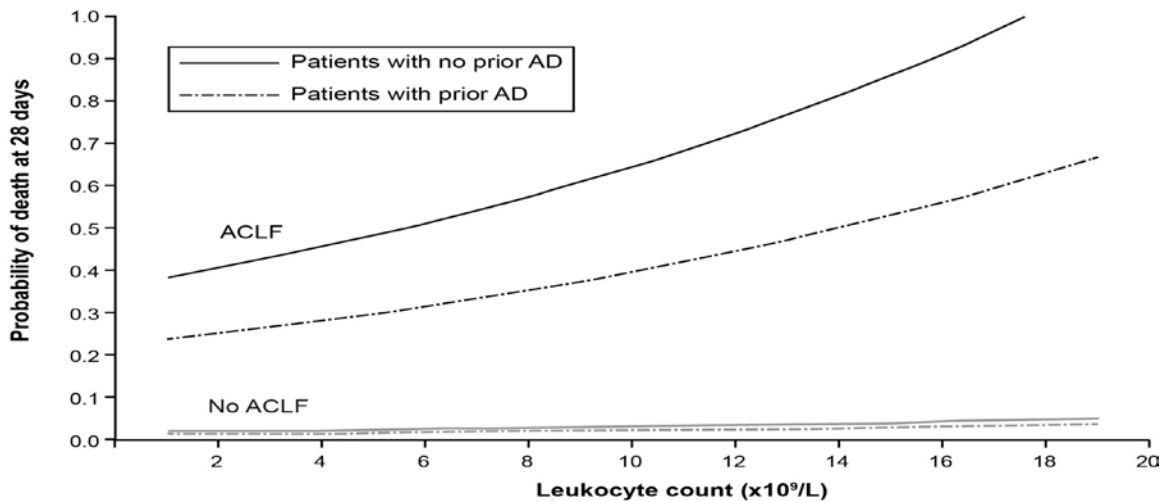
ACLF Grade	Criteria	Additional Criteria
1	Single renal failure	None
	Single liver, coagulation, circulation or respiratory failure	Creatinine 1.5-1.9 mg/dL or mild-moderate encephalopathy
	Single cerebral failure	Creatinine 1.5-1.9 mg/dL
2	2 organ failures	None
3	≥3 organ failures	None

Prognosis was not only determined by ACLF presence, but also by the grade of ACLF[3].
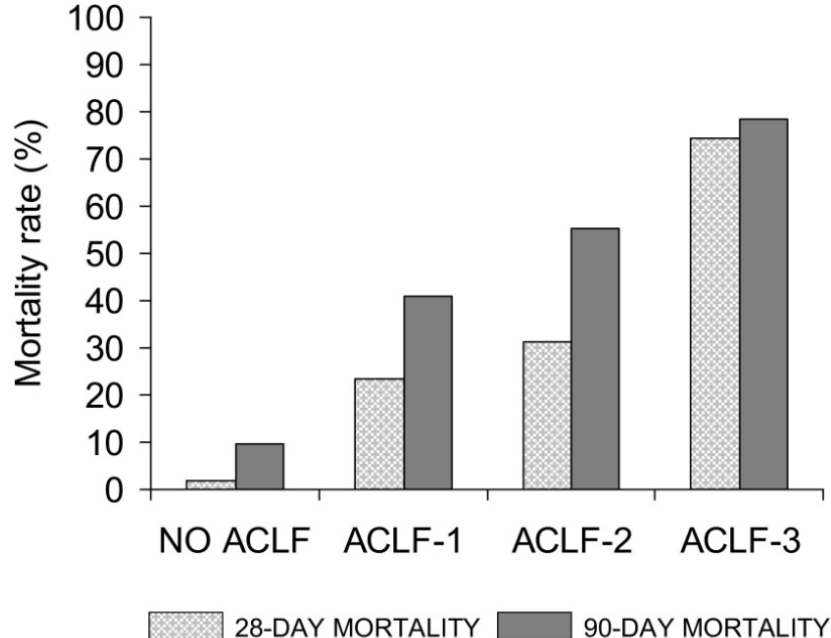
Of note, other factors were found to play a significant role in the prognosis after ACLF development[3]:
1) prognosis declined as white blood cell count (WBC) at presentation increased. This was impactful even in what is presumed to be the "normal range", since patients with cirrhosis tend to have very low WBC counts at baseline[3].

Figure: Probability of death at 28 days versus Leukocyte count (×10⁹/L), with curves for Patients with no prior AD and Patients with prior AD, showing ACLF and No ACLF groups.

2) Probability of death was higher in patients without a prior history of acute decompensation compared to those with a history of acute decompensation. Although this may be counterintuitive, the major driver of ACLF is inflammation and as cirrhosis progresses patients become functionally more immunocomprimised. Therefore, I hypothesize that a patient without a history of decompenation may be able to mount a greater immunologic response to any given insult than one who has a history of prior decompensation.
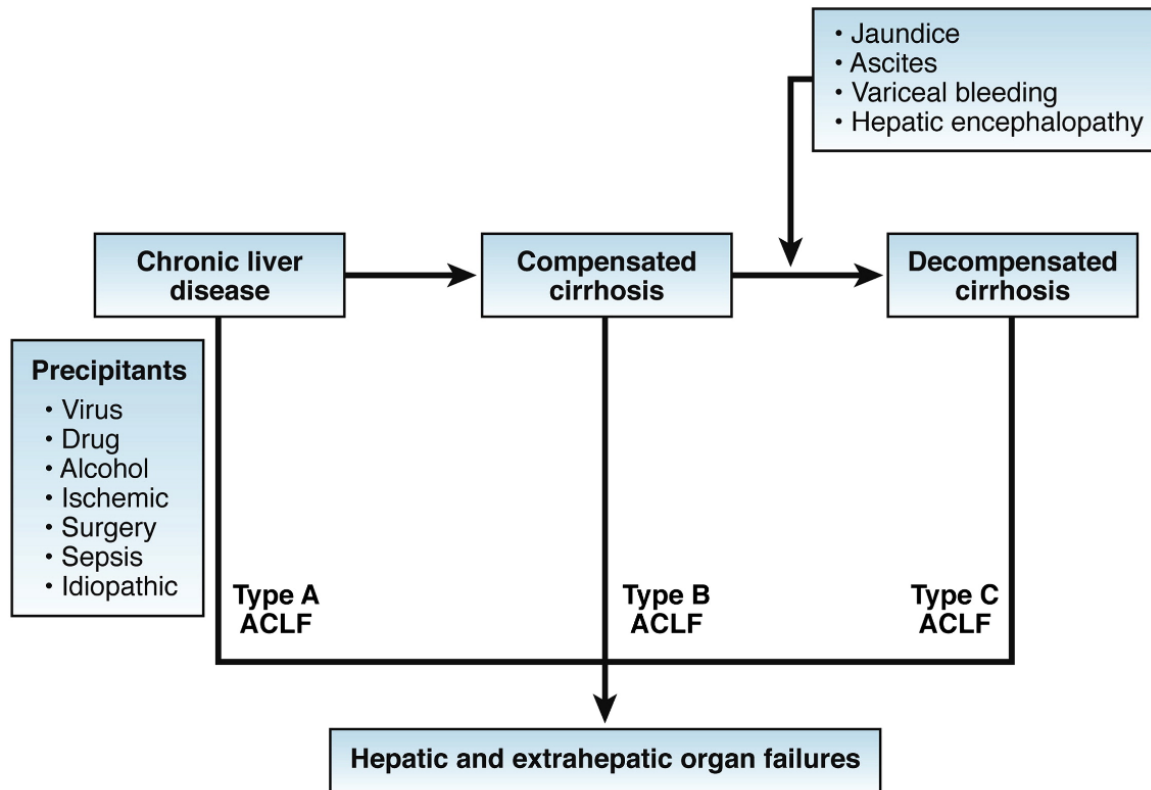
To make the diagnosis more user friendly to clinicians at the bedside the North American Consortium for the Study of End-stage Liver Disease (NACSELD) proposed and validated simplified criteria based on organ failures[4, 5]:
   1) <u>Renal failure</u> = on dialysis
   2) <u>Brain failure</u> = Westhaven grade 3 or 4 encephalopathy
   3) <u>Respiratory failure</u> = bipap use or intubated
   4) <u>Circulatory failure</u> = need for presser support

NACSELD-ACLF was defined as the development of 2 or more organ failures. This was developed on a prospective continent wide cohort of non-electively admitted patients with cirrhosis who were admitted with or developed an infection during their index hospitalization, and validated in a separate prospectively collected cohort of 2,675 patients, 1/3 of whom had or developed an infection. As a result, NACSELD-ACLF is valid in both infected and uninfected cirrhotic patients. A separate group independently validated this definition on the nationwide inpatient sample of 1.9 million admitted cirrhotic patients (Rosenblatt AASLD abstract #284, 2018).

28-day Mortality

Number of Organ Failures
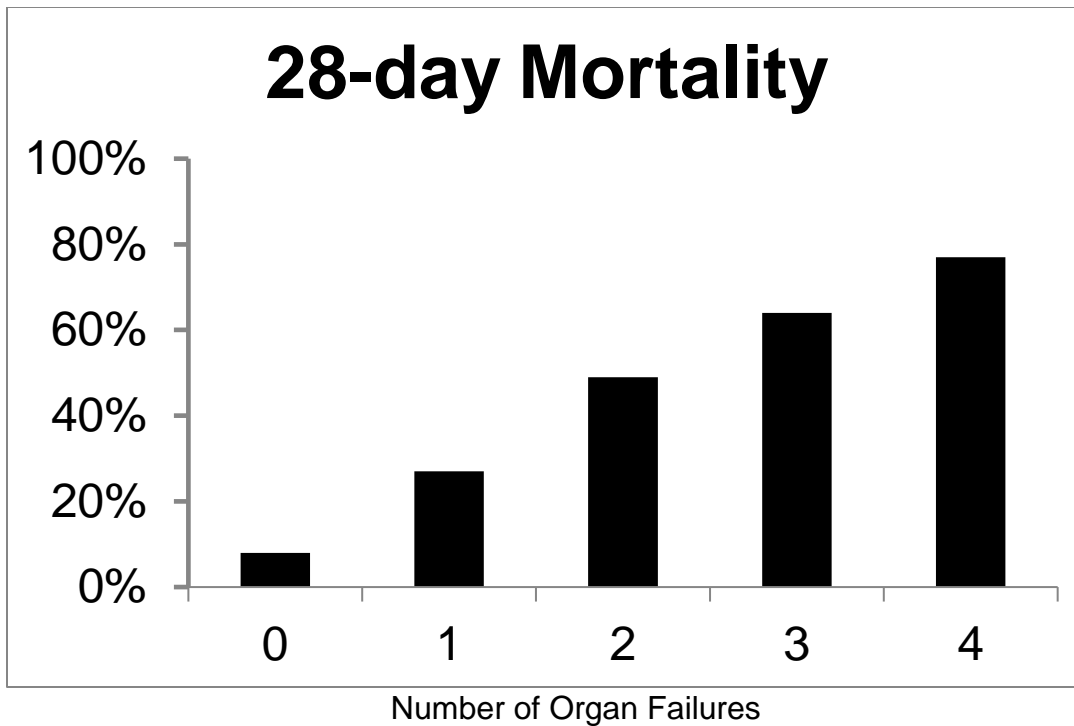
Because of the differences in diagnostic criteria for ACLF between the 3 groups, a consensus conference proposed that instead there be 3 subtypes of ACLF based on the severity of underlying liver disease seen below[1]. The final common pathway of all subtypes results in organ failure, and the number and type of organ failures determine outcome.

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                                              ┌─────────────────────┐
                                              │ • Jaundice          │
                                              │ • Ascites           │
                                              │ • Variceal bleeding │
                                              │ • Hepatic encephalopathy │
                                              └─────────────────────┘
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| Chronic liver disease | Compensated cirrhosis | Decompensated cirrhosis |

Precipitants
- Virus
- Drug
- Alcohol
- Ischemic
- Surgery
- Sepsis
- Idiopathic

Type A ACLF   **Type B ACLF**   **Type C ACLF**

Hepatic and extrahepatic organ failures

No matter how ACLF is defined the number of hospitalizations for patients that have or develop ACLF is increasing nationwide[6]. This is occurring on the backbone of an increasing rate of admissions and readmissions for patients with cirrhosis. Of note, 50% of patients with cirrhosis who are admitted to the hospital experience readmission within 90-days[7].

The precipitants of hospital admission and readmissions are frequently infections; one third of hospitalized patients with cirrhosis have or develop infections during their admission[8]. The immunologic response to infection can be exaggerated and lead to organ failure. After successful resolution of infection the compensatory anti-inflammatory response syndrome (CARS) turns off the inflammatory response to infection[9]. However, this response can leave patients vulnerable to second infections.

SIRS: Systemic inflammatory response

Immune response

— Normal
— ACLF: survivor
— ACLF: non-survivor

CARS: Compensatory anti-inflammatory response
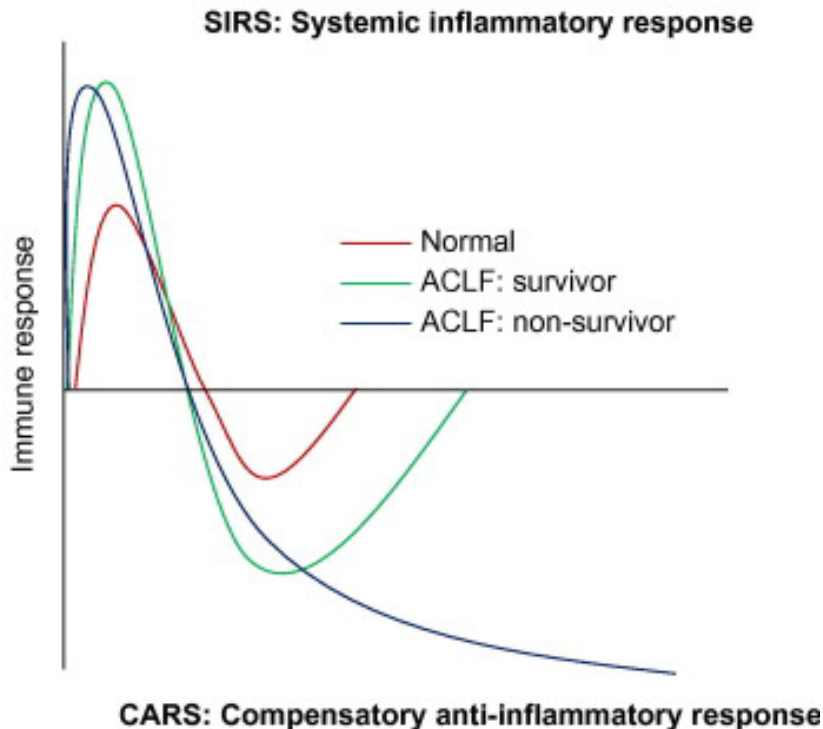
Even after the successful treatment of one infection patients are at a higher risk for death and a second infection. Second infections increase the risk for death ever further. In fact, 45% of patients discharged from the hospital after successful treatment of an infection developed another infection in the next 3-months. 75% of which occurred in a different location from the first infection[10]. Risk factors for recurrent infections include:

       1) Older age,

       2) Proton-pump inhibitor (PPI) use

       3) Development of the first infection while on spontaneous bacterial peritonitis (SBP) prophylaxis

       4) Higher model for end-stage liver disease (MELD) score at admission

Because of the detrimental effects infections can have on prognosis, one may be tempted to start primary SBP prophylaxis earlier in patients with cirrhosis. However, as patients with cirrhosis live longer, they are experiencing more multidrug resistant infections. When outcomes of admitted patients on primary vs. secondary SBP prophylaxis were compared after propensity score matching for MELD and serum albumin, patients on primary prophylaxis had a worse outcome than those on secondary prophylaxis[11]. Specifically, they had a higher risk for acute kidney injury (AKI), death and liver transplant. Therefore it is essential to strictly adhere to the guidelines for initiation of primary SBP prophylaxis[12]:

       Ascites total protein ≤1.5g/dL <u>AND</u>

CTP ≥9 & serum total bilirubin ≥3 mg/dL <u>OR</u>
Serum Creatinine ≥1.2 mg/dL, serum Na ≤130 meq/L <u>OR</u> BUN ≥25

In addition we need to develop new ways of preventing infections without the use of antibiotics.

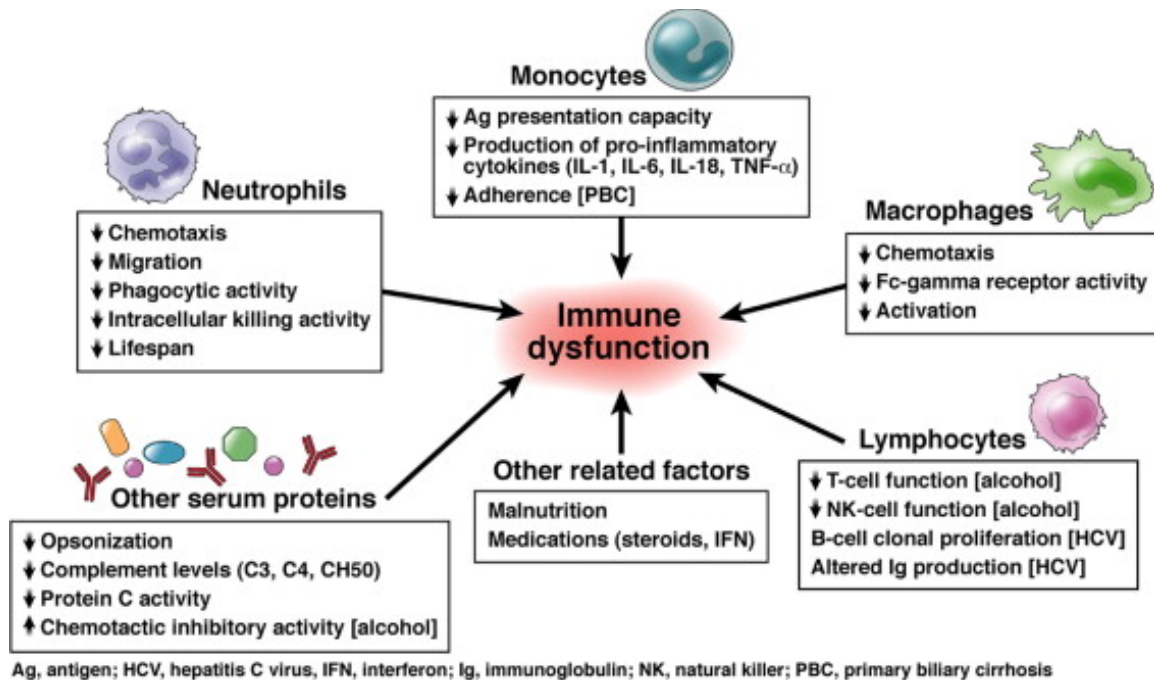# <u>Why are cirrhotic patients at risk?</u>

Cirrhotic patients are at risk for ACLF for a large number of reasons. First, cirrhotic patients have dysbiosis, and it progressively worsens as the liver disease progresses[13]. The cirrhotic dysbiosis ratio was developed to evaluate the severity of dysbiosis in this population, and it was demonstrated that this ratio declines from normal outpatients, to compensated outpatients, to decompensated outpatients, and is the worst in cirrhotic inpatients. Of note, this ratio is also worse in patients with NASH than other types of liver disease.

Second, not only do patients with cirrhosis have dysbiosis, but they are at risk for small intestinal bacterial overgrowth (SIBO). Risk factors for SIBO include[14]:
   a) advancing age
   b) anti-secretory drugs
   c) altered intestinal motility (that worsens with advancing liver disease)
   d) fatty liver

Third, bacterial translocation is seen more commonly in patients with cirrhosis, especially when portal hypertension is present allowing access of the often overgrown dysbiotic gut microbiome to the systemic circulation.

Fourth, patients with cirrhosis are functionally immunocomprimized with portosystemic shunting decreasing bacterial clearance by the retoculoendothelial system as well as intrinsic factors that impair immune function[15]:

Ag, antigen; HCV, hepatitis C virus, IFN, interferon; Ig, immunoglobulin; NK, natural killer; PBC, primary biliary cirrhosis

Gut-Hepatic Axis

The intestinal microbiome composition can be associated with adverse outcomes in patients with cirrhosis. Specifically, increased abundance of the taxa Proteobacteria (Enterobacteriaceae, Campylobacteriaceae, and Pasteurellaceae) on admission was associated with an increased risk of extra-hepatic organ failure, ACLF and death[16].

Prevention of ACLF

Since the outcome of ACLF is poor, it is essential to prevent it when ever possible. Below are some suggested ways to mitigate risk of ACLF in patients with cirrhosis.

1) **Discontinue PPIs:**

   Most patients with cirrhosis are on a PPI for an unknown reason. PPIs block the oxidative burst of the neutrophil thereby causing further immunosuppression in an already immunocomprimised host. Many patients are started on a PPI while hospitalized either as prophylaxis or during a GI bleed. As a result they can and should be discontinued when ever possible. Of note, H2 blockers do not cause immunosuppression, and therefore when acid suppression is required H2 blockers are a good alternative[17]. PPIs are associated with a higher rate of readmissions independent of comorbidities, other medications, age and admission MELD[18]. PPIs alter the gut microbiome; initiation increases the oral-origin

micobiota and discontinuation decreases it[18]. ***Discontinuing PPIs will lower patients risk for infection and readmissions[10, 17, 18].***

2) **Use Non-selective Beta-Blockers (NSBB) as primary prophylaxis for variceal bleeding.**

Options include: Propranolol, Nadolol, and Carvedilol. Although banding to obliteration and NSBB use are both considered equally efficacious to prevent variceal bleeding, NSBB use is more cost effective and may improve outcome in patients with ACLF[19, 20]. EGD screening is indicated in patients with cirrhosis with platelets <150 or with a kPA on elastography of >20[20]. Primary prophylaxis should be started in all patients with Child class A and B cirrhosis with large varices and all patients with Child class C cirrhosis with small or large varices[20]. Patients with refractory ascites with either a systolic blood pressure <90 or type 2 hepatorenal syndrome are at increased risk for death from NSBB use, and therefore require banding to obliteration as therapy instead of NSBB use[21].

Non-selective beta blockers improves the survival of ACLF patients
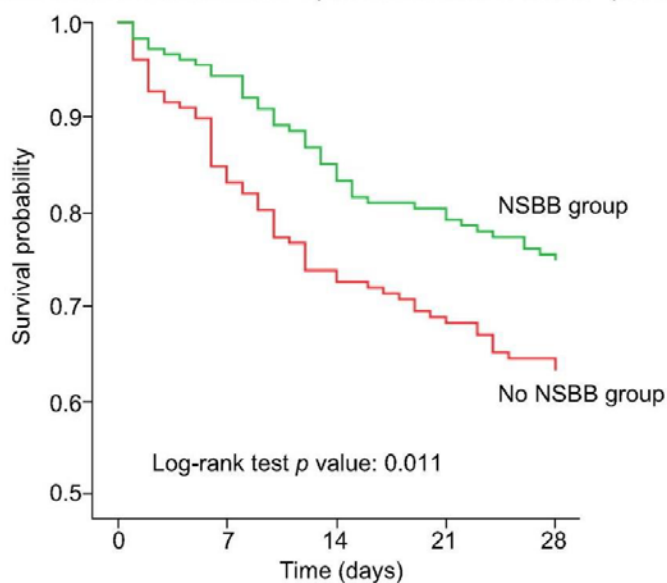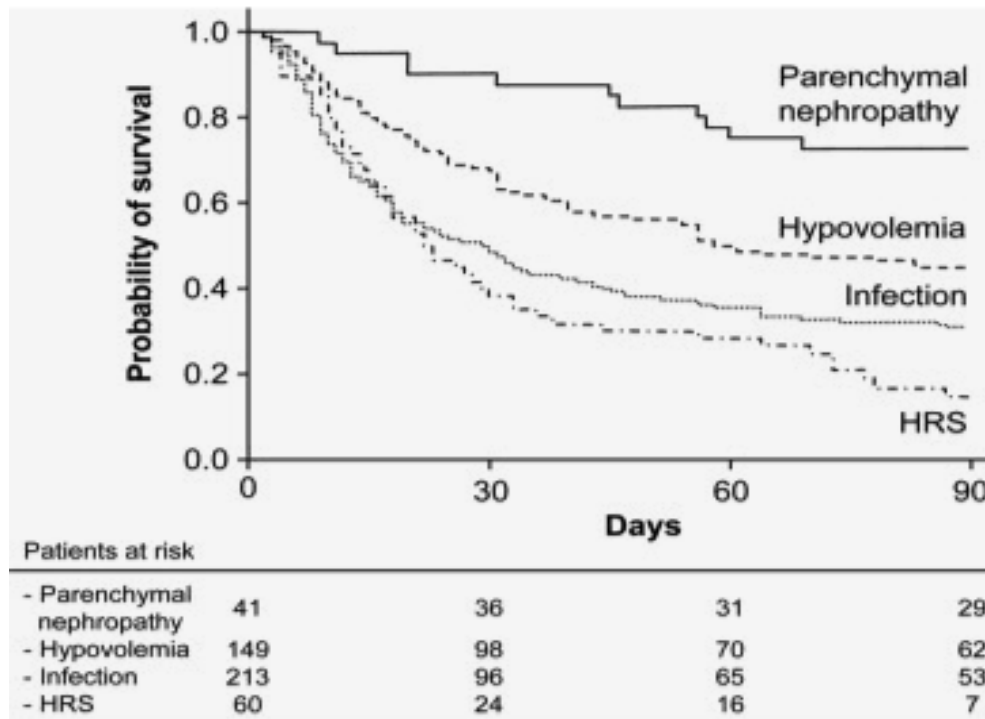
When choosing a NSBB:
    a) Propranolol is the least effective and combined with its inconvenient dosing often leads to noncompliance.
    b) Nadolol is conveniently dosed once per day, and its lower central nervous system penetration decreases the risk for depression.
    c) Carvedilol is the most potent NSBB because of its alpha component; however, this also can exacerbate volume overload in CTP B and C patients. Therefore, carvedilol is usually reserved for CTP A patients.
    d)

3) **Diagnose and Treat Renal Dysfunction Early**:

Cirrhotic patients live and die by their kidneys. The new definition of AKI in patients with cirrhosis is an increase in serum creatinine of ≥0.3 mg/dL in 48 hours or an increase in serum creatinine of ≥1.5 fold over baseline[22, 23]. Even with complete resolution, this small increase has a permanent negative impact on prognosis. Similarly, if the peak serum creatinine is <1.5 mg/dL it also has a negative impact on prognosis[24]. Although all increases in serum creatinine negatively impact prognosis, some are worse than others[25]. AKI-hepatorenal syndrome (AKI-HRS) and infection related AKI have the worst and similar impact, and parenchymal nephropathy has the least negative impact on outcome[26].

Patients at risk				
- Parenchymal nephropathy	41	36	31	29
- Hypovolemia	149	98	70	62
- Infection	213	96	65	53
- HRS	60	24	16	7

When AKI occurs it is essential to remove all nephrotoxins including NSAIDS and aspirin, stop diuretics, and ensure the patient is not intravascular hypovolemic[22].

A low threshold to initiate IV albumin therapy should be utilized even in patients with extravascular hypervolemia as it is the first line therapy for AKI, even in patients whose peak creatinine is ≤1.0 mg/dL[22].

In patients with more advanced AKI with either AKI-HRS or hepatorenal physiology, vasoconstrictors (terlipressin is first line in countries where it is available and norepinephrine in countries where it is not) in combination with IV albumin are indicated[22, 27].

Patients who progress to need dialysis should be considered for liver transplantation. However in inpatients who are not liver transplant candidates, *dialysis is most often considered futile* because[28]:

    a. They can not be adequately dialyzed as an outpatient secondary to low blood pressure limiting fluid removal

    b. The mortality is ~90% at 3-months.

4) **Treat Infections Early**

Most infected cirrhotic patients do not mount a fever, and up to one third of patients with SBP are asymptomatic. As a result, it is imperative to have a high level of suspicion for an infection when any new symptom of decompensation or organ failure develops. Every hour antibiotics are delayed increases mortality[29] and therefore, prompt workup followed by swift antibiotic administration is essential.
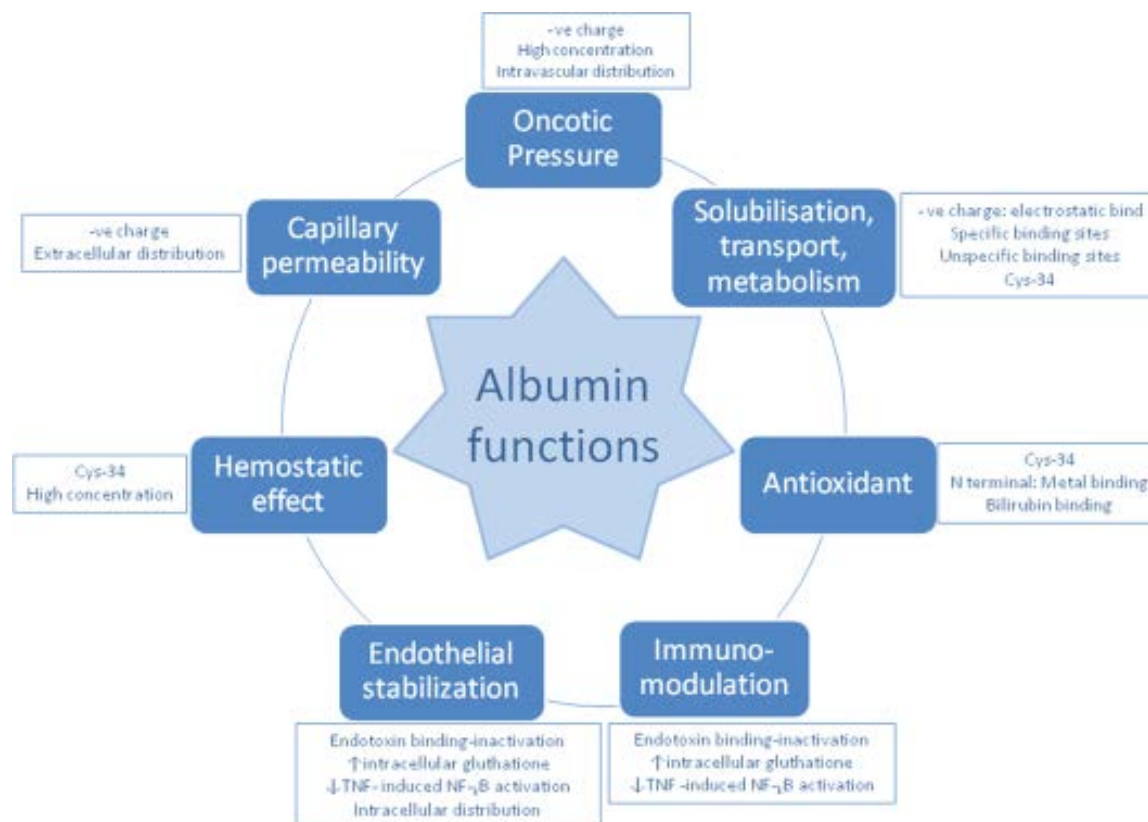
5) **Use IV albumin when indicated**

IV albumin is a drug that should be administered for the following approved indications:

    a) To prevent post-paracenteis syndrome when >5L is removed

    b) To prevent AKI in patients with SBP

    c) To treat AKI

Other unapproved indications include:

    a) Use in hospitalized patients with non-SBP infections to improve survival[30].

    b) Use in combination with diuretics to improve volume status and prevent renal dysfunction.

    c) Use to improve hyponatremia[31].

The myriad functions of albumin are shown below[32], and patients with cirrhosis not only have inadequate levels but poor quality albumin.

Oncotic Pressure
-ve charge
High concentration
Intravascular distribution

Solubilisation, transport, metabolism
-ve charge: electrostatic bind
Specific binding sites
Unspecific binding sites
Cys-34

Capillary permeability
-ve charge
Extracellular distribution

Albumin functions

Antioxidant
Cys-34
N terminal: Metal binding
Bilirubin binding

Hemostatic effect
Cys-34
High concentration

Endothelial stabilization
Endotoxin binding-inactivation
↑intracellular gluthatione
↓TNF-induced NF-⌐B activation
Intracellular distribution

Immuno-modulation
Endotoxin binding-inactivation
↑intracellular gluthatione
↓TNF-induced NF-⌐B activation

IV albumin was first used to treat ascites and edema in patients with cirrhosis in 1946 with some success[33]. Of late, a resurgence of interest in expanding the indication for use of IV albumin has occurred. The recent ANSWER trial documented improved mortality in 440 cirrhotic outpatients with uncomplicated ascites over 18 months with chronic outpatient administration of 40g of IV albumin weekly (HR=0.62; 95%CI 0.40-0.95)[34]. This concept is under further study in the PRECIOSA trial of weight based (up to 100g) IV albumin treatment every 10 days to patients with uncomplicated ascites and recent hospital admission.

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