Towards Better Management of Patients with Acute-On-Chronic Liver Failure

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Acute-on-Chronic Liver Failure Clinical Guidelines

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In patients with cirrhosis and chronic liver disease, acute-on-chronic liver failure is emerging as a major cause of mortality. These guidelines indicate the preferred approach to the management of patients with acute-on-chronic liver failure and represent the official practice recommendations of the American College of Gastroenterology. The scientific evidence for these guidelines was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation process. In instances where the evidence was not appropriate for Grading of Recommendations, Assessment, Development, and Evaluation, but there was consensus of significant clinical merit, "key concept" statements were developed using expert consensus. These guidelines are meant to be broadly applicable and should be viewed as the preferred, but not only, approach to clinical scenarios.

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Important questions

- What is acute on chronic liver disease or failure and how is it it different from decompensated cirrhosis and from acute liver failure?
- How do we define and prognosticate patients with ACLF?
- What are the precipitants and potential prevention strategies?
- What are the individual organ failures that we need to focus on?
- Should ACLF patients be given priority for liver transplant?
- What are the future directions?

Case- ER presentation

- A 59-year-old man is brought to the emergency room (ER) by his wife for new onset confusion and increased abdominal girth. Past medical history is notable for uncontrolled diabetes, obesity, and social alcohol use.
- On examination he is afebrile, alert, and oriented only to place. Abdominal examination revealed a fluid wave.
- He has not sought outpatient care for 3 years due to losing his job and not having insurance, although he underwent emergency surgery for a strangulated inguinal hernia 6 weeks ago.
- Notable admission labs include a serum creatinine 1.3 mg/dL, bilirubin 2 mg/dL, albumin 3.1g/dL, INR 1.4, WBC count 7000/mL, and platelet count $105x10^9/L$.

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Case- Initial Work-up

- The patient has been in the ER for 8 hours and is finally admitted with diagnoses of cirrhosis, ascites, and HE. He is started on lactulose with some improvement in mental status but still has asterixis the next morning.
- Fourteen hours after initial presentation, a diagnostic paracentesis shows spontaneous bacterial peritonitis (SBP).
- His serum creatinine and WBC count have increased to 1.8 mg/dL and 8600/mL respectively.
- The urinalysis is bland, and renal sonogram is normal. He is started on IV ceftriaxone 2gm daily and IV 25% salt-poor albumin.

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Case- 48 hours later

- Still disoriented despite ceftriaxone for 48 hours, with new onset-shortness of breath.
- Creatinine is now 3.0mg/dL, sodium 130 mEq/L, bilirubin 3.5 mg/dL and INR 1.8.
- A repeat tap shows a <25% reduction in PMNs. Blood and ascitic fluid cultures from the ER are negative.
- IV norepinephrine is initiated (since terlipressin was not available then in the US). Antibiotics are escalated to meropenem and vancomycin since the ascites PMNs have not decreased by ≥ 25%.

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Case- Next Morning

- Tachypneic and hypoxic (SpO2: 91%) with a new RLL infiltrate
- Obtunded, anuric with a MAP of 45mmHg. He is transferred to the ICU with a serum creatinine of 4.8 mg/dL and WBC count of 15000/mL.
- Discussions regarding intubation, renal replacement therapy (RRT), and pressor support are undertaken with his wife. Since he now requires organ support to maintain perfusion, oxygenation, and is obtunded, he is a suboptimal candidate for liver transplantation
- Ultimately the patient passes away without liver transplant.

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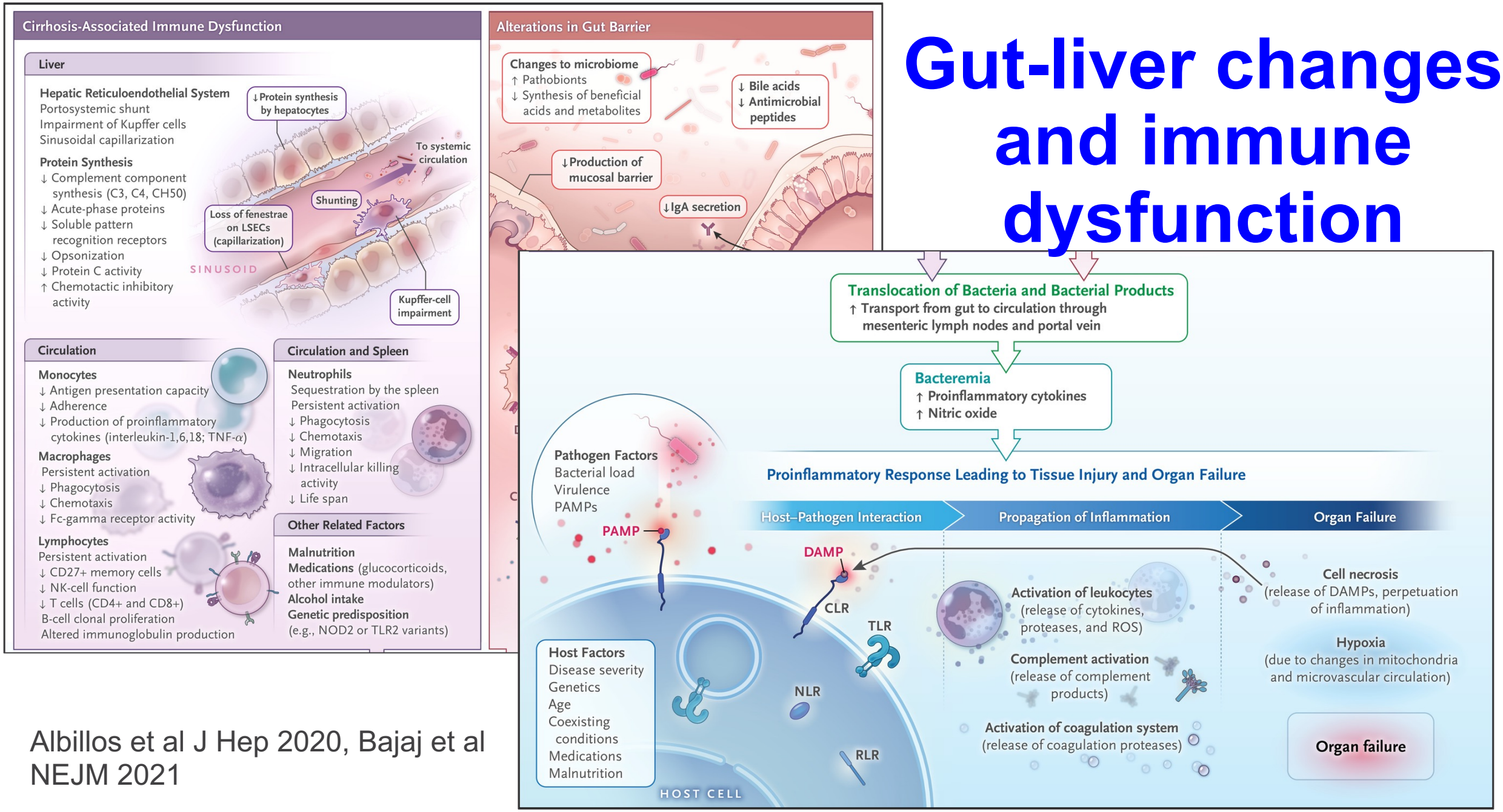
Dominoes fall rapidly if precipitants for ACLF are not recognized early

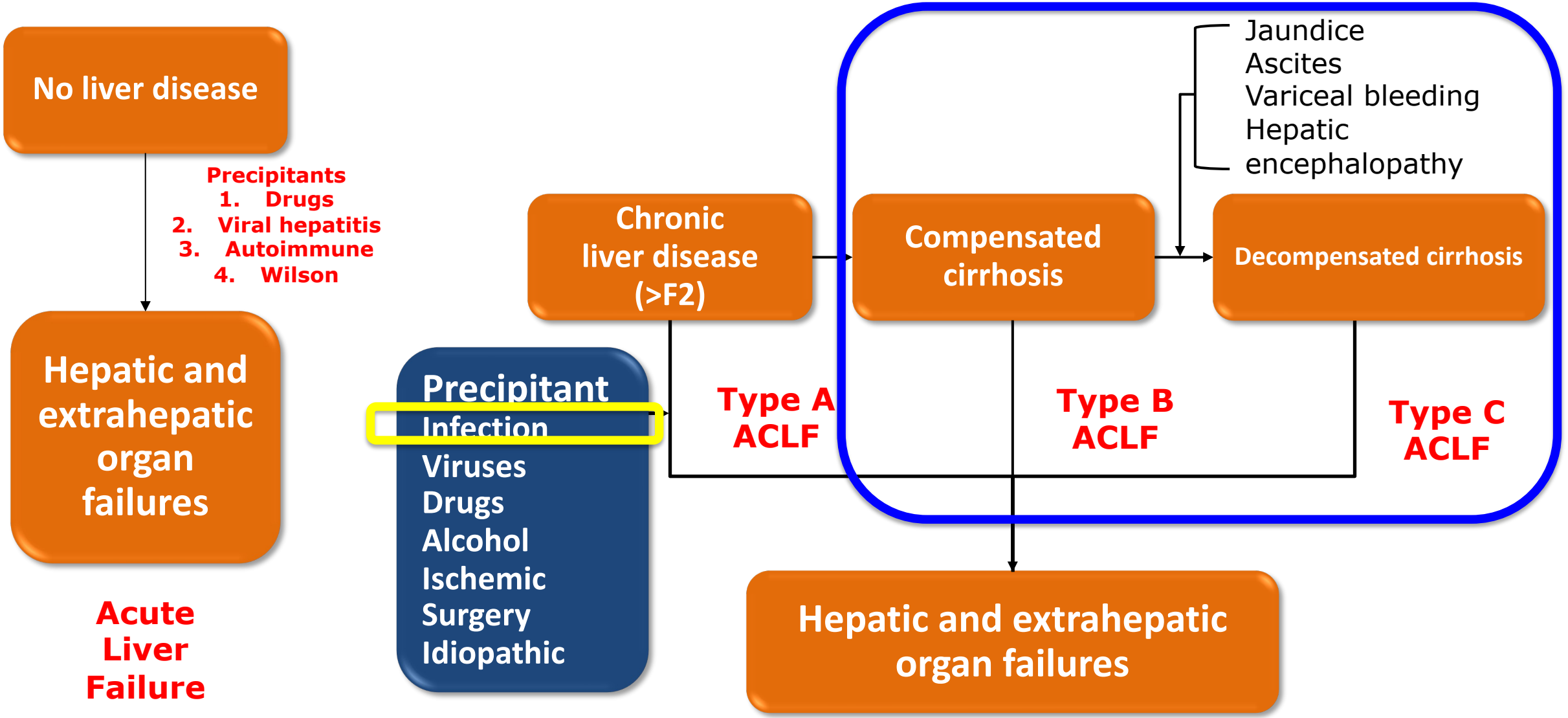
Pathogenesis and Definitions

Gut-liver changes and immune dysfunction



Albillos et al J Hep 2020, Bajaj et al NEJM 2021

Acute liver failure vs ACLF



Jalan R et al ACLF WGO Consensus Gastroenterology 2014

Organ	APASL ACLF Research Consortium	EASL CLIF-C ACLF	NACSELD
Liver	Total Bilirubin PT/INR	Total bilirubin PT/INR	--
Kidney	Creatinine	Creatinine/Dialysis	Dialysis
Brain	HE grade	HE grade	HE grade III/IV
Circulatory	Lactate	MAP, vasopressors	MAP, vasopressors
Respiratory	--	PaO_2 or SpO_2 / FiO_2	Mechanical ventilation
Major Organ failure Category	Predominantly Hepatic failure variables	Combination of hepatic and extrahepatic organ failure variables	Predominantly extra-hepatic organ failure variables
Issues	Diagnosis can be made early enough for intervention to alter disease course. Sensitive but not specific for early mortality	Diagnosis of ACLF may be made too late to impact disease outcome.	Diagnosis of ACLF may be made too late to impact disease outcome.

ACG ACLF definition

ACLF is a potentially reversible condition in patients with chronic liver disease with or without cirrhosis that is associated with the potential for multiple organ failure and mortality within 3 months in the absence of treatment of the underlying liver disease, liver support, or liver transplantation

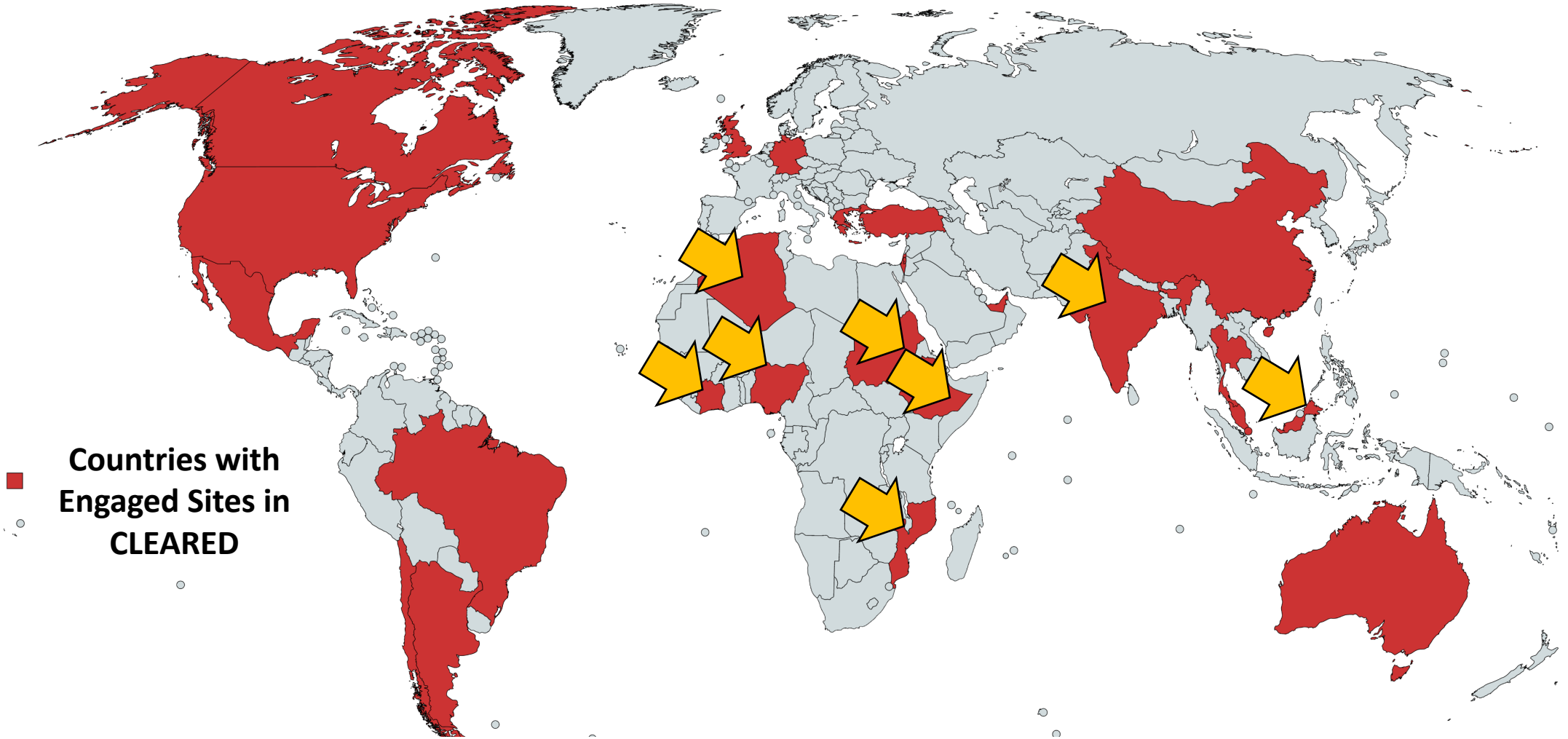
Bajaj JS et al ACG ACLF Guidelines 2021

Issues with current ACLF definitions & biomarkers

- Discordance as to underlying liver disease severity and precipitating factors
- Not prognostic but diagnostic because end-organ failures are likely related to death
- Need to be more pro-active rather than reactive
- **Not generalizable worldwide due to access and affordability issues**

What is needed in a biomarker?

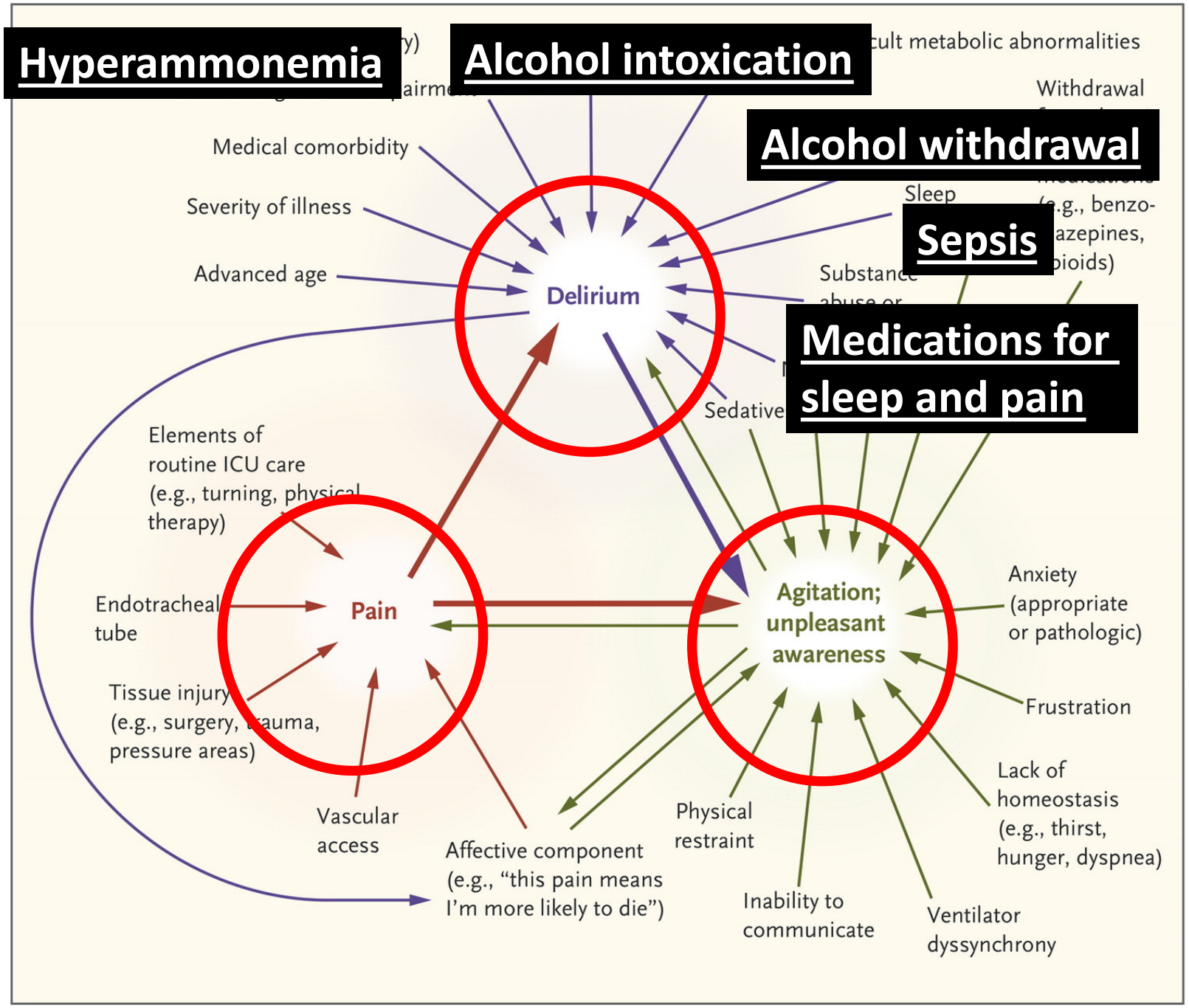
(a) objective,
(b) reliable,
(c) specific to ACLF and distinct from AD and from other patients without cirrhosis requiring critical care,
(d) easily translatable into clinical practice,
(e) determine who is a good candidate for liver transplantation.



- **Death predicted by lack of access to resources, especially in Low and Low-middle income countries**
- **Access to transplant and intensive care and inability to afford medications and outpatient care was predictive of outcomes independent of inpatient events that are traditionally used for ACLF**

Bajaj JS et al CLEARED Consortium Lancet Gastroenterology Hepatology 2023

Individual Organ Failures



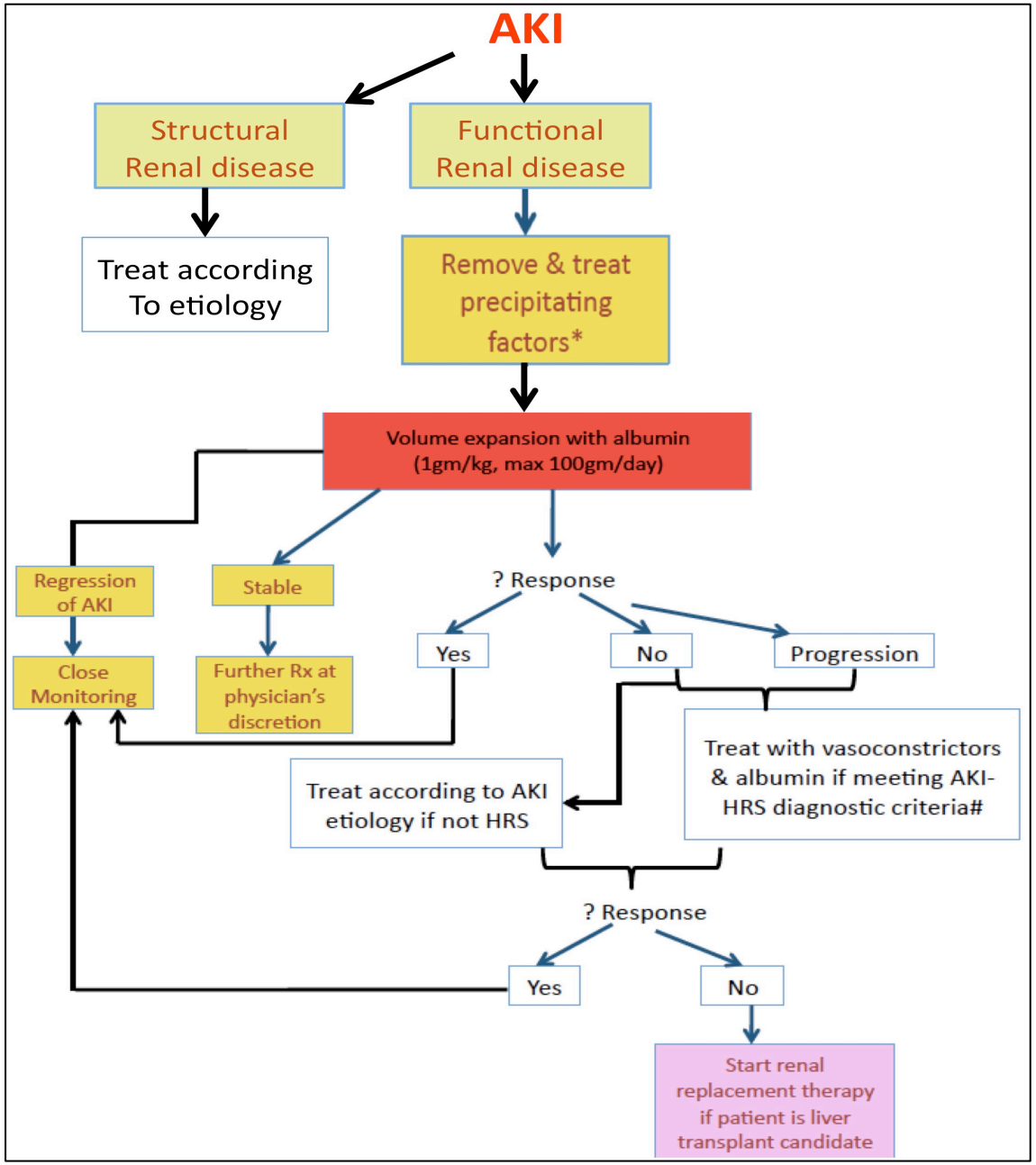
- In ACLF, use of short-acting dexmedetomidine for sedation vs other agents to shorten time to extubation.
- In ventilated patients, we suggest against prophylactic antibiotics to reduce mortality or duration of mechanical ventilation

Reade et al NEJM 2015
ACG ACLF Guidelines 2021

Not all high creatinine is HRS-AKI!

AKI	**Increase in sCr 0.3 mg/dl ≤48 hours or 50% increase from baseline**
AKI Staging	**Stage 1**: Increase in sCr 0.3 mg/dl in ≤48 hours OR Increase in sCr ≥1.5-2.0 times from baseline **Stage 2**: Increase in sCr ≥2.0-3.0 times from baseline **Stage 3**: Increase in sCr ≥3.0 times from baseline OR Serum creatinine 4.0mg/dl with an acute increase of 0.3 mg/dl OR Initiation of renal replacement therapy

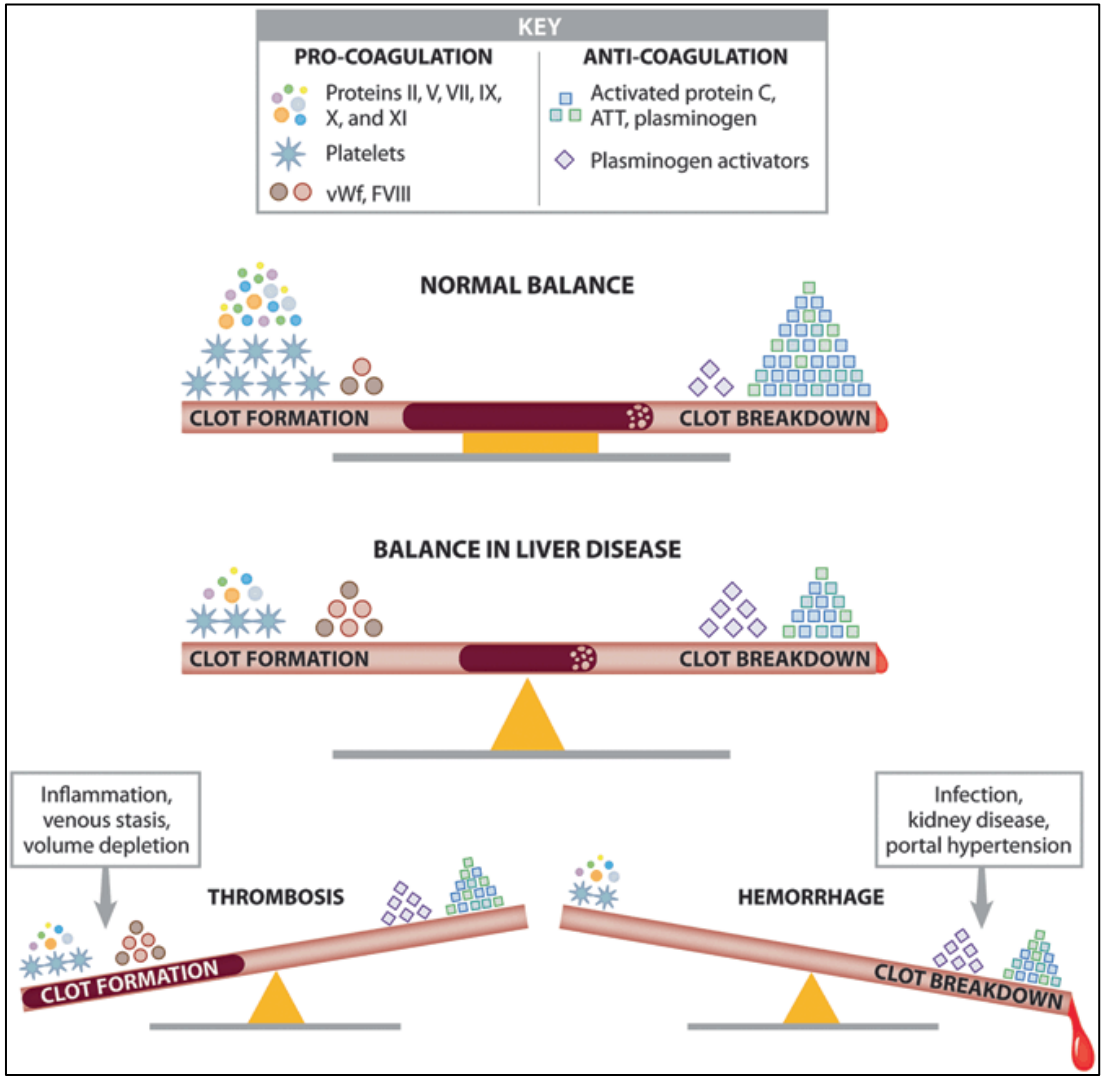
HRS-AKI	
Diagnostic Criteria	-Cirrhosis and ascites; -Stage 2 or 3 AKI; -No improvement of serum creatinine (decrease of creatinine ≤ 0.3mg/dl of baseline) after at least 48 hours of diuretic withdrawal and volume expansion with albumin (1 g/kg body weight/day for 2 days); -Absence of hypovolemic shock or severe infection requiring vasoactive drugs to maintain arterial pressure; -No current or recent treatment with nephrotoxic drugs; -Proteinuria <500 mg/day and no microhematuria (<50 RBCs/ml).



1. In AKI stage 2 & 3 acute kidney injury (AKI), we suggest IV albumin and vasoconstrictors vs albumin alone
2. In hospitalized patients HRS-AKI without high grade of ACLF or major cardiopulmonary or vascular disease, we suggest terlipressin or norepinephrine to improve renal function.

Wong et al 2016, Wong et al NEJM 2021

Coagulation Failure: INR is not the be-all and end-all



1. In ACLF, we suggest against INR to measure coagulation risk
2. In patients with ACLF and altered coagulation parameters, we suggest against transfusion in the absence of bleeding or a planned procedure.
3. In patients who require invasive procedures, we recommend the use of Thrombo-elastography (TEG) or rotational TEG (ROTEM), vs INR, to accurately assess transfusion needs.

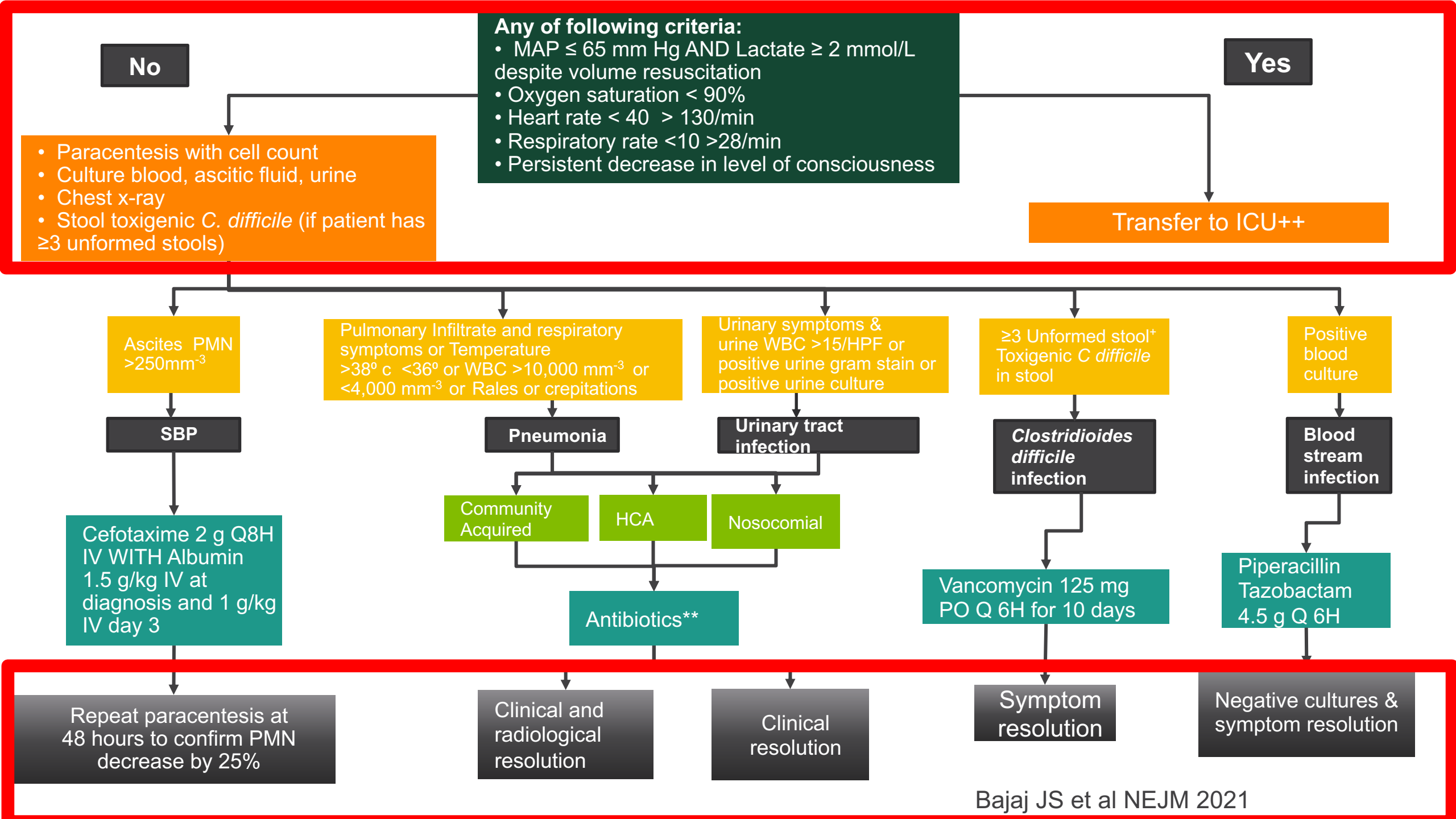
Northup et al 2015, O'Leary et al 2019

Precipitating Factors

- Infections
- Alcohol-related
- Surgery (Mayo Clinic and Vocal Penn Score)
- Drug-induced liver injury
- Viral hepatitis, including reactivation and flare

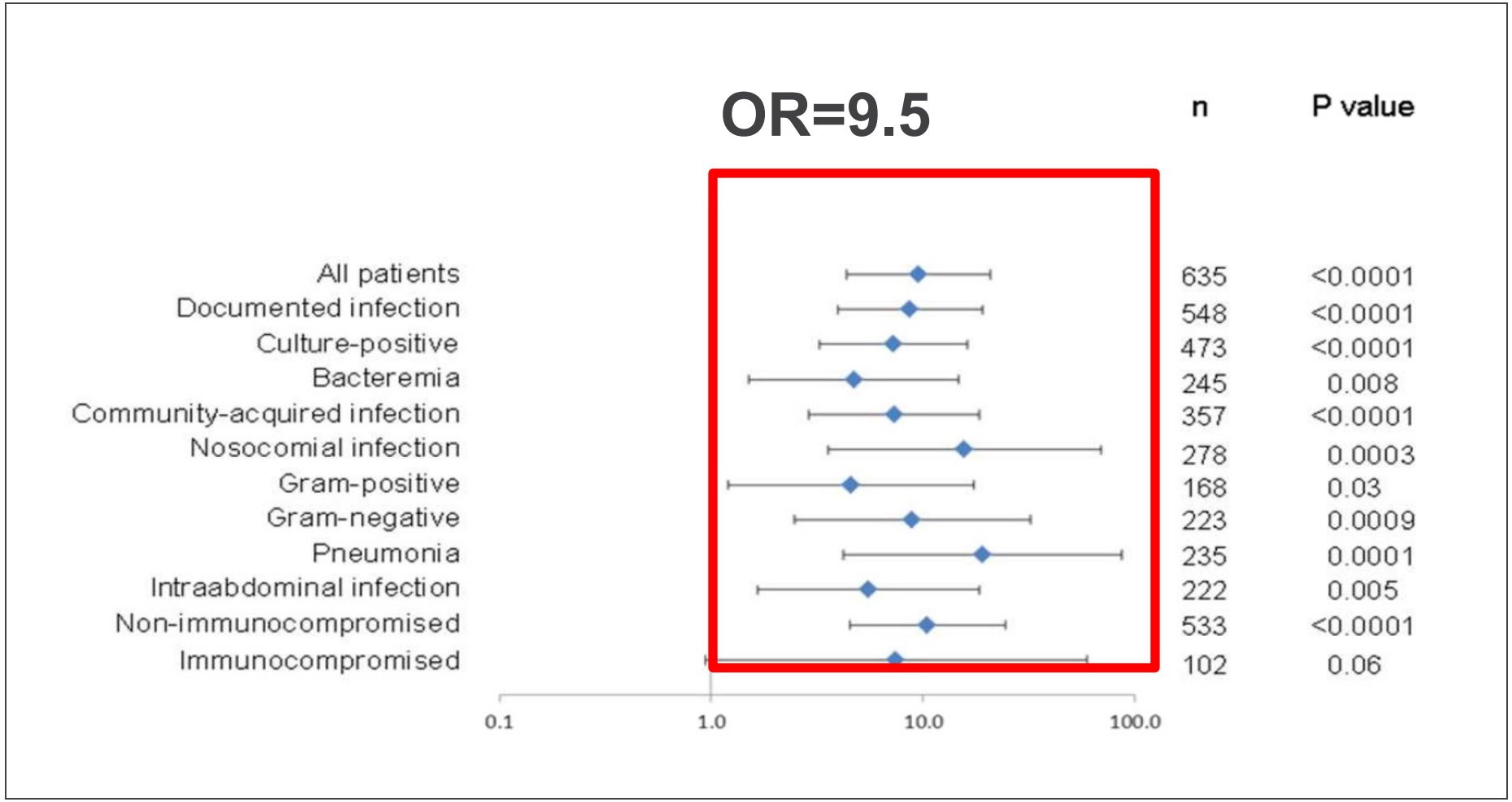
Clues that can indicate infections in cirrhosis

- Usual signs of infection may be absent due to impaired immune response
- Other signs and symptoms could be relevant
  - Altered mental status or hepatic encephalopathy
  - Acute kidney injury
  - Asymptomatic patients with ascites can have “silent” SBP
  - Increase in WBC count may not be dramatic since cirrhotic patients have a lower baseline



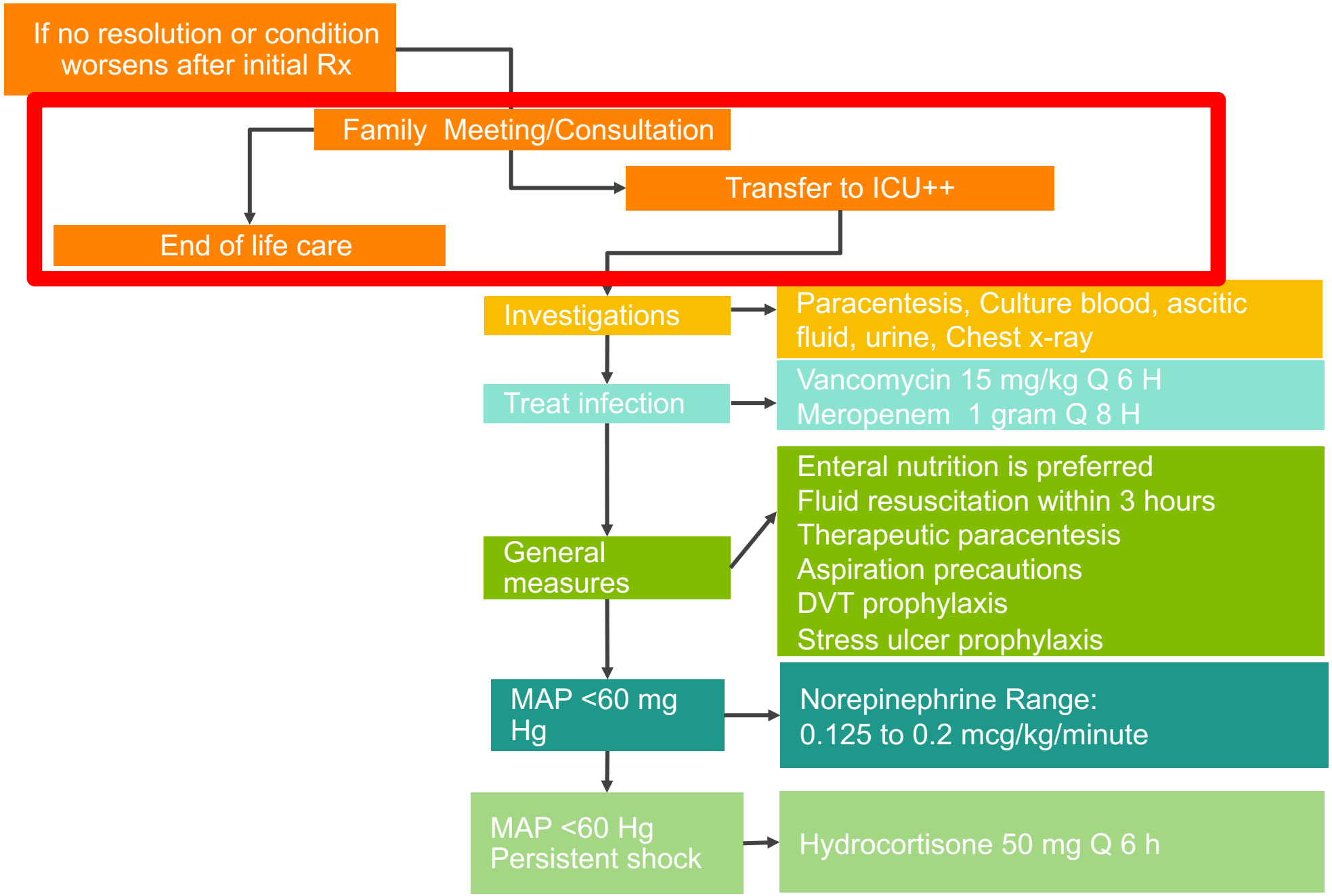
Bajaj JS et al NEJM 2021

Inappropriate antibiotics increase mortality



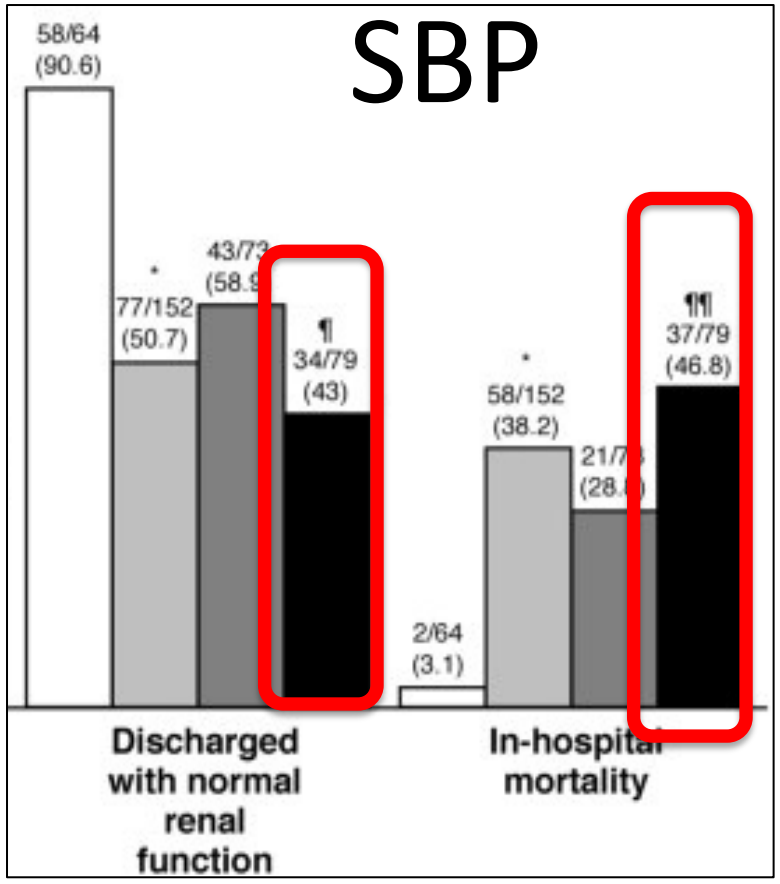
- **Risk factor: Multidrug resistance organism**

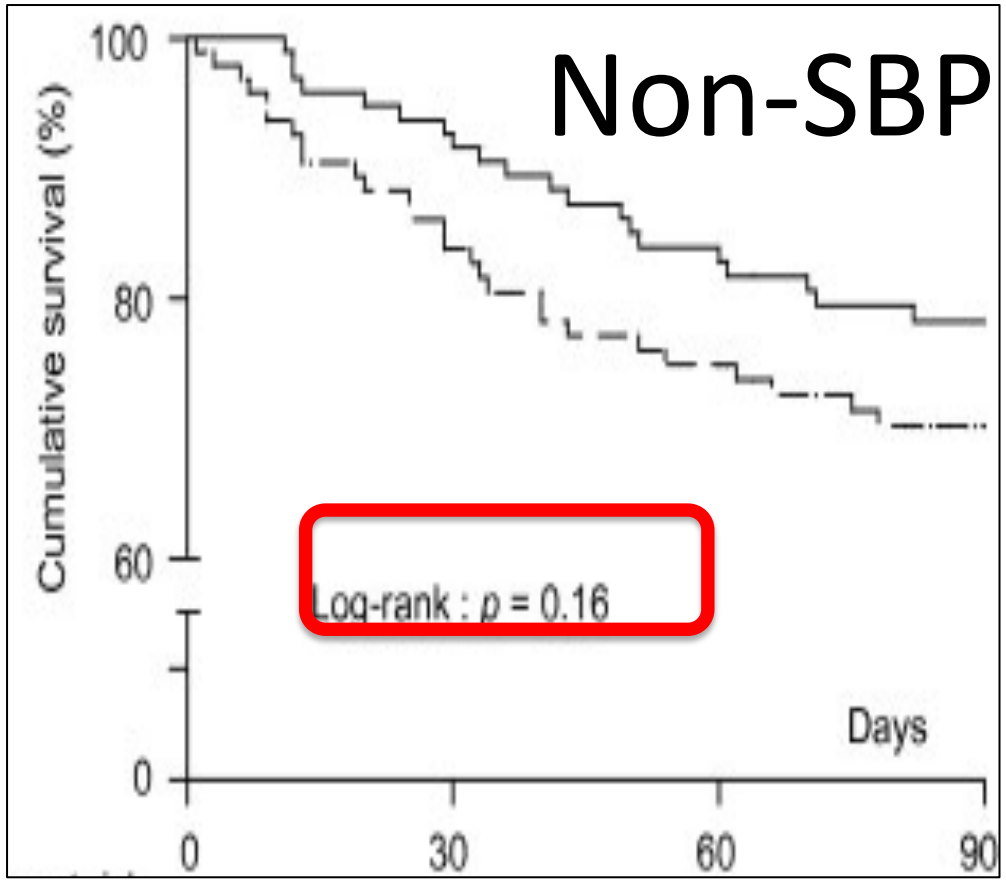
Arabi YM et al. Hepatology, 2012



Bajaj JS et al NEJM 2021

Judicious use of albumin prevents mortality and AKI in SBP but not in other infections and not for all inpatients



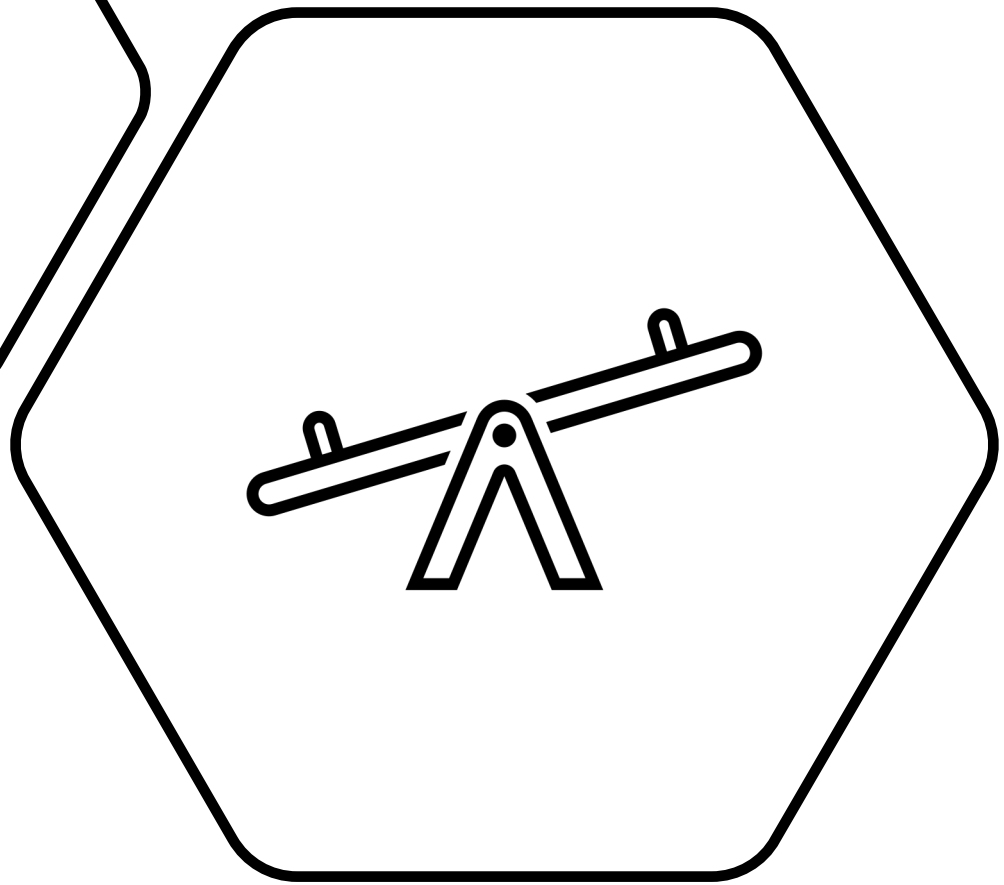


ACG Guideline Recs:
We recommend against daily infusion of albumin to maintain albumin >3 gm/dl to improve mortality, prevention of renal dysfunction or infection

Poca et al J Hepatol 2012, Sort et al N Engl J Med 1999, Thevenot et al J Hepatol 2014, China L et al NEJM 2021

ACG ACLF Guideline Recommendations: Infections

- Check for infection in hospitalized patients.
- In suspected infection, we suggest early antibiotics
- In patients not responding to antibiotic therapy, we recommend suspicion of a resistant organism or fungal infection
- In SBP albumin with antibiotics to prevent AKI and subsequent organ failures but not in other infections.
- In with prior SBP, we suggest use of antibiotics for secondary SBP prophylaxis to prevent recurrent SBP.
- In those needing primary SBP prophylaxis, we suggest daily prophylactic antibiotics, although no one specific regimen is superior to another, to prevent SBP
- We suggest avoiding PPI unless there is a clear indication



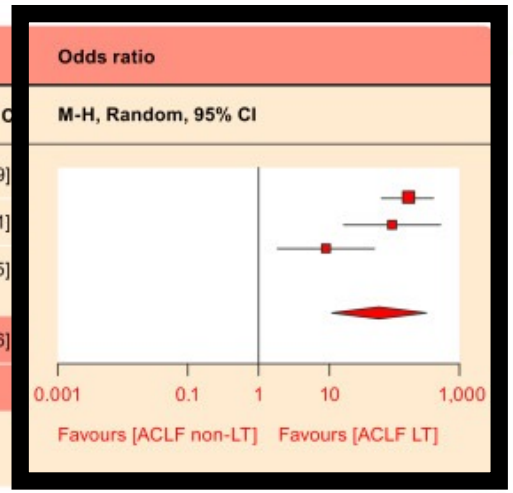
Should ACLF patients get extra listing priority for liver transplant?

Arguments for prioritizing selected ACLF patients

A 30-day mortality

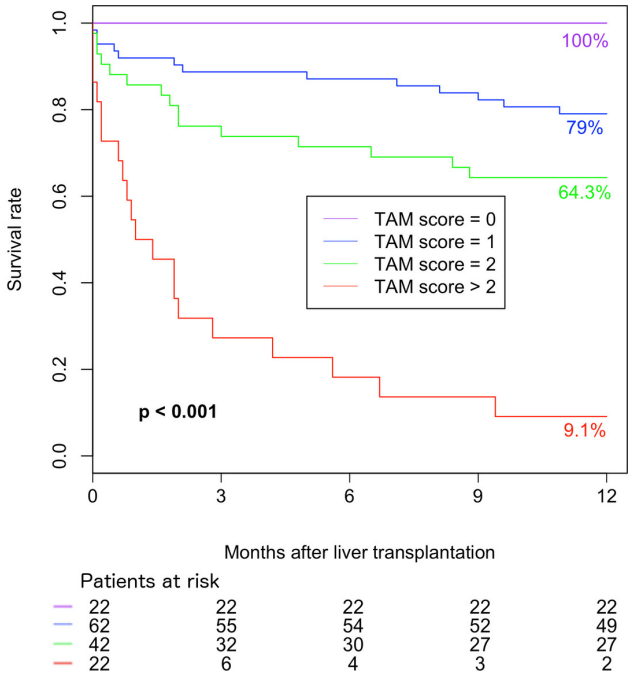
	ACLF LT		ACLF non-LT			Odds ratio
Study or subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C
Artru	318	337	23	119	40.1%	69.86 [36.50, 133.69]
Bhatti	57	60	17	59	31.2%	46.94 [12.92, 170.61]
Hong	42	44	92	123	28.6%	7.08 [1.62, 30.95]
Total (95% CI)		441		301	100.0%	32.02 [8.50, 120.66]
Total events	417		132			

Heterogeneity: Tau² = 1.03; Chi² = 8.45, df = 2 (p = 0.01); I² = 76%
Test for overall effect: Z = 5.12 (p < 0.00001)



1. MELD may not capture the disease severity
2. Acceptable survival post-LT for ACLF-2 and 3
3. Futility rules may need to be specified

	Points
Arterial lactate level (mmol/l)	
<4	0
≥4	1
Mechanical ventilation with PaO_2/FiO_2 ratio ≤ 200 mm Hg	
No	0
Yes	1
Age (years)	
<53	0
≥53	1
Leukocyte counts (G/l)	
>10	0
≤10	1
TAM score	= Σ

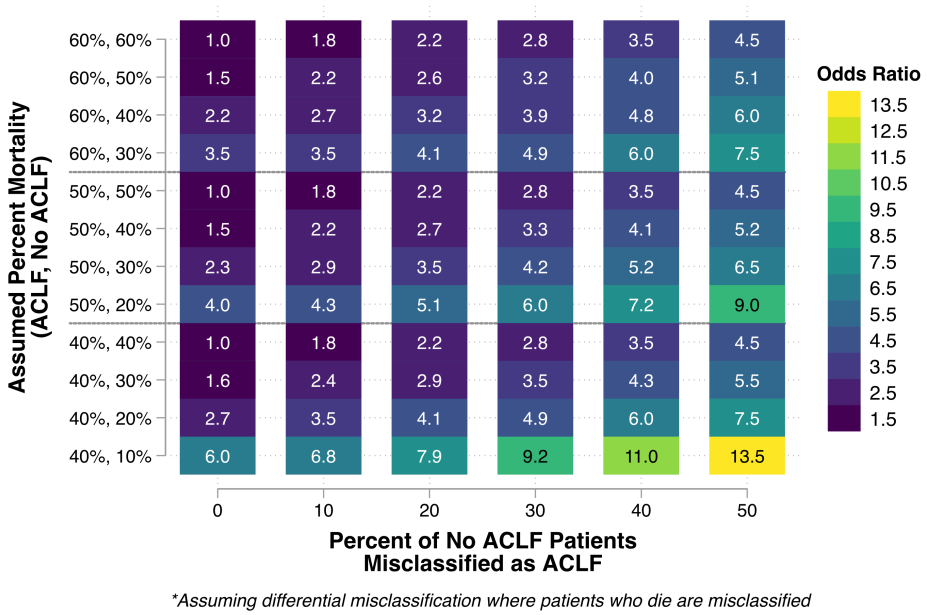


TAM score:

a. Age ≥53 years,
b. arterial lactate ≥4 mmol/L
c. mechanical ventilation with PaO_2/FiO_2 ≤ 200 mm Hg,
d. leukocyte count ≤10 G/L

Jalan et al J Hepatol 2021, Artzner et al AJT 2020

Arguments against prioritizing



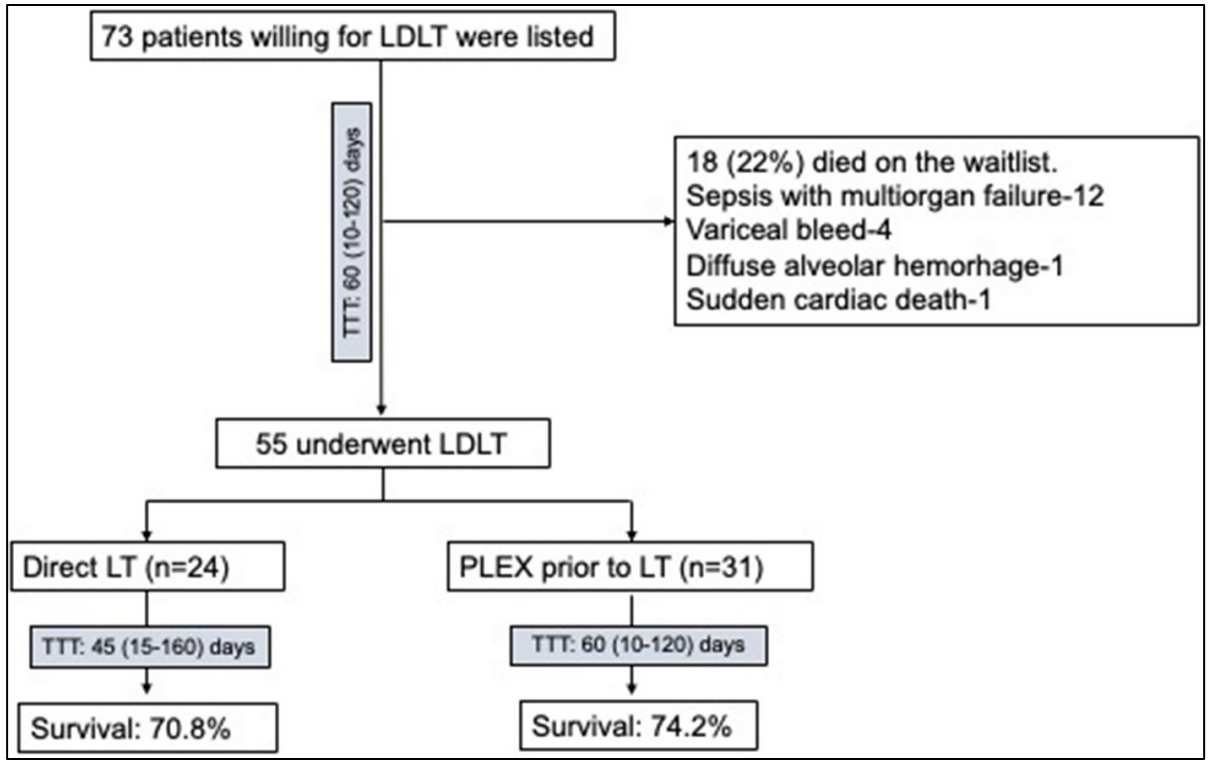
*Assuming differential misclassification where patients who die are misclassified

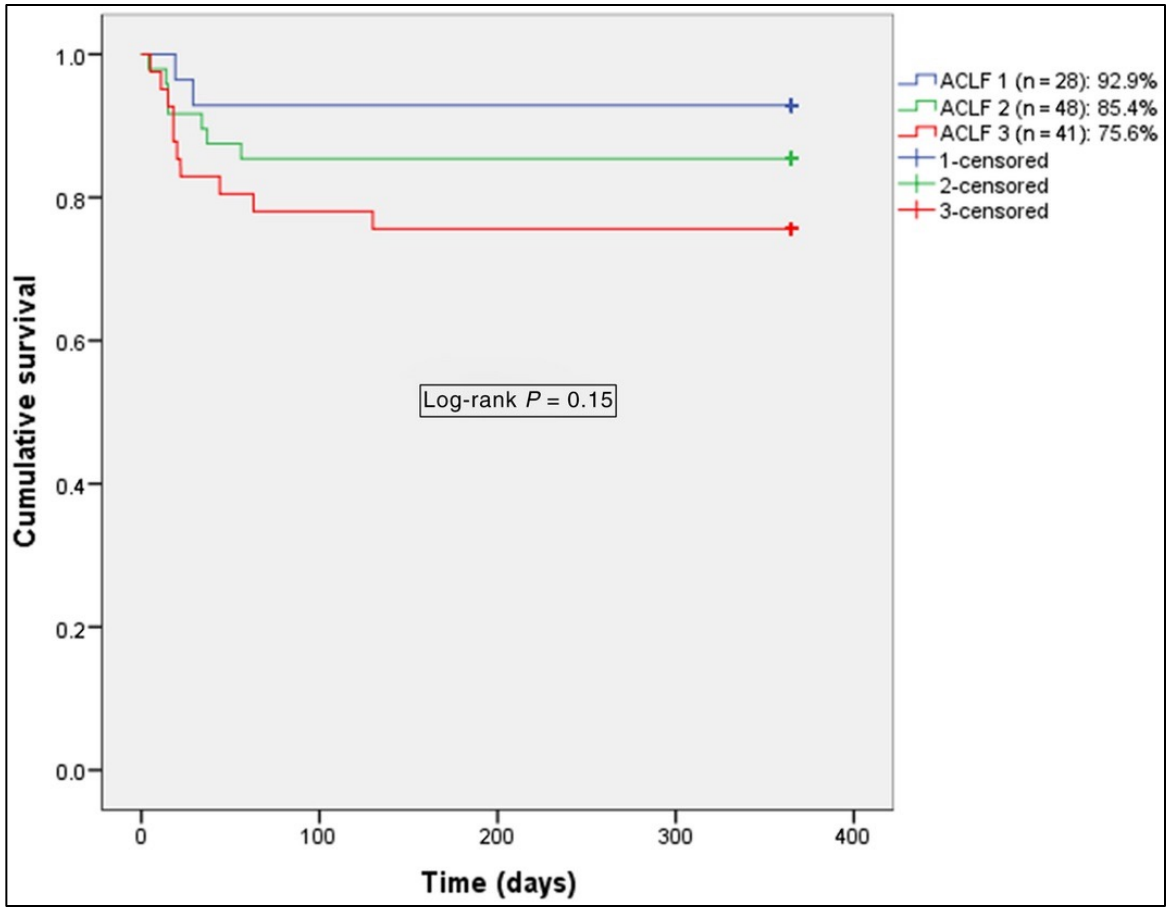
Organ failure	EASL-CLIF	NACSELD	Data in UNOS registry*
Liver	Bilirubin ≥12mg/dL	N/A	Serum bilirubin
Kidney	Creatinine ≥1.5 md/dL (or >2mg/dL)†	Renal replacement therapy	Serum creatinine and dialysis in last week (yes/no)
Brain	HE West Haven grades III/IV	HE West Haven grades III/IV	None, grade 1-2, grade 3-4
Coag	INR ≥2.5	N/A	Serum INR
Respiration	Mechanical ventilation + $PaO_2/FiO_2 \leq 200$ or $SpO_2/FiO_2 \leq 214$	BiPAP or mechanical ventilation	On ventilator (yes/no)
Circulation	Use of vasopressors	Vasopressors + MAP<60mmHg or SBP reduction >40mmHg despite adequate resuscitation	Inotropes (yes/no); life support (yes/no)

1. Potential for misclassification of UNOS data vs ACLF grade
2. Using retrospective data to make prospective decisions
3. Zero –sum game; non-ACLF pts may be affected
4. Currently there is low support to change listing and priority criteria

Goldberg & Bajaj Liver Transpl 2021, Bajaj & Verna Liver Transpl 2020

Living donor LT for ACLF: more challenging





- LDLT was associated with 73% survival
- ↑pre-LT high healthcare resource utilization.

Bangui et al Liver Transpl 2019, Kulkarni et al Hepatol Int 2023

Transplant versus Futility for ACLF: ACG Guideline recommendations

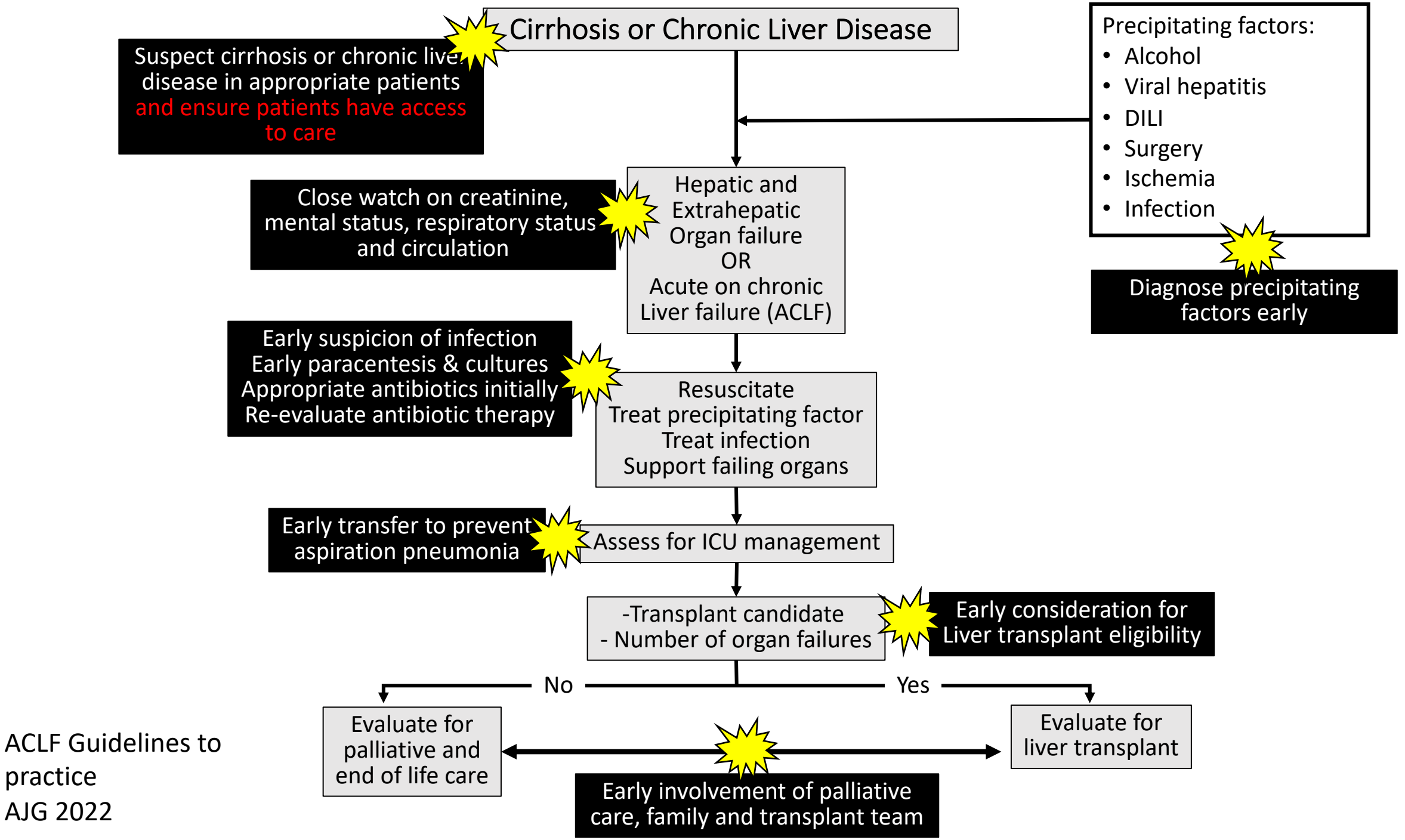
- ACLF patients who continue to require mechanical ventilation due to ARDS or brain-related conditions despite optimal therapy, we suggest against LT listing
- In patients with end-stage liver disease admitted to the hospital, we suggest early goals of care discussion and if appropriate, referral to palliative care to improve resource utilization

Bajaj JS et al ACG ACLF Guidelines 2021

Overall therapeutic strategies

- General (airway, multi-disciplinary team, nutrition, treating precipitating factors, critical care) For each patient
- Specific treatments (G-CSF, Stem cell therapy) Data are not convincing
- Liver-assist devices (MARS, ELAD) Data are not convincing
- Liver transplant (deceased or living donor) Greater evidence for deceased rather than living donor

Back to the case: Opportunities missed that can snowball into ACLF



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Take-Home Messages

- ACLF represents a high burden and prevention strategies including improving access to healthcare are important.
- Infections are one of the major reasons for ACLF, and bacteriology and mycology of infections is changing radically.
- A high index of suspicion, flexible, rapid and appropriate antibiotics and prevention of acute kidney injury is required to prevent ACLF from infections
- Not all high creatinine is HRS-AKI and not all confusion is hepatic encephalopathy
- Use albumin selectively and avoid unnecessary PPIs
- Palliative care should be involved early, and transplant discussions should be approached with care in patients with ACLF
- Better biomarkers to predict ACLF are needed

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