

ACLF

Jacqueline G. O'Leary, MD MPH
Associate Professor of Medicine, UTSW
Chief of Hepatology, Dallas VA Medical Center

Definitions of ACLF

- 3 definitions of ACLF remain
- All focus of organ failures

EASL-CLIF

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

APASL

Cirrhosis is not required
 Acute hepatic insult complicated by:
 Bilirubin ≥5 mg/dL
 Coagulopathy INR ≥1.5
 Complicated <4 weeks by:
 Ascites &/or HE

	NACSELD	EASL-CLIF
Brain	West Haven Grade 3-4	
Circulation	Pressors	Pressors or terlipressin
Renal	Dialysis	Creatinine ≥2 mg/dL
Respiratory	Intubated or Bipap	PaO ₂ /FiO ₂ >100 to ≤200 or SpO ₂ /FiO ₂ >89 to ≤214
Liver	NA	Bilirubin ≥12 mg/dL
Coagulation	NA	INR ≥2.5 or Plts ≤20

NACSELD
 ≥ 2 organ failures

How Common is ACLF?

- VA database -8 years - 80,383 outpatients w/ compensated cirrhosis
 - Incidence:
 - EASL-CLIF ACLF = 2%/year
 - APASL ACLF = 0.6%/year
- VA database from 2004 – 2014
 - 26% of admitted patients with decompensated cirrhosis “met criteria” for EASL-CLIF ACLF
- Number of admitted patients with ACLF is increasing every year.

Definitions of ACLF

Key concept statements

1. In patients with cirrhosis who are hospitalized, the NACSELD score is likely associated with futility, whereas the EASL-CLIF sequential organ failure assessment score is associated with 28-day prognostication.
2. None of the 3 society definitions is optimal for informing management change.

Prevention



You can't prevent if you can't predict...

Can we Predict who will get ACLF?

- 118 pts from NACSELD w/o ACLF on admission had admission microbiome stool analysis.
 - 8% later developed ACLF
 - 21% died
- Marked differences in admission microbiota found between patients who later developed ACLF or died vs. did not.
 - Cirrhosis dysbiosis ratio was lower in patients who developed ACLF.
 - Negative outcomes were associated with a higher % of bacteria from phylum Proteobacteria & higher % of the Firmicutes members Eenterococcaceae and Streptococcaceae.
 - Better outcomes were associated with a higher % of the Firmicutes members Lachnospiraceae and Clostridiales.

Can we Predict who will get ACLF?

- 602 pts from NACSELD w/o ACLF on admission had admission serum metabolomic analysis:
 - 15% later developed ACLF
- Independent predictors of ACLF development and death:
 - After controlling for age, gender, ETOH etiology, & Admission MELD, WBC, Na, Alb
 - ↑ Bile acid intermediates indicative of cholestasis & failure of good microbiota function.
 - ↑ Estrogen metabolites.
 - ↓ Indolepropionic acid, which stabilizes the intestinal barrier.
 - ↓ Microbial metabolites of phenylalanine & tyrosine, which promote local immunity.
 - ↓ Phospholipid moieties, associated with cell membrane integrity.

Can we Predict who will get ACLF?

- Machine learning model based on admission variables and metabolomic analysis to predict of ACLF development during that admission:

Area Under Curve (AUC) = 0.84

Strong link between gut microbial composition and function (or failure) and the metabolomic analysis

Can we Predict who will get Grade 3-4 HE?

- NACSELD multicenter cohort of 602 patients without Brain failure on admission.
 - 144 developed brain failure an average 3 days post-admission.
 - 4 variables that added to clinical predictors:
 - ↓ Thyroxine
 - ↓ Maltose
 - ↑ Methyl-4-hydroxybenzoate sulfate
 - ↑ 3-4 dihydroxy butyrate
- } Microbially derived products

Associated with neuromuscular deficits
Diagnosed dementia
In patients who go on to develop dementia

Can we Predict who will get Grade 3-4 HE?

- Validation cohort—prospective cohort 81 pts
 - 11 developed brain failure
 - Local lab testing

	HE on admission		P value	Developed brain failure		P value
	No (n=65)	Yes (n=16)		No (n=70)	Yes (n=11)	
Total thyroxine (ug/dL)	8.24±3.22	7.11±2.18	0.11	8.35±3.03	5.85±3.03	0.008
Free T4 (uIU/mL)	1.12±0.24	1.03±0.26	0.20	1.13±0.23	0.92±0.26	0.026
Thyroid uptake (%)	36.40±4.44	38.13±3.7	0.12	36.34±4.41	39.27±2.80	0.009
TSH (ng/dl)	2.30±2.65	3.17±5.25	0.53	2.55±3.51	1.96±1.39	0.33

Admission Urinary and Serum Metabolites Predict Renal Outcomes in Hospitalized Patients With Cirrhosis

Jasmohan S. Bajaj , Guadalupe Garcia-Tsao, K. Rajender Reddy, Jacqueline G. O'Leary, Hugo E. Vargas,

- Admission serum metabolites that predict future AKI
 - ↑Uremic toxins
 - ↑Aromatic AA metabolites
 - ↓Lipid Metabolites
- Admission urine metabolites that predict future AKI
 - ↑Tryptophan & Kynurenate metabolites
 - ↑Dopamine metabolites
 - ↓Adrenergic metabolites
 - Δ Cysteine & Methionine metabolites

Adjusted for age, sex, alcohol-related etiology, admission values of MELD, WBC, infection, serum sodium and serum albumin using the false discovery rate adjustment

Treatments for ACLF

- There are no FDA approved treatments for ACLF
- Once ACLF occurs there is a high risk for death (by definition!)
 - Prevention is better
- We will discuss:
 - Prevention
 - Organ failure specific treatments

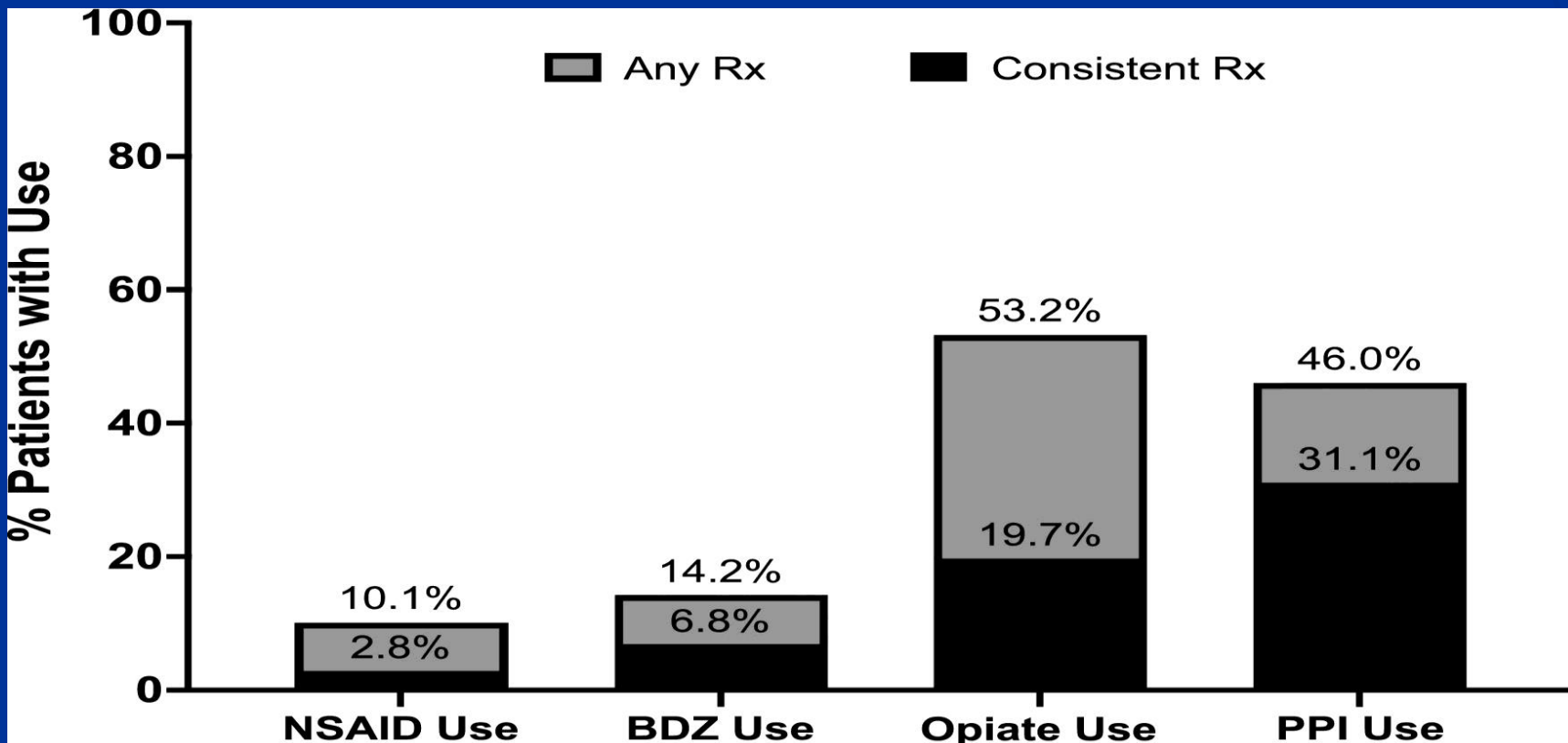
Appropriate and Potentially Inappropriate Medication Use in Decompensated Cirrhosis

Mary J. Thomson ✉, Anna S. F. Lok, Elliot B. Tapper

First published: 10 September 2020 | <https://doi.org/10.1002/hep.31548>

- Retrospective review of outpatient pharmacy claims of a large national managed care organization
- Included 12,621 pts with decompensated cirrhosis

Hepatology, 73; 6: 2429-2440, 2020



Medication-Related Problems in Outpatients With Decompensated Cirrhosis: Opportunities for Harm Prevention

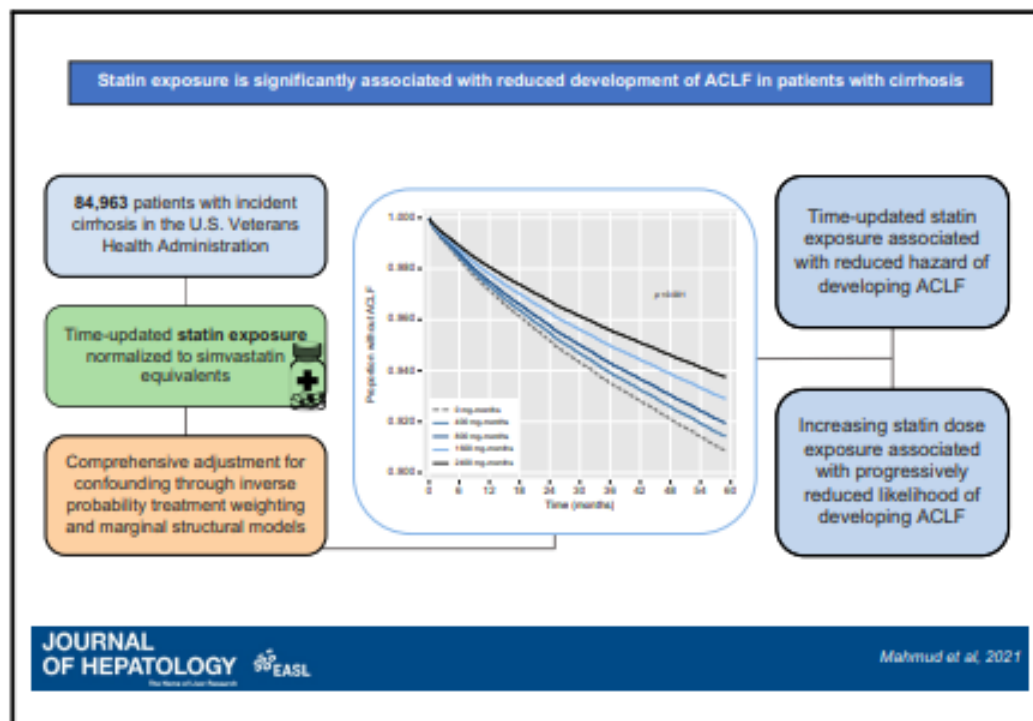
Kelly L. Hayward, Preya J. Patel, Patricia C. Valery, Leigh U. Horsfall, Catherine Y. Li, Penny L. Wright, Caroline J. Tallis, Katherine A. Stuart, Katharine M. Irvine, W. Neil Cottrell ... See all authors ✓

- Cohort of Australians in a multi disciplinary liver clinic – pharmacist led/patient centered medication interventions vs. standard model of care
- Outcomes (N= 116):
 - 96.5% of patients had AT LEAST one medication related problems (MRP) identified at baseline
 - Non-adherence to lactulose was associated with 36% of possibly preventable readmissions
 - Non-adherence to diuretics accounted for 55% of potentially preventable 30-day re-admissions

Statins May Reduce the Risk for ACLF

Statin exposure is associated with reduced development of acute-on-chronic liver failure in a Veterans Affairs cohort

Graphical abstract



Authors

Nadim Mahmud, Sara Chapin, David S. Goldberg, K. Rajender Reddy, Tamar H. Taddei, David E. Kaplan

Correspondence

nadim@pennmedicine.upenn.edu (N. Mahmud).

Lay summary

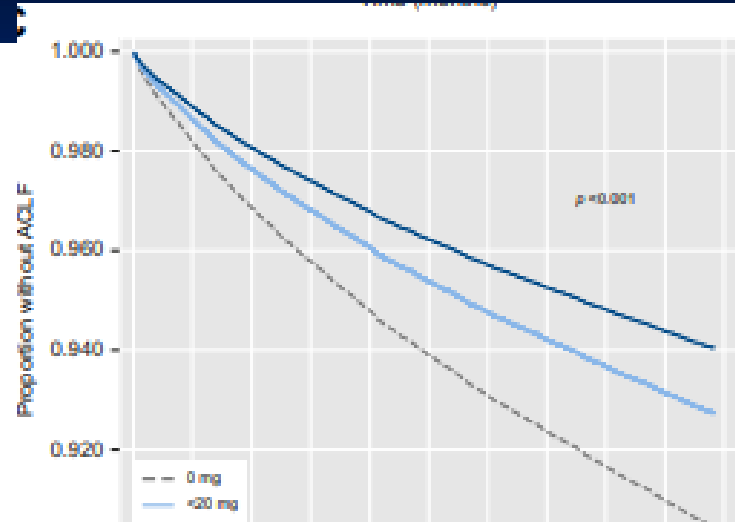
Statin therapy has been shown to have numerous beneficial effects in patients with chronic liver disease. This study demonstrated a strong association between statin therapy and a reduced risk of acute-on-chronic liver failure development in patients with cirrhosis. The re-

Statins May Reduce the Risk for ACLF

Eligible patients with cirrhosis
N = 124,346

Exclusions:
 Transplanted prior to index date n = 527
 FIB-4 <1.45 n = 12,326
 Missing FIB-4 baseline data n = 1,396
 <2 outpatient visits in index year n = 1,687
 <180 days of follow-up n = 10,980
 HCC diagnosis within 180 days n = 7,643
 Missing baseline lipid data n = 4,824

Analytic cohort
n = 84,963

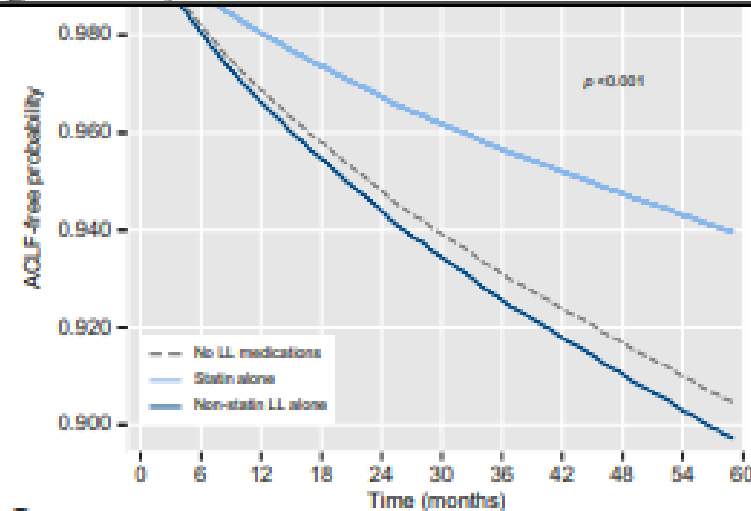
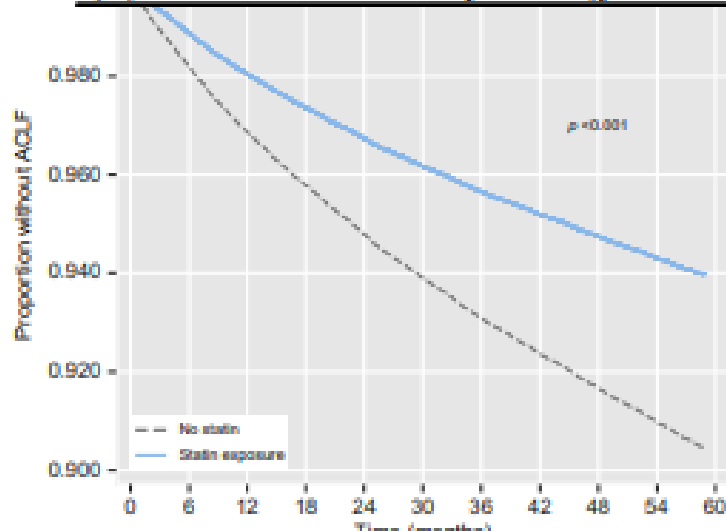


Model

IPTW-adjusted Cox regression†
HR (95% CI)

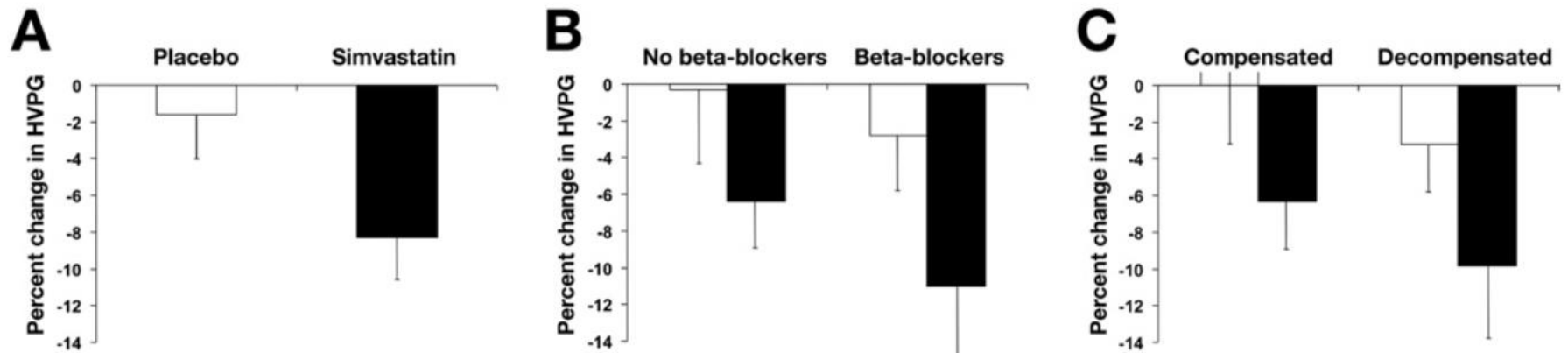
Cumulative exposure models

(1) Statin time exposure (per 5 months)	0.91 (0.90–0.92)*
(2) Statin dose-time exposure (per 400 mg-months)	0.94 (0.93–0.95)*



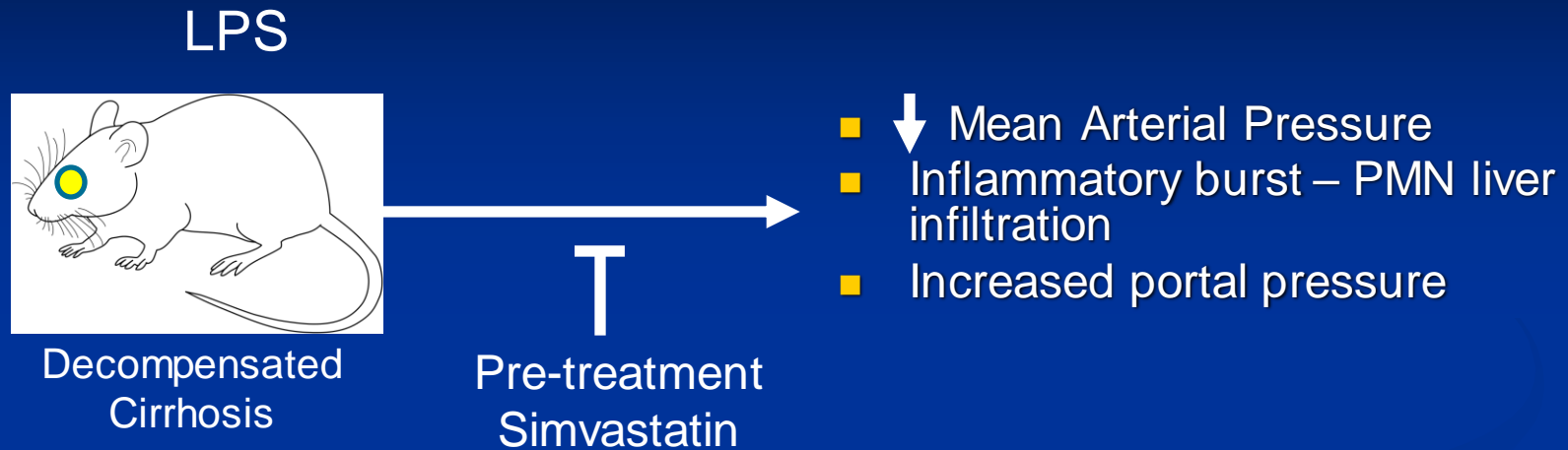
Statins Reduce Portal Pressure

- RCT of patients with cirrhosis and PHTN
 - Independent of NSBB...



- Statin's ↓ lower portal pressures.

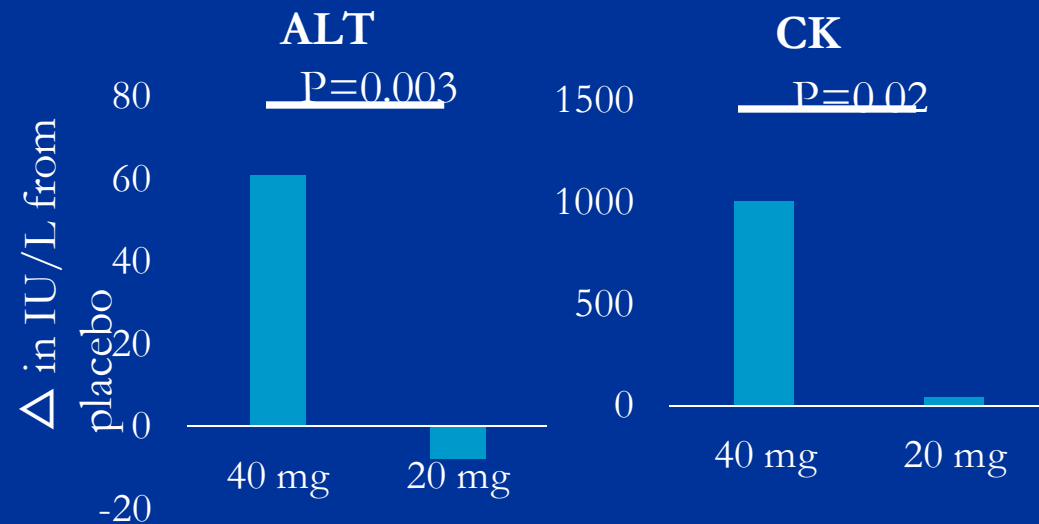
Statin's Dichotomous Effects in ACLF



Statin pre-treatment may decrease the initial injurious effects of infection in patients with decompensated cirrhosis.

Statin Dose Matters...

- LIVERHOPE-SAFETY trial of 50 pts: double-blind, randomized, placebo controlled trial of Simvastatin & Rifaximin in CTP B & C pts.



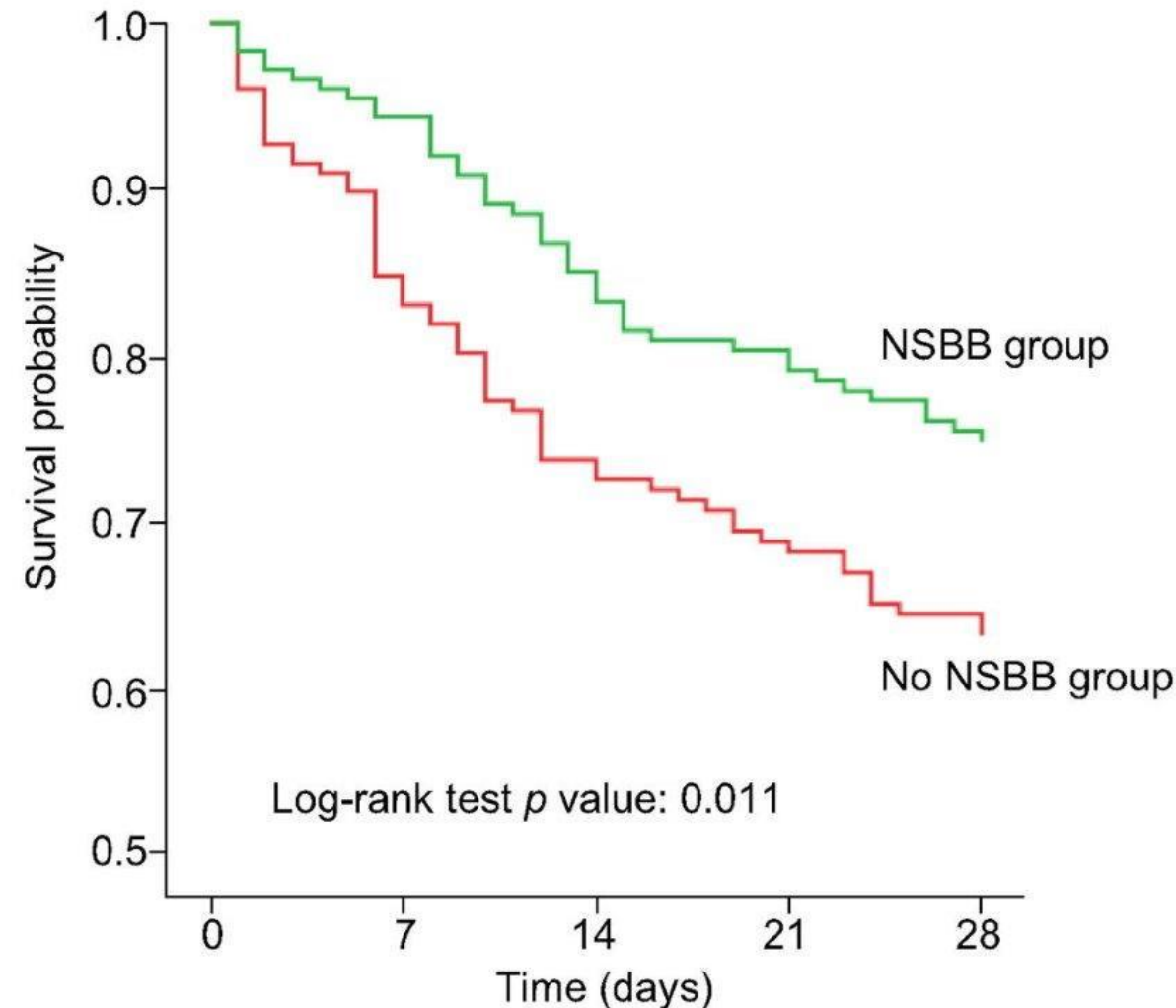
- All pts w/ ALT elevations had CK elevations.
- 1 pt. had elevated INR.
- NACSELD data has shown inferior outcomes in admitted pts. w/ cirrhosis on vs. not on statin.

Statins may help prevent ACLF, but once AC/ACLF occurs hold or decrease the statin.

NSBB

- NSBB may improve outcome in ACLF patients

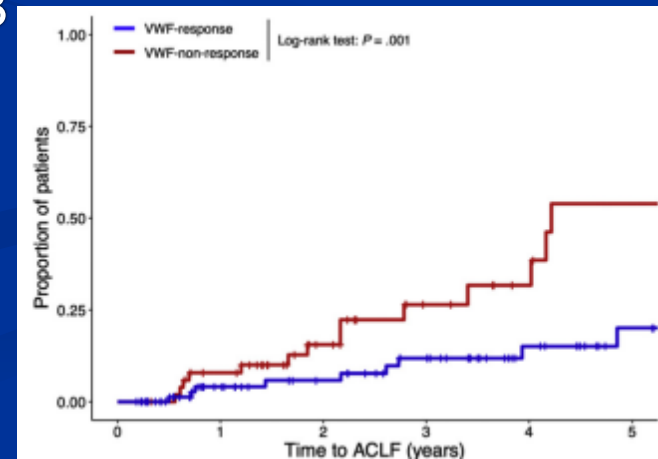
Non-selective beta blockers improves the survival of ACLF patients



*NSBB should be stopped
when SBP < 90*

vWF Response to NSBB may lower risk for ACLF

- vWF is a biomarker of endothelial dysfunction.
 - Increases with increasing severity of liver disease.
- Retrospective evaluation of prospectively collected data on 159 pts who had primary/secondary NSBB treatment.
- vWF response $\geq 5\%$ decrease.
- Responders:
 - Further decompensation aHR = 0.56
 - ACLF aHR = 0.30
 - Liver related death aHR = 0.33
- Responders were more likely to:
 - Carvedilol
 - Smaller decreased in MAP



Appropriate & Early Antibiotics for Infections

- Consistent data shows 1/3 of non-electively admitted cirrhotic patients are infected.
- All admitted cirrhotic patients need to have infection ruled out.
 - When choosing antibiotics:
 - 1) Etiology of infection
 - 2) Severity of infection
 - 3) Local resistance patterns
 - 4) How it was acquired:
 - Community Acquired
 - Health care associated (been admitted <90 days to hospital, long-term care, or getting HD).
 - Nosocomial (>48 hours after admission)
- Early administration of antibiotics in sepsis decreases in-hospital mortality.
 - Each hour delay increased OR Death = 1.04 (95% CI 1.03-1.06)

Primary Norfloxacin Prophylaxis for APASL-Defined Acute-on-Chronic Liver Failure: A Placebo-Controlled Double-Blind Randomized Trial

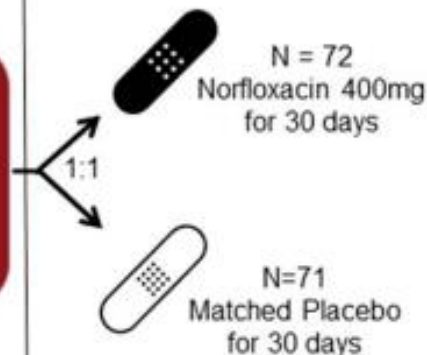
Anand V. Kulkarni, MD, DM¹, Sowmya Tirumalle, MD¹, Madhumita Premkumar, MD, DM², Karan Kumar, MD, DM³, Syeda Fatima, PharmD¹, Bindu Rapole, PharmD¹, Venu Simhadri, PhD⁴, Baqar Ali Gora, MSc¹, Mitnala Sasikala, PhD⁴, Deepika Gujjarlalpuadi, MD⁵, Sadhana Yelamanchili, MD⁶, Mithun Sharma, MD¹, Rajesh Gupta, MD, DM¹, Padaki Nagaraja Rao, MD, DM^{1,*} and D. Nageshwar Reddy, MD, DM^{1,*}

Primary Norfloxacin Prophylaxis for APASL-defined Acute-on-Chronic Liver Failure: A Placebo-Controlled Double-Blind Randomized Trial




Inclusion criteria








Patients with acute-on-chronic liver failure identified by the Asian Pacific Association for the Study of the Liver (APASL) criteria

Interventions



Results

			P
At day 30	18.1%	33.8%	0.03
At day 90	46%	62%	0.02

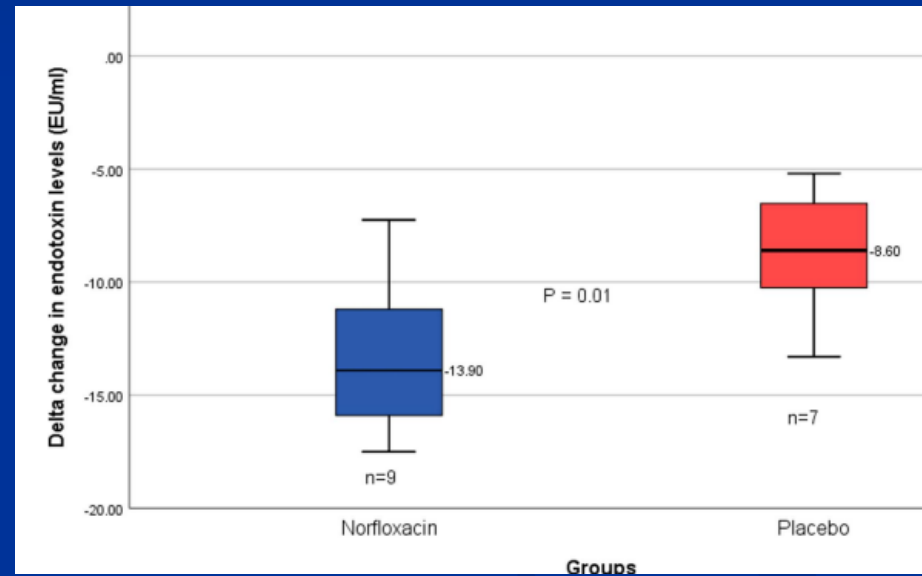
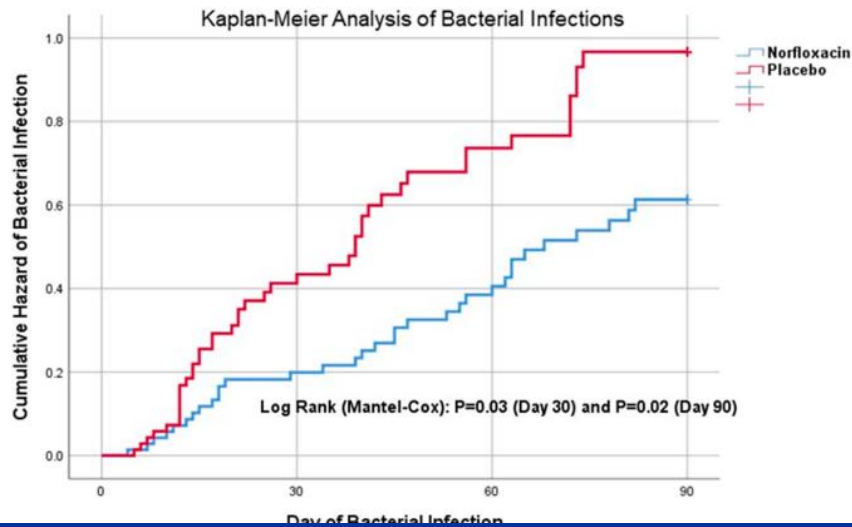
-  Transplant-free survival with 
-  HE/Endotoxin with 
-  Multi-drug resistant organisms-30%
-  Candiduria with 

Kulkarni et al. *Am J Gastroenterol*. 2021. doi:10.14309/ajg.0000000000001611

AJG The American Journal of GASTROENTEROLOGY

Primary Norfloxacin Prophylaxis for APASL-Defined Acute-on-Chronic Liver Failure: A Placebo-Controlled Double-Blind Randomized Trial

Anand V. Kulkarni, MD, DM¹, Sowmya Tirumalle, MD¹, Madhumita Premkumar, MD, DM², Karan Kumar, MD, DM³, Syeda Fatima, PharmD¹, Bindu Rapole, PharmD¹, Venu Simhadri, PhD⁴, Baqar Ali Gora, MSc¹, Mitnala Sasikala, PhD⁴, Deepika Gujjarlappudi, MD⁵, Sadhana Yelamanchili, MD⁶, Mithun Sharma, MD¹, Rajesh Gupta, MD, DM¹, Padaki Nagaraja Rao, MD, DM^{1,*} and D. Nageshwar Reddy, MD, DM^{1,*}



Terlipressin in ACLF

- AKI in patients with cirrhosis increases the risk for death even with recovery.
- Open-label RCT in AAPASL-ACLF

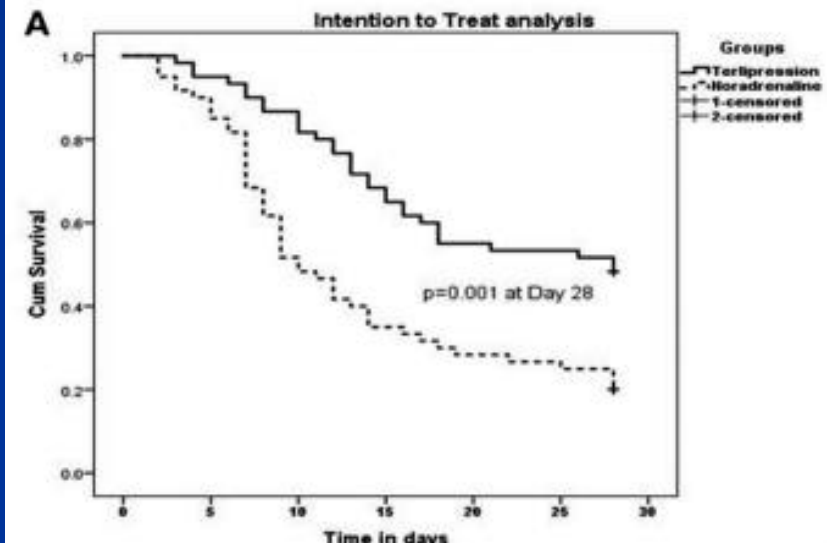
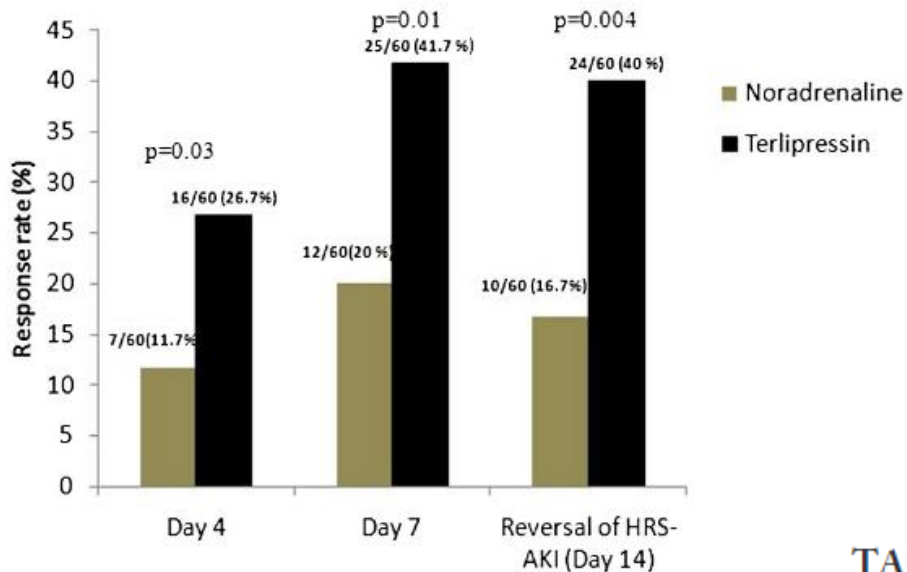


TABLE 3. Table Depicting Predictor of Nonresponse and Mortality Using Uni- and Multivariate Analysis

Predictor of Nonresponse

Variable	OR	95% CI	P Value
HE	1.88	1.20-2.94	0.002
Noradrenaline compared to terlipressin	2.08	1.32-3.30	0.002
MELD	1.08	1.02-1.13	0.003

Early Diagnosis and Tx are essential

Terlipressin in ACLF

- Open label evaluation of Terlipressin in patients with EASL-CLIF ACLF.
 - ACLF-3 was the biggest predictor of Terlipressin non-response.

Parameters	Univariate HR (95%CI)	P	Multivariate HR (95%CI)	P
Age	0.99 (0.96-1.02)	0.51		
MAP at baseline	0.97 (0.93-1.02)	0.33		
Change in MAP at day 3	0.85 (0.76-0.96)	0.009		
Presence of sepsis at baseline	1.4 (0.79-2.48)	0.24		
Hemoglobin	1.05 (0.91-1.2)	0.48		
Total leucocyte counts	1	<0.001		
Platelets	0.99 (0.99-1.003)	0.5		
Total bilirubin	1.03 (1.01-1.06)	0.001		
Serum albumin	0.53 (0.25-1.1)	0.09		
Blood urea	1.005(1-1.009)	0.03		
Serum creatinine	1.38 (1.18-1.62)	<0.001		
Serum sodium	0.95 (0.91-0.99)	0.01		
Serum potassium	0.98 (0.66-1.44)	0.92		
INR	1.42 (1.06-1.9)	0.01		
HE at baseline	2.55 (1.37-4.74)	0.003		
Terlipressin non-response	5.67 (3.13-10.3)	<0.001	3.49 (1.85-6.57)	<0.001
Ischemic adverse events	2.95 (1.5-5.82)	0.002		
MELD NA	1.14 (1.09-1.2)	<0.001	1.12 (1.06-1.18)	<0.001
CLIF-C ACLF	1.03 (1.01-1.06)	0.005		
AARC score	1.34 (1.2-1.49)	<0.001		
ACLF grade II vs. I	3.18 (1.59-6.36)	0.001		
ACLF grade III vs. I	5.83 (2.81-12.06)	<0.001		

Table 5. Predictors of mortality on univariate and multivariate stepwise cox regression analysis

Guidelines

Kidney Recommendations

1. In patients with cirrhosis and stages 2 and 3 acute kidney injury (AKI), we suggest intravenous (IV) albumin and vasoconstrictors as compared to albumin alone, to improve creatinine (low quality, conditional recommendation).
2. In patients with cirrhosis, we suggest against the use of biomarkers to predict the development of renal failure (very low quality, conditional recommendation).
3. In patients with cirrhosis and elevated baseline serum creatinine (sCr) who are admitted to the hospital, we suggest monitoring renal function closely because elevated baseline creatinine is associated with worse renal outcomes and 30-day survival (but no data that closer monitoring improves these outcomes) (very low quality, conditional recommendation).
4. In hospitalized patients with cirrhosis and HRS-AKI without high grade of ACLF or disease, we suggest terlipressin (moderate quality, conditional recommendation) or norepinephrine (low quality, conditional recommendation) to improve renal function.

Circulation

Key concept statements

1. Higher mean arterial blood pressure (MAP) may decrease the risk of ACLF.
2. Norepinephrine is the vasopressor of choice in patients with ACLF.

IV Albumin Vs. Plasmalyte in Sepsis

Induced Hypotension

- Primary endpoint = MAP >65 at 3 hrs.
 - Open label RCT
- 20% Albumin was superior
 - 62% vs. 22% (p<0.001)
 - More rapid normalization of arterial lactate
 - No change in 28-day Mortality
- IV albumin group – 22% need to DC therapy for AEs
 - Albumin dose was 0.5-1.0 gm/kg over 3 hrs.
 - Plasmalyte dose was 30 ml/kg over 3 hrs.

Key concept statements

1. Albumin has several potential benefits beyond the oncotic effect.
2. IV albumin is recommended to prevent AKI and subsequent organ failures in patients diagnosed with SBP.
3. IV albumin is not recommended to prevent organ failures in patients with cirrhosis who have infections other than SBP.
4. Five-percent albumin is often used for rapid volume resuscitation, whereas for more sustained volume expansion, we recommend 25% albumin.

CME

Acute-on-Chronic Liver Failure Clinical Guidelines

Jasmohan S. Bajaj, MD, MS, FACG¹, Jacqueline G. O'Leary, MD, MPH, FACG², Jennifer C. Lai, MD, MBA³, Florence Wong, MD, FACG⁴, Millie D. Long, MD, MPH, FACG (Methodologist)⁵, Robert J. Wong, MD, MS, FACG (Methodologist)⁶ and Patrick S. Kamath, MD⁷

Summary

- Prevention of ACLF is essential
 - Review medications in all patients with cirrhosis
 - Non-compliance with lactulose & diuretics causes preventable re-admission.
 - NSAIDS, benzos, narcotics...
 - PPI –DC?
 - Statin therapy may be beneficial
 - Watch the dose
 - Hold in admitted patients
 - NSBB – carvedilol
- Diagnose and treat infection early – appropriate Abx
- Diagnose and treat AKI early
 - Probably best to avoid Terlipressin in ACLF-3