3RD ANNUAL NCSCG POST-AASLD SYMPOSIUM

Rehoboth McKinley Christian Health Care Services

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Northern California Society for Clinical Gastroenterology

AASLD 2017: Portal Hypertension and Complications of Cirrhosis

R. Todd Frederick, MD
California Pacific Medical Center
fredertz@sutterhealth.org

Disclosures

- Consultant/Advisor: Gilead, Abbvie, Salix
- Investigator: Ocera, Conatus, Mallinckrodt, Gilead, Sequana

Outline

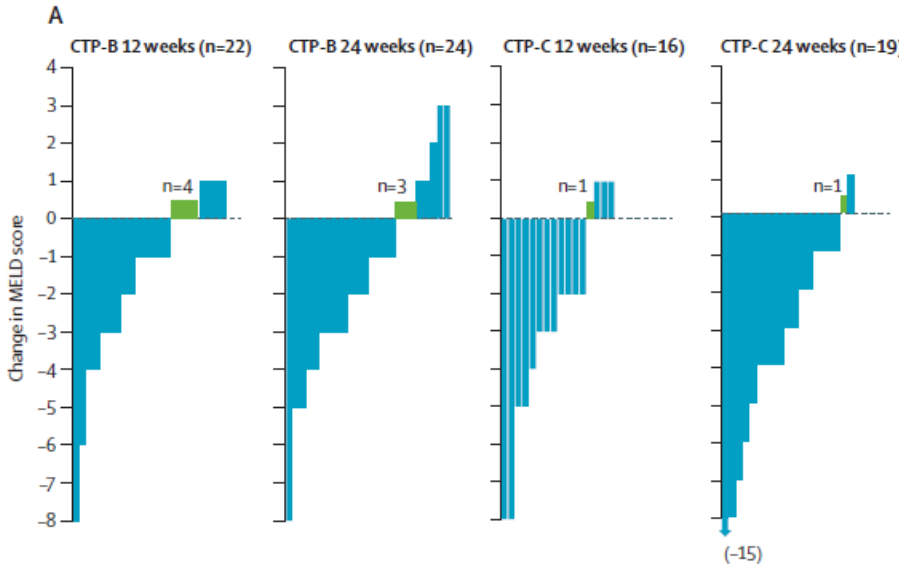
- Mortality benefit of HCV Rx in Decompensated Cirrhosis (LB-27)
- Hepatic Vein Pressure Gradient (HVPG)
  - In NASH (445 and 458)
  - Changes in HVPG for Prognosis (451)
- Hepatic Encephalopathy
  - RCT with OCR-002 (219)
  - Portosystemic Shunt Embolization (465)
  - Sarcopenia and Opiates (222)
- Beta-blockers

Survival benefit of direct-acting antiviral therapy in patients with decompensated cirrhosis – Abstract LB-27

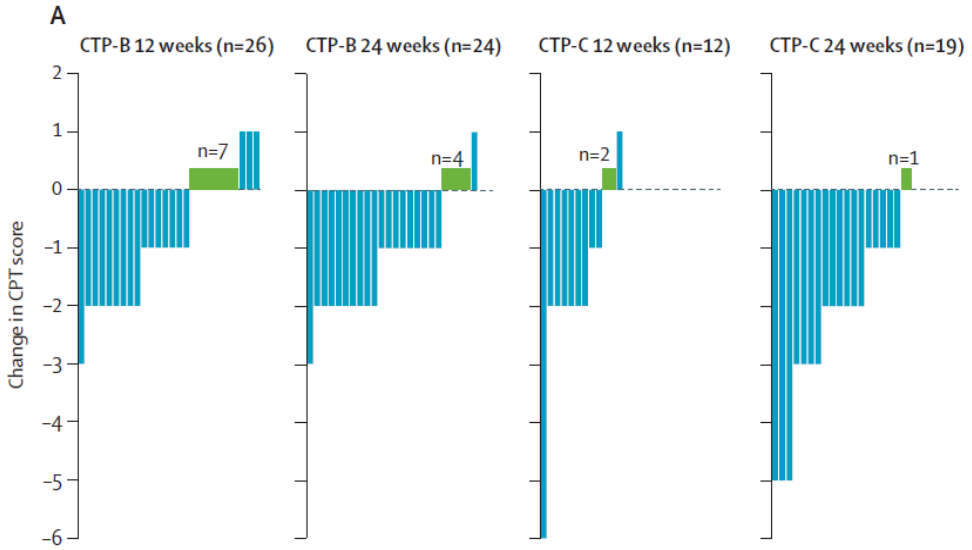
- Kim WR, Mannalithara A, Lee H, et al.
- Background: SVR for HCV results in improved liver function in decomp cirrhotics; mortality benefit unknown
- Follow up of Child B (n=123)/C (n=89) cirrhotics treated from SOLAR[1,2] studies (LDV/SOF/RBV)
- Mortality at 1yr compared to that predicted by Survival Models derived from OPTN data (pre-DAA)
  - Multivariable proprotional hazards regression analysis

1) Charlton M, Everson GT, Flamm SL, et al. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. Gastroenterology. 2015;149:649-659.
2) Manns M, Samuel D, Gane EJ, et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. Lancet Infect Dis. 2016;16:685-697.

SVR Improves Liver Function: MELD and CPT



Baseline MELD 6-25

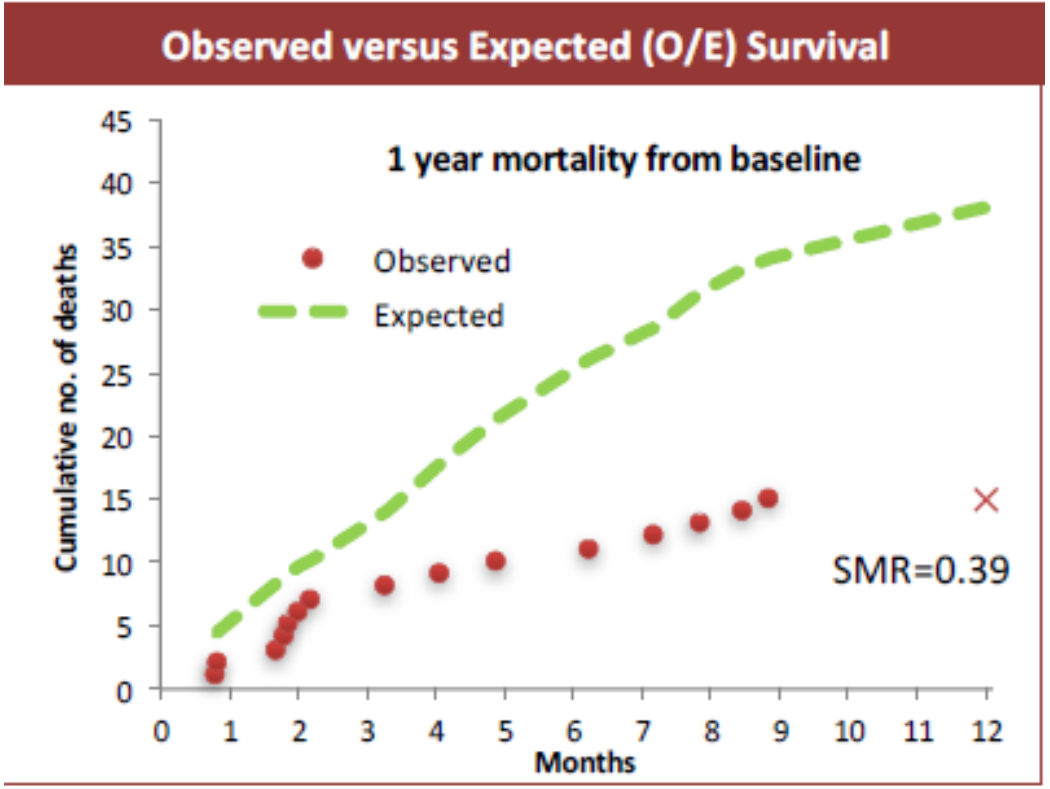


Baseline CTP 7-12

1) Manns M, Samuel D, Gane EJ, et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. Lancet Infect Dis. 2016;16:685-697.

Methods and Results

- SMR, Standardized Mortality Ratio 0.39
  - 61% less likely to die compared to historical control
- 15 deaths in the SOLAR study
- Statistically significant at ~4 months post-treatment

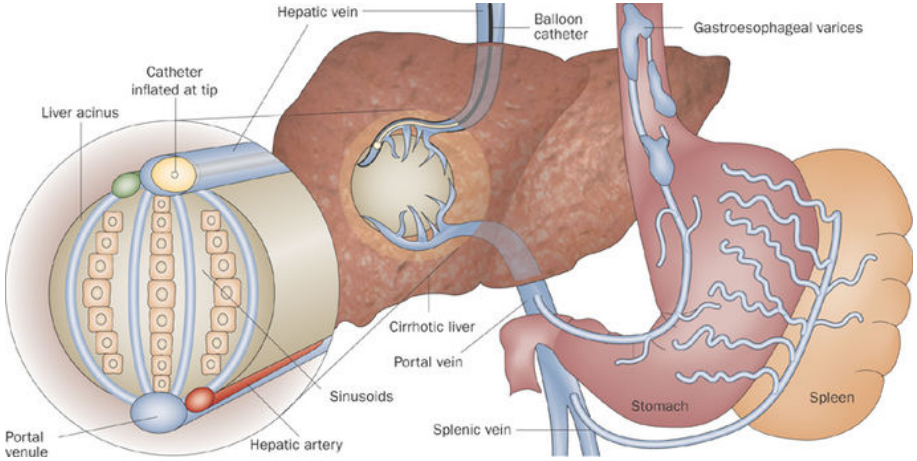


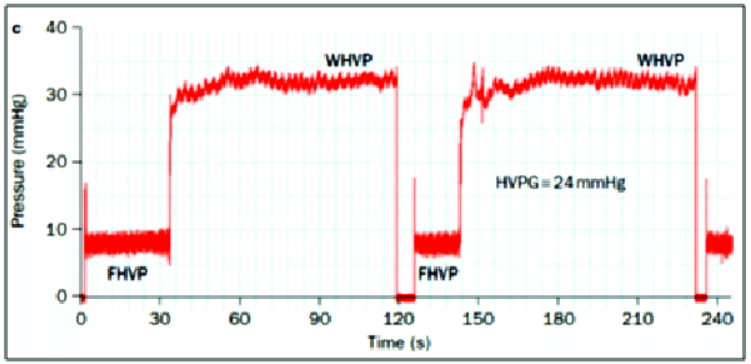
Conclusions & Questions

- DAA therapy appears to significantly decrease mortality risk in decompensated cirrhotics
- Questions:
  - Is there a “point of no return” or futility?
  - Differences between Child B vs C?
  - What about those patients awaiting liver transplant?
    - MELD Purgatory?

HVPG in NASH Cirrhosis

- Hepatic Vein Pressure Gradient (HVPG)
  - WHVP – FHVP
  - Eliminates effect of intra-abd pressure
  - Gold standard for measuring portal HTN
  - Predicts development of varices (HVPG≥10)
  - Predicts variceal bleeding (HVPG≥12)
  - Predicts decompensation (HR 1.11, ROC 0.71) (only 10% w/ NASH/Crypto)
  - Predicts HCC in cirrhosis (HR 1.18; HVPG>10 = 6-fold risk HCC)





Clinical Use of HVPG. Bosch et al. Nature 2009
Groszmann et al. Hepatology 2003
Ripoll et al. Gastroenterology 2007
Ripoll et al. J Hepatology 2009

HVPG Predicts Clinical Disease Progression in Patients With Compensated Cirrhosis Due to NASH – Abstract 445

- Bosch J, Harrison SA, Abdelmalek MF et al.
- Background: Studies primarily in alcoholic and viral cirrhosis demonstrate HVPG predicts decompensation
  - Data with NASH cirrhosis are limited
- 256 patients with NASH cirrhosis
- Prospective trial (simtuzumab) w/ HVPG at weeks 0, 48, 96
- Adjudicated liver-related clinical events (ascites, varices +/-bleeding, MELD $\geq$15, HE, CTP rise $\geq$2, LT, death)
- Baseline MELD 6-9, baseline HVPG 6-18mmHg
  - Stratified HVPG < 10mmHg vs. $\geq$ 10mmHg

HVPG Predicts Clinical Disease Progression in Patients With Compensated Cirrhosis Due to NASH – Abstract 445

Liver-Related Clinical Events

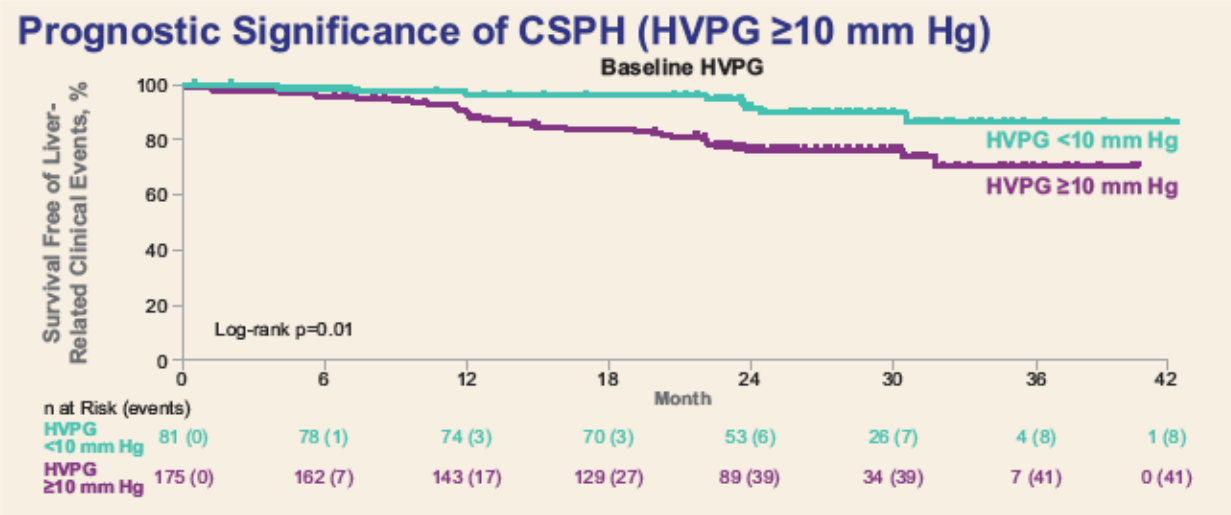
Patients With Adjudicated Liver-Related Clinical Events, n (%)*	Last HVPG Prior to Event		Total n=256
	<10 mm Hg	≥10 mm Hg	
Total	7 (14)	42 (86)	49 (19)
Ascites	2 (11)	17 (89)	19 (7)
Hepatic encephalopathy	3 (23)	10 (77)	13 (5)
Variceal hemorrhage	2 (33)	4 (67)	6 (2)
Newly diagnosed varices	0	4 (100)	4 (2)
≥2-point increase in Child-Pugh score and/or MELD ≥15	0	6 (100)	6 (2)
Death	0	1 (100)	1 (<1)

Prognostic Significance of HVPG and Other Factors*

Parameter	Hazard Ratio (95% CI)	p-Value
Baseline HVPG, per mm Hg	1.13 (1.06, 1.21)	**<0.001**
Change in HVPG, per mm Hg	1.10 (1.03, 1.17)	**<0.01**
Baseline albumin, per g/dL	0.27 (0.12, 0.58)	**<0.01**

*Model adjusted for age, sex, diabetes, BMI, Ishak stage, MELD, and serum albumin. CI, confidence interval.

HVPG Predicts Clinical Disease Progression in Patients With Compensated Cirrhosis Due to NASH – Abstract 445



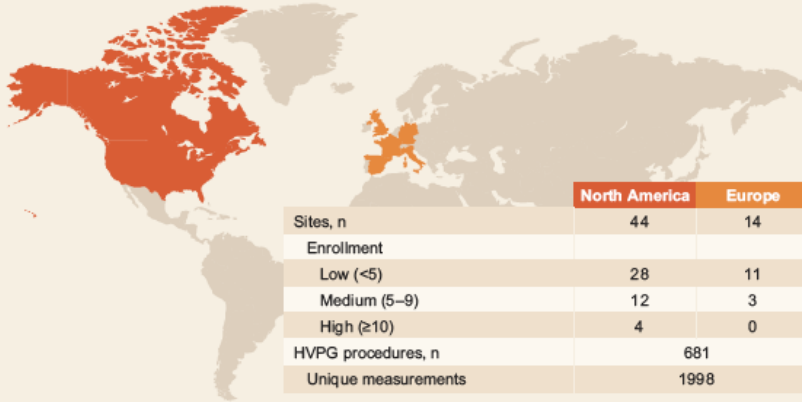
- At 24 mo, estimated survival free of clinical events was 92% (95% CI 82%, 96%) in patients with HVPG <10 mm Hg compared with 75% (68%, 81%) in patients with CSPH (hazard ratio 2.79; 95% CI 1.31, 5.96; log-rank p=0.01)

Variability in Measurement of HVPG in Patients With Compensated Cirrhosis Due to NASH: Results From a Randomized, Controlled Trial – Abstract 458

- Bosch J, Abdelmalek MF, Shiffman ML et al.
- Background: Variability in HVPG due to deep sedation, catheter placement, operator and interpreter experience, equipment/monitor
- All sites trained in HVPG; approved only after submitting 2 acceptable tracings; central reader; measured in triplicate
- Assessed intraclass correlation coefficient (ICC)

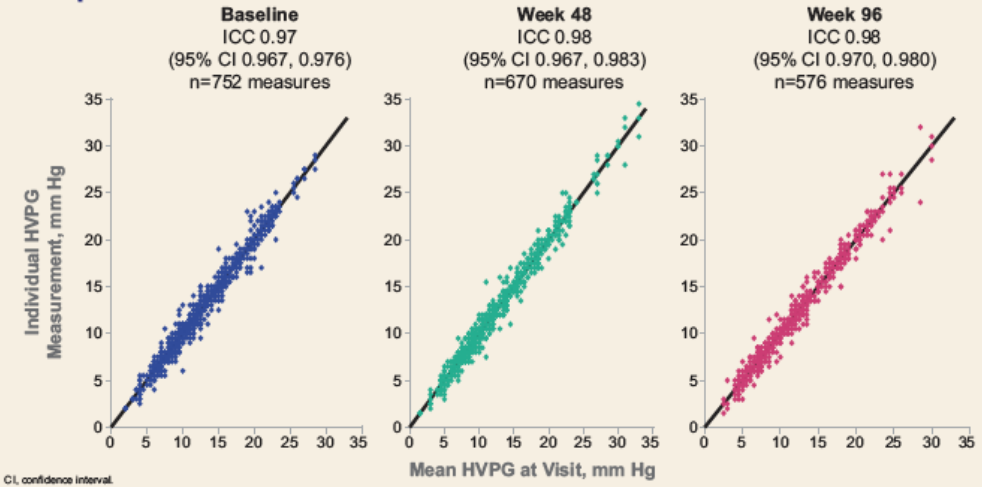
Variability in Measurement of HVPG in Patients With Compensated Cirrhosis Due to NASH: Results From a Randomized, Controlled Trial – Abstract 458

HVPG Measurements and Site Volume



	North America	Europe
Sites, n	44	14
Enrollment		
Low (<5)	28	11
Medium (5–9)	12	3
High (≥10)	4	0
HVPG procedures, n	681	
Unique measurements	1998	

HVPG Measurements Were Reproducible in Patients With Compensated Cirrhosis Due to NASH



CI, confidence interval.

Conclusions & Questions

- HVPG is a robust prognostic variable
  - Both baseline and change over time
- HVPG is reproducible in a clinical trial setting
- HVPG is a viable clinical trial endpoint in patients with advanced liver disease, including NASH cirrhosis
- Are there acceptable (non-invasive) surrogates?

STOP-HE: A Randomized, DB, Pbo-controlled study of OCR-002 in Hepatic Encephalopthy – Abstracts 219 and 502

- Rahimi RS, Safadi R, Thabut D et al.
- Background: Ammonia contributes to the AMS of HE. Ammonia scavengers may help reduce ammonia and improve outcomes in HE
- 231 inpatients with HE stage $\geq$2 randomized to SOC + OCR-002 vs. Pbo. Primary endpoint: median time to “meaningful” improvement

SOC = lactulose +/- rifaximin

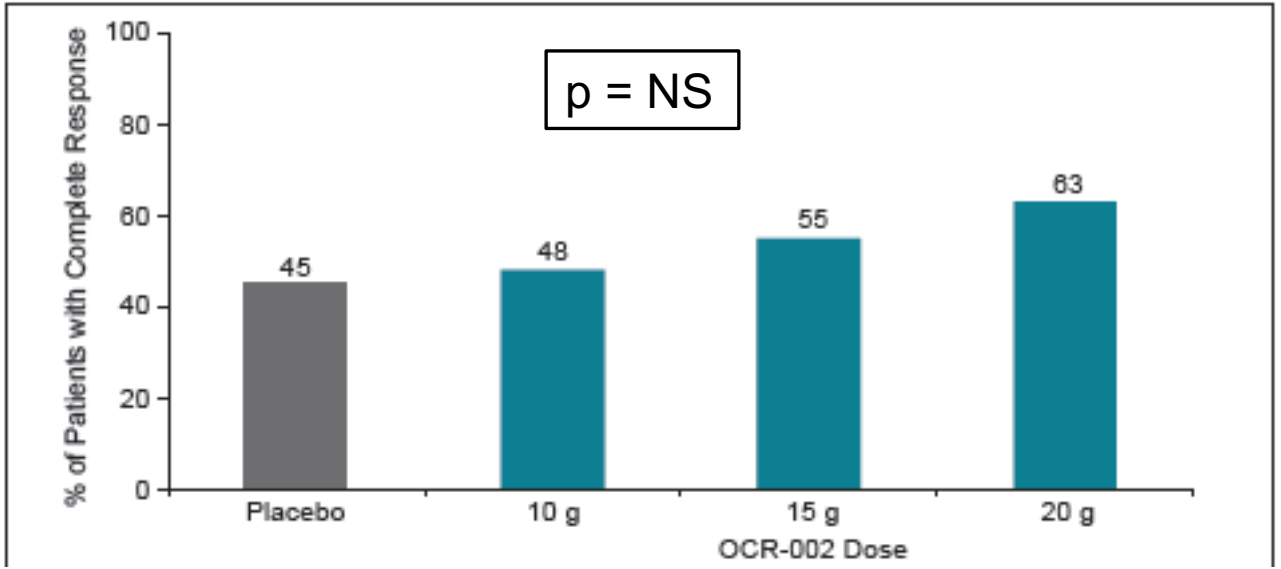
Baseline Characteristics

Characteristic	OCR-002 (n=116)	Placebo (n=115)
Male	62%	68%
Mean age, y (range)	59 (26,74)	60 (27,79)
Child-Pugh and MELD		
Child-Pugh A	2%	<1%
Child-Pugh B	33%	24%
Child-Pugh C	66%	75%
MELD (Median)	18	18
HE Stage		
Stage 2	60%	61%
Stage 3	34%	32%
Stage 4	5%	7%
Inciting Factors (most common)		
Bacterial infection	15 (13%)	14 (12%)
Poor compliance (lactulose)	15 (13%)	13 (11%)
Dehydration	16 (14%)	9 (8%)
TIPS	7 (6%)	9 (8%)

HEST Score	Mean Ammonia Levels at Screening (µmol/L)
2	90
3	100
4	143

p = 0.003

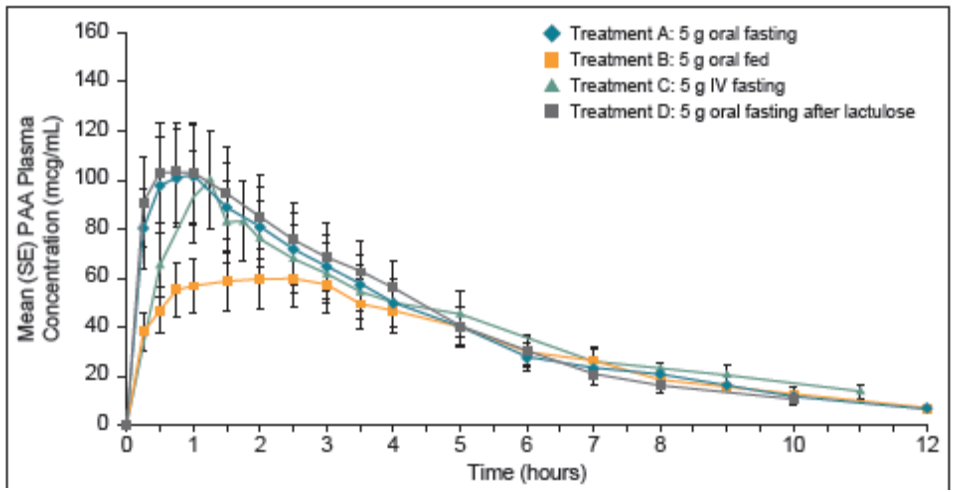
Complete Response to Stage 0/1 HE

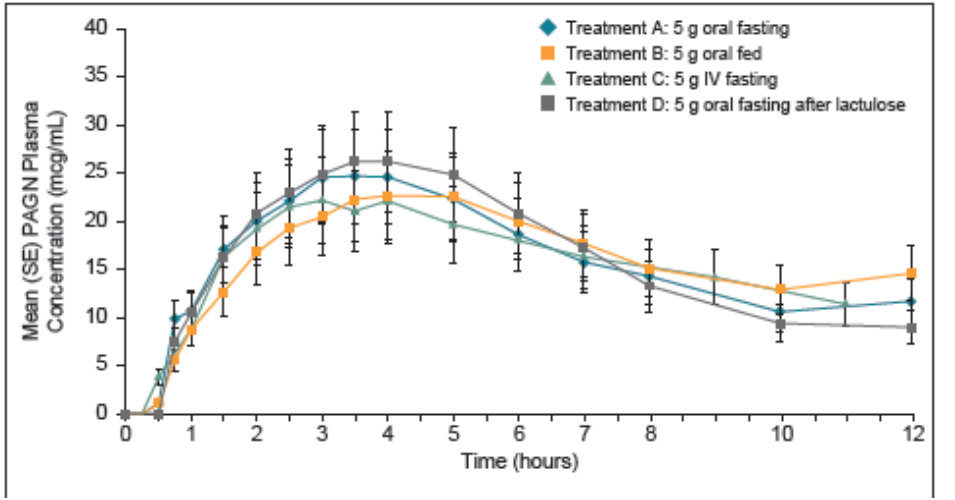


- Dose proportional complete response noted
- Unfortunately, many patients did not achieve complete response

OCR-002 Bioavailability – Abstract 501

- Hassanein TI, Wang L, Barakat F et al.
- Background: Oral formulation of OCR-002 may be more suitable for management of HE
- PK study in Child A (n=6) and C (n=6) cirrhotics comparing IV vs. oral dosing
  - PO: fed vs. fasting vs. after lactulose
  - IV
- Demonstrated excellent bioavailability (≥95%)
- Dosing w/ food may be advantageous, avoid C_{max} of PAA (side effects)





Another ammonia scavenger: Glycerol Phenylbutyrate (GPB, Ravicti)

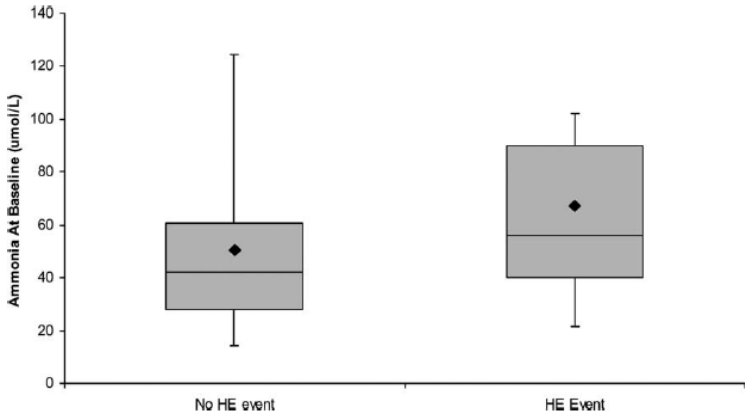
HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Randomized, Double-Blind, Controlled Study of Glycerol Phenylbutyrate in Hepatic Encephalopathy

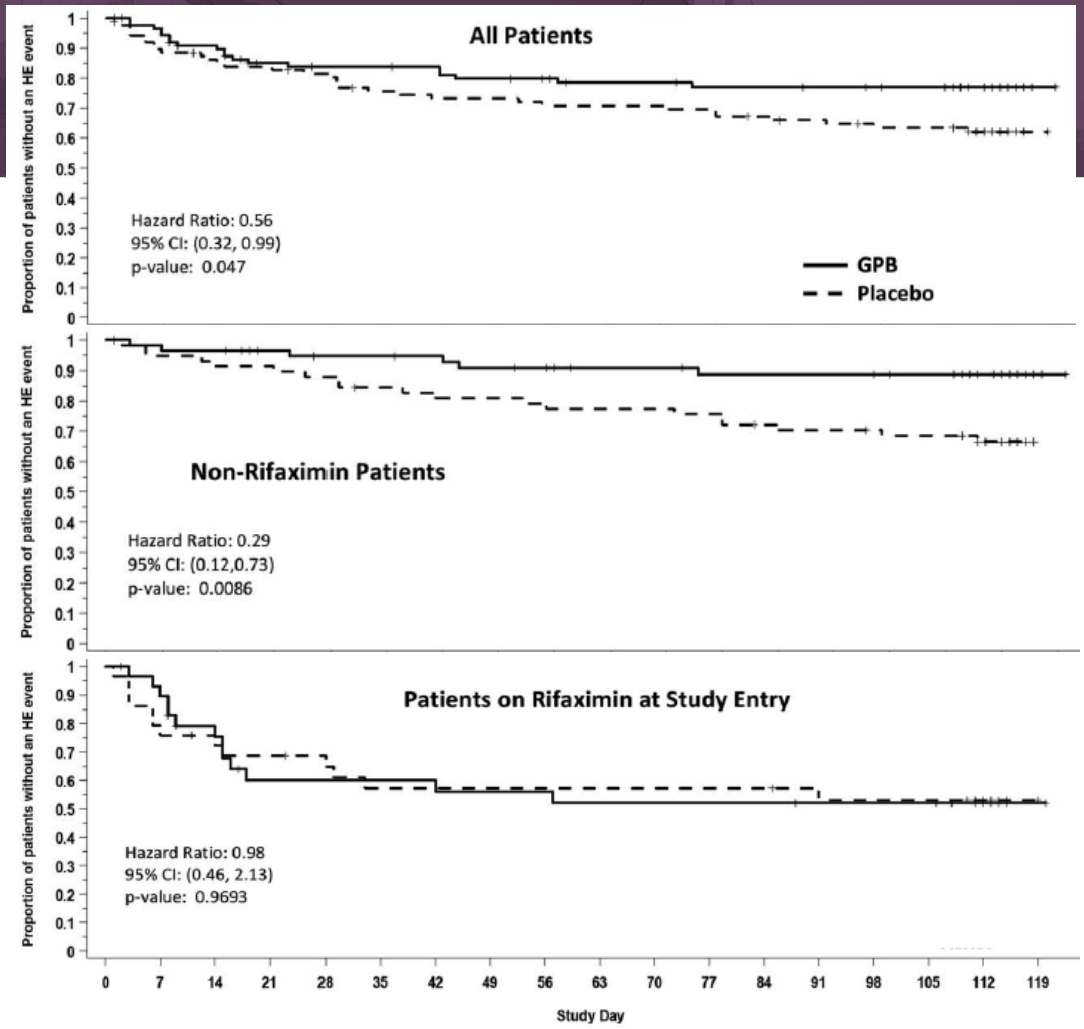
Don C. Rockey,[1] John M. Vierling,[2] Parvez Mantry,[3] Marwan Ghabril,[4] Robert S. Brown, Jr.,[5] Olga Alexeeva,[6] Igor A. Zupanets,[7] Vladimir Grinevich,[8] Andrey Baranovsky,[9] Larysa Dudar,[10] Galyna Fadieienko,[11] Nataliya Kharchenko,[12] Iryna Klaryts'ka,[13] Vyacheslav Morozov,[14] Priya Grewal,[15] Timothy McCashland,[16] K. Gautham Reddy,[17] K. Rajender Reddy,[18] Vasyl Syplyviy,[19] Nathan M. Bass,[20] Klara Dickinson,[21] Catherine Norris,[21] Dion Coakley,[21] Masoud Mokhtarani,[21] and Bruce F. Scharschmidt,[21] for the HALT-HE Study Group

- Phase 2 study for Prevention of Overt HE Recurrence

GPB Results



- Overall successful
- Not for patients on Rfx
- Sold to Horizon
- No Phase 3



Rockey DC et al. Hepatology 2014

Conclusions & Questions

- Ammonia remains an important part of the pathogenesis of HE
- OCR-002, an ammonia scavenger, effectively reduces ammonia levels and is well tolerated
- Reduction of ammonia correlates with improvement in HE
- OCR-002 leads to faster clinical improvement of HE in patients with confirmed hyperammonemia
- Is the benefit similar with and without rifaximin?
- What about those patients with AMS but normal ammonia?
- What about those with persistent HE and hyperammonemia?

Multicenter Study of Portosystemic Shunt Embolization for Persistent Hepatic Encephalopathy: From the Consortium on Liver Disease OUTcomes (CLOUT) Group – Abstract

- Leise MD, Rahimi RS, Paluri M et al.
- Background: Refractory HE may be due to severe portosystemic shunting which may be amenable to mechanical obstruction (coil, glue, foam)
- Retrospective review of 59 cases in 7 centers for effect on HE improvement: marked, moderate, mild, none
- Cirrhosis: HCV(29%)/NASH(24%)/ALD(10%)/AIH(10%)
- Mean MELD 14 (10-16) and CTP 9 (8-11)

Multicenter Study of Portosystemic Shunt Embolization for Persistent Hepatic Encephalopathy: From the Consortium on Liver Disease OUTcomes (CLOUT) Group – Abstract

- Access: Venous (76%); Transhepatic (24%)
- Improvement in HE at 12 months in 19% (mild); 63%(moderate); 15%(marked)
- No significant change in MELD or CTP
- Peri-procedural complications in 15% (AMS, Shock, Thrombosis, Bleeding, Pancreatitis, contrast nephropathy)
- Long-term consequences: worsening ascites in 22%, new EV or GV in 15% (33% of these with bleeding and 1 death)

Portosystemic Shunt Embolization

Study	n	MELD or CTP	Follow-up (days)	HE free	PHTN Complications EV	Ascites
Lynn AM, *et al. Liver Transpl* 2016	20	13.1 ± 3.4	365	8/12 (67%)	1 (8%)	6 (50%)
Laleman W, *et al. Hepatology* 2013	37	13.2 ± 0.9	100 697 ± 157	22/37 (59%) 18/37 (49%)	Non-Significant	
Naeshiro N, *et al. Hepatol Res* 2014	14	CTP: 8 (6–10)	455	13/14 (93%)	4 (29%)	-
Leise MD, *et al.* CLOUT Abst # 465 (256A)	59	14 (10–16)	60 365	25/35 (71%) 21/27 (78%)	3 (5%) 9 (15%)	4 (7%) 13 (22%)

CLOUT: Consortium on Liver Disease OUTcomes Group; CTP: Child-Turcotte-Pugh; EV: Esophageal varices

Slide courtesy of Dr. Robert Rahimi

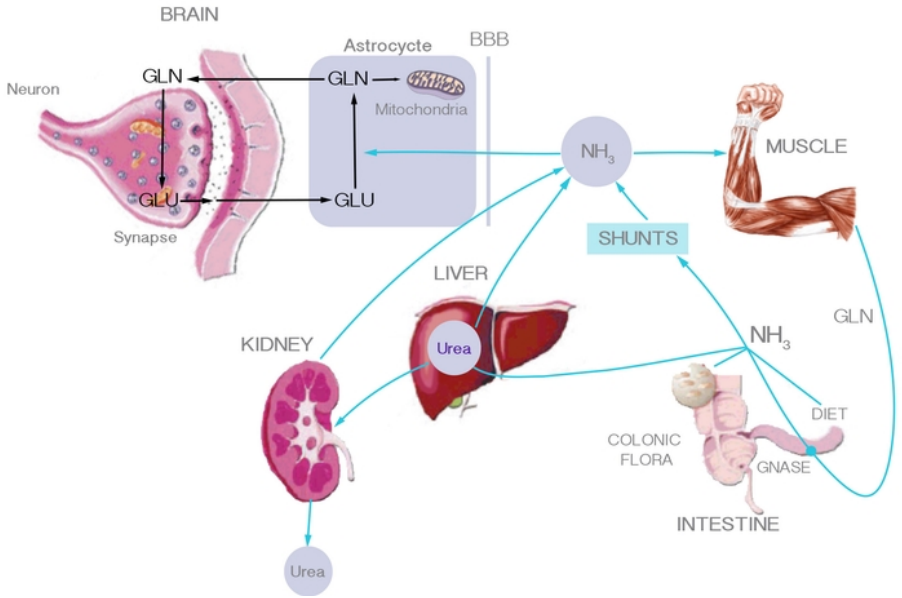
Conclusions & Questions

- Refractory HE can be improved with embolization of large portosystemic shunts
- Beware of downstream implications of worsening portal HTN: ascites, varices
- Pre-emptive surveillance and treatment of varices may improve overall outcomes

Sarcopenia and Opiate Use May Be Modifiable Risk Factors for Overt Hepatic Encephalopathy: A Prospective Study – Abstract 222

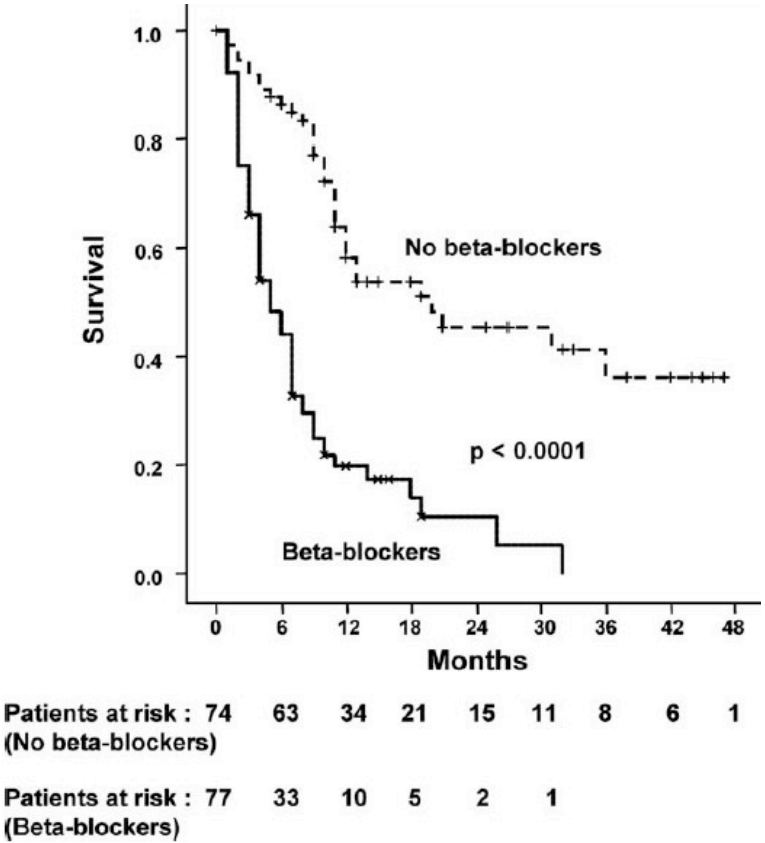
- Tapper E and Lok A.
- Background: Skeletal muscle may have an important role in ammonia disposal. Medications that alter the sensorium likely contribute to HE.
- Single center prospective 6-month assessment of predictors of altered cognition and falls in a cirrhotic population (n=136, Child A/B, without baseline HE, mean MELD 10)
- 12 patients developed overt HE (9%)
- Midarm muscle area (MAMA) predicted overt HE; OR 1.37 for every 10cm^2 of muscle mass (normal 23 – 85mm^2)
- Also noted risk with opiate use (OR 2.88) and Child B vs. A (OR 3.39)

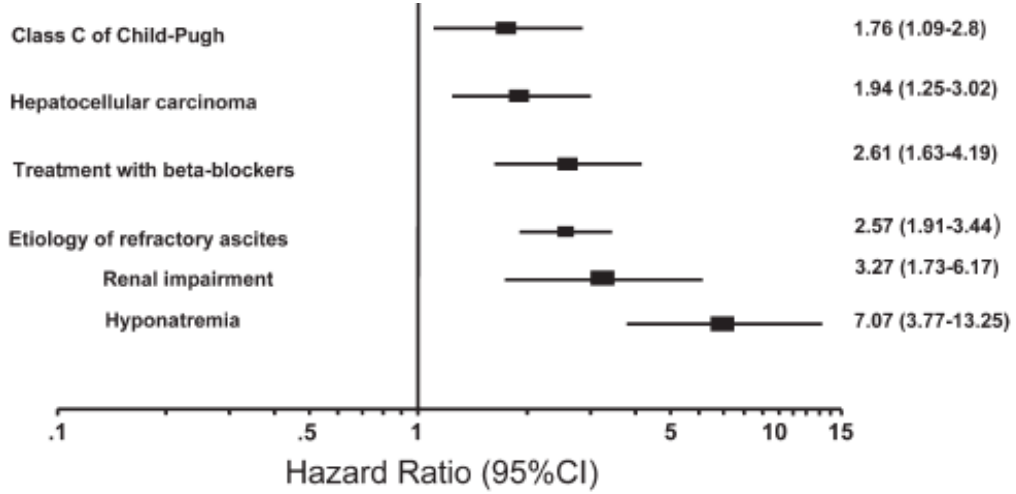
Inter-organ Ammonia Trafficking



Córdoba J, Minguez B. Hepatic encephalopathy. Semin Liver Dis. 2008;28:70–80

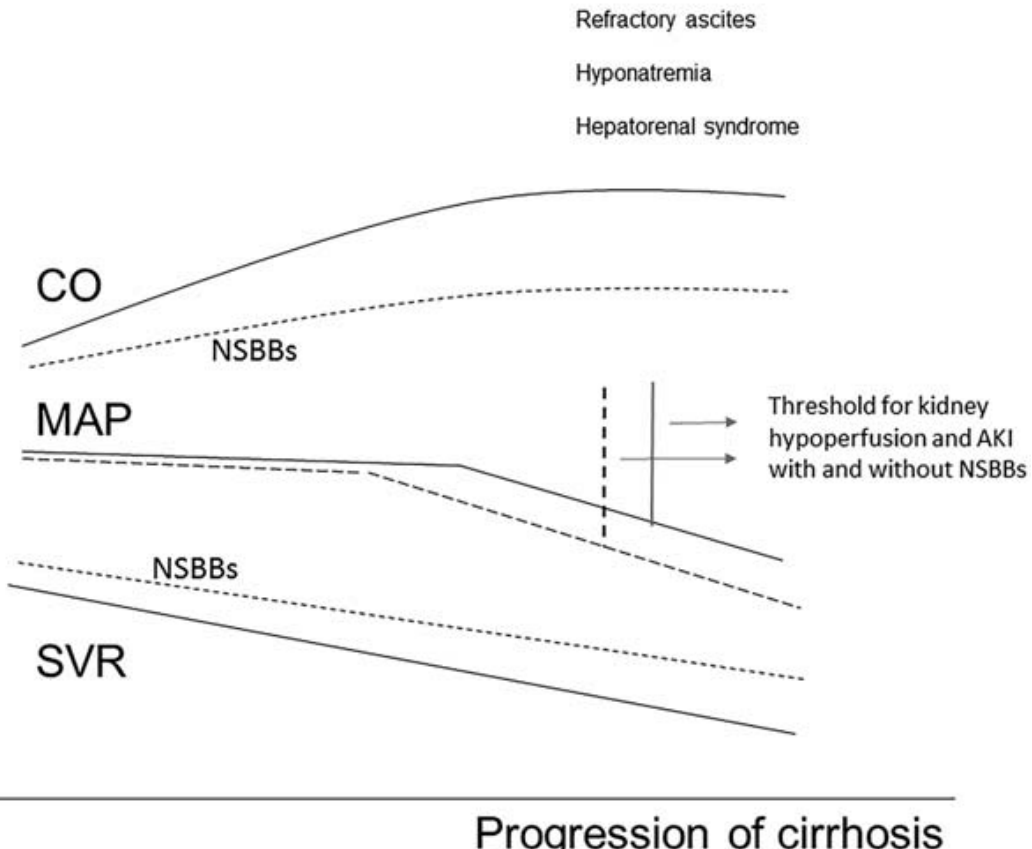
Beta Blockers in Refractory Ascites – Observational Study





Serste et al. Hepatology 2010

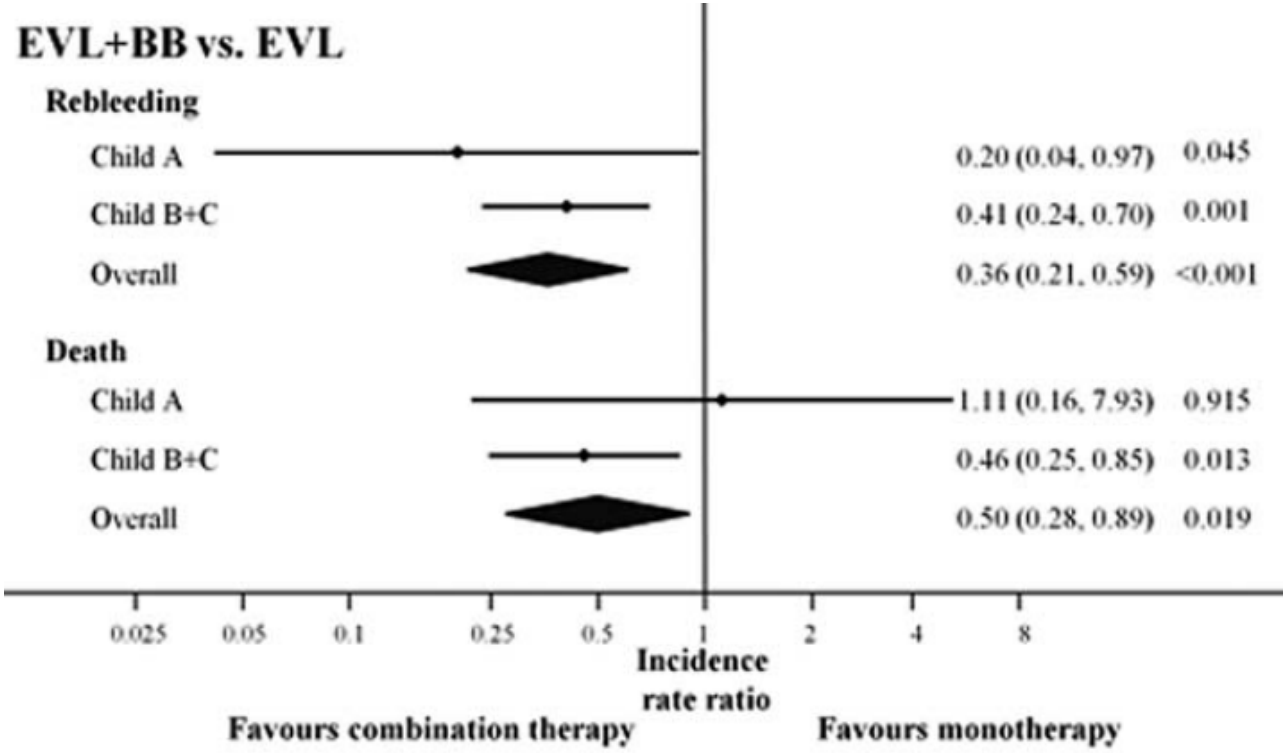
Beta Blockers: Role in Hyperdynamic Circulation of Portal Hypertension



- Progressive splanchnic vasodilation
- Decrease in SVR
- Compensatory increase in CO
- NSBB may shift threshold for AKI

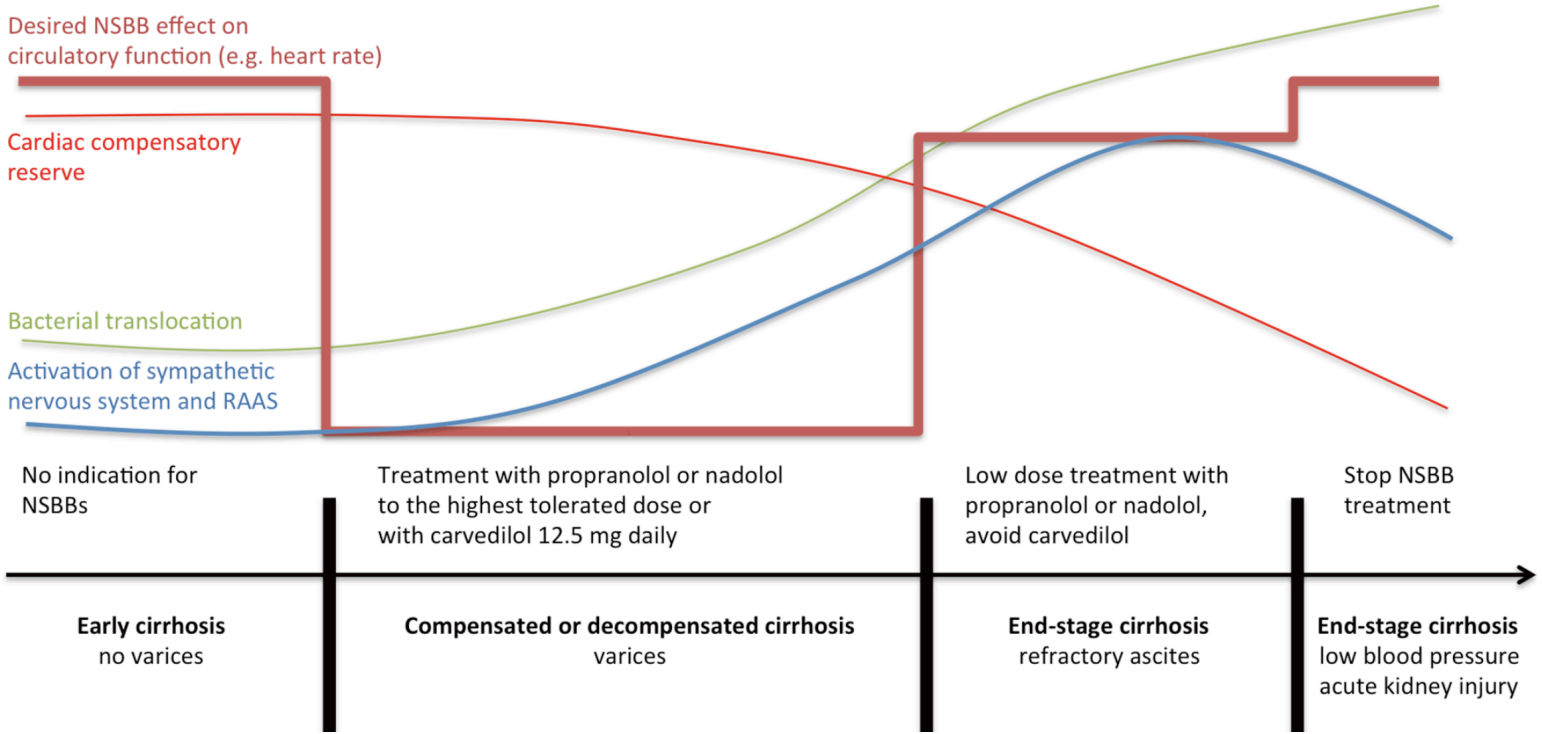
Moctezuma-Velazquez et al. Liv Transpl 2017

Beta blockers favorable for Secondary Prophylaxis



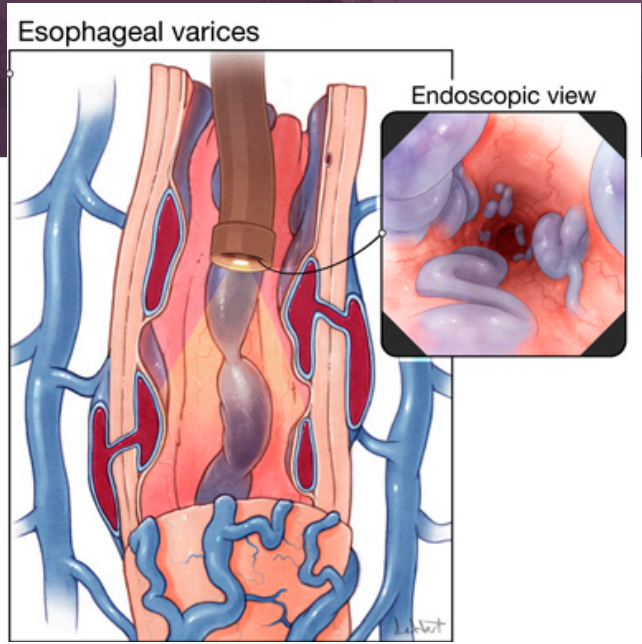
Albillos et al. Hepatology 2017

Natural History of Portal Hypertension



Engelman and Jalan AMJ 2017

AASLD Guidance



- NSBB require careful titration
  - Avoid SBP < 90 mmHg
- Reassess risks/benefits frequently
  - Refractory ascites
  - Hyponatremia
  - Hypotension
  - SBP
  - AKI
- Consider re-institution of NSBB after stabilization from acute event
- In the presence of ascites:
  - Propranolol max dose 160mg/d – worsening liver function – dose reduce
  - Nadolol max dose 80mg/d – worsening renal function – dose reduce
  - Carvedilol max dose 12.5mg/d (use with caution)

Garcia-Tsao et al. Hepatology 2016

Take Home

- Treat your decompensated patients with HCV
  - avoid protease inhibitor containing regimens
  - questions remain for Child C and those awaiting LT
- HVPG remains a valuable tool for prognosis in advanced chronic liver disease; non-invasive surrogates needed
  - AASLD: <20kPa (TE) and Plt > 150 = <5% risk of having varices needing treatment
- Refractory HE
  - consider portosystemic shunt embolization
  - higher risk with sarcopenia; does nutritional therapy help?
  - additional agents needed (ammonia scavengers in development)
- Non-selective Beta Blockers (NSBB) – Controversy continues
  - continually reassess appropriateness in your patients

Questions?