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Northern California Society for Clinical Gastroenterology

Updates in Portal Hypertension and Liver Failure

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Disclosures

- Consultant: Mallinckrodt, Dova, Shionogi, Vital Therapies, Salix, Evidera
- Research Funding: Mallinckrodt, Gilead, Sequana, Conatus
- Off – label use of medications

Outline

- Acute liver failure
- Portopulmonary Hypertension
- Aortic Stenosis Management in Cirrhosis
- Hepatic Encephalopathy
- Ascites
- Stem cell therapy
- Portal Vein Thrombosis

Case

- 28 yo female brought in by family after found in the bathroom with empty bottle of acetaminophen; recent breakup with BF
- 105/62, HR 88, RR 18, SpO2 94% on RA, afebrile. Lethargic but arousable, +asterixis, confused and disoriented, brisk reflexes
- AST 7532, ALT 6298, Tbili 2.3, INR 6.8, pH 7.25, Factor V 15%, Creat 2.2, APAP 110 mcg/ml approx. 18hr after estimated ingestion
- Head CT – normal
- Abd US – normal

Questions:

- What should you do first?
- What is her prognosis?
- Any other therapies available?

Acute liver failure – High-Volume Plasma Exchange, Abstract #288

- ALF – high mortality rate, limited therapeutic options
- Plasma exchange may remove cytokines, “toxins” allowing for reduced HE, reduced ICH, improved regeneration, improved survival
- Prior RCT (n=182), Larsen et al. (JHep 2016) demonstrated improved survival

High Volume Plasma Exchange for ALF

Maiwall R et al. Institute of Liver and Biliary Sciences, New Delhi, India

Primary Aim –

- Assess efficacy of HVPE compared to SMT in ALF

Secondary Aims –

- Improve SIRS, cytokines
- Improve hemodynamics
- Improve SOFA score
- Duration of mech vent, ICU

Methods – Patients with ALF (n=40) randomized 1:1 to:

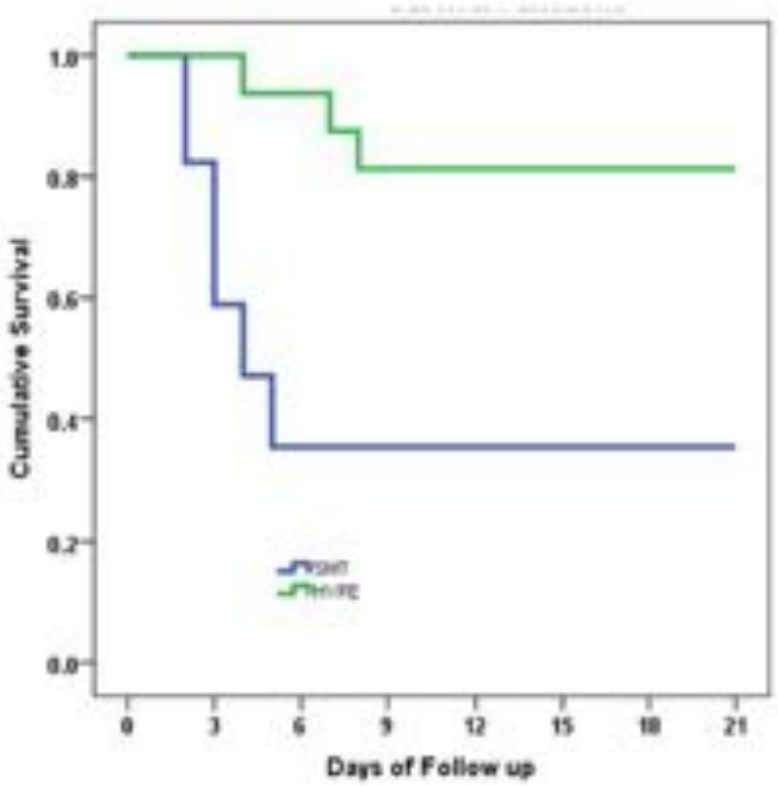
- HVPE (5% of IBW replaced with FFP) + SMT vs.
- SMT alone

High Volume Plasma Exchange for ALF

Maiwall R et al. Institute of Liver and Biliary Sciences, New Delhi, India

Results

- Mean # HVPE sessions = 2 (range 1-5)
- Treated patients noted reduced lactate, reduced SOFA sore, reduced MELD, increased systemic vascular resistance (SVR), decreased ammonia, favorable cytokine shifts (pro- vs anti-inflammatory)
- HVPE improved 21-day transplant-free survival (75% vs 38%, HR 0.15, 0.04-0.55)
- No major adverse effects of HVPE



HVPE for ALF

- The only extracorporeal treatment to show mortality benefit in ALF (Larsen et al 2016 and now Maiwell et al 2018)
- High resource utilization (liters of FFP/session)
- Clarify what “high volume” means (5% vs 15% of IBW)
- Need to clarify best candidates for treatment

Case #2

- 56 yo male with alcohol related cirrhosis, refractory ascites and severe LE edema presents to your clinic.
- Describes severe fatigue, forgetfulness, and very winded after walking up the hill to your clinic
- Exam – BP 92/50, HR 65, RR 16, SpO2 96%, Pronounced second heart sound on cardiac exam, lungs are clear, 3+ edema, large ascites, muscle wasting
- MELD 16
- Abd US – cirrhosis, no masses, patent and dilated PV, enlarged spleen
- Echo done as part of LT eval: LVEF 55%, RVSP 55, RA severely enlarged, RV dilated
- What do you do now?

PORTICO trial: efficacy and safety of macitentan in portopulmonary hypertension (POPH)

Krowka M et al. International study, Abstract #111

Background –

- POPH is a severe disease without clear clinical guidelines
- No RCT data as cirrhotic patients excluded from trials

Aim –

- Evaluate safety and efficacy of endothelin receptor antagonist macitentan in POPH

Methods

- 12 week RCT (1:1), double blind, macitentan 10mg QD vs placebo
- mPAP > 25mmHg, PVR > 320
- Exclude Child C or MELD $\geq$ 19
- Primary endpoint – reduction in PVR
- Secondary – Safety

PORTICO trial: efficacy and safety of macitentan in portopulmonary hypertension (POPH)

Krowka M et al. International study

Results

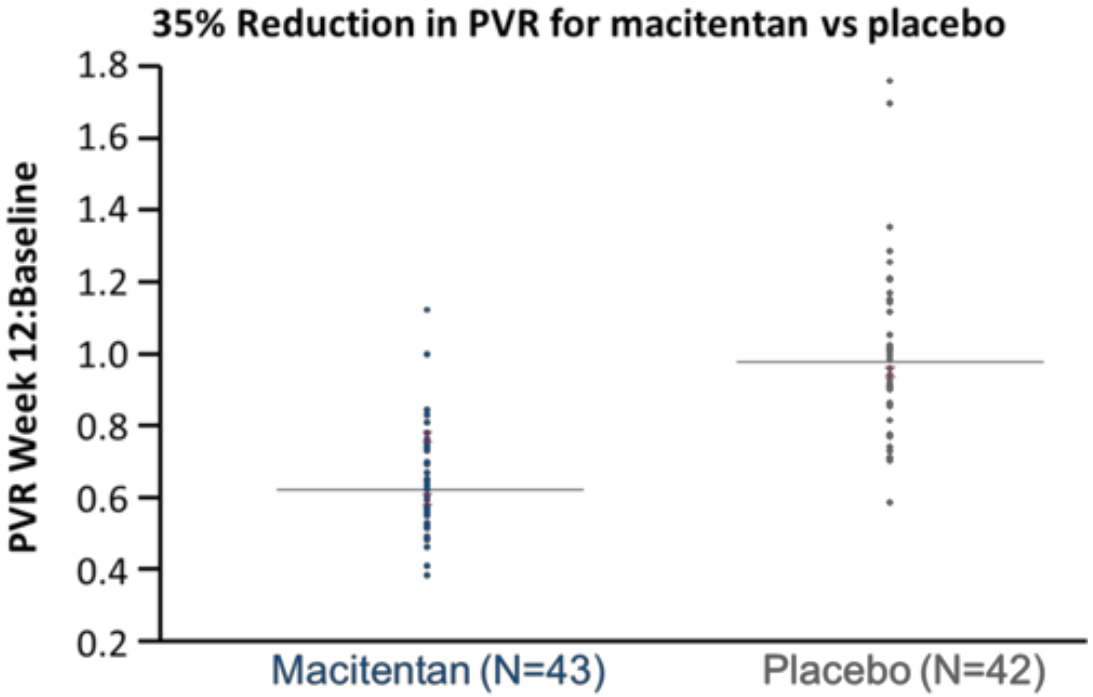
- 85 patients, mostly ALD and HCV
- 63.5% receiving background POPH treatment
- Macitentan reduced PVR by 35% compared with placebo
- No change in BP or HVPG
- Peripheral edema 26% vs 12%
- Mean decrease Hgb 1.8g/dL
- One pt w/ AST > 3xULN and Tbili > 2xULN
- “No hepatic safety concerns”

	Baseline		Week 12		Ratio of baseline, geometric mean (95% CL)		Treatment effect
Primary endpoint	Macitentan N=43	Placebo N=42	Macitentan N=43	Placebo N=42	Macitentan N=43	Placebo N=42	Ratio* (95% CL); *p* value
PVR, dyn·sec/cm^5	552±193	522±163	350±133	515±170	0.63 (0.58, 0.67)	0.98 (0.91, 1.05)	0.65 (0.59, 0.72); *p*<0.0001
	Baseline		Week 12		Change from baseline		Treatment effect
Other hemodynamic endpoints	Macitentan N=43	Placebo N=42	Macitentan N=43	Placebo N=42	Macitentan N=43	Placebo N=42	Difference* (95% CL); *p* value
mRAP, mmHg	7.3±3.7†	6.7±3.6	9.0±5.3‡	7.0±2.9	1.6±5.6‡	0.3±3.3	1.67 (-0.10, 3.44), *p*=0.0637
mPAP, mmHg	46.4±7.9	43.8±8.5	40.0±7.6	44.2±8.3	-6.4±4.9	0.4±7.0	-5.99 (-8.40, -3.57), *p*<0.0001
Cardiac Index, L/min/m^2	3.1±0.8	2.9±0.8	3.7±1.0	3.0±0.8	0.6±0.8	0.1±0.6	0.52 (0.22, 0.81), *p*=0.0009
HVPG, mmHg	10.5±3.5§	10.5±3.8**	10.0±2.8§	12.1±5.5**	-0.5±3.4‡	1.5±4.1**	-2.1 (-5.1, 0.9)††

Plus-minus values are mean±SD *ANCOVA model with factors for treatment, background PAH-specific therapy at baseline and region as factors in the model and variable at baseline as covariates. †n=42; ‡n=15; **n=11; ††Exploratory endpoint; HVPG data were reviewed centrally. CL, confidence limit; HVPG, hepatic venous pressure gradient; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; SD, standard deviation.

PORTICO trial: efficacy and safety of macitentan in portopulmonary hypertension (POPH)

Krowka M et al. International study



POPH Treatment

- Remains very difficult disease to treat
- Endothelin antagonists a mainstay in non-cirrhotics
- Target mPAP < 35mm Hg for LT
- Encouraging data to incorporate use of macitentan for POPH
- Caution with edema, anemia, and possible hepatotoxicity
- Balance the risks of not effectively treating POPH

Case #3

- 69 yo male with NASH cirrhosis found to have severe aortic stenosis during LT eval
- MELD 12
- What do you do now?

Comparison Outcomes Surgical vs Transcatheter Aortic Valve Replacement in Cirrhosis

Peeraphatdit T et al. Mayo Clinic Rochester, Abstract #219

- Aortic stenosis increasingly common in aging population
  - 5-7% of those > 65 have moderate-to-severe AS
  - 2-4% of patients with severe AS have cirrhosis
- Frequent topic of discussion at liver transplant selection conference
- Newer less invasive method of transcatheter valve replacement (TAVR) is appealing – FDA approved 2011
- Aim – Compare outcomes between TAVR vs Surgical AVR (SAVR) in cirrhotic patients with Aortic Stenosis

VALVULAR AND STRUCTURAL HEART DISEASES

WILEY

Editor's Choice

Outcomes and readmissions after transcatheter and surgical aortic valve replacement in patients with cirrhosis: A propensity matched analysis

Abhijeet Dhoble, MD, MPH[1,2] | Viraj Bhise, MBBS, MPH[1,3] | Moises I. Nevah, MD[2,4] | Prakash Balan, MD[1,2] | Tom C. Nguyen, MD[2,5] | Anthony L. Estrera, MD[2,5] | Richard W. Smalling, MD, PhD[1,2]

Review of National Inpatient Database – Short term outcomes

TABLE 2 Outcomes of transcatheter and surgical valve replacement procedures in cirrhosis patients

	TF TAVR (n = 113)	TA TAVR (n = 13)	SAVR (n = 157)	Difference
In-hospital mortality	6 (5.31%)	3 (23.08%)*	7 (4.46)%	0.020
Post-procedure length of stay	6.41 days*	8.31 days	10.83 days	<0.001
Discharge to home	73.45%	69.23%	66.88%	0.511
In-hospital complications				
Permanent pacemaker (PPM) implantation	7.08%	0.00%	6.37%	0.921
Time to PPM (Median)	3.5 days	NA	13 days	0.123
Blood transfusion	27.43%	23.08%	40.76%	0.05
Time to blood transfusion (Median)	1 day	2 days	1 day	0.827
Cost of hospitalization	$57,099.7	$64,260.12	$63,524.75	0.379

*Indicates a significant difference when compared to the SAVR (reference) group in individual sub-group analyses.

Characteristics and demographics	Post-propensity match		
	TAVR (n = 55)	SAVR (n = 55)	P-value
Age (years)	67.2	67.0	0.893
Female Sex	34.5%	34.5%	1.000
Charlson comorbidity index	3.9	3.9	1.000
Diabetes mellitus	58.2%	54.5%	0.704
Coronary artery disease	61.8%	43.6%	0.057
Congestive heart failure	56.4%	54.5%	0.850
Peripheral artery disease	21.8%	10.9%	0.124
Type of hospital (teaching)	98.2%	98.2%	1.000
In-hospital mortality	6.3%	3.6%	0.406
In-hospital complications			
Blood transfusion	21.8%	58.2%	<0.001
PPM placement	3.6%	7.3%	0.406
Post-procedure length of stay	6.3 days	10.2 days	0.002
Total hospital costs	$59,752	$55,604	0.462
Discharge disposition to home	76.4%	70.9%	0.521

Dhoble et al. Catheter Cardiovasc Interv 2018

Comparison Outcomes Surgical vs Transcatheter Aortic Valve Replacement in Cirrhosis

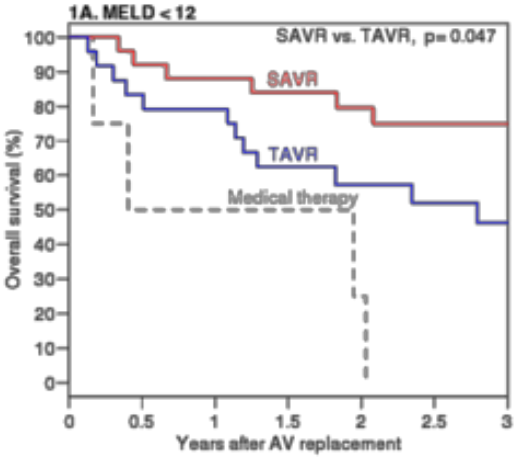
Peeraphatdit T et al. Mayo Clinic Rochester

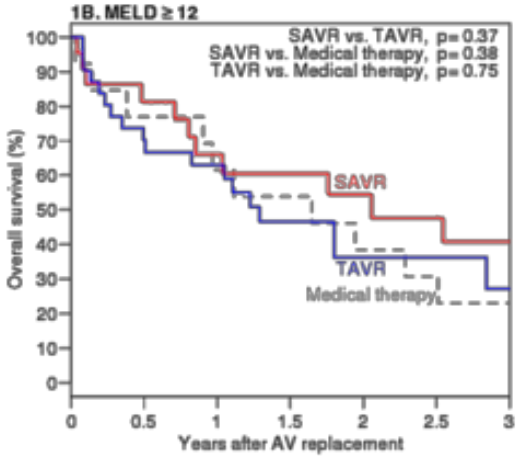
Methods –

- Retrospective review of TAVR (n=55), SAVR (n=50), and medical mngmt (n=17) from 2008-2016
- Covariates: age, gender, year of surgery, MELD, surgical risk score

Results –

- 105 consecutive cirrhotic pts, mean 72y, 68% male, MELD 12 (9-14)
- Short-term: similar mortality at 30d (3.6% v 4.2%); shorter stay (5 vs 6 days, p<0.001), fewer transfusions w/ TAVR
- Median f/u 3.8y: 63 deaths (60%)
- Long-term: higher mortality with TAVR on MELD<12 group





Comparison Outcomes Surgical vs Transcatheter Aortic Valve Replacement in Cirrhosis

Peeraphatdit T et al. Mayo Clinic Rochester

Conclusions:

- Short-term outcomes similar with TAVR vs SAVR although shorter LOS and fewer transfusions with TAVR
- In patients with MELD < 12, TAVR may result in worse long-term outcomes
- In patients with MELD $\geq$ 12, interventions similar to medical management
- TAVR may be best used as a bridge to liver transplant

Limitations:

- Unclear causes of death in long-term. Are these CVD or liver related?
- Does this reflect a learning curve related to TAVR?
- What about our patients with MELD > 14? (excluded from this series)

Periodontal Disease Implications in Cirrhosis

- Systemic inflammation and endotoxemia may propagate progression of cirrhosis and contribute to pathophysiology of portal hypertension and hepatic encephalopathy
- GI tract is commonly attributed as the source but the oral cavity may also be important

Periodontal Therapy Improves Cognitive Function in Cirrhosis

Bajaj J et al. VCU, Abstract 2019

Aim –

- Define the effect of routine periodontal therapy in cirrhosis on endotoxemia, cognition, QOL, and hospitalizations

Methods –

- Age-matched cirrhotic and non-cirrhotic patients with mild/moderate periodontitis
- Pts underwent root planning & scaling and f/u at 30 and 90 days
- Saliva and stool for baseline and f/u microbial composition, MELD, endotoxin, cytokines
- Psychometric testing (PHES, Stroop App) and QOL at baseline and 30 days
- 90 day hospitalizations

Periodontal Therapy Improves Cognitive Function in Cirrhosis

Bajaj J et al. VCU

Results –

- 26 cirrhotics (56yrs, 10 HE, MELD 10) and 20 controls included
- Separate age-matched control group of 24 cirrhotics followed for 30 days without therapy
- Significant improvement in cognition (PHES and Stroop) and QOL in treated cirrhotics and no change in controls
- Significant reduction in endotoxin, IL-1b, IL-6 in treated cirrhotics
- Changes in salivary and stool microbiota in treated cirrhotics noted

Conclusions –

- Endotoxemia and systemic inflammation can be reduced after periodontal therapy likely due to improvement in oral microbiota.
- The oral cavity should be considered a viable target for inflammation reduction in cirrhosis

Take Home –

- Send your cirrhotic patients to see their dentists!

Bajaj J et al. AJP GI and Liver, 2018

Management of Refractory Ascites

- A difficult clinical problem
- Serial large volume paracentesis vs. TIPS or LT
- Alfapump approved in Europe
- Indwelling Pleurex catheters for palliative care

Long-Term Follow-up of Ascites Treated with Alfapump

Wong F et al. Multicenter North America

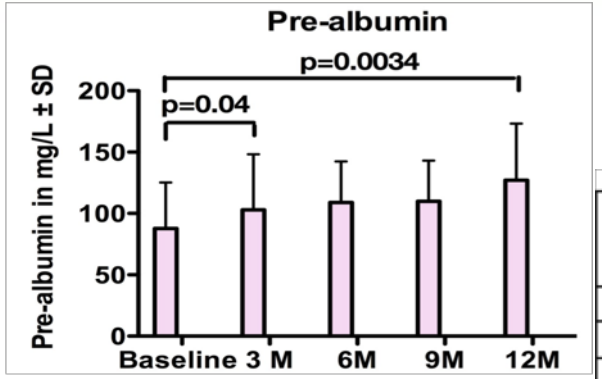
Aim – Assess the NA experience with alfapump as part of a multicenter prospective study for treatment of refractory ascites not amenable to TIPS or LT

Methods – Prospective f/u of 30 patients for ascites control, adverse events, QOL, and mortality over 12 months

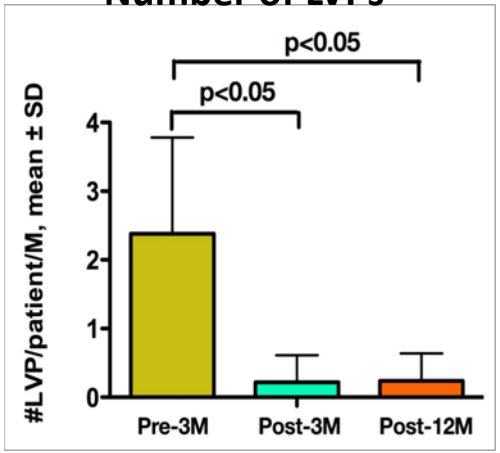
Long-Term Follow-up of Ascites Treated with Alfapump

Wong F et al. Multicenter North America

Results



Number of LVPs



	3 months		12 months	
	# of events	# of patients n/30 (%)	# of events	# of patients
Total	12	10/30 (33.3%)	27	13/30 (43.3%)
Postoperative bleeding	1	1/30 (3.3%)	1	1/30 (3.3%)
Leakage of fluid into pump pocket	2	2/30 (6.7%)	2	2/30 (6.7%)
Wound dehiscence	1	1/30 (3.3%)	1	1/30 (3.3%)
Pump malfunction	2	2/30 (6.7%)	4	3/30 (10%)
Bladder catheter malfunction	1	1/30 (3.3%)	3	3/30 (10%)
Peritoneal catheter dislodgement	0	0	1	1/30 (3.3%)
Hematuria	1	1/30 (3.3%)	1	1/30 (3.3%)
Infection	3	3/30 (10.0%)	9	8/30 (26.7%)
Hyponatremia	1	1/30 (3.3%)	2	1/30 (3.3%)
Acute kidney injury	0	0	2	2/30 (6.7%)
Skin erosion over pump	0	0	1	1/30 (3.3%)

Long-Term Follow-up of Ascites Treated with Alfapump

Wong F et al. Multicenter North America

Conclusions –

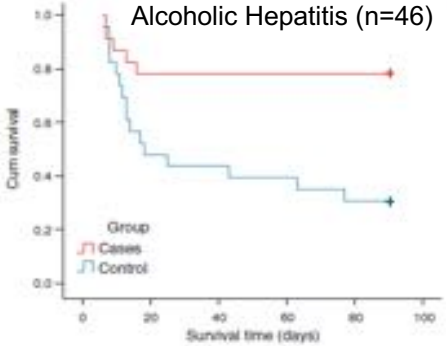
- Alfapump is effective in removing ascites and reduces LVP requirement significantly
- Patients had improved nutritional status and quality of life
- Pump and catheter dysfunction - Company working on improved pump and catheter designs
- Renal dysfunction, electrolyte abnormalities, and infections remain concerns, but can be improved by eliminating diuretic use and adding albumin infusions
- Alfapump may be a definitive treatment for recurrent ascites, especially in patients who are not TIPS candidates

Efficacy of Hematopoietic Stem Cell Therapy in Decompensated Cirrhosis: Open Label RCT

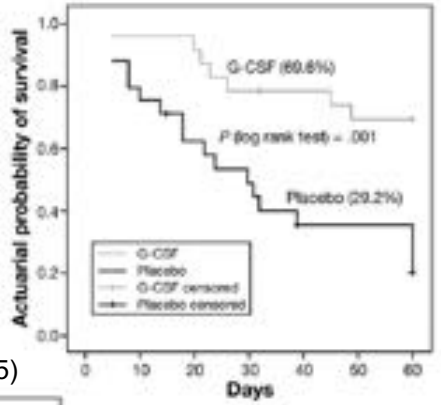
Singh V et al, Chandigarh, India. Abstract #110

Evolving data suggesting improvements in decompensated liver disease with GCSF…

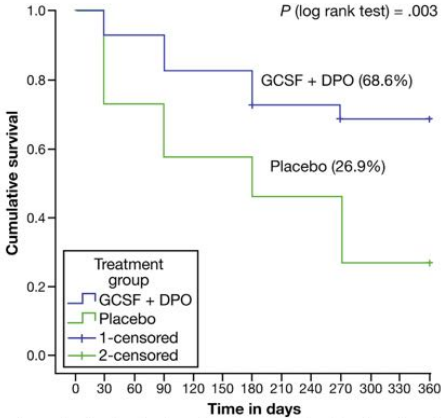
Alcoholic Hepatitis (n=46)



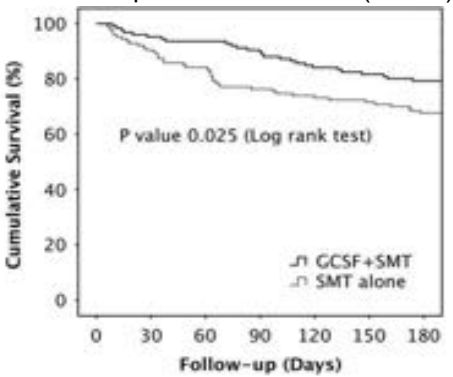
ACLF (n = 47)



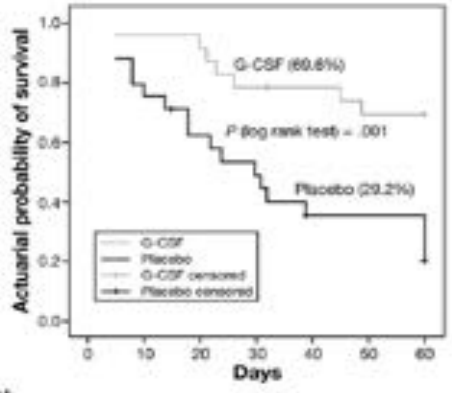
Decompensated Cirrhosis (n = 55)



Decompensated Cirrhosis (n=253)



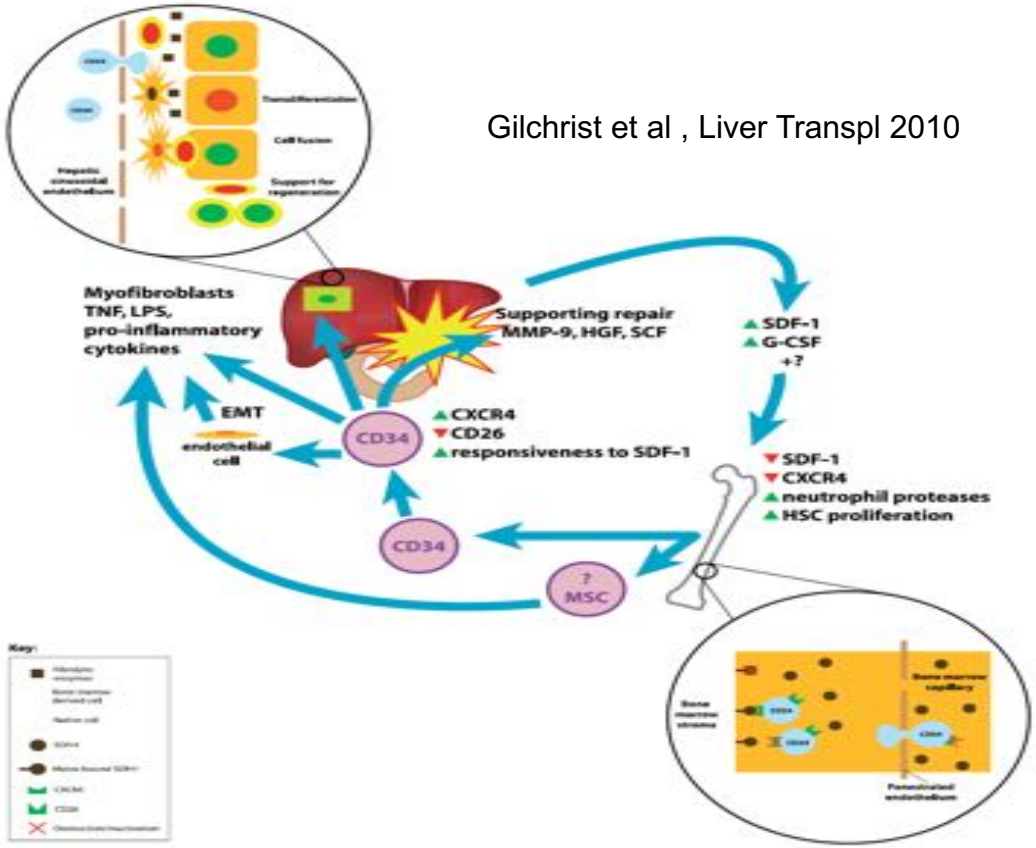
Decompensated Cirrhosis (n = 65)



Garg V et al. CGH 2012;
Singh V et al. AJG 2014;
Kedarisetty et al. Gastroenterology 2015
Prajapati R et al. EurJGastro 2017
Verma N et al. Hepatology 2018

Proposed MOA of G-CSF in Liver Disease

- Production of more neutrophils
- Restoration of neutrophil function
- Recruitment of CD34+ stem cells to liver tissue
- Increase in hepatocyte growth factor
- Proliferation of hepatic progenitor cells
- Facilitation of tissue repair



Gilchrist et al , Liver Transpl 2010

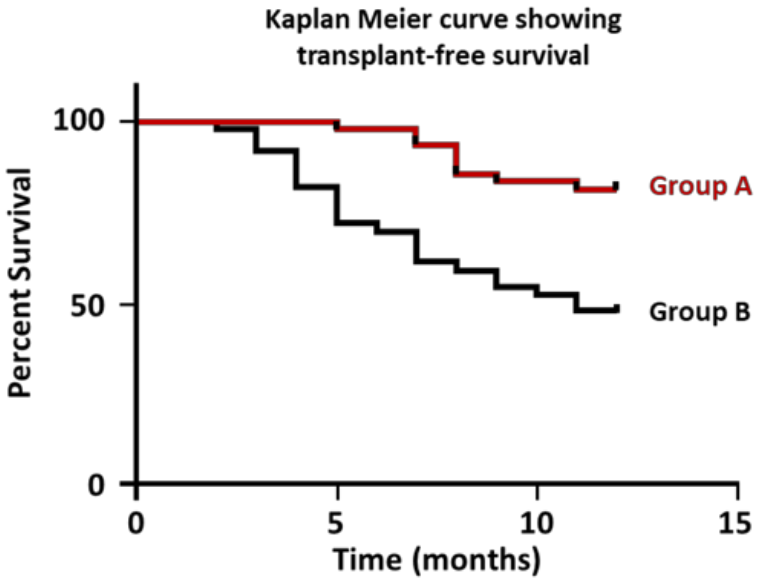
Efficacy of Hematopoietic Stem Cell Therapy in Decompensated Cirrhosis: Open Label RCT

Singh V et al, Chandigarh, India. Abstract #110

Aim – Study safety and efficacy of GCSF for 1 year transplant-free survival (TFS) in patients with decompensated cirrhosis

Methods – 100 patients openly randomized to either four cycles of 5d GCSF (5mcg/kg Q12h) q3M + SMT (n=50) vs SMT alone (n=50)

Conclusions – Multiple cycles of GCSF improved 1-year TFS, mobilized CD34+ cells, improved liver stiffness, imporved MELD and CTP, improved QOL, and reduced liver related complications



Transplant-Free Survival - 12 Months		
Group A	Group B	*P*-value
74%	42%	<0.001

Portal Vein Thrombosis

- A common complication in cirrhosis
- Potentially devastating consequences
- Difficult management with unclear guidelines
  - Watch and wait vs. anticoagulation vs. TIPS
  - AASLD 2009 – Insufficient data for AC
  - EASL 2015 – Consider AC for at least 6 months; In LT candidates with progressive PVT not responding to AC, consider TIPS

Anticoagulation and TIPS for PVT: Meta-Analysis

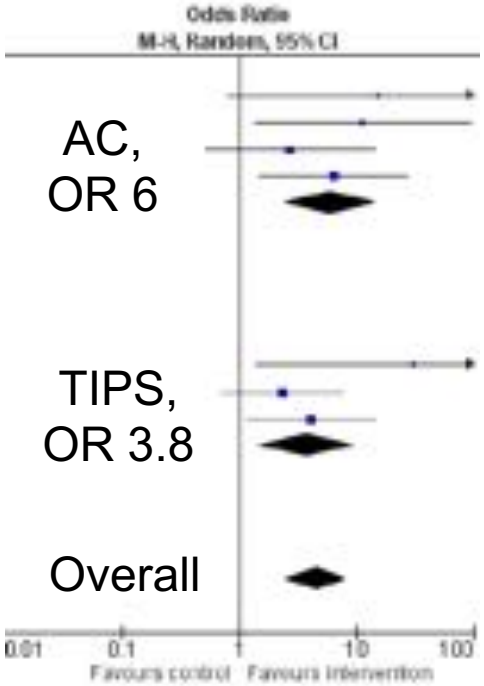
Davis J et al. UVA. Abstract #815

Aim – Compare recanalization rates and mortality benefit of AC or TIPS for chronic PVT in cirrhosis

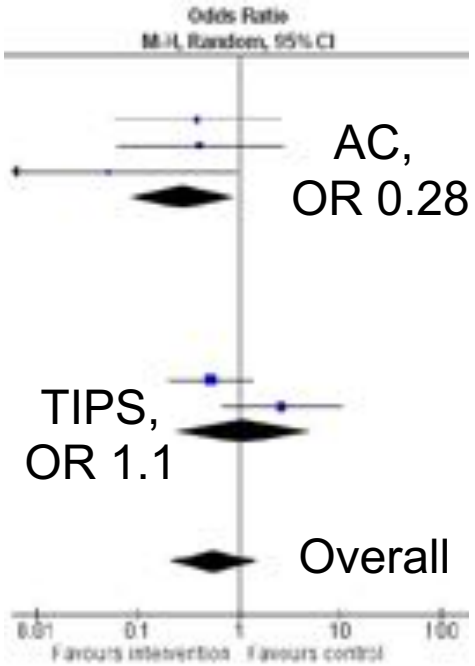
Methods – Included studies evaluating adult cirrhotic patients with PVT treated with AC or TIPS vs untreated controls; excluded malignant PVT or application of both AC+TIPS

Conclusions – Treatment of PVT increases recanalization and may improve survival; AC appears more favorable

Impact on Recanalization



Impact on Mortality



Take Home

- Consider HVPE for patients with ALF
- Consider screening for POPH in your cirrhotic patients and consider macitentan for therapy
- TAVR may be a bridge to LT for cirrhotic patients with AS but SAVR appears to have favorable long-term outcomes with MELD < 12
- Look in your cirrhotic patients mouths and encourage dental care
- Look for potential new therapies for refractory ascites in near future
- A U.S. multicenter trial of G-CSF in decompensated liver disease is needed
- Strongly consider anticoagulation or TIPS for your patients with PVT

Thank You!