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Reversal of Hepatorenal Syndrome Type 1 (HRS-1) with Terlipressin plus Albumin versus Placebo plus Albumin - Not All Responses Are Created Equal - An Analysis of the REVERSE and OT-0401 Trials

Arun J. Sanyal[1], Thomas D. Boyer[2], R Todd Frederick[3], Fredric Regenstein[4], Lorenzo Rossaro[5], Victor Araya[6], Hugo E. Vargas[7], K. Rajender Reddy[8], Khurram Jamil[9], Stephen Chris Pappas[10]; [1]Virginia Commonwealth University, Richmond, VA; [2]University of Arizona, Tucson, AZ; [3]California Pacific Medical Center, San Francisco, CA; [4]St. Luke's Hospital, Kansas City, MO; [5]University of California, Davis Medical Center, Sacramento, CA; [6]Albert Einstein Medical Center, Philadelphia, PA; [7]Mayo Clinic, Scottsdale, AZ; [8]University of Pennsylvania, Philadelphia, PA; [9]Ikaria, Hampton, NJ; [10]Orphan Therapeutics, Lebanon, NJ

Background and Aims: Renal function affects outcomes in patients with HRS-1. Terlipressin plus albumin has been shown to improve renal function in HRS-1 to a greater degree than placebo plus albumin. However, it is unclear whether outcomes following reversal of HRS-1 are the same when reversal is achieved by terlipressin plus albumin vs. albumin alone. The aim of this study was to review data from two pivotal, Phase 3 trials in HRS-1 and evaluate outcomes of those patients who achieved reversal of HRS-1. **Methods**: Serum creatinine (SCr), renal replacement therapy (RRT), and survival data from the REVERSE and OT-0401 trials, both randomized, placebo-controlled trials of terlipressin and albumin versus placebo plus albumin with similar designs and patients enrolled, were pooled to analyze: incidence of confirmed HRS reversal (CHRSR), use of RRT, overall survival, and survival at Day 90 without RRT. CHRSR was defined as 2 SCr values ≤1.5 mg/dL, at least 48 hours apart, on treatment, without RRT or liver transplant. **Results**: Data from 308 patients were analyzed; 153 were randomized to terlipressin, 155 to placebo. Baseline characteristics were similar across the two studies and between treatment groups. CHRSR was achieved in 37/153 patients (24.2%) in the terlipressin group vs. 20/155 patients (12.9%) in the placebo group ($p = 0.0108$). Survival was significantly higher in patients with CHRSR vs. those without CHRSR ($p<0.0001$). Patients with CHRSR received RRT significantly less often compared to patients without CHRSR (4/57 (7%) vs. 109/251 (43%), $p<0.0001$). While Day 90 survival in patients with CHRSR was similar, 27/37 (73%) in the terlipressin group who achieved CHRSR were alive without RRT at Day 90 vs. 9/20 (45%) in the placebo group ($p<0.05$). No patient with CHRSR in the terlipressin group received RRT; 4/16 (25%) of patients with CHRSR in the placebo group received RRT. **Summary**: Pooled data from two large trials show that terlipressin plus albumin treatment was associated with an increased frequency of CHRSR compared to placebo and albumin. Survival in patients with CHRSR was significantly higher, and use of RRT significantly lower, than in patients without CHRSR. There were significantly more patients in the terlipressin group with CHRSR alive at Day 90 without RRT compared to placebo. **Conclusion**: Reversal of HRS-1 occurs following treatment with terlipressin plus albumin more frequently than with placebo plus albumin. Achieving CHRSR reduces the need for RRT and improves survival. Furthermore, patients treated with terlipressin and albumin who achieve CHRSR have a better outcome at Day 90 compared to patients achieving CHRSR with albumin alone.

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Khurram Jamil - Employment: IKARIA; Stock Shareholder: IKARIA

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New Multivariate Models to Predict Glomerular Filtration Rate in Patients with Cirrhosis

Ayse L. Mindikoglu[1], Thomas C. Dowling[4], Laurence S. Magder[3], Robert H. Christenson[5], Matthew R. Weir[2], Stephen L. Seliger[2], William R. Hutson[1], Charles Howell[6]; [1]Department of Medicine, Division of Gastroenterology and Hepatology, University of Maryland School of Medicine, Baltimore, MD; [2]Department of Medicine, Division of Nephrology, University of Maryland School of Medicine, Baltimore, MD; [3]Department of Epidemiology and Public Health, Division of Biostatistics and Bioinformatics, University of Maryland School of Medicine, Baltimore, MD; [4]University of Maryland School of Pharmacy, Baltimore, MD; [5]Department of Pathology, University of Maryland School of Medicine, Baltimore, MD; [6]Department of Medicine, Howard University College of Medicine, Washington, DC

Background: It is well established that conventional glomerular filtration rate (GFR) equations underestimate the extent of kidney dysfunction in patients with cirrhosis. The objective of our study was to assess the performance of novel GFR-estimating equations in subjects with cirrhosis. Methods: Between 2010 and 2014, we measured GFR in 91 subjects with cirrhosis by iothalamate plasma clearance simultaneously with serum Cr, cystatin C, beta-trace protein, and beta-2 microglobulin. Multivariate linear regression analysis was performed to develop GFR-estimating models. Performance of the novel prediction models, CrCl, estimated CrCl (eCrCl), and conventional GFR-estimating equations was quantified as the percentage of GFR estimates that differed by greater than 30% ($1\text{-}P_{30}$) or 20% of measured GFR (mGFR) ($1\text{-}P_{20}$) or the root mean square error (RMSE). Results: Among 91 subjects with cirrhosis, female gender was an independent predictor of serum Cr (β=-0.19, P=0.0003) controlling for age and mGFR, but gender did not predict cystatin C (β=-0.04, P=0.553), beta-trace protein (β=-0.10, P=0.173) and beta-2 microglobulin (β=-0.30, P=0.344) levels. Models that included Cr, cystatin C, age and gender (Model 1) and Cr, cystatin C, beta-2 microglobulin, age and gender (Model 2) resulted in the best fit to predict mGFR. Among 59 subjects with cirrhosis and ascites, the accuracy of Models 1 and 2 was significantly superior to conventional GFR-estimating equations (Table 1). Conclusions: Alternative renal function biomarkers, cystatin C, beta-2 microglobulin and beta-trace protein were not dependent on gender in patients with cirrhosis; whereas gender influenced serum Cr indepen-

dent of mGFR. Models developed from subjects with cirrhosis that included serum Cr, cystatin C and beta-2 microglobulin were more accurate predictors of mGFR than CrCl, eCrCl and conventional GFR equations among patients with ascites.

Performance of Altered Renal Hemodynamics in Cirrhosis (ARHC) Research Program Equations in Comparison to Cr Clearance (CrCl), Cockcroft-Gault (GC) and GFR-Estimating Equations Among Subjects with Cirrhosis and Ascites

	CrCl, CG and Cr-Based GFR-Estimating Equations					Cystatin C-Based GFR-Estimating Equations			Combined Cr-Cystatin C-Based GFR-Estimating Equations		ARHC GFR-Estimating Equations Developed from Subjects with Cirrhosis	
	ml/min/1.73m^2											
	CrCl	GC[3]	4-Variable MDRD[2]	6-Variable MDRD[2]	CKD-EPI Cr (2009)[6]	LARSSON[4]	HOEK[5]	CKD-EPI Cystatin C (2012)[6]	STEVENS[7]	CKD-EPI Creatinine-Cystatin C (2012)[6]	Model 1*	Model 2*
Accuracy (1-P_{30})[§]	18.00	30.00	25.00	19.00	24.00	18.00	15.00	17.00	18.00	15.00	12.00	11.00
P Value[†]	0.144	<0.0001	0.001	0.022	0.001	0.189	0.388	0.180	0.039	0.219		
Accuracy (1-P_{15})[§]	25.00	39.00	33.00	27.00	34.00	31.00	22.00	29.00	28.00	28.00	22.00	21.00
P Value[†]	0.572	0.001	0.012	0.146	0.004	0.076	1.000	0.096	0.065	0.065		
Accuracy (RMSE)[§]	28.67	32.52	28.93	24.43	24.81	27.13	24.00	23.51	22.45	20.72	17.62	17.38
P Value[†]	0.010	0.0001	0.003	0.023	0.002	0.011	0.053	0.004	0.013	0.002		

*Model 1=$e^{(5.52295+((-0.70075)*(\log Cr))+((-0.3174\&)*(\log \text{cystatin C}))+((-0.31042)*(\log age))+((-0.14802)*(\text{gender})))}$

*Model 2=$e^{(5.65375+((-0.67375)*(\log Cr))+((-0.25106)*(\log \text{cystatin C}))+((-0.09800)*(\log \text{beta-2 microglobulin}))+((-0.30776)*(\log age))+((-0.14565)*(\text{gender})))}$

Gender=1 if female; Gender=0 if male

§Lower values for accuracy indicate higher accuracy

†P values compare the performance of Model 2 to CrCl, CG and GFR-estimating equations

RMSE=root mean square error; MDRD=Modification of Diet in Renal Disease; CKD-EPI=Chronic Kidney Disease Epidemiology

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No evidence of reduced mortality due to albumin substitution in HCC-free cirrhotic patients undergoing large volume paracentesis: a systematic review and meta-analysis

Fabian Kütting[1], Jens Schubert[1], Jeremy Franklin[2], Agnes Pelc[1], Andrea Bowe[1], Vera Hoffmann[1], Münevver Demir[1], Dirk Nierhoff[1], Ulrich Toex[1], Hans-Michael Steffen[1]; [1]Department of Gastroenterology and Hepatology, University Hospital of Cologne, Cologne, Germany; [2]Institute of Medical Statistics, Informatics and Epidemiology, University of Cologne, Cologne, Germany

Objectives: Cirrhosis of the liver is a disease that occurs worldwide. Current guidelines for clinical practice recommend the infusion of human albumin after large volume paracentesis. After inspecting the actual evidence behind this recommendation, we decided to conduct a systematic review and meta-analysis to address whether or not, albumin infusion has an effect on mortality and morbidity in the context of large volume paracentesis. Methods: We performed a comprehensive search of large databases and abstract books of conference proceedings up to Dec. 31st 2013. We were finally able to include 21 randomized controlled trials, testing the infusion of human albumin against alternatives (vs. no treatment, vs. plasma expanders; vs. vasoconstrictors) in HCC-free patients suffering from cirrhosis, totaling 1108 patients. We then analyzed them with regard to mortality, changes in plasma renin activity (PRA), hyponatremia, renal impairment, recurrence of ascites with consequential re-admission into hospital and "additional complications" (bleeding from esophageal varices, infections, sepsis and multiple-organ dysfunction-syndrome). Additionally, we employed trial sequential analysis in order to calculate the number of patients required in controlled trials in order to be able to determine a statistically significant advantage of the administration of one agent over another with regard to mortality. Results: While the administration of albumin effectively prevents a rise in PRA as well as hyponatremia, strong clinical endpoints, especially mortality are not significantly improved. Trial sequential analysis showed that at least 1337 additional patients need to be recruited into RCTs and analyzed with regard to this question in order to detect or disprove a 25% mortality effect. Conclusions: There is no evidence that the infusion of albumin after large-volume paracentesis significantly lowers mortality in HCC-free patients with advanced liver disease.

Number of trials that registered events for each endpoint out of the 22 total trials included, patients with HCC included in analysis as indicated

Primary endpoint	trials (n) (without HCC)	P - value (without HCC)	Odds ratio (CI) (without HCC)	trials (n) (with HCC)	P - value (with HCC)	Odds ratio (CI) (with HCC)
Mortality	14	0.14	0.77 [0.54, 1.09]	15	0.06	0.73 [0.53, 1.01]
Secondary endpoints	**trials (n)**	**P-value**	**Odds ratio (CI)**	**trials (n)**	**P-value**	**Odds ratio (CI)**
PRA > 50%	10	0.002	0.50 [0.32, 0.78]	10	0.002	0.50 [0.32, 0.78]
Hyponatremia	15	0.008	0.59 [0.40, 0.87]	16	0.008	0.60 [0.41, 0.88]
Creatinine increase	12	0.24	0.75 [0.46, 1.22]	13	0.25	0.75 [0.46, 1.22]
Additional complications	15	0.09	0.74 [0.52, 1.05]	16	0.19	0.80 [0.57, 1.12]
Recurring ascites	11	0.45	0.88 [0.64, 1.22]	12	0.63	0.93 [0.68, 1.27]

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Serum creatinine within 48 hours after hospitalization is a strong predictor of mortality in patients with cirrhosis with complications provided the peak creatinine is above 1.2 mg/dl

Anantha Nuthalapati[3], Nicholas Schluterman[2], Deborah Greenberg[2], Anuj Khanna[3], Paul J. Thuluvath[1]; [1]Medicine, Mercy Medical Center & University of Maryland School of Mediicine, Baltimore, MD; [2]Epidemiology & Public Health, University of Maryland School of Medicine, Baltimore, MD; [3]Medicine, Mercy Medical Center, Baltimore, MD

Recently, it has been suggested that acute kidney injury (AKI) is an independent predictor of mortality in patients with cirrhosis. In this study, we examined the impact of AKI in 636 consecutive admissions in 339 patients who were admitted to the hospital (Jan 2009-Dec 2013) for a complication(s) of cirrhosis (patients admitted for elective procedures or surgery excluded). Methods: The data from Jan 2013 to Dec 2013 were prospectively entered and the rest were entered retrospectively using electronic medical records. Serum creatinine levels were recorded at baseline, defined as the average of all creatinine measurements within 90 days prior to admission, on admission, peak within 48 hours, peak during admission and at discharge. Mortality data after discharge from the hospital were obtained from social security database. Data were analyzed for in-hospital, 30-day, 90-day and overall mortality. The Cox regression analysis combined all admissions and allowed adjustment for covariates. Results: In-hospital, 30 day and 90-day mortality rates were 6%, 15% and 23%, respectively, for patients' first admission. 90-day survival in those with AKI was 67% versus 91% without AKI. Increment in peak creatinine within 48 hours from admission creatinine (peak 48 hours – admission creatinine) was a very strong predictor of mortality, but only if peak creatinine reached above 1.2 mg/dl. If peak creatinine levels were below 1.2 mg/dl, there was no impact on survival due to increment in peak creatinine. In admissions with peak creatinine above 1.2 mg/dl, every 0.1 mg/dl incre-

ment was associated with a higher mortality, and with 0.4mg/dl increment, 90-day survival was only 58% versus 75% with those with less than 0.4 mg/dl increment (p=0.03). Cox regression analysis showed that 48-hour peak creatinine of 1.2 mg/dl or more had 1.7 higher hazard of death (CI 1.2-2.5), and 0.4 mg/dl increment had the worst outcome (HR 5.2, CI 2.9-9.4). Reason for admission persisted as a predictor of survival, but etiology of cirrhosis, or the use of PPI, beta blockers or rifaxamin did not predict mortality. Other independent predictors of mortality were white race, age, MAP less than 70mm/Hg, hyponatremia, INR and bilirubin. Conclusion: Increments in serum creatinine within 48 hours from hospitalization predict the survival provided the peak serum creatinine within 48 hours is above 1.2mg/dl. Increase in serum creatinine did not have an impact if peak creatinine did not reach 1.2 mg/dl or more. Early renal protection strategies after hospitalization may improve the outcome of patients with cirrhosis admitted with complications.

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Unprecipitated acute kidney injury can occur amongst stable patients with cirrhosis and ascites but no other complications

Florence Wong[1], Peter Jepsen[2], Hugh R. Watson[3], Hendrik V. Vilstrup[2]; [1]Medicine, University of Toronto, Toronto, ON, Canada; [2]Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark; [3]Internal Medicine, Sanofi-Aventis, Chilly-Mazarin, France

Acute kidney injury (AKI) occurs frequently in decompensated cirrhosis both in an ambulatory (Tsien et al, Gut 2013) and in a hospital setting (Garcia-Tsao et al, Hepatology 2008). Most AKI episodes are functional renal disorders, precipitated by an acute event such as infection that perturbs the hemodynamics. Because the background abnormal hemodynamics and compromised renal circulation in decompensated cirrhosis can further deteriorate, it is possible that AKI can occur without any precipitant. Aim: to determine the prevalence of unprecipitated AKI (acute ↑ in serum creatinine (SCr) by ≥0.3mg/dL (26.4μmol/L) in ≤48 hours or ↑ by 50% from baseline) (Wong et al, Gut, 2011) in a large cohort of ambulatory & hospitalized decompensated cirrhotic patients. Methods: Database containing 1115 stable decompensated cirrhotics with ascites and no other complications (early ascites or Gp A: n=434, diuretic responsive ascites or Gp B: n=451, refractory ascites or Gp C: n=230) from several randomized controlled vaptan trials was assessed. Two SCr readings ≤7 days apart taken at screening and at randomization into the vaptan studies were used to determine AKI prevalence. No precipitating event was reported between the 2 SCr readings. Results: AKI had a prevalence of 1.8% in the entire cohort. The prevalence of unprecipitated AKI increases with worsening ascites severity (Gp A: 4/434 or 0.9%; Gp B: 7/451 or 1.6%; Gp C: 9/230 or 3.9%; p=0.019). AKI patients had a mean screening SCr of 89±24μmol/L (±SD), increased to 130±31μmol/L (p<0.001) at AKI diagnosis. All patients except one had stage 1 AKI defined as ↑ in SCr by ≥26.4μmol/L or by 1.5-1.9X from screening. One patient had stage 2 AKI (2.0-2.9X ↑ in SCr from screening). Within a 7-day period, the AKI in 3 stage 1 patients progressed, two to stage 2, and 1 to stage 3 (>3.0 X ↑ in SCr from screening). There was no significant difference in terms of age, gender, liver cirrhosis etiology, history of diabetes or systemic hypertension, screening mean arterial pressure, heart rate, blood work or Child-Pugh and MELD scores, between those who developed AKI versus those who did not. However, there was a significant negative correlation between the screening serum Na and SCr (p=0.0008). Summary: AKI, unprecipitated by any acute event, still occurs in 1.8% of stable decompensated cirrhotic patients. Those with more severe ascites, especially refractory ascites are at a higher risk for developing unprecipitated AKI, Conclusion: Patients with cirrhosis and refractory ascites need to be monitored more closely for the development of unprecipitated AKI, since AKI has a negative impact on the outcome of these patients.

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Evaluation of serum cystatin C as a marker of early renal impairment in patients with liver cirrhosis

Mahmoud S. Omar[1], Wael Abdel-Razek[1], Gamal Abo-Raia[2], Medhat Assem[1], Gasser El-Azab[1]; [1]Hepatology, National Liver Institute, Shebeen El-Kom, Egypt; [2]Clinical Pathology, National Liver Institute, Shebeen El-Kom, Egypt

Background: Early detection of renal impairment (RI), one of the major complications of liver cirrhosis, using the current markers and equations could be challenging. Serum cystatin C (CysC) was proposed as an effective reflection of the glomerular filtration rate (GFR). However, its role in patients with liver cirrhosis has not been extensively verified especially in the detection of early RI. Patients and Methods: Seventy consecutive potential candidates for living donor liver transplantation were included in this prospective study as they fulfilled: age 18-80 years, serum creatinine (Cr) <1.5 mg/dL and no dehydration, sepsis or GI bleeding during the month before enrollment. CysC, Cr and estimated GFR [creatinine clearance (CCr), Cockcroft-Gault formula (C-G) and MDRD equations with 4 and 6 variables] were all correlated to isotopic GFR. Early RI was defined as GFR of 60-89 mL/min/1.73 m2. Results: Patients included 61 (87.1%) males, and had a mean age of 47.4±9.3 years and mean body weight of 78.2±14.7 kg. Liver cirrhosis was mostly due to chronic viral hepatitis, HCV in 51 (72.9%) and HBV in 12 (17.1%) patients, and 20 (28.6%) patients had hepatocellular carcinoma. The mean MELD was 16.2 (range 8-31); 18 (25.7%) and 52 (74.3%) patients were Child-Pugh class B and C, respectively. GFR was ≥90, 60-89 and 30-59 mL/min/1.73 m2 in 22 (31.4%), 45 (64.3%), and 3 (4.3%) patients, respectively. The mean Cr was 0.8±0.3 mg/dL and mean CysC was 1.9±1 mg/L. The GFR (mL/min/1.73 m2) was measured isotopically as 84.5±16.6, and estimated as: C-G 132.9±65, CCr 82.4±31.3, MDRD4 119.2±63.5 and MDRD6 97.4±50.4. All markers and equations, except C-G (p=0.100), were significantly correlated to GFR: 1/CysC (r=0.437, p<0.0001), CCr (r=0.367, p=0.002), 1/Cr (r=0.287, p=0.016), MDRD4 (r=0.260, p=0.030) and MDRD6 (r=0.286, p=0.017). The table shows the area under the curve (AUC) for discriminating early RI. At a cutoff value of 1.2 mg/L, CysC was 89.6% sensitive and 63.6% specific in detecting early RI. Conclusion: In patients with liver cirrhosis, CysC showed the highest significant correlation to GFR and was the test that best discriminated early RI especially at a cutoff of 1.2 mg/L.

	AUC	95% CI	P
CysC	0.785	0.663-0.907	<0.0001
CCr	0.674	0.533-0.815	0.020
Cr	0.642	0.500-0.784	0.058
MDRD4	0.646	0.506-0.787	0.051
MDRD6	0.644	0.503-0.784	0.054
C-G	0.562	0.413-0.710	0.411

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Chronic Kidney Disease Epidemiology Collaboration Equation combining Creatinine and Cystatin C is superior to other Creatine- and Cystatin C-based Equations in Assessing Renal Function in Patients with Cirrhosis

Elisabeth Krones[1], Sabine Zitta[2], Stefan Neunherz[1], Katharina Artinger[2], Tatjana Stojakovic[3], Gilbert Reibnegger[4], Franziska Durchschein[1], Juliana Buchgrabner[2], Vanessa Stadlbauer[1], Peter Fickert[1], Alexander R. Rosenkranz[2]; [1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Medical University of Graz, Graz, Austria; [2]Clinical Division of Nephrology, Department of Internal Medicine, Medical University of Graz, Graz, Austria; [3]Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Graz, Austria; [4]Institute for Physiological Chemistry, Medical University of Graz, Graz, Austria

Background: The prognostic value of renal function in cirrhosis is reflected by the inclusion of serum creatinine (SCr) levels in the model for end-stage liver disease (MELD) a predictor of 3-month mortality. Accurate measurement of renal function in cirrhotics however remains a clinical challenge. Although SCr is easily measurable and available, it has numerous limitations in patients with cirrhosis (e.g. reduced hepatic synthesis, increased tubular secretion, negative correlation with muscle mass) and may consequently be of limited value in determining GFR. Measurement of GFR using inulin clearance (IC) as the currently accepted gold standard is cost-intensive, time-consuming and of inferior role in daily clinical practice. Aim: To compare IC to SCr- and cystatin C (CysC)-based equations for GFR in patients at different stages of cirrhosis. Material and Methods: We determined IC in 50 patients with cirrhosis [divided by Child-Pugh A(18),B(18) and C(14)] and 24 age-matched healthy living kidney donors using the bolus method, which is superior over continuous inulin infusion since neither urine samples nor steady state conditions are required. Therefore, a bolus of 2500 mg sinistrin, an inulin-like polyfructosan, was administered over 3 minutes and GFR was calculated on the basis of sinistrin concentrations at different time points using a two compartment model. GFR determined by IC was furthermore compared to different SCr- and/or CysC-based equations (Cockcroft-Gault, MDRD, Hoek, Larson, CKD-EPI equations using SCr, CysC and/or both) using bias, precision, and "Root Mean Square Error" (RMSE). Results: Compared to IC, SCr-based equations generally overestimated GFR in patients with liver cirrhosis (e.g. bias 11.5, precision 21.8, RMSE 24.7 for MDRD and bias 9.4, precision 20.5, RMSE 22.5 for CKD-EPI). SCr-based overestimation of GFR correlated with progression of liver disease and was not observed in healthy living kidney donors. CysC-based equations showed better results but rather underestimated GFR compared to IC, especially in patients with Child Pugh C (e.g. bias -8.2, precision 17.5, RMSE 19.3 for CKD-EPI). Conclusion: All equations used for estimating GFR showed a high bias. Amongst all, CKD-EPI equation combining SCr and CysC was superior to all other equations in assessing GFR in cirrhosis (bias -0.12, precision 16.1, RMSE 16.1, accuracy 10%: 49%, accuracy 30%: 84%). Our results show the critical importance of cross validation of different tests to accurately determine GFR in cirrhotics. Determination of IC seems to be reasonable in patients with cirrhosis, especially those being evaluated for liver transplantation. Disclosures: none.

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Bile pigment nephropathy and acute tubular necrosis in decompensated cirrhotics and acute on chronic liver failure

Suman Nayak[1], Rajendra P. Mathur[1], Sivaramakrishnan Ramanarayanan[1], Gyan Prakash[1], Shiv K. Sarin[2], Chitranshu Vashishtha[2], Manoj Kumar[2], Rakhi Maiwall[2], Ajeet S. Bhadoria[2]; [1]nephrology, institute of liver and biliary science, New Delhi, India; [2]hepatology, Institute of liver and biliary science, New Delhi, India

Background While functional renal dysfunction is assessed by using Acute Kidney Injury Network (AKIN) criteria, the true spectrum of kidney injury remains speculative. Since majority of patients are very sick and coagulopathic, there is paucity of data on renal biopsies and structural renal pathologies in patients with cirrhosis and acute on chronic liver failure (ACLF). Patients and Methods: We reviewed the post-mortem kidney biopsy reports of patients with severe liver dysfunction who died with acute kidney injury (AKI). Biopsy tissues were processed and subjected to light microscopy and immunofluorescence. In patients with pigment casts in tubules, additional special stains for iron (Pearl's stain) and bile (Fouchet's) were used to characterise the pigments. Results: Total of 43 renal biopsies of patients with complete clinical details and death with AKI were included; 18 patients had ACLF and 25 were decompensated cirrhotics. Mean age of study population was 43.26±11.44 years. All 43 (100%) patients had renal structural anomalies. Bile pigment nephropathy was found in 20/43 (46.51%) and acute tubular necrosis (ATN) in 23/43 (53.49%) patients. ACLF patients had significantly more number of bile pigment nephropathy as compared to cirrhotics (72%vs 27.8%, p value = 0.004). The mean urea (98.80±55.78 vs 90±44.68 mg/dl, p value = 0.294) and creatinine (4.02±2.3 vs 3.42±1.5 mg/dl, p value = 0.081) were higher in bile pigment nephropathy group compared to ATN group. The Mean CTP score was higher in bile pigment nephropathy group compared to ATN group (12.6±1.1 vs. 11.9±1.2, p value = 0.046). The Mean MELD score (39.3±7.9 and 31.35±7.7) and bilirubin (26.06±9.3 and 9.2±5.2 mg/dl) were higher in bile pigment nephropathy group as compared to ATN group (p value = 0.002 and <0.001 respectively). On multivariate logistic regression analysis, high bilirubin was found to be an independent predictor of bile pigment nephropathy. Conclusion: Patients with decompensated cirrhosis and ACLF, who develop severe AKI, do have renal structural anomalies. Bile pigment nephropathy is a common pathological finding; more so in ACLF patients with high serum bilirubin. ATN should be suspected early enough in decompensated cirrhotics.

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Plasma Renin concentration is associated with portal hypertension, liver dysfunction, ascites and hyponatremia and may predict mortality in cirrhosis

Rafael Paternostro[1,2], Simona Bota[1,2], Philipp Schwabl[1,2], Remy Schwarzer[1,2], Thomas Reiberger[1,2], Mattias Mandorfer[1,2], Monika Ferlitsch[2], Michael Trauner[2], Markus Peck-Radosavljevic[1,2], Arnulf Ferlitsch[1,2]; [1]Vienna Hepatic Hemodynamic Laboratory, Divison of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; [2]Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria

Background & Aims: Plasma renin concentration (PRC) has been reported to be elevated in patients with liver cirrhosis. It remains to be established if PRC is associated with portal hypertension (PHT), degree of liver dysfunction, and mortality in cirrhosis. Methods: PRC (in μIE/mL) was measured in 116 patients with liver cirrhosis undergoing measurement of hepatic venous pressure gradient (HVPG) when Child-Pugh-Score (CPS), MELD score, and grade of ascites were evaluated. Mortality was recorded during follow-up. Results: Main patient characteristics were as following; age: 56+-10years; gender:75% male; CPS-A:37%, CPS-B:40%, CPS-C: 23%, MELD: 8.9+-5.5, HVPG: 16+-6.6 mmHg, Ascites: absent/grade1: 73%, Grade2: 15%, Grade3: 12%. Median PRC for CPS-A was: 16.6μIE/mL (IQR:8.6-29), for CPS-B 41μIE/mL (IQR:11.9-198.1) and in C 175.2μIE/mL (IQR:705-1855.4) (A vs. B p=0.003, A vs. C p<0.0001, B vs. C p=0.01).In patients with clinical significant portal hypertension (CSPH, defined as a HVPG ≥10mmHg), median PRC was 43.7μIE/mL (IQR: 14.6-219.9) as compared to 10.1μIE/mL (IQR: 5.02-31.5; p=0.001) in patients without CSPH. The median PRC significantly increased (p<0.001) with the degree of ascites: no ascites 19.5μIE/mL (IQR:2.2-50.1), grade 1 ascites: 40.6μIE/mL (IQR:2.69-149.5), grade 2 106μIE/mL (IQR:38.2-316.6), and grade 3 ascites: 248.3μIE/mL (IQR:151.7-2021).PRC significantly correlated with absolute CPS values (p<0.0001, r=0.414), MELD score (p<0.0001, r=0.422), grade of ascites (p<0.0001, r=0.476), and HVPG (p=0.0001, r=0.358). In addition, PRC correlated with serum sodium (p<0.0001, r=-0.574) and creatinine levels (p=0.002, r=0.283).Median transient elastography values were 41+-22 and were available in 74 patients, significant correlation with PRC was found (p<0.0001, r=0.400). Multivariate analysis found independent correlations of PRC and sodium-levels (p<0.0001), MELD score (p=0.008), CPS (p=0.009), and grade of ascites (p=0.02). 20 patients (17.2%) died during follow-up (median 519 days (IQR:26.6-844.2)) . Median PRC was higher in patients who died during follow-up: 112.4μIE/m (IQR:31.8-270.3) vs. 28.4μIE/m (IQR:9.3-110.9;p=0.02).Logrank test showed significant difference in survival between those patients with elevated PRC (>39.9 μIE/mL)and those with normal PRC levels (p=0.022). Conclusions: PRC correlates with portal hypertension, severity of liver dysfunction (CPS and MELD), the degree of ascites, and lower serum sodium levels in patients with liver cirrhosis. It seems that higher PRC is also associated with mortality, but prospective studies are needed if dynamic changes of PRC are of independent prognostic value in liver cirrhosis.

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Alpha-2a Adrenoceptor Subtype Stimulation by Guanfacine Restores Diuretic Efficiency in Experimental Cirrhosis and Refractory Ascites: Comparison with Clonidine Effects

Giovanni Sansoe[1], Manuela Aragno[2], Raffaella Mastrocola[2], Maurizio Parola[2]; [1]Gastroenterology Unit, Gradenigo Hospital, Torino, Italy; [2]Department of Clinical and Biological Sciences, University of Torino, Torino, Italy

Background. In liver cirrhosis, adrenergic hyperfunction causes proximal tubular fluid retention and reduces the response to diuretics, leading to refractory ascites. Clonidine, a sympatholytic drug, plus diuretics improve natriuresis in refractory ascites. Aim. To compare diuretic efficiency of clonidine (aspecific α2-adrenoceptor agonist) and SSP-002021R (specific α2A-receptor agonist and prodrug of guanfacine) when associated with diuretics in experimental cirrhotic refractory ascites. Methods. Eight groups of rats were studied: controls (group G1); controls receiving furosemide and potassium canrenoate (G2); rats with ascitic cirrhosis due to 14 CCl4 weeks (G3); cirrhotic rats treated with furosemide and canrenoate over the 11th-14th CCl4 weeks (G4); cirrhotic rats treated with canrenoate and clonidine (0.5 mcg three times a week) over the 11th-14th CCl4 weeks (G5); cirrhotic rats treated with furosemide, canrenoate and clonidine (0.5 mcg) (G6); cirrhotic rats treated with diuretics and low-dose clonidine (0.3 mcg) (G7); cirrhotic rats treated with diuretics and SSP002021R (5 mg/kg b.w. three times a week) (G8).Three rats in each group, before sacrifice, had their hormonal status and renal function assessed at the end of 11th, 12th, 13th, and 14th CCl4 weeks. Results. Cirrhotic rats in G3 and G4 gained weight over the 11th-14th CCl4 weeks. In G4, after a brief increase in sodium excretion due to diuretics (11th week), rapid worsening of inulin clearance (GFR) and natriuresis occurred in the 12th-14th CCl4 weeks (diuretic resistance). The addition of low-dose clonidine (G7) or guanfacine (G8) to diuretics increased, respectively, electrolytes excretion over the 11th-12th CCl4 weeks, or GFR and urinary excretion of electrolytes over the 13th-14th CCl4 weeks. Natriuretic responses in G7 and G8 were ushered by reduced catecholamine serum levels. Conclusions. Clonidine reduces adrenergic function and potentiates diuretics-dependent natriuresis before occurrence of refractory ascites. Specific α2A-receptor agonists preserve GFR, increase natriuresis, and prevent refractory ascites in this model.

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Albumin Infusions in Patients with Cirrhosis who Present with Acute Kidney Injury and its Effect on Renal Function

Derek J. Feussner, Amy P. Myers, James C. Slaughter, Andrew Scanga; Vanderbilt University, Nashville, TN

During an admission for AKI in patients with cirrhosis, individuals at Vanderbilt University Hospital are given an albumin challenge to improve their intravascular volume in hopes of increasing blood flow delivered to the kidneys and improving their renal function. There is limited evidence to guide albumin dosing in this clinical scenario. Current recommendations are to give 1gm/kg/day of albumin up to 100gm/day. Our goal in performing this retrospective chart review is to identify differences in outcomes among patients with cirrhosis who present with AKI and who receive differing daily doses of albumin. Using Vanderbilt University Hospitals EMR, 1,124 charts were reviewed from all patients admitted to the Hepatology service from 2010–2013 with 149 subjects identified. Patients with an admission diagnosis of AKI were included if their admission serum creatinine was >2.0mg/dL and had increased from their prior baseline by ≥0.3mg/dL, or their admission serum creatinine was 1.5 times their baseline value. Subjects who met these criteria were excluded if they were diagnosed with spontaneous bacterial peritonitis during their hospital stay. We then looked at the admission creatinine, and creatinine after a 48hour albumin challenge to assess for improvement in renal function. Our results show no evidence that increasing doses of albumin are associated with increasing degree of change in creatinine from pre-to-post intervention (p=0.49). In a multivariable model including MELD scores, PRBC administration and urine sodium; there is no evidence that MELD scores, PRBCs, urine sodium or albumin are associated with changes in creatinine. For subjects receiving less than or equal to 0.5 g/kg of albumin BID, creatinine decreased by 0.44 units from pre to post intervention; in subjects receiving more than 0.5 g/kg of albumin, creatinine decrease by 0.42 units. This is a difference of 0.02 units (95% CI: [-0.24 to 0.28]) due to albumin dosing. While we were unable to show that increasing albumin dose had a greater effect on improving renal function, in general there was an improvement. This study shows no association between albumin dose and effect on improving kidney function, glomerular filtration rate or hospital length of stay in patients with known cirrhosis. These results allowed us to develop a hypothesis that larger doses of albumin are no more effective than low dose albumin regimens in effecting change in overall kidney function. Moving forward it is our goal to create a prospective study with the aim of more effectively using albumin as a hospital resource given Vanderbilt University Hospital as a whole spent 4.6 million dollars on albumin from 2010–2013.

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Nosocomial spontaneous bacterial peritonitis is associated with increased mortality compared to community-acquired spontaneous bacterial peritonitis

Nicolas M. Intagliata, Zachary Henry, Nitin K. Ahuja, Neeral L. Shah, Curtis K. Argo, Stephen H. Caldwell, Patrick G. Northup; Gastroenterology and Hepatology, University of Virginia, Charlottesville, VA

Introduction: Hospital-acquired infections in cirrhosis patients are associated with significant morbidity and mortality. We aimed to examine the relative impact of nosocomial versus community-acquired spontaneous bacterial peritonitis (SBP) among patients hospitalized at a tertiary liver transplant center. Methods: Adult cirrhosis patients with SBP admitted over four years (2009-2012) were identified through a clinical database. SBP was defined as ascites fluid with >250 PMN/mm3. Nosocomial cases were defined as SBP occurring greater than 48 hours after hospitalization. Patients with non-neutrocytic bacterascites, SBP diagnosed prior to transfer, and secondary peritonitis were excluded. Results: Of 341 patients with cirrhosis and peritonitis, 99 patients met criteria for SBP; 23 cases (23%) were identified as nosocomial (NA-SBP) and 76 cases (77%) as community-acquired (CA-SBP). Patients with NA-SBP had significantly higher admission MELD scores (NA-SBP 28, 95% CI 22.9-32.8, vs. CA-SBP 22, 95% CI 19.6-23.9, p=0.02), driven primarily by higher bilirubin levels (NA-SBP 13.0 mg/dL, 95% CI 7.4-18.6, vs. CA-SBP 5.9 mg/dL, 95% CI 4.3-7.5, p=0.01). Exposure to antibiotics prior to paracentesis was more common among patients with NA-SBP than those with CA-SBP (91.3% vs. 56.2%, p=0.002). Patients with NA-SBP had significantly longer hospitalizations (NA-SBP 16.9 days, 95% CI 12.1-21.7, vs. CA-SBP 8.4 days, 95% CI 6.4-10.3, p =0.0001) with longer intervals preceding diagnostic paracentesis (NA-SBP 6.2 days, 95% CI 4.3-8.0, vs. CA-SBP 0.5 days, 95% CI 0.4-0.7, p= 0.0001). Ascites culture yield was low in this cohort (21/99, 21%), with a large proportion of culture-positive ascites growing multi-drug resistant organisms (9/21, 43%). Among NA-SBP patients, only 2/23 (9.5%) yielded positive ascites cultures. 12/23 (52%) of NA-SBP patients had a separate infection noted prior to SBP diagnosis. Kaplan-Meier survival analysis revealed 30-day mortality was significantly higher in patients with NA-SBP (p=0.004, Figure 1). A multivariate Cox proportional hazards model indicated NA-SBP (HR 3.2, p=0.002) was a significant predictor of mortality. Conclusions: NA-SBP carries a high 30-day risk of mortality relative to CA-SBP. After controlling for other important mortality correlates, NA-SBP was found to be an independently significant predictor for death. As hospitalized cirrhotic patients are prone to systemic infections, it is unclear if elevated ascites neutrophils represent true SBP; rather, these counts may be a surrogate marker for overall systemic infection and consequently a higher risk of death. Further prospective study is now needed to better characterize NA-SBP.

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Microscopic Urinanalysis May Represent a Sensitive Test for Kidney Injury in Cirrhotic and Cholestatic Patients with Preserved Kidney Function

Elisabeth Krones[1], Julia Fritz[1], Christoph Schwarz[2], Franziska Durchschein[1], Kathrin Eller[2], Gernot Zollner[1], Werner Ribitsch[2], Tatjana Stojakovic[3], Sabine Zitta[2], Juliana Buchgrabner[2], Alexander R. Rosenkranz[2], Peter Fickert[1]; [1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Medical University of Graz, Graz, Austria; [2]Division of Nephrology, Department of Internal Medicine, Medical University of Graz, Graz, Austria; [3]Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Graz, Austria

Background: Acute kidney injury (AKI) in cirrhosis represents a high-risk situation. It is increasingly recognized that cirrhotic or cholestatic patients show abnormal renal histology with glomerular and tubulointerstitial lesions that may not be noted by routine renal function tests. Microscopic urinanalysis is readily available, inexpensive and noninvasive, and currently considered to be a well-suited surrogate parameter for structural kidney damage. We hypothesized that cirrhotic or cholestatic patients with preserved renal function (eGFR >60 ml/min) upon routine laboratory evaluation frequently show structural renal injury reflected by a pathologic urine cytology. This may represent a herald of subsequent impaired renal function. Aim: To find a useful non-invasive clinical test to identify early structural kidney injury in liver patients. Material and Methods: We collected blood and urine samples from a total of 150 patients [liver cirrhosis Child Pugh score class A (n=41), B (n=38), C (n=28), obstructive cholestasis (n=19), and age-matched healthy living kidney donors (n=24]. Patients with diabetes, insufficiently treated arterial hypertension or pre-existing kidney disease were excluded. Freshly voided urine samples were analyzed by automatic flow cytometry (Sysmex UF 1000) and microscopic urinanalysis after Papanicolaou staining of a smear preparation of the urine sedimentation. The specimens were analyzed for presence and number of renal tubular epithelial cells (RTEC) and granular casts (GC). Results: Serum creatinine (SCr) concentrations (in mg/dL) and GFR determined by the CKD-EPI equation (in ml/h/1.73m^2) were normal amongst all groups (0.76±0.16 and 102±15 in Childs A group, 0.78±0.17 and 101±12 in Childs B group, 0.84±0.23 and 95±19 in Childs C group, 0.85±0.2 and 93±21 in cholestasis group, 0.78±0.11 and 93.6±12.4 in living kidney donors). RTEC and GC as sensitive markers of tubular epithelial kidney injury were frequently found in liver cirrhosis (RTEC in 15%, GC in 8%) and cholestasis (RTEC in 33%, GC in 20%), whereas none of the healthy living kidney donors showed RTEC or GC upon urine cytology. Presence of RTEC significantly correlated with serum bile acid levels (correlation coefficient 0.207; p 0.015) Conclusions: Patients with cirrhosis or cholestasis and normal kidney function show RTEC and GC at increased numbers compared to controls. Microscopic urinanalysis may represent a useful, noninvasive and cheap diagnostic test to identify patients at high risk for AKI or subclinical kidney injury which needs to be evaluated in prospective clinical trials. Disclosures: none.

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Relative Adrenal Insufficiency in Cirrhotic Patients with Ascites

Virendra Singh[1], Rajiv R. Singh[1], Rama Walia[2], Naresh Sachdeva[2], Ashish Bhalla[3], Navneet Sharma[3], Yogesh K. Chawla[1]; [1]Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh, India; [2]Endocrinology, Postgraduate Institute of Medical Education and Research, Chandigarh, India; [3]Internal Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Background : Relative adrenal insufficiency (RAI) has been reported in critically ill patients with cirrhosis and is associated with poor outcome. Its prevalence and impact on survival in non-critically ill cirrhosis patients is largely unknown. We evaluated the prevalence of RAI and its relationship to clinical course in non-septic cirrhosis patients with ascites. Methods:The study included 66 consecutive hemodynamically stable, non-septic cirrhosis patients admitted with ascites. A 250-μg adrenocorticotropic hormone stimulation test was performed within 24 hours of admission to detect RAI. Transcortin, calculated free cortisol (cFC), and free cortisol index (FCI) were assessed in all patients, with FCI >12 representing normal adrenal function. Patients were followed up for 3 months. Results: Sixty six patients (56 males and 10 females) with cirrhosis and ascites participated in the study. The mean Child-Pugh(CTP) and model for end stage liver disease (MELD) scores were 10.6 ± 1.9 and 21.5 ± 7.3, respectively. Hepatorenal syndrome (HRS) was present in 9 (13.6%) patients. The prevalence of RAI in patients with cirrhosis and ascites was 47% (31/66). The prevalence of RAI in patients with and without spontaneous bacterial peritonitis (SBP), renal failure and type 1 HRS was comparable. Hyponatremia at inclusion was present in significantly greater number of patients with RAI (42% versus 17%, p=0.026). Patients with RAI had lower serum levels of total cholesterol, high density cholesterol (HDL) and low density cholesterol (LDL) than patients without RAI. There was a significant correlation of prevalence of RAI with the severity of liver disease with significantly higher prothrombin time, international normalized ratio (INR), MELD scores and CTP class in patients with RAI than those without RAI. During follow up, there was no association between RAI and the risk to develop new infections, severe sepsis, type 1 HRS and death. Conclusions: RAI is common in non-septic cirrhotic patients with ascites. It is likely to be a feature of liver disease per se which increases in prevalence with increasing severity of liver disease. However, it does not affect the short term outcome in these patients.

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Urinary NGAL Levels Reflect the Therapeutic Effects of norUDCA in Mice with Cholemic Nephropathy

Elisabeth Krones[1], Dietmar Glaenzer[1], Franziska Durchschein[1], Alexander Kirsch[2], Kathrin Eller[2], Michael Trauner[3], Alexander R. Rosenkranz[2], Peter Fickert[1,4]; [1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Medical University of Graz, Graz, Austria; [2]Clinical Division of Nephrology, Department of Internal Medicine, Medical University of Graz, Graz, Austria; [3]Hans Popper Laboratory, Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; [4]Department of Pathology, Medical University Graz, Graz, Austria

Background & Aims: Long-term common bile duct ligation (CBDL) in mice models cholemic nephropathy with renal tubular cast formation, tubular epithelial cell injury and impaired renal function (Fickert et al. Hepatology 2013). Interestingly, renally excreted norursodeoxycholic acid (norUDCA) protects CBDL mice from cholemic nephropathy, suggesting a pivotal pathogenetic role for urinary excreted bile acids (BA). Neutrophil-gelatinase associated lipocalin (NGAL) is an iron-transporting protein with increased renal excretion in nephrotoxic or ischemic kidney injury. We aimed to test the hypothesis that urinary NGAL measurement is useful to monitor acute kidney injury in cholemic nephropathy. Methods: Chow-fed (controls) or norUDCA (0.125% w/w)-treated CL57/BL6 mice were subjected to CBDL for 8 weeks. Urinary NGAL levels were determined at time of harvesting using a commercially available ELISA kit (Lipocalin-2/NGAL DuoSet Mouse, R&D Systems, DY1857). In brief, samples were incubated with detection antibody, labeled with streptavidin-HRP and subsequently measured at 450 nm. Results: Chow-fed CBDL mice exhibited significantly elevated urinary NGAL levels (29.6 ± 4.2 ng/ml) compared to norUDCA-treated CBDL mice (9.4 ± 1.8 ng/ml, $p<0.05$). NorUDCA treatment significantly ameliorated the degree of nephritis and kidney fibrosis and consequently to a significantly reduced renal hydroxyproline content (466 ± 107 μg/g vs. 797 ± 160 μg/g in controls, $p<0.05$). Conclusions: Urinary NGAL measurement represents a suitable readout for monitoring the degree of cholemic nephropathy in CBDL mice and reflects the therapeutic effects of norUDCA. Future studies should determine urinary NGAL levels in patients with cholemic nephropathy. Disclosures: The Medical University of Graz has filed a patent for the use of norUDCA in the treatment of liver diseases, and P.F. and M.T. are listed as co-inventors (publication number WO2006119803) and P.F. received a research grant and norUDCA from Dr. Falk Pharma GmbH for this project.

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Prevalence of hyperdynamic circulation in cirrhosis: lack of association to presence and severity of ascites

Cristina Ripoll, Phillip Hohaus, Marcus Hollenbach, Robin A. Greinert, Alexander Zipprich; Innere Medizin I, Martin-Luther-Universität Halle-Wittenberg, Halle (Saale), Germany

Patients with cirrhosis develop hyperdynamic circulation with an increase in cardiac output (CO) and a decrease in systemic vascular resistance (SVR). Patients with hyperdynamic circulation can develop circulatory dysfunction(CD) when this compensatory mechanism is insufficient. Although this takes place theoretically in decompensated patients, namely in patients with ascites, its prevalence has never been specifically analysed. The aim was to evaluate the prevalence of hyperdynamic circulation in patients with compensated and decompensated cirrhosis and it association to liver function, portal hypertension and CD. Methods: Secondary analysis of a prospectively collected dataset of patients with cirrhosis who underwent a hepatic hemodynamic study and right heart catheterization. SVR and CO were categorized according to the presence of abnormal values (below 800 dyn.cm.s5 and above 8 l/m, respectively). Hyperdynamic circulation was defined when both parameters were abnormal. CD was defined by the presence of creatinin >1.5 mg/dL and/or hyponatremia <130 mmol/L. Variables are reported as percentages or medians(IQR). Comparison were performed by means of U-mann Whitney and ANOVA. Kaplan-Meyer curves were constructed and compared with the log rank test. Results: 437 patients were included (65% male, 71% had alcohol related disease, Child A 102 (23%), B 182 (42%), and C 130 (30%), 57% with ascites (n=249) and 30% with refractory ascites (n=130). 22% had hyperdynamic circulation, interestingly 18% of patients without ascites and 25 % of patients with ascites had hyperdynamic circulation. Patients with hyperdynamic circulation had greater HVPG [18 (13-20) mmHg vs. 16 (11-19) mmHg](p=0.007) although no difference in creatinin and serum sodium were observed compared to patients without hyperdynamic circulation. Among patients with ascites, no difference in the prevalence of hyperdynamic circulation was observed according to the presence of diuretic responsive (26%) or refractory ascites (23%). CD was observed in 20% of patients, most frequently in patients with refractory ascites (61%). No association was observed between the presence of hyperdynamic circulation and CD. Patients with CD had greater HVPG [19 (16-21) mmHg vs 15 (11-19) mmHg](p<0.001) and lower SVR [834 (683-1057) dyn.cm.s-5 vs. 938 (751-1182) dyn.cm.s-5] (p=0.006), nevertheless no differences in CO [6.9 (5.6-8.4) l/min vs. 6.7 (5.7-8.3) l/min] were observed. Conclusions: Approximately 25% of patients with cirrhosis have hyperdynamic circulation, irrespective of ascites. CD is associated to refractory ascites. Patients with CD have lower SVR, without differences in CO.

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Outcomes in Patients Receiving Rifaximin along with Systemic Antibiotics for the Inpatient Treatment of Spontaneous Bacterial Peritonitis

Jennifer D. Twilla[1], Anuj Sharma[3], Satheesh Nair[2], Emily H. Wong[2], Sanjaya K. Satapathy[2]; [1]Department of Clinical Pharmacy, University of Tennessee Health Sciences Center, Memphis, TN; [2]Department of Surgery, Methodist Transplant Institute, University of Tennessee Health Sciences Center, Memphis, TN; [3]Department of Gastroenterology, University of Tennessee Health Sciences Center, Memphis, TN

Background: Spontaneous bacterial peritonitis (SBP) is the most frequent infection in patients with cirrhosis causing significant mortality which requires rapid recognition and treatment with systemic antibiotic therapy. The purpose of our study was to investigate whether the addition of non-absorbable oral antibiotic rifaximin for selective intestinal decontamination with aim to reduce bacterial translocation from the gut in patients admitted with SBP reduced mortality as well as other secondary outcomes. **Methodology:** A retrospective review of patients admitted to Methodist LeBonheur Healthcare adult hospitals between 4/09-4/14 with an ICD-9 diagnosis code of 567.23 (SBP) was conducted. These patients were reviewed for administration of systemic antibiotics +/- rifaximin during their inpatient stay and divided into two groups: systemic antibiotics alone (SA) and systemic antibiotics + rifaximin (SA+R). Inclusion criteria: ≥ 18 years of age, diagnosis of cirrhosis or chronic liver disease, diagnosis of SBP, and received ≥ 5 days of systemic antibiotics. Patients groups were compared to determine length of stay (LOS), development of hepatorenal syndrome (HRS), bleeding, hepatic encephalopathy (HE), and mortality. **Results:**Eighty patients were included with 44 patients in the SA group and 36 patients in the SA+R group. Overall mortality rate was 36%, with no statistically significant differences between the SA vs SA+R group (38% vs 34%; p=NS). Average LOS was similar between the two groups (SA group 12.3±10.8 days vs SA+R group 14.8±13.7 days; p=NS). Comparison of the SA group vs SA+R group for differences in number of patients that developed HRS, bleeding, or HE did not reveal any statistically significant differences. However, 18 patients had documentation of rifaximin as a home medication prior to admission. Upon review of patients receiving rifaximin prior to admission vs those who did not, there was a statistically significant difference in the development of HRS (11% vs 40%; p=0.02). **Conclusion:The addition of rifaximin to systemic antibiotics for inpatient treatment of SBP did not affect LOS nor did it alter the development of HRS, bleeding, HE, or mortality. Conversely, receiving rifaximin prior to admission significantly reduced the progression to HRS. Larger prospective studies are needed to validate these results.**

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Clinical Predictors of Morbidity and Mortality in Hospitalized Children with Ascites

Grace Felix[1], Thammasin Ingviya[2], Ann O. Scheimann[1], Pavis Laengvejkal[1], Alexandra Vasilescu[1], Hejab Imteyaz[1], Eric C. Seaberg[2], Wikrom Karnsakul[1]; [1]Pediatrics, Johns Hopkins School of Medicine, Baltimore, MD; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

BACKGROUND: Ascites is a common diagnosis in hospitalized children due to its association with a myriad of etiologies. Little is known about factors predictive of morbidity and mortality in this population. METHODS: IRB approved retrospective cross-sectional chart review was performed on children aged 0-21 hospitalized at Johns Hopkins Hospital between 1983-2010 with an ICD-9 diagnosis of ascites (789.5, 789.51, 789.59). Multiple regression analysis was used to identify demographic, laboratory, and clinical features as potential predictors of morbidity and mortality. Study outcomes included hospital length of stay (LOS) as a proxy for morbidity and mortality (defined as death at hospital discharge). Predictors analyzed included demographic data, ascites etiology and grade (I, II or III), co-morbidities (hepatic encephalopathy (HE), hepatorenal syndrome (HRS), portal vein thrombosis, hydrothorax, etc.) and lab markers (thrombocytopenia, anemia, hyponatremia, and leukopenia). RESULTS: A total of 518 children were studied. The average LOS of the population was 23.6 days. Children aged 0-5 had the longest LOS at 27.8 days (p= 0.02), followed by the 6-12 age group and the 13-21 age group, respectively. Grade of ascites did not predict LOS. Children with hepatic venous outflow obstruction had the longest LOS (41 days) while those with nephrotic syndrome had the shortest LOS (10 days) with a p< 0.001. The presence of hydrothorax was the only comorbidity associated with a prolonged LOS, p= 0.016. Thrombocytopenia was the only laboratory feature associated with longer LOS (p= 0.007). Children aged 0-5 had the highest mortality rate (59.2% p=0.003). Regarding etiologies, hepatic venous obstruction, particularly veno-occlusive disease (VOD) had the highest mortality (Adjusted OR = 33.1; 95% CI: (4.9-677.8)) while cancer had the lowest (0.19%). The presence of HE (p=0.004), HRS (p=0.009), thrombocytopenia (p<0.001) and hyponatremia (p=0.035) were also associated with higher mortality. CONCLUSION: Among hospitalized children with ascites, age ≤5, presence of VOD, hyponatremia, thrombocytopenia and leukopenia were associated with greater morbidity and mortality warranting further investigation.

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Beyond Dr. Google: Early results of a personalized weight-tracking smartphone application and alert system for patients with ascites

Chanda Ho[1], Neil Shah[1], Nabil Alshurafa[2], Behnam Shahbazi[2], Hassan Ghasemzadeh[3], Norah Terrault[1]; [1]Hepatology, UCSF, San Francisco, CA; [2]Computer Science, UCLA, Los Angeles, CA; [3]Computer Science, Washington State University, Pullam, OR

Background: Medical management of ascites is currently limited to dietary sodium restriction, diuretics, and large-volume paracentesis (LVP) with few interventions in place to prevent ascites-related complications. We hypothesize close monitoring of weights can prevent ascites complications related to under or overdiuresis and propose utilizing smartphone appli-

cations to test this hypothesis. Smartphone applications have been shown to improve patient outcomes in chronic disease but have not been tested in cirrhotic patients with ascites. Aim: To develop and implement a patient-centered smartphone application in cirrhotic patients with ascites. Methods: We designed an application with the following features: 1) wireless scale connectivity to record weights 2) patient reminders to weigh in 3) provider alerts if the patient had not weighed in at 72 hours and/or if the patient exceeded a pre-defined, personalized target weight range (TWR). Inclusion criteria were as follows: patients with Child class B/C cirrhosis on at least 2 diuretics with an ascites-related complication in the preceding 6 months defined as fluid overload requiring LVP, renal (Cr ≥ 2.0 mg/dL) or electrolyte (Na <128 mEq/L or K> 5.0 mEq/L) dysfunction, or a hospitalization/emergency department (ED) visit for an ascites-related complication. To date, we have recruited 10 subjects in this ongoing study. We report initial results for 6 subjects along with feedback from qualitative interviews. Results: The mean age of the subjects was 53 years (4 male, 2 female) with an average MELD score of 14 (range 9-24). All but one subject used the application. Three subjects remained in their TWR. Two subjects exceeded their TWR and generated provider alerts. These subjects required several episodes of diuretic titration and ultimately underwent scheduled procedures. None of the participating subjects had a hospital/ED visit during the study. From qualitative interviews, subjects identified that the application facilitated their communication with providers and aided in self-empowerment over their medical care. Conclusions: Our experience shows that subjects maintained their weight or successfully used the alerting system to communicate with their provider regarding management. Close, non-invasive monitoring of patient weights provided an opportunity for an early intervention (uptitrating diuretics, scheduling LVP) in this complex patient population and may play a role in the prevention of ascites-related complications such as a hospitalization/ED visit. Further studies are needed to determine the impact of weight monitoring on patient quality of life, longer-term outcomes, and health-care costs.

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Determination of renal function through creatinine and cystatin C-dependent formulas in comparison to DTPA-Tc-99 clearance in Mexican cirrhotic patients

Jonathan Aguirre-Valadez[1], Haydee Verduzco-Aguirre[1], Ariadna K. Flores-Balbuena[1], Octavio R. García-Flores[1], Ricardo Macías-Rodríguez[1], Cristino Cruz-Rivera[2], Jose A. Niño-Cruz[2], Ignacio Garcia[1], Aldo Torre[1]; [1]Gastroenterology, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Mexico DF, Mexico; [2]Nephrology, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Mexico DF, Mexico

We studied 95 patients with liver cirrhosis of different etiologies. GFR (glomerular filtration rate) was estimated by Cockroft-Gault (CG), MDRD-4 (Modification of Diet in Renal Disease), MDRD-6, Hoek's CysC formula and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) based on serum creatinine (sCr), CysC and sCr plus CysC. We used as standard GFR measured by DTPA-Tc99 (diethylene-triamine-pentaacetate technetium) renal clearance. We divided patients in 3 groups according to MELD (Model for End-Stage Liver Disease) score: <10, 11-14 and >15. Nutritional status was assessed with the Royal Free Hospital Subjective Global Assessment (RFH-SGA) and bioelectrical impedance analysis (malnutrition = phase angle <4.9°). Data was analyzed with SPSS ver. 21. Results: 44 men and 51 women were evaluated. 36.8% of patients had a MELD score <10, 32.6% between 11-14 and 30.5% >15. Mean sCr was 0.74 ± 0.26 mg/dL, with no difference between groups. Mean CysC was 1.19 ± 0.37 mg/L in all patients; in MELD <10 it was 1.02 ± 0.27, MELD 11-14 it was 1.17 ± 0.30, MELD >15 was 1.42 ± 0.42 (p = 0.004). Mean GFR by DTPA-Tc99 for all groups was 67.7 ± 30.14 ml/min/1.73m2. For MELD <10: 78.57 ± 25.6; MELD 11-14: 68.49 ±29.57; MELD >15: 53.66 ± 31.03. SCr formulas overestimated GFR for all groups. Mean GFR by CG was 110.6±50.63. CysC formulas showed a better performance. Mean GFR by Hoek's CysC formula was 68.7 ±21.44, and by CKD-EPI CysC 69.3±25.89. In the MELD >15 group, DTPA-Tc-99 detected a GFR <60 in 65% of patients and a GFR <30 in 27%. CG detected a GFR <60 in 14% and none <30. Similar results occured for all sCr formulas. Hoek's CysC formula detected 58% of GFRs <60 (concordance with DTPA 73%, underdiagnosis 26%) and 3% <30 (concordance 14%). CKD-EPI CysC showed the best performance, detecting 66% of GFRs <60 (concordance 79%, underdiagnosis 21%) and 25% of GFRs <30 (concordance 25%). Severe malnutrition increased with MELD score. By RFH-SGA: 5.7% in MELD <10, 12.9% in MELD 11-14, 24.1% in MELD >15 were malnourished, and by BIA 26%, 29% and 38% respectively. This could contribute to the overestimation of renal function in this population when sCr is used. Conclusion: Estimated GFR by CysC formulas overestimated GFR by DTPA-Tc99 in a lesser degree than sCr formulas. SCr may not be an adequate measure of renal function in this population. Nutritional status could be used to weigh parameters of renal function in malnourished cirrhotic patients. The most benefited group could be patients with MELD >15, candidates for liver transplantation, since an impaired renal function affects postransplant outcomes, and some of them could require liver-kidney transplant.

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Predictors for the Development of Cardiac Ascites in Patients Referred for Cardiac Transplantation

Brian Kim[1], Amy Tan[2], Berkeley N. Limketkai[3], Sean Pinney[4], Thomas D. Schiano[1]; [1]Hepatology, Mount Sinai, New York, NY; [2]Medicine, Mount Sinai, New York, NY; [3]Gastroenterology and Hepatology, Johns Hopkins, Baltimore, MD; [4]Cardiology, Mount Sinai, New York, NY

Background: Cardiac ascites, while frequently diagnosed, has no clear mechanism described in the literature. A portal pressure greater than 10 mmHg is often cited as a requirement for cirrhosis-related ascites. However, there is no minimum right atrial (RA) pressure required for cardiac ascites formation found in the literature. In a group of heart failure (HF) patients referred for cardiac transplantation (CT), we attempted to identify patient characteristics and predictors associated with the development of cardiac ascites. Methods: All adult patients with HF referred to Mount Sinai Medical Center for CT from January 2010 to August 2013 were retrospectively assessed. Patients were divided into two groups based on abdominal imaging: those with and without clinically significant ascites, which was defined as having "moderate" to "large" ascites. Demographic information, serum laboratory values, and results of transtho-

racic echocardiograms (TTE) and right heart catheterizations (RHC) were compared between the groups. Results: Of the 225 patients assessed, 29 patients were excluded due to lack of abdominal imaging. Of the 196 study patients, 29 (14.8%) patients had clinically significant ascites. There were no significant differences in age, gender, ethnicity/race, and etiology of heart disease in the two groups. However, the ascites group had higher creatinine (2.3 vs 1.6 mg/dL, p=0.03), higher BUN (50.1 vs 32.6 mg/dL, p<0.01), higher brain natriuretic peptide (1611 vs 1103 pg/mL, p=0.04), and lower albumin (3.3 vs 3.6 g/dL, p=0.03). On TTE, the ascites group had more severe right ventricular (RV) dilatation (p=0.03) and more tricuspid valve regurgitation (p<0.01). However, this group had a higher left ventricular ejection fraction (33.0 vs 19.9%, p<0.01). On RHC, the ascites group had a higher mean RA pressure (17.1 vs 13.1 mmHg, p=0.01) and a higher RV end diastolic pressure (18.4 vs 12.9 mmHg, p<0.01). There was no difference in pulmonary capillary wedge pressure between the groups (21.8 vs 22.9 mmHg, p=0.57). No clear threshold value of RA pressure was identified for the development of cardiac ascites. Conclusion: Clinically significant ascites was seen in 14.8% of our HF patients referred for CT. Right-sided HF was more commonly seen in the ascites group. In contrast, left-sided HF did not correlate with the presence of ascites. Unlike in cirrhosis, no minimum RA pressure elevation was required for cardiac ascites formation. This is possibly due to other contributing factors in the formation of cardiac ascites, such as worse renal function and lower serum albumin.

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Computer-assisted image analysis of fibrosis on liver biopsy : relationship with portal pressure, histology and clinical data

Nicolas Goossens[1], Sophie Restellini[1], Sophie Clément[2], Laura Rubbia-Brandt[2], Laurent Spahr[1]; [1]Hepatology, Univ. Hospitals of Geneva, Geneva, Switzerland; [2]Clinical Pathology, Univ. Hospitals of Geneva, Geneva, Switzerland

Background : Liver fibrosis (Fib) participates to the development of portal hypertension (PHT). Assessment of Fib is important in the diagnosis and prognosis of patients with chronic liver disease. Hepatic venous pressure gradient (HVPG) evaluates PHT in clinical practice. We aimed to generate a simple cut-off value of liver fibrosis density that would be associated with several clinical, biological and histological endpoints. We quantified liver fibrosis in transjugular biopsies (TJL-101-ET needle set Cook) and determined the relationship with HVPG, elastometry (FS), a non invasive marker of fibrosis/PHT, and other parameters in a large cohort of chronic liver disease. Methods : 86 patients (cirrhosis 67%, MELD 15.4 ± 6, alcoholics (ALD)=61%, HCV=25%, HVPG 19 ± 5.4 mmHg, ascites 45%) and 9 healthy subjects candidates for living donation were included. We used a computer-assisted method to assess the relative proportion of fibrosis (% fibrosis/total biopsy specimen) on Sirius red stained liver sections. The examiner was blinded to patients' characteristics. Results : Fibrosis was higher in patients vs controls (7.8% vs 1%, p<0.001), and in ALD vs HCV (9 vs 4.9%, p<0.01). Table: correlation of fibrosis with variables. On multivariate analysis, only HVPG was associated with fibrosis density (OR 1.3 per unit increase in HVPG, 95% CI [1.1-1.7], p=0.009). Conclusion : In patients with advanced chronic liver disease, density of fibrosis measured on Sirius red stained liver biopsy correlates with PHT, elastometry, and features of liver injury. We determined a threshold useful to identify patients with particular clinical, biological and histological parameters that are commonly measured in clinical practice.

Variable	Low Fib (<4.8%)	High Fib (>4.8%)	p value
HVPG (mmHg)	13.2	17.8	0.01
FS (kPa)	18	40	0.04
MELD	13	18	0.01
ascites	37%	63&	0.04
Histo cholestasis	23%	61%	0.01
Histo ballooned hepatocytes	26%	54%	0.02
Histo steatosis	43%	34%	0.81

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Non-invasive measurement of acute hemodynamic changes using inert gas rebreathing during routine therapeutic paracentesis in tense ascites

Christoph Antoni[1], Joachim Saur[2], Thomas Zimmerer[1], Nenad Suvajac[2], Julia D. Michels[2], Matthias Ebert[1], Frederik Trinkmann[2]; [1]Dept. of Internal Medicine II, University Hospital, Mannheim, Germany., Mannheim, Germany; [2]Dept. of Internal Medicine I, University Hospital, Mannheim, Germany., Mannheim, Germany

Background: In cirrhosis with portal hypertension a decrease in cardiac afterload leads to characteristic hyperdynamic circulation and splanchnic arterial vasodilation. With disease progression, cardiac output (CO) cannot be further increased resulting in arterial hypotension, stimulation of the sympathetic nervous and renin-angiotensin system as well as ascites. Tense ascites decreases venous return and thus CO due to compression of the inferior vena cava and right atrium. Finally, hepatorenal syndrome (HRS) is the extreme expression of this hemodynamic dysfunction. Therapeutic paracentesis acutely increases CO which has been previously identified to be an independent risk factor for the development of HRS. However, the determination of CO is difficult in clinical routine due to invasive, operator dependent or time-consuming standard procedures such as right heart catheterization, echocardiography or cardiac magnetic resonance imaging. The aim of our study was to evaluate hemodynamic changes during paracentesis using non-invasive inert gas rebreathing (IGR). Methods: Routine therapeutic paracentesis was performed in the supine position using ultrasound guidance in 28 patients with tense ascites refractory to therapy. In patients with a volume of ascites removed (VA) > 5 liters albumin was administered. Hemodynamic parameters including CO, stroke volume (SV), heart rate (HR), systolic and diastolic blood pressure (SBP, DBP) were assessed immediately prior to and after the procedure using IGR. Results: The collective (19 men) aged from 42 to 76 years. Mean MELD score was 13 with 15 patients in Child-Pugh class B (CPC) and 13 in C. Most frequent causes of cirrhosis were alcohol (16) and HCV (4) or HBV (3). Mean VA was 4400±1500 ml (range 1900 to 8000 ml). CO significantly increased from 5.7±1.7 to 7.0±2.0 l/min after paracentesis (p<0.001). SV accordingly increased from 81±26 ml to 97±33 ml (p<0.001). Both SBP and DBP significantly dropped from 122±19 to 117±18 mmHg (p=0.04) and 69±12 to 63±13 mmHg (p<0.001). HR remained unchanged at 73±14 and 74±15 mmHg (p=0.69).There was a moderate correlation between VA and change in CO (r=0.36, p=0.12). We neither found differences between change in CO and CPC

(p=0.31) nor the cause of cirrhosis (p=0.25). Conclusion: IGR is safe and feasible in tracking hemodynamic changes non-invasively induced by therapeutic paracentesis. Hyperdynamic circulation further increases acutely showing a moderate association with VA. Further studies are warranted as knowledge of hemodynamics may be beneficial in evaluating patients at risk for e.g. HRS, portopulmonary hypertension or hepatopulmonary syndrome.

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PTFE-covered TIPS position relative to the hepatocaval junction and impact on shunt patency

Charles N. Weber, Gregory J. Nadolski, Michael C. Soulen; Radiology, Hospital of the University of Pennsylvania, Philadelphia, PA

Purpose Distance from the hepatocaval junction (HCJ) to the hepatic venous (HV) end of transjugular intrahepatic portosystemic shunt (TIPS) created with bare metal stents (BMS) has been shown to impact patency. Now, most TIPS are created with polytetrafluoroethylene (PTFE)-covered stent-grafts. Our study investigates the impact of distance from the HCJ on long-term patency of PTFE-covered TIPS. Methods PTFE-covered TIPS placed between 2002 and 2013 were retrospectively reviewed. Clinical and imaging data were collected from the electronic medical record and radiology imaging archive. Distance from HV end to the HCJ was recorded. Primary patency rates were calculated. Differences between groups based on distance from HV end to HCJ were compared using Kaplan-Meier and Cox regression analyses. Results 300 PTFE-covered TIPS were included in the study. 201 were placed with a single stent-graft while 99 were extended at the HV end with additional BMS(N=70) or stent-grafts(N=29). No threshold distance between HV end of the TIPS and HCJ was found to impact long-term patency (p-values at thresholds of 0, 5, 10, 15, and 20 mm were 0.92, 0.79, 0.43, 0.36 and 0.24 respectively). Primary patency in TIPS placed with just a single stent-graft versus those using additional stents was 90% vs 82%, 83% vs 71%, 81% vs 60% 6 months, 1 and 2 years respectively (p = 0.03). In TIPS created with multiple stents, primary patency of those with BMS versus PTFE-covered extensions was 84% vs 78%, 73% vs 69%, and 69% vs 46% at 6 months, 1 and 2 years respectively (p = 0.28). Regression analysis demonstrated the length by which a TIPS was extended and the final distance of the HV end to the HCJ were not predictors of patency failure (p>0.1 and p = 0.06 respectively). Conclusion If the HV end of PTFE-covered TIPS is within 2 cm of the HCJ, the primary patency is not determined by the actual distance from the HCJ nor is it improved by extending the TIPS to the HCJ. If extended, PTFE-covered extensions offer no patency benefit over BMS. The best patency rates occur with single PTFE-covered TIPS.

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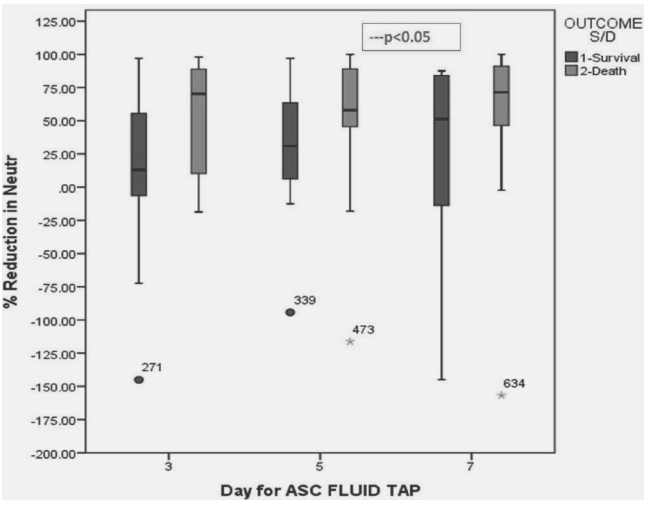
Response guided ascitic tap in spontaneous bacterial peritonitis predicts outcome

Ashok K. Choudhury, Ankur Jindal, Chandan K. Kedarisetty, Tanmay S. Vyas, Ajeet S. Bhadoria, Shiv K. Sarin; Hepatology, Institute of Liver and Biliary Sciences New Delhi, India, NEW DELHI, India

Background and Aims: - Spontaneous bacterial peritonitis (SBP) is the commonest and life-threatening infection in liver cirrhosis. Identification of risk factors, choice and timing of antibiotic in relation to response can improve outcome.We investigated the role of serial ascitic tap for antibiotic response to predict the outcome. Patients and Methods: - Patients of decompensated cirrhosis diagnosed with spontaneous bacterial peritonitis (as per definition) were analyzed retrospectively. As per protocol, the patient underwent ascitic tap after 48hr in all cases and on 5th and 7th day depending upon the clinical parameters. Results:- Total 161 patient of decompensated cirrhosis, mean age 50.8yrs(±11.8SD,) 82% male, with mean CTP =12.3±1.47 and median MELD = 22.7 (range=16-28) were analyzed. Ethanol was the commonest etiology (n=64, 40%), followed by cryptogenic (n=32, 20%) and NASH (n=21, 13%). SBP was associated with hepatic encephalopathy (HE) in 93(57.7%), Variceal bleed (VB) in 16(9.9%), septic shock in 60(37.2%) requiring ventilator support in 47(29.2%) with median hospital stay of 7(range 4-14) days with a high mortality (n=43, 26.7%); predominantly due to sepsis (83.7%), Variceal bleed (11.7%). The predictors of poor survival were presence of HE, Child-C status, MELD >24, persistence of SBP on D3 and D7, low ascitic fluid glucose <92mg/dl%, culture positivity for ascitic fluid (p<0.05). Reduction in ascitic fluid neutrophil count by 13% on D3, was the only predictor associated with improved survival (p<0.05). Conclusions:- The clinical presentation, advanced liver disease, low ascitic fluid glucose with culture positivity at the baseline and the neutrophil count reduction but not the base line ascitic fluid TLC or reduction at 48hr predict the resolution of SBP and overall outcome.

The response tap at 48 hr showing neutrophil count reduction by 13% is associated with better outcome



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Does transjugular intrahepatic portosystemic shunt (TIPS) with covered stents modify the natural course of decompensed cirrhosis?

Xavier Adhoute[1], Paul Castellani[1], Guillaume Penaranda[2], Olivier Monnet[3], Herve Perrier[1], Bernard L. Pol[4], Cyril Muller[3], Arthur Laquiere[1], Valerie Oules[1], Patrick Beaurain[3], Christian Boustiere[1], Olivier Bayle[3], Marc Bourlière[1]; [1]Hepatology, hôpital saint-joseph, Marseille, France; [2]Biostatistics, ALPHABIO Laboratory, Marseille, France; [3]Radiology, hôpital saint-joseph, Marseille, France; [4]Hepatobiliairy Surgery, hôpital saint-joseph, Marseille, France

Purpose : To analyze the impact of TIPS with covered stents on survival of patients with "severe" portal hypertension compared to a control group treated medically. To assess complications associated with implantation of the TIPS. Material and methods : 344 consecutive patients were hospitalized for decompensated cirrhosis (Child-Pugh B 60% / C 40%) from 01/2008 to 12/2012. Covered stent was implanted in 98 patients for refractory ascites or recurrent gastrointestinal bleeding. Assessment of median survival (MS) with and without TIPS, MS according to Child-Pugh score and after matching 1:1 (n=130) for age, Child-Pugh score, MELD score, presence of hepatocellular carcinoma HCC, to a control group having a first decompensation. Results :TIPS implantation was successful in 100% of rates. The mean portosystemic pressure gradient decreased from 18.5±4.5 mmHg to 5.8±2.6 mmHg. MS of patients with TIPS (n=98) was 29.4 months [22-38.6] vs. 12.9 months [10.2-18.3] without TIPS (n=246), p=0.0015 ; MS of child-pugh B patients with TIPS (n=69) was 38.6 months [29.4-48.7] vs. 19.1 months [14.1-35.3] without TIPS (n=137), p=0.0183; MS of child-pugh C patients with TIPS (n=29) was 17.4 months [10.1-25.3] vs. 8 months [6.2-11.2] without TIPS (n=109), p=0.22. TIPS was a prognostic variable associated with survival in univariate analysis (p=0.015). HCC, alcoholic hepatitis were more frequent in patients without TIPS (respectively 31% vs. 8%, p <.0001, 17% vs. 10%, p=0.05). After matching 1:1 for age (61 ±10), Child-Pugh score (B 66%, C 34%), MELD score (17.0±4.2) and presence of HCC (9%), esophageal varices grade 2 or 3 (p=0.003), refractory ascites (p=0.01), an increase in the portosystemic gradient (p=0.008) were significantly more frequent in the TIPS group. Median survival was 26 months in the TIPS group (n=65) vs. 27 months without TIPS (n=65), p=1.00. Median follow up was 12 months. Rate of infection did not differ between the 2 groups. Main complications of TIPS (recurrent encephalopathy 34%, stent dysfunction 24.5%, strangulated umbilical hernia 9%, congestive heart failure 7.5%) did not affect patient survival. Conclusion : in this series, TIPS with covered stents appears to improve the natural history of Child-Pugh B cirrhosis with recurrent decompensation. Conversely, decreasing portosystemic pressure gradient does not alter the progression of Child-Pugh C cirrhosis with prolonged decompensation. Earlier implementation of a tips should be discussed for some child-pugh B patients with recurrent ascites or gastrointestinal bleeding.

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Factors associated with medication adherence in patients living with cirrhosis

Suzanne Polis[1,5], Ling Zhang[1], Amany Zekry[1,3], Ritin Fernandez[2,4]; [1]Gastroenterology & Hepatology, St George Hospital, Kogarah, NSW, Australia; [2]Centre for Research in Nursing and Health, St George Hospital, Kogarah, NSW, Australia; [3]University of New South Wales, St George Clinical School of Medicine, Kogarah, NSW, Australia; [4]School of Nursing and Midwifery, University of Wollongong, Wollongong, NSW, Australia; [5]VHEPP, The Kirby Institute, Randwick, NSW, Australia

Medication adherence is a complex and dynamic interplay of disease specific factors, medication related factors and individual factors such as medication and disease knowledge, beliefs and self efficacy. Improving patient's medication adherence is challenging yet a vital component in the treatment and management of liver cirrhosis. Our study aimed to determine adherence patterns and identify which factors contribute to non-adherence in people living with liver cirrhosis. Methods Participants diagnosed with cirrhosis attending a tertiary based liver clinic were invited to complete a self reported survey. The questionnaire included items relating to demographic information, adherence to medications and knowledge of liver disease and treatment. Data were entered collated, checked and analysed using SPSS version 21. Results Data were obtained from 29 patients (24, 83%) males), median age 57 years (SD 9.2). Eleven (45%) of the patients who were prescribed medications measured low medication adherence using a medication-taking scale. The most commonly reported reasons for this non-adherence included running out of medications, forgetting, being away from home and sleeping through the dose. Mean scores for medication self efficacy, beliefs about medication and social supports were high at 2.58 (SD.0.6), 2.53 (SD 0.6) and 2.2 (SD 0.07) respectively. Overall patients reported good knowledge of liver cirrhosis, individualised care plan and medication regime with approximately 60% of the participants correctly answering nine or more of the thirteen assessment questions. Overall knowledge of prescribed medications was high, however 10 (35%) said that they would adjust medication if their symptoms improved without telling their doctor and 13 (45%) believed that herbal medications would help their liver. Participants 16 (55%) had incorrect knowledge of hepatocellular carcinoma (HCC) surveillance programs and nutritional requirements with 22 (76%) reported that the liver cleansing diet would improve liver health and 11 (38%) had limited knowledge about dietary supplements. Conclusion To our knowledge this is the first study to investigate adherent behaviour in patients diagnosed with cirrhosis. Our study reported low medication adherence in 45% of participants who were prescribed medication. Running out of medications and forgetting were the most common reason for non-adherence. Gaps of patient knowledge related to cirrhosis, nutrition and HCC surveillance were identified. Further research to improve patient knowledge and develop strategies to improve adherence are needed.

Disclosures:

The following people have nothing to disclose: Suzanne Polis, Ling Zhang, Amany Zekry, Ritin Fernandez