Liver Digest

A weekly update of PLRC happenings

September 5, 2019

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Marlies Meisel

In this issue

PLRC Meet and Greet

September 12, 2019
4:30-7:30 p.m.
University Club
Dinner Reception included.

4:30-5:00 – Welcome, Center Overview, Q&A (Dr. Paul Monga)
5:00-5:30 – Drinks & Hors d'oeuvres
5:30-6:00 – Core Directors' presentations – 5 minutes each

- 5:30-5:35 – Pilot & Feasibility (Dr. Gavin Arteel)
- 5:35-5:40 – Enrichment (Dr. Kari Nejak-Bowen)
- 5:40-5:45 – Advanced Cell & Tissue Imaging (Dr. Donna Stolz)
- 5:45-5:50 – Biospecimen Repository & Processing (Dr. Aatur Singhi, Dr. David Geller)
- 5:50-5:55 – Genomics & Systems Biology (Dr. Takis Benos, Dr. Jianhua Luo)

6:00-6:15 – Q&A
6:15-7:00 – Dinner
7:00-7:15 – Path Forward (Dr. Paul Monga)
7:15-7:30 – Q&A

Next Week's Seminar

Liver Seminar - Dr. Gregory Gores
Wed, 09/11/2019

12:00 to 1:00 pm
1104 Scaife

Gregory J. Gores, MD

Professor of Medicine & Physiology
Executive Dean for Research, Mayo Foundation for Medical Education and Research
Mayo Clinic, Rochester, Minnesota

"Cholangiocarcinoma: Mice to Human"

Department of Pathology Seminar, co-sponsored by PLRC

Faculty Highlights

PLRC members collaborating on manuscripts are noted in red.

Original Article:
Sogawa H, Costa G, Armanyous S, Bond GJ, Cruz RJ, **Humar A, Mazariegos G**, Abu-Elmagd KM. Twenty Years of Gut Transplantation for Chronic Intestinal Pseudo-obstruction: Technical Innovation, Long-term Outcome, Quality of Life, and Disease Recurrence. Ann Surg. 2019 Jun 26. doi: 10.1097/SLA.0000000000003265. PubMed PMID: 31274659.

ABSTRACT
OBJECTIVE: To define long-term outcome, predictors of survival, and risk of disease recurrence after gut transplantation (GT) in patients with chronic intestinal pseudo-obstruction (CIPO).

BACKGROUND: GT has been increasingly used to rescue patients with CIPO with end-stage disease and home parenteral nutrition (HPN)-associated complications. However, long-term outcome including quality of life and risk of disease recurrence has yet to be fully defined.

METHODS: Fifty-five patients with CIPO, 23 (42%) children and 32 (58%) adults, underwent GT and were prospectively studied. All patients suffered gut failure, received HPN, and experienced life-threatening complications. The 55

patients received 62 allografts; 43 (67%) liver-free and 19 (33%) liver-contained with 7 (13%) retransplants. Hindgut reconstruction was adopted in 1993 and preservation of native spleen was introduced in 1999. Immunosuppression was tacrolimus-based with antilymphocyte recipient pretreatment in 41 (75%).

RESULTS: Patient survival was 89% at 1 year and 69% at 5 years with respective graft survival of 87% and 56%. Retransplantation was successful in 86%. Adults experienced better patient (P = 0.23) and graft (P = 0.08) survival with lower incidence of post-transplant lymphoproliferative disorder (P = 0.09) and graft versus host disease (P = 0.002). Antilymphocyte pretreatment improved overall patient (P = 0.005) and graft (P = 0.069) survival. The initially restored nutritional autonomy was sustainable in 23 (70%) of 33 long-term survivors with improved quality of life. The remaining 10 recipients required reinstitution of HPN due to allograft enterectomy (n = 3) or gut dysfunction (n = 7). Disease recurrence was highly suspected in 4 (7%) recipients.

CONCLUSIONS: GT is life-saving for patients with end-stage CIPO and HPN-associated complications. Long-term survival is achievable with better quality of life and low risk of disease recurrence.

For full text, please **click here**.

Original Article:
Rich NE, Yang JD, Perumalswami PV, Alkhouri N, Jackson W, Parikh ND, Mehta N, Salgia R, **Duarte-Rojo A**, Kulik L, Rakoski M, Said A, Oloruntoba O, Ioannou GN, Hoteit MA, Moon AM, Rangnekar AS, Eswaran SL, Zheng E, Jou JH, Hanje J, Pillai A, Hernaez R, Wong R, Scaglione S, Samant H, Kapuria D, Chandna S, Rosenblatt R, Ajmera V, Frenette C, Satapathy SK, Mantry P, Jalal P, John BV, Fix OK, Leise M, Lindenmeyer CC, Flores A, Patel N, Jiang ZG, Latt N, Dhanasekaran R, Odewole M, Kagan S, Marrero JA, Singal AG. Provider Attitudes and Practice Patterns for Direct-Acting Antiviral Therapy for Patients with Hepatocellular Carcinoma. Clin Gastroenterol Hepatol. 2019 Jul 26. pii: S1542-3565(19)30786-4. doi: 10.1016/j.cgh.2019.07.042. PubMed PMID: 31357028.

ABSTRACT
BACKGROUND & AIMS: Direct-acting antivirals (DAAs) are effective against hepatitis C virus and sustained virologic response is associated with reduced incidence of hepatocellular carcinoma (HCC). However, there is controversy

over the use of DAAs in patients with active or treated HCC and uncertainty about optimal management of these patients. We aimed to characterize attitudes and practice patterns of hepatology practitioners in the United States regarding the use of DAAs in patients with HCC.

METHODS: We conducted a survey of hepatology providers at 47 tertiary care centers in 25 states. Surveys were sent to 476 providers and we received 279 responses (58.6%).

RESULTS: Provider beliefs about risk of HCC recurrence after DAA therapy varied: 48% responded that DAAs reduce risk, 36% responded that DAAs do not change risk, and 16% responded that DAAs increase risk of HCC recurrence. However, most providers believed DAAs to be beneficial to and reduce mortality of patients with complete responses to HCC treatment. Accordingly, nearly all providers (94.9%) reported recommending DAA therapy to patients with early-stage HCC who received curative treatment. However, fewer providers recommended DAA therapy for patients with intermediate (72.9%) or advanced (57.5%) HCC undergoing palliative therapies. Timing of DAA initiation varied among providers based on HCC treatment modality: 49.1% of providers reported they would initiate DAA therapy within 3 months of surgical resection whereas 45.9% and 5.0% would delay DAA initiation for 3-12 months and >1 year post-surgery, respectively. For patients undergoing transarterial chemoembolization (TACE), 42.0% of providers would provide DAAs within 3 months of the procedure, 46.7% would delay DAAs until 3-12 months afterward, and 11.3% would delay DAAs more than 1 year after TACE.

CONCLUSION: Based on a survey sent to hepatology providers, there is variation in provider attitudes and practice patterns regarding use and timing of DAAs for patients with HCC. Further studies are needed to characterize the risks and benefits of DAA therapy in this patient population.

For full text, please **click here**.

Review Article:

Cohen M, Lamparello AJ, Schimunek L, El-Dehaibi F, Namas RA, Xu Y, Kaynar AM, **Billiar TR, Vodovotz Y**. Quality Control Measures and Validation in Gene Association Studies: Lessons for Acute Illness. Shock. 2019 Jul 30. doi: 10.1097/SHK.0000000000001409. PubMed PMID: 31365490.

ABSTRACT

Acute illness is a complex constellation of responses involving dysregulated inflammatory and immune responses, which are ultimately associated with multiple organ dysfunction. Gene association studies have associated single-nucleotide polymorphisms (SNPs) with clinical and pharmacological outcomes in a variety of disease states, including acute illness. With approximately 4-5 million SNPs in the human genome and recent studies suggesting that a large portion of SNP studies are not reproducible, we suggest that the ultimate clinical utility of SNPs in acute illness depends on validation and quality control measures. To investigate this issue, in December 2018 and January 2019 we searched the literature for peer-reviewed studies reporting data on associations between SNPs and clinical outcomes and between SNPs and pharmaceuticals (i.e. pharmacogenomics) published between January 2011 to February 2019. We review key methodologies and results from a variety of clinical and pharmacological gene association studies, including trauma and sepsis studies, as illustrative examples on current SNP association studies. In this review article, we have found three key points which strengthen the potential accuracy of SNP association studies in acute illness and other diseases: 1) providing evidence of following a protocol quality control method such as the one in Nature Protocols (22) or the OncoArray QC Guidelines (21); 2) enrolling enough patients to have large cohort groups; and 3) validating the SNPs using an independent technique such as a second study using the same SNPs with new patient cohorts. Our survey suggests the need to standardize validation methods and SNP quality control measures in medicine in general, and specifically in the context of complex disease states such as acute illness.

For full text, please **click here**.

Research Report:

Celik N, **Squires JE**, Soltys K, **Vockley J**, Shellmer DA, Chang W, Strauss K, **McKiernan P**, Ganoza A, **Sindhi R**, Bond G, Mazariegos G, Khanna A. Domino liver transplantation for select metabolic disorders: Expanding the living donor pool. JIMD Rep. 2019 Jun 19;48(1):83-89. doi: 10.1002/jmd2.12053. eCollection 2019 Jul. PubMed PMID: 31392117; PubMed Central PMCID: PMC6606984.

ABSTRACT

Domino liver transplantation (DLT) involves transplanting liver from a patient with metabolic disease into a patient with end-stage liver disease with the

expectation that the recipient will not develop the metabolic syndrome or the recurrent syndrome will have minimal affect. The domino donor gets a deceased donor or a segment of live-donor liver through the deceased donor organ allocation system. Waitlist mortality for the domino recipient exceeds morbidity associated with getting the donor disease. Between 2015 and 2017, four patients with three metabolic disorders at UPMC Children's Hospital of Pittsburgh underwent DLT with domino allografts from maple syrup urine disease (MSUD) patients. These included patients with propionic acidemia (PA) (n=1), Crigler-Najjar (CN) syndrome type-1 (n=2), and carbamoyl phosphate synthetase deficiency (CPSD) (n=1). Mean follow-up was 1.6 years (range 1.1-2.1 years). Total bilirubin levels normalized postoperatively in both CN patients and they maintain normal allograft function. The PA patient had normal to minimal elevations of isoleucine and leucine, and no other abnormalities on low protein diet supplemented with a low methionine and valine free formula. No metabolic crises have occurred. The patient with CPSD takes normal baby food. No elevation in ammonia levels have been observed in any of the patients. DLT for a select group of metabolic diseases alleviated the recipients of their metabolic defect with minimal evidence of transferrable-branched chain amino acid elevations or clinical MSUD despite increased protein intake. DLT using allografts with MSUD expands the live donor liver pool and should be considered for select metabolic diseases that may have a different enzymatic deficiency.

For full text, please **click here**.

Funding Opportunities

Career Developement Awards: Advanced/Transplant Hepatology Award
American Association for the Study of Liver Diseases (AASLD)

Research Scholar Award (RSA)
American Gastroenterological Association (AGA)
AGA Research Foundation

Food as Medicine: Food Insecurity and HIV-related Comorbidities, Coinfections, and Complications within the Mission of the NIDDK (R01 Clinical Trial Optional)
(RFA-DK-19-019)

National Institute of Diabetes and Digestive and Kidney Diseases

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****NIAAA - Fellowship and Career Development Awards**

Gary Murray, Program Director for the Division of Metabolism and Health Effects at NIAAA, encourages submissions for fellowships (T and F) and career development (K awards) in this research area. Due to a shortfall in the number of fellowship and training applications related to research on alcohol and metabolism, organ and tissue damage in past years have resulted in a change in the way that NIAAA prioritizes this research. Links to K-awards and fellowships in which NIAAA participates are:

K awards

Fellowship awards (T and F)

Applications in this area have enjoyed funding at ~30th percentile. If you have individuals that may qualify for these awards, now appears to be a very competitive time to submit.

Our mailing address is:
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