Liver Digest

A weekly update of PLRC happenings

April 18, 2019

PITTSBURGH LIVER RESEARCH CENTER

A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Lawrence Vernetti

In this issue

Next Week's Seminars

PLRC Seminar Series:

Tuesday, April 23, 2019

12:00-1:00 pm

S123 BST

Vijay Shah, MD

Professor of Medicine

Professor of Physiology

Mayo Clinic, Rochester, Minnesota

Alcohol-induced fibrosis and portal hypertension: Tales from the Sinusoids

This activity has been approved for AMA PRA Category 1 Credit. #6242 Liver Center Seminars.

Pizza will be provided.

++++++

Registration URL: https://attendee.gotowebinar.com/register/6607572696840938499

For those viewing thru the webinar, please follow the directions below:

- Please Register for the live Webinar ASAP
- After registering, you will receive the confirmation email
- You will be prompt to download the CitrixOnline application and install on your PC or Laptop
- Please contact your local PC Support if you need help installing the application
- Feel free to email Ishtiaque Ahmed (**ahmedi@upmc.edu**) if you have

any questions

NOTE Webinar attendees -- use Telephone/Speakerphone and dial-in instead of using desktop/laptop speakers for better audio quality.

Telephone/Speakerphone Audio option is shown right at the Click to Join Webinar prompt.

Transplantation Grand Rounds:
Friday, April 26, 2019
8:00 a.m. – 9:00 a.m.
LHAS Auditorium
7 Main – MUH

Sandy Feng, MD, PhD
Professor of Surgery in Residence
Director, Abdominal Transplant Surgery Fellowship
University of California San Francisco

"Tolerance in Liver Transplantation: Trials and Tribulations"

Directly Sponsored by
Thomas E. Starzl Transplantation Institute
University of Pittsburgh School of Medicine
Department of Surgery, Division of Transplantation
and
Center for Continuing Education in the Health Sciences

Target Audience: Transplantation fellows and faculty (basic and clinical); research associates and assistants; clinical and research nurses. Overall Goals of the Program: To provide cutting-edge information about research in the transplantation field and related disciplines. This activity is sponsored by the University Of

Pittsburgh School Of Medicine, Center for Continuing Education in the Health Sciences and the Department of Surgery. The University Of Pittsburgh School Of Medicine, as part of the Consortium for Academic Continuing Medical Education, is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians. The Center for Continuing Education in the Health Sciences designates this educational activity for a maximum of 1 hour in Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity. Category 1 Continuing Education Points for Transplant Certification (CEPTCs) have been applied for through the American Board for Transplant Certification (ABTC).

Faculty Highlights

Original Article:

McKiernan PJ, Ganoza A, **Squires JE**, **Squires RH**, **Vockley J**, **Mazariegos G**, Soltys K, Sun Q, **Sindhi R**. Evolving trends in liver transplant for metabolic liver disease in the United States. Liver Transpl. 2019 Feb 12. doi: 10.1002/lt.25433. [Epub ahead of print] PubMed PMID: 30753750.

ABSTRACT

RATIONALE: Indications for liver transplantation (LT) in metabolic disease are evolving. We reviewed the US experience with primary LT for metabolic disease in the Scientific Registry for Transplant Recipients (October 1987 to June 2017) to determine: 1. Temporal changes in indications, 2. long-term outcomes, and 3. factors predicting survival.

METHOD: Subjects were grouped by the presence of structural liver disease and whether the defect was confined to the liver.
RESULTS: 5996 underwent LT metabolic disease, 2354 [39.3%] being children. LT for metabolic disease increased in children but not in adults. Children experienced a six-fold increase in LT for metabolic disease without structural liver disease. Indications for LT remained stable in adults. Living donor LT increased with eras from 5.6 to 7.6% in children, and 0 to 4.5% in adults. Patient and graft survival improved with time. Latest 5-year patient survival were 94.5 and 81.5% in children and adults respectively. Outcomes were worse in adults and in those with extrahepatic disease, ($p<0.01$) while structural liver disease did not affect outcome. Survival improved with younger age at LT until age <2 years. On multivariate analysis; diagnostic category, inpatient status, age at LT and transplant era significantly predicted outcome in all ages, with male gender predicting survival in childhood only. Children without structural disease were less likely to die awaiting LT and had improved post LT survival compared to children with chronic liver disease.
CONCLUSIONS: Liver transplantation for metabolic disease: 1. is increasingly utilized for phenotypic correction in children. 2. Extrahepatic manifestations significantly impact survival at all ages. 3. Where indicated should not be unnecessarily delayed. 4. May require the development of new allocation models.

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

Original Article:

Singhi AD, Nikiforova MN, Chennat J, Papachristou GI, Khalid A, **Rabinovitz M**, Das R, Sarkaria S, Ayasso MS, Wald AI, Monaco SE, **Nalesnik M**, Ohori NP, **Geller D**, Tsung A, Zureikat AH, Zeh H, Marsh JW, Hogg M, Lee K, Bartlett DL, Pingpank JF, **Humar A**, **Bahary N**, Dasyam AK, Brand R, Fasanella KE, McGrath K, Slivka A. Integrating next-generation sequencing to endoscopic retrograde

cholangiopancreatography (ERCP)-obtained biliary specimens improves the detection and management of patients with malignant bile duct strictures. Gut. 2019 Apr 10. pii: gutjnl-2018-317817. doi: 10.1136/gutjnl-2018-317817. [Epub ahead of print]

ABSTRACT

OBJECTIVE: Despite improvements in imaging, serum CA19-9 and pathological evaluation, differentiating between benign and malignant bile duct strictures remains a diagnostic conundrum. Recent developments in next-generation sequencing (NGS) have opened new opportunities for early detection and management of cancers but, to date, have not been rigorously applied to biliary specimens.

DESIGN: We prospectively evaluated a 28-gene NGS panel (BiliSeq) using endoscopic retrograde cholangiopancreatography-obtained biliary specimens from patients with bile duct strictures. The diagnostic performance of serum CA19-9, pathological evaluation and BiliSeq was assessed on 252 patients (57 trainings and 195 validations) with 346 biliary specimens.

RESULTS: The sensitivity and specificity of BiliSeq for malignant strictures was 73% and 100%, respectively. In comparison, an elevated serum CA19-9 and pathological evaluation had sensitivities of 76% and 48%, and specificities of 69% and 99%, respectively. The combination of BiliSeq and pathological evaluation increased the sensitivity to 83% and maintained a specificity of 99%. BiliSeq improved the sensitivity of pathological evaluation for malignancy from 35% to 77% for biliary brushings and from 52% to 83% for biliary biopsies. Among patients with primary sclerosing cholangitis (PSC), BiliSeq had an 83% sensitivity as compared with pathological evaluation with an 8% sensitivity. Therapeutically relevant genomic alterations were identified in 20 (8%) patients. Two patients with ERBB2-amplified cholangiocarcinoma received a trastuzumab-based regimen and had measurable clinicoradiographic response.

CONCLUSIONS: The combination of BiliSeq and pathological evaluation of biliary specimens increased the detection of malignant strictures, particularly in patients with PSC. Additionally, BiliSeq identified

alterations that may stratify patients for specific anticancer therapies.

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

The study is featured in UPMC "Inside Life Changing Medicine": **Sudden, Deadly Diagnosis Swiftly Cured with Precision Medicine**, by Erin Hare, which is **available here**.

Original Article:
Zamora R, Barclay D, Yin J, Alonso EM, Leonis MA, Mi Q, **Billiar TR**, Simmons RL, **Squires RH**, **Vodovotz Y**. HMGB1 is a Central Driver of Dynamic Pro-inflammatory Networks in Pediatric Acute Liver Failure induced by Acetaminophen. Sci Rep. 2019 Apr 12;9(1):5971. doi: 10.1038/s41598-019-42564-5. PMID: 30979951 DOI: 10.1038/s41598-019-42564-5

ABSTRACT
Acetaminophen (APAP) overdose (APAPo) is predominant in the NIH Pediatric Acute Liver Failure (PALF) Study. We assayed multiple inflammatory mediators in serial serum samples from 13 PALF survivors with APAPo + N-acetylcysteine (NAC, the frontline therapy for APAPo), 8 non-APAPo + NAC, 40 non-APAPo non-NAC, and 12 non-survivors. High Mobility Group Box 1 (HMGB1) was a dominant mediator in dynamic inflammation networks in all sub-groups, associated with a threshold network complexity event at d1-2 following enrollment that was exceeded in non-survivors vs. survivors. We thus hypothesized that differential HMGB1 network connectivity after day 2 is related to the putative threshold event in non-survivors. DyNA showed that HMGB1 is most connected in non-survivors on day 2-3, while no connections were observed in APAPo + NAC and non-APAPo + NAC survivors. Inflammatory dynamic networks, and in particular HMGB1 connectivity, were associated with the use of NAC in the context of APAPo. To recapitulate hepatocyte (HC) damage in vitro, primary C57BL/6 HC and

HC-specific HMGB1-null HC were treated with APAP+NAC. Network phenotypes of survivors were recapitulated in C57BL/6 mouse HC and were greatly altered in HMGB1-null HC. HC HMGB1 may thus coordinate a pro-inflammatory program in PALF non-survivors (which is antagonized by NAC), while driving an anti-inflammatory/repair program in survivors.

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

Original Article:
Sujan R, Cruz-Lemini M, Altamirano J, Simonetto DA, Maiwall R, Axley P, Richardson T, Desai V, Cabezas J, Vargas V, Kamath PS, Shah VH, Sarin SK, **Bataller R**, Singal AK. A Validated Score Predicts Acute Kidney Injury and Survival in Patients With Alcoholic Hepatitis. Liver Transpl. 2018 Dec;24(12):1655-1664. doi: 10.1002/lt.25328. PubMed PMID: 30153377.

ABSTRACT
Identifying patients at high risk for acute kidney injury (AKI) during hospitalization among patients admitted with severe alcoholic hepatitis (AH) is an unmet clinical need. We performed a multicentric prospective cohort study using data from 4 different cohorts on well-characterized patients hospitalized with severe AH. Data collected on 773 AH patients from 4 cohorts across the globe were randomly split into test (n = 390) and validation (n = 383) cohorts. We found that 32% of the patients developed inpatient AKI in the test cohort. Approximately 60% of patients met criteria for systemic inflammatory response syndrome (SIRS) at admission. Hepatic encephalopathy, SIRS, and Model for End-Stage Liver Disease score at admission predicted inpatient AKI with odds ratios of 3.86, 2.24, and 1.14, respectively. The AKI risk score developed using these predictors stratified risk of inpatient AKI to low (score <3), moderate (3-4), and high (>4). These findings were replicated in the validation cohort. In the whole study cohort, patients with AKI had a lower 90-day survival (53% versus 77%;

P < 0.001). Those with AKI risk score of >4 had significantly lower 90-day survival as compared with those with risk scores between 3 and 4 and <3 (47% versus 68% versus 88%; P < 0.001). In conclusion, AKI occurs frequently in AH patients and negatively impacts short-term mortality. The AKI risk score is useful in identifying patients at high risk for inpatient AKI and may be useful for developing new therapeutic strategies to prevent AKI in patients with AH.

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

Our mailing address is:
Pittsburgh Liver Research Center
200 Lothrop St. | Pittsburgh, PA 15261