Community Liver Update #1 - Best of AASLD.
General Hepatology Debrief
Saturday, February 10th, 2018 from 1:30 - 3:00 pm

Michael R. Lucey MD
Professor of Medicine
University of Wisconsin School of Medicine and Public Health

Moving Targets

• Receiving attention at 2017 AASLD liver meeting and in the Hepatology Journals
• I won't cover topics that are fully covered elsewhere at CASL 2018: viral hepatitis; NAFLD; hepatocellular cancer; liver transplantation.
• Moving Targets
  • Changing clinical practice
  • Clarifying current practice
Moving Targets

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• I won't cover topics that are fully covered elsewhere at CASL 2018: viral hepatitis; NAFLD; hepatocellular cancer; liver transplantation.
• Moving Targets
  • Changing clinical practice
  • Clarifying current practice
  • Provide a ‘take-away’ message that you can put to use.

‘What oft was thought, but ne'er so well express'd’
Six Moving Targets in Clinical Hepatology

- Acute on Chronic liver failure (ACLF)
- Alcohol-related liver disease
- Microbiome and hepatic encephalopathy
- Predicting variceal hemorrhage
- Frailty
- Palliative care

Acute on Chronic Liver Failure

- Patients with *cirrhosis* who are admitted to hospital with organ failure have a high mortality have been said to have Acute on Chronic Liver Failure (ACLF).
- Organ failure: CLIF-SOFA score
  - Liver
  - Kidney
  - Cerebral (HE)
  - Coagulation
  - Circulation
  - Respiratory
Outcome in ACLF in 1,343 Patients with Cirrhosis, who were Hospitalized

Mortality rate at 28 days and 90 days a/c to the grade of ACLF.

Moreau R et al, Gastro 2013: 144: 1426-1437

Cause of Renal Failure in Patients with Cirrhosis Affects Short-term Survival


- History of chronic dialysis and/or renal transplant (n = 3600)
- Known baseline SC > 3.5 (n = 147)
- No history of chronic liver disease (n = 37,435)
- SC or UO not available for AKI staging (n = 928)

**Source Population**
45,568

**Study Population**
3,458

- No cirrhosis
  - 461 (13.3%)
    - No AKI
      - 141 (30.6%)
    - AKI
      - 320 (69.4%)
  - Cirrhosis
    - 2,997 (86.7%)
      - No AKI
        - 463 (15.4%)
      - AKI
        - 2,534 (84.6%)

AKI (Δ se Cr) in first 7 days in ICU
UO= persistent oliguria
AKI-SC+UO = both criteria

- CLD patients have a high incidence of AKI
- Incorporating Urinary Output into the diagnostic criteria increased the measured incidence of AKI.
- Stage 2-3 AKI-UO has a high negative impact on hospital mortality

RRT, renal replacement therapy; CLD, chronic liver disease; AKI, acute kidney injury; SC, serum creatinine; UO, urine output.
• CLD patients have a high incidence of AKI
• Incorporating Urinary Output into the diagnostic criteria increased the measured incidence of AKI.
• Stage 2-3 AKI-UO has a high negative impact on hospital mortality

In ICU-bound patients with CLD and evidence of deteriorating kidney function, monitor the urinary output.

Alcoholic Liver Disease is a World Health Problem:
• 493,000 deaths in 2010
• 0.9% of all deaths
• 47.9% of all cirrhotic deaths
• ALD-associated liver cancer: 80,600 deaths

New Clarity regarding Severe Alcoholic Hepatitis (SAH)

- Atkinson SR et al. J. Hepatol 2017. Genetic Analysis of samples from the STOPAH
  - PNPLA3A polymorphism (re738409:G) -> increased risk of SAH
  - PNPLA3A ~ late but not early mortality

  - All 3 studies show that alcohol relapse has no impact on 28-day mortality
  - Alcohol relapse is the most significant factor in determining intermediate and long-term survival after an episode of SAH
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Abstinence is life-saving

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Esophageal Varices


- EGD in patients with compensated cirrhosis is time consuming, expensive and carries some risk.
- The most recent thresholds (a platelet count >150 × 10⁹ cells/L and a liver stiffness measurement (LSM) <20 kPa) avoids few EGDs. The goal in this study was to identify non-invasive indicators of which patients were at very low risk (<5%) of having varices needing treatment.
- 3 cohorts: study 499 patients with cACLD of different etiologies; and 2 validation cohorts: London (309 patients) and Barcelona (117 patients).
- The Expanded-Baveno VI criteria (platelet count >110 × 10⁹ cells/L and LSM <25 kPa) would potentially spare 367 (40%) endoscopies with a risk of missing varices needing treatment of 1.6% (95% CI: 0.7%-3.5%) in patients within the criteria and 0.6% (95% CI: 0.3%-1.4%) in the overall population of 925 patients evaluated.
Esophageal Varices


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- the Expanded-Baveno VI criteria (platelet count >110 × 10⁹ cells/L and LSM <25 kPa) would potentially spare 367 (40%) endoscopies with a risk of missing VNT of 1.6% (95% CI: 0.7%-3.5%) in patients within the criteria and 0.6% (95% CI: 0.3%-1.4%) in the overall population of 925 patients evaluated.

Use of platelet count and fibroscan reduces the need for surveillance EGDs.
Key numbers: platelet count >110 × 10⁹ cells/L and LSM <25 kPa.

Fecal Microbiota Transplant (FMT) from a Rational Stool Donor Improves Hepatic Encephalopathy (HE): A Pilot RCT


- Rationale: recurrent HE is associated with microbial dysbiosis. FMT may improve dysbiosis and thereby HE.
- An open-label, 1:1, RCT in 20 outpatient men with cirrhosis and recurrent HE on SOC (standard of care). 10 FMT-randomized patients received 5 days of broad-spectrum antibiotic pretreatment, then a single FMT enema from the same donor with the optimal microbiota deficient in HE. Follow-up occurred on days 5, 6, 12, 35, and 150 postrandomization.
- Primary Outcome: safety of FMT V. SOC. Secondary outcomes were AEs, cognition, microbiota, and metabolomic changes.
- 8 (80%) SOC participants had a total of 11 SAEs compared to 2 (20%) FMT participants with SAEs (both FMT unrelated; \( P = 0.02 \)). Five SOC and no FMT participants developed further HE \( (P = 0.03) \). Cognition improved with FMT, but not SOC.
Cognitive Function Changes Following Fecal Microbiota Transplant in Patients with Hepatic Encephalopathy

(A) EncephalApp Stroop in the SOC group shows no significant change in OffTime+OnTime in seconds compared to baseline.
(B) EncephalApp Stroop in the FMT group showed significant improvement (reduction) in OffTime+OnTime in seconds compared to baseline.
(C) PHES score in the SOC group did not show any change in the SOC group.
(D) PHES score in the FMT group significantly improved (decreased) compared to baseline.

Conclusion: FMT from a rationally selected donor reduced hospitalizations, improved cognition, and dysbiosis in cirrhosis with recurrent

Although needing validation, FMT shows promise…
Frailty

- Frailty: a distinct biological syndrome of decreased physiological reserve, initially recognized in geriatric medicine
- It encompasses what was previously referred to a ‘muscle loss’, now called sarcopenia, malnutrition, and functional abilities.
- Liver Frailty Index: a simple method to measure frailty.

Liver Frailty Index: a simple method to measure frailty:
- Grip strength: the average of three trials, measured in the subject’s dominant hand using a hand dynamometer;
- Timed chair stands: measured as the number of seconds it takes to do five chair stands with the subject's arms folded across the chest;
- Balance testing: measured as the number of seconds that the subject can balance in three positions (feet placed side-to-side, semitandem, and tandem) for a maximum of 10 s each.
- Administered by trained study personnel. the Liver Frailty Index was calculated using http://liverfrailtyindex.ucsf.edu
- Much superior to ‘the eyeball test’. ‘The addition of the LFI to the subjective assessment by the physician significantly improved mortality risk prediction, reclassifying 34% of patients.’

Lai JC et al. The Liver Frailty Index Improves Mortality Prediction of the Subjective Clinician Assessment in Patients With Cirrhosis, Am J Gastroenterol. 2017 Dec 1
Reversing Frailty?

- Optimization of comorbid medical conditions
  - Avoiding polypharmacy, benzos
  - Managing ascites, encephalopathy
- Smoking cessation
- Physical activity programs
- Nutritional intervention
  - High protein and calories
  - Assistance in food preparation
  - Afford nutritious food
  - Frequent small meals
  - Repeated measurement of frailty

Reversing frailty through early postoperative nutrition and mobility?
Bernal W. Clinical Liver Disease. 2017.10, pages 4-8, 28 JUL 2017

Frailty is real, measurable and can be changed
Palliative Care in Liver Patients

- ‘Palliative care is medical care focused on improving quality of life for patients with serious disease.’
  Steven Z. Pantilat. MD. ‘Life after the Diagnosis’.

- In 2014, Poonja et al reported a retrospective study of 102 consecutive adult patients (67% men; mean age, 55 years) who were removed from the LT list for or declined LT from January 2005 through December 2010. Only 11% were referred for palliative care.

- In the US, in an analysis of the Nationwide Inpatient Sample, the rate of palliative care referral in ESLD increased from 0.97% in 2006 to 7.1% in 2012. Referral was influenced by race, insurance status, presence of cancer, DNR status, being in a large teaching hospital. Rush B et al, Hepatology 2017; 66: 1585-1591

The Utilization of Palliative Care Services in Patients with Cirrhosis who have been Denied Liver Transplantation: A Single Center Retrospective Review. Kelly SG et al. Ann Hepatol 2017,

- 116 patients
  - presented for transplant selection 2007-2012
  - considered unsuitable for LT
  - subsequently died.

- Palliative consultation: 40 patients (34.4%) of whom 24 patients were referred to hospice or transferred to the palliative care service.
  - 41 patients (35.3 %) were referred directly to hospice
  - a total of 64 patients (55.2%) received inpatient or residential hospice care with an average LOS of 20 days.
  - 32 patients (27.6%) received comfort measures without palliative consultation, though this occurred on the date of death in 16 patients (13.8%).
  - The median interval between denial of LT listing and palliative care consultation or hospice referral was 28 days, while the median interval between denial and comfort care only was 4 days, P = 0.24.
  - Median survival after palliative care consult or hospice referral was 15 days, compared to 0 days for patients who received comfort care only, P = 0.0023.
Palliative Care in Liver Patients


Palliative care is about life not death. A palliative care approach should be introduced early in patients with decompensated cirrhosis

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• Predicting variceal hemorrhage
• Frailty
• Palliative care
‘Take-away’ Messages

- In ICU-bound patients with CLD and evidence of kidney failure, monitor the urinary output.
- Abstinence is life-saving for patients with ALD.
- Use of platelet count and fibroscan reduces the need for surveillance EGDs. Key numbers: platelet count >110 × 10⁹ cells/L and LSM <25 kPa.
- Although needing validation, FMT shows promise...
- Frailty is real, measurable and can be changed.
- A palliative care approach should be introduced early in patients with decompensated cirrhosis.