Best of AASLD & DDW 2019

December 14th, 2019
# Best of AASLD and DDW 2019

## Table of Contents

<table>
<thead>
<tr>
<th>Item</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agenda</td>
<td>3</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>4</td>
</tr>
<tr>
<td>Speaker Biographies</td>
<td>5</td>
</tr>
<tr>
<td>Speaker Disclosures</td>
<td>9</td>
</tr>
</tbody>
</table>

**Presentation Handouts:**

- Liver Transplantation                    | 10   |
- Non-Viral Liver Disease                  | 18   |
- Liver Cancer                             | 23   |
- Pancreas-Biliary Tree                    | 28   |
- Portal Hypertension                      | 38   |
- Motility and Functional Bowel Disease   | 49   |
- Colon Cancer                             | 55   |
- Inflammatory Bowel Disease               | 65   |
# Best of AASLD and DDW 2019

## Agenda

<table>
<thead>
<tr>
<th>Start</th>
<th>End</th>
<th>Topic</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:30 AM</td>
<td>8:00 AM</td>
<td>Registration/Breakfast</td>
<td></td>
</tr>
<tr>
<td>8:00 AM</td>
<td>8:05 AM</td>
<td>Opening Remarks</td>
<td>Dekey Lhewa, MD</td>
</tr>
<tr>
<td>8:05 AM</td>
<td>8:30 AM</td>
<td>Liver Transplantation</td>
<td>Michael Chang, MD, MS, MBA</td>
</tr>
<tr>
<td>8:35 AM</td>
<td>9:00 AM</td>
<td>Non-Viral Liver Disease</td>
<td>Arnab Mitra, MD</td>
</tr>
<tr>
<td>9:05 AM</td>
<td>9:30 AM</td>
<td>Liver Cancer</td>
<td>Janice Jou, MD MHS</td>
</tr>
<tr>
<td>9:35 AM</td>
<td>10:00 AM</td>
<td>Pancreas-Biliary Tree</td>
<td>Jessica Yu, MD</td>
</tr>
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<td>10:00 AM</td>
<td>10:30 AM</td>
<td><strong>-Break-</strong></td>
<td></td>
</tr>
<tr>
<td>10:30 AM</td>
<td>10:55 AM</td>
<td>Portal Hypertension</td>
<td>Scott Naugler, MD</td>
</tr>
<tr>
<td>11:00 AM</td>
<td>11:25 AM</td>
<td>Motility and Functional Bowel Disease</td>
<td>Sarah Diamond, MD</td>
</tr>
<tr>
<td>11:30 AM</td>
<td>11:55 AM</td>
<td>Colon Cancer</td>
<td>David Lieberman, MD</td>
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<td>11:55 AM</td>
<td>12:15 PM</td>
<td><strong>-Lunch Break-</strong></td>
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<tr>
<td>12:15 PM</td>
<td>12:40 PM</td>
<td>Inflammatory Bowel Disease</td>
<td>Anthony Sofia, MD</td>
</tr>
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<td>12:45 PM</td>
<td>1:45 PM</td>
<td>Viral Hepatitis (Keynote Speaker)</td>
<td>Norah Terrault, MD, MPH</td>
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<td>1:45 PM</td>
<td>2:00 PM</td>
<td>Closing Remarks, Summary</td>
<td>Joseph Ahn, MD, MS, MBA/Anthony Sofia, MD</td>
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Best of AASLD and DDW 2019

ACKNOWLEDGMENTS

We thank the following companies for their support of the Best of AASLD and DDW 2019:

Silver Level Supporter:
- AbbVie HCV

Bronze Level Supporter:
- Gilead

EXHIBITORS

- AbbVie GI Care
- Alexion
- Boston Scientific
- Capso
- Cook
- Gilead HepB
- Intercept
- Johnson + Johnson
- Merck
- Pfizer
- Retrophin Inc.
Norah Terrault, MD, MPH, FAASLD, is the Chief of Gastroenterology & Hepatology at Keck Medical Center of University of Southern California. Dr. Terrault is world renowned for her expertise on her work related to viral hepatitis, especially in the setting of liver transplantation. After earning her medical degree from the University of Alberta, Dr. Terrault completed medical training in Internal Medicine and Gastroenterology at the University of Toronto, Canada followed by post-doctoral fellowship in hepatology and viral hepatitis at University of California, San Francisco along with a concurrent master’s degree in public health from University of California, Berkeley.

Dr. Terrault has authored numerous original articles, reviews and book chapters on viral hepatitis, including the most recent AASLD Hepatitis B treatment Guidelines. She is an investigator on several NIH-funded clinical studies in hepatitis B, C and NASH. She has served as deputy editor for Liver Transplantation, associate editor for Hepatology, is current Associate Editor for Hepatology Communications and Councilor for the AASLD Governing Board.

In addition, Dr. Terrault will serve as the president of the AASLD in 2023 and has been the recipient of many prestigious awards in the field of hepatology.
Joseph Ahn, MD, MS, MBA is Professor of Medicine, Section Chief and Director of Clinical Hepatology at OHSU. Dr. Ahn received his medical degree from Northwestern University and completed his internal medicine residency at the University of Chicago and gastroenterology fellowship at Northwestern. Dr. Ahn treats patients with chronic liver diseases, and liver transplant candidates and recipients. His research interests are focused on hepatitis B, hepatitis C, and PSC.

Michael Chang, MD, MS, MBA completed medical school, internal medicine residency, gastroenterology fellowship, and a Master of Science at Boston University, followed by training in Transplant Hepatology at Harvard’s Beth Israel Deaconess Medical Center, and an MBA at Oregon Health and Science University / Portland State University. He is the Section Chief for gastroenterology and hepatology at the VA Portland Health Care System, Associate Professor of Medicine at OHSU and the Program Director for the Transplant Hepatology Fellowship program. Dr. Chang’s areas of clinical interest include quality initiatives in Advanced Liver Disease, non-invasive assessment of liver fibrosis, and the use of ECHO to improve specialty care access. Dr Chang is a co-investigator on an NIH funded study looking at symptom burden in patient-caregiver dyads with end stage liver disease to better understand the trajectory of symptoms and how best to support this challenging population.

Sarah Diamond, MD is an Assistant Professor of Medicine. Dr. Diamond attended The University of Miami, Miller School of Medicine in Miami, FL and then completed her internal medicine residency, chief residency and gastroenterology fellowship at Oregon Health and Science University. She joined the OHSU GI faculty in 2015. She is the medical director of the Digestive Health Center and the associate fellowship director for the GI program. Her clinical interests include nutrition and gastrointestinal motility.
Janice Jou, MD, MHS is an Associate Professor in the Division of Gastroenterology and Hepatology at OHSU, and is primarily based in the VA Portland Health Care System. Dr. Jou is the program director for the OHSU Gastroenterology fellowship. She completed medical school at Northwestern University, internal medicine residency and chief residency at the University of Wisconsin, and gastroenterology and transplant hepatology fellowships at Duke University. Her clinical and research interest is in hepatocellular carcinoma. She is also an active member on education and training committees of the American Association for the Study of Liver Diseases and American Gastroenterological Association.

Dekey Lhewa, MD earned her medical degree from the University of Washington School of Medicine where she also completed her internal medicine residency. This was followed by a fellowship in gastroenterology and hepatology at the University of California San Francisco-Fresno program and a transplant hepatology fellowship at the University of Michigan. She has special interests in the management of liver tumors along with issues regarding access to care and outcomes of chronic liver disease and liver transplantation especially among underserved populations. She has spent majority of her life in the Pacific Northwest and is very happy to be back home.

David Lieberman MD, is a Professor of Medicine and Chief of the Division of Gastroenterology and Hepatology at OHSU and the Portland VA Medical Center. Dr. Lieberman is internationally recognized as an expert on colon cancer screening with landmark publications in the New England Journal of Medicine, Gastroenterology and Annals of Internal Medicine. He is Chairman for the VA Cooperative Study # 380, which utilized colonoscopy to screen asymptomatic subjects for colorectal cancer. Dr. Lieberman was the Chairman of the Multi-Society Task Force on Colorectal Cancer (2006-2012), and authored colon cancer screening recommendations in 2008 and the polyp surveillance guideline in 2012 as well as colonoscopy quality indicators in 2007. He is the Director of the Clinical Outcomes Research Initiative (CORI), supported by NIH since 1999. The project has created a national endoscopic data repository for research, with more than 90 peer-reviewed publications to date, including papers in JAMA, Gastroenterology and Gastrointestinal Endoscopy. From 2006 to 2008, Dr. Lieberman served as a member of the National Commission on Digestive Diseases. Dr. Lieberman was President of the American Society for Gastrointestinal Endoscopy (ASGE) in 2001-2002. He was the Associate Editor of Gastroenterology (2011-2013). He was the Clinical Research Councilor on the board of the American Gastroenterological Association (2012-2015), and is the current President of the AGA.
Arnab Mitra, MD is an Assistant Professor at OHSU who specializes in caring for patients with liver disease, including those who have undergone liver transplant. He received his medical degree from the University of Alabama, internal medicine residency at the University of Wisconsin, and gastroenterology and transplant hepatology fellowships at Oregon Health and Science University. He joined the OHSU Hepatology faculty in 2019.

Scott Naugler, MD is one of the transplant hepatologists at OHSU. He serves at the Medical Director for Liver Transplant as well as the Multi-Disciplinary Liver Tumor group, with clinical interests in Hepatocellular Carcinoma and liver transplantation. He also works in the lab on liver regeneration and HCC. Scott graduated from Rhodes College in Memphis, TN with a B.A. in Creative Writing. He then attended medical school in Little Rock, AR, followed by internal medicine residency first at Washington University then OHSU (including a chief residency), after which he completed a Gastroenterology fellowship at UC San Diego. He joined the OHSU faculty as a Transplant Hepatologist in 2007.

Anthony Sofia, MD is a gastroenterologist that specializes in the care of patients with inflammatory bowel disease. Anthony earned his degree in medicine from the University of Chicago Pritzker School of Medicine. After medical school, he continued at the University of Chicago Medicine for internal medicine residency and gastroenterology fellowship. His research focuses on ways to deliver optimal clinical care for people with inflammatory bowel disease, including clinical trials of emerging therapies and the use of intestinal ultrasound for bedside disease activity assessments. He joined the faculty at OHSU in 2018.

Jessica Yu, MD focuses on patients with diseases of the bile duct and pancreas, gastrointestinal cancer and pre-cancerous conditions. She performs procedures including ERCP, EUS, small bowel enteroscopy, endoscopic mucosal resection, and enteral stenting. She has a special interest in bariatric endoscopy and endoscopic suturing. Her research focuses on understanding and improving the outcomes of endoscopy.
Best of AASLD and DDW 2019
Saturday, December 14, 2019

FACULTY DISCLOSURE INFORMATION

In accordance with the requirements of the Standards for Commercial Support of the Accreditation Council for Continuing Medical Education, each instructor and member of the planning committee has been asked to disclose any relevant financial relationships with commercial interests (defined as: any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients). The information disclosed for this activity is listed below.

In addition, the planners and instructors listed have agreed that all recommendations involving clinical medicine will be based on evidence that is generally accepted within the profession as adequate justification for their indications and contraindications in the care of patients; that all scientific research used in support or justification of a patient care recommendation will conform to the generally accepted standards of experimental design, data collection and analysis; and that material to be presented will be made available for advance peer review if requested.

INSTRUCTORS/MODERATORS

Joseph Ahn, MD, MS, MBA  Consultant to Gilead, for which he receives consulting fees.
Janice Jou, MD, MHS  Nothing to disclose
Dekey Lhewa, MD  Nothing to disclose
Sarah Diamond, MD  Nothing to disclose
David Lieberman, MD  Consultant, Scientific Advisory Boards for CEGX, Freenome, Check-Cap, Ironwood, for which he receives consulting fees.
Mark Anthony Sofia, MD  Nothing to disclose
Arnab Mitra, MD  Nothing to disclose
Jessica Yu, MD  Nothing to disclose
Michael Chang, MD, MSc  Nothing to disclose
Willscott Naugler, MD  Nothing to disclose
Norah Terrault, MD, MPH  Nothing to disclose

PROGRAM PLANNING COMMITTEE

Janice Jou, MD, MHS  Nothing to disclose
Dekey Lhewa, MD  Nothing to disclose
Mark Anthony Sofia, MD  Nothing to disclose
Rebecca Matro, MD  Advisory board for Pfizer for which she receives an honorarium.
Best of AASLD
Liver Transplant

Michael F. Chang, MD, MSc, MBA
Section Chief GI & Hepatology
Associate Professor of Medicine
VA Portland Healthcare System

• No Disclosures

Outline
• HCV and Transplant
• HCC and Transplant
• High risk transplant
• Changing landscape of liver transplant and liver cancer
• Current state of transplant re-districting

HCV AND TRANSPLANT
• Abstract 3: Multicenter Experience Evaluating Outcomes of HCV Seropositive Donors to HCV Seronegative Recipients Liver Transplantation
• Abstract 38: Transplantation from HCV Infected Donors to HCV-Uninfected Recipients: Short Course Therapy to Prevent Transmission
• Abstract 117: Transplantation of Hepatitis C Positive Kidneys Into HCV Naïve Patients Reveals Early Development of a Robust Viral Burden: Implications for the Initiation of Therapy

HCC AND TRANSPLANT
• Abstract 15: US Multicenter Analysis of 2529 HCC Patients Undergoing Liver Transplant: 10 year Outcome Assessing the Role of Downstaging to Within Milan Criteria
• Abstract 225: Six-month Waiting Rule Lowered Waitlist Mortality/Dropout and Decreased Regional Disparity in Liver Transplant Candidates with HCC
• Abstract 226: Acceptable Liver Transplantation Outcomes Among Older Recipients with HCC Despite Higher Risk Features on Explant in a Large Multicenter US Cohort

High Risk Transplant
• Abstract 91:
• Abstract 92: Simultaneous Liver Kidney Transplant in the Elderly: Is There an Appropriate Age Cut Off?
• Abstract 94: Liver transplant recipients with BMI 40-50 have excellent patient and graft survival
• Abstract 1142: Outcomes of Liver Transplantation in Patients with Pre-existing Coronary Artery Disease
• Abstract 1148: Presence of Any Degree of Coronary Artery Disease Among Liver Transplant Candidates is Associated with Decreased Transplant Eligibility and Increased Rate of Post-Transplant Major Cardiac Adverse Event
CHANGING LANDSCAPE OF LIVER TRANSPLANT AND LIVER CANCER

Liver allocation for HCC

This is the “MELD elevator” – a stepwise increase in MELD score in a patient with a MELD exception (most common is HCC) that ultimately results in the patient getting to the top of the list.
Liver allocation for HCC

Liver
HCC

MELD elevator in effect (after 6 month wait)

1996 Listing 3 months 6 months 9 months
MMAT - Median MELD at Transplant (= 32 in Portland now, thus MMAT -3 = 29

OHSU “A” LT waitlist, Nov 3, 2019

HCC patients with MMAT-3 MELD exceptions

This is where a new patient with HCC (who has already waited 6 months) would be placed
UPDATE ON DOWNSTAGING

Current national down-staging policy

- One tumor ≤ 8 cm
- Two or three tumors, all ≤ 5 cm, total ≤ 8 cm
- Four or five tumors, all ≤ 3.0 cm, total ≤ 8 cm

After locoregional treatment, tumor burden is within Milan (“down-staged”)*

*Based on hypervascular/washout tumor size

Timeline for down-staging

Patient presents
- Out of Milan
- Inside down-staging
- Inside Milan

1 month

List for LT

“ASAP”
Current national down-staging policy

Timeline for down-staging

- Patient presents
- Out of Milan
- Inside down-staging
- 1 month
- 3 months
- 3 months
- 6 months
- 12 months
- Scan
- MMAT – 3 until transplanted

*Must stay within Milan entire time

Current national HCC policy

- Milan criteria as noted
- Down-staging into Milan as noted
- AFP must be ≤1000 ng/mL*

*In CTP A patients who are within Milan, if the AFP is >1000 ng/mL, and locoregional treatment brings it to ≤500 ng/mL, the standard exception can be granted

Caveats to HCC policy

If HCC present (in or out of Milan) and last locoregional treatment was ≥ 2 years prior, the lesions are considered dead and will not count toward a MELD exception.

But if new HCC (within Milan, etc) appears, an exception based on the new tumors is acceptable.

Caveats to HCC policy

HCC tumors for purposes of LT policy are not cumulative.

Patient 1: outside down-staging, can never be transplanted

Patient 1: outside down-staging, can never be transplanted

Patient 2: always within Milan, can get standard exception

Realities of HCC at MMAT -3

Intended
1. More sick cirrhotics will be transplanted, and at lower MELD scores

4 cm HCC
5 cm HCC

4 cm HCC
4 cm HCC non-viable
New 5 cm in Milan

8 cm HCC
4 cm HCC
Realities of HCC at MMAT -3

Intended
1. More sick cirrhotics will be transplanted, and at lower MELD scores

The necessary corollary
1. Fewer HCC patients will get transplanted
   - There is a "log-jam" of patients listed at MMAT -3
   - Those at MMAT -3 are ordered by time on list with an exception (not by HCC burden, etc.)

HCC Landscape

Realities
1. Increasing incidence of HCC
2. More patients eligible for transplant listing
3. Fewer patients getting transplant for HCC

Manifestations
More and more HCC management without transplant

Need to move away from “bridging”

From: "Bridging" to an uncertain transplant
To: Chronic disease that must be managed indefinitely

Transplant in select few

Practical differences in approach?

Very little…but
1. Transplant will no longer be a near-guarantee for patients, and should be communicated as such even to patients within transplantable criteria
2. We may want to consider treating patients with T1 disease (HCC < 2 cm) immediately
   • Rather than observe them until they grow into T2 (transplantable) criteria

AASLD Guidelines HCC management

6. Should adults with cirrhosis & T1 HCC on the transplant list get treatment or be observed?

Recommendation: Observe with imaging in hopes/anticipation of HCC growth to T2, thus qualifying for priority on the list.
   • Quality of evidence: very low
   • Strength of recommendation: conditional

CURRENT STATE OF TRANSPLANT REDISTRICTING
Geographic disparities in allocation

Burden of liver disease vs those on transplant lists

Goldberg, Liv Transplant, 2016

% deaths from liver disease captured with waitlist deaths, 2012

> 11.5%

6.2–9.9%

3–5.9%

≤ 2.7%

Geographic disparities in allocation

- More doctors
- More centers
- Better access

More listed patients/donor = higher MELD at transplant

Move donor livers

More listed patients/donor = higher MELD at transplant

Not listed = Not advantaged

- More doctors
- More centers
- Better access
Geographic disparities in allocation

MELD at transplant may not reflect all disparities

1. MELD exceptions vary widely among regions
   • Affects overall allocation MELD
2. Regions with better health care access list a higher percentage of the population
   • Increases local MELD on waitlist
3. Center competition affects listing practices
   • Increases local MELD on waitlist

Deceased donor liver allocation

Redistricting proposal went for regional vote fall 2016
Non-viral liver disease
Arnab Mitra, MD
Assistant Professor of Medicine
OHSU Department of GI/Hepatology

Disclosure
- I have no financial relationships to disclose

Learning Objectives
- Updates in:
  - NAFL and NASH
  - Cholestatic and Autoimmune liver disease

Non-Alcoholic Fatty Liver Disease
- Evidence of hepatic steatosis without secondary causes of fat accumulation
- Risk Factors
  - Central obesity
  - Hypertension
  - Dyslipidemia
  - Type 2 Diabetes
  - Metabolic syndrome
  - Advancing age
- Spectrum of disease
  - Normal
  - Steatosis 20-40% of general population
  - NASH 15-25%
  - Cirrhosis 10-20% in 10 years
  - HCC

Non-Alcoholic Fatty Liver Disease
Worldwide estimated prevalence of NAFLD and distribution of PNPLA3 genotypes

Pathogenesis

- Cardiovascular disease is the most common cause of death
- Cancer-related mortality is among top 3 causes of death in patients with NAFLD
- NAFLD is 3rd most common cause of HCC
- Histological feature associated with long-term mortality is fibrosis (particularly zone 3 sinusoidal fibrosis)

Mortality

- Cardiovascular disease is the most common cause of death
- Cancer-related mortality is among top 3 causes of death in patients with NAFLD
- NAFLD is 3rd most common cause of HCC
- Histological feature associated with long-term mortality is fibrosis (particularly zone 3 sinusoidal fibrosis)

Non-Invasive Tests for Fibrosis

- NAFLD Fibrosis Score
- FIB-4
- ELF (available in Europe)
- Elastography
- MR
- VCTE

Machine learning models accurately interpret liver histology in patients with NASH

Hypothesis:
A machine learning approach (method) could be utilized to train models to accurately interpret NASH histology.

Methods:
The method research platform used to train and test a deep learning model to interpret liver histology from MRI liver images from a phase II clinical trial (PHILS).

Main Findings:
Machine learning predictions in the test set were highly correlated with pathology readings for the NAFLD (n = 62) and fibrosis staging spectra (n = 62, Fig 3) and for the components of the NAFLD activity score

Conclusions:
Machine learning models showed high concordance with pathologic interpretations of the morphological features of NASH.

Management

- Lifestyle Interventions
  - 5% body weight loss had improved hepatic steatosis
  - 7% body weight loss associated with improvement in NAFLD activity score, with 7-10% body weight loss being associated with higher likelihood of reversing histopathologic features/fibrosis of NASH
  - Medications
    - Pioglitazone
      - Improves liver histology with biopsy-proven NASH with or without DM
    - Vitamin E
      - Improvement in aminotransferases and steatosis, inflammation, and ballooning have previously been seen
      - Consideration for use in biopsy-proven NASH in those who are non-diabetic or non- alcoholic
    - Bariatric Surgery
      - Improvement in fibrosis and NAS, resolution of NASH in some cases
      - Increased mortality in those with cirrhosis, particularly decompensated

Persistence of severe liver fibrosis despite substantial weight loss after bariatric surgery

- Although liver histology remains improved in most of the patients, severe fibrosis persists in 1/3 of the patients even after bariatric surgery
Treatments on the Horizon

- Obeticholic Acid
  - FXR agonist approved for PBC
  - Awaiting FDA approval for NASH
    - Phase 3 REGENERATE study – 25 mg daily demonstrated improvement in liver fibrosis (> or = 1 stage) without worsening NASH (achieved primary endpoint)
  - Saroglitazar
    - PPAR alpha/gamma agonist
  - Tropifexor
    - FXR agonist

Assessment of disease severity

- ALT is not a reliable indicator of disease severity

- 2018 AASLD Guidelines
  - Metabolic syndrome predicts the presence of steatohepatitis
  - NFS or FIB-4 index can be used to identify NAFLD patients with higher likelihood of having bridging fibrosis (stage 3) or cirrhosis (stage 4)
  - VCTE or MRE are clinically useful tools for identifying advanced fibrosis in patients with NAFLD

Saroglitazar, a novel dual PPAR α/γ agonist, for NAFLD/NASH: a phase-2 RCT (EVIDENCES IV study)

On the definition of sarcopenia within NAFLD – results from the large UK biobank imaging study

On the definition of sarcopenia within NAFLD – results from the large UK biobank imaging study
CHOLESTATIC AND AUTOIMMUNE LIVER DISEASE

Primary Biliary Cholangitis (PBC)
- Female >> Male
- Prevalence: ↑
- Diagnosis:
  - Elevated alkaline phos
  - AMA (seen in 95% of pts)
  - Biopsy → PBC
- Treatment
  - Ursodiol 1st line
  - Obeticholic acid 2nd line (approved in 2016)

Clin Gastro Hepatology 2018

Emerging PBC Therapies: Fibrates
- 1 RCT
  - Benazafibrate
    - In addition to urs in inadequate urs response patients
  - Adverse events:
    - Hepatoxicity
    - CPK elevation
- Advance disease?

Corpicot C et al, NEJM 2018

Durable response in the markers of cholestasis through 5 years of OLE study of OCA in PBC patients

Objectives:
- Open-label extension (OLE) of the phase 3, randomized, double-blind placebo-controlled study in patients with PBC to assess long-term safety of obeticholic acid (OCA) and durability of effects on serum markers of cholestasis
- Methods:
  - Following the 3-year double-blind phase, patients on placebo started OCA and were then transitioned to OCA treatment to evaluate the efficacy and safety of up to 5 years of OCA treatment.
- Main findings:
  - ALT, AST, GGT, and other inflammatory markers were significantly reduced.
  - Reductions were sustained for the duration of treatment.
  - Total bilirubin was maintained within the normal range.
- Conclusions:
  - Six years of treatment with OCA resulted in sustained improvement in markers of cholestasis and inflammation and stabilization of liver function with no new safety observations.

Fibrates
- Only approved by FDA as lipid-lowering medications
- Activate PPAR-alpha, gamma and delta
  - PPAR-alpha – regulates bile acid synthesis and detoxification
  - PPAR-delta and PPAR-gamma – anti-inflammatory and anti-fibrotic properties

Bezafibrate is superior to placebo in improving pruritus in chronic cholestatic liver disease: the FITCH trial

Hypothesis:
- Bezafibrate may relieve cholestasis-associated pruritus by affecting the liver’s metabolism of lipid, bile acids, and plasma proteins.
- Methods:
  - Double-blind, randomized, placebo-controlled trial in patients with PBC (n=48), PSC (n=9), or primary biliary cirrhosis (n=12) with moderate to severe cholestatic-associated pruritus.
  - Findings:
    - Bezafibrate (400 mg, daily) led to 80% of the patients to 75% improvement of pruritus whereas patients treated with placebo reached the primary endpoint in 12% (p<0.01, see figure).
- Conclusions:
  - Bezafibrate is superior to placebo in improving pruritus in chronic cholestatic liver disease such as PBC and PBC.
Safety and efficacy of seladelpar in PBC related cirrhosis: 52-week analysis from a randomized phase 2 study: Abstract LB-3

- **Aim**
  - To assess safety and efficacy of daily seladelpar

- **Method**
  - Randomized open-label, dose ranging, phase 2 study
  - Patients with inadequate response or intolerance to ursodeoxycholic acid (UDCA)

- **Conclusion**
  - Good anti-cholestatic efficacy
  - Well tolerated
  - Phase 3 study

Bowlus C, et al, Abstract LB-3

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Results - 52 weeks

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<tr>
<th>Seladelpar</th>
<th>5/10 mg</th>
<th>10 mg</th>
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<tr>
<td>Responders</td>
<td>59%</td>
<td>71%</td>
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| AP Mean Change | 47% | 46% |
| AP Normalization | 24% | 29% |

Update:
Seladelpar moved to phase 3 study given positive safety results

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Potential role of heavy metals in the pathogenesis of autoimmune liver diseases (AILD)

- **Aim**
  - To explore the relationships between social deprivation and environmental triggers for the development of AILD

- **Methods**
  - Structural equation modelling (SEM) was used to evaluate pathways linking poverty variables for disease development.

- **Main Findings**
  - The main sociocultural factors were unemployment and education (Figure 4).
  - In primary sclerosing cholangitis (PSC), there was a cultural transition path (Figure 5) and disease prevalence (Figure 6).

- **Conclusions**
  - Toxic metals may relate to the development of AILD potentially by causing immune dysregulation and epithelial injury through valvular stress.

---

Primary Sclerosing Cholangitis

- **Aim**
  - Male >> Female
  - 2/3rds: concurrent IBD

---

Bile acid profiles predict hepatic decompensation in primary sclerosing cholangitis

- **Aim**
  - Patients with PSC other than those who have been exposed to bile acids (BAs) are not included.
  - We aim to establish whether bile acid profiles are predictive of hepatic decompensation (HD) based on the history, genetic factors, and environmental factors.

- **Methods**
  - Plasma BA profiles and other contributory risk factors were assessed using the Clinical Predictive Score and to phenotypes.
  - The study was conducted in a cohort of 324 patients with PSC over a period of 3 years.

- **Main Findings**
  - Bile acid profiles are independently associated with predicting future liver cirrhosis (LC) in patients with PSC.

- **Conclusions**
  - Bile acid profiles have prognostic value and should be considered in disease management and a possible endpoint in future clinical trials.

---

Prospective validation of the prognostic value of liver stiffness (LS) (FibroScan®) in PSC: the FICUS study

- **Aim**
  - To assess prospectively the prognostic value of liver stiffness (LS) as evaluated by FibroScan® in patients with PSC.

- **Methods**
  - 13 institutions, across 11 countries.
  - 525 patients enrolled, analysis at 2 years in 444 with valid LS data.

- **Main Findings**
  - LS was highly independent (adjusted for bilirubin, ALT, and Mayo Risk Score) for predicting risk of LC.

- **Conclusions**
  - This study validates the prognostic value of LS FibroScan® in PSC and supports the role of LS as a novel, non-invasive, and powerful surrogate endpoint in clinical trials.

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Weismuller, T et al, Gastro 2017

Bowlus C, et al, Abstract LB-3

---

Figure 4: HD model for PSC

Figure 6: Anti-tissue-associated AILD concentrations

Figure 8: Anti-smooth muscle antibodies for PSC

transplant-free survival
Best of AASLD 2019: Update in HCC

Janice Jou, MD MHS
Associate Professor
Division of Gastroenterology and Hepatology
Oregon Health and Science University
Portland VA Medical Center

Conflict of Interest Disclosures

• I have nothing to disclose.

**Impact of Healthy Lifestyle on HCC and cirrhosis risk**

- Nationwide prospective cohort adult men and women without known liver disease at baseline, 1986-2012
- N=121,893
  - 121 HCCs
- Low risk lifestyle met all criteria
  - Never smoker (pack years <5)
  - No/moderate EtOH (<1 drink/day women, <2 drinks/day men)
  - BMI 18.5-24.9
  - Weekly physical activity ≥6 MET hours
  - Healthy diet (upper 40% of the Alternative Healthy Eating Index)
- High risk lifestyle- all other patients

Simon TG et al. AASLD Abstract #16

**Prevention of HCC**

<table>
<thead>
<tr>
<th>Healthy Lifestyle Score</th>
<th>Age-adjusted Incidence, per 100,000 person years</th>
<th>Adjusted HR, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-Risk Group</td>
<td>High-Risk Group</td>
</tr>
<tr>
<td>Pooled cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incident HCC</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Liver-related Mortality</td>
<td>5</td>
<td>17</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incident HCC</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Liver-related Mortality</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incident HCC</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Liver-related Mortality</td>
<td>5</td>
<td>27</td>
</tr>
</tbody>
</table>

HR 3.59 (95% CI 1.50-7.43) for HCC.
HR 4.27 (95% CI 2.06-11.03)

Single modifiable risk factor with largest Population attributable risk was overweight/obesity BMI ≥25, INT 36% (95% CI 22-50), 42%

(95% CI 1.83-5.4)

Simon TG et al. AASLD Abstract #16
AASLD Guidelines for HCC Surveillance

- Ultrasound with or without AFP, every 6 months
- Do not perform surveillance in Child’s class C cirrhosis unless they are on the transplant waiting list, given the low anticipated survival for patients with Child’s C cirrhosis
- Comorbidities precluding diagnosis, surveillance, or treatment (renal failure)
- Randomized controlled trials supporting surveillance/screening for HCC are sparse

AASLD Guidelines for HCC Surveillance

- Multiphase CT and MRI are generally equivalent
- Choose test based on center expertise
- Breath holding, patient movement, ascites make MRI more variable
- Discourage biopsy of every indeterminate lesion
- Patients with Child’s A cirrhosis with T1 or T2 HCC should undergo resection over ablation (Quality: Mod, Strength: conditional)
- In the absence of portal hypertension

GALAD for early detection of HCC

LI-RADS: Liver Imaging Reporting and Data System - 2018

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AASLD guidelines regarding HCV after DAA therapy

- The risk of HCC for patients with HCV-related cirrhosis who develop SVR after DAA treatment is lowered, but not eliminated, and therefore patients with cirrhosis and treated HCV should continue to undergo surveillance.
- The risk of HCC is significantly lower in those with HCV or NAFLD and no cirrhosis compared to those with cirrhosis, and surveillance is not recommended for these patients.

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- In the absence of portal hypertension
HCC AASLD Guidance: Diagnostic algorithm

- Ultrasound +/- AFP every 6 months

  - If a lesion is >1cm or new AFP>20: Multiphase CT or MR
  - If benign, LI-RADS 1-2: Resume U/S every 6 months
  - If a lesion is >2cm or new AFP>20: Multiphase CT or MR
  - If a lesion is >3cm or new AFP>20: Multiphase CT or MR

  - If indeterminate, LI-RADS 3: Repeat CT/MR in 3-6 months
  - If probable HCC, LI-RADS 4: Multidisciplinary discussion to consider biopsy or CT/MR in 3 months

  - If diagnostic of HCC, LI-RADS 5: Multidisciplinary discussion of possible treatment options

Adapted from Dr. Julie Heimbach, AASLD 2019, HCC Guidance Summary

Direct-Acting Antiviral Therapy Is Associated With Improved Survival in Patients With a History of Hepatocellular Carcinoma: A Multicenter North American Cohort Study

- Does DAA therapy improve survival in patients with a history of complete response to HCC treatment?

  - HCV-associated HCC
    - Complete response to HCC treatment

  - Design:
    - 245 patients with HCV-associated HCC with complete radiographic response 320: 12, 12% received DAA therapy

  - Outcomes in North America including 79 patients with HCV-associated HCC with complete radiographic response

Gastroenterology

Bolondi L et al. Semin Liver Dis 2012

TARE

- Conventional Y-90
- Lobar
- Radiation segmentectomy
  - Superselective delivery of an ablative dose of radiation [≥ 190 Gy] to segmental artery feeding the tumor
  - Assumes that there is an equal distribution of the Y-90 dose to the entire volume of liver perfused, and perhaps higher concentration to a hypervascular tumor like HCC

https://ervaldays.com/articles/2018-ctc/
**TARE vs TACE: Meta-analysis**

- 18 studies included
  - 1 RCT
  - 4 prospective cohort studies
  - N=2561 patients
- Child’s A 63.6%, B 33.1%, C 2.1%
- BCLC A 26.1%, BCLC B 43.8%, BCLC C 30.2%
- Significant heterogeneity
- Time to progression was 17.5 months (TARE) vs. 9.8 months (TACE)
- TARE with a longer TTP than TACE, but no significant difference in overall survival

---

**Lenvatinib-induced thyroiditis**

- N=60
- Subclinical hypothyroidism n=7 (11.7%)
- Overt hypothyroidism n=26 (43.3%)
- Thyrotoxicosis n=5 (8.3%)
- Of those with hypothyroidism, N=27, 84% developed symptoms within 2 weeks
- Patient with hypothyroidism had better prognosis
- Mechanism is unknown: VEGF inhibition leading to decreased thyroid blood flow?

---

**Systemic Treatment for Advanced HCC**

<table>
<thead>
<tr>
<th>HCC</th>
<th>First-line treatments</th>
<th>Second-line treatments</th>
<th>Third-line treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC</td>
<td>Sorafenib</td>
<td>Regorafenib</td>
<td>Cabozantin</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**CheckMate 459: Nivolumab First line**

- Multinational study
- Nivolumab 400mg IV q2weeks
- Sorafenib 400mg po BID
- Primary endpoint: overall survival
- N=743 randomized 1:1
- Minimum F/U 22.8 months
- Did not meet primary endpoint
- Less side effects Grade 3/4 22% vs 49%
- Discontinuation 4% vs 8%

Atezolizumab

- PD1 Inhibitor
- Used previously in lung and bladder, breast CA

IMbrave 150: Atezolizumab/Bevacizumab vs. Sorafenib

- 1st line treatment for HCC
- 2:1 randomization
- 336 patients treated with atezolizumab 1200 mg IV plus bevacizumab at 15 mg/kg IV q3 weeks
- 165 patients treated with sorafenib 400 mg twice daily
- Primary endpoints: overall survival and progression free survival by independent review facility (IRF)-assessed RECIST v1.1
- Secondary endpoints: IRF-assessed objective response rate (ORR) per RECIST v1.1 and IRF-ORR per HCC modified (m) RECIST v1.1.

Cheng A-L et al. ESMO 2019 Abstract LBA3

IMbrave 150: Atezolimab/Bevacizumab vs. Sorafenib

- Median follow-up of 8.6 months
- ORR 27% Atezo+bev vs 12% Sor (p < 0.0001) per IRF RECIST v1.1.
- ORR 33% versus 13% (p < 0.0001) IRF HCC mRECIST criteria
- Atezolizumab/bevacizumab delayed deterioration of quality of life compared to sorafenib
- Median treatment 7.4 mos Atezo+bev and 2.8 mos sorafenib
- Grade 3-4 AEs: 37% atezo+bev patients vs 55% of sor patients
- Grade 5 Aes: 5% Atezo+bev and 6% Sor

Cheng A-L et al. ESMO 2019 Abstract LBA3

Management of elevated liver tests with immunotherapy

- AST or ALT > 3x and 5.5x ULN and/or Total Bilirubin > 3.0 x ULN
  - Rule out other causes (infection, malignancy)
  - Monitor LFTs 1-2 weekly until resolution < grade 2 (or baseline)
  - For patients continuing to trend up, or no resolution within 2 mos start steroids at 0.5-1.0 mg/kg prednisone
- AST or ALT > 3.0x ULN and/or Total Bilirubin > 3.0 x ULN
  - As above
  - Start steroids at 1-2 mg/kg prednisone

* In patients with abnormal LFTs at baseline, monitor for increase of LFTs and treat based on the parameters above.
** For patients with persistently elevated LFTs or that are refractory to steroids, consider hepabiliary consult, consider mycophenolate

Slide Credit: Dr. Edward Loftus, DDW Postgrad Course 2018

Questions?
Best of DDW: Pancreas and biliary
Jessica Yu, MD, MS
Assistant Professor of Medicine
Division of Gastroenterology
Oregon Health and Science University

Agenda
- Pancreatic cyst
- Pancreatitis
- Biliary and therapeutic EUS

Pancreas Cysts
- Pancreatic cysts are often detected on imaging with incidence of 2.4-13.5% and increases with age
- Some pancreatic cysts have malignant potential but some do not

Who to survey?
- Management of pancreatic cyst needs to take into account risk of malignancy versus frequency of detection
- Costs of surveillance and the morbidity/mortality of surgical resection is high and benefits of surveillance is unproven
- Patient not fit for surgery should not have further evaluation of incidentally found cyst regardless of cyst size

How to survey?
- MRI/MRCP is the of choice. EUS or pancreas protocol CT are alternatives
  - Diagnostic accuracy relatively low for cyst type (40%)
- Look for high risk features
  - Jaundice, pancreatitis due to cyst, elevated Ca19-9 without explanation, mural nodule/solid component, MPD > 5mm, ductal dilation with upstream atrophy, size 7 3cm, size > 3mm/year, high grade dysplasia on cytology
  - FNA reserved for indeterminant cysts when results may change management

Fluid analysis
- CEA helps to determine mucinous vs. other types. Not helpful for HGD or cancer
  - CEA > 192: 63% sensitive, 93% specific
  - CEA < 5: >95% specific for non-mucinous cyst
- Cytology: only 35% have adequate cellularity
- Molecular markers: better sensitivity/specificity for mucinous cyst. Not helpful for cancer risk
Endoscopic Ultrasound-Guided Fine Needle Biopsy Has a High Diagnostic Yield in Providing a Histologic Diagnosis for Pancreatic Cysts

Jennifer Phan MD, David Dawson MD, Alireza Sedarati MD, M Phillip Feuجمل MD, Neil Marys MD, Aadarsh Thaker MD, Melinda Rogers MD, Stephen Kim MD, V Raman Muthusamy MD

TATON AND TANNER MANSHOUR DIVISION OF GASTROENTEROLOGY AND GASTROINTESTINAL PATHOLOGY DAVID GEFFEN SCHOOL OF MEDICINE AT UCLA LOS ANGELES, CA

Study Conclusion

- A combination of molecular and clinical markers guides pancreatic cyst management more accurately than standard of care
- 60% reduction of unnecessary surgery
- Additional validation necessary
Study Conclusion

- EUS-guided FNA, MFB, nCLE appear safe
- Significant improvement of diagnostic yield with MFB (79.5%) or nCLE (88.6%)
- Significant change in management from MFB (38.6%) and nCLE (43.2%) use
- Limited number of endosonographers, operator dependent

When to stop Surveillance?

- Surveillance intervals if no concerning features and stable size.
  - Risk of malignant transformation does not decrease with time, no justification to stop after 5 years of stability (AGA guidelines)
- Surveillance should be discontinued if a patient is no longer a surgical candidate
- It is reasonable to assess utility of ongoing surveillance for those aged > 75 years though this needs to be individualized.

Take home message

- Pancreatic cysts are common, statistically, it is a side branch IPMN
- Survey only if surgical candidate.
- New techniques for improved diagnosis are being evaluated

Pancreatitits

AGA SECTION

American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis

Seth D. Crockett, Sachin Wani, Timothy B. Gardner, Yingye Falck-Ytter, and Alan N. Barkun; on behalf of American Gastroenterological Association Institute Clinical Guidelines Committee

Recommendation 3. In patients with acute biliary pancreatitis and no cholangitis, the AGA suggests against the routine use of urgent ERCP. Conditional recommendation, low quality evidence.

Abstract presentation:
Early endoscopic retrograde cholangiography with biliary sphincterotomy or conservative treatment in predicted severe acute biliary pancreatitis: A multicenter randomized controlled trial

Nicolien J. Schepers
Study details

- 232 patients from 26 Dutch centers with predicted severe acute biliary pancreatitis randomized to early ERCP within 24hr or conservative management
- Severity based on APACHE score ≥ 8, Imrie score ≥ 3 or CRP > 150 within 24 hrs of admission

Findings

- Death or severe complications occurred in 39% of patients in the ERCP group and 44% of conservative management group (p=0.37)
- Lower rates of cholangitis in ERCP group (2% vs. 10%, p = 0.01
- No significant differences in new onset organ failure, death or other endpoints
- Emergent ERCP in gallstone pancreatitis without cholangitis does not improve outcomes

Results:

The diagnostic work-up and outcomes of “presumed” idiopathic acute pancreatitis
A post-hoc analysis of a multicenter observational cohort

Nina Hellersleben, Device Umans, Steffen Bouwense, Robert Verdonk, Tessa Romkes, Bas Wittenberg, Matthijs Schwartz, Marcel Spantjer, Robert Laheij, Hjalmar van Santvoort, Marc Besselink, Jeanin van Hooft, Marco Bruno
on behalf of the Dutch Pancreatitis Study Group

Results: Etiological factors

<table>
<thead>
<tr>
<th>Etiological factor</th>
<th>No. (percentage) – n=176</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute pancreatitis</td>
<td>12 (7%)</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>43 (27%)</td>
</tr>
<tr>
<td>- Pancreatic cancer</td>
<td>9 (5.1%)</td>
</tr>
<tr>
<td>- Ampullary carcinoma</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td>- Neuroendocrine tumor</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>- IPMN</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>8 (4.6%)</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>5 (2.8%)</td>
</tr>
<tr>
<td>Pancreas divisum</td>
<td>1 (0.6%)</td>
</tr>
</tbody>
</table>

Conclusions

- Additional diagnostic work-up detects an etiology in one-third of patients
  - More than half binary
  - 7% neoplasms
- EUS and MR/MRCP have a high diagnostic yield (33-35%)
- Detection of etiology and subsequent treatment can prevent recurrences
Complications after pancreatitis

- Interstitial Pancreatitis
- Acute Fluid Collection
- Acute Necrotic Collection
- Walled-off Necrosis (WON)

Indications For Treatment of Pancreatic Necrosis

- Proven infected necrosis – rare early on
- Suspected infected necrosis with persistent organ failure or failure to improve
- Symptomatic walled off necrosis (> 4 weeks)
  - Gastric, intestinal or biliary obstruction
  - Persistent symptoms – pain, anorexia, weight loss, failure to thrive
  - Disconnected pancreatic duct syndrome (DPDS)

Endoscopic cystgastrostomy and necrosectomy

Endoscopic transluminal approach preferred

Death or major complication: Endoscopy 11.8% vs. Surgery 40.6%, p =0.007

Take home messages

- Emergent ERCP should be reserved for patient with acute biliary pancreatitis and cholangitis
- Additional work-up, in particular EUS, MRI can help improve identification of etiology for presumed “idiopathic” acute pancreatitis
- Endoscopic step-up approach is preferred for the management of pancreatic fluid collections though a multi-disciplinary approach should be taken and a standardize protocol for stent removal may help limit bleeding risk
Biliary disease

Biliary Dilation in Patients with Normal Liver Function Tests: Association with Opiate Use

Monique T. Barakat, MD, PhD, Subhas Banerjee, MD

Division of Gastroenterology & Hepatology
Stanford University Medical Center
May 18, 2019, Digestive Disease Week

Conclusions

- Bile duct dilation is increasingly detected
- Opiate use is associated with biliary dilation in the setting of normal bilirubin
- Opiate use and Cholecystectomy modulate bile duct diameter to a greater extent than age
- Known opiate users with normal LFTs may not require expensive and potentially risky endoscopic evaluation for biliary dilation

Therapeutic EUS

Biliary Rendezvous  Cholecchoduodenostomy  Hepaticojejunostomy

TEMPORARY EUS-GUIDED ANASTOMOSES (TEA) WITH COVERED SELF-EXPANDABLE METAL STENTS (CSEMS) AS THERAPEUTIC ACCESS FISTULAS (TAF) IN BENIGN BILIARY OBSTRUCTION (BBO) NOT AMENABLE TO ERCP

Hospital Universitario Rio Hortega, Valladolid, Spain
Endoscopic gallbladder drainage

Results: treatment
Success

87 patients

Drainage success n (%): 72 (84.2%)

18 (20.7%) In progress Follow-up for 60 days Indefinite TEA

69 (79.3%)

Final therapeutic success

Yes 54/69 (78.2%)

No 15/69 (21.8%)

PTBD or Surgery

Endoscopic gallbladder drainage

Table 4. Logistic regression analysis factors related to clinical success, technical success, recurrent cholecystitis, and adverse events in EUS-guided versus transpapillary gallbladder drainage for endoscopic patients (p = .16).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>EUS-guided</th>
<th>Transpapillary</th>
<th>Drainage modality</th>
<th>Odds ratios (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical success</td>
<td>1.1 (1.02, 1.19)</td>
<td>1.0 (1.00, 1.02)</td>
<td>1.0 (1.00, 1.02)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Technical success</td>
<td>1.1 (1.03, 1.17)</td>
<td>1.0 (1.00, 1.02)</td>
<td>1.0 (1.00, 1.02)</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Recurrent cholecystitis</td>
<td>1.1 (1.03, 1.17)</td>
<td>1.0 (1.00, 1.02)</td>
<td>1.0 (1.00, 1.02)</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>1.1 (1.03, 1.17)</td>
<td>1.0 (1.00, 1.02)</td>
<td>1.0 (1.00, 1.02)</td>
<td>0.17</td>
<td></td>
</tr>
</tbody>
</table>

Endoscopic Gallbladder Stenting (n=96)

Transpapillary (n=83) | Complete cystic duct obstruction (n=9) | Post sphincterotomy bleeding (n=10)

Success (n=65) | Failure (n=18)

EUS-guided (n=13) | Complete cystic duct obstruction (n=4) | Post sphincterotomy bleeding (n=5)

Success (n=17)

Technical Success Rate | Transpapillary 78% | EUS-guided 100% | p-value 0.04

Adverse events and long-term success rates are similar

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Transpapillary (n=50)</th>
<th>EUS-guided (n=17)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure-related adverse events, n (%)</td>
<td>5 (8)</td>
<td>1 (6)</td>
<td>1.00</td>
</tr>
<tr>
<td>- Post sphincterotomy bleeding</td>
<td>3 (5)</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>- Guide wire perforation</td>
<td>2 (3)</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>- Fever</td>
<td>1 (1)</td>
<td>1 (6)</td>
<td>0.37</td>
</tr>
<tr>
<td>Length of stay, days, median (range)</td>
<td>7 (1-60)</td>
<td>10 (4-30)</td>
<td>0.73</td>
</tr>
<tr>
<td>Follow-up time, days, median (range)</td>
<td>68 (3-180)</td>
<td>252 (10-886)</td>
<td>0.10</td>
</tr>
<tr>
<td>Clinical success rate, n (%)</td>
<td>61 (64)</td>
<td>17 (100)</td>
<td>0.58</td>
</tr>
</tbody>
</table>
Outcomes

<table>
<thead>
<tr>
<th></th>
<th>EUS-GBD N=35</th>
<th>PT-GBD N=34</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year adverse events (%)</td>
<td>1/12/30</td>
<td>1/14/34</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Recurrent acute cholecystitis (%)</td>
<td>3/12 (35)</td>
<td>3/26/34 (9.26%)</td>
<td>0.129</td>
</tr>
<tr>
<td>Restenosis after 30 days (%)</td>
<td>1/14</td>
<td>0/22</td>
<td>0.001</td>
</tr>
<tr>
<td>Retreatment of PT-GBD</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Cleaning blocked stent</td>
<td>3</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Unplanned admissions (%)</td>
<td>6 (17.1)</td>
<td>20 (59)</td>
<td>0.002</td>
</tr>
<tr>
<td>30-day adverse events (%)</td>
<td>1 (2.9)</td>
<td>39 (47)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Conclusions

- At 1 year, EUS-GBD reduced adverse events, recurrent acute cholecystitis, re-interventions and unplanned admissions.
- In the shorter term, it reduced 30-day adverse events, had lower post-procedural pain scores and analgesic requirements.
- These findings support the use of this modality as a definitive treatment for acute cholecystitis in those patients that cannot receive cholecystectomy.
- EUS-GBD should be the procedure of choice in these patients provided that the expertise is available.

Take home message

- EUS-guided direct gallbladder drainage has high success rates.
- Endoscopic guided gallbladder drainage should be considered for patients who are not candidate for surgery.

Altered Anatomy ERCP

1) Laparoscopy assisted ERCP
2) Enteroscopy assisted ERCP
3) EUS-guided ERCP (EDGE)
4) Percutaneous transcutaneous biliary drainage (PTBD)

ERCP with Roux-en-Y anatomy
Methods

- International multi-center retrospective study
- Primary outcomes: Technical success
- Secondary outcomes: adverse events, rates of persistent fistula, success of fistula closure

Results

- 98% technical success rate
- Complications:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Persistent Pneumoperitoneum</th>
<th>LAMR migration, retroperitoneal</th>
<th>LAMR migration, edgewise</th>
<th>Bleeding requiring ERCP/DHAT</th>
<th>Post-LAMR Pancreatitis</th>
<th>Crosswalk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (3)</td>
<td>Moderate (2)</td>
<td>Closed retroperitoneally (1), intraoperative (1), Closed retroperitoneally (3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>Conservative management</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Take home message

- EDGE procedures have high rates of technical success, and is relatively safe. Persistent fistulas are uncommon and can be managed endoscopically
- Choice depends on local expertise and indication

Persistent fistulas

- Suggestive of chronic pancreatitis
- EUS-guided Sphincterotomy
- Endoscopic sump drainage

Final Thoughts

- Pancreatic cysts are common and surveillance should be pursued only if patients are surgical candidates. FNA if cyst is indeterminant and monitor for high risk features.
- Urgent ERCP for acute biliary pancreatitis should be reserved for cholangitis
- Therapeutic EUS is an expanding field with indications including biliary drainage, pancreatic fluid collection drainage, disconnected duct syndrome.
- Multidisciplinary approach is imperative
The Best of AASLD 2019: Complications of Liver Disease

Scott Naugler, MD
Assoc. Professor of Medicine
Medical Director of Liver Transplantation
Division of Gastroenterology and Hepatology
Oregon Health & Science University

Alcoholic Liver Disease

Learning Objectives

1. Increasing incidence of alcohol-related illness
2. Liver transplant for chronic alcoholic liver disease
3. Liver transplant for Acute Alcoholic Hepatitis
4. Liver Transplant at OHSU for alcoholic liver disease

COFFEE AND ALCOHOL CONSUMPTION AND SOCIAL STATUS: EFFECTS ON ADVANCED LIVER FIBROSIS IN THE ERA OF HCV CURE (ARNS CO22 HEPATHER COHORT)

- Study: French multi-center (ARNS CO22)
- Purpose: HCV eradication with DAAs
- Time: 5 year follow up
- Patients: 7,791
- HCV cure: 94%

Results: HCV cure results in
- Decreased liver cancer
- Decreased overall mortality

Real Results: Dose dependent decreased chance for advanced fibrosis for each additional cup of coffee per day (OR 0.6)
OR 3.4 for advanced fibrosis for elevated alcohol consumption

COFFEE AND ALCOHOL CONSUMPTION AND SOCIAL STATUS: EFFECTS ON ADVANCED LIVER FIBROSIS IN THE ERA OF HCV CURE (ARNS CO22 HEPATHER COHORT)

- Source: Framingham Heart Study
- Groups: Patients with fatty liver presumed NAFLD
**In those with binge drinking, the odds of steatosis increased in dose-dependent manner with # drinks per week.**

**The Best of AASLD 2019: Alcoholic Liver Disease**

**Alcohol Conclusions #1**

1. Coffee good, alcohol bad (for the liver)
2. Alcohol is more common than we think, even in patients with “clear” NAFLD

**The Best of AASLD 2019: Alcoholic Liver Disease**

TRENDS AND OUTCOMES ASSOCIATED WITH ALCOHOL-RELATED HOSPITALIZATIONS IN THE UNITED STATES: A RETROSPECTIVE COHORT STUDY

- **Db:** National Inpatient Sample
- **Time:** 2005-2014
- **Groups:**
  - 417,605 adult, alcohol related causes
  - 290,233 adult, alcoholic liver disease
  - 114,120 adult, acute alcohol intoxication

Over 2005-2014, there was an average 1.1% increase in annual hospitalizations for:
- All alcohol-related causes
- Alcoholic liver disease
- Alcohol intoxication

Odds-ratio for in-hospital mortality

Increasing hospitalizations for alcohol-related causes, but decreasing in-hospital mortality over time

Highest risk for in-hospital mortality in patients with ALD is the development of HRS
Alcohol Conclusions #2

1. Coffee good, alcohol bad (for the liver)
2. Alcohol is more common than we think, even in patients with “clear” NAFLD
3. Alcohol-related medical problems (including liver disease) are on the rise in the US

Acute Alcoholic Hepatitis versus Decompensated Alcoholic Cirrhosis (ACLF)

Yes, it is important to distinguish between AAH and ACLF

**AAH**
- **Treatment:** steroids
- **Outcomes:** 70% mortality if no response to steroids (usually in first 1-2 months); complete recovery possible
- **LT:** more recidivism risk

**ACLF**
- **Treatment:** ACLF precipitant
- **Outcomes:** depends on # organ failures; reversal of ACLF possible, but not complete recovery
- **LT:** less recidivism if abstinent at time of decompensation

Liver transplant for chronic alcoholic liver disease

- **Retrospective, single center**
- 155 patients transplanted for chronic ALD
- 20% relapse rate post-LT (58% of which was sustained)
- Relapse was significantly associated with rejection
  - HR 2.33
  - Median time to rejection 11 months
Liver transplant for chronic alcoholic liver disease

Predictors of relapse post-LT:
1. History of recurrent relapse prior to LT
2. Failure to engage in recommended alcohol treatment
3. Inability to stop drinking despite diagnosis of liver disease

Compared to other etiologies, patients with ALD are:
1. Less likely to die on the waitlist
2. Just as likely to get transplanted
3. More likely to recover
Alcohol Conclusions #3

1. Coffee good, alcohol bad (for the liver)
2. Alcohol is more common than we think, even in patients with “clear” NAFLD
3. Alcohol-related medical problems (including liver disease) are on the rise in the US
4. ACLF in alcoholic liver disease is the leading indication for LT listing in the US
5. Patients listed for LT for ACLF from alcohol die less, recover more compared to other etiologies

Liver Transplantation for Acute Alcoholic Hepatitis

Mathurin, NEJM, 2011

OVERALL

NO recidivism

OVERALL

Recidivism

Predictors of post-LT alcohol use:
• Younger age
• Alcohol-related legal issues

Lee, Gastroenterology, 2018

Predicting low-risk for sustained alcohol use after early transplant for alcoholic hepatitis: The SALT score

• Source: ACCELERATE study
• Groups: 146 patients who got liver transplant for AAH at 12 US centers from 2006-17

Sustained Alcohol use post-LT = SALT

Lee, Hepatology, 2019

Sustained Alcohol use post-LT = SALT
SALT ≥ 5 had 25% PPV for sustained drinking post-LT
SALT < 5 had 95% NPV at low risk for sustained drinking

Lee, Hepatology, 2019
The Best of AASLD 2019: Alcoholics Liver Disease

Patterns of Alcohol Use After Early Liver Transplantation (LT) for Alcoholic Hepatitis (AH): Implications for Selection and Monitoring

- **Source:** ACCELERATE study
- **Groups:** 146 patients who got liver transplant for AAH at 12 US centers from 2006-17

Defined **four** patterns of alcohol use post-LT

1. Abstinence/late slip (101/146, 69%)
2. Abstinence/early slip (16/146, 11%)
3. Early sustained harmful use (15/146, 10%)
4. Early fluctuating harmful use (14/146, 10%)

Hazard Ratio for increased risk of post-LT death

Early sustained harmful use: 12.4
Early fluctuating harmful use: 5.7

---

Kitajima, Abstract #1350, Liver Meeting 2019

Waitlist Outcomes in Patients with Alcoholic Hepatitis: An Analysis of UNOS Registry

- **Db:** UNOS
- **Time:** 2009-18
- **Groups:** Patients listed for liver transplant
  Alcoholic Hepatitis vs HCV, NASH, Cholestatic (and alcoholic cirrhosis)

**Outcome:** Waitlist Mortality

---

Kitajima, Abstract #1350, Liver Meeting 2019

### Waitlist Mortality

- **p < 0.001**
- **Hepatitis C**
- **Alcoholic Hepatitis**

---

Kitajima, Abstract #1350, Liver Meeting 2019

### Waitlist Mortality

- **p < 0.001**
- **NASH**
- **Alcoholic Hepatitis**
- **Nonalcoholic Fatty Liver Disease (NASH)**
- **Alcoholic Hepatitis**
6. In highly selected patients, LT for AAH works and has excellent outcomes
7. Patients with AAH have better waitlist outcomes (presumably due to recovery) than patients listed for other liver diseases
8. Return to sustained drinking after LT for AAH leads to a significant risk of post-LT mortality

New treatments on the horizon for AAH?
DUR-928 (an oxysterol)
19 patients with AAH meeting criteria for steroid rx

Results:
1. 100% 28 day survival
2. 17/19 (89%) responded (decrease in Lille score)
3. No toxicity noted

Too good to be true?

Corticosteroids + NAC

Recommendation arises from 2015 network meta-analysis, and suggests this combination can reduce short-term mortality in AAH

...and that no treatment is effective for reducing medium-term mortality.

 Liver Transplant for Alcoholic Liver Disease at OHSU

NOTE

There are simply too many patients with alcoholic liver disease for us to evaluate them all. We want to consider those who would benefit and are good candidates, but we need your help in determining which candidates are the right ones.

Many/most will not be good candidates.
Liver Transplant for Alcoholic Liver Disease at OHSU

Acute Alcoholic Hepatitis

Admitted to hospital acutely ill, AAH or ACLF*

Severe Acute Alcoholic Hepatitis (DF >32, MELD >20)

Steroids if no contraindications*

Transplant candidate

Call for potential transfer

Not transplant candidate

Palliative Care

*Send urine ethyl glucuronide and PETH, always and immediately.

**May add NAC for 3 days if hospitalized.

Requirements for transplant evaluation for AAH at OHSU

1. No period of abstinence required
2. First hospitalization for liver-related alcohol illness
3. Non-response to 1 week of corticosteroids
4. Excellent social support
5. Absence of severe psychiatric disease
6. ≤ 1 prior failed rehab attempts
7. Willingness to undergo rehab, engage in long-term recovery support if recommended by team

Requirements for transplant evaluation forAlcoholic ACLF at OHSU

1. Two months out of hospital abstinence required*
2. Willingness to undergo rehab, long-term recovery support, etc. if recommended by group
3. Stop all addictive drugs
   - Marijuana, opiates, nicotine, benzos

OHSU Substance Abuse policy for liver transplantation

<table>
<thead>
<tr>
<th>Treatment needed</th>
<th>List for LT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Refer for inpatient transfer evaluation if candidate</td>
<td>Call for inpatient transfer evaluation if candidate</td>
</tr>
</tbody>
</table>

Unacceptable post-LT compliance risk
- Combination of:
  1. High risk of nonadherence
  2. Significant psychiatric co-morbidity
  3. Past social situation
     a. Unstable living environment
     b. Unacceptable support network

Acceptable post-LT compliance risk
- 1. No significant psychiatric co-morbidity
- 2. Good social situation
- 3. Stable living environment
- 4. Good support network

Stop all addictive substances unless strong clinical indication exists as determined by team
- Marijuana, opiates, benzos, etc.

Too ill to benefit from treatment
- Formal evaluation by treatment program
- Patient may be listed after treatment plan reviewed by team, with patient and support person agreement that patient will enter program – 6 months after LT

Not too ill to benefit from treatment
- Review for listing pending successful completion of recommended treatment program
- Satisfactory completion/progress?
**Hepatic Encephalopathy: Standard of Care**

- **Avoid precipitants**
  - Dehydration
  - Renal dysfunction
  - CNS Medications
  - GI bleeding
  - Infections (SBP)

- **Treat Episode**
  - Identify and treat precipitant
  - HE treatment *

- **Prevention**
  - Lactulose
  - Rifaximin if recurrence on lactulose
  - Avoid precipitants

**Study: RCT, double-blind, placebo**

- **Patients:** Getting TIPS (86% ascites, 16% bleeding)
- **Number:** 186 total
- **Notes:** 20% had an episode of HE prior to TIPS
- **Method:** Start rifaximin 15 days before TIPS
  - End rifaximin 6 months after TIPS
- **Outcome:** Encephalopathy within 6 months of TIPS

- **Results:**
  - 6 month HE free: 59% (rifaximin) vs 44% (placebo)
  - LT-free survival: 93% (rifaximin) vs 84% (placebo)

**Hospitalized, cirrhosis plus AKI**

- **Stop diuretics; lactulose, vasodilators if ascites**
- **Investigate for infection, blood or fluid loss**

**Fluid bolus (500-2000 mL)**
- **Albumin (1g/Kg QD or BID)**

**FENa < 1%**
- **Casts in urine**
- **H/o shock**
- **Contrast**

**Treat as HRS**

**Treat as ATN**

- **HRS (1 or 2) treatment**
  - **Albumin 1 g/kg 1st day, then 25-50 grams daily**
  - **Vasoconstrictor**
    - **Octreotide**
      - 100-200 mcg SQ tid or
      - 50 mcg/hr IV
    - **Midodrine**
      - 7.5 to 15 mg PO tid
    - **Noradrenaline**
      - 0.5 mg/hr
      - Inc MAP ≥ 10 mm Hg or
      - UOP ≥ 200 mL/4 h
      - Inc by 0.5 mg q 4h
      - Max dose 3 mg/hr

- **Monitor for ischemic complications**
- **Maximum treatment = 15 days**
- **Discontinue vasoconstrictor if creatinine < 1.5 mg/dL**
The Best of AASLD 2019: Alcoholic Liver Disease

Beta-blocker “window”

<table>
<thead>
<tr>
<th>No Varices</th>
<th>Varices, No ascites</th>
<th>Varices, Ascites*</th>
<th>Varices, Ascites**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Full dose Beta blockers</strong></td>
<td><strong>Half dose Beta blockers</strong></td>
<td><strong>- SBP &gt; 90</strong> -Na+ ≥ 130 -No AKI</td>
<td><strong>- SBP &lt; 90</strong> -Na+ &lt; 130 -AKI</td>
</tr>
<tr>
<td>NO Beta blockers Banding for primary prophylaxis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Banding for primary prophylaxis

- Full dose Beta blockers
- Half dose Beta blockers

| No Varices, No ascites | Ascites specific treatments
<table>
<thead>
<tr>
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<th></th>
</tr>
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<tbody>
<tr>
<td>Lactulose</td>
<td>NSBB, limited dose</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>Banding</td>
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</table>

The Best of AASLD 2019: Alcoholic Liver Disease

Acute-on-Chronic Liver Failure (ACLF)

Cirrhosis, hospitalized with decompensation

- One organ failure, not renal
- Renal failure, or 1 organ + renal dysfunction
- 2 organ failure
- 3+ organ failure

<table>
<thead>
<tr>
<th>No ACLF</th>
<th>ACLF, Grade 1</th>
<th>ACLF, Grade 2</th>
<th>ACLF, Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>14%</td>
<td>41%</td>
<td>52%</td>
<td>79%</td>
</tr>
</tbody>
</table>

90 day mortality

Moreau, Gastroenterology, 2013

The Best of AASLD 2019: Alcoholic Liver Disease

Diuretic responsive ascites

Portal hypertension

- Vasodilation
- Decrease in effective arterial blood volume
- Neurohormonal activation

Sodium retention

| Ascites | Ascites specific treatments
<table>
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</table>

Treatment of complications

- Lactulose
- NSBB, limited dose

The Best of AASLD 2019: Alcoholic Liver Disease

Hyponatremia

Portal hypertension

- Vasodilation
- Decrease in effective arterial blood volume
- Neurohormonal activation

Sodium retention

| Ascites | Ascites specific treatments
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Treatment of complications

- Lactulose
- NSBB, limited dose

Moreau, Gastroenterology, 2013
Hepatorenal Syndrome

- Portal hypertension
- Vasodilation
- Decrease in effective arterial blood volume
- Neurohormonal activation

Ascites specific treatments:
- Sodium/water, Albumin
- Diuretics
- Midodrine
- TIPS

Treatment of complications:
- Lactulose, Rifaximin
- NSBB, Banding

- Sodium retention
- Water retention
- Renal vasoconstriction

- Refractory ascites
- Hyponatremia
- Hepatorenal syndrome
Overview

- Novel therapies for gastroparesis
- Rome IV Classification for functional GI disorders
- Non-pharmacologic approach to functional dyspepsia
- Updates in treatment of IBS
- Highlights of our approach to management at OHSU

GASTROPARESIS

Novel promotility agents

- Relamorelin
- Prucalopride
- Velusatrag
Velusetrag Improves Gastrroparesis Both in Symptoms and Gastric Emptying in Patients with Diabetic or Idiopathic Gastroparesis in a 12-Week Global Phase 2b Study

Thomas L. Abell,1 Braden Kuo,2 Tuba Esfandyari,3 Daniel Canafax,4* Roberto Camerini,5 Maria Grimaldi,5 Giuseppe C. Viscomi,5 Cecilia Renzulli,5 Kefei Zhou,4* Deanna D. Nguyen,4 Chris N. Barnes,4* Richard McCallum6
1University of Louisville, Louisville, KY, USA; 2Massachusetts General Hospital, Boston, MA, USA; 3University of Kansas Medical School, Kansas City, KS, USA; 4Theravance Biopharma US, Inc., South San Francisco, CA, USA; 5Alfasigma S.p.A., Bologna, Italy; 6Texas Tech University, El Paso, TX, USA; *Former employee

Our approach to gastroparesis
- 4 hour, solid meal gastric emptying study or wireless Smartpill motility capsule
- Domperidone
  - 10mg TID with meals
  - Blue sky Drugs in Canada
  - Baseline EKG and q 6 months for QTc
- Prucalopride
  - FDA approved for chronic idiopathic constipation
  - Starting dose of 2mg daily except in patients > 65 yo (start 1mg daily)

Functional GI Disorders (FGID)
- Evolving definition and classification with Rome Foundation update in 2016 (Rome IV)
  - Absence of structural disease
  - Disorder of GI function
- Development of symptoms due to
  - Motility disturbances
  - Visceral hypersensitivity
  - Altered mucosal and immune function
  - Altered gut microbiota
  - Altered central nervous system (CNS) processing

Rome IV Classification
- Functional gastroduodenal disorders
  - Functional dyspepsia
  - Belching disorders
  - Nausea and vomiting disorders
  - Rumination syndrome
- Centrally mediated disorders of gastrointestinal pain
  - Centrally mediated abdominal pain syndrome
  - Narcotic bowel syndrome
- Functional bowel disorders
  - IBS
  - Functional bloating
  - Functional constipation
  - Functional diarrhea
- Functional anorectal disorders
  - Functional fecal incontinence
  - Functional anorectal pain
  - Functional defecation disorders
Rome IV Classification

**Functional Esophageal disorders**
- Functional heartburn
- Reflux hypersensitivity
- Chest pain, esophageal origin
- Functional dysphagia
- Globus

**Functional gastroduodenal disorders**
- Functional dyspepsia
  - Belching disorders
  - Nausea and vomiting disorders
  - Rumination syndrome

**Centrally mediated disorders of gastrointestinal pain**
- Centrally mediated abdominal pain syndrome
- Narcotic bowel syndrome

**Functional bowel disorders**
- IBS
  - Functional bloating
  - Functional constipation
  - Functional diarrhea
- IBS
  - Functional bloating
  - Functional constipation
  - Functional diarrhea

**Functional anorectal disorders**
- Functional fecal incontinence
- Functional anorectal pain
- Functional defecation disorders

---

**Curcuma Longa Linn versus Omeprazole in Treatment of Functional Dyspepsia: A Randomized Double-Blind Placebo-Controlled Trial**

- Randomized, double-blind, placebo-controlled trial at an outpatient Thai clinic, 2017-2018
- Included pt 18-80 years old with functional dyspepsia based on Rome IV criteria
- Randomized to 4 weeks of treatment with curcumin, omeprazole or placebo
- Primary outcome: pain and non-pain score (severity of dyspepsia assessment-SODA) change after 4 weeks of treatment
- Secondary outcome: satisfaction score, quality of life score, adverse events

- Curcumin improved pain scores at 2 weeks and 4 weeks compared to placebo
- No statistically difference between omeprazole and placebo
- Similar degree of improvements seen in non-pain score (bloating, belching, heartburn, etc) compared to placebo

**Transcutaneous auricular vagal nerve stimulation improves functional dyspepsia by enhancing vagal efferent activity**

Primary outcome:
- Dyspeptic symptom scale (DSS)

Secondary outcomes:
- Max tolerable volume on a satiety drinking test
- Gastric slow waves (measured by EEG)
- Hospital anxiety and depression scale (HADS)
Rifaximin for Improving Abdominal pain and Bloating Symptoms in Patients with IBS-D

- Post-hoc analysis of phase 3 trial evaluated rifaximin treatment in improving abdominal pain and bloating symptoms in IBS-D

Rome IV: Functional Bowel Disorders

Visceral hypersensitivity

- New Device in development: Non-invasive vagus N stim.

Gut-brain modulators for Functional Bowel Disorders

Rifaximin for Improving Abdominal pain and Bloating Symptoms in Patients with IBS-D

- Post-hoc analysis of phase 3 trial evaluated rifaximin treatment in improving abdominal pain and bloating symptoms in IBS-D
Rifaximin provided consistent and durable improvement in abdominal pain and bloating symptoms vs placebo in patients with IBS-D

- Response measured at various thresholds for improvement of abdominal pain (≥30%, ≥40%, ≥50% decrease from baseline) combined with improvement in bloating ≥1-point decrease from baseline
- 2579 patients (68% women) IBS > 10-11 years

Robustness and Safety profile of eluxadoline in patient with IBS-d reporting inadequate symptom control with loperamide: a phase 4 study

- Eluxadoline is a µ- and K- opioid agonist and delta-opioid receptor antagonist approved by the FDA for treating IBS-D
- Post-hoc analysis of original phase 3 study had shown symptom improvement in patients who had not responded to loperamide
- This phase 4 RELIEF study prospectively aimed to assess the efficacy and safety of eluxadoline in this group of patients
- Endpoint: 30% reduction in worse abdominal pain (WAP) and normalization of stool texture

FMT with or without antibiotic pretreatment in patients with IBS-D: results of a double-blind, randomized, placebo-controlled trial

- A single dose of 19 capsules containing a frozen fecal material (OpenBiome, Somerville, MA) was orally administered.
- Assessed at week 1 and week 10 after the randomization.

Symptom Assessment at Week 10

<table>
<thead>
<tr>
<th>Parameters</th>
<th>FMT alone (N=39)</th>
<th>Rifaximin EB/FMT (N=40)</th>
<th>Cipro/Metro 1/b FMT (N=28)</th>
<th>Placebo (N=12)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mea change in IBS-SXs</td>
<td>-4.9</td>
<td>-7.4</td>
<td>-1.4</td>
<td>0.3</td>
<td>0.65</td>
</tr>
<tr>
<td>Mea change in IBS-QoL</td>
<td>14.7</td>
<td>6.8</td>
<td>20.9</td>
<td>10.3</td>
<td>0.49</td>
</tr>
<tr>
<td>Mea Global Improvement score</td>
<td>4.9</td>
<td>4.5</td>
<td>4.7</td>
<td>4.2</td>
<td>0.80</td>
</tr>
<tr>
<td>Adequate relief</td>
<td>33.3%</td>
<td>40%</td>
<td>57.1%</td>
<td>33.3%</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Conclusions: FMT (with or without antibiotic pretreatment) did not improve IBS-related symptoms in patients with IBS-D
Our approach to IBS

• Patient education — FGID and visceral hypersensitivity
• Treatment
  • Diet, exercise, fiber, antispasmodics
  • Rifaximin (often from Canadian pharmacy due to $$)
  • Neuromodulators (e.g.: nortriptyline) when pain predominates
• Not currently performing FMT for IBS at OHSU

Thank you!
Are we ready for risk stratification in Colorectal Cancer Screening and Surveillance?

University of Washington
Gi Division
10-18-19

David Lieberman MD
Chief, Division of Gastroenterology and Hepatology
Oregon Health and Science University
Portland VA Medical Center

Disclosures
• Scientific Advisory Boards
  – Freenome
  – CEGX
  – Cap-Check
  – Ironwood

Once upon a time . . .

CRC Incidence by Age

Pre-1969: Evaluation of the Colon
Turbulent
Disruptive

1960's

Basil Hirschowitz
Fiberoptic Endoscopy

William Wolff
Colonoscopy 1969

1969 – 1st polypectomy

Hiromi Shinya
1971 – 1st polypectomy

2019: 50 year Anniversary of Colonoscopy

Lieberman et al; NEJM 2000; 343:162-8
Zuber et al; NEJM 2012; 366: 687-96
CRC Mortality over time

Robertson, Ladabaum; Gastroenterol 2019; 156:904‐17

CRC Incidence in USA

Other Trends:
- Longer life span
- Obesity

Screening contributes

ACS Recommends CRC Screening

Lieberman et al; NEJM 2000; 343:162-8

USA Screening Guidelines 2016-2018

What age to initiate screening?

<table>
<thead>
<tr>
<th></th>
<th>USPSTF 2016</th>
<th>MSTF 2017</th>
<th>ACS 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age to initiate</td>
<td>50 yrs for all</td>
<td>45 yrs for African Americans 50 yrs; all others</td>
<td>45 yrs for all</td>
</tr>
</tbody>
</table>

American Cancer Society 2018 Recommendation:
- Screen at age 45 to 75: **Qualified** Recommendation
- Screen age 50 to 75: **Strong** Recommendation

Does it make sense to screen everyone at the same age with the same tests?

CRC Screening:
- Same age, Same test

Familial Risk

<table>
<thead>
<tr>
<th>Family History</th>
<th>Risk Level (relative to average risk)</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>One FDR with CRC</td>
<td>&gt;2.0</td>
<td>1. Initiate at age 40 or 10 years younger than index 2. Colonoscopy preferred 3. Interval 5–10 yrs</td>
</tr>
<tr>
<td>&gt; 2 FDRs with CRC</td>
<td>&gt;4.0</td>
<td>1. Initiate at age 40 or 10 years younger than index 2. Colonoscopy preferred 3. 5 year interval</td>
</tr>
</tbody>
</table>

Key points:
1. Begin taking FHX before age 40 years
2. Update FHX every 1–2 years

Leddin, Lieberman et al; Gastroenterol 2018; 155:1325-47

CRC Incidence and Mortality (2006-2010)

Men
- Incident:
- Mortality:

Women
- Incident:
- Mortality:

CA Cancer J Clin 2014; 64: 104-117
### Race/Ethnicity and CRC

**Figure 3.** Long-term trends in United States colorectal cancer incidence (1999–2015), stratified by race, based upon SEER 18 registry data and created using seer.cancer.gov/explore application spar.

Robertson, Ladabaum; Gastroenterol 2019; 156:904-17

### Racial Gap: CRC Incidence

Multi-Society Task Force 2017:

Initiate Screening in African Americans at age 45 yrs

**Rex et al:** MSTF-CRC; Gastroenterol 2017; 153:307-23

**SEER 2009-2013**

### CRC Incidence by Sex

**Sex Differences:**
- **Age:**
  - Male rates: Location – more prox in men
  - Female rates: Location – more prox in women

**Rate per 100,000 population**

**Age at diagnosis, years**

### Risk Factors

**Tobacco Use**

- **Ever use:** 1.18 (1.11-1.25)
- **Current use:** 2.04 (1.56-2.66)

**>50g/d:** 1.21 (1.01-1.46)

### 2016 – USPSTF

- **Aspirin use and CRC**
  - Reduces CRC deaths by **33%**
  - Reduces CRC incidence by **40%**
  - Requires 5-10 yrs for protective effect
  - Low dose effective
- **Mechanism?**
  - Inhibition of Cox-2, but lack of dose-dependence
  - ? Anti-platelet action

**Bibbens-Dimingo/USPSTF Ann Intern Med doi:10.7326/M16-0577**

- **BMI >35 vs <25:** 1.07 (0.98-1.17)
- **Exercise:** 0.87 (0.78-0.97)

**Exercise:** 0.87 (0.78-0.97)
低剂量ASA

减低风险：总体 0.83 (0.78-0.89)
>1yr 0.79 (0.73-0.85)

Claudogrel 和 CRC

减低风险：总体 0.80 (0.69-0.93)
>1yr 0.65 (0.55-0.78)

基因组学 - SNPs

结直肠癌筛查和监视

精确医学 — 一个时代已经到来？

结直肠癌风险因素

- 种族/民族
- FHX
- 吸烟？
- ASA/NSAID 使用？
- 肥胖？
- 饮食？
- FIT 定量
- 遗传学？
CRC Risk Score

Risk Prediction Models for Colorectal Cancer (CRC)

AUC Estimates

<table>
<thead>
<tr>
<th>Model</th>
<th>AUC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model I: Family history &amp; C-score</td>
<td>0.68</td>
<td>(0.59 to 0.78)</td>
</tr>
<tr>
<td>Model II: Family history &amp; G-score</td>
<td>0.68</td>
<td>(0.58 to 0.78)</td>
</tr>
<tr>
<td>Model III: Family history &amp; C-score &amp; G-score</td>
<td>0.68</td>
<td>(0.56 to 0.80)</td>
</tr>
</tbody>
</table>

Risk Score

Age to start CRC screening

International Clinical Practice Guideline:

Qcancer.org/15yr/colorectal/

Helsingen et al; BMJ 2019; 367:l5516

International Clinical Practice Guideline

Helsingen et al; BMJ 2019; 367/l5516
**Incidence Reduction based on Individual Risk over 15 yrs**

- FIT q2yrs: RR 0.95
- FIT q1yr: RR 0.85
- FS once: RR 0.73
- CSP once: RR 0.66

**Mortality Reduction**

- FIT q2yrs: RR 0.5
- FIT q1yr: RR 0.41
- FS once: RR 0.48
- CSP once: RR 0.37

**Question: Will Patients accept this level of risk reduction?**

**Can we target screening more effectively?**

- Timing of screening
- Type of screening
  - Invasive
  - Non-invasive

**Risk-Based CRC Screening**

**Higher Risk**
- Who:
  - African American
  - Smoker
  - Obese
- When:
  - Start age 45
- What test:
  - Invasive test: colonoscopy

**Lower Risk**
- Who:
  - Non-African American women
  - Normal BMI
  - Aspirin/NSAID use
- When:
  - 7 start at 50
- What Test:
  - Non-invasive test until age 55-60
What about Risk-Based Surveillance?

- gFOBT
- FIT
- Genetic/Proteomics
- Imaging

Colonoscopy

Surveillance

Post-Colonoscopy CRC

- Biology
- Polyp detection (ADR)
- Completeness of polyp resection
- History of Surveillance
  - 1970’s – annual f/u after adenoma detection
  - 2019 – new recommendations based on studies which stratify patients based on risk of developing CRC

What about Risk-Based Surveillance?

- Biology
- Polyp detection (ADR)
- Completeness of polyp resection
- History of Surveillance
  - 1970’s – annual f/u after adenoma detection
  - 2019 – new recommendations based on studies which stratify patients based on risk of developing CRC

Surveillance after polypectomy:

<table>
<thead>
<tr>
<th>Baseline: Most advanced finding</th>
<th>Recommended Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>No polyp</td>
<td>10 yrs</td>
</tr>
<tr>
<td>Hyperplastic, left-sided</td>
<td>10 yrs</td>
</tr>
<tr>
<td>1-2 Tubular Adenomas ≤10mm</td>
<td>5-10 yrs</td>
</tr>
<tr>
<td>3 or more tubular adenomas</td>
<td>3 yrs</td>
</tr>
<tr>
<td>Tubular adenomas &gt;10mm</td>
<td>5 yrs</td>
</tr>
<tr>
<td>Villous adenoma (&gt;25% villous)</td>
<td>3 yrs</td>
</tr>
<tr>
<td>Adenoma with HGD</td>
<td>3 yrs</td>
</tr>
<tr>
<td>&gt;10 adenomas</td>
<td>&lt;3 yrs</td>
</tr>
<tr>
<td>Piecemeal resection</td>
<td>2-6 months</td>
</tr>
<tr>
<td>Cancer</td>
<td>1 year</td>
</tr>
</tbody>
</table>

Outcome in most studies: Advanced Adenoma

Surveillance: New Studies with Cancer Endpoints

<table>
<thead>
<tr>
<th>Baseline Colonoscopy</th>
<th>New Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>No neoplasia</td>
<td>Nishihara 2012; Lee 2018 Reduced risk of CRC incidence and mortality for at least 10 years</td>
</tr>
<tr>
<td>Low-risk Adenoma</td>
<td>Loberg 2014; Click 2018 Low risk of CRC incidence and death similar to no neoplasia</td>
</tr>
<tr>
<td>High-risk Adenoma</td>
<td>Loberg 2014; Click 2018; Atkin 2017 High risk of incident and fatal CRC Surveillance reduced risk</td>
</tr>
</tbody>
</table>

2019 Surveillance Recommendations

<table>
<thead>
<tr>
<th>Baseline</th>
<th>2012 Recommendation</th>
<th>2019 Recommendation</th>
<th>Strength of new evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>No adenoma</td>
<td>10 yrs</td>
<td>10 yrs</td>
<td>Stronger</td>
</tr>
<tr>
<td>1-2 tubular adenomas &lt;10mm</td>
<td>5-10 yrs</td>
<td>7-10 yrs</td>
<td>Stronger</td>
</tr>
</tbody>
</table>

New Data this month:
- Hartstein et al; GIE 2019 Risk of Advanced neoplasia

<table>
<thead>
<tr>
<th>Baseline</th>
<th>% with advanced adenoma at surveillance</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 TA ≤6mm</td>
<td>3.6%</td>
<td>Ref</td>
</tr>
<tr>
<td>1-2 TA 6-9mm</td>
<td>6.9%</td>
<td>1.63 (0.78-3.39)</td>
</tr>
<tr>
<td>≥3 TA at least one 6-9mm</td>
<td>10.4%</td>
<td>3.31 (1.92-7.38)</td>
</tr>
</tbody>
</table>

2019 Surveillance Recommendations

<table>
<thead>
<tr>
<th>Baseline</th>
<th>2012 Recommendation</th>
<th>2019 Recommendation</th>
<th>Strength of new evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>No adenoma</td>
<td>10 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2 tubular adenomas ≤10mm</td>
<td>5-10 yrs</td>
<td>7-10 yrs</td>
<td>Stronger</td>
</tr>
</tbody>
</table>

New Data this month:
- Meester; Ann Intern Med 2019
  Risk of Advanced neoplasia

Model assumes 10.4% CRC risk for LRA

Model assumes Low High
High-risk

Current high-risk defined as HGD or ≥ 3 or villous or ≥ 10 mm

No. of subjects in risk groups

36.5% of patients with adenomas are high-risk

33.2

Risk in 1000 per year

68.7

New definition of high-risk

High-risk defined as ≥ 20 mm or HGD

9.5% high-risk

Risk of CRC: (c/w patients with no adenomas)

** >20mm HR 9.25 (6.39-13.39)

** HGD <20mm HR 3.58 (1.96-6.54)

2019 Surveillance Recommendations

<table>
<thead>
<tr>
<th>Baseline</th>
<th>2012 Recommendation</th>
<th>2019 Recommendation</th>
<th>Strength of new evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>No adeno</td>
<td>10 yrs</td>
<td>10 yrs</td>
<td>Stronger</td>
</tr>
<tr>
<td>1-2 TA &lt;10</td>
<td></td>
<td></td>
<td>Stronger</td>
</tr>
<tr>
<td>3-4 TA &lt;10</td>
<td></td>
<td></td>
<td>Stronger</td>
</tr>
<tr>
<td>5-10 adeno</td>
<td></td>
<td></td>
<td>Similar</td>
</tr>
<tr>
<td>TA ≥10mm</td>
<td></td>
<td></td>
<td>Stronger</td>
</tr>
<tr>
<td>Villous/hid</td>
<td></td>
<td></td>
<td>Stronger</td>
</tr>
</tbody>
</table>

2019 Surveillance Recommendations

Sessile Serrated Polyps (SSP)

<table>
<thead>
<tr>
<th>Baseline</th>
<th>2012 Recommendation</th>
<th>2019 Recommendation</th>
<th>Strength of new evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>HP &lt;10mm</td>
<td>10 yrs</td>
<td>10 yrs</td>
<td>Moderate – no new evidence</td>
</tr>
<tr>
<td>HP &gt;10mm</td>
<td></td>
<td></td>
<td>Weak</td>
</tr>
<tr>
<td>1-2 SSP &lt;10mm; no dysplasia</td>
<td>5 yrs</td>
<td>3-5 yrs</td>
<td>Weak</td>
</tr>
<tr>
<td>3-4 SSP &lt;10mm</td>
<td>3 yrs</td>
<td>3-5 yrs</td>
<td>Weak</td>
</tr>
<tr>
<td>5-10 SSP &lt;10mm</td>
<td>3 yrs</td>
<td>3 yrs</td>
<td>Weak</td>
</tr>
<tr>
<td>SSP ≥10mm or Dysplasia or Traditional SSP</td>
<td>3 yrs</td>
<td>3 yrs</td>
<td>Weak</td>
</tr>
</tbody>
</table>

Post-Colonoscopy CRC

- Biology matters
  - Definitions of high-risk evolving
- Quality may be more important
  - Good Prep
  - Complete exam
  - Adenoma Detection Rate
- Other possible factors – no evidence
  - Aspirin/NSAID use
  - Smoking
  - Obesity

Information Gaps: Surveillance

- Growing evidence that colon polyp surveillance is beneficial based on CRC outcomes
- Current risk stratification based on Biology
- With improved quality of colonoscopy:
  - More adenomas detected
  - Risk could be lower
- Genomics of polyp could allow tailoring of surveillance interval
- Long-term f/u studies are still needed
Precision Medicine

Risk-Based, Personalized Screening

CRC screening is effective if performed with high-quality

end
5-ASA Overuse in Crohn’s Disease

- **Background:** 2018 ACG Guidelines
  - Oral mesalamine is not recommended for induction or maintenance of remission
- **Methods**
  - National database of commercially insured patients between 2009 and 2014
  - Ages 18-65 years
  - Analyzed trends in prescribing and factors associated with 5-ASA use

- **Results**
  - 132,804 patients
  - Declining use over time
  - Use associated with:
    - Younger age
    - Male
    - More comorbidities
    - HMO > PPO
    - Western US > NE

Stopping 5-ASA in Crohn’s Disease During Biologic Induction

- **Methods**
  - US database of commercially insured patients between 2007 and 2016
  - Danish cohorts derived from national patient register, national health registers, and prescription registry between 1995 and 2014
  - **Inclusion:**
    - Crohn’s disease treated with anti-TNF for ≥90d duration
    - Baseline 5-ASA prescription ≥90d before anti-TNF

Disclosures

- None
High Dose vs. Low Dose Methotrexate as Combination Therapy

- **Methods**
  - Retrospective cohort of UC/CD on combination of mtx + anti-TNFα
  - Low dose ≤ 15mg weekly
  - High dose > 15mg weekly

- **Primary Outcome @ 1 year**
  - Composite of need for IBD hospitalization, surgery, steroids use or change in biologic agent

<table>
<thead>
<tr>
<th></th>
<th>Low Dose (n = 113)</th>
<th>High Dose (n = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite outcome</td>
<td></td>
<td>p = 0.44</td>
</tr>
<tr>
<td>42%</td>
<td>47%</td>
<td></td>
</tr>
</tbody>
</table>

Withdrawal of Azathioprine from Adalimumab in Crohn’s Disease

- **Methods**
  - Randomized, open-label, superiority study of continued combination therapy versus azathioprine withdrawal
  - Crohn’s disease with steroid free clinical remission ≥6m
  - Patients randomized to:
    - Continued azathioprine + adalimumab (n=22)
    - Continue adalimumab and withdraw azathioprine (n=28)

- **Results**
  - No differences in ADA trough level
    - 7.08 v. 6.48, p=0.5
  - No differences in anti-drug antibody positivity
    - 10% v. 20%, p=0.4

Anti-TNF is Not Associated with Post-op Infection: PUCCINI Study

- **Methods**
  - Prospective registry of IBD patients having intra-abdominal surgery
  - Exposure to Anti-TNF within 12w
  - Detectable pre-op Anti-TNF level

- **Results**
  - 955 patients total
  - 382/955 (40%) exposed to anti-TNF within 12w
  - 224/322 had detectable pre-op anti-TNF level

<table>
<thead>
<tr>
<th></th>
<th>Anti-TNF w/in 12w</th>
<th>Detectable Anti-TNF Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any infection</td>
<td>Anti-TNF exposed</td>
<td>Any infection</td>
</tr>
<tr>
<td>Anti-TNF exposed</td>
<td>Surgical site infection</td>
<td>Anti-TNF exposed</td>
</tr>
<tr>
<td>≤ 12%</td>
<td>20%</td>
<td>Detectable level</td>
</tr>
<tr>
<td>12%</td>
<td>20%</td>
<td>Undetectable level</td>
</tr>
<tr>
<td>p = 0.8</td>
<td>p = 0.7</td>
<td>p = 0.99</td>
</tr>
<tr>
<td>p = 0.5</td>
<td>p = 0.5</td>
<td>p = 0.5</td>
</tr>
</tbody>
</table>
Pre-operative Serum Vedolizumab Levels Do Not Impact Post-operative Outcomes

- **Methods**
  - Prospective registry of IBD patients having intra-abdominal surgery at Cedars-Sinai
  - Pre-op vedolizumab level drawn day of surgery
  - Detectable level (≥1.6 µg/ml) versus undetectable

- **Results**
  - 72 patients total
  - 53% with detectable vedolizumab level

Adalimumab for Crohn's Disease Complicated by Intra-Abdominal Abscess

- **Methods**
  - Prospective observational cohort
  - Ileocolonic CD, age ≥18y
  - Spontaneous intra-abdominal or pelvic abscess on imaging
  - Excluding post-operative, perineal abscess, current TNFα medication, need for emergency surgery
  - All patients received adalimumab within 21 days of confirmed abscess control

Vedolizumab versus Adalimumab in Ulcerative Colitis: VARSITY

- **Methods**
  - Double blind, randomized, double dummy, controlled trial
  - Ages 18-85 with moderate to severe ulcerative colitis

- **Results**
  - 769 patients randomized to vedo (n = 383) or ada (n = 386)

Adalimumab for Crohn's Disease Complicated by Intra-Abdominal Abscess

- **Predictors of success**
  - Non-smoker
  - Normal CRP at beginning
  - High mural signal intensity on T2w MRE
Vedolizumab versus Adalimumab in Ulcerative Colitis: VARSITY


Calprotectin at Week 8 Predicts Endoscopic Response to Vedolizumab and Ustekinumab


Ustekinumab IV Re-Induction Can Re-Capture Response in Crohn’s Disease


Mirikizumab for Maintenance in UC


Mirikizumab for Induction in Crohn’s Disease


Upadacitinib for Induction in UC: U-ACHIEVE

Etrasimod for Induction in UC: OASIS

- **Methods**
  - S1P1 receptor modulator
  - Multi-center, randomized, double-blind, placebo trial
  - Moderate to severe UC
  - 156 patients randomized to 1mg po qd, 2mg po qd, or placebo
- **Safety**
  - Overall similar compared to placebo treated patients

12 Week Outcomes

<table>
<thead>
<tr>
<th>Endoscopic Improvement</th>
<th>Histologic Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1mg</td>
</tr>
<tr>
<td>10%</td>
<td>22%</td>
</tr>
<tr>
<td>16%</td>
<td>24%</td>
</tr>
</tbody>
</table>

* p <0.05  ** p <0.01

** Highlights **

- 5ASA remains overused in CD.
- Anti-TNFs and vedolizumab are not associated with post-operative infections
- Adalimumab can help heal bowel after an intra-abdominal abscess
- Vedolizumab appears superior to adalimumab for ulcerative colitis
- Ustekinumab re-induction can re-capture response
- Even more new therapies are progressing through the pipeline
  - Mirikizumab, upadacitinib, etrasimod

** Thank you **