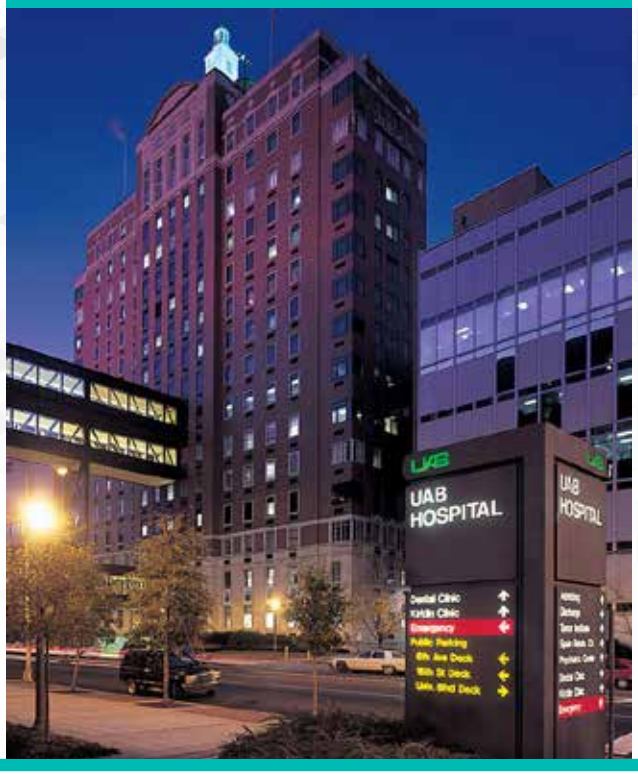
GASTROENTEROLOGY, HEPATOLOGY & ADVANCED ENDOSCOPY



UAB'S 16TH UPDATE IN GASTROENTEROLOGY, HEPATOLOGY & ADVANCED ENDOSCOPY

A CME Event for Physicians, Nurses and Healthcare Professionals

Friday & Saturday, August 13-14, 2021

The Sheraton Birmingham
Birmingham, AL

Sponsored by: Division of Gastroenterology & Hepatology & Division of Continuing Medical Education

UAB MEDICINE
The University of Alabama at Birmingham
uabmedicine.org

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Agenda

Friday, August 13, 2021

6:30 AM……..…….…….....Registration

SESSION I - "Updates in Hepatology"

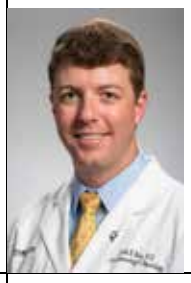
Moderator: Meagan Gray, MD

7:50 AM	Welcome & Opening Remarks		***Meagan Gray, MD*** Assistant Professor UAB Liver Center / Transplant Hepatology UAB Division of Gastroenterology & Hepatology
8:00 AM	**"State of the Art Lecture"** **Alcohol associated hepatitis**		***Patrick Kamath, MD*** Professor and Consultant Division of Gastroenterology and Hepatology Department of Medicine Mayo Clinic Rochester
8:30 AM	Regional and national impact of liver transplant allocation changes		***Robert Cannon, MD*** Assistant Professor UAB Division of Transplant Surgery
8:55 AM	Change in paradigm of pharmacologic treatment of NASH		***Sidney Barritt, MD, MPH*** Associate Professor Director, UNC Liver Center University of North Carolina, Chapel Hill
9:20 AM	Questions & Answers		
9:30 AM	Break / Posters / Exhibitors		Exhibit Area

9:50 AM	Changing landscape of treatment for advanced hepatocellular carcinoma	 ***Mohamed Shoreibah, MD*** Assistant Professor UAB Liver Center / Transplant Hepatology UAB Division of Gastroenterology & Hepatology
10:15 AM	Hepatitis B – Current treatment criteria and can we ever stop treatment?	 ***David Fettig, MD*** Assistant Professor UAB Liver Center / Transplant Hepatology UAB Division of Gastroenterology & Hepatology
10:40 AM	Palliative care in end-stage liver disease	 ***Nicholas Hoppmann, MD*** Assistant Professor UAB Liver Center / Transplant Hepatology UAB Division of Gastroenterology & Hepatology
11:05 AM	Acute on chronic liver failure	 ***Brendan McGuire, MD*** Professor & Medical Director of Liver Transplant Director, UAB Liver Center Program Director, Transplant Hepatology Fellowship UAB Division of Gastroenterology & Hepatology
11:35 AM	Questions & Answers	
11:50 AM	Break / Posters / Exhibits	
12:00 PM	Lunch	

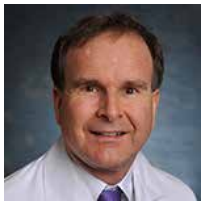
SESSION II – "Updates in Inflammatory Bowel Disease and Enteropathies"

Moderator: Doug Morgan, MD, MPH

12:55 PM	Welcome Back		***Doug Morgan, MD, MPH*** Professor Director, UAB Division of Gastroenterology & Hepatology
1:00 PM	**"State of the Art Lecture"** **Treat to target paradigm in Inflammatory Bowel Disease**		***Millie Long, MD, MPH*** Associate Professor Director of Fellowship Program Division of Gastroenterology & Hepatology Vice-Chair for Education University of North Carolina, Chapel Hill
1:30 PM	Therapeutic drug monitoring in IBD		***Kirk Russ, MD*** Assistant Professor UAB Division of Gastroenterology & Hepatology
1:55 PM	The role of surgery in IBD		***Robert Hollis, IV, MD, MSPH*** Assistant Professor UAB Division of Gastrointestinal Surgery
2:20 PM	Persistent symptoms in celiac disease despite a gluten free diet		***Amanda Cartee, MD*** Assistant Professor UAB Division of Gastroenterology & Hepatology
2:45	Questions & Answers		
2:55 PM	Break / Posters / Exhibitors		

SESSION III – "Updates in General Gastroenterology"

Moderator: Adam Edwards, MD, MS

3:18 PM	Welcome Back		***Adam Edwards, MD, MS*** Assistant Professor UAB Division of Gastroenterology & Hepatology
3:20 PM	Updates in colon polypectomy guidelines		***Chad Burski, MD*** Associate Professor Fellowship Director, UAB Division of Gastroenterology & Hepatology
3:45 PM	Neuromodulators in FGIDs		***Fred Weber, MD*** Clinical Professor UAB Division of Gastroenterology & Hepatology
4:10 PM	Functional lumen imaging in esophageal motility evaluation		***James Callaway, MD*** Assistant Professor Director, Esophageal Motility Program UAB Division of Gastroenterology & Hepatology
4:35 PM	Questions & Answers		
4:45 PM	Closing Remarks		

SESSION IV – "Updates in Pancreaticobiliary Disease and Advanced Endoscopy"

Moderator: Ali Ahmed, MD

7:45 AM	Welcome & Opening Remarks	 ***Ali Ahmed, MD*** Assistant Professor Interventional Gastroenterology UAB Division of Gastroenterology & Hepatology
8:00 AM	Interventional endoscopy – a path to everywhere	 ***Kondal Kyanam, MD, FASGE, FACP*** Assistant Professor Director of Endoscopy, Basil I. Hirschowitz Endoscopic Center of Excellence Program Director, Advanced Endoscopy Fellowship UAB Division of Gastroenterology & Hepatology
8:30 AM	Questions & Answers	
8:35 AM	Management of fistulas, perforations and leaks	 ***Ali Ahmed, MD*** Assistant Professor Interventional Gastroenterology UAB Division of Gastroenterology & Hepatology
8:55 AM	Imaging of the complex GI patient	 ***Samuel Galgano, MD*** Assistant Professor UAB Department of Radiology Sections of Abdominal Imaging and Molecular Imaging & Therapeutics Section Chief, Abdominal Imaging Fellowship Director, Abdominal Imaging
9:15 AM	Questions & Answers	
9:35 AM	Break / Exhibitors	

10:00 AM	**"State of the Art Lecture"** **EndoHepatology: expanding the role of endoscopy in the management of patients with liver disease**		*Kenneth J. Chang, MD, FACG, AGAF, FASGE, FJGES* Professor and Chief, Division of Gastroenterology & Hepatology Executive Director, Digestive Health Institute (DHI) Medical Director, Comprehensive Digestive Disease Center (CDDC) University of California, Irvine
10:30 AM	Questions & Answers		
10:35 AM	Updates in the surgical management of pancreatic cancer		*Vikas Dudeja, MD* Professor & Director of UAB Division of Surgical Oncology Selwyn M. Vickers Endowed Scholar James P. Hayes Jr., Endowed Professor in Gastrointestinal Oncology
10:50 AM	Complex polypectomy: strategies for polyp resection		*Shajan Peter, MD* Associate Professor Director, Small Bowel and Mucosal Therapeutics Programs UAB Division of Gastroenterology & Hepatology
11:15 AM	Update in the treatment of patients with pancreatic ducal adenocarcinoma		*Moh'd Khushman, MD* Associate Professor Section Chief, Gastrointestinal Oncology Medical Director, Clinical Trials Office O'Neal Comprehensive Cancer Center UAB Department of Hematology-Oncology
11:40 AM	Questions & Answers		
11:55 AM	Closing Remarks		

NURSING SYMPOSIUM AGENDA
2021 Update in Gastroenterology & Hepatology

Friday, August 13, 2021

6:30 AM ……..…….....Registration

SESSION I *Moderator: Rachel Mitchell, CRNP*

7:45 AM	Welcome / Opening Remarks		*Meagan Gray, MD* Assistant Professor UAB Liver Center UAB Division of Gastroenterology & Hepatology
8:00 AM	**"State of the Art Lecture"** **Alcohol associated hepatitis**		*Patrick Kamath, MD* Professor and Consultant Division of Gastroenterology and Hepatology Department of Medicine Mayo Clinic Rochester
8:40 AM	Welcome to Nursing Symposium		*Rachel Mitchell, CRNP* Nurse Practitioner Basil I. Hirshowitz Endoscopic Center of Excellence UAB Hospital
8:45 AM	Dysphagia		*Shajan Peter, MD* Associate Professor Director, Small Bowel and Mucosal Therapeutics Programs UAB Division of Gastroenterology & Hepatology

9:15 AM	Management of IBD	 *Emily Roberson, CRNP* Nurse Practitioner Digestive Disease Center The Kirklin Clinic at UAB Hospital
9:40 AM	Break / Exhibitors	
10:10 AM	Pain Management in Chronic Pancreatitis	 *Kondal Kyanam, MD* Associate Professor Director of Endoscopy, Basil I. Hirschowitz Endoscopic Center of Excellence UAB Division of Gastroenterology & Hepatology
10:35 AM	Questions & Answers	
10:45 AM	**Pharmacology Update:** Update in medications for Inflammatory Bowel Disease (IBD)	 *Lindsey DeLoach Flynn,PharmD* Clinical Pharmacist UAB Medicine  *Hibah Missoum, PharmD* Clinical Pharmacist UAB Medicine
11:25 AM	**Pharmacology Update:** Post liver transplant hepatitis C treatment: utilizing hepatitis C viremic donors in uninfected transplant recipients	 *DeAnn Jones, PharmD, BCPS* Clinical Pharmacist UAB Hospital
12:00 PM	Break / Exhibitors / Lunch	

SESSION II — *Moderator: Brooke Little, CRNP*

1:00 PM	**"State of the Art Lecture"** **Treat to target paradigm in IBD**		*Millie Long, MD, MPH* Associate Professor Director of Fellowship Program Vice-Chair for Education Division of Gastroenterology & Hepatology University of North Carolina, Chapel Hill
1:30 PM	Welcome Back		*Brooke Little, CRNP* Nurse Practitioner UAB Liver Center Post-op Liver Transplant Clinic The Kirklin Clinic at UAB Hospital
1:30 PM	Pre Liver Transplant Evaluation		*RaShae Robinson, BSN* Lead Pre-Liver Transplant Coordinator UAB Division of Liver Transplant
	Post Liver Transplant Care		*Michelle Cagle, MSN, BSN* Lead Post-Liver Transplant Coordinator UAB Division of Liver Transplant
2:00 PM	Hepatic Encephalopathy		*Cherie Reed, CRNP* Nurse Practitioner UAB Liver Center Post-op Liver Transplant Clinic The Kirklin Clinic at UAB Hospital
2:25 PM	Break / Posters / Exhibitors		

3:10 PM	Nutrition Recommendations in NAFLD/NASH Patients	 *Barbara Roberts, MS, RDN, LDN, CDE* Diabetes and Nutrition Education The Kirklin Clinic at UAB Hospital
3:35 PM	Benefits of palliative care in end-stage liver disease	 *Nicholas Hoppmann, MD* Assistant Professor UAB Liver Center / Transplant Hepatology UAB Division of Gastroenterology & Hepatology
4:00 PM	Evaluation and treatment of liver lesions	 *Dana Scott, CRNP* Nurse Practitioner UAB Liver Transplant & Hepatobiliary Surgery UAB Liver Tumor Clinic
4:25 PM	Questions & Answers	
4:35 PM	Closing Remarks	

Welcome from the Division Director

UAB SCHOOL OF MEDICINE
Division of Gastroenterology & Hepatology

Douglas R. Morgan, MD, MPH, FACG
Professor of Medicine and Epidemiology
Director, UAB Gastroenterology & Hepatology

As Director of the UAB Division of Gastroenterology and Hepatology, I welcome you to the 2021 Update in Gastroenterology, Hepatology and Advanced Endoscopy. We hope that you will enjoy and profit from this outstanding educational program. We are in an exciting era in Gastroenterology, Hepatology and Endoscopy with the acceleration of diagnostic and therapeutic options for our patients.

UAB's Division of Gastroenterology and Hepatology enters a noteworthy growth phase in terms of faculty and programs. Over the past year, we have added 10 new faculty. We have partnered with Gastrointestinal Surgery in Digestive Health to develop Areas of Excellence in IBD, Foregut, Colorectal Cancer, Bariatrics and Advanced Endoscopy. Hepatology continues to grow with programs in viral hepatitis and NAFLD. These are aligned with the UAB Medical Center's prioritization of Digestive Health, Transplant Medicine and the GI-Hep Cancers. Our Mucosal Immunology group is a leader in IBD and Cancer research. We serve veterans throughout the state with our robust BVAMC GI program.

We welcome your thoughts as to how we can best serve our community partners and our patients in Alabama and the region. Thank you for your daily contributions, and we hope that the 2021 Update course will enhance your patient care and professional advancement.

Doug Morgan, MD, MPH, FACG
Professor of Medicine and Epidemiology
Director, Division of Gastroenterology and Hepatology
University of Alabama at Birmingham

Welcome from the Course Directors

The Faculty and Staff of the Division of Gastroenterology and Hepatology at the University of Alabama at Birmingham Medical Center would like to welcome you to the "2021 Update in Gastroenterology, Hepatology and Advanced Endoscopy ". It is our hope that you will find this conference to be informative and applicable to your daily clinical practice. We are coming back from a year of the Covid-19 pandemic and when compared to previous meetings, we have made a few changes in this year's update by providing Advanced Endoscopy session and a Nursing Symposium that will be simultaneous on Friday. We hope that you will benefit from this format of updates and that these changes will further enhance your learning experience.

Constructive feedback is a very important part of the educational process. Please take time to complete the evaluation forms that are provided to you. We review all of the received feedback in detail and suggestions are often utilized as we continue to develop this annual course.

Also, please remember to visit our exhibitors during the breaks. We rely on their support, and we are grateful for their participation.

Again, welcome to this year's conference and thank you for attending. Please contact us if we can assist you in any way.

Meagan Gray, MD

Adam Edwards, MD, MSc

Ali Ahmed, MD

2021 Update in GI-HEP Co-Directors

Course Faculty

Ali Ahmed, MD
Assistant Professor of Medicine
Interventional Gastroenterology
Division of Gastroenterology & Hepatology
University of Alabama at Birmingham

Sidney Barritt, MD, MPH
Associate Professor of Medicine
Director, UNC Liver Center
University of North Carolina
Chapel Hill

Robert Cannon, MD
Assistant Professor of Sugery
UAB Department of Surgery
Kidney, Liver & Pancreas Transplant Service
University of Alabama at Birmingham

Chad Burski, MD
Associate Professor of Medicine
Director, Fellowship Program
Division of Gastroenterology & Hepatology
University of Alabama at Birmingham

Amanda Cartee, MD
Assistant Professor of Medicine
Division of Gastroenterology & Hepatology
University of Alabama at Birmingham

Kenneth J. Chang, MD
Professor and Chief, Division of Gastroenterology & Hepatology
Executive Director, Digestive Health Institute (DHI)
Medical Director, Comprehensive Digestive Disease Center (CDDC)
University of California, Irvine

James Callaway, MD
Assistant Professor of Medicine
Division of Gastroenterology & Hepatology
University of Alabama at Birmingham

Vikas Dudeja, MD
Professor & Director of UAB Division of Surgical Oncology
Selwyn M. Vickers Endowed Scholar
James P. Hayes Jr., Endowed Professor in Gastrointestinal Oncology

Adam Edwards, MD, MS
Assistant Professor of Medicine
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David Fettig, MD
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University of Alabama at Birmingham

Samuel Galgano, MD
Assistant Professor
Department of Radiology
Sections of Abdominal Imaging and Molecular Imaging & Therapeutics
Section Chief, Abdominal Imaging
Fellowship Director, Abdominal Imaging
University of Alabama at Birmingham

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Nicholas Hoppmann, MD
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Moh'd Khushman, MD
Associate Professor of Medicine
Section Chief, Gastrointestinal Oncology
Medical Director, Clinical Trials Office
O'Neal Comprehensive Cancer Center
UAB Department of Hematology-Oncology

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Program Director, Advanced Endoscopy Fellowship
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Millie Long, MD, MPH
Associate Professor of Medicine
Director, Fellowship Program
Vice-Chair of Education
Division of Gastroenterology & Hepatology
University of North Carolina
Chapel Hill

Brendan M. McGuire, MD
Professor of Medicine
Medical Director, Liver Transplant Program
Director, UAB Liver Center
Program Director, Transplant Hepatology Fellowship
Division of Gastroenterology & Hepatology
University of Alabama at Birmingham

Doug Morgan, MD, MPH
Professor of Medicine & Epidemiology
Director, Division of Gastroenterology & Hepatology
University of Alabama at Birmingham

Shajan Peter, MD
Associate Professor of Medicine
Division of Gastroenterology / Hepatology
University of Alabama at Birmingham

Kirk B. Russ, MD
Assistant Professor of Medicine
Division of Gastroenterology & Hepatology
University of Alabama at Birmingham

Mohamed Shoreibah, MD
Assistant Professor of Medicine
UAB Liver Center
Division of Gastroenterology & Hepatology
University of Alabama at Birmingham

Frederick Weber, MD
Clinical Professor of Medicine
Division of Gastroenterology & Hepatology
University of Alabama at Birmingham

Sponsors / Exhibitors

The support of our exhibitors help to make this conference possible. We encourage you to visit the our exhibitors during the conference.

Abbvie GI Care	**Abbvie Hepatology**
Abbvie Immunology	**Alabama Gastroenterology Society**
Ambu	**Boston Scientific**
Bristol Myers Squibb	**Cook Medical**
CSL Behring, LLC	**Dynavax**
Eisai Oncology	**Eli Lilly**
ERBE-USA	**Exact Science**
Genentech – Roche Group	**Gilead – Hepatitis B**
Gilead – Hepatitis C	**Janssen Biotech**
Medtronic	**Merck**
Merit Medical Systems	**Micro-Tec**
Nestle Health Sciences	**Olympus**
Optum Rx	**Recordati Rare Diseases**
Rumpshaker, Inc	**Salix**
Shire-Takeda	**Takeda**
US Endoscopy – Steris	**UAB Gastroenterology & Hepatology**
UAB Liver Transplant	**UAB Physician Services**

Acknowledgment of Education Grant Support

We gratefully acknowledge the Educational Grant support from the following companies that allowed us to offer this important educational opportunity:

ConMed

Cook Medical

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Overview of the UAB Division of Gastroenterology & Hepatology

The UAB Division of Gastroenterology & Hepatology is dedicated to providing comprehensive clinical, educational, and research services for all digestive and liver related diseases.

Clinical

We provide comprehensive clinical care for the treatment of digestive and liver diseases. Our faculty are trained and equipped with the most advanced techniques and procedural services available in the state and Southeast. We provide inpatient and consultative services at UAB Hospital and the Birmingham VA Medical Center. Our outpatient clinics, located within the Kirklin Clinic and UAB Highlands, report an average of over 12,000 annual patients. Additionally, our endoscopic ultrasound program is one of the highest volume centers in the world. Attending faculty members with the assistance of GI fellows and advanced nurse practitioners sees all of our patients.

Educational

Our goal is to train future gastroenterologists, transplant hepatologists and advanced endoscopists, and provide them with the most advanced knowledge and skills for treating digestive disease and liver diseases. Our faculty are actively involved with the teaching of gastroenterology fellows, house-staff, post-doctoral fellows, and sub-specialty fellows in endoscopy, inflammatory bowel disease, hepatology and transplant hepatology. We are able to provide unique learning opportunities for future gastroenterologists and sub-specialty physicians in the academic setting. All educational activities benefit from our experienced clinical and research faculty members.

Research

Our goal is to advance the management, treatment and therapies for digestive and liver related diseases. With both industry and NIH funded research, we are active in basic science and clinical research to further the treatment and knowledge of digestive diseases. We are able to utilize our diverse research programs and foster collaborative research projects not only at UAB, but also throughout the world. Our Mucosal Immunology group is leader in IBD and Cancer research. Our gastric cancer research program in Central and South America is an example of service to diverse and global populations. Our faculty members provide leadership to the UAB Liver Center and the UAB Pancreaticobiliary Disease Center (PDC). We also utilize an inclusive clinical research program, which provides a specialized infrastructure to facilitate clinical research for faculty members. This has allowed increased efficiency in our clinical research endeavors.

UAB GI/HEP Highlights

- **Publications: Numerous publications in a variety of prestigious journals including:**
  - Gastroenterology
  - Clinical Gastroenterology & Hepatology (CGH)
  - American Journal of Gastroenterology (AJG)
  - Gut
  - Science Immunology
  - Nature Oncogene, Nature ISME
  - Hepatology
  - Journal of Vascular and Interventional Radiology
  - American Journal of Medicine
  - Endoscopy
  - Gastrointestinal Endoscopy (GIE)
  - Video Gastrointestinal Endoscopy
  - World Journal Gastrointestinal Endoscopy
  - New England Journal of Medicine
- **Research: Active research projects including NIH* funded protocols:**
  - GERD and Esophageal Motility
  - Colorectal Cancer Screening
  - *Gastric Cancer prevention and epidemiology
  - Celiac Disease
  - Inflammatory Bowel Disease
  - Gastric Antral Vascular Ectasia (GAVE)
  - Advanced Endoscopy, novel technologies, AI and quality
  - Liver Transplant outcomes and quality
  - NASH with and without cirrhosis
  - Alcoholic Hepatitis
  - *The Porphyria's
  - *ESLD palliative care
- **Procedures for academic year 2020-2021:**
  A total of 17, 196 endoscopic procedures
  - 886 – ERCP
  - 1275 – EUS
  - 63 – POEM (Per Oral Endoscopic Myotomy)
  - 28 – Confocal Microscopy
  - 33 – Cryotherapy for Barrett's
  - 133 – Barrett's RFA
  - 92 – EndoFLip (Impedence Planimetry)
  - 195 – EMR/ESD
  - 228 – DBE (Biliary & Pancreatic)
  - 56 – Ductoscopy (Biliary & Pancreas Duct)
  - 92 – Cystgastrostomy/Necrosectomy (24=necrosectomy, 68=cystogastrostomy)
  - 85 – Celiac Plexus Block/Neurolysis
  - 106 – Luminal Stent
  - 42 – Endoscopic suturing
  - 139 – Bravo Capsule

- Other procedures offered at UAB Medicine are:
  - WATS^{3D} (Wide Area Transepithelial Sample with 3-Dimensional Tissue Analysis)
  - Esophageal function testing including high-resolution esophageal monometry, pH/impedance and BRAVO testing.

- **UAB Pancreatobiliary Disease Center**

  Pancreatobiliary Disease Conference is an interdisciplinary conference with experts in advanced endoscopy, surgical/medical oncology, radiology/interventional radiology, transplant surgery, pathology and genetics which evaluated a total of 443 patients in 2020-21.

  Cases reviewed in 2020-2021:
  - 163 cases of Pancreatic cancer (adenocarcinoma)
  - 54 cases of Pancreatic neuroendocrine tumors
  - 77 cases of Pancreatitis
  - 32 cases of Cholangiocarcinoma
  - 10 cases of Gallbladder cancer
  - 12 cases of Ampullary adenoma/carcinoma
  - 95 miscellaneous cases

- **UAB GI and Liver Tumor Board**: Twenty patients per week discussed at Tumor Board, a combination of new and follow up.

- **UAB Liver Tumor Clinic:** 150 new HCC referrals per year in Liver Tumor Clinic, which makes up 67% of our referral diagnosis (the rest being colorectal metastasis, cholangiocarcinoma, and other miscellaneous benign lesions). About 45% of our patients get liver directed therapy (SBRT, TACE and Y90), 19% will receive an ablation, and 36% undergo resection.

- **Viral Hepatitis Program**: Patients are now seen in our multidisciplinary *ABC Clinic* (viral hepatitis A, B, & C) by our team consisting of liver & infectious disease physicians, along with a dedicated nurse practitioner. We also now have a dedicated patient care coordinator who assists in the scheduling, treatment & followup of this clinic. Greater than 2,000 patients are seen per year. More than half of the patients with Hepatitis C seen at UAB were cured last year.

- **Hepatology and Transplant Outreach Clinics**:
  - Mobile, AL
  - Chattanooga, TN
  - Huntsville, AL

- **Liver Transplant:** Over 650 transplant referrals / over 300 evaluations per year and over 100 liver transplantations per year. Our program is ranked in the top 15 nationally in the number of liver transplants performed annually.

Overview of the UAB Liver Center

Division of Gastroenterology and Hepatology
University of Alabama at Birmingham
Birmingham, Alabama

The mission of the UAB Liver Center is:

- To provide specialized care to children and adults with all types of liver and biliary tract disease;
- To develop clinical and basic research programs to support clinical care activities for such individuals;
- To educate the profession and public about liver disease.

The University of Alabama at Birmingham (UAB) Liver Center specializes in the diagnosis, treatment and research of liver disease. Since 1995, the UAB Liver Center has pioneered numerous new treatments for patients and we offer comprehensive care throughout our outpatient clinics and our inpatient hepatology service. We also have an active clinical research unit.

Advancing the medical management of liver disease through clinical and basic research programs is a major priority for the Liver Center. In 2002, we began a Comprehensive Care Program for Patients with Hepatitis C. The establishment of this program has allowed us to streamline the process of educating, evaluating, treating and following Hepatitis C patients. A team of physicians, nurse practitioners, administrative support staff and clinical staff in the Kirklin Clinic help coordinate the evaluation, long-term management and assimilation of data of the patients who are seen in our ABC Clinic which is a multidisciplinary program with the addition of Infectious Disease. This leads to a more rapid enrollment of patients into therapy, better patient and referring physician satisfaction and improved outcomes.

The establishment of the Cirrhosis Clinic in 2005 continues to provided evaluation and treatment for cirrhotic patients. By coordinating these patients through the clinics of our physicians, we are able to evaluate and plan long-term management, including liver transplantation, with assimilation of data to improve patient outcomes.

We have performed more than 2933 transplants to date. Our one-year patient survival rate is 94.0%, which is the current national outcome of 94%. The median wait time from listing to transplant is only 5.1 months at UAB, compared to a national median of 14.4 months.

Due to the wide geographic area UAB serves, our transplant evaluation process has been streamlined for the convenience of our patients. A multidisciplinary team with expertise in liver transplantation that includes surgeons, transplant hepatologists, liver transplant coordinators, physician assistants, nurse practitioners, nurses, pharmacists, social workers, and therapists provide care for patients. From the beginning of the evaluation process, through the transplant operation and aftercare beyond, this dedicated team of professionals provides an outstanding level of care.

Overview of the Basil I. Hirschowitz Endoscopic Center of Excellence

The Division of Gastroenterology and Hepatology at the University of Alabama at Birmingham (UAB) is dedicated to providing comprehensive clinical care, education, and research for all digestive and liver-related diseases. **The Basil Hirschowitz Endoscopic Center of Excellence** features state-of-the-art facilities for interventional endoscopy procedures in the gastrointestinal and pancreaticobiliary tract. Our physicians are some of the leaders in interventional endoscopy and are world-renowned pioneers with extensive clinical and research experience in the management of complex digestive disorders. We emphasize personalized patient care delivered through our commitment to excellence and endoscopic expertise.

UAB provides a wide range of the most advanced and specialized diagnostic and treatment modalities, including:

- Advanced endoscopic imaging (standard and virtual chromoendoscopy, zoom endoscopy, endomicroscopy)
- ERCP
- Direct cholangioscopy
- Electrohydraulic shock wave lithotripsy
- Endoscopic ultrasound (EUS)
- Double balloon enteroscopy
- Radiofrequency ablation (RFA)
- Cryotherapy
- Enteral stenting & enteral nutrition (direct percutaneous jejunostomy)
- Endoscopic resection (EMR and ESD)
- Photodynamic therapy
- Advanced hemostatic techniques for fistulas and GI-leaks (loops & over-the-scope clip)
- Endoscopic drainage of abscesses and pancreatic pseudocysts/necrosis

Services & Treatment Options

- **Endoscopic Retrograde Cholangiopancreatography (ERCP) & Cholangioscopy**
  Diagnosis of the underlying problem and procurement of tissue in bile duct lesions can be challenging. This often requires an intraductal ultrasound or direct cholangioscopy to visualize the lesion and then perform biopsy. UAB specialists have found that intraductal ultrasound and cholangioscopy can diagnose greater than 90% of these lesions. Our advanced endoscopists at UAB perform the entire spectrum of bile duct stone removal techniques, ERCP procedures, and complex intraductal therapies. Our center is also unique in that we perform ERCP on patients with Roux-en-Y anastomosis and complex post-surgical anatomy.

- **Pancreatic Endotherapy**

  UAB is the leading center in the Southeast in pancreatic endotherapy. Management of pancreatic stones, strictures, and leaks can be technically challenging requiring a multidisciplinary approach. Our team has shown that pancreatic endotherapy techniques improve the outcomes in patients with pancreatic duct leaks. Also, in patients with chronic calcific pancreatitis, laser lithotripsy in conjunction with endotherapy increases the treatment success. Endoscopic necrosectomy is sometimes used in patients with walled-off pancreatic necrosis as definitive therapy or as bridge to surgery. The technique can be lifesaving in critically ill patients who are too sick to undergo surgical debridement.

- **Endoscopic Drainage of Pancreatic Fluid and Pseudocysts**

  UAB endoscopists are pioneers in the technique of EUS-guided drainage of pancreatic fluid collections and pseudocysts. Our team has shown that EUS-guided transluminal drainage results in a treatment success of greater than 90%, hospital stay of less than 48 hours, and a complication rate of less than 1%.

- **Endoscopic Ultrasound (EUS)**

  EUS is extremely important in the diagnosis, staging, and therapy of a large variety of intraluminal and extraluminal GI diseases. UAB performs the largest number of diagnostic and therapeutic EUS in the Southeast. UAB EUS offers on-site cytopathology, providing instantaneous answers when a fine needle aspiration (FNA) is performed. Our program is also at the forefront of research into EUS technology and applications.

- **Double Balloon Endoscopy**

  The double balloon endoscope (DBE), can examine the entire small bowel in real time. This technology allows the ability for both biopsy and provide definitive endoscopic therapy. DBE involves the use of a balloon at the end of a special enteroscope camera and is fitted with an overtube and balloon to drive the scope through the bowel. This helps identify and characterize diseases of the small bowel.

- **Confocal Laser Endomicroscopy (CLE)**

  This cutting-edge technology, often referred to as the "world's smallest microscope," allows for a small probe to be passed via the endoscope imaging through the gastrointestinal tract. It can be used in ERCP to image the bile duct. It can be passed through a needle during EUS – FNA of pancreatic lesions or in standard gastroscopy and colonoscopy to image the gastrointestinal mucosa. Also, early stage cancers can be diagnosed both accurately and instantly without the need for a biopsy, allowing treatment to be delivered immediately during the endoscopy.

- **Barrett's Esophagus and Radiofrequency Ablation Therapy (RFA)**

  RFA therapy for treatment of Barrett's esophagus with dysplasia utilizes endoscopy and a balloon to burn the mutated tissue, thus proactively treating the disorder. An alternative to the once standard esophagectomy, RFA takes only 30 minutes and is a minimally invasive procedure with a short recovery time.

- **Endoscopic Mucosal Resection (EMR) and Endoscopic Submucosal Dissection (ESD)**

  Early esophageal or stomach cancers and large or sessile polyps of the colon can be removed by endoscopic mucosal resection (EMR) or endoscopic sub-mucosal dissection (ESD). Our team has extensive experience in managing these types of patients and we offer the entire spectrum of endoscopic resection methods.

- **Enteral Feeding**

  We perform the entire spectrum of enteral feeding procedures including direct gastropexy, percutaneous endoscopic gastrostomy (PEG), PEG-J and direct endoscopic jejunostomy.

Third Space Endoscopy

- Zenker's myotomy: This is a minimally invasive endoscopic treatment option for dysphagia related to Zenker's diverticulum and an alternative to surgery.

Overview of Clinical Research

The Gastroenterology/Hepatology Research Program partners with the UAB Clinical Research Enterprise which provides research support, management, and oversight of clinical research studies within the Department of Medicine at UAB.

Current research in the Division of Gastroenterology & Hepatology includes:

PI	Protocol Title	Brief Description
CURRENT RESEARCH ENROLLING		
Kyanam, Kondal	A Single-Use Duodenoscope in a Real-World Setting	Evaluate the use of the Ambu® aScope™ Duodeno endoscope in SOC ERCP procedures.
Peter, Shajan	A Multicenter Case-Control Study of the Efficacy of EsoGuard on SamplesCollected Using EsoCheck, versus Esophagogastroduodenoscopy, for the Diagnosis of Barrett's Esophagus with and without Dysplasia, and for Esophageal Adenocarcinoma	Compare results of a new investigational procedure to SoC for diagnosing Barrett's Esophagus and Esophageal Adenocarcinoma.
Kyanam, Kondal	Evaluation of the Clinical Performance of an Investigational Real-Time Colorectal Polyp Clinical Decision Support Device (CDSD)	The study objective is to establish the efficacy of the colorectal polyp CDSD in clinical use.
Morgan, Douglas	Clinical Validation of An Optimized Multi-Target Stool DNA (mt-sDNA 2.0) Test, for Colorectal Cancer Screening "BLUE-C"	Determine the ability of the Exact Sciences mt-sDNA 2.0 stool screening test compared with the other standard ways to screen
Morgan, Douglas	PREEMPT CRC: Prevention of Colorectal Cancer Through Multiomics Blood Testing	Determine the sensitivity (and specificity of Freenome's test for colorectal adenocarcinoma
Elson, Charles	Corrona Inflammatory Bowel Disease (IBD) Registry	Registry to prospectively study natural history of IBD, comorbidities, adverse events, utilization patterns, comparative effectiveness and comparative safety of approved IBD treatments.
Gray, Meagan	A Randomized, Double-blind, Placebo-controlled, Phase 2b study to Evaluate Safety and Efficacy of DUR-928 in Subjects with Alcoholic Hepatitis	Phase 2b to evaluate the safety and efficacy of IV DUR-928 in subjects with severe alcohol-associated hepatitis,
McGuire, Brendan	ELEVATE, a global observational longitudinal prospective registry of patients with acute hepatic porphyria (AHP)	Study long-term safety of givosiran in patients with all types of AHP
Gray, Meagan	A Seamless, Adaptive, Phase 2b/3, Double-Blind, Randomized, Placebo-controlled, Multicenter, International Study Evaluating the Efficacy and Safety of Belapectin (GR-MD-02) for the Prevention of Esophageal Varices in NASH Cirrhosis	Study the safety and efficacy of Belapectin (for the prevention of esophageal varices in NASH Cirrhosis.

Russ, Kirk	A Phase 3, Multicenter, Randomized, Double-Blind, Placebo- and Active- Controlled, Treat-Through Study to Evaluate the Efficacy and Safety of Mirikizumab in Patients with Moderately to Severely Active Crohn's Disease	Phase 3 to evaluate the safety and efficacy of mirikizumab compared to placebo and ustekinumab. with moderate to severe active CD
Gray, Meagan	A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study Comparing the Efficacy and Safety of Tirzepatide versus Placebo in Patients with Nonalcoholic Steatohepatitis (NASH)	Phase 2 to evaluate the safety and efficacy of tirzepatide in patients with nonalcoholic steatohepatitis.
Hoppmann, Nicholas	Introducing Palliative Care (PC) within the Treatment of End Stage Liver Disease (ESLD): A Cluster Randomized Controlled Trial.	Compare effectiveness of two Palliative Care Delivery models for patients with end stage liver disease on improving quality of life.
McGuire, Brendan	Longitudinal Study of the Porphyrias	The purpose of this study is to study the natural history, symptoms, and medical treatment of people with acute and cutaneous porphyria.
Russ, Kirk	Multi-Center African-American IBD (Inflammatory Bowel Disease) Study	Investigate Inflammatory Bowel Disease in individuals and families to help find genes that may be responsible for the development of IBD.
Russ, Kirk	Study of the Immune Regulation of Idiopathic Inflammatory Bowel Diseases: Crohn's Disease, Ulcerative Colitis, and Other Inflammatory Conditions of the Gut	Collect and analyze clinical and research data from enrolled patients in order to generate hypotheses for future studies in IBD
Elson, Charles	An IBD peptide immunochip for diagnosis, prognosis, and immune monitoring in Crohn's disease	Collect clinical, immunological and other health related information related to Inflammatory Bowel Disease.
Russ, Kirk	Theravance Biopharma Ireland Limited / A Phase 2 Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Induction Therapy with 2 Doses of TD-1473 in Subjects with Moderately-to-Severely Active Crohn's Disease	The purpose of the study is to evaluate the effectiveness of TD-1473 in treating Crohn's disease.
RESEARCH IN START UP		
McGuire, Brendan	Effects of Plasma Exchange with Human Serum Albumin 5% (PE-A 5%) on Short-term Survival in Subjects with "Acute-On-Chronic Liver Failure" (ACLF) at High Risk of Hospital Mortality	The purpose of the study is to evaluate the effect of standard medical treatment (SMT) plus PE-A 5% (SMT+PE-A 5%) on 90-day overall survival in Acute on chronic liver failure.
Russ, Kirk	Study of a Prospective Adult Research Cohort with Inflammatory Bowel Disease (SPARC IBD)	The goals of this research are to identify new diagnostic tests that can predict which patient will respond to which treatment and who is most likely to relapse.
Morgan, Douglas	Novel mucosal sampling technology for gastric neoplasia Wide-area Trans-epithelial Gastric Sampling for the Detection of Premalignant Lesions and Early Gastric Cancer	Compare the diagnostic yields of the Wide-area Trans-epithelial Gastric Sampling (WATS) approach to the standard biopsies of the five gastric regions.
Ahmed, Ali	A Prospective, Post-Market, Multicenter, Randomized Controlled Trial to Compare the Performance of the EndoRotor® System Versus Conventional Endoscopic Techniques for Direct Endoscopic Necrosectomy of Walled Off Necrosis - The RESOLVE Trial	This study is being done to compare the EndoRotor System to manual endoscopic instruments for pancreatic necrosis.

Gray, Meagan	Zydus Therapeutics Inc. / "A Phase 2b, Prospective, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate Efficacy and Safety of Saroglitazar Magnesium in Subjects with Nonalcoholic Steatohepatitis and Fibrosis"	Studying Saroglitazar Magnesium as a possible treatment for Nonalcoholic Steatohepatitis and Fibrosis.
Gray, Meagan	A Phase 3, Multinational, Double-Blind, Randomized, Placebo-Controlled Study of MGL-3196 (resmetirom) in Patients With NASH and Fibrosis to Resolve NASH and Reduce Progression to Cirrhosis and/or Hepatic Decompensation	The purpose of this study is to investigate how well MCL-3196 works for the treatment of NASH compared to placebo.

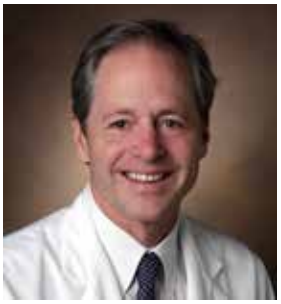
CLOSED TO ENROLLMENT / IN FOLLOWUP

Russ, Kirk	A Long-Term Non-Interventional Registry to Assess Safety and Effectiveness of HUMIRA® (Adalimumab) in Patients with Moderately to Severely Active Ulcerative Colitis	Objective of this Registry is to evaluate the long-term safety of HUMIRA® in active UC adult patients (18 years or older) who are treated per routine clinical practice.
McGuire, Brendan	A Multi-Center Group to Study Acute Liver Failure	Purpose of this study is to obtain samples of blood and urine from patients with acute liver injury and acute liver failure.
McGuire, Brendan	A Placebo-Controlled, Multi-dose, Phase 2 Study to Determine the Safety, Tolerability and Pharmacodynamic Effect of ARO-AAT in Patients with Alpha-1 Antitrypsin Deficiency (AATD) [SEQUOIA]	Study to evaluate the safety, tolerability and pharmacodynamics of the ARO-AAT to patients with Alpha-1 Antitrypsin Deficiency
Gray, Meagan	A Phase 3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Obeticholic Acid in Subjects with Compensated Cirrhosis due to Nonalcoholic Steatohepatitis (NASH)	Objective is to evaluate the effects of OCA treatment compared on histological improvement in fibrosis
McGuire, Brendan	Potential Use of Rotational Thromboelastometry to Explore Hemostatic Abnormalities in Patients with Acute Liver Failure or Acute Liver Injury	Purpose is to learn more about problems with bleeding/blood clotting in patients with ALI and ALF.

Meet the Professors…

GASTROENTEROLOGY

Doug Morgan, MD, MPH



Dr. Morgan, Professor of Medicine and Epidemiology, is the Division Director for the Division of Gastroenterology and Hepatology at UAB. His top priorities include expanding the division's clinical, educational, and research programs to meet the needs of Alabamians and beyond. His central career interest is cancer epidemiology and prevention in Hispanic-Latino populations in Latin America and the US. Dr. Morgan served as a Peace Corps engineer in Central America. This experience guided his career interests in research focusing on gastric adenocarcinoma in the low resource settings of Central America (Honduras, Nicaragua, Guatemala, El Salvador), as well as Colombia and Puerto Rico. Globally, gastric cancer is the leading infection-associated cancer, and represents a major cancer disparity in the US.

Ali Ahmed, MD

Dr. Ahmed is Assistant Professor of Medicine in Interventional Endoscopy in the Basil I. Hirschowitz Center of Endoscopic Excellence within the Division of Gastroenterology and Hepatology at UAB. He also holds an appointment at the Birmingham VA Medical Center. He obtained his medical degree at The State University of New York (SUNY), completed his fellowship at SUNY Downstate Medical Center and received his training in Advanced Endoscopy at Yale University. His interests are in ERCP, therapeutic EUS, EMR, cystgastrostomy, endoscopic suturing, luminal stenting, dilation, enteroscopy, optically enhanced endoscopy, endoscopic obesity management and general gastroenterology procedures.

Katie Alexander, PhD

Dr. Alexander joined the Division of Gastroenterology and Hepatology as Assistant Professor of Medicine in early 2021. She obtained her undergraduate degree in Chemistry from Birmingham-Southern College and completed her Ph.D. postdoctoral studies in immunology at under Dr. Charles O. Elson and Dr. Phillip D. Smith, respectively. She has a long-standing interesting in mucosal immunology and gastrointestinal disorders and a passion for translational research.

Chad Burski, MD

Dr. Burski is Associate Professor of Medicine in the Division of Gastroenterology and Hepatology at UAB. He also holds an appointment at the Birmingham VA Medical Center. He received his medical degree at Louisiana State University Health Science Center in Shreveport, LA, and completed both his Internal Medicine residency and Gastroenterology fellowship at UAB. Dr. Burski currently serves as Program Director of UAB's Gastroenterology and Hepatology Fellowship program and is actively involved in the clinical education of fellows, residents and medical students. He is also the Clinical Gastroenterology Module Director for UAB School of Medicine and is a core faculty member of the Tinsley Harrison Internal Medicine Residency program.

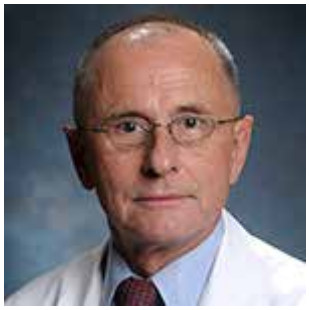
James Callaway, MD

Dr. Callaway is Assistant Professor of Medicine in the Division of Gastroenterology and Hepatology at UAB. He is also the Section Chief of Gastroenterology at the Birmingham VA Hospital. He graduated from the University of Georgia with a BS in Microbiology and received his medical degree from the Medical College of Georgia. Dr. Callaway completed his residency at UAB, where he served as Chief Medical Resident. He remained at UAB to complete his Gastroenterology fellowship and is board certified in both Internal Medicine and Gastroenterology. He serves as the Associate Director of the Gastroenterology Fellowship Program and has an avid interest in the clinical education of both residents and fellows. His major clinical interests include dysphagia, esophageal motility disorders, esophageal strictures and gastroesophageal reflux disease and its complications.

Amanda Cartee, MD

Dr. Amanda Cartee joined our faculty as Assistant Professor of Medicine in the Division of Gastroenterology and Hepatology at UAB in early 2021. Prior to coming to UAB, she was Assistant Professor of Medicine at The University of Michigan. She specializes in treating patients with celiac disease, non-celiac gluten sensitivity, and enteropathies. Her research interests include symptoms despite treatment with a gluten free diet and transition to adult care.

Charles Dasher, MD



Dr. Dasher is Professor of Medicine in the Division of Gastroenterology and Hepatology at UAB. He is also the Medical Director of Gastroenterology at UAB – Highlands. He graduated from the University of Georgia with a BS in Physics and received his medical degree from the Medical College of Georgia. He completed his residency at UAB, where he served as Chief Medical Resident. Following his residency, Dr. Dasher also completed his fellowship at UAB under the guidance of Dr. Basil Hirschowitz. He re-joined the division in 2009, and has built a very robust gastroenterology practice at UAB – Highlands.

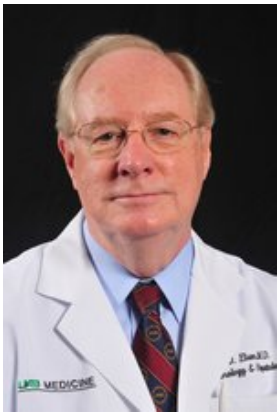
Douglas Dickinson, MD

Dr. Dickinson joined our division in early 2021 as Adjunct Professor and outpatient endoscopist at the Kirklin Clinic. Dr. Dickinson earned his MS in Biophysics and MD degree from the Pennsylvania State University and completed his Internal Medicine Residency and Gastroenterology Fellowship training at UAB Medical Center. He started Birmingham Gastroenterology Associates, PC and served in the private sector until 2013 when he joined the Birmingham VA Medical Center faculty as an attending Gastroenterologist. He also served as a Volunteer Clinical Assistant Professor with our UAB GI fellowship training program.

Adam Edwards, MD, MS

Dr. Edwards is Assistant Professor of Medicine in the Division of Gastroenterology and Hepatology at UAB. He is also the Assistant Section Chief for Gastroenterology and Hepatology at the Birmingham Veterans Affairs Medical Center. He received his medical degree from the University of Alabama at Birmingham School of Medicine. He completed his internal medicine residency training in the Tinsley Harrison Internal Medicine Residency Program at UAB, where he was also a Chief Medicine Resident. He then completed his fellowship training in the Division of Gastroenterology and Hepatology at UAB. He is an active member of the American College of Gastroenterology, American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy.

Charles O. Elson, III, MD



Dr. Elson is Professor of Medicine in the Division of Gastroenterology and Hepatology and Microbiology at UAB. He received his medical degree from Washington University in St. Louis, trained in Internal Medicine at New York Hospital/Cornell and completed his Gastroenterology fellowship at the University of Chicago. After conducting full-time research in Immunology at National Institutes of Health (NIH), he joined the Faculty of the Division of Gastroenterology at the Medical College of Virginia. He moved to the University of Alabama at Birmingham to become Director of the Division of Gastroenterology and Hepatology, and subsequently served as Vice-Chair for Research in the Department of Medicine. He holds the Basil I. Hirschowitz Chair in Gastroenterology and is an active consultant in immune-mediated intestinal disorders. The author of numerous peer-reviewed manuscripts, reviews, and book chapters, Dr. Elson has held major positions in national organizations, and has served on a number of advisory boards, including the Advisory Council of the National Institute of Diabetes and Digestive and Kidney Diseases. He has been elected to many of the most outstanding professional societies in the field of academic medicine and has a long history of service to the Society for Mucosal Immunology for which he is a co-founder and past president.

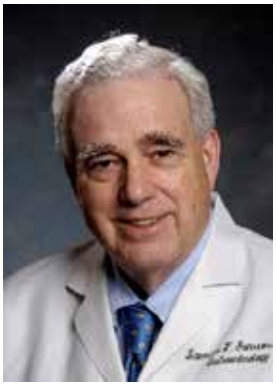
Anam Hameed, MD

Anam Hameed, MD joins the Division of Gastroenterology and Hepatolgoy as Assistant Professor of Medicine at UAB in September 2021. She received her Bachelor of Medicine, Bachelor of Surgery (MBBS) from Aga Khan University Medical College in Karachi, Pakistan. She completed her Internal Medicine residency and a Geriatric Medicine fellowship at McGovern Medical School University of Texas Health Science Center in Houston, TX and her Gastroenterology fellowship at the University of Arkansas for Medical Sciences in Little Rock, AR. Dr. Hameed's focus is nutrition and motility.

Mohamed Saleh Ismail, MD, MSc

Mohamed Saleh Ismail, MD, MSc joins our faculty in September 2021 as Assistant Professor of Medicine in the Division of Gastroenterology and Hepatology at UAB. He received his Bachelor of Medicine and Surgery, Master of Internal Medicine and completed his fellowship in Gastroenterology and Hepatology at Ain Shams University in Cairo, Egypt. He completed his training in inflammatory bowel disease at The Meyerhoff Inflammatory Bowel Disease Center at The Johns Hopkins University. He is a clinician-researcher focused on delivering comprehensive and optimal care for patients with inflammatory bowel disease.

Lawrence F. Johnson, MD
Professor Emeritus



Dr. Johnson is Professor Emeritus of Medicine in the Division of Gastroenterology and Hepatology at UAB. He received his medical degree from the Medical College of Virginia and completed his fellowship training at the Walter Reed Army Medical Center in Washington D.C. Dr. Johnson served for many years at Walter Reed Army Medical Center and in the Department of Medicine, Uniformed Services before coming to UAB in 1996 as the Director of the UAB Esophageal Program and GI Laboratory. He received many service medals and commendations during his time at Walter Reed. He has also served on several editorial boards during his years of practice. While in clinical practice, his interests were in esophageal and swallowing disorders. His scholarly achievements show insightful observations pursued independently with peers/junior staff involving multiple disciplines, culminating in numerous publications in respected peer-reviewed journals. To investigate gastroesophageal reflux, he conceived a groundbreaking technique, 24-hour esophageal pH monitoring, now employed worldwide. Since retiring from clinical practice in 2020, Dr. Johnson is preparing to publish his research.

Kondal Kyanam, MD

Dr. Kyanam is Associate Professor of Medicine in Interventional Endoscopy in the Basil I. Hirschowitz Center of Endoscopic Excellence within the Division of Gastroenterology and Hepatology at UAB. He also holds an appointment at the Birmingham VA Medical Center. Dr. Kyanam serves as the Director of Advanced Endoscopy for the Division. A graduate of Osmania Medical College, Hyderabad, India, he completed an Internal Medicine Residency and a Gastroenterology Fellowship at Louisiana State University Health Science Center, Shreveport. He completed an Advanced Endoscopy Fellowship at Mayo Clinic, Jacksonville, FL. Dr. Kyanam performs diagnostic and interventional endosonography, endoscopic retrograde cholangio-pancreatography, and endoscopic mucosal resection of lesions in esophagus, stomach, duodenum and colon. He has an additional interest in advanced endoluminal endoscopy such as complex stricture dilation, fistula closure, and over the scope clip use for different indications. His research interests include early diagnosis of pancreatic cancer and pancreatic juice markers as surrogates for diagnosis of malignant and benign pancreatic disease.

Ramzi Mulki, MD

Dr. Mulki joins our faculty in September 2021 as Assistant Professor of Medicine in the Division of Gastroenterology and Hepatology after completing his Advanced Endoscopy fellowship at UAB. Dr. Mulki graduated from Cairo University Medical School with a Bachelor of Medicine, Bachelor of Surgery (MBBCh). His post-graduate training consisted of an internship in the Department of Internal Medicine Cairo University and Department of General Surgery Jordan Hospital in Amman. He completed his internal medicine residency at Albert Einstein Medical Center. He completed his fellowship in Gastroenterology at Emory University. Currently, he is a fellow in our Advanced Endoscopy Fellowship Program.

Pranav Patel, MD

Dr. Pranav Patel is Clinical Assistant Professor of Medicine in the Division of Gastroenterology and Hepatology at UAB and sees patients at the UAB Multispecialty Clinic in Montgomery, AL. He received his medical degree from BJ Medical College, Gujarat University, Ahmedabad, India. Before he moved to United States, he completed general surgery training in India. He also worked as an adult cardiac surgery fellow at Yale New Haven Hospital for two years. Dr. Patel completed his internal medicine residency training and gastroenterology fellowship training at East Tennessee State University. He is board certified in Internal Medicine and was awarded the Richard Jordan Trust Fund Research Award for two consecutive Academic Years at East Tennessee State University.

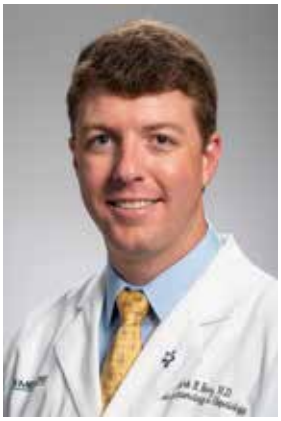
Shajan Peter, MD

Dr. Peter is Associate Professor of Medicine in the Division of Gastroenterology and Hepatology at UAB. He completed a Bachelors of Medicine and Surgery at Madras University in India and a fellowship in Internal Medicine specializing in Gastroenterology at Christian Medical College in Vellore, India. Between 2000 and 2004 he was a Consultant in the Department of Gastroenterology at Christian Medical College. In 2005 he became a Staff Gastroenterologist at the University Hospital of Basel, Switzerland, until he was recruited in 2008 to UAB. He is Board certified in Internal Medicine and Gastroenterology. He directs UAB's complicated Barrett's esophagus and early esophageal cancer program. His clinical interests include esophageal and small bowel disorders. He performs radiofrequency ablation, deep enteroscopy, advanced endoscopic imaging, screening for colorectal cancer, endoscopic mucosal resection and therapies for GI bleeding. His research focuses on endoscopic treatment outcomes of Barrett's esophagus and obscure GI bleeding and he collaborates with scientists and physicians in cell biology and mucosal immunology to better understand esophageal pathobiology.

Nipun Reddy, MD

Dr. Reddy is Assistant Professor of Medicine in the Division of Gastroenterology and Hepatology at UAB. He also holds an appointment at the Birmingham VA Medical Center. He completed his undergraduate studies at Villanova University. Dr. Reddy received his medical degree, completed his Internal Medicine residency, and completed his fellowship training program in Gastroenterology and Hepatology at UAB. He serves as the Medical Director of the Digestive Health Center at The Kirklin Clinic. He serves on various committees in the Department of Medicine. Dr. Reddy is a vital part of the Gastroenterology and Hepatology Fellowship program and also teaches first year medical students in the UAB School of Medicine. His clinical practice is focused on providing comprehensive services to a full range of digestive disorders.

Kirk Russ, MD



Dr. Russ is Assistant Professor of Medicine in the Division of Gastroenterology and Hepatology at UAB. He also holds an appointment at the Birmingham VA Medical Center. Dr. Russ completed his undergraduate studies at the University of Mississippi. He obtained his medical degree from the University of Mississippi School of Medicine in Jackson MS. After completing his residency at the UAB, where he was Chief Medical Resident, Dr. Russ completed a fellowship in Gastroenterology and Hepatology at UAB. Dr. Russ sees patients at The Kirklin Clinic and his clinical and research interests are in Inflammatory Bowel Disease (IBD).

Sergio Sanchez-Luna, MD

Dr. Sánchez-Luna joins UAB in September 2021 as Assistant Professor in the Division of Gastroenterology & Hepatology. He received his medical degree at the Universidad Autonoma de Guadalajara (UAG) in Guadalajara, Jalisco, Mexico. He completed his internal medicine residency at the University of Iowa Hospitals and Clinics (Roy J. and Lucille A. Carver College of Medicine, Department of Internal Medicine) and his Gastroenterology and Hepatology Fellowship at the University of New Mexico School of Medicine in Albuquerque, NM. In addition to performing therapeutic endoscopic procedures including EUS and ERCP, he has a focus on bariatric/metabolic endoscopy and on treating surgical complications of bariatric surgery. He also has a clinical interest in Endo-Hepatology and performs endoscopic therapy for GERD.

Fayez Sarkis, MD

Dr. Sarkis is Assistant Professor of Medicine in the Division of Gastroenterology and Hepatology at UAB. Dr. Sarkis graduated from American University, Beirut, Lebanon with a Bachelor of Science in Biology and received his MD as well as completing an Internal Medicine Internship. He completed his Internal Medicine Residency at University of Miami/JFK Medical Center and a fellowship in Gastroenterology and Hepatology at the University of Kansas Medical Center. Dr. Sarkis' clinical practice is focused on providing comprehensive services to a full range of digestive disorders.

Phillip Smith, MD

Dr. Smith is Professor of Medicine in the Division of Gastroenterology and Hepatology at UAB and past Director of the UAB Mucosal HIV and Immunobiology Center (MHIC). He earned his BA from the University of California at Berkeley in Pre-Medical Sciences and Anthropology and his medical degree from the University of Rochester, NY. After residency in Internal Medicine at Vanderbilt University and a fellowship in Gastroenterology at the University of Colorado. While, which included training in clinical parasitology at the University of Natal in Durban, South Africa. Dr. Smith completed a postdoctoral fellowship in parasite immunology in the Laboratory of Parasitic Diseases, NIAID, NIH and then joined the Laboratory of Cellular Immunology, NIDCR, NIH, where he was a Senior Investigator. Dr. Smith joined the UAB Department of Medicine in 1993. Dr. Smith's current investigative focus to mucosal stem cell organogenesis.

Lesley Smythies, PhD
Professor Emerita

Dr. Smythies is Professor Emerita of Medicine in the Division of Gastroenterology and Hepatology at UAB. She earned her BSc (Hons) and AKC degree at Kings College, London University in England and her PhD at Wye College, London University in England. She completed a Postdoctoral Fellowship in the Department of Physiology and Biophysics at UAB and the Department of Biology at the University of York in England. She returned to UAB to join the Department of Medicine as a Research Associate in 1998, advancing to Research Assistant Professor in 2002, Associate Professor in 2006 and full Professor in 2013. In 2018, she retired from UAB but is still very active with her research as Professor Emerita. She is a Collaborative Research Investigator in the Mucosal HIV and Immunobiology Center, Director of the Human Cells Core and Co-Director of the UAB Organogenesis Unit. Her research focus in human mucosal immunology, in particular the immunobiology of mucosal antigen presenting cells and the host immunological response to parasite and bacterial pathogens.

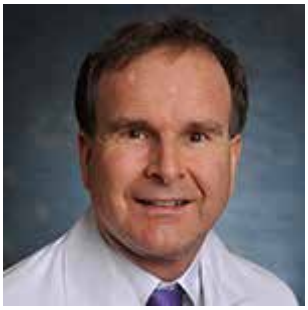
Jerry Spenney, MD

Dr. Spenney is Professor of Medicine in the Division of Gastroenterology and Hepatology at UAB. He received his medical degree from the University of Illinois and completed his residency and fellowship in Gastroenterology at UAB. He holds board certifications in both Internal Medicine and Gastroenterology and is a member of several professional medical organizations related to gastroenterology. Prior to the COVID pandemic, Dr. Spenney's clinical practice included providing inpatient consultative services at UAB.

Christopher Truss, MD

Dr. Truss is Professor of Medicine in the Division of Gastroenterology and Hepatology at UAB. He is an alumnus of the University of Alabama School of Medicine, and completed residency and fellowship training in Gastroenterology at Duke University. Dr. Truss is board certified in both Internal Medicine and Gastroenterology and has been a treating physician at UAB for over 20 years. Dr. Truss provides comprehensive gastroenterological services to patients in the Digestive Health Center located at the Kirklin Clinic.

Frederick Weber, MD



Dr. Weber is Professor of Medicine in the Division of Gastroenterology and Hepatology at UAB. He is the Director of the UAB GI Fellows Clinic, the Director of the UAB Gastric Electrical Stimulator in Gastroparesis Program and the Director of the UAB GI Clinical Nurse Practitioner Program. He received his MD from Tufts University School of Medicine. He completed his internship and residency training at Mount Auburn Hospital, which is located in Cambridge, MA which is affiliated with Harvard University. He completed his fellowship training in Gastroenterology at the University of Virginia Hospital. Dr. Weber was in private practice for many years before joining UAB in 2000. His clinical practice is focused on providing comprehensive services to the full range of digestive disorders at The Kirklin Clinic and UAB Hospital. Dr. Weber has received the Tinsley Harrison Outstanding Teacher Award in the Department of Medicine and the Tinsley Harrison Award for Best Clinical Teacher in the Department of Medicine on multiple occasions.

C. Mel Wilcox, MD, MSPH
Professor Emeritus

Dr. Wilcox is Professor Emeritus of Medicine in the Division of Gastroenterology and Hepatology at UAB. He served as the Division Director from 2001 to 2018. During that time, Dr. Wilcox guided the Division into becoming one of the leaders in the treatment of gastrointestinal and digestive disorders in the region. Dr. Wilcox is also a Major in the Department of the Army serving in the Alabama National Guard. Dr. Wilcox received his medical degree from the Medical College of Georgia. He completed his internship and residency at UAB and fellowship training in Gastroenterology at University of California San Francisco. Dr. Wilcox is a leading expert in the treatment of Zollinger-Ellison syndrome and disorders relating to pancreaticobiliary disease. Dr. Wilcox has served on several editorial boards of scholarly journals including Clinical Gastroenterology and Hepatology (Editor) and American Journal of Medicine (Associate Editor), among others. His current research interests include the role of endoscopic therapy in the treatment of pancreaticobiliary diseases.

HEPATOLOGY / UAB LIVER CENTER

Brendan M. McGuire, MD, MS

Dr. McGuire is Professor of Medicine, Medical Director of Liver Transplant and UAB Liver Center Director. He is also the Medical Director and Consultant of Liver Transplant at Children's Hospital of Alabama. He received his medical degree from the University of Pittsburgh and completed his fellowship training in Gastroenterology at the University of Minnesota. Dr. McGuire is a leading expert in the medical complications of liver disease and liver transplantation. His clinical focus is on the treatment of liver related diseases, cirrhosis and liver transplant. His research focus is in clinical management of complications in patients with end-stage liver disease. He has been involved in industry sponsored multi-center studies using two liver assist devices for treating acute and chronic liver disease. He is the primary investigator at UAB of the Acute Liver Failure Study Group, which is an NIH funded R01 multi-center study at 15 adult liver programs in the U.S. He is also the site investigator for an NIH-R01 for The Porphyrias Consortium Rare Disease Clinical Research Network.

David Fettig, MD

Dr. Fettig is Assistant Professor of Medicine in the Division of Gastroenterology & Hepatology at UAB. He joined our faculty in May, 2020. Dr. Fettig graduated Summa Cum Laude from Florida State University with a Bachelor of Science and received his MD from the University of South Florida College of Medicine. He completed his internship and residency in Internal Medicine and served as Chief Resident, and completed his fellowship in Gastroenterology and Liver Transplant Fellowship at UAB. Dr. Fettig comes back to UAB after having worked in a local private practice gastroenterology group providing hepatology services along with establishing a hepatology satellite office. Dr. Fettig's practice focus is diagnosing and treating diseases of the liver including alcoholic liver disease, liver cancer, viral hepatitis B and C, and liver transplant. He currently practices both at The Kirklin Clinic as well as the UAB Gardendale Primary & Specialty Care.

Meagan E. Gray, MD

Dr. Gray is Assistant Professor of Medicine in the Division of Gastroenterology and Hepatology at UAB. She received her Bachelors of Science and Engineering (Biomedical) from Duke University and her medical degree from the University of Louisville School of Medicine. She completed postdoctoral training at the Medical University of South Carolina and fellowship in Gastroenterology, Hepatology and Nutrition at the University of Cincinnati College of Medicine. She also completed her Transplant Hepatology Fellowship at the University of Cincinnati College of Medicine. Her clinical focus is nutrition, fatty liver disease and transplant hepatology. She also serves as the Associate Director of the Gastroenterology Fellowship Program and has an avid interest in the clinical education of both residents and fellows in liver disease.

Nicholas Hoppmann, MD

Dr. Hoppmann is Assistant Professor of Medicine in the Division of Gastroenterology and Hepatology at UAB. He graduated *Magna Cum Laude* from the University of South Carolina with a Bachelor of Science degree where he also received his MD. He completed his internship and residency in Internal Medicine and served as Chief Resident. He completed his fellowship in Gastroenterology and Transplant Hepatology at UAB. His research interests include palliative care, quality improvement and health system delivery for hospitalized patients with advanced liver disease.

Sujan Ravi, MD

Dr. Ravi joins the Division of Gastroenterology and Hepatology at UAB in September 2021 as Assistant Professor of Medicine. He received his medical degree from the Siddhartha Medical College, India. He moved to the US in 2007 and attained a Master's in Public Health from the University of Massachusetts. He completed his residency at Wayne State University, Detroit following which he worked as a hospitalist for 5 years at UAB. He completed both Gastroenterology and Transplant Hepatology fellowship training in the Division of Gastroenterology and Hepatology at UAB in 2021. Dr. Ravi's research interest is in improving health care delivery systems for patients with chronic liver diseases and he has a clinical interest in autoimmune and cholestatic liver diseases.

Mohamed Shoreibah, MD

Dr. Shoreibah is Assistant Professor of Medicine in the Division of Gastroenterology and Hepatology. He rejoined the faculty of the UAB Liver Center and Division of Gastroenterology and Hepatology in 2018 after completion of his Gastroenterology and Transplant Hepatology Fellowship at UAB. Dr. Shoreibah received his medical degree from Cairo University School of Medicine in Cairo, Egypt and completed an internship at Cairo University Hospital. He completed a residency in Internal Medicine at Atlantic City Medical Center in Atlantic City, NJ. He was in private practice for several years as an Internist before joining UAB as Assistant Professor in the Division of Gastroenterology and Hepatology. Dr. Shoreibah is active in the liver transplant program and serves as Physician Director of Communication and Outreach and is a core faculty member of the Tinsley Harrison Internal Medicine Residency program. His clinical interests are Hepatitis C, cirrhosis and liver transplant.

Joseph R. Bloomer, MD
Professor Emeritus

Dr. Bloomer is Professor Emeritus of Medicine and former Director of the UAB Liver Center. He received his medical degree from Western Reserve Medical School and fellowship training in gastroenterology at Yale University. Dr. Bloomer was a leading expert in the treatment of hepatitis B and porphyria, and is world renowned for his research in genetic diseases of the liver. Throughout his career at UAB, he aided in the growth of services available to patients suffering from liver-related diseases. Dr. Bloomer has retired from UAB.

Meet the Nurse Practitioners…

Amia Bolin, CRNP - Gastroenterology

Amia completed both her bachelors and masters degrees at UAB and has been working at UAB Hospital since 2015. Her love for GI Medicine began when her father was diagnosed with colon cancer.

Devin Harrison, CRNP - Advanced Endoscopy

Devin has been in the medical field for 10 years with experience in Cardiovascular Surgery and Hospitalist Medicine. He works in our Advanced Endoscopy Unit. He received his BSN and MSN degrees from UAB where he met his lovely wife. They now have two little boys.

Brooke Little, CRNP - Hepatology

Brooke graduated with a BSN from University of Alabama, Tuscaloosa and worked as a nurse in Infectious Disease and Cardiac Surgery. She graduated with a MSN from UAB and has been a nurse practitioner for 3 years specializing in general Hepatology and Liver Transplant. She is married and has two little girls.

Rachel Mitchell, CRNP – Advanced Endoscopy

Rachel has worked at UAB Hospital since 2008 after completing her BSN at the University of Alabama Capstone College of Nursing. She worked first as an RN in the TBICU while earning her MSN from UAB in 2013. She has worked as a nurse practitioner with Vascular Surgery, and now with the GI Medicine Advanced Endoscopy team since May 2017. She is married with one little girl.

Cherie Reed, CRNP - Hepatology

Cherie is a two-time graduate of UAB, earning her Bachelor's degree in 2010 and her Master's degree in 2016. Originally, from Asheville, NC, she has enjoyed living in Birmingham for the past 9 years. Cherie started her nursing career as a scrub and circulator in the operating room and progressed to bedside nursing where she found her passion in caring for Hepatology and Liver Transplant patients. Cherie is the proud mother of one boy with one on the way.

Emily Roberson, CRNP – Gastroenterology, IBD

Emily began her nursing journey at UAB in 2003 in the Surgical ICU unit and as an outpatient GI Surgery nurse coordinator. She attended UAB School of Nursing and graduated in 2017 with her MSN in Primary Adult/Gerontology. She joined the Digestive Health Clinic in 2018 and has a passion for Crohn's and Ulcerative colitis. She works with Dr Kirk Russ who focuses on Inflammatory Bowel Disease.

Mallory Rush, CRNP - Gastroenterology

Mallory has been working with GI Medicine in the Digestive Health Center for a little over a year. She obtained both her BSN and MSN from UAB while working on GISU at UAB as a nurse. She is currently seeing general GI patients. She is married, and has a little girl and baby boy.

Richard Ketchum, CRNP – Gastroenterology

Richard received his BS from Auburn in Biomedical Science and and received his BSN and MSN from UAB. Richard previously worked many years at UAB in the Cardiovascular Operating Room before joining the Digestive Health Center in 2020. He sees general GI patients.

2021-2022 Fellows
Division of Gastroenterology & Hepatology

Usman Barlass, MD
Advanced Endoscopy Fellow

Accreditation

PHYSICIANS

The University of Alabama School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The University of Alabama School of Medicine designates this live activity for a maximum of **10.5** ***AMA PRA Category 1 Credits™.*** Physician should claim only the credit commensurate with the extent of their participation in the activity.

PHYSICIAN ATTENDANCE CERTIFICATES:

Registrants will receive their continuing medical education certificates by email from the UAB Continuing Medical Education office within 2-3 weeks following the course. Please make sure that we have your email address correct on your registration. For any questions or concerns, please email the Division of CME at cme@uab.edu.

NURSING

UAB Hospital Center for Nursing Excellence – Nursing Continuing Education

Offering Title: 2021 Nursing Symposium - Update in Gastroenterology & Hepatology

The above Nursing Continuing Education offering has been reviewed and approved for the following contact hours:

ABN: 6.5 ANCC: 5.4 ABN Pharm 1.2 ANCC Pharm 1.0

This offering may be presented during 2021 only. The offering number is **23021**.

Offering Title: 2021 Update in Gastroenterology, Hepatology & Advanced Endoscopy

The above Nursing Continuing Education offering has been reviewed and approved for the following contact hours:

FRIDAY: ABN: 7.2 ANCC: 6.0
SATURDAY: ABN: 3.7 ANCC: 3.1

This offering may be presented during 2021 only. The offering number is **23021-A**.

In order for participants to receive CE credit, they must:

- Sign the roster at the beginning of the offering.
- Attend the offering in its entirety.
- Complete the course evaluation.
- Swipe their nursing license at the conclusion of the offering.
- No partial CE credit will be awarded.

UAB Hospital's Center for Nursing Excellence is an approved provider of continuing nursing education by the Alabama Board of Nursing (Provider No: ABNP0055, Expiration date: May 28, 2025).

UAB Hospital's Center for Nursing Excellence is approved as a provider of nursing continuing professional development by The Alabama State Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.
(Provider No: 5-69, Expiration date: July 7, 2023).
For any questions email nursingce@uabmc.edu .

Patrick Kamath, MD
Professor & Consultant
Division of Gastroenterology & Hepatology
Department of Medicine
Mayo Clinic
Rochester ,MN

"Alcohol associated hepatitis"

Disclosures: NIH-NIAAA (Grant)

Learning Objectives:

- Identify alcohol associated hepatitis
- Understand patient selection and criteria for early liver transplantation

The most common causes of cirrhosis worldwide are alcohol-associated liver disease, also termed alcohol-related liver disease, nonalcoholic fatty liver disease (NAFLD), also termed metabolic-associated fatty liver disease (MAFLD), and especially in developing countries, chronic viral hepatitis B and C. Among the 2 billion people who consume alcohol worldwide, upwards of 75 million are at risk for alcohol-associated liver disease given their high level of alcohol use. Approximately 5% with global burden of all disease is attributable to alcohol consumption. Moreover, 4-25% of specific cancers can be attributed to alcohol. Alcohol is the leading risk factor globally for death and DALY among those less than 20 years of age. Over 50 % of mortality related to cirrhosis is attributable to alcohol. Regions of the world which have higher rates of heavy alcohol consumption have a higher rate of cirrhosis.

Three or more drinks in women and 4 or more drinks in men is considered harmful drinking putting individuals at risk for alcohol associated liver disease. Among heavy drinkers, liver biopsy will demonstrate fatty liver in about 90% of patients. Only about 30% of heavy drinkers will have alcohol associated hepatitis, and only approximately 15% will develop cirrhosis. The rate of progression to hepatocellular carcinoma in patients with cirrhosis is 2-4% per year. Alcohol associated hepatitis (AAH) is the most severe form of alcohol associated liver disease and mortality rates are as high as 50% at 6 months.

Patients with fatty liver disease alone may be asymptomatic or have mild nausea, epigastric discomfort, or vomiting. AAH is considered with the serum bilirubin is greater than 3 mg/dL, the AST is elevated but < 400 u/L, and the AST:ALT ratio is > 1.5. Liver biopsy is not always required for diagnosis of AAH. However, in patients where the amount of alcohol use is uncertain, or if the AST and ALT pattern is atypical, or if there are confounding factors such as drug use or sepsis, and steroids are considered as therapy, liver biopsy is mandatory for diagnosis. Severe AAH is diagnosed when the Maddrey discriminant functions is > 32 or the MELD score is > 20.

Inpatient management is recommended when patients have severe AAH. Prednisolone is recommended in a dose of 40 mg per day for 28 days. Methylprednisolone 32 mg per day intravenously may be used as an alternative in patients who are unable to take medication by mouth. Prior to initiation of steroid therapy, infection and gastrointestinal bleeding should be ruled out. Addiction services should also be involved in the management of these patients. Response to steroid

treatment is determined by Lille score < 0.45 at 7 days. Patients who respond to steroid treatment as determined by the Lille score and will do not resume alcohol use, have good long-term survival.

Highly selected patients who do not respond to medical treatment and are deemed to be at low risk for relapse to alcohol use post-transplant are potential candidates for liver transplantation. Survival in such patients is similar to steroid responders.

Recommended reading:

1. Singal, Ashwani K MD, MS, FACG[1]; Bataller, Ramon MD, PhD, FACG[2]; Ahn, Joseph MD, MS, FACG (GRADE Methodologist)[3]; Kamath, Patrick S MD[4]; Shah, Vijay H MD, FACG[4] ACG Clinical Guideline: Alcoholic Liver Disease American Journal of Gastroenterology: February 2018 - Volume 113 - Issue 2 - p 175-194
2. Crabb DW, Im GY, Szabo G, Mellinger JL, Lucey MR Diagnosis and Treatment of Alcohol-Associated Liver Diseases: 2019 Practice Guidance From the American Association for the Study of Liver Diseases. Hepatology. 2020 Jan;71(1):306-333
3. Singal AK, Mathurin P**.** Diagnosis and Treatment of Alcohol-Associated Liver Disease: A Review. JAMA. 2021 Jul 13;326(2):165-176

Alcohol Associated Hepatitis: Current Management and Future Directions

Patrick S. Kamath MD
Division of Gastroenterology and Hepatology
Mayo Clinic College of Medicine and Science
Rochester MN

Pathogenesis and Management of Alcohol Associated Hepatitis: Current and future perspectives

Quiz
ACG 2018 Guidelines
AASLD 2019 Guidelines

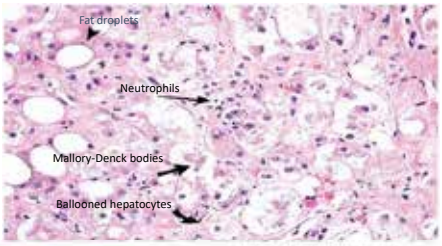
Alcohol and Obesity

- Patients with obesity and/or HCV should be advised to consume no more than 1/2/3 alcoholic drinks per day
- Patients with ALD should not smoke because of increased risk of
- A HCC
- B More severe hepatitis
- C Hepatic fibrosis

Liver Biopsy for Diagnosis of AAH

- Liver biopsy is required for diagnosis of AAH when other liver diseases ruled out if
- A. There is a clear history of alcohol use but normal liver tests
- B. Unclear history of alcohol use and elevated liver tests
- C. Only with clear history of alcohol use AND elevated liver tests

Histopathological Features of AAH



Severe Alcohol Associated Hepatitis

- Severe AH is diagnosed by Maddrey score of
  - ➢32 OR MELD score of:
    - A. > 20
    - B. > 24
    - C. > 28
    - D. > 32

Treatment of Alcohol Associated Hepatitis

- Which of the following is true regarding prednisone/prednisolone therapy for severe AAH:
  - A. Reduces mortality 30 days
  - B. Reduces mortality 180 days
  - C. Reduces mortality 360 days
  - D. Does not reduce mortality

Response to steroid therapy

- After 1 week of 40mg daily prednisone therapy the Lille score is 0.58. You will:
  - A. Stop prednisone
  - B. Increase prednisone to 60 mg
  - C. Add antibiotics
  - D. Add pentoxifylline

Early Liver Transplantation for AAH

- Early liver transplantation for severe AH is associated with survival:
  - A. Similar to steroid responders
  - B. Better than steroid responders
  - C. Better than elective transplantation
  - D. Worse than elective transplantations

Liver Transplantation in Alcohol Associated Hepatitis

- Liver transplantation may be considered for highly selected patients with severe alcohol associated hepatitis. (Strong recommendation, moderate level of evidence.)

Alcohol Associated Hepatitis (AAH)

- **Terminology**
- **Alcohol: facts**
- **Outpatient management**
- **Pathophysiology and management**
- **Liver Transplantation for AAH**
- **Take-home messages**

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Current Terminology

Previous term	Current term	Abbreviation
Alcoholic	Alcohol use disorder	AUD
Alcoholic liver disease	Alcohol-related liver disease	ALD
Alcoholic cirrhosis	Cirrhosis due to alcohol-related liver disease	ALD cirrhosis
Alcoholic steatohepatitis (histologically-defined lesion)	Steatohepatitis due to ALD	ASH
Alcoholic fibrosis	Fibrosis due to ALD	ALD fibrosis
Alcoholic hepatitis	Alcoholic hepatitis*	AH

Term "alcoholic" is stigmatizing and undermines patient dignity and self-esteem.

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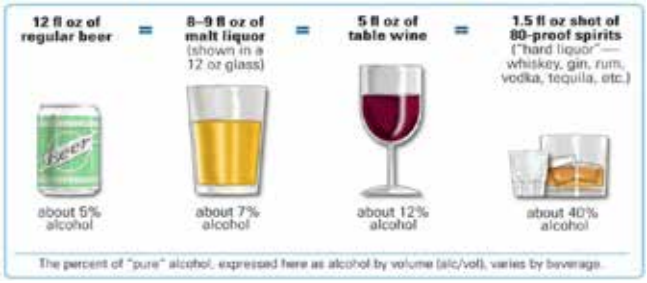
How much is "just one drink"?



Drinkers underestimate alcohol consumption by ~ 40%

NIAAA.gov

Binge Drinking and Liver Disease

- 4-5 drinks over 2 hours (BAL ~ 0.08) – NIAAA
- Social harm, crime, pregnancy
- Effects on liver related complications is less resolved (Askgaard et al and Rehm et al J Hep 2015)

The next crisis: Powdered alcohols

- Palcohol; Booze2go
- Easily carried and dissolved in liquid or snorted
- Regulations ongoing at state and national level

Flying under the influence

Minnesota Residents Call Police On Rowdy Drunk Birds

Elephants Really Can't Hold Their Liquor

Humans and other species have a gene mutation that lets them digest alcohol. So other species, it's missing.

Detecting Alcohol Use: Interpretation of Phosphatidylethanol Levels

• If Peth	Alcohol consumption 28 days
• <10 µg/L	Abstinent or minimal use
• 10-35 µg/L	Low or occasional
• 35-210 µg/L	Social/moderate
• >210 µg/L	Excessive

How much coffee do you have to drink to protect from alcohol associated liver disease?

Alcohol increases risk of death from cirrhosis

N Engl J Med 1997 Dec 11;337(24):1705-14

How Much Should you Drink to Develop Alcohol Associated Liver Disease

- Heavy alcohol :3 drinks per day for women (≥40 grams of alcohol), and four drinks per day for men (≥50-60 grams of alcohol).
- Strong correlation between severity and duration of alcohol use and the presence of cirrhosis.
- Rate of cirrhosis higher in patients consuming ≥ 30 g / d than abstinent controls or consuming <30 g / day (2.2% vs 0.08%)
- Alcohol consumption > 120 g /day highest risk of cirrhosis (13.5%)
- 3% of patients with alcohol associated hepatitis progress to cirrhosis annually

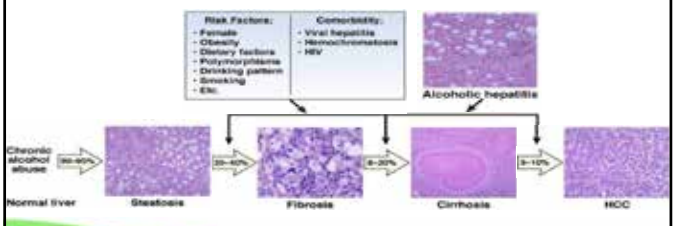
Low Risk Drinking: NIAAA Definitions

National Institute of Alcohol Abuse and Alcoholism Definition of Drinking at Low Risk for Developing Alcohol Use Disorder (AUD):

- For women, low-risk drinking is defined as no more than 3 drinks on any single day and no more than 7 drinks per week.
- For men, no more than 4 drinks on any single day and no more than 14 drinks per week.
- NIAAA research shows that only about 2 in 100 people who drink within these limits have AUD.

Women: 3 OR 7 Rule (Caution: Breast cancer and other risk increases with 1 drink per day
Men: 4 OR 14 Rule

Histopathological progression of ALD: Risk factors and Co-morbidities



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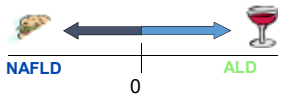
Outpatient management of alcohol associated liver disease

- Differentiating between alcohol associated steatohepatitis and non-alcohol associated steatohepatitis
- Diagnosing alcohol use disorder
- Management

Alcohol associated Steatohepatitis Versus NASH

- Difficult to obtain accurate alcohol consumption history: AUDIT questions and history from multiple sources
- High MCV, male sex, low BMI, and AST > ALT favor Alcohol as factor
- Normal MCV, female sex, obesity, ALT > AST favor NASH diagnosis

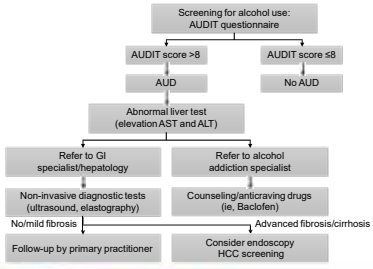


Diagnosing Alcohol Use Disorder

- AUDIT (Alcohol Use Disorders Inventory Test): 10 questions that explore consumption (1–3), dependence (4–6), and alcohol-related problems (7–10)
- C-off points:8-15 "risky drinking"; ≥ 16 "harmful drinking"
- AUDIT-C includes just the first three questions of AUDIT: reliable for the screening of 'risky drinking'.
- NIAAA (National Institute of Alcohol Abuse and Alcoholism) recommends third question of the AUDIT *(How often do you have six or more drinks on one occasion?)* as single screening question, followed by the whole AUDIT in answer is rated positive.

Alcohol Associated Liver Disease

Algorithm for Outpatient Management



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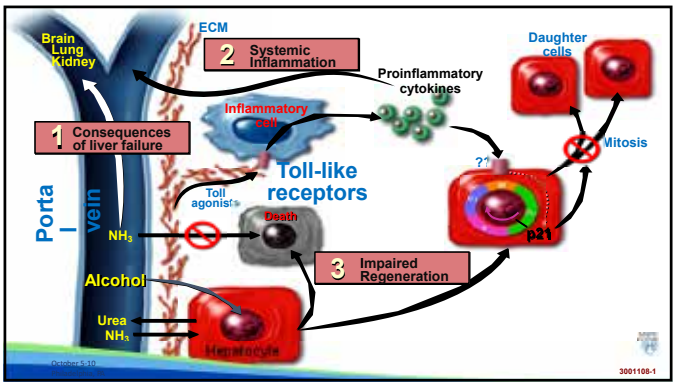
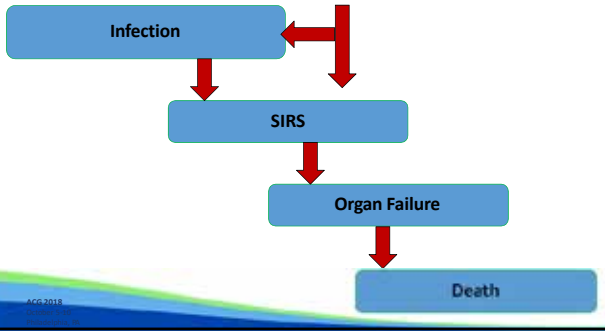


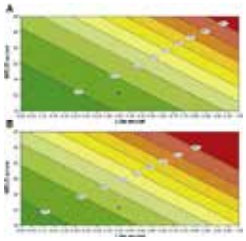
Clinical Manifestations of Alcohol Associated Hepatitis

- Consequences of liver failure: Jaundice
  Ascites
  Encephalopathy
- Systemic Inflammation and sepsis: SIRS
  Multiple organ failure
- Impaired hepatocyte regeneration: Propagation of liver failure
- Features of alcohol withdrawal syndrome

SEVERE AH: COURSE



Combining MELD and Lille for Optimal Prognostic Scoring



2 Month Mortality

6 Month Mortality

MELD score: 21
Lille Score 0.45

www.lillemodel.com

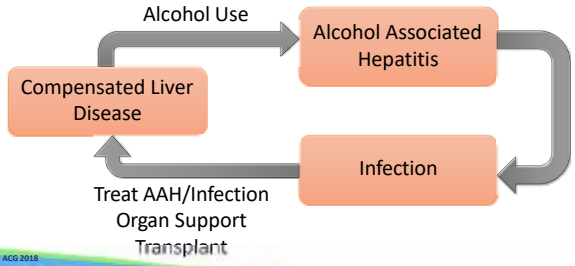
2-month mortality: 15.3%

6-month mortality: 24%

Louvet Gastro 2015

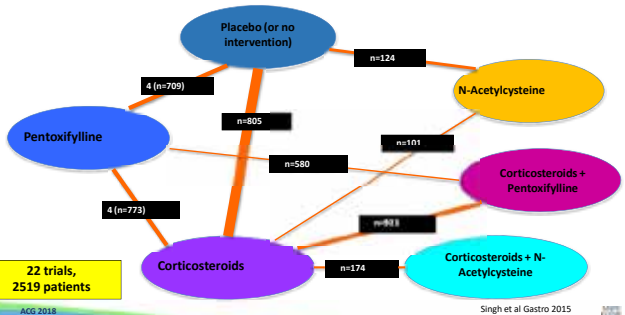
ACG 2018

AAH-ACLF: Therapeutic Targets



ACG 2018

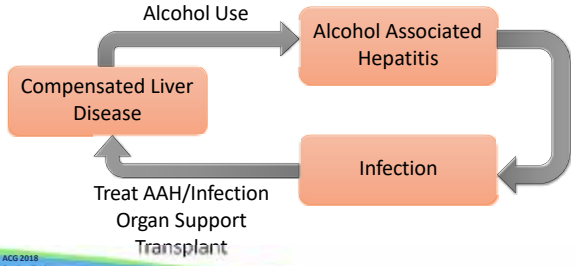
AH Treatment: Which One is Best?



Singh et al Gastro 2015

ACG 2018

AAH-ACLF: Therapeutic Targets



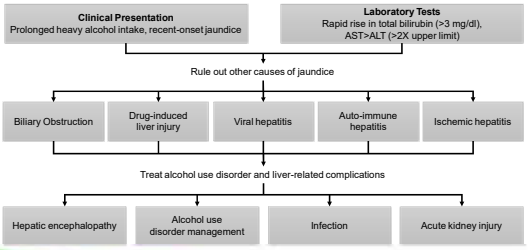
ACG 2018

Treatment of AAH

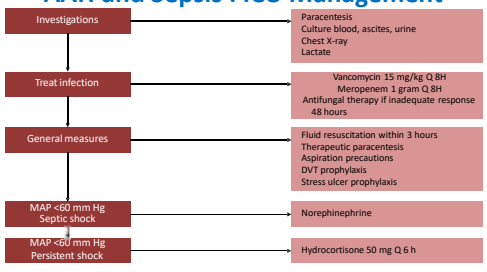
- Network meta-analysis suggests only prednisone/prednisolone is associated with improved survival at 30 days
- No drug improves survival beyond 6 months
- Survival beyond 6 months related to initial response to treatment AND sustained abstinence
- Highly selected patients (first episode of AH), benefit from liver transplant)
- Sustained alcohol use after LT is infrequent but associated with increased mortality.

Alcohol Associated Liver Disease

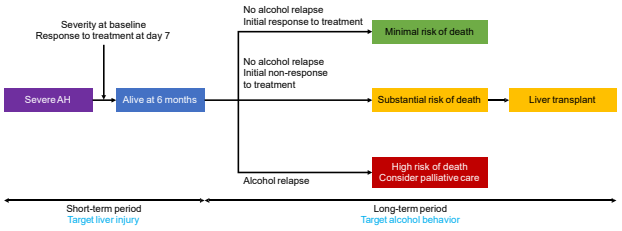
Alcohol Associated Hepatitis Initial Evaluation



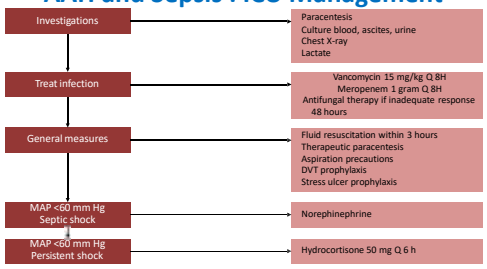
AAH and Sepsis : ICU Management



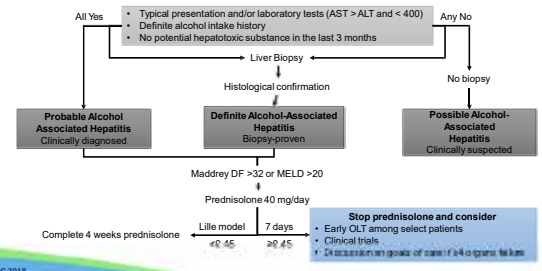
Alcohol Associated Hepatitis: Prognostic Factors



AAH and Sepsis : ICU Management



Alcohol Associated Hepatitis: Management



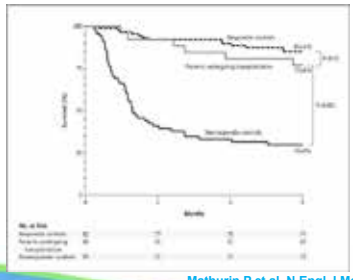
Alcohol Associated Hepatitis (AAH)

- **Terminology**
- **Alcohol: facts**
- **Outpatient management**
- **Pathophysiology and management**
- **Liver Transplantation for AAH**
- **Take-home messages**

Who is a candidate for early transplantation for AAH

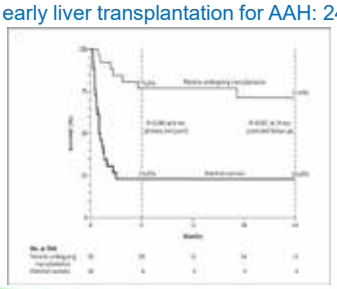
- Very carefully selected patients (10% of all patients with AAH)
- No evidence of ongoing extrahepatic infection
- Limited frailty or sarcopenia; “eyeball test”
- No or decreasing vasopressor requirement
- Experienced liver transplant center
- Limited social and medical risk
- Low risk donor liver

Results of early liver transplantation for AAH: 6 months



Mathurin P et al. N Engl J Med 2011;365:1790-1800

Results of early liver transplantation for AAH: 24 months



Mathurin P et al. N Engl J Med 2011;365:1790-1800

Results of early liver transplantation for AAH: US Experience

Gastroenterology. 2018 August ; 155(2): 422–430

How do you determine risk for alcohol use relapse

High Risk Alcohol Relapse Scale (HRAR)

Table 1. High-Risk Alcoholism Relapse Scale

Item	Score
Duration of heavy drinking, y	
≤11	0
11-25	1
≥25	2
Daily drinks, No.*	
≤9	0
9-17	1
≥17	2
Prior alcoholism inpatient treatments, No.	
0	0
1	1
≥1	2

- N= 387 ALD patients who underwent LTX
- Three factors found to be independently associated with relapse to *harmful drinking*:
  1. Abstinence of less than 6 mo (OR 3.3)
  2. Psychiatric comorbidity (anxiety or depression) (OR 7.8)
  3. High risk alcoholism relapse score (HRAR) greater than 3 (OR 10.7)

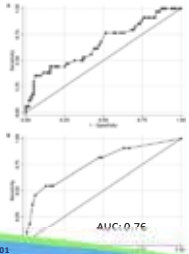
# of criteria met	Relapse rate	# patients
0	5%	13/272
1	18%	16/92
2	64%	14/22
3	100%	3/3

Gottardi et al, 2007

Severe AAH: List for transplantation or not

- List if:
  - HRAR < or = 3 with or without psychiatric comorbidity
  - HRAR =4 without psychiatric comorbidity, other substance abuse
  - Insight and social support acceptable
- Do not list:
  - HRAR > 4
  - HRAR=3 but no insight, social support, additional substance abuse and harmful behavior (multiple DUI within past 3 years)

Sustained Alcohol Use Post-LT (SALT) score



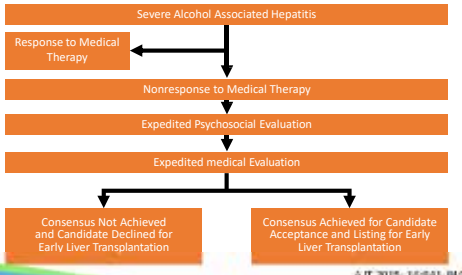
- 10 drinks/day= 4 points
- Multiple prior rehab= 4
- Prior alcohol related legal= 2
- Illicit substance abuse= 1

SALT score ≥5 had a 25% positive predictive value (95% CI: 10%-47%) and a SALT score of <5 had a 95% negative predictive value (95% CI: 89%-98%) for sustained alcohol use post-LT

LIST IF SALT SCORE < 5

Lee et al, Hepatology. 2019 Apr;69(4):1477-1487.

Early Liver Transplantation for Severe AAH Algorithm



AJT 2015; 15:841 8h3.

ACG 2018

Alcohol Associated Hepatitis (AAH)

- **Terminology**
- **Alcohol: facts**
- **Outpatient management**
- **Pathophysiology and management**
- **Liver Transplantation for AAH**
- **Take-home messages**

ACG 2018

Alcohol Associated Hepatitis: Take Home Messages

- More than 3 drinks a day in women and 4 drinks a day in men is harmful drinking
- Caution all your patients irrespective of medical issue to drink only in moderation
- Avoid using term “alcoholic”
- Abstinence works best for long term survival in patients with AAH
- Prednisone/prednisolone for AAH reduces only 30-day mortality
- MELD and Lille score for prognosis
- Early liver transplant in highly selected patients

ACG 2018

Robert Cannon, MD
Assistant Professor
UAB Division of Transplant Surgery
University of Alabama at Birmingham
Birmingham, AL

"Regional and national impact of liver transplant allocation changes"

Disclosures: None

Learning Objectives:

- Identify recent changes to liver allocation
- Recognize impact on waitlist mortality and patient outcomes since change

The Impact of Liver Allocation Changes

UAB Update in Gastroenterology and Hepatology
Robert M. Cannon, MD

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Definitions

- DSA: donation service area. The geographic area served by a single organ procurement organization
- OPO: organ procurement organization. One of 58 federally chartered entities responsible for procurement and placement of organs for transplant. Legacy of Hope is the OPO serving the Alabama
- UNOS: United Network for Organ Sharing. The organization contracted by the federal government to oversee all aspects of organ transplantation in the US
- MELD: model for end stage liver disease. Predicts mortality on liver transplant waitlist and used to prioritize candidates for transplant

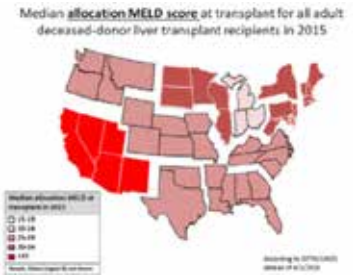
DSAs in the US

UNOS Regions

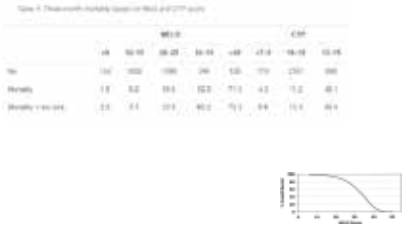
Previous Liver Allocation Sequence

Classification	Candidates that are within the:	And are:
1	OPO's region	Adult or pediatric status 1A
2	OPO's region	Pediatric status 1B
3	OPO's DSA	MELD/PELD of 40
4	OPO's region	MELD/PELD of 40
5	OPO's DSA	MELD/PELD of 39
6	OPO's region	MELD/PELD of 39
7	OPO's DSA	MELD/PELD of 38
8	OPO's region	MELD/PELD of 38
9	OPO's DSA	MELD/PELD of 37
10	OPO's region	MELD/PELD of 37
11	OPO's DSA	MELD/PELD of 36
12	OPO's region	MELD/PELD of 29
13	OPO's DSA	MELD/PELD of 35
14	OPO's region	MELD/PELD of 35
15	OPO's DSA	MELD/PELD of at least 17
16	OPO's region	MELD/PELD of at least 17
17	Nation	Adult or Pediatric status 1A
18	Nation	Pediatric status 1B
19	Nation	MELD/PELD of at least 15

The Geographic Disparity



Mortality by MELD Score



The Pro Wider Distribution View

New York, California, Others

- Patterns of death vary throughout the country, which influences the supply of livers available for transplant
- Patients listed at centers with higher organ availability have a shorter waiting time and are transplanted at lower MELDs than those in regions with higher demand for transplant and lower organ supply
- This places recipients in high MELD areas such as New York and California at an unfair disadvantage simply because of where they live

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The Pro Wider Distribution View

New York, New England, California

- Donor service areas and UNOS regions were never designed to be optimal units of organ allocation. Their borders are generally arbitrary
- Reliance upon DSA boundaries for organ allocation is not only unfair, it is illegal

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The Final Rule

§121.8 Allocation of organs.

(a) Policy development. The Board of Directors established under §121.3 shall develop, in accordance with the policy development process described in §121.4, policies for the equitable allocation of cadaveric organs among potential recipients. Such allocation policies:

(1) Shall be based on sound medical judgment;

(2) Shall seek to achieve the best use of donated organs;

(3) Shall preserve the ability of a transplant program to decline an offer of an organ or not to use the organ for the potential recipient in accordance with §121.7(b)(4)(i) and (e);

(4) Shall be specific for each organ type or combination of organ types to be transplanted into a transplant candidate;

(5) Shall be designed to avoid wasting organs, to avoid futile transplants, to promote patient access to transplantation, and to promote the efficient management of organ placement;

(6) Shall be reviewed periodically and revised as appropriate;

(7) Shall include appropriate procedures to promote and review compliance including, to the extent appropriate, prospective and retrospective reviews of each transplant program's application of the policies to patients listed or proposed to be listed at the program; and

(8) Shall not, [illegible] candidate's place of residence or place of listing, except to the extent required by paragraphs (a)(1)(ii) of this section.

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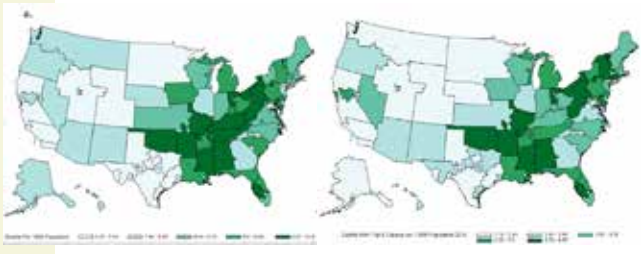
Organ Supply



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The "Answer": Redistribution

Addressing Geographic Disparities in Liver Transplantation Through Redistricting

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The Initial Compromise

- UNOS Tasked by HHS to reduce geographic disparity without increasing waitlist mortality
- Over 4 years of work and several rounds of public comment resulted in a new scheme that was, although controversial in itself, eventually accepted as a reasonable compromise
- 11 regions reduced to 8 mathematically optimized districts, and recipients within 150 miles around the donor hospital are assigned 3 additional MELD points based on proximity.
- Set for implementation in December 2018

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The Initial Compromise

- National Review Board created to review all MELD exception requests
- HCC MELD exception reduced from 28 points to the median MELD at transplant in the DSA minus 3

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Exceptions and MELD Creep

- Patients believed to be a higher risk of waiting list mortality than reflected by their MELD score may be granted "exception" points.
- The most common standard MELD exception is HCC
  - Automatically approved when within Milan Criteria
  - Other standard MELD exceptions are hepatopulmonary syndrome, portopulmonary hypertension, metabolic disease
- Non-standard MELD exception requests were previously approved/denied by a regional review board, leaving wide room for variation in MELD exception points between regions

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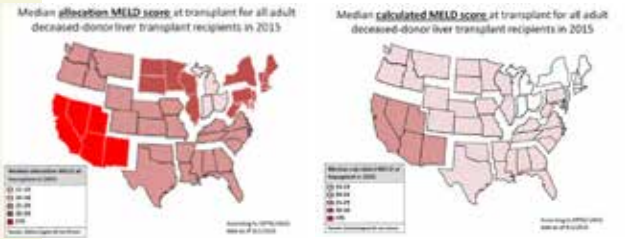
The Geographic “Disparity”

Exceptions, Exceptions, Exceptions



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In Come the Lawyers

BSF BOIES SCHILLER FLEXNER

- Cruz et al. v. U.S Dept. of Health and Human Services filed July, 2018 in Southern District of NY
- HHS Secretary Azar directs the OPTN to eliminate DSA and regions from allocation policy by December 2018 in a letter dated July 31, 2018

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The Liver and Intestine Committee’s Charge

- Devise a new liver allocation system that does not reference DSA or Region
- You have 4 months to do it

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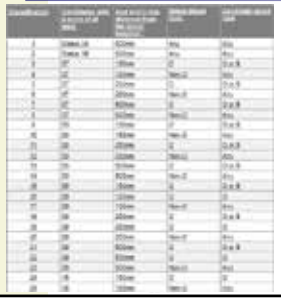
Current Liver Allocation Scheme

Acuity Circles



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The Long Arms of New York

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The Effect of Liver Redistribution on Alabama

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500 Nautical Miles Around Birmingham

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Alabama residents already face Reduced Access to Transplant

Access to liver transplantation has been shown to be significantly decreased for patients in high CHS areas.

The Community Health Score (CHS) is a composite indicator of community health, environmental and behavioral risk factors, poor socioeconomic status, and access to quality healthcare. Higher scores indicate poorer health, higher poverty, and reduced access to care.

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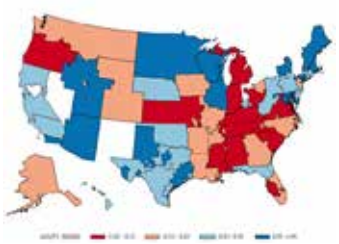
Liver Transplant Volume in Alabama Was Projected to Decrease 22% Under the Current Scheme. The Majority of DSAs were Expected to Perform Less Transplants



Projected percent change in liver transplant volumes under the newly approved liver distribution model. Red/orange areas see decrease, light blue is little change, dark blue is increase. Borders represent DSA boundaries

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Overall Effect of the Proposed Changes

- There will be redistribution of donor livers from Alabama and the much of the South and rural Midwest to more affluent regions with better access to healthcare
- 29% fewer transplants in Alabama
- 27% fewer transplants in Mississippi and South Carolina
- 20% fewer transplants in North Carolina
- 19% fewer transplants in Louisiana
- 8% fewer transplants in Georgia and Tennessee
- This amounts to 186 fewer lives saved over a 1 year period in these 6 states

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Who Gains?

- 29% more liver transplants in New York City
- 87% more liver transplants in upstate New York
- 17% more transplants in Minnesota
- 13% more transplants in Northern Illinois
- 11% more transplants in Massachusetts and New England
- 250 more transplants over a 1 year period in the above 5 areas

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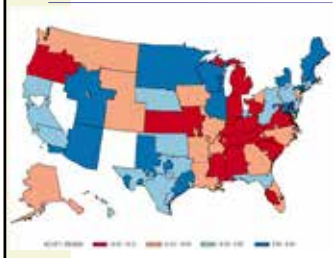
Shifting Disparity



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Effect on UAB's Waitlist

- 54% of all recipients now hospitalized at the time of transplant offer
  - 17% are in the ICU
- The median MELD score of patients being transplanted is now 30

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The Bigger Picture

DONATE LIFE

"We say yes to donation at the worst moment of our lives because we want to help another family not walk through the same heartache that we're walking through"

"When you bicker and fight over organs . . . And you're not kind to one another, that really kind of actually makes me question my decision to be involved in the community"

-Deanna Santana, OPTN Board Member, Donor Mom

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- Inpatient Transfers (UAB MIST): 205-934-6478
- My Cell: 404-405-9329

UAB MEDICINE SURGERY

A. Sidney Barritt IV, MD, MSCR, FAASLD
Associate Professor of Medicine
Director, UNC Liver Center
University of North Carolina, Chapel Hill
Chapel Hill, NC

"Change in paradigm of pharmacologic treatment for NASH"

Disclosures: Grants: Intercept, Allergan, Galmed, Genfit
Consulting Fee: Target PharmaSolutions

Learning Objectives:

- Identify mechanisms of action for NASH drug development
- Understand current options for treatment

Nonalcoholic fatty liver disease (NAFLD) is a highly prevalent chronic liver disease that is driven by the metabolic syndrome. NAFLD encompasses nonalcoholic fatty liver (NAFL), >5% fat in the liver without inflammation or fibrosis, nonalcoholic steatohepatitis (NASH), fat plus varying degrees of inflammation and fibrosis, and cirrhosis of the liver from NASH. As facets of the metabolic syndrome, particularly diabetes and obesity, become more common worldwide, the incidence of new NAFLD is increasing. Current therapies rely on metabolic syndrome risk factor control and lifestyle changes to achieve weight loss. As sustained weight loss is difficult for many patients, there is a critical unmet need for pharmacotherapy to treat NAFLD, especially the progressive form, NASH in order to prevent cirrhosis of the liver. New therapies for NAFLD focus on the subset of patients with NASH and some degree of fibrosis. Novel mechanisms of action including farnesoid X nuclear receptor agonism, C-C motif chemokine receptor 2 and CCR5 antagonism, steroyl-CoA desaturase-1, and thyroid hormone receptor β agonism are currently under investigation as monotherapy. These products also hold the potential for use in combination with and without insulin sensitizers and other established drugs in the future.

While there are multiple potential products under investigation, progress in clinical trials has been fraught with high screen fail rates and drugs with promising phase 2 results succumbing to futility end points during phase 3 clinical trials. Challenges to clinical trials include finding the right NASH patient for participation with few additional comorbid conditions, no contraindicated medications, and the appropriate grade and stage of NASH on liver biopsy. Regulating lifestyle intervention and combating a high placebo response rate make for additional challenges for new agents to show efficacy.

As we wait for new medications to come to market, getting back to basics with a patient centered approach to treating NAFLD and NASH is required. Most patients are aware that they need to lose weight prior to visiting the gastroenterologist or hepatologist. How can we make such advice meaningful to the patient? First, combating all of the overwhelming information and misinformation available to patients in regard to dietary intervention is vital, especially for those patients with lower health literacy. Utilizing a nutritionist/dietician can be extremely helpful in this regard. Second, consider the whole patient. Many overweight and obese patients have a complicated relationship with

food. Stress eating, mood eating, eating out of boredom, eating to mitigate depression or anxiety are all maladaptive coping behaviors that get in the way of adherence to a dietary intervention. A clinical psychologist can be a useful ally to address underlying mental health concerns and to provide motivation for lifestyle interventions. Finally, making NASH relevant to the patient. Abnormal liver enzymes are abstract and many patients are asymptomatic from their liver disease. Teaching the patient that NASH increases cardiovascular and cancer risk are meaningful outcomes that resonate with patients. Framing NASH therapy as mitigating cancer and cardiovascular risks is often useful for the patient in terms of seeing the overall picture.

NAFLD and NASH are common and increasing. There is a critical unmet need for pharmacotherapy to treat NASH and reducing the risk of disease progression to cirrhosis and liver cancer. However, even when new medications are FDA approved, lifestyle intervention and metabolic syndrome risk factor control will remain a cornerstone of therapy. Taking a patient centered approach can help increase the likelihood of success.

Recommended reading

1. Campbell P, Symonds A, Barritt AS 4th. Therapy for Nonalcoholic Fatty Liver Disease: Current Options and Future Directions. Clin Ther. 2021 Feb 11:S0149-2918(21)00048-5. doi: 10.1016/j.clinthera.2021.01.021. PMID: 33583577 Review.
2. R. Loomba, A.J. Sanyal. The global NAFLD epidemic Nat Rev Gastroenterol Hepatol, 10 (2013), pp. 686-690
3. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, Harrison SA, Brunt EM, Sanyal AJ. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases Hepatology . 2018 Jan;67(1):328-357.doi: 10.1002/hep.29367. Epub 2017 Sep

Therapeutic approach to NASH

A. Sidney Barritt IV, MD, MSCR, FAASLD
Director, UNC Liver Center
Division of Gastroenterology & Hepatology
University of North Carolina, Chapel Hill

UNC SCHOOL OF MEDICINE

Disclosures

- Consulting in the last 12 months for:
  - Target RWE
  - Novo Nordisk

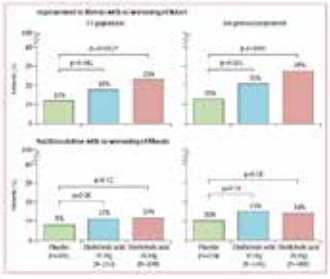
Roadmap

- Phase 3 NASH clinical trial data
- Why do some studies fail?
- Back to the basics

Regenerate Trial – good news?

Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial

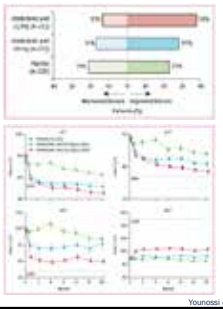
- 1968 patients with NASH and F1-F3 fibrosis
- 1:1:1 Placebo, OCA 10mg, OCA 25mg
- Interim analysis of 931 patients with F2-3 disease



Younossi et al Lancet 2019

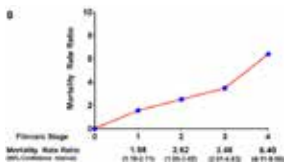
Regenerate Trial

- Secondary end points
  - Fibrosis can progress or regress, important to look at movement in both directions
  - Consistent liver enzyme improvement
- Predictors of response?
  - Will need to wait for final results

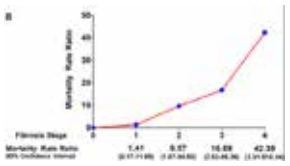


Younossi et al Lancet 2019

Fibrosis progression is associated with increased mortality



All cause mortality



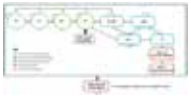
Liver related mortality

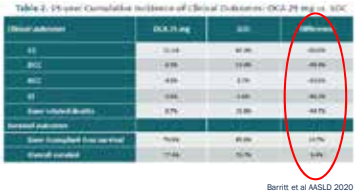
Dulai et al Hepatology 2017

Is a fibrosis improvement in only 23% meaningful?

Predicted Long-Term Clinical Outcomes of OCA for the Treatment of F3 Patients with NASH Compared to Standard of Care

- To evaluate the long-term clinical benefits of using OCA 25 mg vs. SOC in patients F3 NASH
- Markov model based on trial data and literature
- Costs not applied to model





Barritt et al AASLD 2020

Now the bad news...

Genfit's elafibranor en route to NASH graveyard with phase 3 flop

Gilead's selonsertib flunks another NASH phase 3

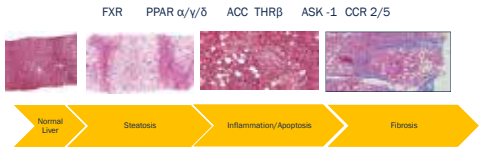
- Genfit released interim analyses in May 2020 for Elafibranor
  - NASH resolution 19% vs. 15%
  - Fibrosis improvement 25% vs 22%
- Gilead's Selonosertib interim analyses from 2019
  - F3 trial: Fibrosis improvement 9-12% vs 13%
  - F4 trial: Fibrosis improvement 14% vs 13%

Al Idrus, various sources, biowire 2020

Why do some studies fail?

- Wrong drug(s)?
- Placebo response?
- Wrong population?

Potential novel targets for therapy in NASH



'Antioxidants' Insulin resistance Dyslipidemia

Weight loss through diet and exercise

Barritt, AASLD Postgraduate Course 2018

Combination Therapy

- Multiple Phase 2 clinical trials currently or in near future
- Until we can better phenotype NASH patients, a multi-faceted approach including addressing insulin resistance is necessary

Drugs	MOA	Company	NASH population
selonsertib simtuzimab	ASK1 inhibitor LOXL2	Gilead	
selonsertib cilofexor firsocostat	ASK1 inhibitor FXR agonist ACC inhibitor	Gilead	NASH with steatosis >10% F3-F4 NASH
PF-xxx PF-xxx	ACC inhibitor DGAT2 inhibitor	Pfizer	Steatosis >8%
cenicriviroc tropifexor	CCR2/5 antagonist FXR agnonist	Allergan Novartis	F2-F3 NASH
cilofexor firsocostat semaglutide	FXR agonist ACC inhibitor GLP-1 inhibotor	Gilead Novo Nordisk	F2-F3 NASH
elafibranor GLP-1 SGLT-2	PPAR a/d GLP-1 SGLT-2	Genfit	

Press releases and Clinical trials.gov accessed July 19 2019

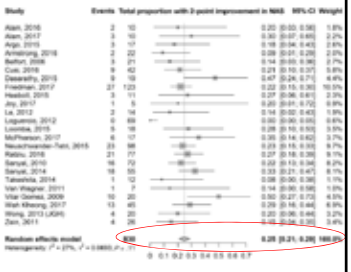
Placebo response

We know that diet and exercise are key to NASH therapy

- Do patients behave differently in a RCT?
- Coordinator support, frequent visits, measurements, diet and exercise advice

Meta Analysis of 39RCT, ~1500 patients on placebo

- 25% improved NAS by ≥2 points
- 33% improved steatosis
- 30% improved ballooning
- 32% improved inflammation
- 21% improved fibrosis



Han et al CGH 2019

Regulating diet and exercise

- Inherent in placebo response is how lifestyle is assessed
- Most industry sponsored phase 3 clinical trials only provide recommendations
- Behavioral interventions left to smaller NIH or investigator initiated studies

Glass et al Jhep 2020

Assessing disease

- Liver biopsy is the gold standard for assessing NASH
- Reviewed how NASH biopsies were reported in academic and community centers and assessed agreement with a centralized pathologist
  - Heterogeneity in the reporting of NASH
  - Many reports missing descriptors of NASH disease activity
  - Only moderate concordance for fibrosis staging
- New modalities may look imperfect when compared to a flawed standard

Histological Characteristic	Pathology Reports Compared	Statistic (95% CI)	Concordance Interpretation
Steatosis	57	0.364 (0.2029, 0.5243)	Fair
Lobular Inflammation	29	-0.081 (-0.1867, 0.0223)	Poor
Portal Inflammation	31	0.216 (-0.0106, 0.4382)	Fair
Hepatocyte Ballooning	31	0.113 (-0.0708, 0.3038)	Slight
Fibrosis Stage	59	0.575 (0.4663, 0.6894)	Moderate
Scoring Systems			
NAFLD Activity Score	38	0.357 (0.0591, 0.6130)	Fair
Brunt Grade (Inflammation)	25	0.364 (0.1591, 0.5882)	Fair
Brunt Stage (Fibrosis)	59	0.590 (0.4775, 0.7028)	Moderate

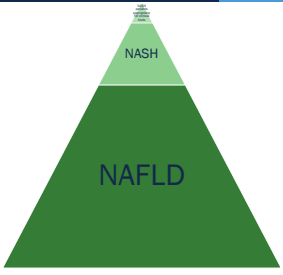
Kim et al AASLD 2020

NASH Trials are difficult

- NASH is a heterogeneous disease
- Screen fail rates range from 50-80% in Phase 2-3 trials
- Allowable HGB A1C can go up to 9.5% in some trials!
- Patients taking newer drugs for insulin resistance/diabetes are often excluded
- Outcome metrics (biopsy) are flawed
- Need to strike a balance between enrolling the trial, finding and accurate result and having the data actually mean something in the end

The challenge to treat NASH will continue

- If/when there are successful FDA approved interventions for NASH, questions and challenges will remain
  - Are these lifetime drugs?
  - Are medications interventions to pause disease while patients fix lifestyle problems?
  - What is the CV risk/benefit?
  - What is the cancer risk/reduction?
  - Clinical trial efficacy vs. real world effectiveness

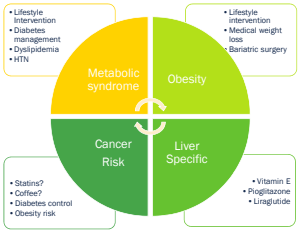


Barritt, AASLD Postgraduate Course 2018

Back to the basics

Current pharmacologic management

- All cause mortality in the patient with NASH
  1. CVD
  2. Cancer
  3. Liver disease
- We can address these risks in a complementary manner with currently available medications
  - Cardiovascular risk
    - Statins
  - Cancer risk
    - Statins, metformin, weight loss
  - Metabolic syndrome
    - HTN, dyslipidemia, diabetes
  - Obesity
  - NASH specific



Adapted from Anstee, AASLD Postgraduate Course 2017

Efficacy of NASH monotherapy in recent trials

Adapted from Rinella, NAFLD Debrief AASLD 2018

How I Manage Disease

- What works:
  - An appeal to the gut
  - I am not a nutritionist/dietician (but there are some really good ones at UNC)
  - There is so much (mis)information about diet available, many patients are overwhelmed
  - Many patients have well meaning but maladaptive dietary strategies
    - Skipping meals, empty calories
  - I counsel about liquid calories, alcohol, portion control
- **I refer any patient who will listen to the nutritionist!**

How I Manage Disease

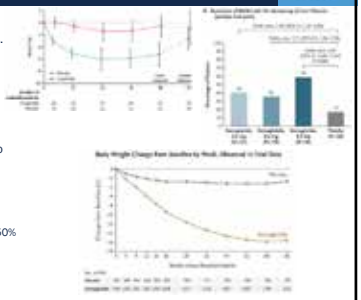
- What works:
  - An appeal to the mind
  - Many of my patients suffer from eating out of boredom, stress, sadness, depression and anxiety
    - We recognize the patient with an alcohol use disorder who does this, so why not the 'comfort eater'
  - Psychological assistance for adherence to diet, exercise and positive coping strategies has been very helpful
    - Philosophy of treating the whole patient, not just liver enzymes
- **I refer any patient who will listen to our clinical psychologist!**

How I Manage Disease

- What works:
  - An appeal to the heart
  - Use the C word
    - Heart disease and cancer are much more meaningful outcomes to the lay public
      - Metabolic risk factors – diabetes, weight, high blood pressure, lipids- are all risk factors for cardiovascular disease and many cancers
      - We are on the same team as the cardiologist and PCP
      - What is good for the heart is good for the liver
      - What is good for the liver reduces cancer risk

Medical weight loss for NASH patients

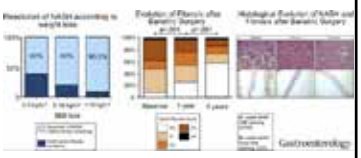
- Liraglutide
  - Resolution of NASH in 9/23 (39%) liraglutide vs. 2/22 (9%) placebo p=0.019
  - Secondary outcomes showed improvements in weight and ALT
- Semaglutide in NASH
  - NASH resolution semaglutide 0.4mg (59%) vs placebo (17%)
  - Fibrosis improvement not different than placebo
  - 13% weight loss vs 1% placebo
- Semaglutide in obesity
  - 15% weight loss after 68 weeks vs 2% in placebo
    - 86% achieved 5% loss, 69% achieved 10% loss, 50% achieved 15% or more weight loss
- Watch for drug induced liver injury with herbal/dietary supplements



Armstrong et al Lancet 2016; Newsome et al NEJM 2021; Wilding et al NEJM 2021; Barritt et al (sub) 2021

Surgical weight loss

- Bariatric Surgery?
  - Multiple studies have shown that weight loss following bariatric surgery leads to biochemical and histological improvement of NASH
    - Improvements occur in those with correction of insulin resistance and metabolic syndrome

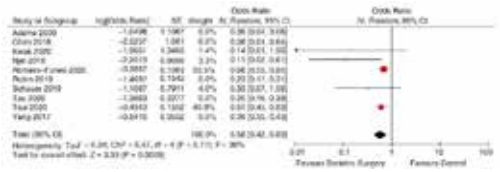


Weiner et al, JAMA Surgery 2013
Lassailly et al Gastro 2020

Surgical weight loss and HCC reduction?

If we improve obesity and insulin resistance, can that change the dynamic for HCC risk?

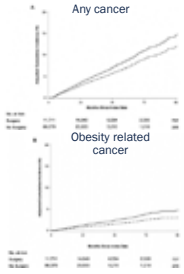
- Systematic review with meta-analysis for bariatric surgery and HCC
- 9 studies of 1M bariatric surgery patients with 18M controls
- Adjusted OR 0.58 (0.42-0.80)



Ramai et al, APT 2021

Surgical weight loss and cancer risk reduction?

- Does weight reduction translate into reduced any cancer risk?
  - Bariatric surgery associated with significant reductions in the risks of any cancer and obesity-related cancer in NAFLD patients BMI >40
  - Diabetes improvement responsible?
- Studies of bariatric surgery are subject to selection bias
- Bariatric surgery is great when it works
  - Weight loss helps heart, liver and cancer risks
  - A viable solution for the general population???



Rustigi et al Gastro 2021
Barritt et al Gastro 2021

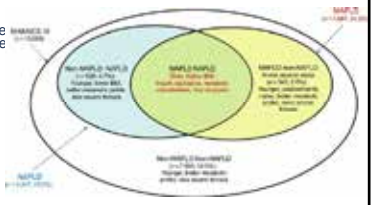
Management challenges

- Battles I fight
  - Diabetes control!
  - Statins are safe!
    - May have pleiotropic effects in liver disease beyond cholesterol reduction
  - Opioid avoidance
    - Increase fibrosis?
    - ~20% of patients with NAFLD are on an opiate
    - ~25% of patients with NASH cirrhosis are on an opiate
    - Significant associations with hepatic encephalopathy
    - Opiates increase length of stay
    - Rarely have I seen that a chronic opiate helps mobility and allows a patient to exercise.
- Battles I avoid
  - Abdominal pain
    - I used to say 'it's not your liver'
    - Now I agree whole heartedly
      - Yes – this is fat in your liver causing the capsule to stretch
      - The only way to fix this is to reduce the fat in the liver through diet, exercise and weight loss

Moon et al Dig Dis 2020
Moon et al APT 2020
Moon et al PLOS One 2020

New Nomenclature?

- Metabolic-dysfunction Associated Fatty Liver Disease (MAFLD)
- Hepatic steatosis and at least one feature among overweight/obesity, type 2 diabete and metabolic dysregulation.
  - "metabolic dysregulation" ≥ 2 increased waist circumference, HTN, hypertriglyceridemia, low HDL-C, prediabetes, insulin resistance and subclinical inflammation.
  - Pros
    - More accurate?
    - Not a "non" condition
    - Can diagnose MAFLD even with AUD
  - Cons
    - May exclude "lean" NAFLD
    - NAFLD/NASH awareness not great as is, change may confuse
    - Clinical trials



Bianco et al Liver international 2020

Summary

- OCA 25 mg reduced fibrosis in 23% of patients in interim results
  - Not yet FDA approved
- 2 large phase 3 trials stopped for futility after interim results reported
- Multiple other phase 2/3 trials underway
  - I suspect that combination therapy will be critical
- NASH trials are difficult and require balance of priorities
  - Enrollment, efficacy, placebo response, real world effectiveness
- Diet and exercise remains the cornerstone
  - Utilize any allied healthcare professional to help

UNC

Thank you!

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"Changing landscape of treatment for advanced HCC"

Disclosures: None

Learning Objectives:

- Recognize of advanced HCC
- Understand new treatments available for advanced HCC

Highlights

- The burden of hepatocellular carcinoma (HCC)
- HCC surveillance
- HCC diagnosis
- Advanced state HCC represents a large number of HCC cases at the time of diagnosis
- Staging of HCC
- Management of advanced stage HCC
- The utility of transarterial radioembolization (TARE)
- Introduction to systemic therapy for HCC treatment: Tyrosine kinase inhibitors and immune checkpoint inhibitors
- The new first line systemic therapy for HCC

Advanced Stage Hepatocellular Carcinoma (HCC)

Mohamed Shoreibah, MD

13 August 2021

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I have no disclosures.

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Advanced Stage HCC

- **Overview**
- HCC Surveillance
- HCC Diagnosis
- HCC Classification
- Management of Advanced Stage HCC

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Overview

- Liver cancer:
  - 6th most common cancer worldwide
  - 4th leading cause of cancer-related death
- By 2025, more than 1M/year will be affected by liver cancer
- HCC accounts for ~90% of liver cancers
- HBV infection accounts for ~50% of cases
- HCV infection risk decreased with the new antiviral drugs
- NASH is becoming the fastest growing etiology (up to 20%)

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Advanced Stage HCC

- Overview
- **HCC Surveillance**
- HCC Diagnosis
- HCC Classification
- Management of Advanced Stage HCC

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HCC Surveillance

TABLE 1. PATIENTS AT THE HIGHEST RISK FOR HCC

Population Group	Threshold Incidence for Efficacy of Surveillance (>0.25 [1Q] % per year)	Incidence of HCC
Surveillance benefit		
Asian male hepatitis B carriers over age 40	0.2	0.4%-0.6% per year
Asian female hepatitis B carriers over age 50	0.2	0.3%-0.4% per year
Hepatitis B carrier with family history of HCC	0.2	Incidence higher than without family history
African and/or North American blacks with hepatitis B	0.2	HCC occurs at a younger age
Hepatitis B carriers with cirrhosis	0.2-1.5	3%-8% per year
Hepatitis C cirrhosis	1.5	3%-5% per year
Stage 4 PBC	1.5	3%-5% per year
Genetic hemochromatosis and cirrhosis	1.5	Unknown, but probably >1.5% per year
Alpha-1 antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably >1.5% per year
Other cirrhosis	1.5	Unknown
Surveillance benefit uncertain		
Hepatitis B carriers younger than 40 (males) or 50 (females)	0.2	<0.2% per year
Hepatitis C and stage 3 fibrosis	1.5	<1.5% per year
NAFLD without cirrhosis	1.5	<1.5% per year

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HCC Surveillance

- Ultrasound w/wo AFP every 6 months
- If ultrasound is inadequate MRI or CT can be utilized
- Surveillance improves overall survival
- Continue surveillance of patients with cirrhosis secondary to HCV who achieve SVR
- Surveillance is not recommended for patients with NAFLD and HCV without cirrhosis
- Patients with Child Pugh C cirrhosis should not undergo surveillance unless they have a path to transplant

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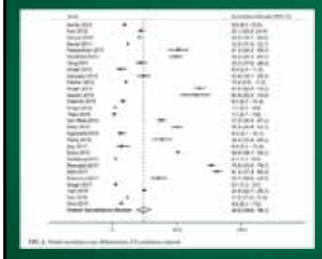
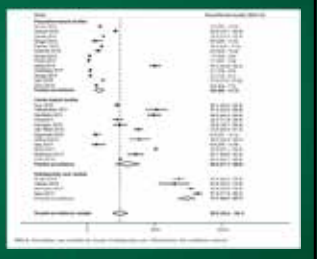
Poor Adherence to Surveillance





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Advanced Stage HCC

- Overview
- HCC Surveillance
- **HCC Diagnosis**
- HCC Classification
- Management of Advanced Stage HCC

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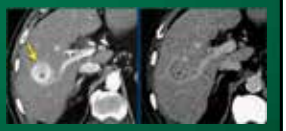
HCC Diagnosis

- 50% are diagnosed incidentally
- Dynamic imaging:
  - CT or MRI (Multiphasic/3 phasic)
  - If one modality is inconclusive order the other
- Biopsy:
  - Sensitivity is ~70%
  - A negative biopsy does not exclude HCC
- Liquid biopsy:
  - Circulating tumor DNA, exosomes or actual tumor cells



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Immune & Molecular Subclasses

- Immune subclasses:
  - Active
  - Exhausted
  - Intermediate
  - Excluded
- Molecular subclasses:
  - ~20-25% of HCC have at least one potential actionable mutation

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Advanced Stage HCC

- Overview
- HCC Surveillance
- HCC Diagnosis
- **HCC Classification**
- Management of Advanced Stage HCC

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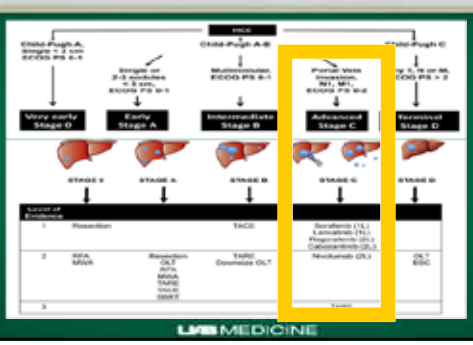
BCLC Classification



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Advanced Stage HCC

- More than 50% of patients present with advanced disease at diagnosis
- Factors associated with advanced stage HCC at the time of diagnosis:
  - African Americans vs. non-Hispanic whites: 63% vs 55%, P < 0.001
  - Lack of health insurance
  - 1945-1965 birth cohort (indicating poor adherence to initial guidelines)
  - Male patients
- Two main reasons as to why we see advanced HCC:
  - Lack of adherence to HCC surveillance
  - A growing population with advanced disease started as early disease and progressed

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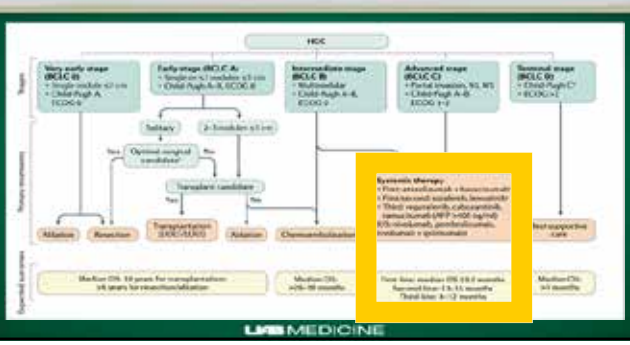
Treatment



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BCLC Classification (Systemic)

- Advanced stage HCC therapy eligibility criteria:
  - Presence of portal vein invasion
  - W/WO extrahepatic metastases
  - Preserved liver function
  - Preserved functional status
- Systemic therapy trials lack sufficient data on Child Pugh class B and C patients

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Advanced Stage HCC

- Overview
- HCC Surveillance
- HCC Diagnosis
- HCC Classification
- **Treatment of Advanced stage HCC**

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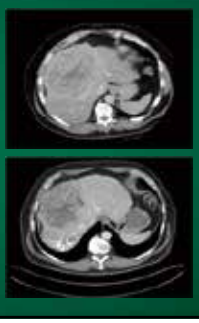
Treatment: Transarterial Radioembolization (TARE)

- Glass microspheres with embedded Y90
- Poor candidates for TACE
- larger tumors (>2 segments)
- Portal vein invasion
- Progressive disease post-TACE



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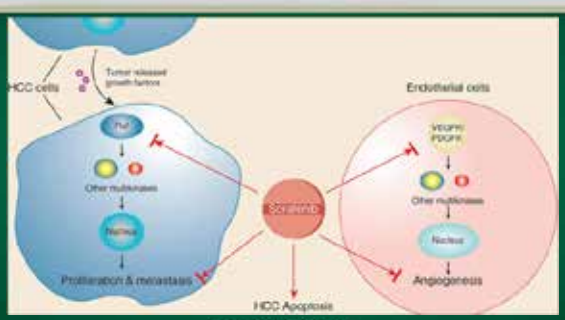
Treatment: Multiple Tyrosine Kinase Inhibitor (TKI)



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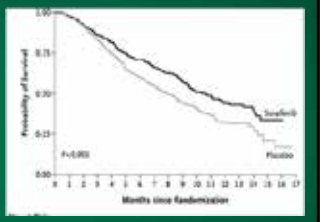
Treatment: TKI/Sorafenib

- 2.8 months survival advantage
- Adverse events:
  - Diarrhea
  - Fatigue
  - Palmar-plantar erythema
- Discontinuation in ~ 20% of patients



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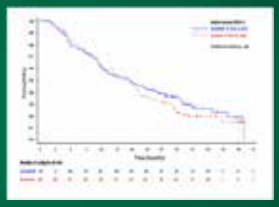
Treatment: TKI/Lenvatinib

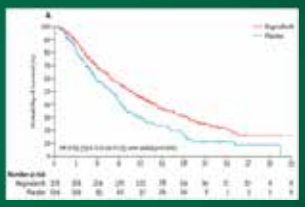
- Noninferior compared to sorafenib
- Side effects:
  - Hypertension
  - Diarrhea, fatigue, and weight loss
  - Hand-foot skin reaction
  - Dysphonia
  - Proteinuria (25%)



LIVER MEDICINE

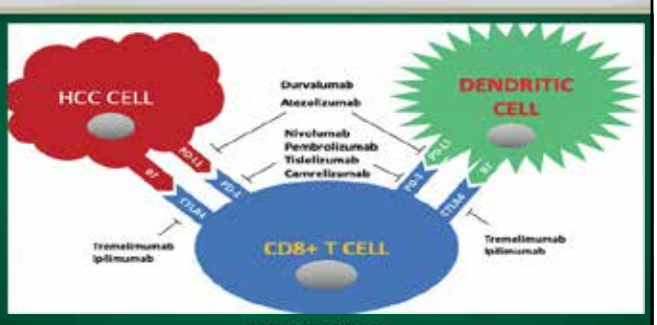
Treatment: TKI/Regorafenib

- Second line following Sorafenib failure
- Side effects:
  - Hypertension
  - Fatigue
  - Diarrhea
  - Elevated AST & ALT
  - Hand-foot skin reaction



LIVER MEDICINE

Treatment: Immune Checkpoint Inhibitor (ICI)



LIVER MEDICINE

Treatment: ICI/Nivolumab

- Human immunoglobulin G4 monoclonal antibody
- Disrupts PD-1 immune checkpoint signaling
- Restores the antitumor activity of T cell
- Side effects:
  - Allograft failure when used post liver transplant
  - Autoimmune disorders: hepatitis, colitis, pneumonitis, & uveitis
- No difference in survival compared to Sorafenib

LIVER MEDICINE

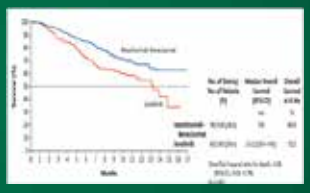
Treatment: ICI Toxicity

- ICIs are used as monotherapy or in combination
- Durable immune responses in a subsets of patients
- Grade 3-4 treatment-related adverse events were 18-22% for single agents and 37% for combination regimens
- Immune-related toxicity (27%) such as rash, joint aches or hypothyroidism, to severe and potentially life-threatening events such as pneumonitis, enterocolitis or myocarditis
- Steroids are used for the management of immune-related toxicity
- Cannot be used post liver transplant patients

UAB MEDICINE

Treatment: Atezolizumab + Bevacizumab

- Atezolizumab+Bevacizumab VS Sorafenib in untreated unresectable HCC
- Atezolizumab: PDL1 inhibitor
- Bevacizumab: VEGF inhibitor
- Overall survival at 12 months
  - 67.2% vs. 54.6%
- Progression-free survival:
  - 6.8 vs. 4.3 months



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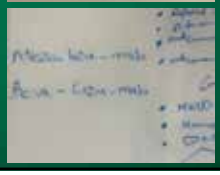
Treatment: Atezolizumab + Bevacizumab

- Adverse effects:
  - Diarrhea & decreased appetite
  - Hypertension, alopecia, and asthenia
  - Elevated ALT and proteinuria
  - Autoimmune complications



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Advanced HCC: $

- The 3-year cost of care of HCC: $154,688
- TARE: $32,500

Cost-Effectiveness Analysis.

Strategy	Costs (US$)	Incremental Costs (US$)	Effectiveness (QALY)	Incremental Effectiveness (QALY)	ICER ($/QALY)	ICER 95% CI ($/QALY)
Atezolizumab + Bevacizumab	321,960	102,648	1.26	0.42	244,213	111,398 – 650,718
Sorafenib	219,312	-	0.84	-	-	-

Base-Case Model | PSA Model

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Future Directions

- Tumor biopsy may emerge as a decision-making tool
- The utility of a liquid biopsy remains to be determined
- Personalized treatment utilizing systemic therapy options depending on molecular and immune classification
- The utility of certain locoregional therapies like SBRT & proton therapy

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Summary

- It is common for patients with HCC to present at an advanced stage
- Adherence to HCC surveillance may change this trajectory
- Systemic therapy offers promising results
- Locoregional therapy with TARE is an attractive treatment option

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The Multidisciplinary Approach

- Dana Scott, CRNP
- Stephanie Steel, RN
- UAB Tumor Clinic:
  - Tel: (205) 996-5970
  - Fax: (205) 996-9037

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THANK YOU

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"Hepatitis B – Current treatment criteria and can we ever stop treatment?"

Disclosures: None

Learning Objectives:

- Understand current criteria for antiviral treatment of HBV
- Understand how to select patients for discontinuation of therapy

With the advent of vaccination, infection with Hepatitis B virus (HBV) has become a preventable disease. However, access to care may limit those who are able to be vaccinated and thus risk exposure and/or transmission of HBV. HBV is spread by way of semen, blood, or other body fluids. The majority of HBV is currently transmitted by intravenous drug use (IVDU) or sexual contact, but transmission via mother-baby or vertical transmission remains an ongoing issue in some regions. If transmission occurs after birth, particularly as an adult, the risk of developing chronic HBV is low, approximately 5%. However, the risk of developing chronic HBV when transmissions occur as a child is approximately 90%.

The most recent data from both census data in the United States of America (USA) and foreign-born migration estimates around 2.2 million people in the US are infected with HBV. The rate of acute HBV has declined since the vaccination became commercially available in 1982. Cases went from 9.6 cases per 100,000 population in 1982 to 1.1 cases per 100,000 population in 2015. The opioid crisis in the US has become an avenue for new cases to emerge, and three states showed new cases increase over 100% due to IVDU.

Treatment of HBV has evolved over the years, but the goal remains the same. Our intent as health care providers is to prevent cirrhosis and hepatocellular carcinoma. We are actively trying to vaccinate all people but that is not accomplished our goal of disease prevention with treatment of patients remains. The new AASLD guidelines were published in 2016 and 2018 with Tenofovir alafenamide (TAF) added to the current treatments. TAF joins the list of preferred medications entecavir, Tenofovir disoproxil fumarate (TDF), and Interferon. In this talk we will discuss treatment rationale for chronic HBV patients and situations where continuation of therapy and possible discontinuation of therapy may be possible.

Recommended Readings:

1. Schillie S, Vellozzi C, Reingold A, et al. Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2018;67:1-31.
2. Terrault NA, Lok ASF, McMahon BJ, et al. Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance. Clin Liver Dis (Hoboken) 2018;12:33-4.
3. Harris AM, Iqbal K, Schillie S, et al. Increases in Acute Hepatitis B Virus Infections - Kentucky, Tennessee, and West Virginia, 2006-2013. MMWR Morb Mortal Wkly Rep 2016;65:47-50.

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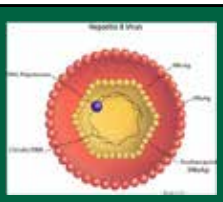
Hepatitis B- Current treatment criteria, can we ever stop treatment?

David M. Fettig M.D.
Assistant Professor of Medicine
UAB Liver Center
Comprehensive Transplant Institute

Educational Objectives

1. Phases of Chronic HBV
2. Treatment recommendations of Chronic HBV
3. Strategies and considerations of stopping therapy

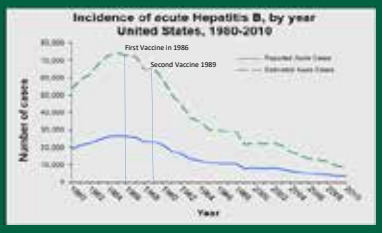
Hepatitis B Virus (HBV)



1. DNA virus (ccc)
2. Worldwide: 240 million with CHB
3. 1.2 million persons in the US with chronic HBV infection(700k US born)
4. 1 million deaths annually worldwide

Prevalence of Chronic HBV Infection

Incidence of Acute HBV



IOM 2010 HBV Findings

1. Internal Medicine doctors had significant gaps in knowledge of Hepatitis B
2. Doctors did not know whom to screen
3. Doctors did not know what tests to order
4. Doctors where not clear as to correctly evaluate those with positive tests
5. Doctors where unsure who to send to a specialist for care

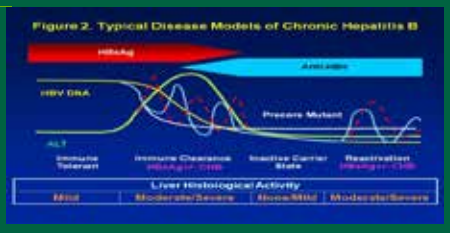
In response the US Department of Health issued an action plan for all Viral Hepatitis in 2011 for Primary Care doctors

Key aspects of Chronic HBV

1. HBsAg present for >6 months
2. HBV is not directly cytopathic to the hepatocytes, host response to virus are what drive inflammation and chronic disease
3. HBV is a Dynamic disease: transition through different clinical phases variable lab levels
4. Labs, imaging, and biopsy help stage severity and project outcomes.

Terrault, N. et al. Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B guidance. Hepatology Vol 67, No 4, 2018

Phases of Chronic HBV



Yim HJ, et al. Hepatology. 2006;43:S173-S181

Immune Tolerant

1. Definition: HBeAg +, Normal ALT, High DNA, HBsAg + greater than 6 month
2. Perinatal Transmission
3. Biopsy: Non-inflammatory
4. Lasts anywhere from 1-4 decades
5. Some who have "High Normal" ALT may actually go on to develop cirrhosis earlier

Immune Clearance

1. Definition: HBsAg + greater than 6 month
   HBeAg + with variation in ALT and DNA >20,000
   HBeAg – with variation in ALT and DNA <2000
3. Chronic Active Inflammation
   -Rise of DNA/Fall in ALT
   -Fall of DNA/Rise in ALT
4. Spontaneous HBsAg Seroconversion 1% per year
5. Length of phase is variable but ends with HBeAg Seroconversion

Exacerbations and Flares

1. Some are actually asymptomatic
   -Lok et al→ about 40% are sub-clinical
2. Exacerbations: may be associated with an elevation in the IgM anti-HBc titer, which may lead to misdiagnosis of acute HBV infection
3. Exacerbations are believed to be due to a sudden increase in immune-mediated lysis of infected hepatocytes.
   -Preceded events: Rise in HBV DNA and Core Ag from nuclear to cytoplasmic sites
   -This suggests that immune clearance may be triggered by an increase in viral load or a change in the presentation of viral antigens.
4. Risk factors: Male gender, ALT >200 at diagnosis, Age >20

Acute exacerbations in Chinese patients with chronic hepatitis B virus (HBV) infection. Incidence, predisposing factors and etiology.
Lok AS, Lai CL
J Hepatol. 1988;7(1):29

Inactive Carrier

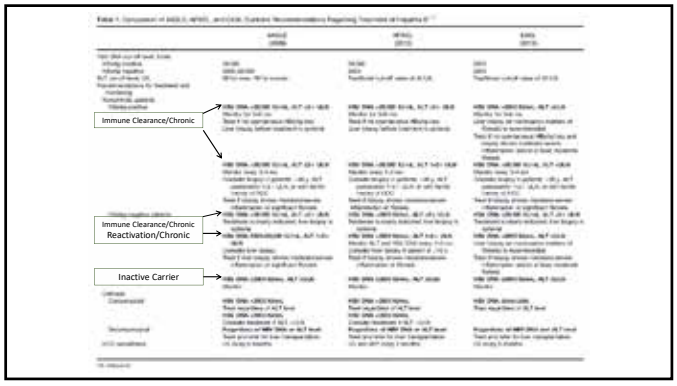
1. Definition: HBeAg Negative/ HBeAb Positive with Normal ALT and Low/Undetectable DNA (less than 2000 IU/mL). HBsAg + greater than 6 months.
3. Biopsy: variable depending on length of Immune Clearance phase, number of flares, and length of flare
4. Can be entire life of patient
5. Three Normal ALT levels and three DNA levels (DNA persistently<or=2000 IU/mL) in one year period

Goals of Evaluation and Therapy

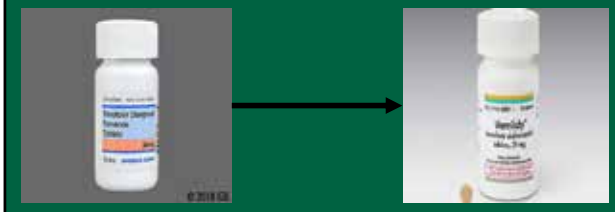
1. Prevent Cirrhosis and Complications

2. Prevent HCC and improve quality of life

Who do I treat now?
Who do I treat later?
Who should I monitor closely/from a distance?
When can I stop treatment?
Who must continue treatment?



Whats new since 2016 Guidelines



Tenofovir disoproxil fumarate (TDF) vs Tenofovir alafenamide(TAF)

1. Nucleotide analogue that inhibits reverse transcription of pregenomic RNA to HBV DNA.

1. TAF is more stable than TDF: thus, lower dose is used

1. TAF has less systemic exposure thus minimal renal/bone disease as compared to TDF

Initial Comparisons of TDF vs TAF

1. Phase 3 trial of 873 patients
   -HBeAg positive patients (75% naïve to NUC therapy)
   -Randomized to either TDF vs TAF

   <u>48 weeks (TAF vs TDF)</u>
   HBV DNA <30 IU/mL: 64% vs 67%
   ALT normalization: 72% vs 67%
   HBeAg loss: 14% vs 12%
   HbsAg loss: 1% vs 0.3%

Agarwal K et al. A phase 3 study comparing TAF to TDF in patients with HBeAg positive, chronic hepatitis: efficacy and safety results at 48 weeks and 96 weeks. J Hepatol 2017; 66(suppl 1): S478

Safety and Switching

1. TAF overall has better safety profile
   -No significant Renal Disease or discontinuation due to renal impact
   -Less impact on bone mineral density and fracture risk

2. Switching TDF to TAF (data mostly in HIV)
   -Improvement in proteinuria, albuminuria, renal tubule dysfunction
   -Improved bone mineral density

Raffi F et al. Brief Report: Long Term (96 week) Efficacy and Safety After Switching from TDF to TAF in HIV Infected, virologically suppressed adults. J Acquir Immune Defic Syndr 2017; 75: 226-231

Nucleos(t)ide analogues (NUCs)

- 1. Tenofovir- Nucleotide
- 2. Entecavir-Nucleoside
- 3. Telbivudine-Nucleoside
- 4. Lamivudine- Nucleoside
- 5. Adefovir-Nucleotide

Immune Tolerant Follow up and Treatment

1. Monitor every 3-6 months with DNA, ALT, and HBeAg
2. Test ALT levels more often if ALT trend increases
3. No treatment indicated in this phase

-Risk of resistance long term and low yield in clinical outcomes

-Data supports if by 4th decade ALT still normal to begin treatment as increasing age has been show to predict adverse outcomes.

Attar, b. Clinical Liver Disease, Vol 15, No1, January 2020

REVEAL Study:

-Push for treatment of HCV high VL, irrespective of ALT level to prevent HCC

-11 year study, 3500 patients with CHB followed every 6 months. Study consisted of untreated patients looking at natural history of disease (Study was done prior to national insurance instituted HBV treatment in Taiwan)

Findings:

-Higher levels of DNA correlated with higher risk of HCC and cirrhosis

-Many had normal ALT levels (similar to Immune tolerant) however 85% were HBeAg negative not HBeAg positive

-Median Age 45

Chen CJ, Yang HI
Risk of Hepatocellular Carcinoma across a biological gradient of serum Hepatitis B virus DNA level
REVEAL Study: JAMA 2006;295

REVEAL Study as it relates to Immune tolerant

Patient 1: 45-year-old HBeAg negative immune active with high rise in Viral load and elevated ALT

Patient 2: 20-year-old HBeAg positive Immune tolerant with normal ALT and high viral load

Very different patients thus discussing correlation between high viral load and risk of cirrhosis and HCC, the REVEAL study does not work for immune tolerant patient

Tran, T. Immune Tolerant Hepatitis B: A clinical Dilemma. Gastroenterology and Hepatology 2011 Aug; 7(8) 511-516

Treatment in Non-Cirrhosis Immune Clearance

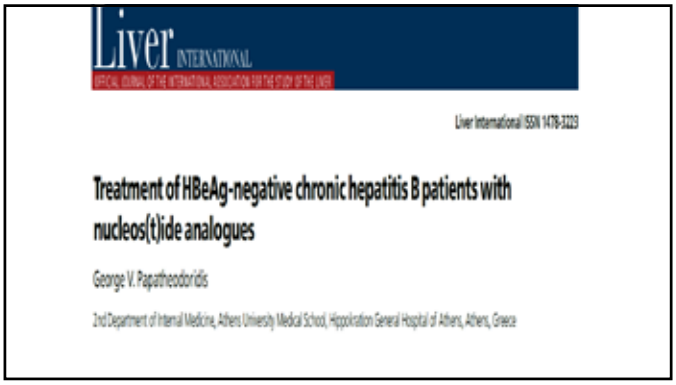
1. HBeAg (+): Elevated DNA and rise ALT
2. HBeAg (+): Elevated DNA and mild rise in ALT
3. HBeAg (-): Elevated DNA and rise ALT
4. HBeAg (-): Elevated DNA and mild rise in ALT

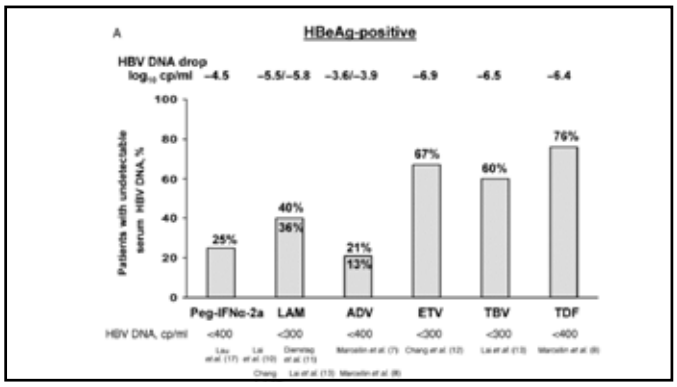
Immune Clearance Treatment

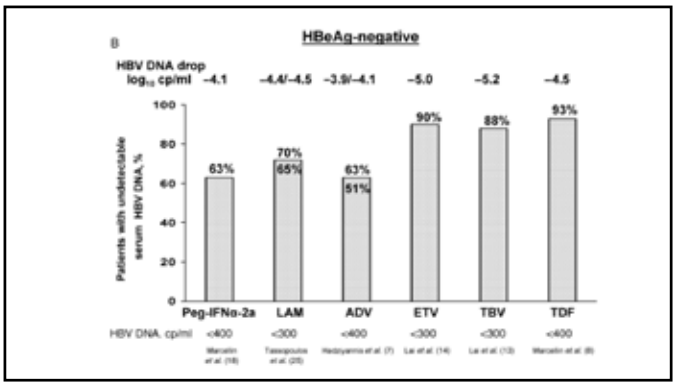
1. HBeAg positive , ALT >2x ULN or fibrosis, DNA >20,000: Treat with NUC therapy
2. HBeAg negative, ALT >2x ULN or fibrosis, DNA >2000: Treat with NUC therapy

Immune Clearance Treatment: Criteria not fully met

1. ALT elevated but not 2x ULN or VL level does not fit into criteria
   - -Age: >40 associated with worse disease
   - -Family history of cirrhosis or HCC in setting of HBV
   - -Previous treatment history
   - -Presence of extrahepatic manifestations
   - -Presence of cirrhosis







HBsAg and Viral suppression with NUCs

1. HBsAg loss rate: 1%
2. DNA suppression: 93%
3. ALT normalization: 76 %

Monitoring Treatment

1. HBV DNA: Q3 months then Q6months once undetectable
2. If HBeAg (+): Q6 months HBeAg and Anti-HBe
3. If HBeAg (-): Yearly HBV DNA

Can we stop treatment safely?

HBeAg positive to HBeAg negative CHB on THERAPY

Treatment consolidation to HBeAg negative/HBeAb positive on THERAPY

How to consider it and do it:
-Treat for 12 months with normal ALT, Undetectable DNA, HBeAg negative
-Must be a non-cirrhotic with no other forms of liver disease
-Monitor after NUC cessation every three months for 1 year.

AASLD: Quality/Certainty of evidence is LOW
Strength is CONDITIONAL

HBeAg negative CHB

-HBeAg negative/HBeAb positive/HBsAg Positive with no cirrhosis
-Viral Load that are not in category to treat
-Vast majority of patients we encounter in USA/Europe

How to consider it and do it:
-Not recommended unless compelling reason

AASLD: Quality/Certainty of evidence is LOW
Strength is CONDITIONAL

Chronic HBV in patients with Cirrhosis

Do not recommend stopping therapy

AASLD: Quality/Certainty of evidence is MODERATE
Strength is STRONG

Stopping Therapy with NUCs

HBeAg (+): Can give 12 months of consolidation therapy
- -Stop Therapy if: HBeAg seroconverion and undectable DNA
- -If Cirrhotic: Treat until HBsAg loss (essentially forever)

HBeAg (-):
- -EASL/AASLD: Treat until HBsAg loss (essentially forever)
- -APASL: after 2-5 years undetectable DNA at 2 separate occasions 6 months apart then can STOP: (cost issue)
- -If Cirrhotic: Treat until HBsAg loss (essentially forever)

Right Endpoints

1. Inactive Carrier: HBsAg positive, HBeAg negative, Low/Undetectable DNA, Normal ALT
2. Functional Cure: HBsAg negative and Undetectable DNA
1. Complete Cure: absence cccDNA

Norah Terrault MD
AASLD Liver Meeting 2017
UCSF

ABC Clinic

Providers: David Fettig, Ricardo Franco, Turner Overton, Mike Saag, and Brooke Little
Clinical Coordinator: Ashonte McCray
Pharmacy: DeAnn Jones

Referrals:
Fax: 866-408-1445
Phone: 205-377-3584
Email: almccray@uabmc.edu
Inside UAB: Please use message system in pool- ABC clinic scheduling

Questions ?

UAB LIVER CENTER and COMPREHENSIVE TRANSPLANT INSTITUTE

Nicholas Hoppmann, MD
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"Palliative care in end-stage liver disease"

Disclosures: Grant: PCORI-Pal Liver Study

Learning Objectives:

- Discuss current lack of palliative care in ESLD
- Discuss patient impact of collaboration between hepatology and palliative care

Palliative care (PC) is an integral part in the management of patients with chronic disease especially those with high symptom burden. Patients with end-stage liver disease (ESLD) experience a poor quality of life (QOL) related to a fluctuating clinical course with episodes of high symptom burden, however, patients with ESLD are rarely referred for PC and when they are it is often very late in the disease course. Several major barriers have been identified in providing PC to patients with ESLD including inadequate access to PC providers, discomfort with end of life discussions, preferential focus on life saving interventions, and clinical time constraints of providers. As the prevalence of ESLD continues to increase, providing optimal care for these patients, which includes components of PC, continues to be a challenge. In addition to patients, family caregivers (FCGs) –an integral part of the ESLD management team – have supportive care needs that are also under-recognized and poorly understood. The AGA recently provided a clinical practice update for PC in the care of patients with ESLD, highlighting 10 best practices regarding palliative care integration into practices. Currently, multiple ongoing studies are hoping to provide evidence-based guidance for PC in patients with ESLD. UAB is part of a larger national-effort to determine how to integrate PC into ESLD management through the PAL Liver study, a multi-institution cluster-randomized comparative effectiveness trial comparing hepatologist *vs* PC specialist-delivered PC. As a member of the PAL Liver network, UAB is aiming to define optimal PC delivery for patients with ESLD and their FCGs and to guide providers in ways to integrate PC into their clinical practice.

Suggested readings:

- Peng JK, Hepgul N, Higginson IJ, Gao W. Symptom prevalence and quality of life of patients with end-stage liver disease: a systematic review and meta-analysis. Palliat Med 2019;33:24-36
- Poonja Z, Brisebois A, van Zanten SV, Tandon P, Meeberg G, Karvellas CJ. Patients with cirrhosis and denied liver transplants rarely receive adequate palliative care or appropriate management. Clin Gastroenterol Hepatol. 2014 Apr;12(4):692-8. doi: 10.1016/j.cgh.2013.08.027. Epub 2013 Aug 24. PMID: 23978345.
- Mudumbi SK, Bourgeois CE, Hoppmann NA, Smith CH, Verma M, Bakitas MA, Brown CJ, Markland AD. Palliative Care and Hospice Interventions in Decompensated Cirrhosis and Hepatocellular Carcinoma: A Rapid Review of Literature. J Palliat Med. 2018 Aug;21(8):1177-1184. doi: 10.1089/jpm.2017.0656. Epub 2018 Apr 26. PMID: 29698124; PMCID: PMC6104656.
- Verma M, Tapper EB, Singal AG, Navarro V. Nonhospice Palliative Care Within the Treatment of End-Stage Liver Disease. Hepatology. 2020 Jun;71(6):2149-2159. doi: 10.1002/hep.31226. PMID: 32167615.
- Tandon P, Walling A, Patton H, Taddei T. AGA Clinical Practice Update on Palliative Care Management in Cirrhosis: Expert Review. Clin Gastroenterol Hepatol. 2021 Apr;19(4):646-656.e3. doi: 10.1016/j.cgh.2020.11.027. Epub 2020 Nov 19. PMID: 33221550.

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Palliative Care for End-Stage Liver Disease

Nicholas Hoppmann
Transplant Hepatology

Objectives

- End-Stage Liver Disease in the US
- Palliative Care in End-Stage Liver Disease – Current state of affairs
- Palliative Care in End-Stage Liver Disease – What's on the horizon
- PAL-LIVER Study
- Integration of PC – What can we do now?

End-Stage Liver Disease: Increasing in the US

Prevalence

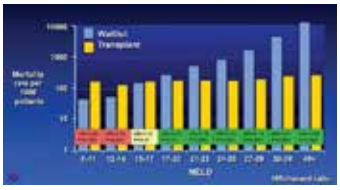
- 600,000 patients w/ cirrhosis in US
- ESLD doubled from 2001- 2013
- Younger (25-34 years)
  - Men increase 7.9%
  - Women increase 11.4%

Mortality

- 36,427 deaths in 2013
  - 66,000 deaths per year
- 12th leading cause of death
  - 7th for aged 25-64 years
  - Mortality rate increased 65% from 1999- 2016

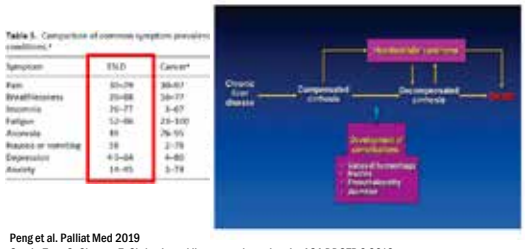
Scaglione et al. J Clin Gastroenterol 2015
Asrani SK et al. Gastroenterology 2013
Tapper EB, Parikh ND. BMJ 2018
U.S. Department of Health and Human Services; CDC; National Center for Health Statistics, 2019.

End-Stage Liver Disease: A Unique Position



Garcia-Tsao G. Chapter 7: Cirrhosis and liver transplantation. In: AGA DDSEP 9 2019

End-Stage Liver Disease: A Unique Position



Peng et al. Palliat Med 2019
Garcia-Tsao G. Chapter 7: Cirrhosis and liver transplantation. In: AGA DDSEP 9 2019

End-Stage Liver Disease: A Unique Position

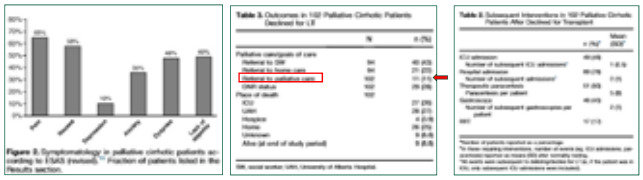
SUPPORT Study (2000)

- Similar symptoms to patients with lung and colorectal cancer
- Pain, dyspnea, confusion, depressed mood, anxiety
- Perceived QOL – fair or poor > 70%
- Understanding Prognosis: 160 (27%) patient who died during index hospitalization predicted their likelihood of 2-month survival at 75% or greater

Roth et al. J Am Geriatr Soc. 2000

End-Stage Liver Disease: A Unique Position

- Retrospective EMR review of 102 adult patients
  - Removed from LT or declined from 2005-2010 at their institution



Poonja et al. Clin Gastroenterol Hepatol. 2014

End-Stage Liver Disease: A Unique Position

- Family Caregivers (88% had FCG at home)
  - 15% quit work to care for patient
  - 37% loss major source of family income
  - 32% exhausted savings
  - 9% gave up or deferred education
  - 10% answered yes to “Has anyone else in the family become ill or unable to function normally in part because of stress and strain” of the illness

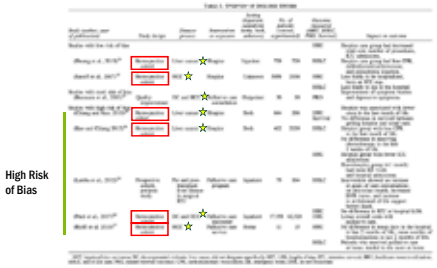
Roth et al. J Am Geriatr Soc. 2000

ESLD & Palliative Care

- Infrequent
- Delayed until the very end of life
- Stigmatized

- Major barriers
  - Inadequate access to PC providers
  - Episodes of decompensation occur with increased frequency over time
  - Discomfort with end of life care discussions
  - Preferential focus on life saving interventions
  - Time and training for palliative care

Palliative Care in ESLD: Rapid Review



High Risk of Bias

3 Main Outcome Groups

Healthcare Resource Utilization (HRU)
End-of-life Care (EOLC)
Patient-reported outcomes

Mudumbi SK et al. J Palliat Med. 2018

Palliative Care in ESLD: Prospective Studies

Verma M et al. Hepatology. 2020

Aren't PC providers better?

- Depends!
  - No standard model for integrating PC services within hepatology
- *Numbers game?*
  - PC providers: overburdened, not enough
- *"Who is this?"*
  - Another specialist may "unintentionally undermine existing therapeutic relationships"
- *"Talk to your [insert: Liver or Palliative Care] doctor?"*

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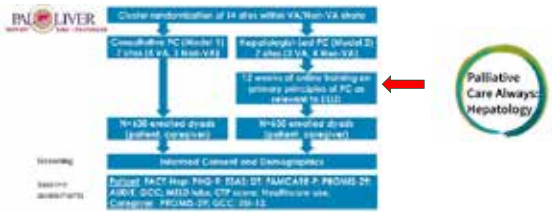
PAL LIVER

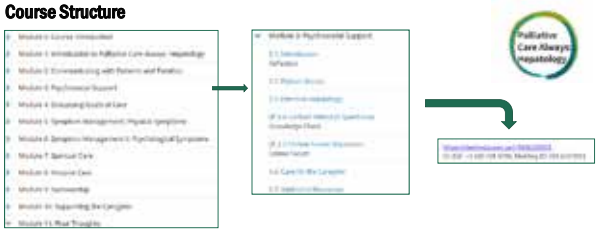
Introducing Palliative Care (PC) within the Treatment of End Stage Liver Disease: A Cluster Randomized Controlled Trial

Enrolling Protocol



Hepatology-Palliative Care Training

Course Structure



Intervention & Follow-Up

Evaluating Patients & Caregivers Experiences with Each Model: Qualitative Sub-Study
Patient-Caregiver Experiences

What can we do now?

AGA Clinical Practice Update – 10 Best Practice Advice (BPA)

1. Care with palliative care principles should be provided to any patient with advanced serious chronic illness or life-limiting illness such as cirrhosis, irrespective of transplant candidacy; this care should be based on needs assessment instead of prognosis alone, delivered concurrently with curative or life-prolonging treatments, and tailored to stage of disease.
2. Care inclusive of palliative care principles may be delivered by healthcare providers from any specialty within any healthcare setting.
3. Providers caring for persons with cirrhosis should assess for the presence and severity of symptoms within physical, psychological, social, and spiritual domains related to their liver disease, its treatment, and prognosis.
4. Across the spectrum of cirrhosis, excellence in communication is integral to high quality advance care planning, goals of care conversations, and the cultivation of prognostic awareness with patients and caregivers.
5. Routine care for patients with cirrhosis, and particularly those with decompensated disease, should include assessment of caregiver support and screening for caregiver needs.
6. Prognosis should be evaluated by gastroenterology/hepatology providers during routine care visits and at sentinel events.
7. Goals of care discussions in patients with cirrhosis should be repeated at sentinel events including hospital or intensive care admission, before initiation of lifesupporting therapies, before surgery, on new onset of cirrhosis-related complications, and after determination of transplant eligibility.
8. Because lack of time is one of the major barriers to administering palliative care, healthcare providers should consider how they can optimize efficiencies in palliative care delivery (identifying local billing codes, prescreening surveys carried out by ancillary staff, development of multidisciplinary teams).
9. Dedicated specialist palliative care services are often a limited resource. As such, healthcare providers should work together with local specialist palliative care teams to establish clear triggers and pathways for referral.
10. Healthcare providers caring for patients with cirrhosis should provide timely referral to hospice for patients who have comfort-oriented goals and prognosis of 6 months or less.

Tandon P, Walling A, Patton H, Taddei T. Clin Gastroenterol Hepatol. 2021

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Palliative Care: Anyone, anywhere.

AGA: PC in ESLD Best Practice Advice

1. Care with palliative care principles should be provided to any patient with advanced serious chronic illness or life-limiting illness such as cirrhosis, irrespective of transplant candidacy; this care should be based on needs assessment instead of prognosis alone, delivered concurrently with curative or life-prolonging treatments, and tailored to stage of disease.
2. Care inclusive of palliative care principles may be delivered by healthcare providers from any specialty within any healthcare setting.

Consider the palliative care measures you can provide for your patients with cirrhosis at any time.

Tandon P, Walling A, Patton H, Taddei T. Clin Gastroenterol Hepatol. 2021

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Beyond Decompensation Management

AGA: PC in ESLD Best Practice Advice

3. Providers caring for persons with cirrhosis should assess for the presence and severity of symptoms within physical, psychological, social, and spiritual domains related to their liver disease, its treatment, and prognosis.

Consider incorporating new symptom assessment and management into your practice.

Tandon P, Walling A, Patton H, Taddei T. Clin Gastroenterol Hepatol. 2021

Communication is Key

AGA: PC in ESLD Best Practice Advice

4. Across the spectrum of cirrhosis, excellence in communication is integral to high quality advance care planning, goals of care conversations, and the cultivation of prognostic awareness with patients and caregivers.

6. Prognosis should be evaluated by gastroenterology/hepatology providers during routine care visits and at sentinel events.

7. Goals of care discussions in patients with cirrhosis should be repeated at sentinel events including hospital or intensive care admission, before initiation of life supporting therapies, before surgery, on new onset of cirrhosis-related complications, and after determination of transplant eligibility.

Find resources to improve communication about goal of care, advanced care planning, prognosis.

The Conversation Project

Your Conversation Starter Guide
What Matter to Me Workbook
Your Guide to Choosing a Heath Care Proxy
Your Guide to Being a Health Care Proxy

Tandon P, Walling A, Patton H, Taddei T. Clin Gastroenterol Hepatol. 2021

Caregivers are critical

AGA: PC in ESLD Best Practice Advice

5. Routine care for patients with cirrhosis, and particularly those with decompensated disease, should include assessment of caregiver support and screening for caregiver needs.

Consider caregiver needs and establish resources to provide.

https://www.liver.ca/patients-caregivers/for-caregivers/

https://liverfoundation.org/caregivers/caregiver-support/

http://www.cirrhosis-caregivers.com/

https://www.caregiving.org/resources/

Tandon P, Walling A, Patton H, Taddei T. Clin Gastroenterol Hepatol. 2021

Plan for Palliative Care

AGA: PC in ESLD Best Practice Advice

8. Because lack of time is one of the major barriers to administering palliative care, healthcare providers should consider how they can optimize efficiencies in palliative care delivery (identifying local billing codes, prescreening surveys carried out by ancillary staff, development of multidisciplinary teams).

9. Dedicated specialist palliative care services are often a limited resource. As such, healthcare providers should work together with local specialist palliative care teams to establish clear triggers and pathways for referral.

10. Healthcare providers caring for patients with cirrhosis should provide timely referral to hospice for patients who have comfort-oriented goals and prognosis of 6 months or less.

Take time to plan incorporation of PC into your practice and establish easy avenues for referral.

Tandon P, Walling A, Patton H, Taddei T. Clin Gastroenterol Hepatol. 2021

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Thank you!

Nicholas Hoppmann
NHoppmann@uabmc.edu

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- Verma M, Tapper EB, Singal AG, Navarro V. Nonhospice Palliative Care Within the Treatment of End-Stage Liver Disease. Hepatology. 2020 Jun;71(6):2149-2159. doi: 10.1002/hep.31226. PMID: 32167615.
- Tandon P, Walling A, Patton H, Taddei T. AGA Clinical Practice Update on Palliative Care Management in Cirrhosis: Expert Review. Clin Gastroenterol Hepatol. 2021 Apr;19(4):646-656.e3. doi: 10.1016/j.cgh.2020.11.027. Epub 2020 Nov 19. PMID: 33221550.

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"Acute on chronic liver failure"

Disclosures: Grants: Gilead, Arrowhead Pharmaceuticals

Learning Objectives:

- Understand definition of acute on chronic liver failure
- Understand current treatment and mortality risk predictors

Introduction

Acute-on-chronic liver failure (ACLF) is a clinical syndrome, for patients with cirrhosis who develop both hepatic and extra-hepatic organ failure. The most common precipitating events are bacterial infection, active alcohol abuse and reactivation of, or, superimposed viral hepatitis. In approximately 40% of patients a precipitating event is not identified, but the precipitant has neither been linked to disease severity, nor mortality. ACLF is associated with a high mortality. Patients with ACLF have a greater degree of organ dysfunction on admission when compared to the general ICU population and this may explain their increased mortality. Nonetheless, in ACLF organ dysfunction is often reversible and these patients should be considered candidates for admission to ICU. Evidence-based guidance on management of these patients are limited, but recent guidelines have been created to assist with management of patients with ACLF admitted to an ICU. These guidelines involve the best clinical practice using a comprehensive multi-disciplinary and systems-based approach based on a combination of accepted ICU practice and evidence from trials in this cohort.

Hemodynamics

The hyperdynamic circulation of cirrhosis, which is associated with a high cardiac-output circulation with decreased systemic vascular resistance and subsequent low mean arterial pressure (MAP) is common in these patients. In addition, cirrhotic cardiomyopathy and relative adrenal insufficiency can further contribute to this circulatory failure state. Volume resuscitation is the first priority in management for these patients as they are managed in the ICU. The preferred agents are crystalloids, albumin and if necessary, blood if hemoglobin is less than 7 mg/dL. Avoid hydroxyethyl starch such as HESPAN and HEXTEND. For liver patients that require fluid resuscitation and have a serum albumin less than 3 mg/dL, albumin-based resuscitation is recommended over isotonic crystalloid. The MAP target should be individualized to the patient and account for their pre-morbid physiology. A target MAP of 65 mmHg is generally accepted and should be used to titrate vasopressors and norepinephrine is the recommended first-line vasopressor and can be given in combination with fluid resuscitation.

Pulmonary

Intubation and mechanical ventilation is indicated in patients with severe hepatic encephalopathy (HE) and to facilitate endoscopy following a variceal bleed. Administration of sedation to tolerate a definitive airway should be minimized in HE given the prolonged hepatic clearance of some agents. Acute respiratory failure secondary to pulmonary pathology, predominantly infection and acute lung injury, often requires ventilatory support. Pulmonary pathology may be pre-existing and can precipitate or exacerbate respiratory failure. Porto-pulmonary hypertension (POHTN) and hepato-pulmonary syndrome (HPS) are specific to cirrhosis but are rare causes of hypoxemia. POHTN is defined as the presence of pulmonary artery hypertension that evolves because of portal hypertension and HPS is characterized by intra-pulmonary arterio-venous dilatations and hypoxemia. It is an important differential to consider POHTN or HPS in patients in whom hypoxemia is either out of proportion to the clinical condition.

Ascites and hepatic hydrothorax can equally impede ventilation and drainage of either is indicated to improve pulmonary status. Management of refractory hepatic hydrothorax should include transjugular intrahepatic portosystemic shunt (TIPS), video assisted thoroscopic surgery (VATS) with pleurodesis, or pleurex catheters. TIPS has a success rate in about 75% of cases. However, TIPS is complicated by hepatic encephalopathy (HE) and cannot be used in all patients. VATS with pleurodesis can also be used in most patients with similar success rates to TIPS. Traditionally, chest tubes for hepatic hydrothorax were considered a relative contraindication due to fear of infection and loss of excessive fluids and electrolytes. However, the newer pleurex catheters can be used as a bridge until liver transplant is available or for patients being placed on hospice.

Renal

Renal failure is the most common extra-hepatic organ failure in ACLF and occurs in over half of cases. The International Club of Ascites defines acute kidney injury (AKI) in cirrhosis to include a change from baseline serum creatinine, of greater than 0.3 mg/dL within 48 hours. In ACLF, AKI is predominantly a pre-renal problem, accounting for a majority of cases. While hepatorenal syndrome (HRS) is a pre-renal cause and accounts for 15–20% of all cases of AKI. HRS is diagnosed following exclusion of shock, structural kidney disease and recent exposure to nephrotoxics, in patients with cirrhosis and ascites and low systemic blood pressure. The approach to management is to remove nephrotoxic medications, excluded obstructive pathology, identification and treatment of infections and intravascular volume replacement, with albumin (1 g/kg/body weight), for 48 hours, if no response in renal function, HRS is considered higher in the differential. Treatment include using vasopressors, if the patient is outside of an ICU bed use midodrine & octreotide or for patients in an ICU use norepinephrine. Renal replacement therapy may be necessary to remove toxins and volume or to correct electrolyte disturbances or acidosis. In cases of low blood pressure, continuous renal replacement therapy is the only option available as a bridge to liver transplantation.

Infection

Infection occurs in over commonly in patients with cirrhosis and ACLF. Infection is both a precipitant and complication of this syndrome. The most common presentations are spontaneous bacterial peritonitis, pneumonia and urinary tract infections. Bacterial infections dominate, while fungal infections can occur. Patients with cirrhosis admitted to a hospital or transferred to an ICU, should be considered as having underlying infection driving progression to ACLF. An infection work-up should be done on these patients and empirical broad-spectrum antibiotic therapy should be given early to enhance treatment efficacy. The infection work-up should include a diagnostic

paracentesis even in the absence of classical sepsis clinical features. Empirical anti-fungal use is not recommended initially.

Coagulation

Clotting parameters, including prothrombin time (PT), international normalized ratio (INR), fibrinogen and platelet count, are invariably abnormal in ACLF. Despite concerns of increase risk of bleeding in patients, hemostasis is re-balanced in patients with cirrhosis, since there are reductions in both anti- and pro-coagulant factors. In patients with cirrhosis, they display hypocoagulable and hypofibrinolysis. Hypocoagulable state, is countered by an increase in von Willibrand factor, which increases the risk of hemostasis. Hypofibrinolysis is caused by reduction in plasminogen, which is counteracted by elevated tissue plasminogen activator and reduced factor VIII, alpha-2 anti-plasmin and thrombin-activatable fibrinolysis inhibitor. Prolonged INR correlates with liver disease severity, but does not correlate with bleeding or thrombosis. Empirical correction of clotting abnormalities is not recommended. In patients undergoing invasive procedures, if platelets $<50\times10^9$/l consider platelet transfusion and if fibrinogen <120 mg/dl consider replacement with cryoprecipitate. In addition, thrombo-elastography (TEG) should be used to stratify bleeding risk. In small RCTs the use of TEG reduced blood product transfusions, in cirrhotic patients undergoing invasive procedures, without increased bleeding complications. TEG use should be considered, alongside a standard clotting profile, to guide transfusion for high risk procedures.

Referral to liver transplant centers

On admission, patients who are on the transplant waiting list should be discussed with their transplant center to update the patient's clinical condition as offers are accepted at any time and the status on the list may change quickly in these sick patients. For patients not listed for a liver transplant with acute liver failure or ACLF, an early conversation with the transplant center should occur to determine if the patient has the potential to be an appropriate candidate for transplant and may need to be transferred. If the clinical trajectory is improving a transplant evaluation may be delayed until discharge from ICU or hospital and set up at a later date. Conversations are generally centered around transplantation and hospital to hospital transfer, but, if necessary, discussions on management issues can be obtained with the transplant center. An alternative reason for referral to transplant center is for additional resources offered by the transplant center, such as management of gastric varices, placement of TIPS, or initiation of CRRT.

Recommended readings:

1. Nanchal R, Subramanian R, Karvellas CJ, Hollenberg SM, et al. Guidelines for the Management of Adult Acute and Acute-on-Chronic Liver Failure in the ICU: Cardiovascular, Endocrine, Hematologic, Pulmonary and Renal Considerations: Executive Summary. Critical Care Medicine 2020;48(3):415-419.
2. Asrani SK, SImonetto DA, Kamath PS. Acute-on-Chronic Liver Failure. Clin Gastroenterol Hepatol 2015;13(12):2128-2139.
3. MacDonald AJ, Olson J, Karvellas CJ. Critical Care Considerations in the Management of Acute-on-Chronic Liver Failure. Curr Opin Crit Care 2020;26(2):171-179.

ICU Management of the Patient with Acute on Chronic Liver Failure

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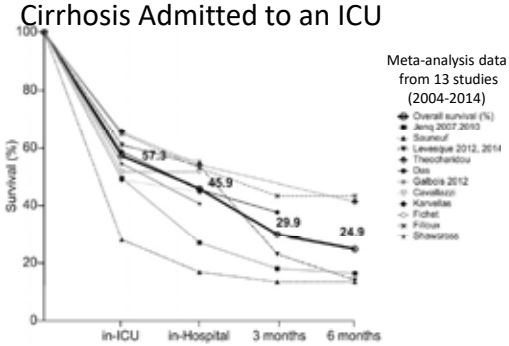
Medical Director of Liver Transplant

Survival (N=2523) Patients with Cirrhosis Admitted to an ICU



J of Hepatology 2021;75:S163-S177

Introduction

- Resuscitation
- Nutrition
- Glucose Control
- Venous Thromboembolism (VTE) Prophylaxis
- Hepatorenal Syndrome (HRS)
- Hepatic Hydrothorax
- Assessing Bleeding Risk for Invasive Procedures

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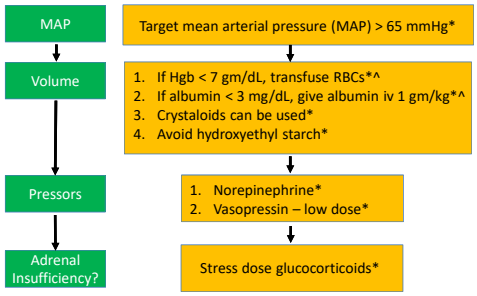
Resuscitation



*Guidelines based on critically ill ICU patients
^Guidelines based on ACLF patients

Crit Care Med 2020;48:415-419

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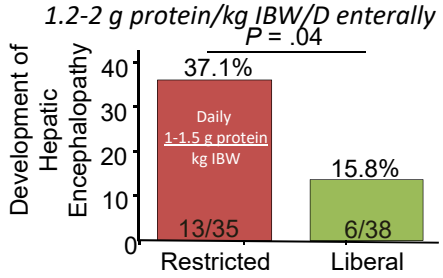
Target Protein Goals Comparable to Critically Ill Patients

1.2-2 g protein/kg IBW/D enterally



Intensive Care Med 2017;43:1-15

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Target Glucose Control between 110-180 mg/dL in ACLF Patients

- Data supports shorter hospital stay & provide an effective transition out of the hospital that prevents acute complications & readmission
- Retrospective analysis of 312 patients with ACLF showed hypoglycemia is associate with increased mortality.[1]

1. J Crit Care 2014; 29:316.e7–e12

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Use Low Molecular Weight Heparin (LMWH) for VTE Prophylaxis is Safe

- Retrospective study (N=235 patients with 355 discrete hospitalizations to non-ICU beds between 2007-2010) received prophylactic to LMWH (15%) or unfractionated heparin (77%).
- Despite thromboprophylaxis, 5 patients (1.4%) were diagnosed with VTE (3 non-splanchnic DVT, 2 PE).
- 9/355 (2.5%) with GI bleeding
  - 5 required blood transfusion
  - 6/9 had EGD±COL (2 esophageal ulcers, 2 GAVE, 1 COL CA)
  - 2 had heparin induced thrombocytopenia
  - No patients died from VTE related complications

Liver Int. 2014;34:26-32

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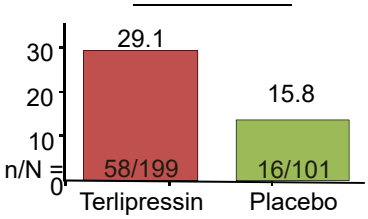
Vasopressors in HRS

- Vasopressors should be used with intravenous albumin in HRS.
  1. Terlipressin
  2. Norepinephrine
  3. Midodrine & Octreotide
- Meta-analysis comparing terlipressin vs norepinephrine (4 RCT) shows no differences in reversal of HRS
  - (58 vs 59%) with lower rates of SE with norepinephrine[1]
- Reversal of HRS with Terlipressin (phase 3) trial – Terlipressin 29.1% vs Placebo 15.8%[2]

1. PLOS ONE 2014;9(9): e107466
2. NEJM 2021;384:818-828

Reversal of HRS with Terlipressin – Phase 3 Trial



Liver Transplantation @ 90 Days	23%	29%
Mortality @ 90 Days	51%	45%

NEJM 2021;384:818-828

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Hepatic Hydrothorax

Medical Options

- Sodium restriction
  - 2000 mg/day
- Diuretics
  - Furosemide 80 mg BID
  - Spironolactone 400 mg QD
  - Metolazone 5 mg QD

Surgical Options

- Liver Transplant
- Frequent Thorocenteses
- Transjugular Intrahepatic Portosystemic Shunt (TIPS)
- Video Assisted Pleurodesis
- Indwelling Pleural Catheter

Hepatology 2020;72:1851-1863

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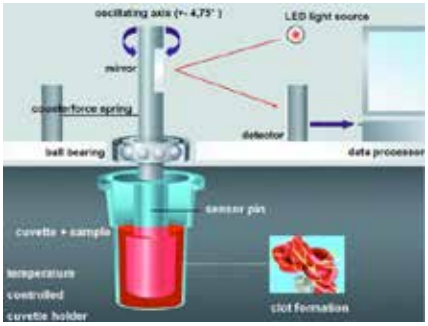
Viscoelastography (TEG/ROTEM) should be used over INR, platelets, or fibrinogen in patients undergoing an invasive procedure

- Single center RTC in 60 patients undergoing an invasive procedure
  - Treatment group had therapy guided by TEG
  - Control group used standard of care
  - No difference in bleeding or 90 day mortality
  - Treatment group received less blood products (RR 0.18, 95% CI 0.08 - 0.39)

Hepatology 2016;63:566-573

Viscoelastography



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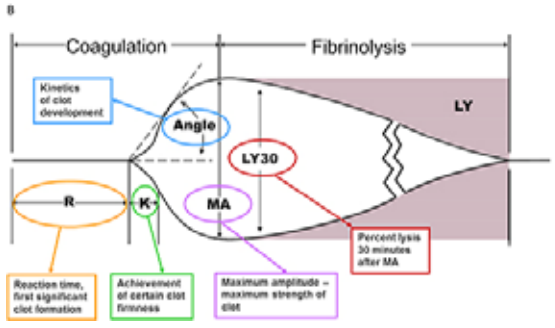

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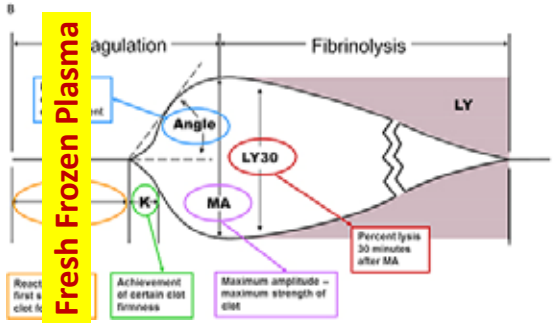
Viscoelastogography



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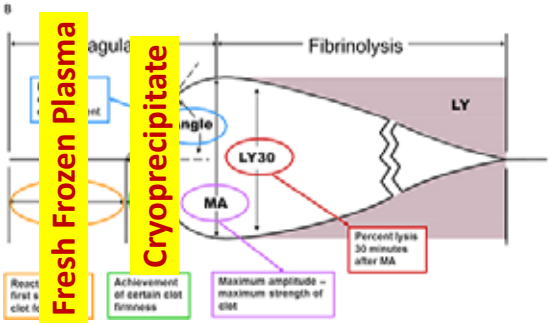

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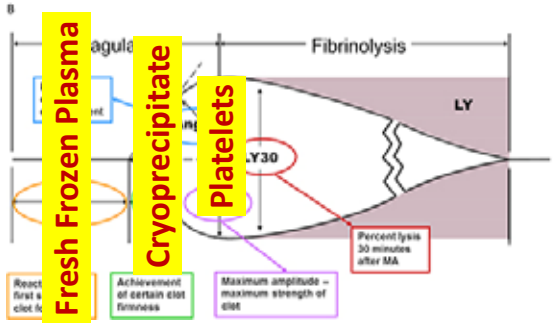

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QUESTIONS

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"Treat to Target" Paradigm in Inflammatory Bowel Disease

Disclosures: Grants: Pfizer, Takeda
Consulting Fee: Pfizer, Takeda, Janssen, AbbVie, Roche, Genentech, Lilly, Salix, Valeant, Theravance, Prometheus, Target Pharmasolutions, Bristol Myers Squibb, Calibr

Learning Objectives:

- To summarize new treatments available in inflammatory bowel disease (IBD)
- To review treat to target paradigms in IBD

Crohn's disease and ulcerative colitis, forms of inflammatory bowel disease (IBD), are inflammatory disorders of the gastrointestinal tract that can lead to significant complications and disability if not fully treated. Historically, indications for IBD treatment have been based on clinical symptoms. Therapeutic options were first utilized in a step-up approach, requiring failure of one class of medication to initiate the next. Treatment options initially consisted of corticosteroids and 5-aminosalucylic acid therapies, which did little to prevent progression of Crohn's disease and were only effective in a portion of patients with ulcerative colitis. With the advent of novel therapeutics such as biologics and small molecules, a greater therapeutic armamentarium became available. However, response to therapy continued to be measured by improvement in clinical symptoms. Unfortunately, targeting symptom control does not appear to alter the natural history of the disease. Several cohort studies have demonstrated that Crohn's disease patients in clinical remission who have elevated c-reactive protein (CRP) have an increased rate of relapse within 1-2 years. Symptoms do not necessarily correlate with overall inflammatory burden, particularly in Crohn's disease. Therefore, this conventional management paradigm has now evolved.

This new paradigm, entitled "treat to target," utilizes objective and biologic measures of inflammation as markers of response. Example "targets" in this paradigm include endoscopic scales of severity of inflammation, radiology, CRP and fecal calprotectin. The focus has shifted to a) selecting the right patient for advanced therapy earlier in disease course b) measurement of response via patient reported outcomes AND a biologic measure (preferably endoscopy) and c) tight control and monitoring of the patient to maintain remission with biologic and symptom-based measurements.

Utilization of clinical and objective risk factors for severe disease can inform earlier treatment of appropriate individuals with IBD, prior to development of any structural damage. Poor prognostic factors in Crohn's disease include young age at diagnosis, extensive bowel involvement, perianal disease, severe rectal disease, or penetrating/stenosing disease at diagnosis. Risk factors for severe disease (defined as colectomy) in ulcerative colitis include young age at diagnosis, extensive colitis, severe endoscopic disease, hospitalization for colitis, elevated CRP and low albumin. The greater the number of risk factors, the more likely it is that the patient's disease progress. Therefore, these risk factors can be utilized to recommend earlier advanced therapies in patients with IBD. Patients and physicians can then discuss which targets to assess after treatment initiation, and how to monitor for continued control once targets are reached. The STRIDE panel recommends a target of both patient reported outcome (PRO) remission (resolution of rectal bleeding and diarrhea) and endoscopic remission (defined as a Mayo endoscopic score of 0 or 1) for ulcerative colitis. For Crohn's disease, STRIDE

recommends a target of PRO remission (defined as resolution of abdominal pain and diarrhea) and endoscopic remission (resolution of ulceration on ileocolonoscopy or radiologic resolution of inflammation when ileocolonoscopy cannot reach the inflammation).

The highest level of data for treating Crohn's disease to an objective target comes from the CALM trial, where individuals with Crohn's disease were randomized to clinical management (titration of medications based on clinical symptoms) versus tight control group (measuring biomarkers and symptoms to titrate medications). The primary outcome was endoscopic remission at week 48. The tight control group achieved a significantly higher rate of endoscopic remission at week 48 (46% vs. 30%, p=0.010). In longer term follow up of this trial, patients achieving endoscopic or deep remission after 1 year of tight control were less likely to have disease progression (defined as a composite of new internal fistula/abscess, stricture, perianal fistula/abscess, hospitalization or surgery) over a median of 3 years.

In summary, providers should determine disease severity to guide the management of IBD. Goals of treatment include endoscopic as well as PRO remission. Untreated "silent" inflammation is associated with disease related complications. Utilizing a "tight control" approach can improve endoscopic remission rates in Crohn's disease. Monitoring strategies should include biomarkers like fecal calprotectin, CRP and repeat endoscopic evaluation at intervals determined through shared decision making. By utilizing these strategies, providers can improve long-term outcomes for patients with IBD.

Recommended readings:

1. Colombel JF, Panaccione R, Bossuyt P, et al. Effect of tight control management on Crohn's disease (CALM): a multicentre, randomised, controlled phase 3 trial. Lancet 2017;390:2779-2789.
2. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining Therapeutic Goals for Treat-to-Target. Am J Gastroenterol 2015;110:1324-38.
3. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. Gastroenterology 2021;160:1570-1583.
4. Ungaro RC, Yzet C, Bossuyt P, et al. Deep Remission at 1 Year Prevents Progression of Early Crohn's Disease. Gastroenterology 2020;159:139-147.
5. Darr U, Khan N. Treat to Target in Inflammatory Bowel Disease: An Updated Review of Literature. *Curr Treat Options Gastro* **15,** 116–125 (2017).

Treat to Target Paradigm in IBD

August 13, 2021

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Disclosures

- Consultant:
  - AbbVie, Pfizer, Takeda, Janssen,Target PharmaSolutions, Prometheus, Valeant, Salix, Genentech, Roche, Theravance, BMS, Lilly, Calibr
- Grant support
  - Takeda, Pfizer

Outline: Treat to Target in Inflammatory Bowel Disease

- Case Presentation
- Defining severity and treatment goals in IBD
  - Definitions of endoscopic targets
- Does “mucosal healing” improve outcomes?
- Treat to Target: where do the data stand?
  - CALM trial
  - STARDUST trial
- Strategies for monitoring
- Summary

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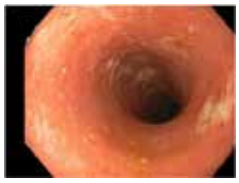
Case 1: Ulcerative Colitis

- Left-sided Ulcerative Colitis x 15 years
- Mesalamine 4.8g/day & lactobacillus daily
- Flare-ups ~ twice a year, uses rectal and intermittent oral steroids (total of 4 courses)

- **MHx:** breast cancer, lumpectomy 6 yrs ago
- **SHx:** Driver for delivery company

- **Currently:**
  - 2-3 formed stool per day, occasional blood
  - CRP 2.8mg/L FC 180ug/g



Patient Concerns:

"Do I need to do anything else for my colitis? Why?"

"I just want to stay healthy, and keep working to pay the bills"

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Old and New Definitions of UC Disease Severity

Old: Symptoms Only

- **Mild:** up to 4 loose stools daily, may be bloody, mild abdominal pain
- **Moderate:** 4–6 stools daily, moderate abdominal pain, anemia
- **Severe:** over 6 bloody stools daily, fever, anemia
- **Fulminant:** over 10 stools daily, continuous bleeding, abdominal pain, distension; potentially fatal

New: Consider Context

Poor Prognostic factors
Age<40 years at diagnosis
Extensive colitis
Severe endoscopic disease (Mayo endoscopic subscore 3, UCEIS >=7)
Hospitalization for colitis
Elevated CRP
Low serum albumin

The greater the number of poor prognostic factors, the worse the prognosis as measured by likelihood of colectomy

Modified from: Kornbluth A, et al. Am J Gastroenterol 2010; 105:501-523 and Dassopoulos T, et al. Gastro 2015; 149: 238-245. Rubin DT, et al. Am J Gastroenterol. 2019 Mar;114(3):384-413.

Endoscopic Scales and Disease Severity

New: Include Endoscopic Scoring

Mayo Score
0-3

Photo Credit: Nature Rev Gastroenterol Hepatol 2009

ACG Guideline UC Severity Definitions (Symptoms and Endoscopy)

	Remission	Mild	Moderate-Severe	Fulminant
Stools (#/day)	Formed stools	<4	>6	>10
Blood in stools	None	Intermittent	Frequent	Continuous
Urgency	None	Mild, occasional	Often	Continuous
Hemoglobin	Normal	Normal	<75% of normal	Transfusion required
ESR	<30	<30	>30	>30
CRP (mg/L)	Normal	Elevated	Elevated	Elevated
Fecal calprotectin (µg/g)	<150-200	>150-200	>150-200	>150-200
Endoscopy (Mayo subscore)	0-1	1	2-3	3
UCEIS	0-1	2-4	5-8	7-8

Modified from: Kornbluth A, et al. Am J Gastroenterol 2010; 105:501-523 and Dassopoulos T, et al. Gastro 2015; 149: 238-245.
Rubin DT, et al. Am J Gastroenterol. 2019 Mar;114(3):384-413.

Crohn's Disease: Progressive Disease

Window of Opportunity?

Phenotypes of CD

- Inflammatory (only 20%)
- Stricturing
- Penetrating
- Perianal disease

CDAI, Crohn's disease activity index; CDEIS, Crohn's disease endoscopic index of severity; CRP, C-reactive protein
Pariente B, … Lemann M. *Inflamm Bowel Dis* 2011; Colombel JF et al. *Gastroenterology* 2017

Old and New Definitions of CD Disease Severity

Old: Symptoms Only

– CDAI and other indices

New: Include endoscopy

– Deep ulcerations on endoscopy
– SES-CD >6 is mod/severe

New: Consider Prognosis

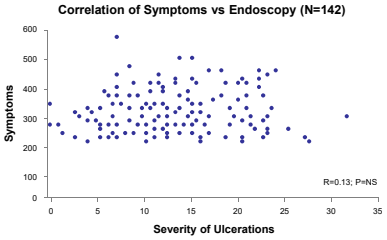
Poor Prognostic factors
- Young age
- Extensive bowel involvement
- Perianal/ Severe Rectal Disease
- Penetrating/stenosing at diagnosis

The greater the number of poor prognostic factors, the worse the prognosis

Only 20-30% of CD patients will have an indolent course

Lichtenstein GR, et al. Am J Gastroenterol. 2018 Apr;113(4):481-517.

Symptoms Often Do Not Correlate with Inflammation

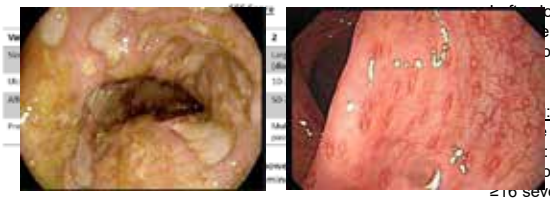


NS = not significant.

Modigliani R, et al. *Gastroenterology*. 1990;98(4):811-818.

Endoscopic Scoring

Simple endoscopic score (SES-CD)



Segments:
Rectum
…on
…erse
…olon

…: mild
…oderate
…≥16 severe

Daperno, M et al. Gastroinestin Endosc. 60, 505-512 (2004)

ACG Crohn's disease guideline: Treatment Goals

- Mucosal healing as a goal of therapy
  - Endoscopic scores to monitor response due to lack of correlation between symptoms and endoscopy
  - Evaluation within 1 year of resection for postoperative endoscopic recurrence to guide therapy
  - Fecal biomarkers (calprotectin, lactoferrin) may have a role in non-invasive monitoring of response to therapy
- Patient QoL as a goal of therapy
  - Attention to management of stress, anxiety and depression

Lichtenstein GR, et al. Am J Gastroenterol. 2018 Apr;113(4):481-517.

Definitions of Endoscopic Targets

- Mucosal healing: complete absence of mucsal ulceration in the bowel
  - For UC: absence of friability, blood, erosions, and ulcers in all visualized segments of the gut mucosa
  - For CD: absence of ulcers
- Endoscopic remission: typically defined as cut offs on various scores
  - For UC: Mayo endoscopic score 0 or 1
  - For CD: CDEIS of <3
- Histo-endoscopic healing: lack of mucosal ulceration + Geboes score based criteria (neutrophil infiltration is <5% of crypts)
- Deep remission: clinical (PRO based) remission + complete mucosal healing

Treat-to-Target in UC: STRIDE Guidelines

Composite Endpoint

Clinical/PRO Remission AND **Endoscopic Remission**

Clinical/PRO Remission

Defined as resolution of rectal bleeding and normalization of bowel habit
- Should be assessed at minimum of 3 mos during active disease
- Patients' individual goals (eg, QoL< mood disorders, fatigue, work productivity) should also be addressed: normalization of QoL as ultimate goal

Endoscopic Remission

Defined as resolution of friability and ulceration at flexible sigmoidoscopy or colonoscopy (Mayo 0–1)
- Should be assessed within 3–6 mos after start of therapy

Adjunctive Measures of Disease Activity That May Be Useful in Selected Cases
- **Biomarkers:** CRP and fecal calprotectin are adjunctive measures of inflammation, not targets, for monitoring UC
- **Histology** is a sensitive measure of inflammation but is not a target due to lack of evidence of clinical utility

Adapted from Peyrin-Biroulet L, et al. *Am J Gastroenterol*. 2015;110(9):1324-1338.

Treat-to-Target in CD: STRIDE Guidelines

Composite Endpoint

Clinical/PRO Remission AND **Endoscopic Remission**

Clinical/PRO Remission

Defined as resolution of abdominal pain and normalization of bowel habit
- Assessed at minimum of 3 mos during active disease
- Patients' individual goals should also be addressed

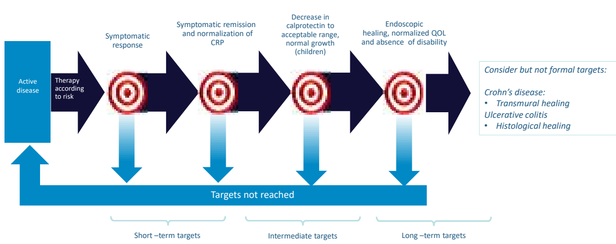
Endoscopic Remission

Defined as resolution of ulceration
- Should be assessed within 6–9 mos after start of therapy
- When endoscope cannot adequately evaluate inflammation, assess resolution inflammation by cross-sectional imaging

Adjunctive Measures
- **Biomarkers:** CRP and fecal calprotectin are adjunctive measures of inflammation, not targets, for monitoring CD
- **Histology:** Histologic remission is not considered a target

Adapted from Peyrin-Biroulet L, et al. *Am J Gastroenterol*. 2015;110(9):1324-1338.

Proposed Update to STRIDE: (STRIDE 2) Treatment Targets in Both CD and UC



Turner D, et al. *Gastroenterology*. 2020

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Are We Ready to Apply Treat-to-Target to IBD?

- Shared decision-making between patient and provider
- Primary goal: maximize health-related quality of life
  - Control of symptoms
  - Prevention of progressive structural damage
  - Normalization of function and social participation
- Reduction of inflammation is the most important means to achieve goals
- *Treatment to target by measuring disease activity and adjusting therapy accordingly optimizes outcomes*

Smolen JS, et al. *Ann Rheum Dis*. 2010;69(4):631-637.

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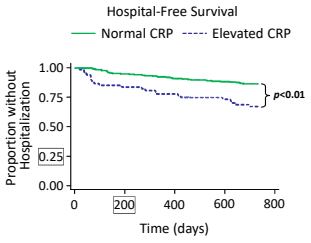
Histologic + Endoscopic Remission as a Predictor of Reduced Oral Steroid Use and Hospitalization in UC

N=91	ENDO Remission + HISTO Activity N=14	HISTO + ENDO Remission N=42	P-value
Patients requiring oral CS (63% overall)	79% (11/14)	43% (18/42)	*P*=0.02
Patients requiring hospitalization (22% overall)	36% (5/14)	12% (5/42)	*P*=0.04

Bryant RV et al. *Gut.* 2016 Mar;65(3):408-14.

'Silent' Crohn's Patients Have 2-Fold Higher Risk of Hospitalizations

- 351 CD patients with clinical remission
- More patients with elevated CRP admitted compared to normal CRP
  - (33% vs 13%, P<0.0001)
- Quiescent patients with CRP elevation at increased risk of relapse within 1-2 years



Click B, et al. *Inflamm Bowel Dis.* 2015;21(10):2254-61.

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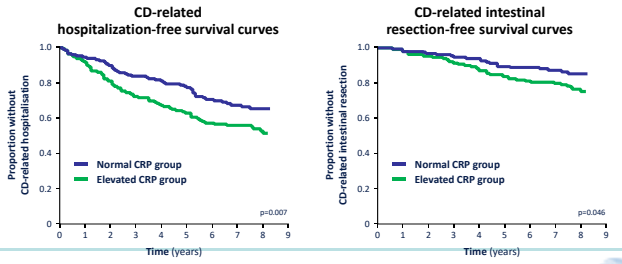
Impact of Subclinical Inflammation on CD-related Outcomes



Oh K, et al. *PLoS One* 2017;12:e0179266.

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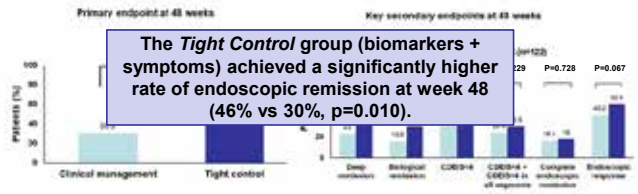
CALM: Substitution of Biomarkers for Endoscopy-based Monitoring to Optimize Mucosal Healing

Clinical Management (CM) vs Treat-to-Target (Tight Control, TC)
Importance of Noninvasive Biomarkers



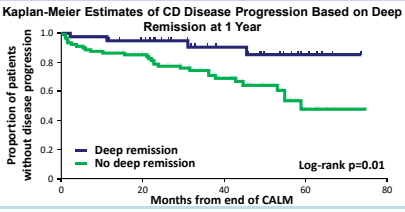
The *Tight Control* group (biomarkers + symptoms) achieved a significantly higher rate of endoscopic remission at week 48 (46% vs 30%, p=0.010).

Mucosal Healing: (CDEIS<4) and no deep ulcerations

Colombel et al. *Lancet* 2017; 390: 2779-2789.

CALM Follow-up: Impact of Induction of Deep Remission on Disease Progression in CD

CD patients achieving endoscopic or deep remission after 1Y of tight control are less likely to have disease progression* over a median of 3Y



*Disease progression defined as composite of new internal fistula/abscess, stricture, perianal fistula/ abscess, CD hospitalization, or CD surgery since end of CALM

Ungaro R et al Gastroenterology. 2020 Mar 26:S0016-5085(20)30390-.

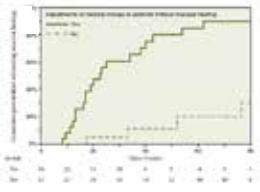
CALM: Lessons Learned and Clinical Implications

- ✓ "The CALM trial demonstrated better clinical and biochemical outcomes by utilizing a tight control algorithm, including C-reactive protein and fecal calprotectin (FCP), compared to symptom-driven decision-making alone in patients with moderate-to-severe CD"
- ✓ Majority of biomarker-based adjustments occurred due to elevations in FCP as opposed to CRP
- ✓ We should incorporate non-invasive markers of disease activity in order to achieve this goal

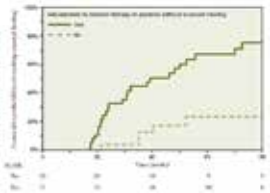
Pouillon L and Peyrin-Biroulet L J Crohns Colitis. 2018 Mar 28;12(4):509
Colombel et al., Effect of tight control management on Crohn's disease (CALM): a multicenter, randomized, controlled phase 3 trial. Lancet 2018; 390: 2779-2789.

Retrospective Assessment of Treatment Adjustments Demonstrates Feasibility of Achieving MH in UC and CD

Ulcerative Colitis[1]



Crohn's Disease[2]



Bouguen G, et al. *Inflamm Bowel Dis*. 2014;20(2):231-239.[2] Bouguen G, et al. *Clin Gastroenterol Hepatol*. 2014;12(6):978-985.

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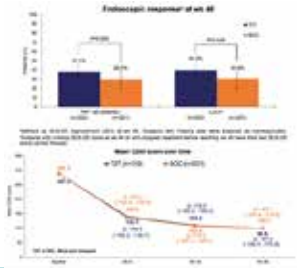
STARDUST: Treat-to-target vs standard of care with ustekinumab in CD

- Phase 3b trial of moderate/severe CD patients who failed conventional therapy or 1 biologic treatment
- **Treat to Target Arm:**
  - Wk 16 endoscopy: ΔSES-CD
    - <25%→q8w; ≥25%→q12w
  - Maintenance goals
    - CDAI <220 and ≥70-point decrease from BL
      AND
      Normal CRP or FC
    - Interval decreased if not met
- **Standard of Care Arm**
  - q12w maintenance if wk 16 response
    - No wk 16 endoscopy
  - If no wk 16 response, can receive 90 mg SC dose at clinician discretion
  - Flare evaluation and dose adjustment as per clinician and label

BL, baseline; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; EU SmPC, European Union Summary of Product Characteristics; FC, fecal calprotectin; LOCF, last observation carried forward; LTE, long-term extension; NRI, nonresponder imputation; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease; SOC, standard of care; T2T, treat-to-target
Danese S, et al. UEG 2020, LB11

STARDUST: Treat-to-target vs standard of care with ustekinumab in CD

- Primary endpoint:
  - Wk 48 endoscopic response (defined as ≥50% reduction in SES-CD from baseline)
- 441/500 pts re-randomized at wk 8
  - T2T n=220
  - SOC n=221
- Wk 48 completion: 79.1% T2T vs 87.3% SOC
  - Similar improvements in SES-CD, mucosal healing, steroid-free endoscopic response, CDAI, and biomarkers between groups
  - No new safety signals



CDAI, Crohn's Disease Activity Index; LOCF, last observation carried forward; NRI, nonresponder imputation; NS, nonsignificant; SES-CD, Simple Endoscopic Score for Crohn's Disease; SOC, standard of care; T2T, treat-to-target
Danese S, et al. UEG 2020, LB11

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  - CALM trial
  - STARDUST trial
- **Strategies for monitoring**
- Summary

Treatment of Inflammatory Bowel Disease (IBD)

- Medical management focuses on:
  - Symptom relief
  - Mucosal (and histological healing)
  - Preventing bowel damage
  - Preventing long-term complications
    - Prevent dysplasia or colectomy in UC
    - Prevent stricturing disease/surgery in CD
- Stages of medical therapy:
  - Achieve clinical/endoscopic remission
  - Maintain remission and prevent flares

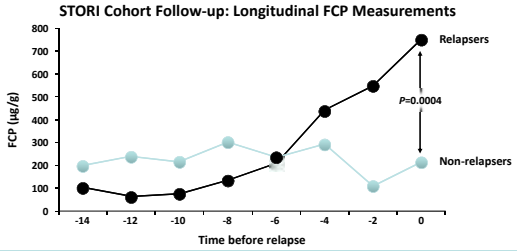

Colon with Mayo 3 Ulcerative Colitis


Ileum with Crohn's disease


Normal colon


Normal ileum

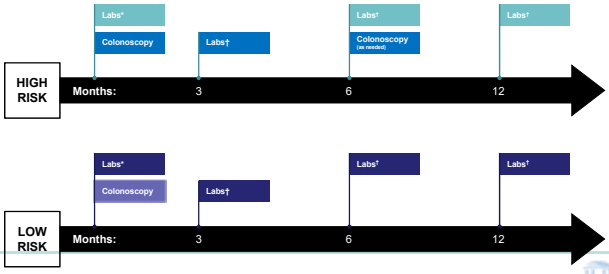
Consecutive FCP Measurements for Early Prediction of Clinical Relapse



N=113; Luminal CD patients; ≥1 year on IFX plus immunosuppressant; in stable remission without steroids ≥6 months.
FCP, fecal calprotectin.

Louis E, et al. *Gastroenterology*. 2012;142:63–70.

Sample Monitoring Algorithm for Adjusting Treatment to Treat to Target



*Baseline CRP and/or fecal calprotectin levels. †Including follow-up CRP and/or fecal calprotection levels.

Summary: Treating to Target in IBD Clinical Practice

- Determine disease severity to guide management of IBD
  - Risk factors for more aggressive disease as well as clinical symptoms
- Goals include endoscopic as well as PRO remission
  - While histologic healing is associated with good prognosis – not a goal at this time
- "Silent" inflammation is associated with disease related complications
- CALM demonstrated that treat to target utilizing a "tight control" approach w/ anti-TNF and thiopurine improved endoscopic remission in CD
  - Those in deep remission were less likely to progress over the subsequent 3 years
- STARDUST demonstrated that treat to target with ustekinumab was not associated with a significant improvement in clinical or endoscopic response at 48 weeks
- Monitoring strategies should include biomarkers like CRP, fecal calprotectin and repeat endoscopic evaluation at intervals determined through shared decision making

UNC Multidisciplinary IBD Center

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"Therapeutic drug monitoring in IBD"

Disclosures: Consulting Fee: Pfizer

Learning Objectives:

- Recognize the different inflammatory bowel diseases
- Describe the role of therapeutic d rug monitoring

Therapeutic drug monitoring (TDM) is an important tool in caring for patients with inflammatory bowel disease (IBD) on biologic therapies and is defined as the measurement of drug concentrations and anti-drug antibodies (ADA). Biologic therapies are potentially immunogenic, and the development of ADA can result in drug discontinuation. With anti-TNF therapy, up to 1/3rd of patients experience primary non-response and up to 50% experience secondary loss of response at 1 year, often due to ADA and low drug levels.

There is little controversy in using reactive TDM in response to primary nonresponse or secondary loss of response with biologic therapy. Reactive TDM helps guide therapeutic decisions going forward when there is a lack of response to biologic therapy. Conversely, proactive TDM in patients who are experiencing response or remission to biologic therapy has been controversial. However, there is growing evidence supporting proactive TDM use with anti-TNF agents. The use of proactive TDM for non-anti-TNF biologic therapies is not currently supported.

The accompanying slides will provide an overview of the role of TDM in patients with IBD including definitions, review of society guidelines/consensus statements, review of the evidence for proactive TDM, optimal drug levels, and strategies to reduce immunogenicity (ADA).

Recommended readings:

1. Papamichael K, et al. Appropriate Therapeutic Drug Monitoring of Biologic Agents for Patients With Inflammatory Bowel Diseases. Clin Gastroenterol Hepatol. 2019 Aug;17(9):1655-1668.e3. doi: 10.1016/j.cgh.2019.03.037. Epub 2019 Mar 27. PMID: 30928454; PMCID: PMC6661210.
2. Feuerstein JD, et al. American Gastroenterological Association Institute Clinical Guidelines Committee. American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. Gastroenterology. 2017 Sep;153(3):827-834. doi: 10.1053/j.gastro.2017.07.032. Epub 2017 Aug 3. PMID: 28780013.
3. Kennedy NA, et al; UK Inflammatory Bowel Disease Pharmacogenetics Study Group. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. Lancet Gastroenterol Hepatol. 2019 May;4(5):341-353. doi: 10.1016/S2468-1253(19)30012-3. Epub 2019 Feb 27. PMID: 30824404.

THERAPEUTIC DRUG MONITORING IN IBD

UAB Division of Gastroenterology & Hepatology 2021 Update

Kirk Russ, MD
Assistant Professor

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

OBJECTIVES

- Define and understand the role of therapeutic drug monitoring (TDM) in inflammatory bowel disease (IBD)
- Understand the evidence behind proactive TDM
- Learn optimal drug levels for available biologic agents
- Learn strategies to reduce immunogenicity (anti-drug antibodies)

DEFINITION

Therapeutic drug monitoring (TDM) is the assessment of drug concentration +/- anti-drug antibodies (ADA)

PROACTIVE VS REACTIVE

- Reactive TDM – measurement of drug concentration and ADA in patients with loss of response
- Proactive TDM –measurement of drug concentration and ADA in responders during induction and/or maintenance

WHY DO WE DO TDM?

- Biologic medications are proteins and thus potentially immunogenic
- Positive correlation between drug concentration and favorable therapeutic outcomes
- Up to 1/3rd of patients experience primary non-response to anti-TNFs
- 50% of patients experience secondary loss of response at 1 year to anti-TNFs
- ADAs and suboptimal PK (low levels) are most common causes for loss of response for anti-TNF therapies

APPROPRIATE TIMES FOR TDM

- Appropriate (i.e. reactive TDM):
  - End of induction in primary non-responders
  - Secondary non-responders
  - Restarting after drug-holiday (before 2nd infusion)
  - Treatment cessation in deep remission
- Less certain (i.e. proactive TDM)
  - At end of induction in responders
  - During first year of maintenance in responders

Melmed GY et al. CGH 2016.

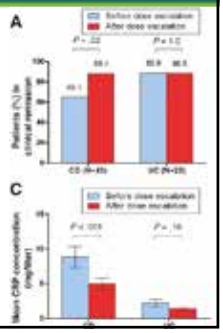
WHAT DO THE EXPERTS SAY?

- AGA Guideline TDM in IBD 2017
  - In adult patients with quiescent IBD treated with anti-TNF agents, the AGA makes **no recommendation regarding the use of routine proactive therapeutic drug monitoring**.
- Australian TDM Consensus 2017:
  - In patients in clinical remission following anti-TNF induction and periodically in patients in clinical remission, **TDM should be considered to guide management**
- ACG Guideline UC 2019
  - There is **insufficient evidence** supporting a benefit for proactive therapeutic drug monitoring **in all unselected patients with UC in remission.**
- BRIDGe Group Consensus Panel 2019
  - **For anti-TNF therapies, proactive TDM was found to be appropriate after induction and at least once during maintenance therapy**, but this was not the case for the other biologics

WHAT IS THE EVIDENCE FOR PROACTIVE TDM?

TAXIT TRIAL

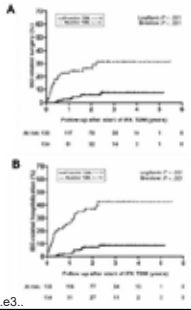
- Proactive TDM of infliximab vs Clinically-based dosing
- Failed to meet primary endpoint: clinical and biochemical remission at 1 year (64.3 vs 62.3%, p=0.79)
- Proactive TDM was associated with ↓ frequency of undetectable drug concentrations, ↓ risk of relapse; also ↓ CRP, and ↑ remission rates in CD but not UC
- Also cost effective



Vande Casteele et al. Gastroenterology. 2015 Jun;148(7):1320-

PAPAMICHAEL K, ET AL. CGH 2017.

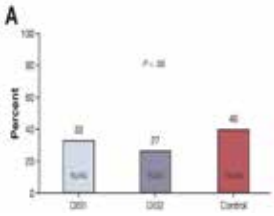
- Retrospective, real-world study of 264 patients with IBD receiving infliximab maintenance therapy.
- Compared proactive (n = 130) vs reactive (n = 134) drug monitoring
- Proactive TDM with reduced risk for:
  - treatment failure HR 0.16; *P* < .001
  - IBD-related surgery HR, 0.30; *P* = .017
  - IBD-related hospitalization HR, 0.16; *P* < .001
  - Antibodies to infliximab HR, 0.25; *P* = .025
  - Serious infusion reaction HR, 0.17; *P* = .023



Papamichael K, et. al. Clin Gastroenterol Hepatol. 2017 Oct;15(10):1580-1588.e3..

TAILORIX TRIAL

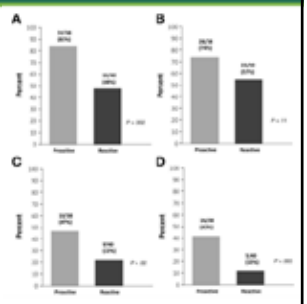
- Double-blind trial in 122 biologic-naïve adult patients with CD receiving infliximab + immunomodulator
- Dose escalation of infliximab based on TDM + biomarkers vs symptoms alone
- The primary endpoint was sustained corticosteroid-free clinical remission from weeks 22 through 54 with no ulcers at week 54



D'Haens G, et. al.. Gastroenterology. 2018 Apr;154(5):1343-

PAILOT TRIAL

- Pediatric CD trial, 80 patients randomized to proactive or reactive drug monitoring of adalimumab
- Primary endpoint: sustained corticosteroid free clinical remission (PCDAI<10) from week 8 to week 72
- Proactive TDM + tight control superior to reactive TDM + tight control



Assa A, et. al. Gastroenterology. 2019 Oct;157(4):985-99

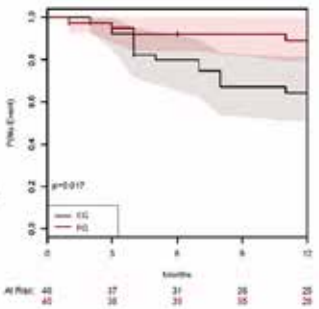
OPTIMIZED MONOTHERAPY

- Retrospective study, 83 patients with IBD, comparing proactive TDM with monotherapy infliximab (n=16) vs control group on monotherapy infliximab (n=32) vs patients on combination therapy with infliximab + immunomodulator (n=35)
- Examined the frequency of IFX discontinuation, ADAs, infusion reactions, and IFX concentrations during the first year of treatment
- No difference in IFX discontinuation between proactive TDM with monotherapy infliximab and combination therapy groups
- More antibodies in control group on monotherapy infliximab

Lega S, Dubinsky, M, et. al. Inflamm Bowel Dis. 2019 Jan 1;25(1):134-

PRECISION TRIAL

- Randomized 80 IBD patients in clinical remission receiving IFX maintenance treatment to IFX dosing guided by proactive TDM vs continued treatment without dose adaptations.
- Primary endpoint was the proportion of patients in sustained clinical remission after 1 year.



Strik AS, et al. Scand J Gastroenterol. 2021

WHAT ABOUT OTHER BIOLOGICS?

- Low rates of immunogenicity (ADA) with vedolizumab (4%) and ustekinumab (2.3%) in phase 3 clinical trials
- Evidence for TDM mostly dose-response relationship studies
- No strong evidence to support proactive TDM with these agents at this time
- Reactive monitoring still appropriate in patients with primary nonresponse or secondary loss of response

A NOTE ABOUT LAB ASSAYS

- Some lab assays can measure antibodies in presence of drug
- Some only measure drug level and reflex to antibody testing if drug level undetectable
- Use caution when interpreting drug tolerant assays

WHAT ARE THE OPTIMAL DRUG LEVELS?

- It depends…
  - Disease activity
  - Type of disease (e.g. perianal Crohn's disease)
  - Outcome of interest
  - Induction vs Maintenance

Papamichael K, et. al. Clin Gastroenterol Hepatol. 2019 August;17(9): 1655–1668.e3

TDM CHEAT SHEET

- With a goal of mucosal healing on maintenance therapy:

Drug	Goal Trough Concentration (µg/ml)
Infliximab	>10
Adalimumab	>10
Certolizumab pegol	>15
Golimumab	Unknown; >1-2.5?
Vedolizumab	>15
Ustekinumab	>4.5

Papamichael K, et. al. Clin Gastroenterol Hepatol. 2019 August;17(9): 1655–1668.e3

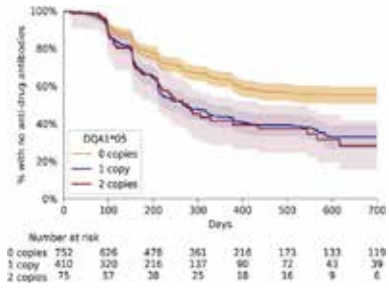
PANTS CONSORTIUM

- Personalized Anti-TNF Therapy in Crohn's Disease (PANTS)
- Prospective cohort study, 1610 eligible patients with active CD from 120 UK sites
- Optimal week 14 drug levels associated w/ week 54 clinical remission
  - Infliximab 7mg/L
  - Adalimumab 12 mg/L
- Anti-drug antibodies at week 54
  - Infliximab 62.8%
  - Adalimumab 28.5%
- Immunomodulators reduced risk of ADAs by 60% for both infliximab and adalimumab

Kennedy NA, et. al. Lancet Gastroenterol Hepatol. 2019 May;4(5):34

HLA DQA1*05 ALLELE

- GWA study from PANTS study to identify variants associated with immunogenicity
- HLA-DQA1*05 allele, carried by approximately 40% of Europeans, increased the rate of immunogenicity by hazard ratio of 1.90
- Prometheus RiskImmune



Sazonovs A, et al; PANTS Consortium. Gastroenterology. 2020 Jan;158(1):

SUMMARY

- TDM is an important and helpful tool for IBD patients on biologic therapies
- Reactive TDM helps determine which direction to go when treatment not working
- Growing evidence for proactive TDM with anti-TNF therapy and makes sense
- Don't give up on therapies without dose-escalation to try and achieve adequate drug levels
- Immunomodulators reduce immunogenicity for anti-TNFs
- Consider HLA DQA1*05 testing for biologic naïve patients

QUESTIONS?

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"The role of surgery in IBD"

Disclosures: **None**

Learning Objectives:

- Describe surgical approaches to the management of IBD complications
- Understand optimal outcomes in IBD-related surgeries

A. Crohn's Disease and Surgery

a. Surgery continues to play an important role in the treatment of Crohn's Disease. Metanalysis results estimate that the cumulative rate of surgery is 16% at 1 year after diagnosis, 33% at 5 years, and 47% at 10 years.

b. The medical treatment for Crohn's disease has significantly changed with the introduction of biologic therapies beginning in 1998 (infliximab). It remains controversial whether these new therapies have actually decreased the percentage of patients undergoing surgery for Crohn's disease or whether this has simply changed the presentation and timing for surgery.

c. The various ages, presentations, location, and behavior types of Crohn's disease mandate flexibility and individualized treatment strategies from the Crohn's disease surgeon.

d. Indications for surgery in Crohn's Disease include:

i. Acute indications: Severe enteritis/enterocolitis, hemorrhage, perforation

ii. Chronic: Fistula, stricture, neoplasia/malignancy, resistance to medical therapy

e. Principles of Surgery in Crohn's Disease

i. Surgery is not curative: Leave asymptomatic disease and perform conservative resection margins. There is no benefit to extended resections or obtaining microscopic negative margins.

ii. Crohn's mesentery can be challenging: the surgeon should be prepared to deal with intraoperative techniques to control blood loss in thick and fragile mesentery.

iii. Be prepared with all reconstructive options for unexpected scenarios. In general, anastomotic type does not impact long-term outcomes. Emerging data on use of Kono-S anastomosis for decreasing recurrence needs to be monitored.

iv. Bowel can be an innocent bystander. Preoperative endoscopy plays an important role in the decision for repair or resection of sigmoid colon in treatment of an ileal-sigmoid fistula.
v. Preoperative abscess should be drained and considered for delayed surgery.
vi. Surgery should be performed using minimally invasive approaches as possible.

f. Management of Medications around surgery:

i. Preoperative steroid use increases postoperative complications and should be weaned before surgery as possible.
ii. Immunomodulators are not associated with increase postoperative complications and do not have to be weaned.
iii. The risk of biologic therapy for postoperative complications is controversial. A typical perioperative management strategy includes holding the preoperative dose and/or timing surgery following one-half life of the drug.

g. Postoperative recurrence: ¼ of patients will require a second surgery within 5 years of their first surgery. Postoperative medical therapy should be considered for high risk patients which include: Age < 30, active smoking, penetrating disease phenotype, history of 2 or more surgery, perianal disease.

B. <u>Ulcerative Colitis and Surgery</u>

a. Surgery remains an important tool for the treatment of ulcerative colitis. Rates of colectomy in ulcerative colitis have been reported as 4.8% within 1 year after diagnosis, 9.5% within 5 years of diagnosis, and 15.2% within 10 years of diagnosis.

b. Indications for surgery in Ulcerative Colitis:

i. Acute indications: Toxic colitis refractory to meds, hemorrhage, perforation
ii. Chronic indications: Refractory Symptoms, Neoplasia/Malignancy

c. Surgical Option in Ulcerative Colitis

i. Preferred: Total proctocolectomy with ileal anal j pouch (stapled vs. hand-sewn). Can be done in three or two stages based on patient disease presentation.
ii. Total Proctocolectomy with end ileostomy. Can be done in 1-2 stages.
iii. Other options that are much less frequently used include total proctocolectomy with continent ileostomy, total abdominal colectomy with ileal-rectal anastomosis, and Turnbull blow-hole (historical).

d. Pouch Function

i. Despite patient age or age of the pouch, patients can have excellent function (on average 6 bowel movements/day with 1-2 being at night).
ii. Patients are overall very satisfied with having a pouch: 96-98% would recommend the surgery to others or would undergo surgery again.
iii. To optimize pouch function and obtain fewer number of stools per day, the pouch needs to completely empty. This is best achieved by maintaining liquid stools, allowing the time for pouch to empty by gravity, and having a proper pouch construction without stenosis or twists.

Suggested readings:

The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Surgical Management of Crohn's Disease. Dis Colon Rectum 2020; 63:1028-1052. https://fascrs.org/ascrs/media/files/downloads/crohns-CPG-2020.pdf

Practice Parameters for the Surgical Treatment of Ulcerative Colitis. Dis Colon Rectum 2014; 57:5-22. https://fascrs.org/ascrs/media/files/downloads/Clinical%20Practice%20Guidelines/practice_parameters_for_the_surgical_treatment_of-3.pdf

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Department of Surgery

UAB 2021 UPDATE IN GASTROENTEROLOGY, HEPATOLOGY, & ADVANCED ENDOSCOPY:

Role of Surgery in IBD

Robert Hollis MD MSPH
Assistant Professor
Division of Gastrointestinal Surgery

@UABSurgery

Disclosures

None

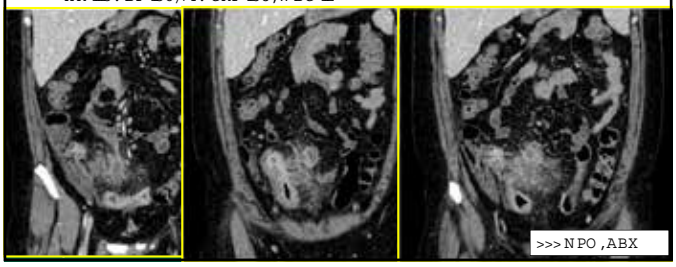
Role of Surgery in IBD

- Crohn's Disease
- Ulcerative Colitis

- ✓ Case scenarios
- ✓ Indications
- ✓ Surgical Considerations

Crohn's Disease Case

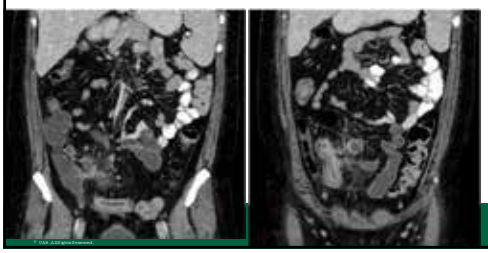
30 YO F with no PMH presented with 2 weeks of abdominal pain with worsening nausea/vomiting and new fevers.
HR 115. BP 136/74. CRP 188, WBC 12



Crohn's Disease Case

5

7 days later.. still unable to tolerate PO intake, AFVSS, CRP 22



Crohn's Disease Case 1

6

- TPN
- Preoperative ostomy marking
- Laparoscopic ileocectomy, takedown of ileal-ileal fistula with small bowel resection/anastomosis, end ileostomy
- 3 months later:
  - Ileoscopy/Colonoscopy
  - Laparoscopic end ileostomy takedown with end to side anastomosis
- Postop medical therapy: ADA + AZA

Crohn's Disease and Surgery

7

Results of Meta analysis for Risk of Intestinal Surgery in Crohn's disease

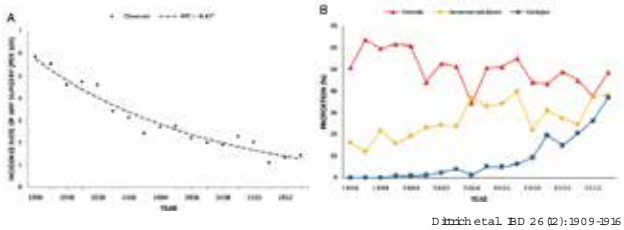
Cumulative risk of surgery:

1 year after diagnosis: 16%
5 year after diagnosis: 33%
10 year after diagnosis: 47%

Frolkis et al. Gastroenterology 2013;145 (5):996-1006

Crohn's Disease and Surgery

8



Dittrich et al. IBD 26 (12):1909-1916

Montreal Classification

Variable	
Age at diagnosis (yr)	A1, ≤ 16
	A2, 17–39
	A3, ≥ 40
Location	L1, ileal
	L2, colonic
	L3, ileocolonic
	L4, isolated upper disease*
Behavior	B1, non-stricturing, non-penetrating
	B2, stricturing
	B3, penetrating
	p, perianal disease modifier*

Crohn's Disease: Surgical Indications

Acute

- Severe enteritis/enterocolitis
- Hemorrhage
- Perforation
  - Free
  - Contained

Chronic

- Fistula
- Stricture
- Neoplasia/Malignancy
- Resistance to medical therapy

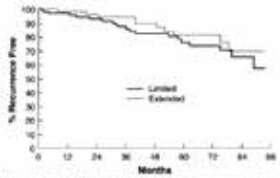
PRINCIPLES OF SURGERY IN CROHN'S DISEASE

- SURGERY IS NOT CURATIVE
  - Leave asymptomatic disease
  - Conservative resection margins

Effect of Resection Margins on the Recurrence of Crohn's Disease in the Small Bowel

A Randomized Controlled Trial

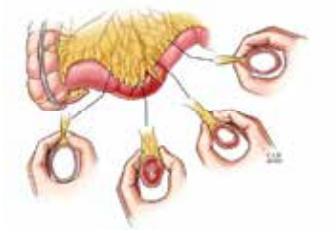
Fazio et al. Ann Surg. 1996;224(5):563-71.



Conclusion

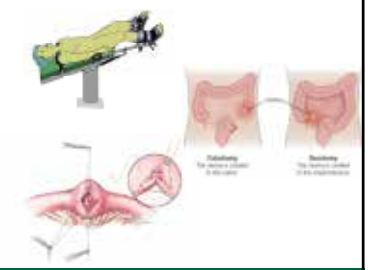
Recurrence of CD is unaffected by the width of the margin of resection from macroscopically involved bowel. Recurrence rates also do not increase when microscopic CD is present at the resection margins. Therefore, extensive resection margins are unnecessary.

PRINCIPLES OF SURGERY IN CROHN'S DISEASE



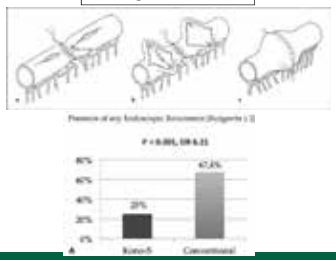
PRINCIPLES OF SURGERY IN CROHN'S DISEASE

- SURGERY IS NOT CURATIVE
  - Leave asymptomatic disease
  - Conservative resection margins
- CROHN'S MESENTARY CAN BE CHALLENGING
- BE PREPARED FOR ALL RECONOPTIONS



Surgical Prevention of Anastomotic Recurrence by Excluding Mesentery in Crohn's Disease: The SuPREMe-CD Study - A Randomized Clinical Trial

Ann Surg 2020;272:210-217

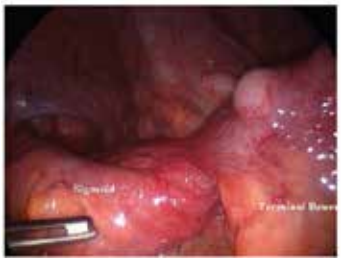


The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Surgical Management of Crohn's Disease

4. Following ileocecal resections, reconstruction using side-to-side, side-to-end, or end-to-end handsewn or stapled anastomosis based on surgeon preference and experience is reasonable. Grade of recommendation: Strong recommendation based on low-quality evidence; 1C.

DCR 2020;63:1028-1052

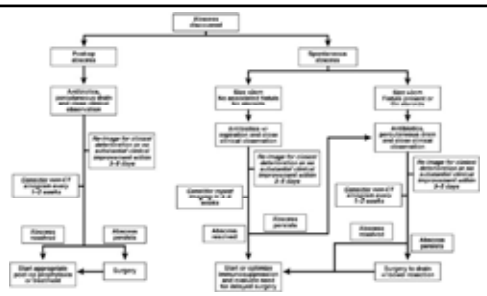
PRINCIPLES OF SURGERY IN CROHN'S DISEASE



- BOWEL CAN BE AN INNOCENT BYSTANDER

PRINCIPLES OF SURGERY IN CROHN'S DISEASE

- SURGERY IS NOT CURATIVE
  - Leave asymptomatic disease
  - Conservative resection margins
- CROHN'S MESENTARY CAN BE CHALLENGING
- BE PREPARED WITH ALL OPERATIVE OPTIONS
- BOWEL CAN BE AN INNOCENT BYSTANDER
- PREOP ABSCESS SHOULD BE DRAINED AND CONSIDERED FOR DELAYED SURGERY



Clinical Gastroenterology and Hepatology 2011;9:842-850.

PRINCIPLES OF SURGERY IN CROHN'S DISEASE

- SURGERY IS NOT CURATIVE
  - Leave asymptomatic disease
  - Conservative resection margins
- CROHN'S MESENTARY CAN BE CHALLENGING
- BE PREPARED WITH ALL OPERATIVE OPTIONS
- BOWEL CAN BE AN INNOCENT BYSTANDER
- PREOP ABSCESS SHOULD BE DRAINED AND CONSIDERED FOR DELAYED SURGERY
- MINIMALLY INVASIVE AS POSSIBLE

SURGICAL RISKS WITH MEDS?

1. Preoperative high-dose glucocorticoids increase the risk of postoperative infectious complications and attempts should typically be made to wean glucocorticoids before surgical intervention. Immunomodulators are not associated with increased risk of postoperative infectious complications and do not typically need to be held before surgery. Grade of recommendation: Strong recommendation based on low-quality evidence, 1C.

2. Whether or not preoperative exposure to monoclonal antibody therapy influences outcomes remains controversial, but delaying surgical intervention based on monoclonal antibody therapy alone is not typically recommended. Grade of recommendation: Weak recommendation based on low-quality evidence, 2C.

WEAN STEROIDS PREOP
CONTINUE IMMUNOMODULATORS PREOP

BIOLOGICS = CONTROVERSIAL
>>> typically hold preop dose or time surgery after one-half life

The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Surgical Management of Crohn's Disease

Importance of postop medical therapy

- ¼ of patients will require a second surgery within 5 years.

HIGH RISK FOR POSTOPERATIVE RECURRENCE:

- Age < 30
- Active Smoking
- Penetrating Disease
- 2 or more Surgery
- Perianal Disease

Baumgart and Sandborn. Lancet 2012. 380 (9853):1590-1605.
AGA Guidelines, ASCRS Guidelines

Ulcerative Colitis Case

- 28 YOM with UC
  - Diagnosed 2 months prior with rectal bleeding + diarrhea, endoscopic confirmation
    - PO steroid + mesalamine
    - Hospitalization #1 (7 days): IV steroids, entyvio
    - Hospitalization #2 (6 days): IV steroids
    - Returns with recurrent severe symptoms:
      - Abdominal tenderness, 50 lbs weight loss
      - 8 bloody BM/24 hrs
      - Afebrile, HR 117
      - Hg 7.0, CRP 200
      - CT = no perforation

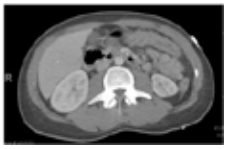


TABLE 17-2 Clinical Criteria for the Severity of Ulcerative Colitis

Criterion	Mild Disease	Severe Disease	Fulminant Disease
Stools per day	<4	>6	>10
Blood in stool	Infrequent	Frequent	Continuous
Temperature, °C	Normal	>37.5	>37.5
Heart rate, beats per minute	Normal	>90	>90
Hemoglobin	Normal	<75% of baseline	Transfusion required
Erythrocyte sedimentation rate, mm/hr	<30	>30	>30
Abdominal radiograph	—	Edema	Dilation of colon
Clinical signs	—	Abdominal tenderness	Abdominal tenderness and distention

Modified from Truelove SC, Witts LJ. Cortisone in ulcerative colitis: final report on a therapeutic trial. BMJ. 1955;2:1041-1048.

Ulcerative Colitis Case

- Urgent Laparoscopic total abdominal Colectomy

6 months later:

+50 lbs, energetic, working

- Laparoscopic completion proctectomy with ileal anal pouch anastomosis, diverting loop ileostomy

Ulcerative Colitis and Surgery

Results of Meta analysis for Risk of Colectomy in Ulcerative colitis

Cumulative risk of surgery:

1 year after diagnosis: 4.8%
5 year after diagnosis: 9.5%
10 year after diagnosis: 15.2%

Clinical Gastroenterology and Hepatology
2020;1542-3565(20)31497

Ulcerative Colitis: Surgical Indications

Acute

- Toxic colitis refractory to meds
- Hemorrhage
- Perforation

Chronic

- Refractory symptoms
- Neoplasia/Malignancy

Surgical Options

- Total proctocolectomy with ileal anal pouch anastomosis
  - 3-stg vs 2 stg
- Total proctocolectomy with end ileostomy
  - 2-stg vs 1 stage
- Other
  - Total proctocolectomy with continent ileostomy
  - Total abdominal colectomy with ileal rectal anastomosis
  - Turnbull blow hole

Prospective, Age-Related Analysis of Surgical Results, Functional Outcome, and Quality of Life After Ileal Pouch-Anal Anastomosis

Annals of Surgery 2003;238(2):221-228

Prospective, Age-Related Analysis of Surgical Results, Functional Outcome, and Quality of Life After Ileal Pouch-Anal Anastomosis

Annals of Surgery 2003.238 (2):221-228

TABLE 7. Social, Work and Sexual Restrictions in Patients Undergoing Proctocolectomy and IPAA, Grouped by Age at Time of Surgery

	Age (Year)							
	≤45	46–55	56–65	>65	Total	P	Test?	Multivariable
Social restrictions (%)	12	13	11	28	13	0.13	F	0.23
Work restrictions (%)	11	12	10	14	12	0.70	F	0.34
Sexual restrictions (%)	12	16	17	33	14	0.013	F*	0.035*
Would undergo surgery again (%)	96	96	96	89	96	0.24	F	0.59
Recommend IPAA to others (%)	98	97	96	96	98	0.30	F	0.80

TECHNICAL NOTE

The Implications of Pouch Physiology

James Church, M.B., Ch.B., F.R.A.C.S. Disease of Colon and Rectum 2019;62:510-512

Suggestions for Surgeons:

- Stapled J pouch is best design
- Avoid any twists
- S pouch needs short spout
- If very frequent stools – look out for stenosis or twists

Suggestions for Patients

- Pouch empties by gravity and works best with liquids stools
- Better emptying = fewer stools
- Miralax can actually help
- Undigested food can block pouch

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM Department of Surgery

UAB 2021 UPDATE IN GASTROENTEROLOGY, HEPATOLOGY, & ADVANCED ENDOSCOPY:

Role of Surgery in IBD

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"Persistent symptoms in celiac disease despite a gluten free diet"

Disclosures: None

Learning Objectives:

- Be able to name 4 diagnostic criteria for celiac disease
- Discuss the role of HLA typing
- Utilize a systematic approach to evaluate symptoms despite treatment

Diagnostic Criteria of Celiac Disease

1. History and physical
    a. Symptoms, physical findings, and abnormal labs, tests prompt further evaluation for celiac disease, including:
        i. Gastrointestinal symptoms (Remember: non classical symptoms such as constipation)
        ii. Extra-intestinal symptoms
        iii. Lab, test abnormalities: anemia, elevated LFTs, osteoporosis
    b. Screening the general population for celiac disease is *not* recommended at this time
    c. Patients with family history of first degree relative with celiac disease should be screened for celiac disease
2. Serologic testing*
    a. Tissue transglutaminase (tTG) IgA is the best serologic test
        i. Not reliable in patients with IgA deficiency → Check serum IgA level
    b. Deamidated gliadin peptide (DGP) IgG is the best test in patients with IgA deficiency
3. Biopsies confirm diagnosis*
    a. Three histologic characteristics
        i. Villous atrophy
        ii. Crypt hyperplasia
        iii. Increased intraepithelial lymphocytes (IELs)
    b. Small bowel involvement is patchy
    c. Take 4 bites from the distal duodenum and 1-2 bites from the duodenal bulb
4. Response to treatment (gluten free diet)
    a. Clinical, serologic, and histologic response

*These tests are dependent on adequate gluten exposure (i.e., at least once slice of wheat bread per day for at least 2 weeks)

Role of HLA Typing in Celiac Disease Diagnosis and Management

- Celiac Disease only occurs in people with genetic predisposition

- Thus, patients with celiac disease must carry at least one copy of HLA-DQ2 or HLA-DQ8
- HLA status does not change over a person's life
- HLA-DQ2/DQ8 is common in the US population
    - 30-40 people out of 100 people in the US carry at least one copy of HLA-DQ2 or HLA-DQ8
    - Only 1 of these 30-40 people go on to develop Celiac Disease in their lifetime
- Other genetic and environmental factors contribute to Celiac Disease diagnosis
- HLA status is best used to *exclude* Celiac Disease when negative

Systematic Approach to Evaluate Symptoms on a Gluten Free Diet

- Symptoms are common on a gluten free diet
- Symptoms can result from
    - Acute or chronic gluten exposure
    - A complication of Celiac Disease or its treatment (i.e., refractory sprue, post inflammatory IBS, metabolic syndrome)
    - A condition related to Celiac Disease (i.e., hypothyroidism, adrenal insufficiency)
    - Another gastrointestinal condition (i.e., functional gastrointestinal disorder, heartburn)
    - Unrelated conditions (i.e., fibromyalgia, migraines)
- Consider the following key steps in evaluating symptoms in a patient with treated Celiac Disease

1. Confirm Celiac Disease Diagnosis
    - Review symptoms, signs, serologies, initial pathology from diagnosis
        - Look for histologic features of Celiac Disease Mimickers
    - Consider HLA typing
        - If HLA typing is not permissive, evaluate for another condition
2. Obtain thorough history of symptoms, medication review, and dietary adherence
3. Are symptoms from chronic, ongoing gluten exposure?
    - Dietitian referral to identify sources of gluten exposure
    - Labs that may indicate non-adherence (i.e., tTG, CBC, vitamin levels)
    - Repeat EGD with duodenal biopsies to assess for histologic remission which is typically achieved within 2 years of a gluten free diet
4. Are symptoms from a complication of celiac disease or a gluten free diet?
    - Exocrine pancreatic insufficiency
    - Refractory sprue
    - Pelvic floor dysfunction
    - Thiamine deficiency
    - Weight gain, metabolic syndrome leading to obstructive sleep apnea, type 2 diabetes
5. Are symptoms from a functional gastrointestinal disorder?
    - Patients with celiac disease should also undergo empiric trials of PPIs, anti-spasmodics, neuromodulators, etc as indicated

Recommended readings:

1. Silvester JA, Therrien A, Kelly CP. Celiac Disease: Fallacies and facts. Am J Gastroenterol. 2021;116(6):1148-1155.

2. Oxentenko AS, Murray JA. Celiac Disease: Ten things that every gastroenterologist should know. Clin Gastroenterol Hepatol. 2015;13(8):1396-404.
3. Caio G, Volta U, Sapone A, Leffler DA, De Giorgio R, Catassi C, Fasano A. Celiac disease: A comprehensive current review. BMC Med. 2019;17(1):142.

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Persistent Symptoms in Celiac Disease

Amanda Cartee, MD
Assistant Professor

Disclosures

- None

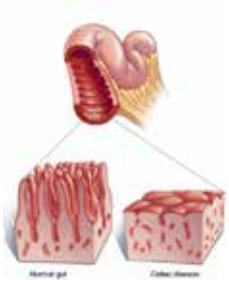
Objectives

1. Name 4 diagnostic criteria
2. Discuss the role of HLA typing
3. Utilize a systematic approach to evaluate symptoms

Celiac Disease

- Immune-mediated inflammation of the small intestine
- Gluten exposure
- At-risk genes
  - HLA-DQ 2,8
- Completely resolves when gluten is removed

The only autoimmune disorder in which we know the environmental stimulus (gluten)!



1970s shag carpet

Tile floor

mayoclinic.org

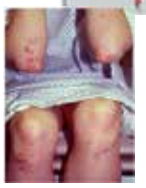
Celiac Disease Epidemiology

- 1% US population
- Any age
- Various racial groups[1,2]
  - Even described in China[3]
- Diverse symptoms
  - Malabsorptive symptoms
  - Constipation
  - Extra-intestinal
    - Headaches
    - Arthralgias
    - "Brain fog"
  - No symptoms

But abnormal tests (labs, DEXA)

Personal, family hx high risk condition

China: 2.85% in IBS patients



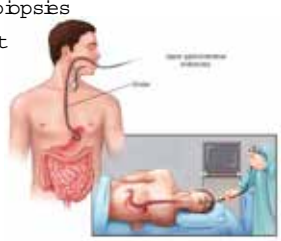
Dermatitis herpetiformis

Murray. Mayo Clinic Going Gluten Free. 2014
[2]Singh P. Clin Gastroenterol Hepatol. 2013;[illegible]
[3]Kou. J Dig Dis. 2013;[illegible]
[illegible].com

Multiple Findings Contribute to Diagnosis

1. History and physical (a reason to test)
2. Serologic test(s)
3. Endoscopy with small bowel biopsies
4. Response to a gluten free diet
   - Clinical, symptomatic
   - Serologic
   - Histologic

HLA testing may aid in diagnosis in certain circumstances



Rubio-Tapia et al. Am J Gastroenterol. 2013

Serologies Are the First Diagnostic Test

Test	Sensitivity (%)	Specificity (%)
Tissue Transglutaminase (tTG)		
tTG IgA	98	98
tTG IgG	70	95
Deamidated Gliadin Peptide (DGP)		
DGP IgA	88	95
DGP IgG	80	98
Anti-Gliadin Antibody (AGA)		
AGA IgA	85	90
AGA IgG	85	80
Endomysial Antibody (EMA)	95	99

Lefler DA. Am J Gastroenterol. 2010;105(2):2520-2524.

Serology Take Home Points: the tTG

- tTG IgA is the test of choice
- Different lab kits for tTG
  - Variation in lab reference range
  - Not always comparable between labs
- Must first obtain IgA levels
  - tTG IgA will not be elevated in someone with IgA deficiency
- Limited utility of tTG IgG
  - May be helpful in IgA deficiency
  - Can be elevated in non-celiac gluten sensitivity

Rubio-Tapia et al. Am J Gastroenterol. 2013

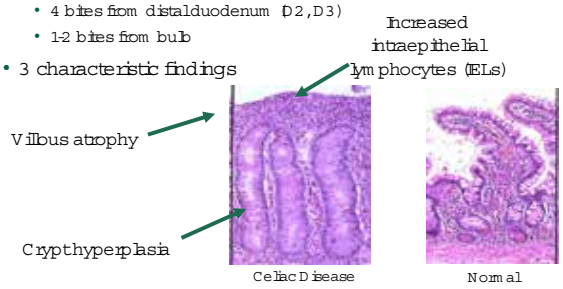
Serology Take Home Points: Deamidated Gliadin Peptide (DGP) IgG

- Best test in patients with selective IgA deficiency
  - tTG IgG may be elevated in this scenario
- Confusing nomenclature
  - Some labs call this test the anti-gliadin peptide

Rubio-Tapia et al Am J Gastroenterol 2013

Small Bowel Biopsies are Confirmatory

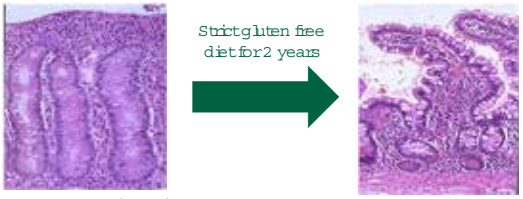
- Villous atrophy is patchy
- Multiple biopsies from multiple sites are needed
  - 4 bites from distal duodenum (D2, D3)
  - 1-2 bites from bulb
- 3 characteristic findings



Rubio-Tapia et al Am J Gastroenterol 2013.
Latorre M et al Gastrointestinal Endoscopy. 2015

Response to a Gluten Free Diet

- Clinical, serologic, and histologic response
- Symptoms, signs resolve (~weeks to months)
- tTG returns to normal (~1 year)
- Small bowel heals



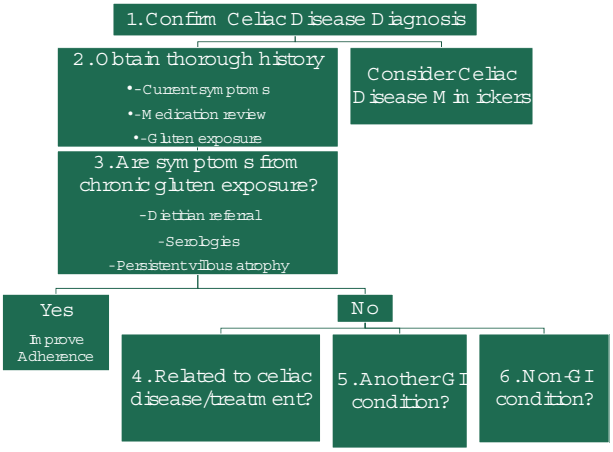
Persistent Symptoms Are Common

- Many people report symptoms despite a gluten free diet
  - Chronic, daily vs intermittent
  - Gastrointestinal +/- extra-intestinal
- Follow up is poor
- Persistent or recurring symptoms are a common reason for consultation

Edwards George JB. J Clin Gastroenterol 2021
Herman ML. Clin Gastroenterol Hepatol 2012.

Five Categories of Causes of Persistent Symptoms

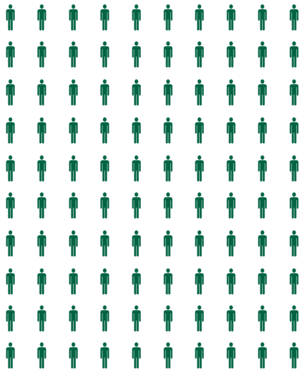
1. Acute or chronic gluten exposure
2. Complication of celiac disease or gluten free diet
3. Condition related to celiac disease
4. Another gastrointestinal condition
5. Another extra-intestinal condition



1. Confirm Celiac Disease Diagnosis

- Review symptoms prior to diagnosis
- Review serologies at diagnosis
  - 5% seronegative celiac disease
- Review EGD, path results at diagnosis
  - Subtle histologic findings suggest another etiology
- Improvement in symptoms, serologies
- HLA testing helpful to exclude celiac disease

Celiac Disease Genetic Predisposition



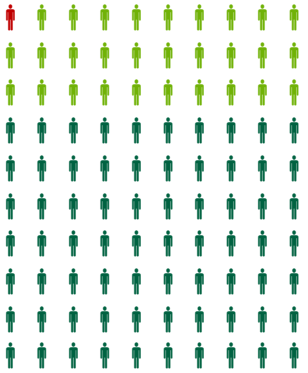
100 people

Celiac Disease Genetic Predisposition

100 people

30 people carry HLA-DQ2/8

Celiac Disease Genetic Predisposition



100 people

30-40 people carry HLA-DQ2/8

1 has Celiac Disease

High Negative Predictive Value

Never develop celiac disease

What are you most likely to see on pathology review?

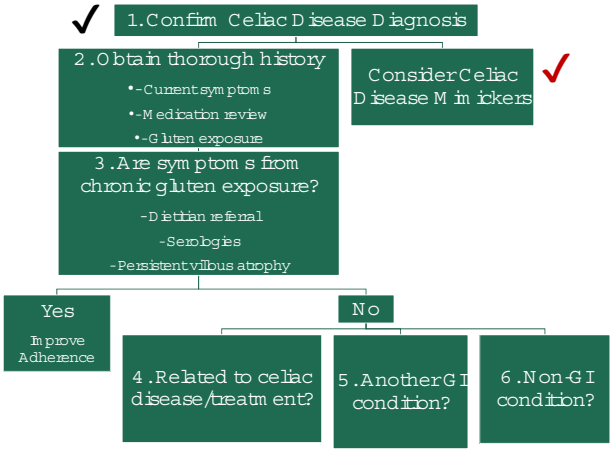
- 56 year old woman
- Frequent sinus infections and pneumonias
- At diagnosis 3 years ago, 20 bowel movements/day
- Index EGD with biopsy showed villous atrophy
- No symptomatic or histologic response on a strict gluten free diet
- HLA testing is negative

A. Clonal population of T cells
B. Lack of plasma cells
C. Lack of goblet cells
D. Collagenous band

Know "Celiac Mimickers"

- Olmesartan associated enteropathy (OAE) is a cause of non-celiac villous atrophy
  - Collagenous sprue
  - Collagenous colitis
  - Other high potency ARBs: irbesartan, telmisartan, valsartan
- Autoimmune enteropathy
  - Lack of goblet cells
  - Anti-enterocyte antibody (serum)
- Common Variable Immunodeficiency (CVID)
  - Lack of plasma cells
  - Low serum immunoglobbulins

Jansson-Knodell Mayo Clin Proc. 2018.



2. Obtain Detailed History

- Relation to eating
- Similar to "celiac symptoms"
  - Before diagnosis
  - With known gluten exposure
- New medications
  - Can develop medication associated villous atrophy
  - Gluten in prescription medications – rare
  - Supplements claiming to break down gluten
    - Not FDA Approved
- Ask about inadvertent and intentional gluten exposure
  - Ask several always

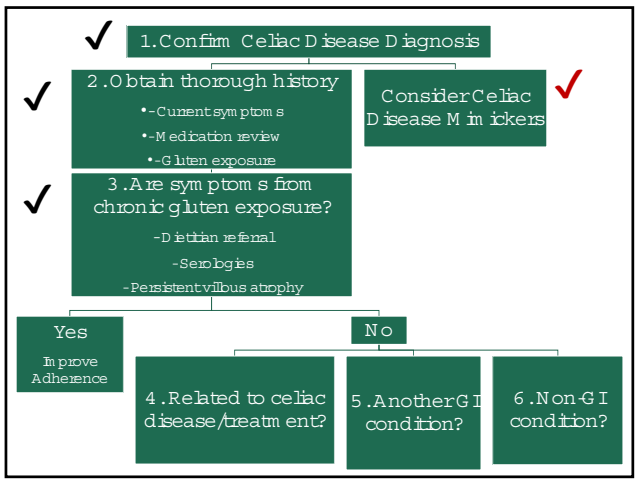
3. Are symptoms from gluten exposure?

Chronic Exposure

- Non-specific symptoms
  - New onset if previously asymptomatic
- Dietary history
- Elevated tTG IgA
- Villous atrophy
- Tx: Improve adherence

Acute Exposure

- Intermittent
  - Nausea +/- vomiting
  - Bloating
  - Fatigue
  - Headaches
- 0.5-2 hours of exposure
- Normal tTG IgA
- Normal histology
- Tx: Symptomatic



4. Are Symptoms Related to Celiac Disease or Its Treatment?

- Celiac Disease Related Conditions
  - Microscopic colitis
  - Autoimmune thyroid disease: Annual TSH
- Celiac Disease Complications
  - Refractory celiac disease
  - Exocrine pancreatic insufficiency
  - Post-inflammatory IBS
- Gluten Free Diet Complications
  - Weight gain
  - Thiamine deficiency (gluten free alternatives not fortified)

Patient with Celiac Disease and Recurrent Fatigue x 6 months

Diagnosis 5 years ago
• Fatigue, diarrhea, anemia • Serologies 4X ULN • Total villous atrophy

Patient with Celiac Disease and Recurrent Fatigue x 6 months

Diagnosis 5 years ago	5 years ago - Now
• Fatigue, diarrhea, anemia • Serologies 4X ULN • Total villous atrophy	• Strict gluten free diet • Symptoms, anemia resolved • Serologies normalized • Small bowel healed

Patient with Celiac Disease and Recurrent Fatigue x 6 months

Diagnosis 5 years ago	5 years ago - Now	Now
• Fatigue, diarrhea, anemia • Serologies 4X ULN • Total villous atrophy	• Strict gluten free diet • Symptoms, anemia resolved • Serologies normalized • Small bowel healed	• No changes in diet • No diarrhea or weight loss • Normal Hb • Serologies, histology normal

Patient with Celiac Disease and Recurrent Fatigue x 6 months

On further history and exam

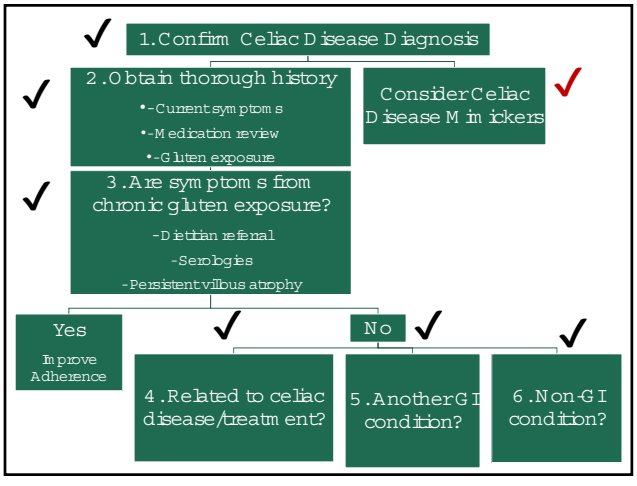
- Gained 30 pounds on a gluten free diet, now overweight
- New onset snoring
- Witnessed apneic episodes
- Diagnosed with obstructive sleep apnea

Take Home Points

- Counsel patients about potential for weight gain
- Consider complications of weight gain, metabolic syndrome

5. Symptoms From Another GI Condition
6. Symptoms from Non-GI Condition

- Patients can have conditions unrelated to celiac disease
- Gastrointestinal conditions
  - GERD
  - IBS
  - Eosinophilic gastroenteritis
  - Gastroparesis
  - Trial PPI, anti-spasmodic, neuromodulators
- Non-Gastrointestinal conditions
  - Migraines, tension headaches
  - Fibromyalgia



Evaluating Persistent Symptoms Summary

1. Confirm the diagnosis
   - The patient may have been misdiagnosed with celiac disease
2. Determine if the symptoms are from gluten exposure
   - Detailed history and physical is key!
3. Patients with celiac disease can have other GI and non-GI medical conditions
4. Metabolic syndrome can be a consequence of the gluten free diet

Questions?

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University of Alabama at Birmingham
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"Updates in colon polypectomy guidelines"

Disclosures: Stock/shareholder (directly purchased): Merck, Johnson & Johnson, Astra Zeneca, Kimberly Clark, Proctor & Gamble

Learning Objectives:

- Understand updates on new recommendations for intervals between colonoscopies
- Review updates on recommended polypectomy techniques

Colon cancer is the third most common malignancy affecting both men and women despite seeing a steady decline. (1) It is thought that colonoscopy has helped decrease the risk of colon cancer and mortality. A common clinical scenario encountered by physicians is determining the timing of surveillance interval after completing colonoscopy. In 2020, a consensus update by the US Multi-Society Task Force on Colorectal Cancer released updated guidelines on recommendations for follow up after colonoscopy and polypectomy. The aim of this talk is to highlight important changes from the previous 2012 guidelines and rational for those changes.

An important update and consistent theme is the importance of high-quality colonoscopy. Features that are highlighted to ensure high quality colonoscopy include examination complete to the cecum, attention to complete polypectomy and proportion of examinations with adequate preparation. (2) The update also recommends ensuring achievement and monitoring of adequate adenoma detection rates for the endoscopist. (2)

There were several surveillance interval changes with a major change to extend the interval for patients with 1-2 tubular adenomas <10mm in size. The previous 2012 guidelines suggested an interval between 5-10 years, however the 2020 guidelines recommend extending this to 7 to 10 years. (2, 3) This recommendations stems from several studies showing the risk of metachronous advanced adenoma was similar to patients with a normal colonoscopy. (2) Other interval changes include patients with 3-4 adenomas <10mm in size which allowed for the option to extend the interval to 3 to 5 years rather than 3 year interval recommended in 2012. This option also extends from studies suggesting that the risk of metachronous advanced adenoma for patients with 3-4 <10mm adenomas was similar to those patients with 1-2 low risk adenoma. (2) Most of the recommendations in the 2020 guideline update extended intervals, however in patients with >10 tubular adenomas the interval decreased to 1 year. In 2012, this was previously set at less than 3 years, but due to the concern of patients with >10 polyps having an association with a polyposis syndrome and one study suggesting the risk for metachronous advanced adenoma was ~26 % the interval was changed to 1 year.(2)

Further details and expanded review can found with review of the ***"Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer."***

Suggested readings:

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin. 2021 Jan;71(1):7-33. doi: 10.3322/caac.21654. Epub 2021 Jan 12. Erratum in: CA Cancer J Clin. 2021 Jul;71(4):359. PMID: 33433946.
2. Gupta S, Lieberman D, Anderson JC, Burke CA, Dominitz JA, Kaltenbach T, Robertson DJ, Shaukat A, Syngal S, Rex DK. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2020 Mar;91(3):463-485.e5. doi: 10.1016/j.gie.2020.01.014. Epub 2020 Feb 7. PMID: 32044106; PMCID: PMC7389642.
3. Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2012 Sep;143(3):844-857. doi: 10.1053/j.gastro.2012.06.001. Epub 2012 Jul 3. PMID: 22763141.

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Review of Updated Recommendations for Follow up After Colonoscopy and Polypectomy

Chad Burski, MD

Previous Guidelines 2012

Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2012 Sep;143(3):844-857. doi: 10.1053/j.gastro.2012.06.001. Epub 2012 Jul 3. PMID: 22763141

Caveat to the Guidelines

- Applied to patients with Average Risk
  - Not applied to patients with:
    - Family history of colon cancer
    - Inflammatory Bowel Disease
    - Hereditary syndromes
    - Personal history of colon cancer
- High Quality Examination

Gupta S, Lieberman D, Anderson JC, Burke CA, Dominitz JA, Kaltenbach T, Robertson DJ, Shaukat A, Syngal S, Rex DK. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2020 Mar;91(3):463-485.e5. doi: 10.1016/j.gie.2020.01.014. Epub 2020 Feb 7. PMID: 32044106; PMCID: PMC7389642

High Quality Examination

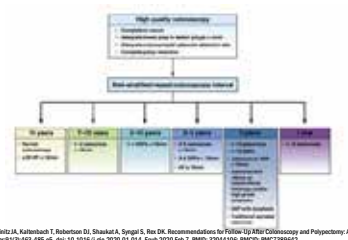
- Must have a high-quality colonoscopy
  - Adequate bowel Prep
  - Complete exam to the cecum
  - Complete polypectomy
- Completed by a high quality endoscopist
  - Adenoma detection rate >30% in men
  - Adenoma detection rate >20% in women

Gupta S, Lieberman D, Anderson JC, Burke CA, Dominitz JA, Kaltenbach T, Robertson DJ, Shaukat A, Syngal S, Rex DK. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2020 Mar;91(3):463-485.e5. doi: 10.1016/j.gie.2020.01.014. Epub 2020 Feb 7. PMID: 32044106; PMCID: PMC7389642

Risk for Colon Cancer

- Colonoscopy reduces risk for the incident of Colorectal Cancer
- Studies suggest that in patients with adenoma, even with resection, are at increased risk of CRC when compared to the general population.
  - When stratifying for advanced vs non-advanced polyps, patients with the advanced adenoma was associated with a 2.2 fold increase in CRC when compared to the general population.
  - Patient's with nonadvanced adenoma was associated with a reduced risk of CRC compared to the general population.
- Leading to the statement:
  - Surveillance colonoscopy after baseline removal of adenoma with high risk features may reduce the risk for incident CRC but impact on fatal CRC is uncertain.

Gupta S, Lieberman D, Anderson JC, Burke CA, Dominitz JA, Kaltenbach T, Robertson DJ, Shaukat A, Syngal S, Rex DK. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2020 Mar;91(3):463-485.e5. doi: 10.1016/j.gie.2020.01.014. Epub 2020 Feb 7. PMID: 32044106; PMCID: PMC7389642



Gupta S, Lieberman D, Anderson JC, Burke CA, Dominitz JA, Kaltenbach T, Robertson DJ, Shaukat A, Syngal S, Rex DK. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2020 Mar;91(3):463-485.e5. doi: 10.1016/j.gie.2020.01.014. Epub 2020 Feb 7. PMID: 32044106; PMCID: PMC7389642

Repeat in 10 years

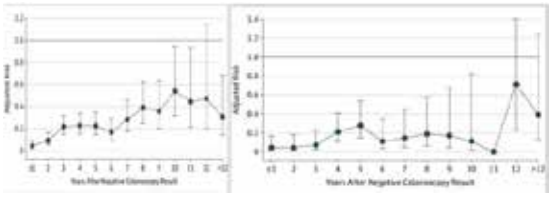
- Normal Colonoscopy
  - Including ≤20 Hyperplastic polys <10mm
- No Change from Prior Recommendations
- Modeling studies still support repeat colonoscopy.

Gupta S, Lieberman D, Anderson JC, Burke CA, Dominitz JA, Kaltenbach T, Robertson DJ, Shaukat A, Syngal S, Rex DK. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2020 Mar;91(3):463-485.e5. doi: 10.1016/j.gie.2020.01.014. Epub 2020 Feb 7. PMID: 32044106; PMCID: PMC7389642

Normal Colonoscopy

Several studies show decreased rate of CRC and mortality in patients who had normal colonoscopy.

One study:



Lee JK, Jensen CD, Levin TR, et al. Long-term Risk of Colorectal Cancer and Related Deaths After a Colonoscopy With Normal Findings. *JAMA Intern Med.* 2019;179(2):153-160. doi:10.1001/jamainternmed.2018.5565

<20 Hyperplastic Polyps less than 10mm

- No new data to suggest increased risk
- Prior data suggested similar risk to a normal colonoscopy

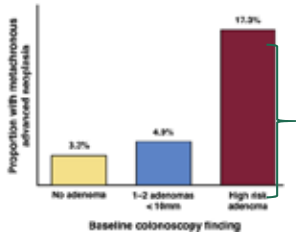
Gupta S, Lieberman D, Anderson JC, Burke CA, Dominitz JA, Kaltenbach T, Robertson DJ, Shaukat A, Syngal S, Rex DK. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2020 Mar;91(3):463-485.e5. doi: 10.1016/j.gie.2020.01.014. Epub 2020 Feb 7. PMID: 32044106; PMCID: PMC7389642

Repeat in 7-10 years

- 1-2 Tubular Adenoma, <10mm
- Previous recommendations repeat in range of 5-10 years
- UPDATED: Repeat in 7-10 years
- New evidence suggest that patients with low-risk adenoma have reduced risk of advanced neoplasia as well as the incident of CRC.

Gupta S, Lieberman D, Anderson JC, Burke CA, Dominitz JA, Kaltenbach T, Robertson DJ, Shaukat A, Syngal S, Rex DK. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2020 Mar;91(3):463-485.e5. doi: 10.1016/j.gie.2020.01.014. Epub 2020 Feb 7. PMID: 32044106; PMCID: PMC7389642

1-2 Tubular Adenoma <10mm



Size >10mm
High risk pathology
>3 polyps <10mm

Gupta S, Lieberman D, Anderson JC, et al. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. *Gastrointest Endosc* 2020;91(3):463-485.e5. doi:10.1016/j.gie.2020.01.014

Repeat in 5-10 years

- 1-2 Sessile Serrated Polyps <10mm

Gupta S, Lieberman D, Anderson JC, Burke CA, Dominitz JA, Kaltenbach T, Robertson DJ, Shaukat A, Syngal S, Rex DK. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2020 Mar;91(3):463-485.e5. doi: 10.1016/j.gie.2020.01.014. Epub 2020 Feb 7. PMID: 32044106; PMCID: PMC7389642

Repeat in 3- 5 years

- 3-4 Adenomas, <10mm
- 3-4 Sessile Serrate Polyps, <10mm
- Hyperplastic polyp ≥ 10mm

Gupta S, Lieberman D, Anderson JC, Burke CA, Dominitz JA, Kaltenbach T, Robertson DJ, Shaukat A, Syngal S, Rex DK. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2020 Mar;91(3):463-485.e5. doi: 10.1016/j.gie.2020.01.014. Epub 2020 Feb 7. PMID: 32044106; PMCID: PMC7389642

≥3 Adenomas, <10mm

- Previous 3-10 tubular adenoma repeat in 10 years
- UPDATED:
- 3-4 Tubular Adenomas <10mm repeat in 3-5 years
- 5 to 10 Tubular Adenomas repeat in 3 years

- Several studies looking at patients with 3-10 tubular adenoma <10mm
  - Consistent show increased risk of advanced polyps and CRC

Gupta S, Lieberman D, Anderson JC, Burke CA, Dominitz JA, Kaltenbach T, Robertson DJ, Shaukat A, Syngal S, Rex DK. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2020 Mar;91(3):463-485.e5. doi: 10.1016/j.gie.2020.01.014. Epub 2020 Feb 7. PMID: 32044106; PMCID: PMC7389642

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3-4 Adenoma, <10mm

- Task force reviewed several studies looking at this particular category
- Felt the risk for advanced neoplasia and CRC was low and in a few of the studies similar to those patients with 1-2 low risk adenoma
- Therefore recommended 3-5 year interval, with favor to five year but recognized the limited data

Gupta S, Lieberman D, Anderson JC, Burke CA, Dominitz JA, Kaltenbach T, Robertson DJ, Shaukat A, Syngal S, Rex DK. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2020 Mar;91(3):463-485.e5. doi: 10.1016/j.gie.2020.01.014. Epub 2020 Feb 7. PMID: 32044106; PMCID: PMC7389642

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Sessile Serrated Polyps

- Prior recommendations:
  - Sessile Serrated Polyps <10mm with no dysplasia - 5 years
  - Sessile Serrated Polyps ≥ 10mm or Sessile Serrated Polyp with dysplasia - 3 years

  Updated:

- New Recommendations:
  - 1-2 Sessile Serrated Polyps <10mm – 5 to 10 years
  - 3-4 Sessile Serrated Polyps <10mm – 3 to 5 years

Gupta S, Lieberman D, Anderson JC, Burke CA, Dominitz JA, Kaltenbach T, Robertson DJ, Shaukat A, Syngal S, Rex DK. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2020 Mar;91(3):463-485.e5. doi: 10.1016/j.gie.2020.01.014. Epub 2020 Feb 7. PMID: 32044106; PMCID: PMC7389642

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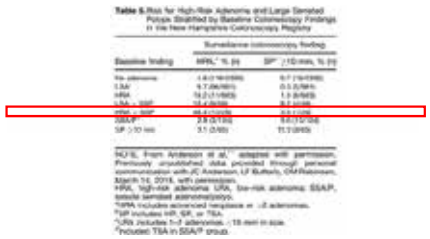
Sessile Serrated Polyps



Gupta S, Lieberman D, Anderson JC, Burke CA, Dominitz JA, Kaltenbach T, Robertson DJ, Shaukat A, Syngal S, Rex DK. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2020 Mar;91(3):463-485.e5. doi: 10.1016/j.gie.2020.01.014. Epub 2020 Feb 7. PMID: 32044106; PMCID: PMC7389642

Repeat in 3 years

- 5-10 Adenomas
- 5-10 Sessile Serrated Polyps
- Polyp >10mm
- High Grade Pathology
  - Villous or Tubulovillous Histology
  - High Grade Dyspasia
- Traditional Serrated Adenoma

- All unchanged from prior update

Gupta S, Lieberman D, Anderson JC, Burke CA, Dominitz JA, Kaltenbach T, Robertson DJ, Shaukat A, Syngal S, Rex DK. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2020 Mar;91(3):463-485.e5. doi: 10.1016/j.gie.2020.01.014. Epub 2020 Feb 7. PMID: 32044106; PMCID: PMC7389642

Repeat in 1 year

- ≥ 10 Adenomas

Gupta S, Lieberman D, Anderson JC, Burke CA, Dominitz JA, Kaltenbach T, Robertson DJ, Shaukat A, Syngal S, Rex DK. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2020 Mar;91(3):463-485.e5. doi: 10.1016/j.gie.2020.01.014. Epub 2020 Feb 7. PMID: 32044106; PMCID: PMC7389642

≥ 10 Adenomas

- Prior Recommendations repeat in < 3years
- UPDATED:
- Repeat in 1 year
  - Concern for increased risk of polyposis syndrome
  - One study showed risk of metachronous advanced adenoma was ~26%

Gupta S, Lieberman D, Anderson JC, Burke CA, Dominitz JA, Kaltenbach T, Robertson DJ, Shaukat A, Syngal S, Rex DK. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2020 Mar;91(3):463-485.e5. doi: 10.1016/j.gie.2020.01.014. Epub 2020 Feb 7. PMID: 32044106; PMCID: PMC7389642

Summary of Tubular Adenoma

Gupta S, Lieberman D, Anderson JC, Burke CA, Dominitz JA, Kaltenbach T, Robertson DJ, Shaukat A, Syngal S, Rex DK. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2020 Mar;91(3):463-485.e5. doi: 10.1016/j.gie.2020.01.014. Epub 2020 Feb 7. PMID: 32044106; PMCID: PMC7389642

Summary of Sessile Serrated Polyps

Gupta S, Lieberman D, Anderson JC, Burke CA, Dominitz JA, Kaltenbach T, Robertson DJ, Shaukat A, Syngal S, Rex DK. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2020 Mar;91(3):463-485.e5. doi: 10.1016/j.gie.2020.01.014. Epub 2020 Feb 7. PMID: 32044106; PMCID: PMC7389642

Key Updates

- Importance of high quality endoscopy
- 7-10 year option rather than 5-10 year for 1-2 tubular adenoma <10mm
- 1 year recommendation for >10 tubular adenoma removed
- Option for 3-5 year instead of 3 year for 3-4 tubular adenoma

Gupta S, Lieberman D, Anderson JC, Burke CA, Dominitz JA, Kaltenbach T, Robertson DJ, Shaukat A, Syngal S, Rex DK. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2020 Mar;91(3):463-485.e5. doi: 10.1016/j.gie.2020.01.014. Epub 2020 Feb 7. PMID: 32044106; PMCID: PMC7389642

Questions?

References

- 1. Gupta S, Lieberman D, Anderson JC, Burke CA, Dominitz JA, Kaltenbach T, Robertson DJ, Shaukat A, Syngal S, Rex DK. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2020 Mar;91(3):463-485.e5. doi: 10.1016/j.gie.2020.01.014. Epub 2020 Feb 7. PMID: 32044106; PMCID: PMC7389642
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- 3. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin. 2021 Jan;71(1):7-33. doi: 10.3322/caac.21654. Epub 2021 Jan 12. Erratum in: CA Cancer J Clin. 2021 Jul;71(4):359. PMID: 33433946.

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"Central neuromodulators in functional gastrointestinal disorders: is there method to the madness?"

Disclosures: **None**

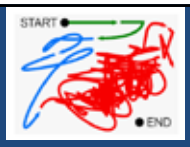
Learning Objectives:

- Define functional gastrointestinal disorders
- Understand the role of neuromodulators in treating FGIDs

Central neuromodulators (antidepressants, antipsychotics, other CNS targeted agents) are increasingly used in functional gastrointestinal disorders (FGIDs), now recognized as disorders of gut brain interaction (DGBI). However, the available evidence and guidance for the use of central neuromodulators in these conditions is scant and incomplete. The accompanying slides which follow will summarize the rationale for use and clinical experience to thereby provide a roadmap as guidance for therapy in these challenging disorders. This will include a summary of the pharmacology of central neuromodulation followed by recommendations for clinical use guided by the available clinical evidence. This evidence-based review on neuromodulators in FGID remains limited by small numbers of available controlled trials integrated with open-label studies and case series. General summary guidelines include:
(1) Low to modest dosages of tricyclic antidepressants provide the most convincing evidence of benefit for treating chronic gastrointestinal pain and painful FGIDs and serotonin noradrenergic reuptake inhibitors can also be recommended, though with less available data.
(2) Augmentation with the addition of a second treatment (adding quetiapine, aripiprazole, buspirone, or delta ligand agents) is recommended when a single medication is unsuccessful or produces side effects at higher dosage.
(3) Treatment should be continued for 6-12 months to potentially prevent relapse.
(4) Successful treatment requires effective communication skills to optimize the patient-provider relationship to thereby improve patient acceptance and adherence.

Suggested readings:

1. Drossman D, et al. Neuromodulators for Functional Gastrointestinal Disorders (Disorders of Gut-Brain Interaction): A Rome Foundation Working Team Report. Gastroenterology 2018;154:1140-1171
2. Tornblom H, et al. Psychotropics, Antidepressants and Visceral Analgesics in Functional Gastrointestinal Disorders. Current Gastroenterology Reports 2018;20:58
3. Sobi HW, et al. Central Neuromodulators for the Treatment of Functional GI Disorders: A Primer. Am J Gastroenterol 2017;112;693-702



Central Neuromodulator Primer for Use in Functional GI Disorders: Is there a Method to the Madness?

Frederick H. Weber Jr., M.D.
Clinical Professor
Division of Gastroenterology and Hepatology
2021

No disclosures

Outline

- Define FGID
- Rationale for central neuromodulators
- Important clinical pharmacology
- Literature review by disorder
  - Functional chest pain/heartburn
  - Functional dyspepsia
  - Chronic nausea and vomiting
  - Functional bowel disorders

FGID definition and background

- Symptoms arising in the absence of a defineable structural or biochemical abnormality
- Commonplace
- Often refractory to peripherally acting agents
- Psychiatric comorbidity common
- May respond to central neuromodulation

FGID (DGBI)

- Rome IV (2016): FGID as "disorders of *gut-brain interaction* with any combination of dysmotility, visceral hypersensitivity, altered mucosal and immune function, altered microbiota, and altered CNS processing"
- ENS & CNS hardwired → share similar neurotransmitters
- Stigma and perceptions of "antidepressants" limit effective pharmacotherapy
- Better: "neuromodulators" or "centrally targeted agents"

Rationale for central neuromodulator use in FGID

- Second line: augmenting peripheral agents
- Treat comorbid anxiety, depression, hypervigilance
- Reduce pain by down regulating visceral signals
- Capitalize on effects on GI motor function
- Some target nausea
- Neurogenesis: "rewire" CNS & ENS

FGID and central neuromodulation

- None FDA approved
- Knowledge of neurogastroenterology → outpaced regulatory approval
- Rationale: limited meta-analyses and clinical studies, expert opinion, and extrapolation from chronic somatic pain literature
- *Engage patient re-Rx rationale-"not psych med"*
- ** Goal = reduce symptom burden and improve QOL *rather than* complete symptom resolution

Central neuromodulator key treatment principles

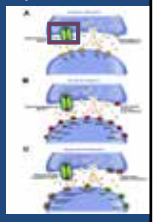
- Confident diagnosis
- Effective therapeutic relationship
- Legitimize disorder/ early side effects may dissipate /Rx effect delay
- Address perceptions about neuromodulators
- Know prior neuromodulator history

Central neuromodulator key treatment principles

- Negotiate treatment plan based on:
  - target symptoms
  - side effect profile
  - cost/availability
  - patient's prior experiences/preferences
- Early phone / portal contact to assess compliance and side effects

Central neuromodulators

- Act on neurotransmitter receptors and transporters
- Key monoamines released by neurons
  - serotonin
  - norepinephrine
  - dopamine
- Transporters allow reuptake into neurons
- Transporter reuptake blockade raises levels in synaptic cleft→ prolonged activity



Central neuromodulators

- Agents that ↑ serotonin or norepinephrine promote analgesia
- Agents that ↑ DA are stimulating and reduce sedation
- SERT inhibition: potent in SSRIs, SNRIs, and to lesser extent all TCAs
  - benefits depression
  - associated with nausea and diarrhea
- NET inhibition: SNRIs, TCAs, *NOT* SSRIs
  - promotes analgesia
  - treats depression
  - activation/sympathomimetic
  - mildly constipating

Central neuromodulators

- DAT inhibition:
  - activation/sympathomimetic
  - treats: depression
    - nausea
    - psychosis
- D2 receptor inhibition: ie; metoclopramide, domperidone, most antipsychotics
  - improves nausea
  - extrapyramidal side effects

Central neuromodulators

- 5HT1 receptor stimulation: ie; buspirone, sumatriptan
  - aids anxiety and depression
  - improves gastric compliance/accomodation
- 5HT3 receptor stimulation linked to pain, nausea, diarrhea
  - inhibitors benefit nausea (ondansetron, dolasetron, granisetron, mirtazepine, olanzapine) and diarrhea (ondansetron, alosetron)

Central neuromodulators

- M1 receptor inhibition: TCAs, paroxetine
  - may give anticholinergic side effects
  - dry mouth & constipation
  - distinguishes paroxetine from other SSRIs
- H1 receptor inhibition: all TCAs, atypical antipsychotics
  - sedation
  - weight gain

Central neuromodulators for GI TCAs

- Begin at 10-12.5 mg HS and increase weekly ("low and slow"); assess at 8-12 weeks
- HS to minimize sedation and orthostasis
- Carefully after age 65
- Minimum analgesic dose 25 mg/d
- IBS-D
- CAPS
- Functional CP/HB
- Functional dyspepsia
- Abdominal wall pain
- Anorectal pain

Central neuromodulators for GI TCAs

Benefits

Inhibit SERT and NET

Better than SSRIs for pain

Anticholinergic action benefits diarrhea

H1 action benefits insomnia

Liabilities

M1, H1, alpha 1 adrenergic, cardiac fast channel Na inhibition

Tertiary amines (amitriptyline, imipramine) → more side effects

Secondary amines favored for pain(?)

Side effects early and benefit may take 1 month +

Avoid if cardiac disease; baseline ECG if patient with cardiac conduction risk

Central neuromodulators in GI SSRIs

- *Not for pain* but adjunctive use for comorbid anxiety, phobias, depression, hypervigilance, somatization
- IBS-C
- Sertraline, citalopram, escitalopram
  - fewest drug-drug interactions
  - less cytochrome P450 effects
- Fluoxetine and paroxetine
  - Strong P450 isoenzyme 1A2 and 2D6 inhibition
  - more drug-drug interactions
  - SSRI discontinuation syndrome
    - fluoxetine long half life of 10-12 days- lowest risk
    - paroxetine half life < 1 day - highest risk

Central neuromodulators in GI SSRIs

- May be anxiogenic initially
  - start half usual starting dose 1st week
- Benefit delayed 3-4 weeks
- If severe functional impairment, consider clonazepam bridge
  - 0.25-0.5 mg BID for 4 weeks, then taper off

Central neuromodulators in GI SNRIs

- Evidence for effect on somatic pain
- Extrapolated use to visceral pain
- Similar pain benefit with less side effects than TCAs→ TCA failures or side effects limiting dose escalation
- CAPS
- Functional CP/HB
- IBS-C: less constipating than TCAs and pain relief > SSRIs
- Abdominal wall pain

Central neuromodulators in GI SNRIs

- Duloxetine best in FGID
- Venflaxine
  - SSRI at low doses→ need 150 mg/d + for NET inhibition for pain
  - more nausea than duloxetine
- Milnacipran (Savella) may be used for pain

Central neuromodulators in GI atypical antipsychotics

- Quietiapine, aripiprazole, olanzapine
- Pain relief via NET inhibition; D2 inhibition helps nausea
- Less risk of EPS side effects than typical antipsychotics ie; haloperidol
- Second line in GI as augmenting agents in FGID after TCA and/or SNRI failure
- May help anxiety and disordered sleep
- Painful IBS
- CAPS
- Metabolic effects (wt gain, DM, lipid elevation) and sedation greatest with quietiapine
- Olanzapine 5HT3 and D2 inhibition helps nausea

Central neuromodulators in GI miscellaneous agents

- Buspirone: 5HT1A agonist that enhances gastric fundic relaxation→ 15-45 mg/d in FD and postprandial distress syndrome, gastroparesis, rapid GE?
- Trazodone: blocks 5HT2/SERT/H1 receptor→ functional CP dosing at 75-150 mg HS
- Mirtazapine (15-45 mg HS): alpha 2 adrenergic agonist and blocks 5HT2, 5HT3 and H1 receptors
  - chronic nausea
  - dyspepsia
  - weight loss
  - insomnia

Central neuromodulators in GI miscellaneous agents

- Naltrexone
- mu receptor antagonist
- 50 mg/d originally used for narcotic antagonism in opioid addiction
- 50 mg/d used for refractory cholestatic pruritis
- Possible use for chronic pain at 0.5-4.5 mg/d
- Mechanism of action unknown-→ ? glial/immune cell modulator

Central neuromodulators side effect tips

- N/V with SSRIs, SNRIs less if taken with food
- Paroxetine if SSRI for IBS-D (anticholinergic)
- Fluoxetine, sertraline, bupropion less sedating
- Priapism rarely with trazodone
- Unmasking a bipolar disorder
- GIB with SSRIs – platelet dysfunction
  - OR 1.7-2.4 but 4.3-6.3 combined with NSAIDs

    Loke YK. APT 2007;27:31-40 Anglin R. AJG 2014;109:811-819
  - OR 4 for post-PEG bleeding on SSRIs

    Richter JA. GIE 2011;74:22-34

Central neuromodulators side effect tips

- Serotonin syndrome
  - fever, muscle rigidity, tachycardia, Sz, dilated pupils
  - high doses or multiple serotinergic medications
  - triptans, tramadol, ondansetron, linezolid can contribute
- Hepatotoxicity rare: dose adjustment in decompensated cirrhosis
  - DILI Network: 7/899 cases due to duloxetine

    Chalasani NP . AJG 2014;109:950-66
- Discontinuation
  - if SSRI/SNRI > 4 weeks, taper by 25% /week

FGID general treatment principles

- Begin with peripheral agents acting directly on gut
- Add central neuromodulators as second line especially if pain or comorbid psychiatric cofactors
- Augment with dual TCA/SNRI/SSRI third line
- Miscellaneous agents or atypical antipsychotics selectively targeting dominant symptom ie;
  - quietiapine for pain
  - olanzapine for nausea
  - buspirone for PDS, satiety, postprandial fullness
  - mirtazapine for PDS with weight loss, anorexia, nausea/vomiting, dyspepsia

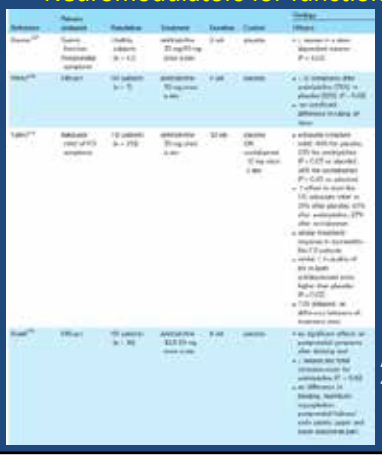
Table 2. Randomized Controlled Trials of Neuromodulators for the Treatment of Functional Esophageal Disorders

Class of drug	Dose	Disorder	Response rate	Side effects
TCAs				
Imipramine[117]	50 mg/d	NCCP	52%	QT prolongation
Imipramine[118]	50 mg/d	NCCP	Significant	Dry mouth, dizziness
Imipramine[119]	50 mg/d	FH, RH	57.2%	Constipation
Amitriptyline[116,121]	10, 25 mg/d	NCCP, globus	52%, significant	Excessive sleeping, dizziness
SNRIs				
Venlafaxine[122]	75 mg/d	NCCP	62%	Sleep disturbances
SSRIs				
Sertraline[120]	50–200 mg/d	NCCP	57%	Nausea, restlessness
Sertraline[120]	50–200 mg/d	NCCP	Modest	Dry mouth, diarrhea
Paroxetine[123]	10–50 mg/d	NCCP	Modest	Fatigue, dizziness
Paroxetine[124]	10–50 mg/d	NCCP	21.7%	None
Citalopram[117]	20 mg/d	FH	Significant	None
Fluoxetine[125]	20 mg/d	FHRH	Significant	Headache, dry mouth
Other				
Melatonin[126]	6 mg/d	FH	75%	Diarrhea
Ranitidine[106]	300 mg/d	FH	Significant	None
Theophylline[130]	200 mg twice/d	NCCP	58%	Nausea, insomnia, tremor
Gabapentin[131]	300 mg 3 times/d	Globus	66%	None

FH, functional heartburn; NCCP, noncardiac chest pain; RH, reflux hypersensitivity; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
Reprinted with permission from Cyrowski and Rao.[111]

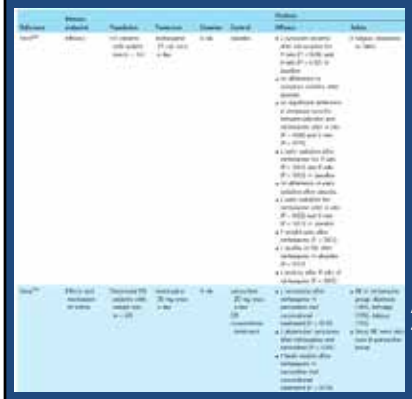
Patel D. CGH 2021;19:1314-1326

Neuromodulators for functional dyspepsia



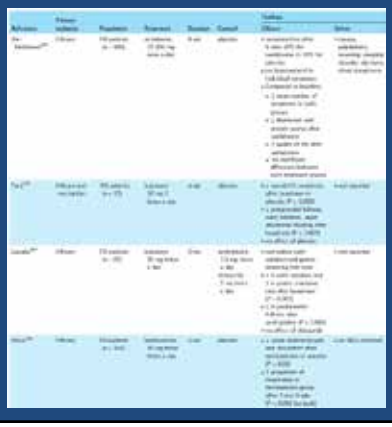
Adapted from Masuy I. APT 2019; 49:1134-1172

Neuromodulators for functional dyspepsia



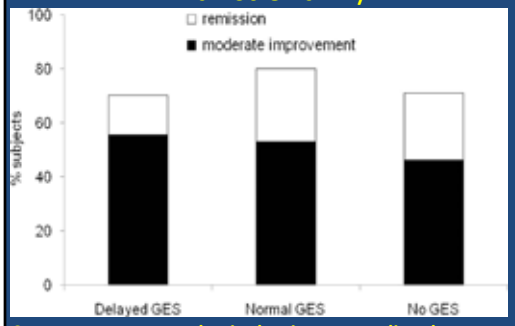
Adapted from Masuy I. APT 2019; 49:1134-1172

Neuromodulators for functional dyspepsia



Adapted from Masuy I. APT 2019; 49:1134-1172

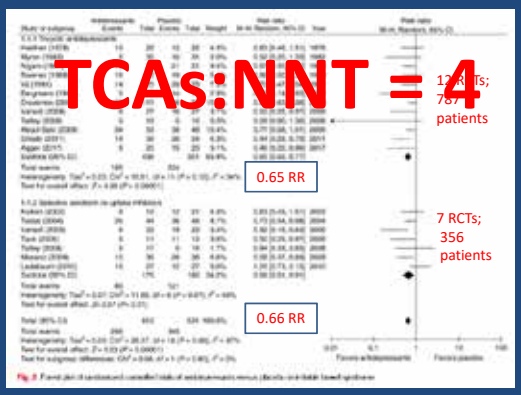
Central neuromodulator therapy in functional N/V



Severe symptoms and pain dominance predicted nonresponse

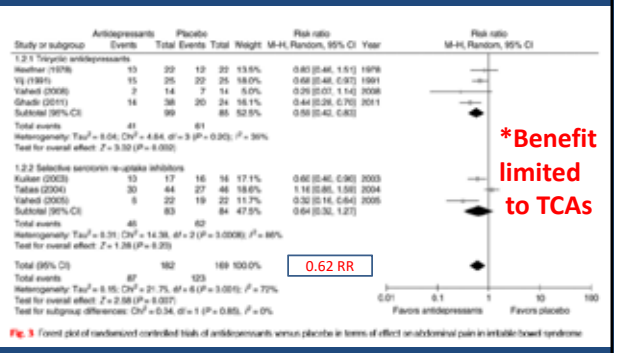
Amit Patel et al. Postgrad Med J 2013;89:131-138

TCAs and SSRIs for IBS symptoms

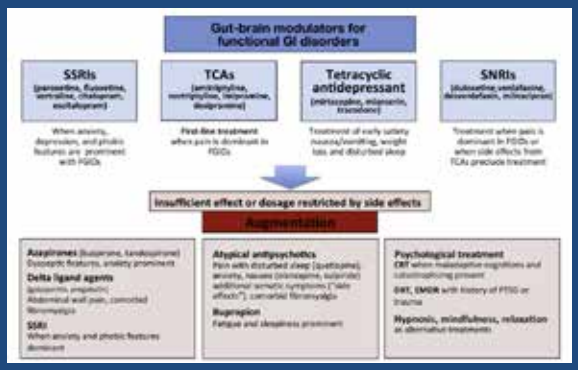


Ford AC. AJG 2019;114:21-39

TCAs and SSRIs for IBS *abdominal pain*



Ford AC. AJG 2019;114:21-39



Drossman D. Gastroenterology 2018;154:1140-1171

Central neuromodulators in FGID: future needs

- Pharmacogenomics data
- SNRI RCTs
- Delta ligand RCTs
- Trials in SOD, CVS, CUNV, anorectal pain
- Trials of dual therapy/treatment augmentation
- RCTs of communication techniques and clinical outcomes, patient satisfaction, adherence, and cost

Central neuromodulators in GI Summary

- FGID: most convincing evidence→ low to moderate dose TCAs, but SNRIs may also be recommended (and may combine….)
- Augmentation with a second agent (atypical antipsychotic, buspirone, mirtazapine) or peripheral neuromodulators (gabapentin/pregabalin) may be useful when above unsuccessful or limited by side effects
- "Low and slow"; treat > 6-12 months to avoid relapse
- Effective provider communication skills → key to patient acceptance and clinical success
- Avoid opioids

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"Don't FLIP Out! The use of Functional Lumen Imaging Probe in Esophageal Motility Evaluations"

Disclosures: **None**

Learning Objectives:

- Identify EndoFLIP technology
- Understand role and position of EndoFLIP in esophageal motility testing

Technical Aspects:

The functional lumen imaging probe (FLIP), marketed as EndoFLIP™ (Medtronic, Minnesota, US) is a catheter based device which measures the luminal cross sectional area (CSA) and esophageal pressure using impedance planimetry. There are two main configurations for FLIP catheters (EF 325: 8cm catheter with 16 impedance sensors spaced 0.5 cm apart and EF-322: 16cm catheter with 16 impedance sensors spaced 1 cm apart). The EF 325 (shorter) catheter is primarily used in the evaluation of the esophagogastric junction (EGJ), whereas the EF 322 (longer) catheter also provides contractility/peristalsis patterns in addition to the EGJ measurements provided by the EF 325 catheter. The catheters have numerous impedance sensors, as above, and are encased within a balloon which is distended with a fluid of known conductivity and volume. The FLIP 2.0 module displays diameter changes over the length of the esophagus (y-axis) and over time (x-axis) to create topographic patterns which demonstrate motility patterns of the esophageal body and the EGJ. This technology utilizes the known contractile response that occurs with esophageal body distension, known as secondary peristalsis, to stimulate the esophagus during sedation.

The FLIP catheter is placed transorally into the esophagus after the endoscope has been removed. It has an atraumatic tip which is guided across the EGJ based on measurements obtained during the immediately preceding endoscopy and 2-3 sensors are typically kept in the stomach during the testing. There are separate protocols for each catheter (max fill 50mL on the EF 325; max fill 70mL on the EF 322) as previously described (Savarino & Gyawali, 2020).

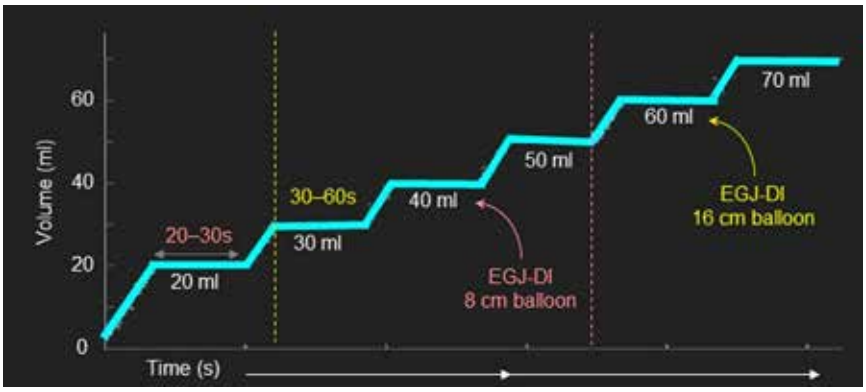

Image from Savarino et al, AJG, 2020

Clinical Use:

The EndoFLIP device is novel in that it is performed during a sedated endoscopy. This has a primary advantage of being better tolerated than the typical unsedated esophageal manometry study. Additionally, since an endoscopy is performed at the same time, if the catheter is having difficulty getting across the EGJ or through a hernia, the endoscope can be used in real-time to help ensure correct placement. Despite these advantages, FLIP is not equivalent to formal high-resolution esophageal manometry as they are measuring different aspects of esophageal function and anatomy. FLIP planometry measures the diameter and distensibility (stiffness) of the esophagus and the EGJ, whereas esophageal manometry is measuring pressures. Additionally, FLIP panometry, and this type of testing, is done in response to distension, whereas esophageal manometry is performed during patient initiated, volitional swallows. The relationship between primary (patient-initiated) peristalsis and secondary (distension response) peristalsis continues to be elucidated with FLIP technology being at the forefront of this research.

FLIP technology has numerous applications in clinical gastroenterology, and numerous additional applications are being developed. FLIP topography gives additional insight into the EGJ by providing a measured distensibility index (DI) which is calculated by dividing the CSA by the intra-bag pressure (Pandolfino, 2013) (Carlson & Pandolfino, 2019). Esophageal body contractility patterns (defined as luminal diameter changes over space-time continuum) have been described and repetitive anterograde contractions(RACs) at a rate of 6/minute is considered to be normal contractility (Savarino & Gyawali, 2020). Additional patterns of contractile response have been defined, including repetitive retrograde contractions (RRCs), absent contractility, and diminished or disordered contractile response which is defined as other contractile patterns that does not meet the criteria for the above three categories.

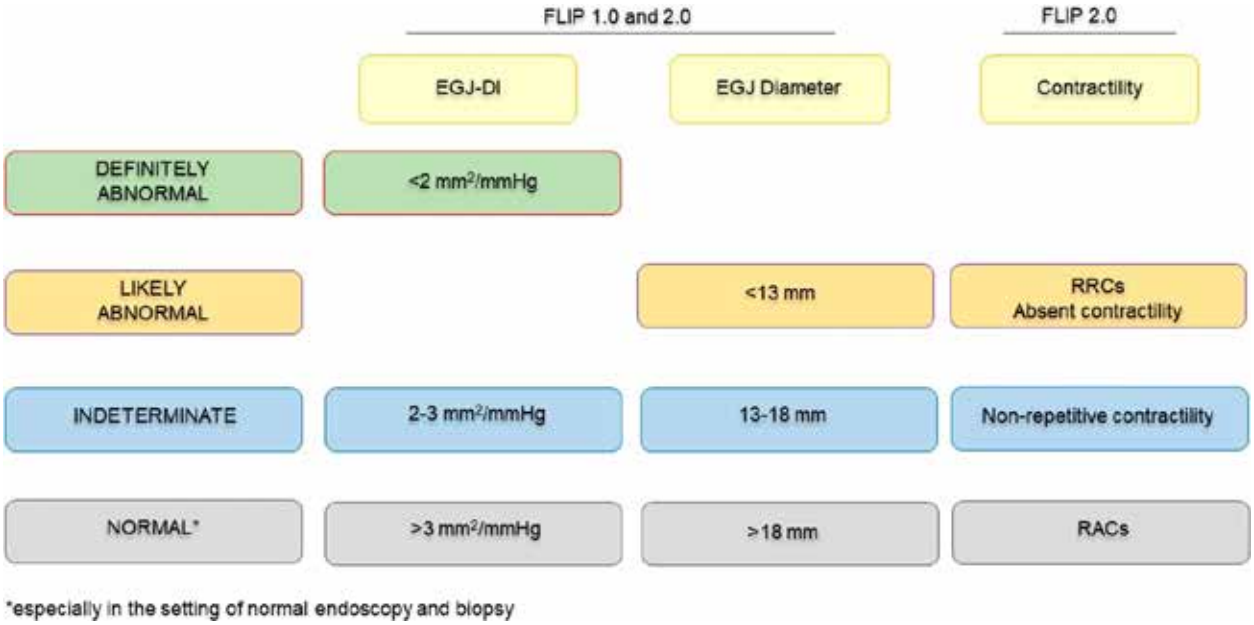

Image from Savarino et al, AJG, 2020

Clinical Scenarios:

Achalasia: FLIP has wide applicability in both the diagnosis of treatment naïve patients with suspected achalasia and also in the surveillance of achalasia patients who have undergone EGJ directed therapy (POEM, Heller myotomy, or pneumatic dilation). A DI cut off of 2 is considered diagnostic of outflow obstruction, with a DI between 2-3 being indeterminate and a DI greater than 3 being considered normal. Additionally, FLIP is commonly used in manometrically indeterminate cases who have a strong clinical presentation and suspicion for achalasia.

In patients who have undergone definitive treatment for achalasia, the EGJ-DI carried a stronger association with outcome than manometric LES pressure – compared to either the integrated relaxation pressure (IRP) or basal EGJ pressure (Jain, Carlson, & Pandolfino, 2019). In patients who have undergone pneumatic dilation for achalasia, a EGJ-DI > 1.8 mm^2/mmHg was predictive of immediate clinical response in patients, defined as an Eckardt score < 4 at 2 weeks. Similar data has been shown in patients whom underwent surgical or endoscopic myotomy.

EGJ Outflow Obstruction (EGJOO): In the recent update of the Chicago Classification (version 4.0), FLIP has taken a larger role in helping to distinguish and confirm the diagnosis/physiology of EGJ Outflow Obstruction (Yadlapati & Kharilas, 2020). If a patient has an elevated median IRP in both the primary and secondary positions (typically supine and upright), then a confirmatory test, either a timed barium esophagram or EndoFLIP is suggested to confirm the outflow obstruction physiology. With the previous version of the Chicago Classification, the Chicago committee found that EGJOO was being over-diagnosed, resulting in patients undergoing potentially unnecessary surgical interventions. FLIP panometry accurately identified clinically relevant conclusive EGJ outflow obstruction when compared to HRM testing and may provide value as an tool at index endoscopy or as complimentary testing to manometry (Carlson & Pandolfino, 2021). FLIP may provide additional strength to recommendations for or against surgical intervention in cases of EGJOO.

Dysphagia: In patients who present with dysphagia and a normal upper endoscopy, additional testing may be clinically indicated and could include an barium esophagram to assess for subtle stenosis missed on endoscopy, or esophageal manometry testing to exclude esophageal motility disorders. In patients with a normal endoscopy, FLIP may provide *immediate* insight to the presence or absence of an esophageal motility disorder as it can be performed at the time of the index endoscopy. In patients with abnormal motility on esophageal manometry, FLIP was abnormal in 95% of the cases (Carlson & Pandolfino, 2016). In this study, all patients with achalasia were accurately identified. Depending on the FLIP finding, FLIP may help triage which patients would benefit the most from formal motility testing and potentially reduce the number of patients who undergo manometry which is more likely to be associated with patient discomfort. Further prospective research is needed to assess the use of FLIP at the index endoscopy prior to its widespread use early in the diagnostic algorithm in patients with dysphagia.

Conclusions:

FLIP continues to emerge as a useful tool in the management of patients presenting with esophageal dysphagia. The ability to accurate triage patients at the time of index endoscopy could reduce the need for esophageal manometry although further research is needed prior to widespread adoption. FLIP panometry is highly accurate in diagnosing achalasia and likely provides the most accurate assessment of the efficacy of LES directed therapies. The EGJ Distensibility Index (EGJ-DI) is the most well understood metric in FLIP panometry and has a high degree of correlation with symptomatic patients. In patients with suspected outflow obstruction physiology, FLIP testing can be used both independently and as a complimentary test to manometry, endoscopy, and barium esophagram to help guide management decisions.

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Don't FLIP Out!
The use of Functional Lumen Imaging Probe in Esophageal Motility Evaluations

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UAB Division of Gastroenterology

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Objectives

1. Review the technical aspects of the functional lumen imaging probe (FLIP)
2. Discuss differences between FLIP and manometry
3. Review common indications and clinical scenarios where FLIP testing provides useful diagnostic information

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Functional Lumen Imaging Probe (FLIP)

- **Catheter based test performed during a sedated endoscopy**
- **Utilizes impedance planimetry to measure:**
  - Luminal cross sectional area (CSA)
  - Intra-balloon pressure
- **Key metrics and results**
  - EGJ Distensibility Index
  - Maximum luminal diameter
  - Contractile patterns

Image from medtronic.com

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EndoFLIP™

- **Catheters have 16 impedance sensors spaced out over 8 or 16cm which is encased with a balloon that is distended with a substance with a known conductivity and volume**
- **Two sizes**
  - EF 325 – 8 cm, 16 sensors
    - EGJ evaluation
  - EF 322 – 16 cm, 16 sensors
    - EGJ + Esophageal body eval

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Why refer for FLIP?

- **Initial motility evaluation**
- **Clarification of EGJ**
- **Pre- and Post- Achalasia treatment**
- **Others:**
  - Anti-reflux surgery assessment
  - EoE assessment
  - Pharyngoesophageal junction measurement

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FLIP: Concepts

- **Measure the distensibility of the EGJ and esophageal body during volumetric distension**
- **Conceptual advantage lies in the distinction between sphincter relaxation (manometry) and sphincter opening (FLIP)**

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FLIP ≠ HRM

- **FLIP Panometry measures diameter and distensibility**
- **Esophageal Manometry measures pressures**
- **FLIP Panometry – response to distension**
- **Esophageal Manometry – response to volitional swallows**

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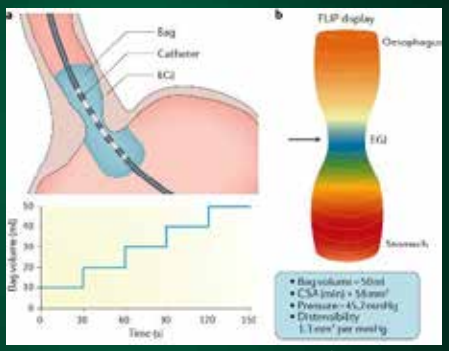
FLIP EGJ assessment

- **EJG- DI**
  - **≤ 2 mm²/mmHg abnormal**
  - **> 3 mm²/mmHg normal**
  - **2–3 mm²/mmHg indeterminate**



Kahrilas, P. J. *et al. Nat. Rev. Gastroenterol. Hepatol.* 2017.

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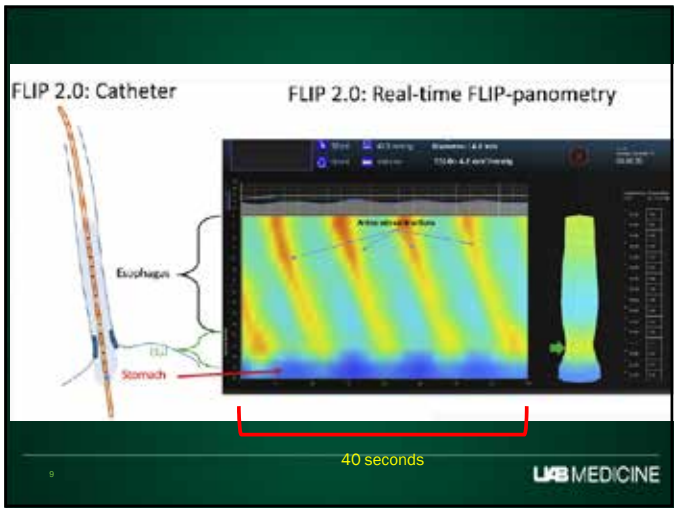


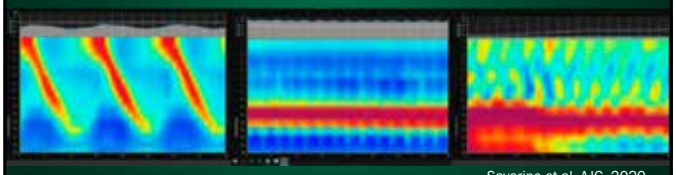
FLIP Contractility Assessment

Normal – Rapid Antegrade Contractions (RACs)

- 3 or more consecutive and consistently spaced antegrade contractions, typically occurring at a rate of 6/minute in healthy volunteers

Abnormal - Rapid Retrograde Contractions (RRCs)

- 3 or more consecutive and consistently spaced retrograde contractions, typically occurring a faster rate of 12/minute in achalasia



Savarino et al. AJG. 2020.

10

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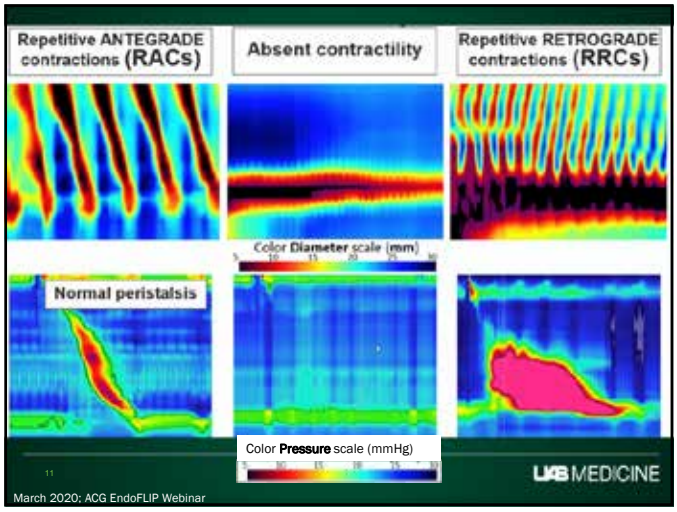

Clinical Scenarios

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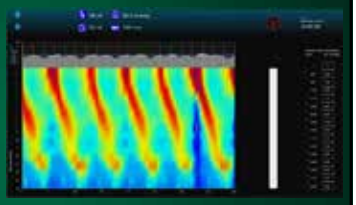
62 year-old with pyrosis and regurgitation

Symptoms well controlled on PPI but concerned of possible long term side effects

PMH: Osteoporosis, HTN, BMI 19
Surg Hx: Deviated septum X 2

EGD: Class A esophagitis

Unable to tolerate manometry probe



Maximum diameter – 21mm
EGJ DI – 6.0 mm^2/mmHg

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145 patients who underwent EGD with FLIP and Esophageal Manometry

Table 3. FLIP topography classification by manometric motility diagnosis

HRM motility diagnosis	n	FLIP topography motility classification, n (%)						
		Achalasia without contractility	Spastic achalasia	EGJOO (achalasia or subtle mechanical obstruction)	Spastic motor disorder	Absent contractility	Diminished contractility	Normal motility
Type I achalasia	19	13 (68)	2 (11)	3 (16)	0	1 (5)	0	0
Type II achalasia	20	14 (70)	13 (65)	12 (60)	1 (5)	0	0	0
Type III achalasia	12	0	10 (83)	2 (17)	0	0	0	0
EGJOO	38	2 (5)	13 (34)	18 (47)	0	0	0	5 (13)
Jackhammer	3	0	3 (100)	0	0	0	0	0
IEM	5	0	0	1 (20)	1 (20)	0	1 (20)	2 (40)
Normal	29	0	4 (14)	8 (28)	3 (10)	0	0	14 (48)
Controls (10.11)	30	0	0	0	0	0	2 (20)	8 (80)

EGJOO, esophagogastric junction outflow obstruction; FLIP, functional lumen imaging probe; HRM, high-resolution manometry; IEM, ineffective esophageal motility. Values represent number of patients and percentage within each HRM motility diagnosis. Previously evaluated asymptomatic controls are included as a reference (10,11).

FLIP was able to rule out a major disorder of motility 95% of time

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Carlson, D. American Journal of Gastroenterology, 2016

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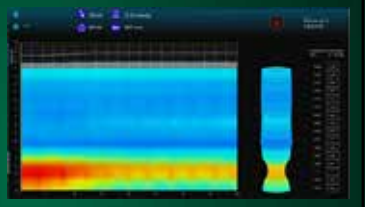
49 year-old with GERD, now with new regurgitation

Longstanding 'GERD'
BMI 29

PMH:
Raynauds
SLE

Barium Swallow – Holds column up at 5 minutes

EGD – Stasis and reflux changes with normal caliber esophagus



Maximum diameter – 13mm
EGJ DI – 6.0 mm^2/mmHg

Anti – SCL70 (+)

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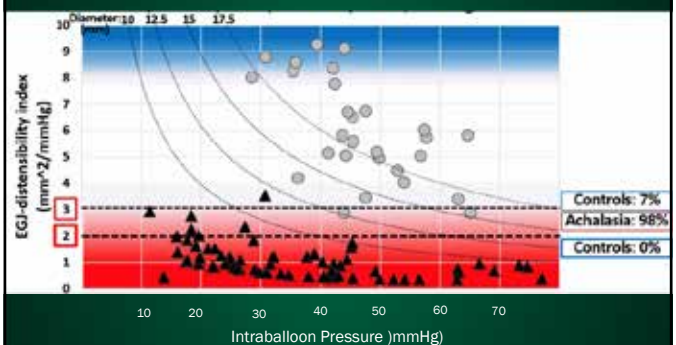
EGJ-DI in Achalasia Patients



16 Carlson et al. AJG, 2016; Rohof et al, Gastroenterolgoy, 2012; Pandolfino et al. Neurogastro Motility, 2016

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52 year old with EGJOO/achalasia, s/p POEM

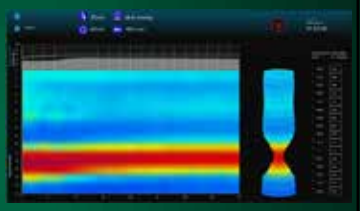
Solid and liquid dysphagia X 5 years
Chest pain
Eckardt score 8

BaSwallow – Column at 5 minutes
HRM with EGJOO + some spastisity

POEM difficult but dysphagia resolved X 8 months

Now with recurrent dysphagia and chest pain

No response to EGD with TTS 18-20 dilation



Maximum Diameter 7mm
EGJ DI 0.9 mm^2/mmHg

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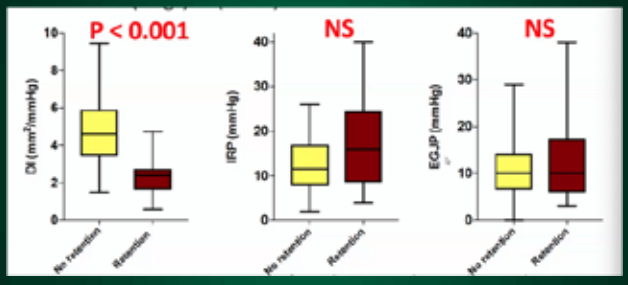
Post-Treatment Achalasia: FLIP > HRM



*In patients with normal anatomy

EGJ-DI carried stronger association with outcome than manometric LES pressure

Jain et al, AJG, 2019

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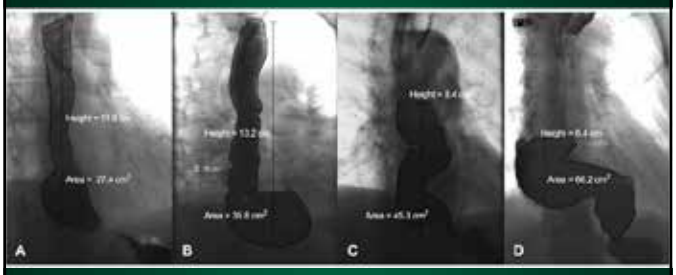
Post-Treatment Achalasia: Anatomy Matters



Pseudo-diverticulum At myotomy site | Epiphrenic diverticulum | Sigmoid deformity | Sinktrap deformity

Jain et al, AJG, 2019

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52 year old with EGJOO/achalasia, s/p POEM

Large interval development of an epiphrenic diverticulum, likely at site of prior myotomy

Plan: Laparoscopic Heller Myotomy with epiphrenic diverticulectomy

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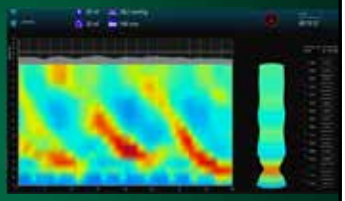
77 year-old with solid food dysphagia X 5 years

No difficulties with liquids.

EGD with paraesophageal hernia, otherwise, non-obstructive EGD

Manometry with EGJOO, and minor evidence of outflow obstruction on rapid drink challenge.

BaSwallow – column held at 1 min minutes, cleared at 2 minutes, tablet hung.



Maximum diameter – 19mm
EGJ DI – 8 mm²/mmHg

PEH repair alone, no myotomy

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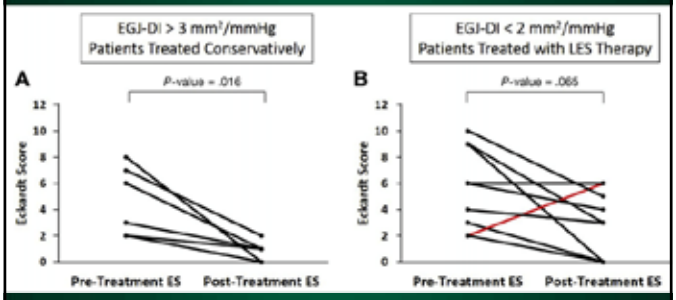
FLIP in EGJOO



 Triggs et al, Clinical Gastroenterology and Hepatology, 2020

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Key Points

- **FLIP is a novel test which allows for assessment of EGJ distensibility and peristalsis during sedated endoscopy**
- **A normal FLIP assessment (RACs + Normal EGJ-DI) suggests normal esophageal motility**
- **EGJ-DI may predict trajectory of patients with EGJOO and in post-treatment achalasia patients**

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Director, Basil I. Hirschowitz Endoscopic Center of Excellence
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Birmingham, AL

"Interventional endoscopy – a path to everywhere"

Disclosures: Grants: Olympus, AMBU

Learning Objectives:

- Review the innovation of LAMS and its impact in launching interventional EUS
- Recognize new frontiers for interventional EUS

This presentation endeavors to explore the limits of the interventional endoscopy and the new procedures that can be performed to enable access to various organ systems through the upper and lower gastrointestinal tracts. The lecture will also elucidate new and revolutionary methods to resect lesions, including cancers previously addressed by surgery.

We will review the current state of various procedures, indications, complications, and success rates. We also attempt to evaluate new related technology, published research, availability, learning curve, and robustness. Finally, we will compare these procedures to standard of care and assess both short term and long-term outcomes.

EUS guided drainage of pseudocyst and necrosis:

1. Pseudocyst drainage
2. EUS guided necrosectomy

EUS guided access:

1. Hepaticogastrostomy
2. Choledochoduodenostomy
3. EUS guided pancreatic duct access

EUS guided luminal anastomosis creation

EUS guided tumor therapy:

1. EUS guided chemotherapy mediated cyst ablation
2. EUS guided RFA treatment of solid lesions

Endoscopic surgery or resection:

1. Peroral endoscopic myotomy (esophageal and gastric)
2. Endoscopic Mucosal Resection
3. Endoscopic Submucosal Dissection
4. Endoscopic Full Thickness Resection

Suggested readings:

1. Clin Gastroenterol Hepatol. 2017 May;15(5):738-745. doi: 10.1016/j.cgh.2016.12.021. Epub 2016 Dec 30.
2. Gastrointest Endosc. 2017 May;85(5):904-914. doi: 10.1016/j.gie.2016.12.023. Epub 2017 Jan 4.
3. Endosc Int Open. 2017 Apr; 5(4): E275–E281.
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5. World J Gastrointest Endosc. 2017 Aug 16; 9(8): 378–388
6. Gastrointest Endosc. 2016 Jun;83(6):1164-72. doi: 10.1016/j.gie.2015.09.040. Epub 2015 Oct 9
7. Gastrointest Endosc. 2017 May;85(5):996-1001. doi: 10.1016/j.gie.2016.09.026. Epub 2016 Sep 29

Interventional Endoscopy—a path to everywhere

Kondal Kyanam
Assistant Professor
Director of Endoscopy
University of Alabama at Birmingham

Conflict of Interest

- Olympus: Institutional grant recipient
- Ambu: Institutional grant recipient

Objective

- To understand new endoscopic procedures:
- Therapeutic EUS procedures as alternatives to endoscopy, ERCP, IR procedures, and surgery
- Endoscopic Oncology—Endoscopic therapy of cancers
- “Third space” endoscopy

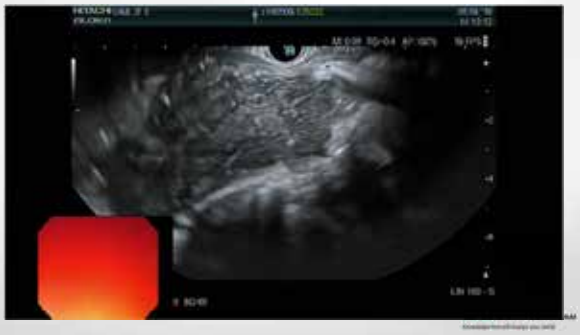
Objectives

- Current state of knowledge
- Comparison to current care
- Outcomes
- New uses
- Appropriate indications and patient selection
- Complications and management

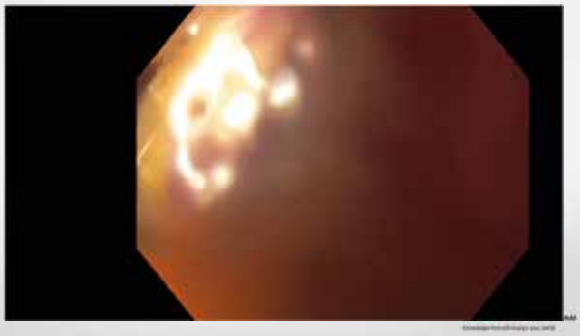
EUS guided necrosectomy

- Large systematic review:
- 455 patients with acute complicated pancreatitis
- Organ failure (23%), infected necrosis (57%)
- Successful resolution--81%
- Complications—36% (bleeding)
- Mortality--6%
- RCTs ongoing but comparison is fraught

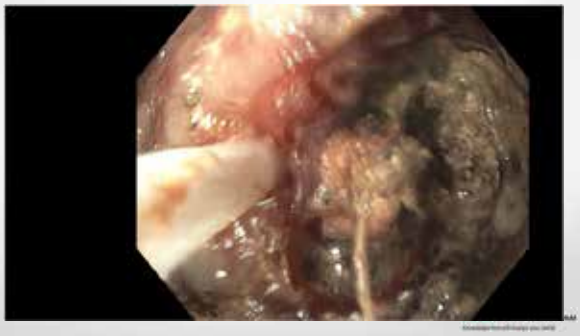
EUS LAMS placement



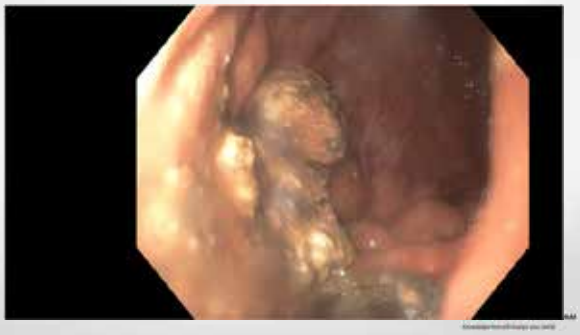
Drainage



Necrosectomy

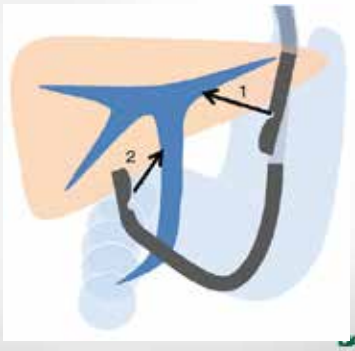


Post necrosectomy



EUS guided biliary drainage—distal malignant obstruction

- Failed ERCP
- Failed cannulation
- Tumor involving ampulla
- Ampulla not accessible—duodenum obstructed



Approaches

- Preferred: choledocho—duodenostomy if obstruction is distal
- Distal choledocho--gastrostomy is an alternative if duodenal bulb is not accessible

Issues to consider

- Resectability—potential effect of stent on surgery
- Location of stent
- Duodenal obstruction

Evidence—large review/meta-analysis

- No difference in technical success between 2 procedures (OR, 1.78)—EUS-BD vs ERCP
- EUS-BD was associated with better clinical success (OR, .45),
- Fewer post-procedure adverse events (OR, .23)
- Lower rate of re-intervention (OR, .13).
- No difference in length of hospital stay
- EUS-BD was more cost-effective

Video

- https://doi.org/10.1016/j.vgie.2017.11.003

Complications

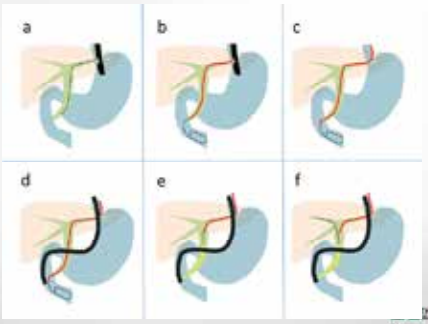
- Failed appropriate stent placement
- Perforated duodenum
- Injury to bile duct, cystic duct, and gallbladder.
- Vascular injury
- Bile leak
- Bile peritonitis
- Rescue techniques—access using traditional ERCP tools and place FCSEMS

EUS guided biliary drainage—proximal malignant obstruction

- Failed ERCP/cannulation
- Antrum/pylorus/duodenum inaccessible
- Altered surgical anatomy of the main bile duct, distal stomach, duodenum

- Hepaticogastrostomy

Hepatico-gastrostomy approaches



Significantly more challenging

- Fully intra-peritoneal
- Along lesser curve sometimes very close to GEJ
- Dilation of the liver parenchyma required
- Respiratory Motion
- Stent migration into peritoneum during deployment and later by migration

Video

- https://www.youtube.com/watch?v=w0Byu6-MHPs

EUS guided gallbladder drainage

- Acute cholecystitis--unfit for surgery/IR:
- Critically ill
- Multiple comorbidities
- Unstable for transport
- Inoperable pancreatico-biliary malignancy (susceptible to cholecystitis)
- Internal drainage preferred

Evidence—prospective data lacking:

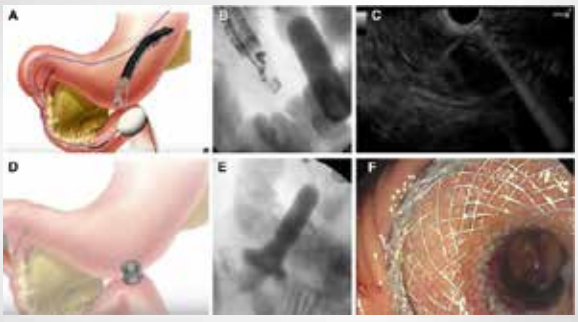
- NO large randomized trials
- Large retrospective study showed—EUS vs PTC
- Technical success—98% vs 100 (NS)
- Clinical success—96% vs 91% (NS)
- Complications—11% vs 32% (NS--trend)
- Shorter LOS and repeat interventions

Video

- https://www.youtube.com/watch?v=--I-1nX6WJ4

EUS guided gastrojejunostomy

- Palliative procedure for malignant GOO
- Alternative to surgery in poor operative candidates—some benign indications
- Altered anatomy from prior surgery
- Hostile surgical abdomen



Large retrospective comparison--malignant

- EUS-GE (n=30) or SGJ (n=63)
- Peritoneal carcinomatosis 43% vs 11%(P<0.001)
- Technical success rate was significantly higher in the SGJ group vs EUS-GE group (100% vs. 87%, P=0.009)
- Clinical success rate was not different (90% vs. 87%, P=0.18, OR 0.8, 95%CI 0.44–7.07)
- AEs was lower in the EUS-GE group (NS)
- LOS, recurrent GOO, re-intervention rate similar

Large case series—benign indication

- Overall, 26 patients (46.2% female; mean age 57.7±13.9 years) underwent EUS-GE for benign GOO
- Etiology: chronic pancreatitis (n=11), surgical anastomosis (n=6), peptic ulcer disease (n=5), acute pancreatitis (n=1), superior mesentery artery syndrome (n=1), caustic injury (n=1), and hematoma (n=1).

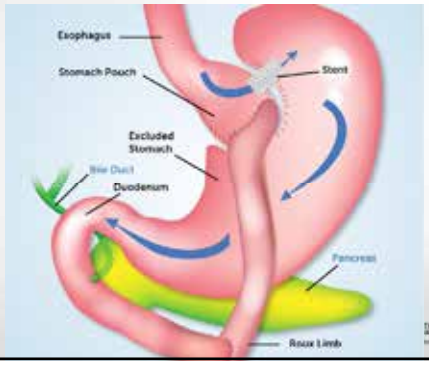
Continued

- Technical success--96.2%.
- Dilation of the lumen apposing metal stent was performed in 13/25 (52%) with a mean maximum diameter of 14.6±1.0mm.
- Procedure time was 44.6±26.1min.
- Clinical success was observed in 84.0%
- Time to oral intake-2 d, and F/U—median 6 m.
- Rate of unplanned re-intervention was 4.8%.

Video

- https://www.youtube.com/watch?v=-o3tjOAeRYc
- https://www.youtube.com/watch?v=eA1ylZg0hkk

EUS guided trans-gastric access



EUS guided tumor therapy

- Chemotherapy
- RFA
- Other thermal therapy
- Ablative agents

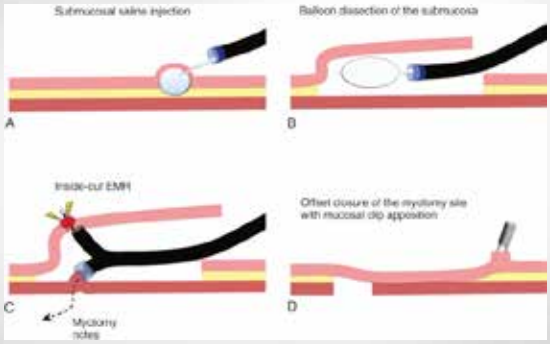
Recent review of case series

- Total of 28 cases
- Technical success—100%
- Clinical success—not defined
- Resolution of symptoms of insulinoma
- Tumor size reduction
- Decrease CA 19.9 level
- AE: Mild abdominal pain-30%
- Mild pancreatitis—1 case

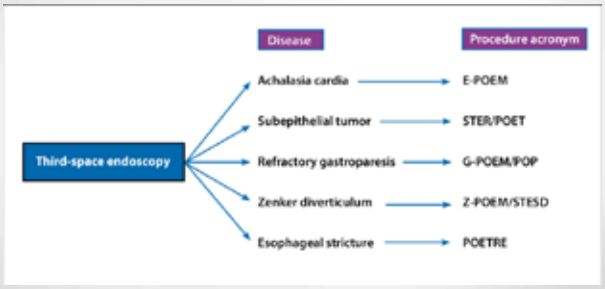
EUS RFA probe

Third space endoscopy

- "Third space" endoscopy, also commonly referred as submucosal endoscopy, is founded on the principle that the deeper layers of the gastrointestinal (GI) tract can be accessed by tunneling in the submucosal space without compromising the integrity of the overlying mucosa.



Classification



Third space endoscopy

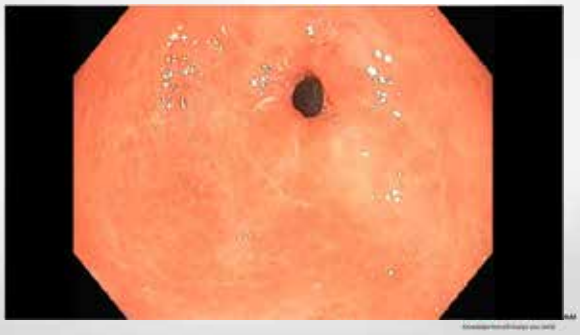
- Peroral endoscopic myotomy—POEM
- Endoscopic submucosal dissection—ESD

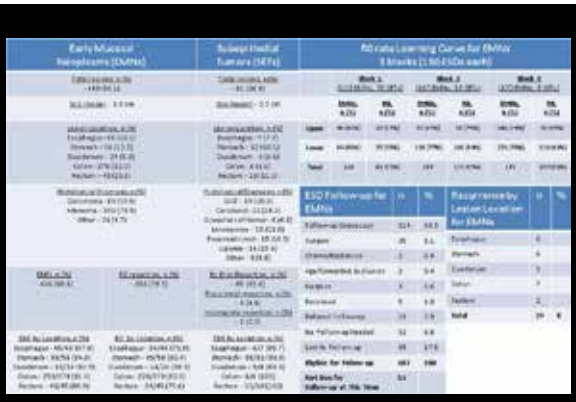
POEM--achalasia

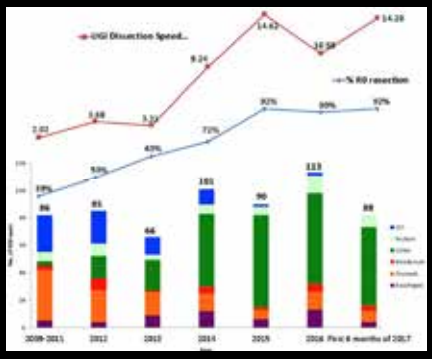
	1 year	2 years	3 years	4 years	5 years
Total # of assessable pts	316	246	173	99	53
No. pts on whom f/up obtained	306	219	152	87	49
% of pts Lost to f/up	5%	11%	14%	12%	8%
CLINICAL SUCCESS	289 /306 94%	204 /219 93%	142 /152 93%	80/87 92%	44/49 90%

ESD

Gastric cancer resection

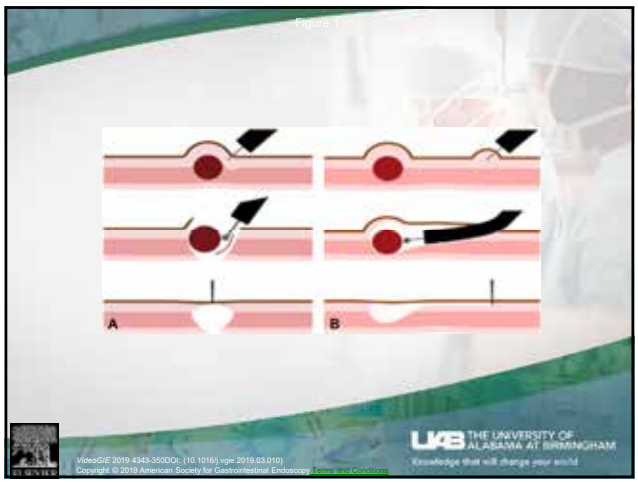


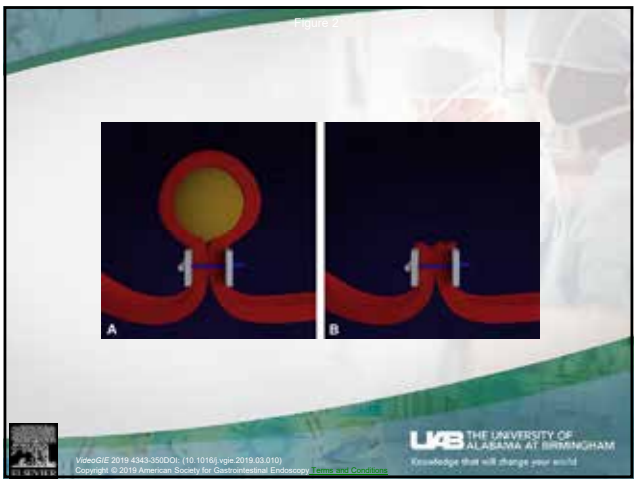




Endoscopic full thickness resection

- Fundamentally different
- Similar to surgical approach
- Training and endoscopy skill set
- Technical support
- Surgery buy in
- Multidisciplinary approach





Other issues

- Education and review of literature
- Training—ex-vivo, animal models, courses
- Mentoring and proctoring
- Credentialing
- Standardized protocols
- Clinical support from division and ancillary departments
- Surgery and IR support
- Billing

- Questions?
- Comments?

References

- Clin Gastroenterol Hepatol. 2017 May;15(5):738-745. doi: 10.1016/j.cgh.2016.12.021. Epub 2016 Dec 30.
- Gastrointest Endosc. 2017 May;85(5):904-914. doi: 10.1016/j.gie.2016.12.023. Epub 2017 Jan 4.
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"Management of fistulas, perforations and leaks"

Disclosures: Consulting fee: Boston Scientific, Cook Medical, Olympus

Learning Objectives:

- Identify types of gastrointestinal defects
- Recognize devices and techniques for endoscopic closure

Introduction

Recent advances in endoscopic therapy provide non-surgical interventions for complicated diseases. This offers therapy for a wide-array of patients who were at one time deemed poor candidates for the conventional surgery. Concomitant innovation in endoscopic procedures and devices have ushered the new era of interventional endoscopy. This now comes with the responsibility to manage the complications of such procedures which at one time was limited to surgery. This presentation will focus on perforation, leaks and fistulas of the upper GI tract and the tools to help manage such patients.

Objectives

- Differentiate perforations, leaks and fistulas
- Recognize 3 specialized closure devices/techniques for managing luminal defects
- Take away a general treatment paradigm for managing such complications

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Management of Fistulas, Perforations and Leaks

Ali Mir Ahmed, MD
Assistant Professor, Division of Gastroenterology & Hepatology
UAB 2021 Update in Gastroenterology & Hepatology
August 14, 2021

Disclosures

- Boston Scientific – Consultant
- Cook Medical – Consultant
- Interscope, Inc. - Consultant
- Olympus Corp of America – Consultant

- I declare no conflicts of interest with this presentation

Executive Summary

Introduction

- Advances in endoscopic therapy provide more options in complication management
- We will focus on perforations, leaks and fistula and different treatment approaches

Objectives

- Differentiate perforations, leaks and fistulas
- Identify a general treatment paradigm for these complications
- Recognize three specialized closure devices/tools

Table of contents

Overview of Transmural Defects

- Leaks
  - Typically arise after surgery
- Perforations
  - Most often after endoscopic procedure
- Fistulas
  - Represent chronic effect of disease or the delayed effect of surgical leaks

Gastroenterology, 2018

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Perforations

Upper GI Procedure Complication Rates

- Low Risk Procedures
  - Diagnostic EGD
    - Complication rate of 0.03%
    - Most perforations occur in the thoracic esophagus
  - Diagnostic EUS
    - Complication rate of 0.01%
    - Most perforations occur in the duodenum
- ERCP is more commonly associated with duodenal perforations
- Duodenal perforations are seen in the duodenum from muscular trauma from multiple biopsies of the same site

Upper GI Procedure Complication Rates

- High Risk Procedures
  - EMR/ESD
    - Esopahgus – EMR perforation risk up to 3%
    - Esopahgus – ESD perforation risk up to 4%
    - Gastric – EMR perforation risk reported at 0.5%
    - Gastric – ESD perforation rate 4%
    - Gastric ESD Perforation risk factors
      - Procedure time (increased)
      - Proximal stomach location (thinner wall); Prior Radiation tx or location near ulcer
      - Lesion size
      - Patient Age > 80

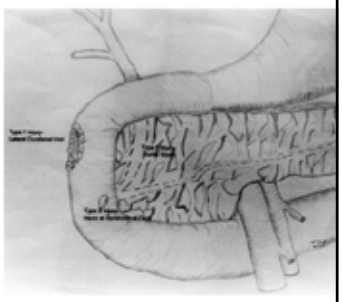
Upper GI Procedure Complication Rates

- Duodenal EMR immediate/delayed perforation (1.6% and 0.6%)
- Duodenal ESD immediate/delayed perforation (12% and 4.0%)

- UPPER ENDOSCOPY DILATIONS
  - Perforation rates 2-3% (greater for duodenal, malignant, caustic and achalasia strictures)
  - No perforation difference between bougie vs balloon dilators
    - Variability due to stricture length, physician preference, cost, availability
    - Non-wire guided (Malnoney) dilators have been largely replaced by wire guided options (Savary) due to better safety profile

Stapfer Classification

Defect	Location (etiology)
Type I	Lateral Duodenal wall (direct scope)
Type II	Sphincter of Oddi (Sphincterotomy)
Type III	Bile duct injury (guidewire, basket)
Type IV	Barotrauma (compressed air)



Annals of Surgery, 2000

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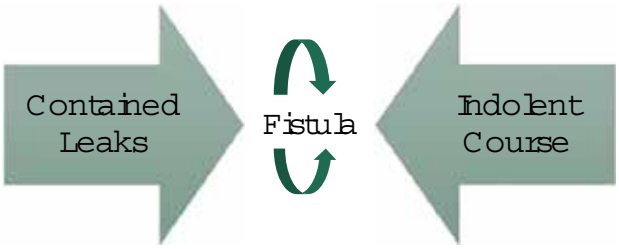
Fistulae & Leaks

Upper GI Tract Fistulae & Leak

- Dreaded complication from upper GI tract surgery
- Surgical re-intervention for leaks and fistulae is associated with significant morbidity
- Risk Factors for Anastomotic Leaks
  - Tobacco/Alcohol Dependence
  - Steroid Use
  - Malnutrition
  - Age
  - Diabetes
  - Advanced tumor stage; Emergent Surgery
  - Renal failure

Upper GI Tract Fistulae & Leak



Esophageal Fistulas

- Acquired
- Present with recurrent aspiration PNA
- Usually due to malignancy
- Trauma, Infection, Iatrogenic (esophageal stent, EGD, Tracheal tubes)
- Foreign bodies (Button Batteries)
- Caustic Ingestion

- Most commonly Tracheo-esophageal (TEF)
- But Broncho-esophageal and Pulmo-esophageal also observed

Gastroduodenal Fistulas

- Rare usually secondary to GI surgery (85-90%)
- Also associated with malignancy, IBD, trauma and infection
- Gastro-cutaneous fistula can occur
  - (ie) post-PEG removal

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Treatment Tools & Devices

Through the Scope (TTS) Clips

Comments

- Easiest/Fastest to use
- Cost effective if use < 3
- Best for defects < 10mm
- Challenging to deploy on chronic lesions (fistulae)
- Stem length may pose a challenge in some lesions

Cook Medical Instinct Clip

Source: Cook Medical

TTS Clips

- Multiple Vendors with Differentiating Features
  - Multiple vendors
  - Size
  - Rotation
  - Tensile and Closure strength

Over-The-Scope-Clip (OTSC)

- OTSC System (Ovesco Ag)
- Padlock (Steris Corp)

- Advantages
  - Close larger defects (best up to 20mm)
  - Greater compressive force vs TTS Clips
  - Ability to close chronic fistulae/leaks
- Disadvantages
  - Must remove endoscope for over the scope deployment
  - Increased diameter makes luminal passage/intubation more challenging

Luminal Stent

- Bridge the defect and direct luminal content within the GI Tract
- Covered, Partially covered metal stents most often used
- Goal to cover 3 to 5 cm proximal and distal to the defect
- Stent Deployment utilizing fluoroscopy with guidewire and direct visualization
- Stent is often left for 6 to 8 weeks
- Contrast oral studies performed at 48 to 72 hours to confirm presence of no leak
- Best effect for defects < 3cm, adjacent tissue viable with limited angulation in order to obtain optimal stent-tissue approximation
- Most often used for mid, distal esophageal defects
- Stent fixation with suturing or fixation device can be employed to minimize migration

Endoscopic Vacuum Therapy

- Utilized porous polyurethane sponge placed endoscopically within/adjacent to the cavity
- Sponge promotes granulation tissue growth
- Negative pressure removes secretion, reduces edema and promotes healing
- Success rates of up to 90% reported, limited by publication bias
- Best for contained cavity < 8cm
- Requires sponge change every 72 hours

Endoscopic Suturing

- Disposable device affixed on a double channel therapeutic scope
- Provides full thickness suture
- Adjacent tissue viability is key for effective tissue approximation
- Best for acute perforations not amenable to over the scope closure
- Reduced efficacy for fistulae
- Cost-prohibitive

Tissue Sealants

- Fibrin or cyanoacrylate
  - Monotherapy
  - Combined with clips, mesh or stents
- Epithelium primed with APC
  - Promotes fistula closure

General Principles "DIRT"

- Discuss
  - Informed consent identifying high risk procedure
- Interdisciplinary Approach
  - Hospital/Practice protocol for managing complications
- Recognize
  - High quality inspection during therapeutic endoscopy to efficiently identify any defects
- Treat
  - Best outcomes achieved with immediate rescue intervention

General Principles: Intraprocedure

- Complete intervention if possible
- Ensure use of CO2 insufflation
- Communicate with anesthesia provider and maintain close eye on hemodynamic parameters
- Consider needle decompression as required
- Consider post pyloric/defect feeding (NJ tube placement)
- Early antibiotics with broad spectrum coverage
- Close PACU monitoring
- Prepare patient, team, family for likely hospital admission for elective procedures

General Principles

- Conservative Management
  - NPO
  - IV ABX
  - NGT
  - Analgesia
  - PPI
  - Hemodynamic Monitoring / Suppport
  - Increased success for defects in the cervical esophagus due to lower risk of mediastinal contamination

Acute Perforation

- < 1cm : TTS Clips
- 1 – 3cm : OTSC; Suturing
- > 3cm : Luminal Stent, Vacuum Therapy
- Upper Esophagus: Consider conservative therapy

- Consider surgery for endoscopic failure, uncontained perforation, unstable pt
- Duodenal perforation have limited role for suturing

Chronic Fistulas/Leaks

- Absence of sepsis, contained, < 3cm, viable surrounding tissue
  - Manage as acute perforation
- Fistulae
  - OTSC as first line therapy
  - Rescue therapy with luminal stent/Endoscopic Vacuum Therapy
- Presence of sepsis, uncontained, > 3cm, devitalized tissue
  - Consider Endoscopic Vacuum Tx +/- Percutaneous drainage
  - Surgery

Suggested Closure Device/Techniques

Location	Defect < 10mm	Defect < 20mm	Defect > 20mm	Diversion Tx
Esophagus	TTS Clips	OTSC	Stents	Stents / EndoVac
Stomach	TTS Clips	OTSC	Suture/Loop	Surgery
Non-Ampullary Duodenum	TTS Clips	OTSC	Surgery	Stent/Surgery
Jejunum / Ileum	TTS Clips	TTS Clips	TTS Clips	Surgery
Colon / Rectum	TTS Clips	OTSC	Vacuum Therapy	Surgery/Vacuum Tx

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Thank you!

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"Imaging of the complex GI patient"

Disclosures: **None**

Learning Objectives:

- Identify radiologic findings of complex hepatobiliary disease
- Understand the role of multi-disciplinary approach to pacreatico-biliary disease

Imaging is a cornerstone of diagnosis and treatment of many patients suffering from gastrointestinal disease. For some, the choice of imaging modality is clear, but for others there is uncertainty about how best to image these patients to obtain the desired information. In particular, the choice of imaging modality may differ depending on if the patient is ill and admitted to the hospital or being evaluated in the outpatient clinic. The primary aim of this lecture is to briefly discuss three common clinical scenarios: evaluation of cirrhosis/hepatic fibrosis, chronic nausea and vomiting with suspected delayed gastric emptying, and the evaluation of post-operative or post-procedural patient. The goal of the lecture is to gain understanding of the various strengths and weaknesses of differing imaging modalities in each of these clinical scenarios.

For many patients with suspected gastrointestinal problems, abdominal ultrasound is one of the initial imaging studies ordered. It is preferred as it is quick, cheap, and widely available in both the inpatient and outpatient settings. In the ultrasound evaluation of the liver, the diagnosis of cirrhosis can be suggested and largely relies on surface nodularity of the liver and/or heterogeneous hepatic echotexture. For many radiologists, the exact laboratory abnormalities of the patient are not known at the time of diagnosis and in some instances, grayscale ultrasound alone may erroneously suggest cirrhosis in the setting of normal LFTs and no risk factors. Unlike other cross-sectional imaging modalities, other structural changes in the liver commonly seen in cirrhosis (such as caudate lobe hypertrophy) are not as easily visualized to help further evaluate possible cirrhosis. Ultrasound elastography is an imaging exam that allows for evaluation of liver stiffness, which in turn can help diagnosis and monitor hepatic fibrosis or rule out significant hepatic fibrosis. The exam focuses the ultrasound on a selected portion of the liver and does approximately 10 repeated measurements to determine the stiffness. While this improves upon the performance of grayscale ultrasound alone, a main issue is that it only focuses on one area of the liver and in patients who have heterogeneous fibrosis, it may underestimate or overestimate the degree of overall liver fibrosis. MR elastography is a newer imaging modality for the evaluation of hepatic fibrosis and steatosis and provides whole liver

stiffness evaluation in addition to calculation of hepatic fat and iron deposition. This is clearly advantageous when compared to ultrasound, but this exam is more expensive and not as widely available. Additionally, in patients with hepatic iron deposition, MR elastography will not be suitable due to artifacts generated by the hepatic iron. Thus, each of these modalities have their strengths and weaknesses and may play a more significant role in certain patient populations. Finally, the results of these studies should be taken in context of the overall patient presentation and lab profile, as the diagnosis of significant fibrosis or cirrhosis suggested on ultrasound may not be accurate.

Chronic nausea and vomiting is a commonly encountered clinical scenario in the gastroenterology clinic and delayed gastric emptying is a major consideration. Particularly, due to rising rates of obesity and poorly controlled diabetes, gastroparesis remains a major diagnostic consideration. Frequently, if presenting to the emergency room, these patients are often first evaluated with CT scan. The strength of CT is that it is widely available and quick, but largely serves a role in these patients to rule out bowel obstruction or structural causes of gastric outlet obstruction. Subsequently, patients may undergo a GI fluoroscopic evaluation to evaluate gastric emptying. Although quick and widely available, fluoroscopy is often unrevealing in these patients and assessment of delayed gastric emptying cannot be quantified or truly evaluated on this exam. However, in patients who have undergone prior upper gastrointestinal surgeries, including partial gastrectomy, Roux-en-Y gastric bypass, sleeve gastrectomy, or pancreaticoduodenectomy, fluoroscopy may play a more significant role and outperform nuclear medicine, owing to high-resolution assessment of post-surgical anatomy and possible stricture and the lack of clear normal values on gastric emptying studies for these patients. For patients with no prior surgical history, nuclear medicine gastric emptying studies are the study of choice to evaluate gastric emptying, as they can quantitate gastric emptying and compare to established normal values in the literature. These studies can be performed both as solid or liquid meals, but are challenging to interpret correctly (particularly in the inpatient setting) due to a number of interactions between medications and their effect on gastric emptying.

Frequently the most complex patients, evaluation of the post-surgical/post-procedural patient is challenging and often necessitates a multidisciplinary approach. While many of these patients may be admitted to a surgical service, it is not uncommon to see gastroenterology consulted for problems (such as elevated bilirubin). Depending on the suspected problem, either CT or ultrasound will likely be the initial imaging modality of choice. Both of these modalities are widely available at all medical centers and offer key information about possible intra-abdominal abscess or bile leak, biliary obstruction, bowel obstruction, and patency of hepatic vasculature. For patients who have recently undergone surgery, ultrasound may be limited due to intra-abdominal free air (which obscures visualization) and abdominal tenderness, which may limit sonographers from obtaining optimal images. MRI can also be utilized for detection of post-operative/post-procedural complications, but performs best on outpatients and patients otherwise healthy. The acquisition of MR images relies on adherence to breathing instructions and minimal patient motion, both of which are often a challenge in inpatients. Additionally, surgical clips and intra-abdominal air produce artifacts on MRI which limit visualization of adjacent structures. However, in patients with suspected retained calculi seen on CT or US with biliary ductal dilation, MRCP can be useful in evaluation prior to ERCP. Finally, the evaluation for possible biliary leak is often best performed with nuclear medicine HIDA scan which

can be performed as a SPECT/CT in many centers to confirm the presence or absence of excreted tracer in the peritoneum or fluid collection.

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Imaging of the Complex GI Patient

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Knowledge that will change your world

Disclosures

None relevant to this lecture.

Objectives

- To understand the strengths and weakness of grayscale ultrasound, ultrasound elastography, and MR elastography in the diagnosis of liver fibrosis and cirrhosis
- To outline the advantages and disadvantages of different imaging modalities in patients with suspected delayed gastric emptying
- To illustrate the advantages and disadvantages of CT, MRI, US, and NM in the evaluation of the post-operative/post-procedural patient

Patient Scenarios

35 y/o obese male with elevated LFTs

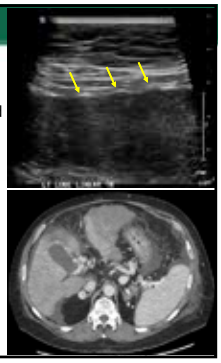
52 y/o female with hepatitis C

44 y/o male with hemochromatosis and elevated LFTs

How best to screen for cirrhosis/liver fibrosis?

Ultrasound for Diagnosis of Cirrhosis

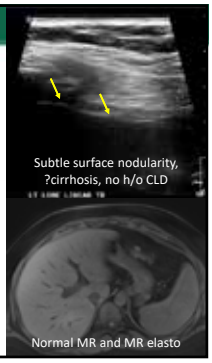
- For patients with chronic liver disease, ultrasound is often the first imaging study obtained
- Additionally, many patients with nonspecific GI complaints also undergo abdominal US as an initial diagnostic imaging test
  - Widely available, cheap, quick
- The diagnosis of cirrhosis on ultrasound can be challenging due to lack of visualization of the entire liver to assess morphology
  - Typically relies on presence of surface nodularity



Ultrasound for Diagnosis of Cirrhosis

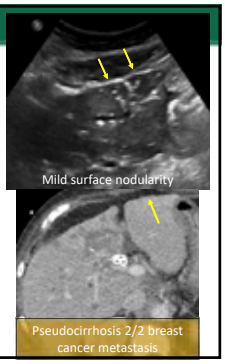
- In patients without evidence of portal hypertension undergoing abdominal US, only moderate utility of US in predicting advanced liver disease on biopsy
  - PPV 68%
  - False positive diagnosis of cirrhosis in 20%
- Data is mixed, with some studies reporting sensitivities of only 50-57% but specificities of 94% or greater
- However, liver surface nodularity can be observed in patients without chronic liver disease (including acute liver disease) and lead to misclassification as cirrhosis
  - Particularly true as ultrasound image quality improves

Kelly EMM et al. Gastroenterol Hepatol (NY). 2018. Poff JA et al. Radiology. 2008. Colli A et al. Radiology. 2003.



Ultrasound for Diagnosis of Cirrhosis

- Slightly lobular surface contour
  - Likely normal variant if no risk factors
- Pseudocirrhosis
  - Due to hepatic metastatic disease mimicking a cirrhotic liver morphology
- Performance of US in diagnosing cirrhosis significantly improves in setting of additional evidence of portal hypertension



Ultrasound Elastography

- Initially approved by the FDA in 2013, US elastography allows for non-invasive detection of hepatic fibrosis
  - Can be done in conjunction with screening abdominal US
- Two techniques
  - Transient elastography (FibroScan)
    - No real time imaging, requires separate device
  - Shear wave elastography (point SWE)
    - Real time imaging, utilizes normal US probe
- Uses ultrasound waves to assess liver stiffness

Ultrasound Elastography

- In a meta-analysis in patients with HBV and HCV, accuracy of pSWE for differentiating early fibrosis (≥ F2), advanced fibrosis (≥ F3), and cirrhosis (F4) was 0.88, 0.94, and 0.91, respectively
- In a meta-analysis including nine studies and 982 patients with NAFLD, the mean accuracy of pSWE for differentiating early fibrosis (≥ F2), advanced fibrosis (≥ F3), and cirrhosis (F4) was 0.86, 0.94, and 0.95
- A meta-analysis comparing pSWE and transient elastography in 1163 patients found a significantly lower rate of unreliable measurements with pSWE (2.1% vs 6.6%, p < 0.001)

Bota S et al. Liver Int. 2013.
Jansen C et al. Liver Int. 2017.

Ultrasound Elastography – Pros/Cons for TE vs. pSWE

Transient Elastography

Pros

- Widely available
- Relatively high accuracy
- Available at POC
- Low equipment cost

Cons

- Requires special device
- Smaller ROI than other techniques
- Higher technical failure rate
- No real-time imaging to avoid confounding structures
- Relative contraindications of ascites and obesity

Smith AD et al. Am J Roentgenol. 2019.

Ultrasound Elastography – Pros/Cons for TE vs. pSWE

Point Shear Wave Elastography

Pros

- Real-time imaging to avoid confounding structures
- High accuracy and precision
- Low failure rate
- Widely available

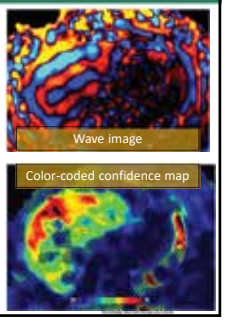
Cons

- Small ROI (compared to new SWE techniques)
- Requirement for patient fasting
- Relatively contraindicated in obesity
- Relatively high expense for deploying at multiple sites

Smith AD et al. Am J Roentgenol. 2019.

MR Elastography

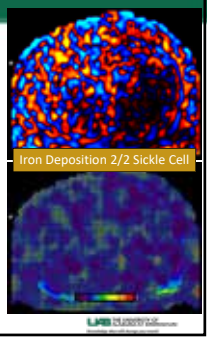
- Noninvasive MR technique allowing for assessment of hepatic fibrosis
  - Evaluates the whole liver rather than a specific area
- Can be performed on 1.5 or 3 T scanners
- Requires specialized software and hardware
  - Acoustic driver
  - Passive driver
- Driver generates mechanical waves through liver
  - Faster wave propagation = increased stiffness



Smith AD et al. Am J Roentgenol. 2019.

MR Elastography

- Excellent performance with meta-analysis demonstrating accuracies of differentiating early fibrosis (≥F2), advanced fibrosis (≥F3), and cirrhosis (F4) of 0.88, 0.93, and 0.92, respectively
- Also allows for simultaneous quantification of hepatic iron and fat deposition
  - Useful in patients with NAFLD
- Comparison between MR elastography and SWE US elastography found similar diagnostic performance but increased reliability of measurements with MR



Yoon JH et al. Radiology. 2014.
Singh S et a. Clin Gastroenterol Hepatol. 2015

MR Elastography

Pros

- Very high accuracy and precision
- Analysis of large portion of liver
- Low technical failure rate

Cons

- Contraindications to MRI
- Requirement for patient fasting
- Limited availability
- Cost
- Limited expertise in some centers

Smith AD et al. Am J Roentgenol. 2019.

Patient Scenarios

35 y/o obese male with elevated LFTs

MR Elastography

52 y/o female with hepatitis C

Gray Scale US +/- US Elastography

44 y/o male with hemochromatosis and elevated LFTs

US Elastography

Patient Scenario

46 y/o female with chronic nausea and vomiting after eating. No prior surgical history. History of poorly controlled DM.

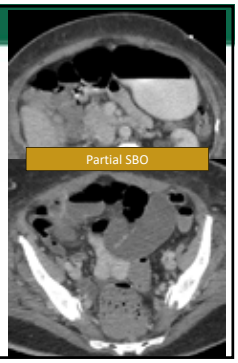
Delayed Gastric Emptying

- Chronic nausea and vomiting is a common complaint in patients presenting to gastroenterology clinic
- Gastroparesis (or delayed gastric emptying) is a potential etiology of these patients complains, particularly in diabetics
  - Prevalence of close to 5% in T1DM and 2% in T2DM
- The imaging algorithm in patients with suspected DGE is unclear and often leads to redundant/potentially unnecessary imaging

Santhanam P et al. Curr Diabetes Rev. 2018.

Delayed Gastric Emptying

- Given the overlap between symptoms of DGE and partial small bowel obstruction, CT may be the initial diagnostic imaging obtained
- Strengths
  - Quick, widely available, helpful in identifying alternate etiology of patient symptoms or evaluation of multiple symptoms in complex histories
- Weaknesses
  - May not provide a diagnosis, not a functional imaging modality, not great for intraluminal disease



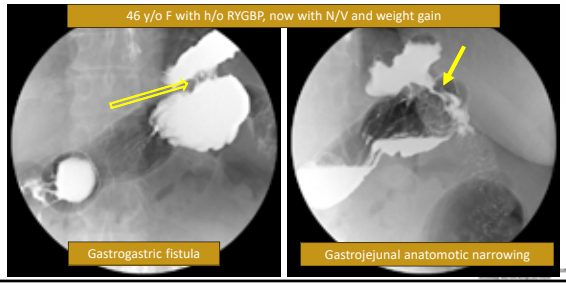
Delayed Gastric Emptying

Delayed Gastric Emptying

- Another imaging test for evaluation of N/V and DGE is upper GI fluoroscopy (single or double contrast)
- Patients will drink contrast and can evaluate intraluminal abnormalities and structural abnormalities
  - Problematic if very nauseated w/o NG tube
- No quantitation of DGE, so diagnosis is not possible on fluoro
- Helpful in post-surgical patients, patients with potential structural abnormalities
- Only intraluminal imaging, operator dependent

Delayed Gastric Emptying

46 y/o F with h/o RYGBP, now with N/V and weight gain



Delayed Gastric Emptying

- Nuclear medicine gastric emptying study is gold standard for quantification of gastric emptying
- Patient consumes a standardized meal composed of all food groups and imaged hourly with established normal values at each time point
  - Traditionally four-hour protocol, two-hour protocol and alternative meals have been validated over time
- Problematic if patient cannot eat or on medications that alter motility
  - Can create issues in inpatient setting
- Offers little information beyond quantification of gastric emptying, no normal values in postsurgical patients

Pelletier-Galarneau M et al. J Nucl Med. 2015.
Sachdeva P et al. Dig Dis Sci. 2013.

Delayed Gastric Emptying

35 y/o F with h/o T1DM, now with N/V

New Bonta criteria

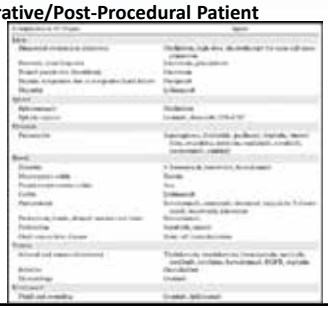
- Gastric retention <45% at 2 hours indicates normal gastric emptying
- Gastric retention >65% at 2 hours is diagnostic of DGE
- Gastric retention <30% at 1 hour is consistent with rapid gastric emptying

The Post-Operative/Post-Procedural Patient

73 y/o male with history of colon cancer on chemotherapy status post left hepatectomy, now with elevated total bilirubin and abdominal pain

The Post-Operative/Post-Procedural Patient

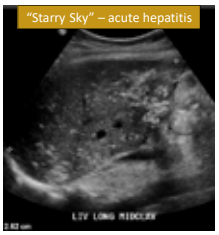
The Post-Operative/Post-Procedural Patient



Viswanathan C et al. Radiographics. 2014.

The Post-Operative/Post-Procedural Patient

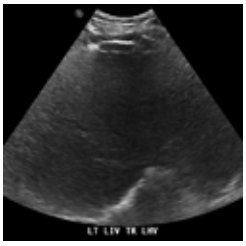
- Ultrasound - Strengths
  - Frequently the first-line imaging test of the abdomen (particularly the liver)
  - Cheap, quick, can be done portable
  - Obtains dynamic imaging (e.g. Doppler) when compared to CT
  - Can determine the presence of obstructive jaundice by depicting dilated bile ducts, with reported sensitivities ranging from 32% to 100% and specificities of 71% to 97%



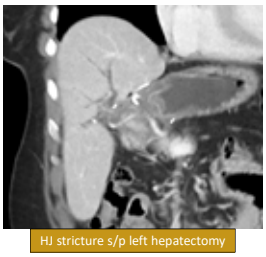
Posanen PA et al. Eur J Surg. 1993.
Mitchell SE et al. AJR Am J Roentgenol. 1984.

The Post-Operative/Post-Procedural Patient

- Ultrasound - Weaknesses
  - May not be conclusive in etiology of findings and lead to additional imaging studies
  - May be technically limited in patients who are recently post-operative
    - Bowel gas and/or free intraperitoneal air frequently limit visualization of CBD
  - Operator dependent and prone to artifact
  - Visualization of structures is often limited in larger patients
  - Does not image the entire abdomen



The Post-Operative/Post-Procedural Patient

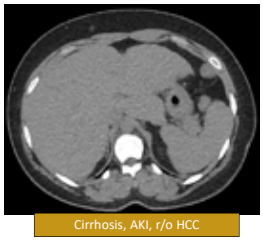


HJ stricture s/p left hepatectomy

- CT – Strengths
  - Widely available, quick
  - Excellent spatial resolution
  - Not as sensitive to motion as MRI
  - Images the entire abdomen and may offer alternative diagnoses in cases of abdominal pain
  - For biliary obstruction, CT outperforms US in characterizing the location of the obstruction and if the obstruction is malignant or benign

Maurea S et al. Radiol Med. 2009.

The Post-Operative/Post-Procedural Patient

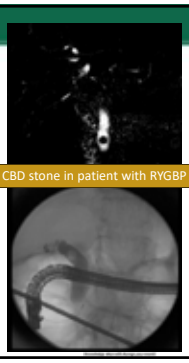


Cirrhosis, AKI, r/o HCC

- CT – Weaknesses
  - Requires transport to the radiology department
  - Less useful without use of intravenous contrast
    - May be limited in patients with renal dysfunction
  - Ionizing radiation (less of an issue with adults)
  - Static imaging

The Post-Operative/Post-Procedural Patient

- MRI/MRCP – Strengths
  - Most sensitive test for detection of choledocholithiasis than CT or US
  - May provide additional information about hepatic parenchymal disease, early manifestations of PSC, and underlying cholangitis
  - For diagnosis of CBD stones, MRI has sensitivity 77-88% and specificity 50-72%

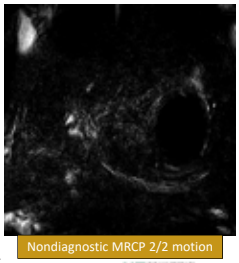


CBD stone in patient with RYGBP

Kolodziejczyk E et al. Pancreas. 2016.

The Post-Operative/Post-Procedural Patient

- MRI/MRCP – Weaknesses
  - Highly motion sensitive
    - MRCP sequences require multiple breath holds of ~20 seconds
    - Severely limits its sensitivity
  - Expensive, long exam (30-60 min), limited availability
  - Limited utility in cases with elevated bilirubin and negative US (non-obstructive jaundice)
    - AGA guidelines recommend additional laboratory testing and no additional imaging



Nondiagnostic MRCP 2/2 motion

Kwo PY E et al. Am J Gastroenterol. 2017.

Take Home Points

- Noninvasive evaluation of liver fibrosis
  - Grayscale ultrasound is an excellent, widely available screening modality that is capable of diagnosing cirrhosis but does not allow for quantification of fibrosis
  - US Elastography is a specialized US technique that allows for evaluation of liver fibrosis, but typically only evaluates a single portion of the liver
  - MR Elastography is the most comprehensive method of evaluation fibrosis throughout the liver, but requires special hardware and software and post-processing
    - May not be available at all imaging centers

Take Home Points

- Delayed Gastric Emptying
  - CT may serve as initial imaging modality in patients with N/V, particularly if low-grade or partial SBO is being considered
  - Fluoroscopy provides high-resolution images of intraluminal structural abnormalities of the UGI tract, but is operator-dependent and cannot quantify gastric emptying
    - Likely more appropriate in post-surgical patients
  - Nuclear medicine gastric emptying study is gold standard for diagnosis of DGE, but many medications can affect the results and offers no other information

Take Home Points

- Post-procedural/Post-operative patients with jaundice
  - US is an excellent screening modality for potential biliary obstruction, but may be limited in larger patients or patients who are recently post-operative
  - CT is the mainstay of diagnosis in post-operative complications and can often provide a rapid, accurate diagnosis
  - MRI is the most sensitive imaging technique for evaluating the liver and biliary tree, but is highly motion sensitive and likely suboptimal in the inpatient setting

Thank you for your time!

Questions?

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"EndoHepatology: expanding the role of endoscopy in the management of patients with liver disease"

Disclosures:

Grants: Cook Medical, Erbe, EndoGastric Solutions, Pentax, Olympus, Medtronic, Creo Medical, Aqua Medical
Consulting fee: Apollo, Aqua Medical, Boston Scientific, Cook Medical, Creo Medical, Endogastric Solutions, Erbe, Medtronic, Mauna Kea, Olympus, Ovesco, Pentax
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Support for travel to meetings: Cook Medical, Endogastsric Solutions, Erbe, Medtronic, Olympus
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Royalties: Cook Medical

Learning Objectives:

- Recognize the emerging field of endo-hepatology and early evidence
- Understand future paradigms for the endoscopic evaluation of the liver patient

The application of EUS for liver indications is now termed "Endo-hepatology."[1, 2] The initial indication for Endo-hepatology was EUS-guided liver biopsy (EUS-LB). This is followed by EUS-guided portal pressure gradient (PPG) measurement and EUS-guided shear wave elastography (SWE). *EUS-guided Liver Biopsy:* The arguments in favor of EUS-LB over conventional percutaneous approaches include: 1) real-time ultrasound guidance of the needle into the liver, with Doppler confirmation of no blood flow within the needle track prior to removing the needle from the liver, 2) the ability to make several needle actuations within the liver with a single puncture through the liver capsule, 3) rapid recovery time (no need to have the patient lie over their right side for long periods), 4) the ability to sample both lobes of the liver and 5) potential for simultaneous endoscopy, EUS-guided shear wave elastography, and EUS-guided portal pressure gradient measurement (see below). Cost analyses also suggest a lower over-all cost of the EUS strategy when factors such as recovery time, non-diagnostic yield, and complications are factored in.[3]

EUS-guided portal pressure gradient (PPG): Portal hypertension (PH), resulting from increased resistance of hepatic sinusoids to blood flow, is a severe complication of liver cirrhosis increasing the risk of esophageal varices, gastric varices, portal hypertensive gastropathy, ascites, and hepatorenal syndrome. Measurement of PH has been useful in determining the stage, progression, and prognosis of cirrhosis in individual patients. Using a trans-jugular approach, the hepatic vein pressure may be measured directly (called the free hepatic venous pressure, or FHVP). However, the portal vein pressure is usually determined indirectly from the wedged hepatic venous pressure (WHVP). HVPG

has been shown to predict the likelihood of clinical decompensation in patients with compensated cirrhosis.[4] A portal pressure gradient (PPG) measurement of 0-5 mmHg is considered normal, between 6-9 mmHg is considered portal hypertension, ≥10 mmHg is considered "clinically significant" portal hypertension and associated with development of esophageal varices; and finally, a PPG of ≥12 mmHg is associated with variceal hemorrhage. Reduction of PPG by 20% or to below 12 mmHg with pharmacotherapy has been found to decrease risk of future bleeding or re-bleeding episodes. The portal pressure gradient is also useful in assessing response to B-blockers, response to anti-viral agents, and risk for post-hepatectomy liver failure in patients with HCC. In clinical practice, portal hypertension is most often diagnosed by percutaneous transjugular pressure measurements. This method is relatively invasive, requires ionizing radiation, intravenous contrast, and provides only indirect measurements. The procedure is performed by placing a radiopaque catheter into the right jugular vein and advancing it into the hepatic vein tributaries under fluoroscopic guidance. A free and a wedged hepatic vein pressure are then obtained. The HVPG, an indirect measurement of the portal vein pressure, is estimated by subtracting the FHVP former from WHVP. This estimation can be inaccurate in cases of pre-hepatic portal hypertension, such as portal vein thrombosis, and duplex ultrasonography is often also required. In addition, patients with hepatic, pre-sinusoidal portal hypertension, such as in myeloproliferative disorders, can have an inaccurate HVPG.

EUS-guided PPG measurement was initially developed using a 25-gauge needle and a novel compact manometer in an animal model[5] demonstrating excellent accuracy and strong correlation with pressure values obtained by the gold standard transjugular wedged and free hepatic venous pressure measurements by interventional radiology. The initial pilot study in humans demonstrated safe and accurate direct portal pressure gradient measurements**.** A total of 28 patients underwent EUS-guided portal pressure manometery in this study and pressure measurements were successfully achieved in all 28 patients. EUS-PPG values ranged from 1.5-19mmHg with a mean of 8.2mmHg. 15/28 (57.1%) had evidence of PH based on EUS-PPG of which 10/15 (66.7%) had clinically significant portal hypertension (CSPH). Eleven of 28 subjects had endoscopic evidence of either esophageal or gastric varices with all 11 (100%) having PH and 10 (90.9%) patients having CSPH based on EUS-PPG measurement.[6,7] This study showed that EUS-guided portal pressure measurement using a 25-g needle and compact manometer was feasible and appeared to be safe in humans. An updated abstract was published with 51 patients undergoing EUS-PPG, with 100% technical success, no adverse events, and a PPG range of 0-27 mmHg with strong correlation with clinical markers of portal hypertension.[8] A study in a cohort of patients who underwent both EUS-PPG as well as EUS-guided liver biopsy demonstrated that the two procedures could be conveniently combined in one setting.[9] EUS-PPG can also overcome the issue of accurately diagnosing hepatic, pre-sinusoidal portal hypertension – by directly measuring the pressure in the portal vein. While EUS-PPG in clinical trials being compared to the "gold-standard" HVPG, one can argue that EUS-PPG could become the new "gold-standard" with direct measurements of both vessels. This technique represents a promising breakthrough for procuring indispensable information in the management of patients with liver disease. With the expansion of EUS to the liver and the emergence of the field of "Endo-Hepatology," there is now potential for "one-stop-shop" diagnosis and staging of liver disease.

Suggested readings:

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3. Mony S, Shah I, Vyas N, et al. EUS-guided Liver Biopsy is more cost-effective than percutaneous liver biopsy in patients with non-alcoholic fatty liver disease (NAFLD). Gastroinest Endosc 2018;87:AB326-327.
4. Ripoll C, Groszmann R, Garcia-Tsao G, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology 2007;133:481-8.
5. Huang JY, Samarasena JB, Tsujino T, et al. EUS-guided portal pressure gradient measurement with a novel 25-gauge needle device versus standard transjugular approach: a comparison animal study. Gastrointest Endosc 2016;84:358-62.
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Knowledge that will change your world

EndoHepatology:

Expanding the role of endoscopy in the management of liver disease

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Vincent & Anna Kong Chair, GI Endoscopic Oncology
University of California, Irvine

Disclosures

- Apollo
- Boston Scientific
- Cook
- Covidien
- Erbe
- Endogastric Solutions
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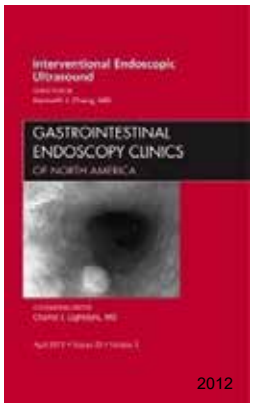


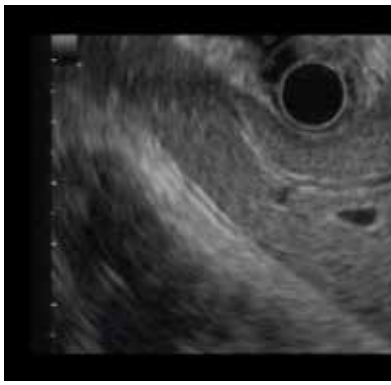
Preface
Interventional Endoscopic Ultrasound

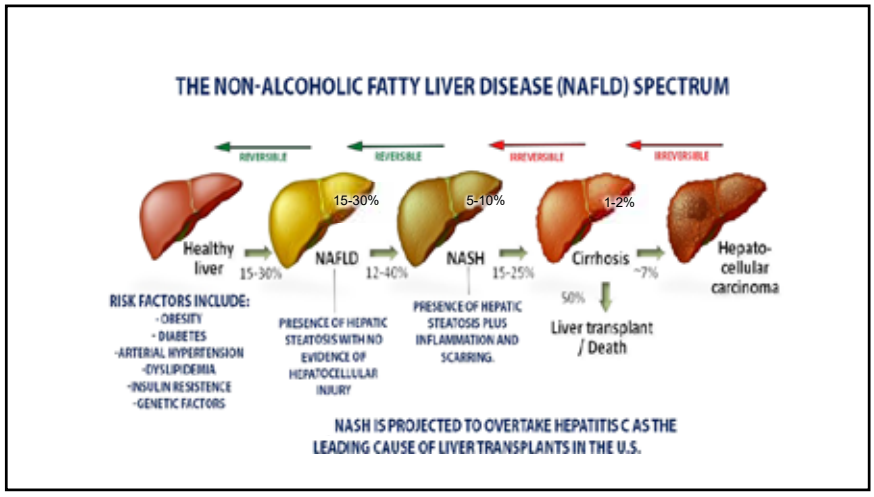
Kenneth J. Chang, MD
Guest Editor

Endo-Hepatology: A New Paradigm

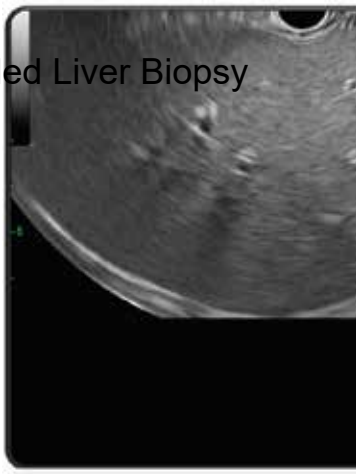
Kenneth J. Chang, MD[a,*], Jason B. Samarasena, MD[a], Takuji Iwashita, MD, PhD[b,c], Yosuke Nakai, MD, PhD[a,d], John G. Lee, MD[a]

"EUS Liver Palpation"

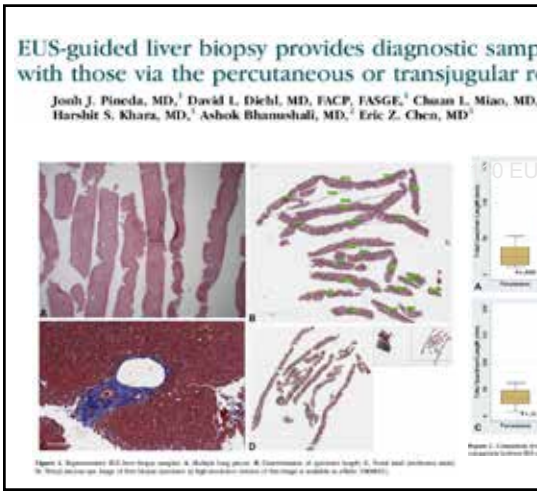




EUS-guided Liver Biopsy



Multiple To-Fro, Fanning

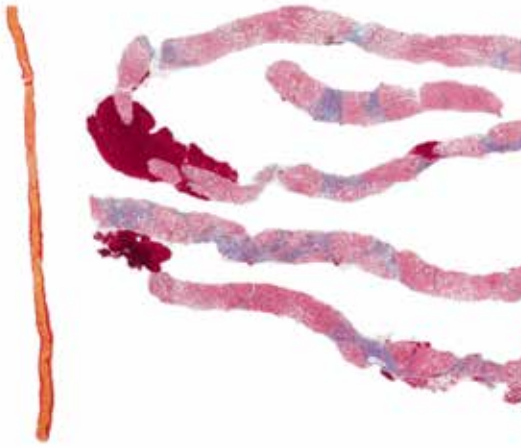


Specialized Tip Core needles

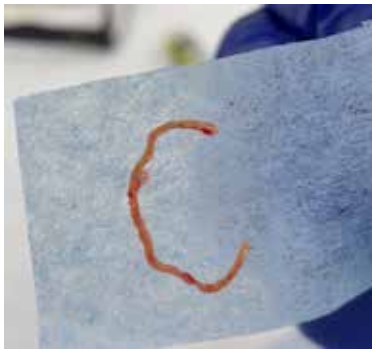
Fork-tip

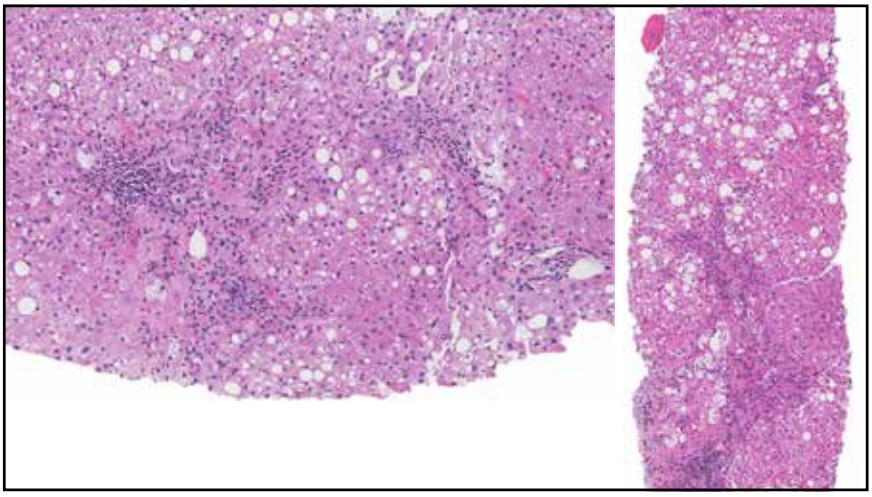
Franseen

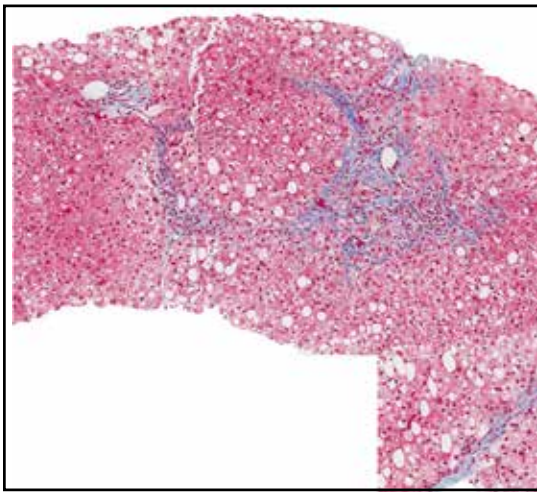
Menghini



Very long cores…..







19G aspiration needle versus 19G core biopsy needle for endoscopic ultrasound-guided liver biopsy: a prospective randomized trial

Take Home:

- **19G Franseen tip better than 19G standard needle**
- Both Left and Right lobe
- (7-10 to/fro); heparinized, suction
- EUS-LB using the FNB needle delivered longer liver biopsy specimens with more CPTs than the regular (non-core) needle.

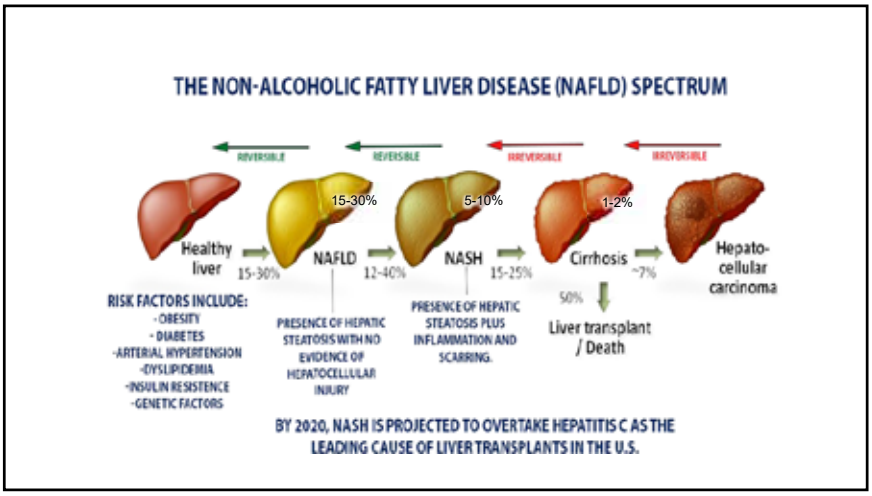
Ching-Companioni RA et al.
Endoscopy 2019; 51: 1059–1065

▶ Table 1 Quantitative outcomes comparing fine-needle aspiration versus core biopsy needles.

	FNA (n = 20)	FNB (n = 20)	P value
Aggregate specimen length, mean (SD), cm			
• Pre-processing	18.89 (4.38)	15.78 (5.19)	0.003*
• Post-processing	11.4 (5.55)	10.32 (5.24)	0.028*
Length of longest piece, mean (SD), cm			
• Pre-processing	1.47 (0.40)	2.09 (0.41)	<0.001*
• Post-processing	1.05 (0.42)	1.76 (0.66)	<0.001*
Length of the longest piece			
• <2 cm	17 (85)	10 (50)	0.04*
• ≥2 cm	3 (15)	10 (50)	0.04*
Total specimen complete portal triads			
• Mean (SD)	18.1 (9.3)	42.6 (25.0)	<0.001*
• Median (range)	16.5 (6–38)	38.0 (9–81)	0.004*
Portal triads groups, n (%)			
• <11	6 (30)	2 (10)	0.24
• ≥11	14 (70)	18 (90)	0.24
No. of fragments ≥ 9 mm, mean (SD)			
• Pre-processing	3.5 (2.4)	7.7 (3.7)	<0.001*
• Post-processing	1.1 (1)	4.8 (3.6)	<0.001*

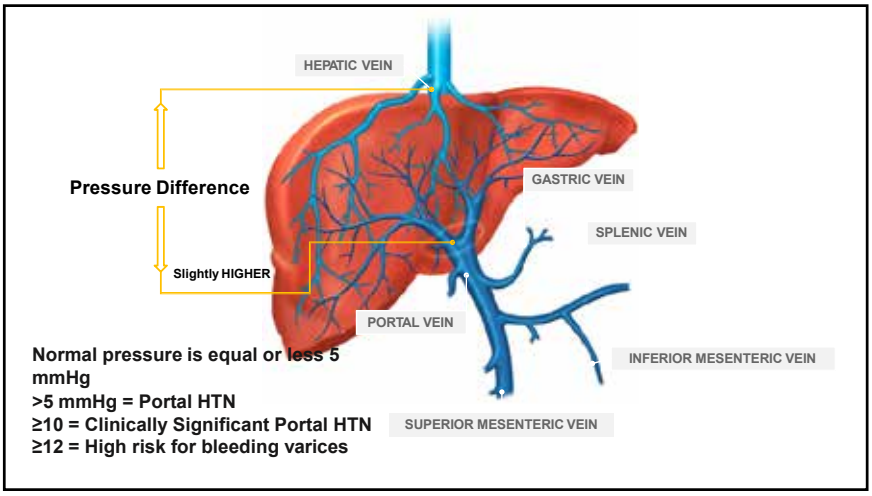
Comparison of Two Specialized Histology Needles for Ultrasound (EUS)-Guided Liver Biopsy: A Pilot Study
Hashimoto, Chang, et al Dig Dis Sci 2020 (in-press)

	19G Franseen (n=22)	19G Fork-tip (n=22)
Randomized to first pass, n (%)	11 (50%)	11 (50%)
Left lobe vs Right Lobe, n:n	11:11	11:11
Pre-fix aggregate specimen length, mm	51.7	45
Post-fix aggregate length specimen, mm	44.9	34.6
Post-fix longest length specimen, mm	19.9	13.7
Complete portal tracts (CPTs), mm	14.4	9.5
Adequate specimen, n		
Pathologist Qualitative Assessment	22	21
NEJM 2001, n(%)[CPT≥5; length≥15mm]	21 (96)	17 (77)
AASLD 2009, n(%) [CPT≥1; length≥20mm]	15 (68)	6 (27)

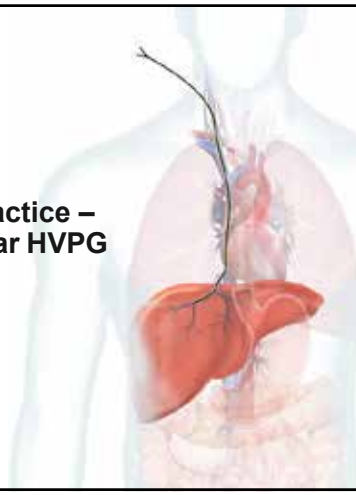


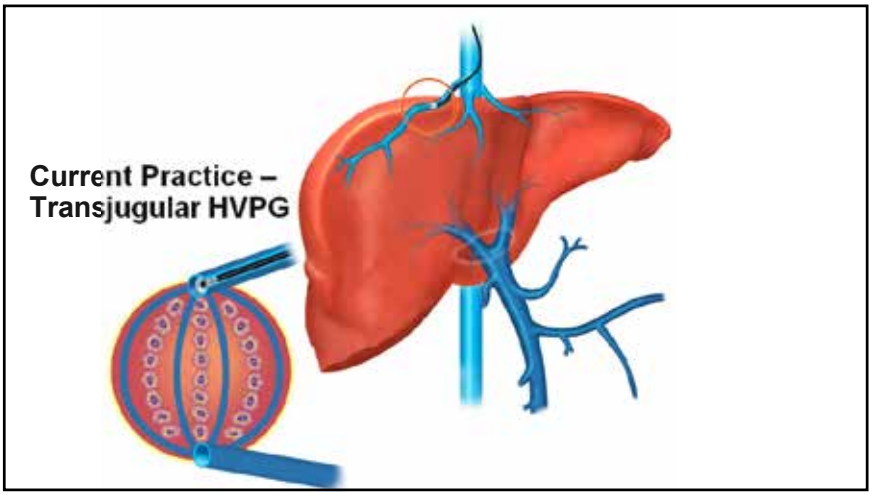
EUS-guided porto-systemic press

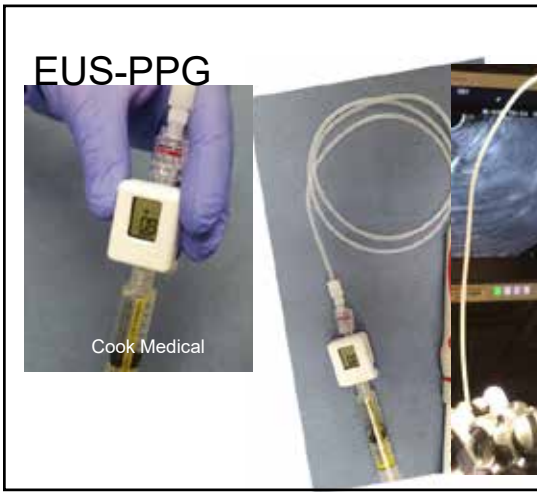
- Portal hypertension (PH) is a se liver cirrhosis.
- The hepatic venous pressure gr accurately reflects the degree of
- Single best prognostic factor in l
- Guides medical therapy
- Predicts liver decompensation &



Current Practice – Transjugular HVPG



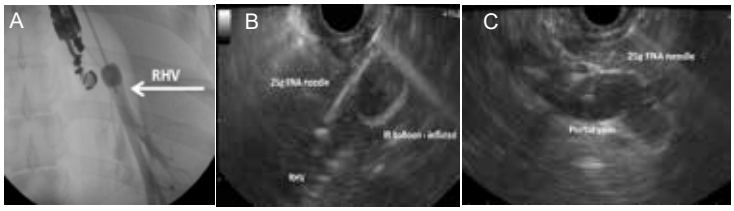




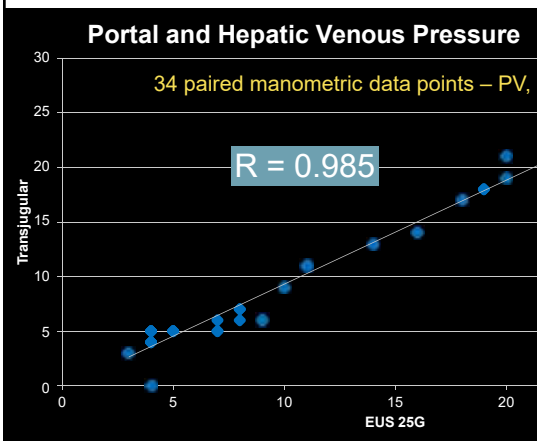
EUS-guided portal pressure gradient measurement with a novel 25-gauge needle device versus standard transjugular approach: a comparison animal study

Jason Y. Huang, FRACP, Jason B. Samarasena, MD, Takeshi Tsujino, MD, Kenneth J. Chang, MD

- Compared EUS-PPG vs
- Simultaneous Transjugular balloon catheter



GIE 2016:84:2: 358-62



EUS-guided portal pressure gradient measurement with a simple novel device: a human pilot study

Jason Y. Huang, FRACP,[1] Jason B. Samarasena, MD,[1] Takeshi Tsujino, MD, PhD,[1] John Lee, MD,[1] Ke-Qin Hu, MD,[1] Christine E. McLaren, PhD,[2,3] Wen-Pin Chen, MS,[3] Kenneth J. Chang, MD[1]

Irvine, California, USA

AIMS:

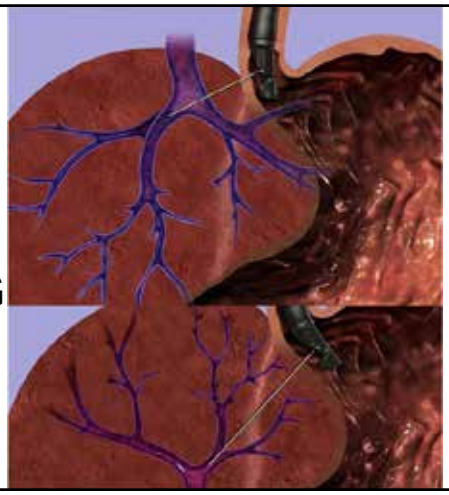
- To evaluate the feasibility and safety of EUS–PPG technique in humans
- To correlate EUS-PPG with endoscopic and clinical evidence of PH in patients with liver disease

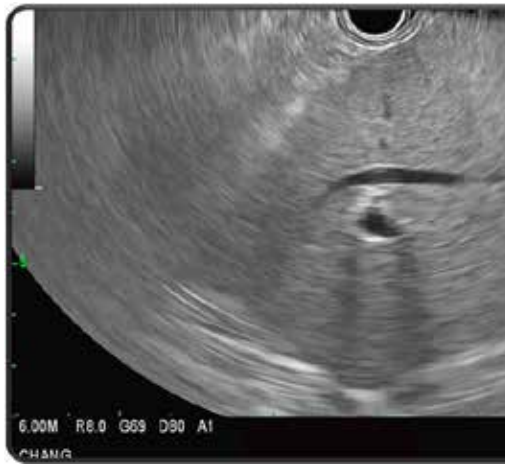
GIE 2017;85:996-1001

Results

- All 28 subjects underwent EU 100% technical success
  - *Identifying and accessing targ*
  - *Obtaining Manometric pressu*
- There were no complications
- PPG range was 1.5-19mmHg

EUS-PPG





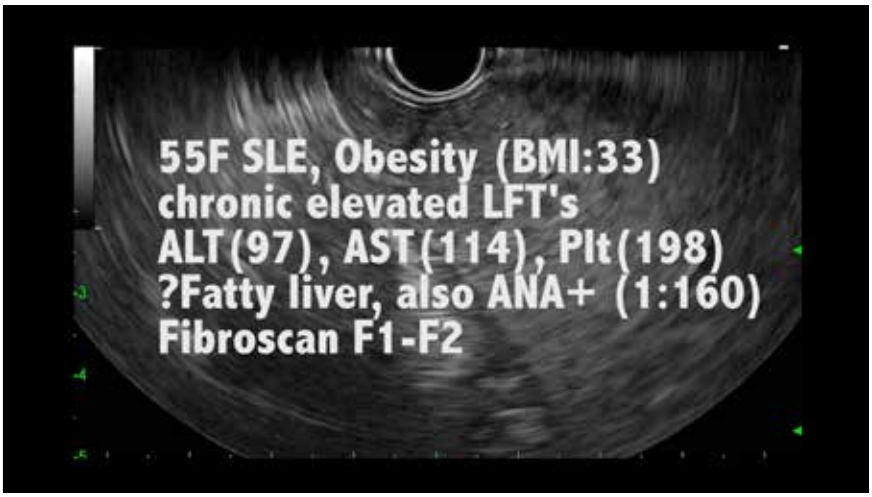
Study Conclusions

- In this human pilot study, the novel technique of EUS-guided PPG using a 25G needle and compact manometer was feasible and appeared safe.
- EUS-PPG values showed excellent correlation with clinical parameters of PH.

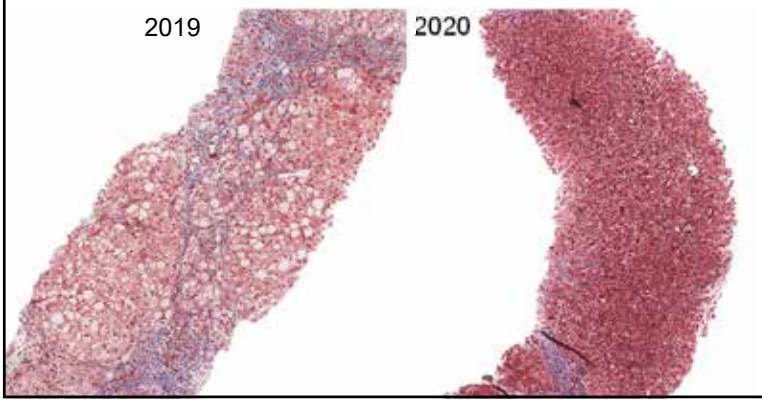
Safety and feasibility of combination EUS-guided po gradient measurement and liver biopsy the realization of Endo-Hepatology

Takeshi Tsujino, MD, PhD, Jason Y. Huang, MD, Jason B. Samarasena, M Miller, FRCPA, Andrew Clouston, FRCPA, Kenneth J. Chang, MD, FASGE

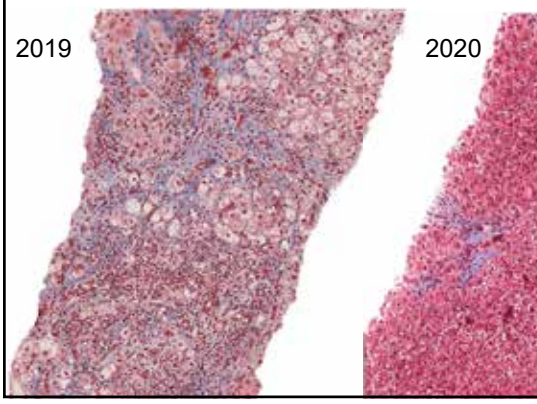
- In 22 patients, both EUS-guided PPG m liver biopsy performed during the same
- 100% technical success. Mean PPG = 6
- Subjective and objective histological ade guided liver biopsy was 91% and 73%,
- Mean number of complete portal tract w
- Mean PPG was significantly higher in pa F3 and F4 compared to those with Meta



1 year after ESG – 60 lb weight loss

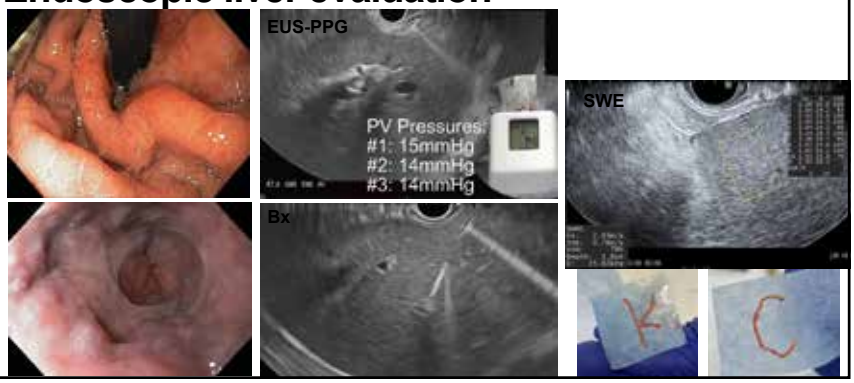


1 year after ESG – 60 lb weight loss



One-stop shop

Endoscopic liver evaluation



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EndoHepatology

Expanding the role of e
in the management of liv

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Birmingham, AL

"Updates in the surgical management of pancreatic cancer"

Disclosures: **None**

Learning Objectives:

1) Recognize risk factors for pancreatic cancer
2) Understand surgical options in pancreatic cancer

Summary of presentation: Pancreatic Cancer: A Surgeon's Perspective

1. The incidence rate of pancreatic cancer is increasing in United States
2. Pancreatic cancer has recently overcome breast cancer and has become the 3rd most common cause of cancer related deaths in United States.
3. If the current trend continues, pancreatic cancer will soon become the 2nd most common cause of cancer related deaths.
4. Risk factors of pancreatic cancer include Smoking, Diabetes Mellitus, Obesity, Alcohol intake and pancreatitis.
5. Weight loss and pain are the most common symptoms of pancreatic cancer.
6. Unfortunately, most patients with pancreatic cancer present with locally advanced and/or metastatic disease.
7. Only about 20% of patients with pancreatic cancer are eligible for some sort of surgical resection.
8. Data suggest that an aggressive approach to surgical resection improves outcomes.
9. Pancreatic cancer, based on the involvement of the surrounding vascular structures and presence/absence of metastases can be classified into
    a. Resectable disease
    b. Borderline resectable disease
    c. Locally advanced resectable
    d. Metastatic disease
10. In the past, patients who had resectable or borderline resectable disease underwent upfront surgery. Such approach, unfortunately, was associated with early relapse with upto 30% developing local/systemic recurrence within 1 year after surgery. The surgery led to decreased performance status with decreased ability to tolerate adjuvant chemotherapy. Nationally, as high as 60% of patients undergoing surgery first approach did not receive adjuvant therapy.
11. Now, patients are increasingly being treated with neo-adjuvant approach. Neoadjuvant treatment is in the form of either FOLFIRINOX or GEM/Abraxane.
12. Adjuvant therapy

   a. ESPAC-3 trial demonstrated Gemcitabine and 5-FU were equivalent as adjuvant therapy
   b. ESPAC-4 demonstrated combination of gemcitabine with capecitabine was better then gemcitabine alone.

13. Radiation Treatment: No data till date has shown radiation to equivocally benefit patients with pancreatic cancer. We consider radiation in cases where the disease is localized but the patient is unable to undergo surgery due to performance status or in locally recurrent disease.
14. Surgical treatment
   a. Tumor in the head of the pancreas: Whipple operation
   b. Tumor in the tail of the pancreas: Distal pancreatectomy and splenectomy
15. Staging laparoscopy: We consider staging laparoscopy in almost all patients as if we find micrometastatic disease which was not evident on the staging scans, we can avoid laparotomy.
16. Involvement of portal vein/SMV not a contra-indication, if there is options for reconstruction available
17. Short segment involvement of hepatic artery: not a contra-indication. Recommend neo-adjuvant treatment.
18. <180 involvement of SMA, not a contra-indication. After neo-adjuvant treatment.

Updates on Pancreatic Cancer

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Financial Disclosures

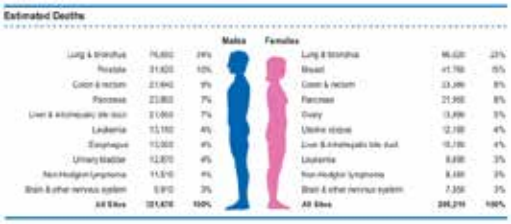
- Nothing to disclose

Agenda

- What's new with pancreatic cancer
- A little bit of history
- Discuss the work of the Pancreatobiliary Disease Center (PDC)

Background

Epidemiology



- 56,770 will be diagnosed in 2019
- 45,750 will die of PDAC in 2019 (770 in Alabama)
- M:F 1.1:1

Risk Factors

Risk Factor	Risk Estimate (95% CI)
Current Cigarette Smoking	OR= 2.20 (1.71–2.83)
Past Cigarette Smoking 1–10 years since quitting 15–20 years since quitting	OR=1.64 (1.36–1.97) OR=1.12 (0.86–1.44)
Diabetes Mellitus <3 years >10 years duration	RR=7.94 (95% CI, 4.70–12.55) OR 1.51 (95% CI=1.16–1.96)
BMI (>35 vs 18.9–24.9)	OR =1.55 (95%CI=1.16 – 2.07)
Heavy Alcohol (> 6 drinks/day)	OR 1.46 (95%CI=1.16–1.83)
Pancreatitis (>2 years)	2.71 fold (95% CI 1.96–3.74)

Wolfgang. CA Cancer J Clin. 2013

Genetic Risk

Gene/Risk Group	Risk Estimate (95% CI)	Estimated Lifetime Pancreatic Cancer Risk
General Population	1	0.9%(by age 80)[225]
Familial Pancreatic Cancer Overall 3 or more first-degree relatives with pancreatic cancer	RR= 6.79 (4.34 to 9.75) RR= 17.02 (7.34 to 33.3)	Varies with youngest age of onset
High Penetrance		
BRCA2	RR = 3.35(1.87–6.38)[228]	3.36% (age 80) [4]
PALB2	Elevated	Elevated
BRCA1	OR=2.26 (1.26 to 4.06)[33]	2.16% (age 80) [4]
Mis-Match Repair (HNPCC)	RR=8.6 (4.3–15.7) [34]	3.68%(3.41%–3.89%)(age 70)[29]
Hereditary Pancreatitis (*PRSS1*)	RR=50 (23–107)[47]	30–40%(age 70) [4748]
Peutz-Jeghers (*STK11*)	RR=132 (44, 281)[227]	11%-32%[28, 29]
Familial Melanoma(*CDKN2A*)	RR=38 (10–97)[49]	17% (age 75)
ATM	Unknown	Unknown

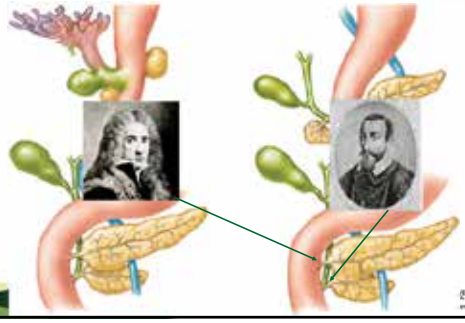
Wolfgang. CA Cancer J Clin. 2013

Presenting Symptoms

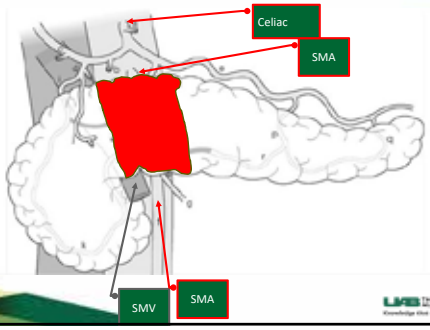
Sign/Symptom	Incidence (%)
Weight loss	50–90
Pain	75–80
Malnutrition	50–75
Jaundice	70
Anorexia	60
Diabetes	15–40
Ascites	5
Gastric outlet obstruction	5

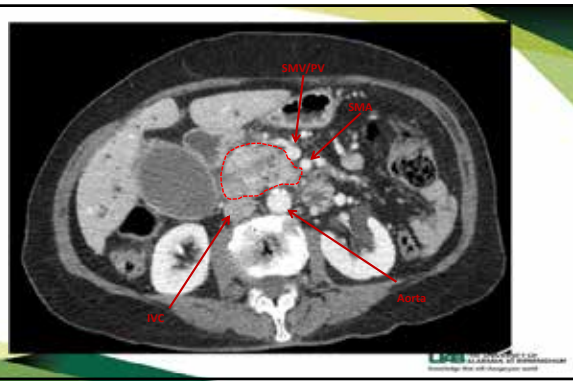
Thomas and Ahmad SOCNA 2010

Development

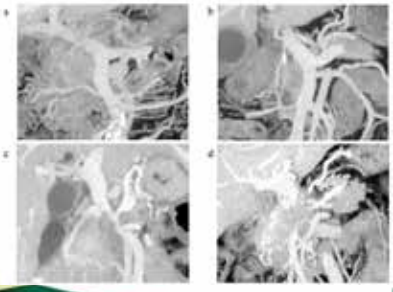


Pancreatic Neck –surgical anatomy





Venous involvement

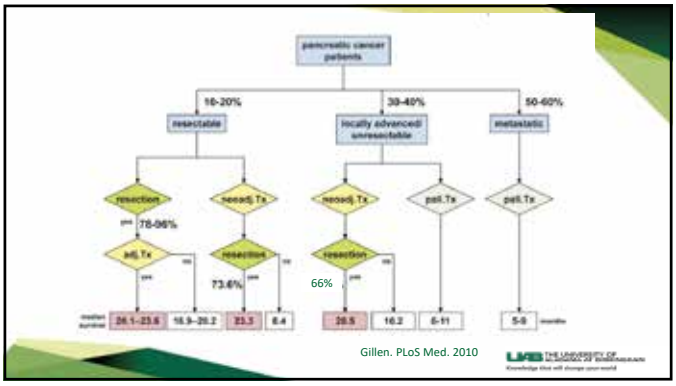


Isaji. Pancreatology. 2017

Anatomic classification

Isaji. Pancreatology. 2017

Gillen. PLoS Med. 2010



What's driving poor survival?

- 80% of patients with pancreatic cancer die from metastatic disease
- Pancreatectomy is associated with significant morbidity—short- and long-term
- How do we control distant disease?
- Should we be more selective on whom we operate?

Adjuvant

Study	N	Design	Results	P-value
5yr actual survival was 21% vs 10% (HR 0.76 [95% CI 0.61 – 0.95]; p=0.01)				
Neoptolemos, 2009 (ESPAC-3)	1030	Gem vs 5FU	23.6 vs 23	NS
Neoptolemos, 2017 (ESPAC-4)	732	Gem + Cap vs Gem	28 vs 25.5	0.032

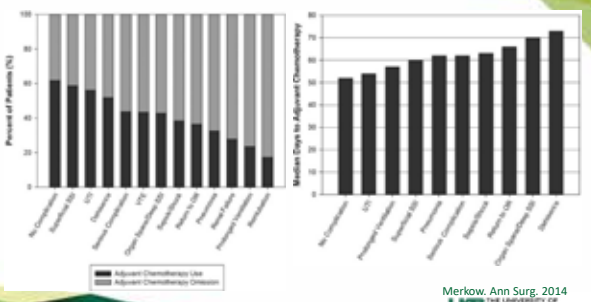
Oettle. JAMA. 2013

Completion of Adjuvant Therapy

- Only 75% will even start adjuvant treatment
- 25-50% of patients in a surgery first approach complete subsequent chemotherapy or chemoradiotherapy
- Adjuvant is typically single agent

Spitz. J Clin Onc. 1997

Reasons for Adjuvant Omission



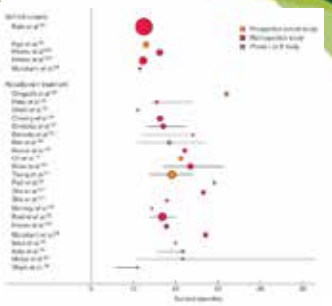
Merkow. Ann Surg. 2014

Rationale for Upfront Therapy (Neoadjuvant)

- *In vivo* assessment of tumor response to chemotherapy
- Patient selection prior to surgery
- Tumor regression (margin or LN negative resection)
- More likely to complete multidrug therapy
- Have better peri-operative outcomes?

Neoadjuvant for borderline disease

- Surgery 1st (n=927)
  - 12.8mo OS, 81% resected
  - 15mo OS if resected, 64% R0
- Neoadj (n=819)
  - 19.2mo OS, 65% resected
  - 26.9mo if resected, 87% R0
- So it's settled right?



Versteijne. Br J Surg. 2018

Not Really…

- Most data is moderate quality
- Still unclear if benefit is systemic treatment vs selection bias
- Most studies based on old regimens

Multidrug Regimens

- For metastatic pancreatic cancer

Study	N	Design	Results	P-value
Von Hoff, 2013	861	Gemcitabine +nab-Paclitaxel vs. Gemcitabine	8.7 vs. 6.6 mo	<0.001
Conroy, 2011	342	FOLFIRINOX vs. Gemcitabine	11.1 vs. 6.8 mo	<0.001
Moore, 2007	569	Erlotinib + Gemcitabine vs. Gemcitabine	6.24 vs. 5.91	0.038

10 days!!

FOLFIRINOX with Locally Advanced Disease

Study	N	Full Dose	Resection	Grade 1/2	Grade 3/4
Hosein, 2012	18	83%	44%	100%	44%
Peddi, 2012	23	18%	35%	NR	34%**
Gunturu, 2013	16	83%*	12%	NR	26%
Vasile, 2013 (abstract)	32	NR	42%	NR	65%**
Blazer, 2015	43	58%	51%	NR	30%

53/132 = 40% Conversion rate into resectable disease

*Of the first cycle, virtually everyone in subsequent cycles got dose reduction
**True toxicity not reported, these are admission rates for G3/4 toxicity

What about radiation?

Adjuvant

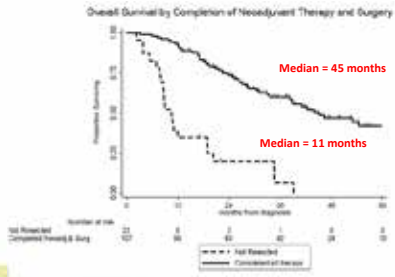
- ESPAC-1: 5FU vs 5FU+XRT vs CRT+CT vs Obs (17.9 vs 15.9 mo)
  - Poor adherence (70% got full 20Gy EBRT dose)
- Hopkins+Mayo: 5FU CRT vs Obs (MOS 21.1 vs 15.5 mo; p=<0.001)
  - Best for R1 or R0 w/ LN+

Neoadjuvant

- NCT01458717: Gem+XRT vs Upfront resection (21 vs 12 mo)
  - Low dose Gem. Not modern chemo.
- LAP07 trial: Gem vs Gem/Erb -> CT vs CRT.
  - No survival benefit (only 4% resected).
  - Improved local control (32% vs 46%)

Hsu. Ann Surg Onc, 2010 Hammel. JAMA. 2016
Jang. Ann Surg. 2018 Neoptolemos. NEJM. 2004

Molecular Profiling To Guide Neoadjuvant



Profile
1. TYMS
2. ERCC1
3. RRM1
4. SPARC
5. TOP1
6. hENT1

Tsai S. Ann Surg 2018

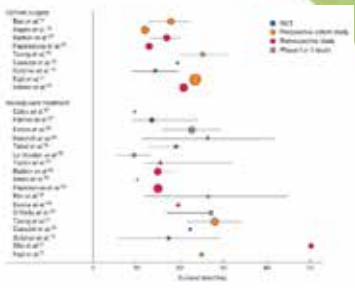
Ongoing Neoadjuvant Trials

- ESPAC-5F: Surg vs GEMCAP vs FOLFIRINOX vs Cap-EBRT (BRPC)
- Alliance 021501: mFOLFIRINOX +/- SBRT

Trial is halted as of 8/7/18 for interim analysis

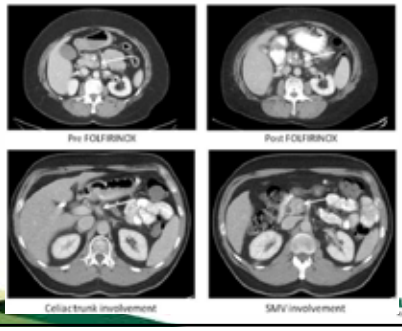
Upfront Therapy for Resectable Patients?

- Surgery vs neoadj
  - MOS: 17.7 vs 18.2mo
  - Resected: 77 vs 67%
  - R0: 71 vs 85%
- SWOG S1505: FOLFIRINOX vs Gem/Abx (Resectable)



Versteijne. Br J Surg. 2018

Why push the boundaries?



Ferrone. Ann Surg. 2016

Drawbacks of Upfront Chemotherapy

- A resectable tumor can become unresectable
  - Tumors slower growing than we think.
  - 12 years to form, 7 years to met, 3 years to death
- Decline in performance status
  - 80% + will complete neoadjuvant regimen
- Development of metastases
  - Likely already there if seen after 2-3 months

Iacobuzio-Donahue. Nature. 2010

Resection

Operative planning

Important questions:

- Mets?
  - Neg on CT and/or PET
- Major comorbidities
  - No issues
- Functional status
- Age
- Staging laparoscopy?

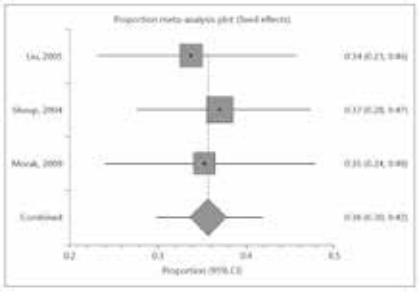
Procedures for right-sided PDAC:

- Pancreatoduodenectomy (Whipple)

Procedures for left-sided PDAC:

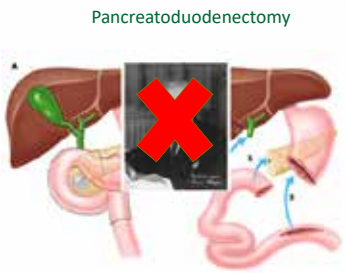
- Distal pancreatectomy/splenectomy
- Radical Antegrade Modular pancreatosplenectomy (RAMPS)
  - Anterior
  - Posterior

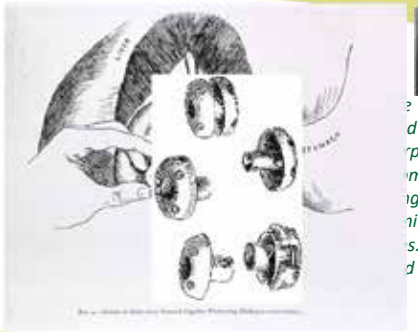
Staging Laparoscopy



Ta. Dig Surg. 2018

Pancreatoduodenectomy





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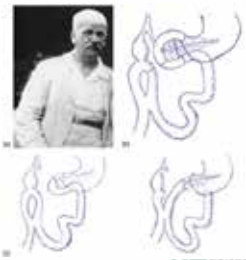
August 21, 1909

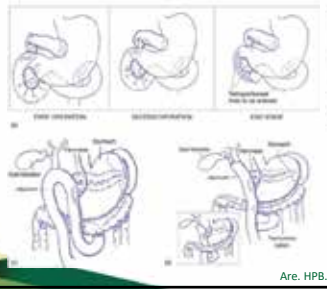
(Walther Kausch)

- *'Adhesions from prior (cholecystoenterosomy) operation add to the difficulty. After Kocherization, I verified resectability. Having confirmed that it was resectable, I went on to, fashion a gastroenterostomy, close the pylorus, resect the duodenum and part of the pancreatic head the size of a walnut, ligate the choledochus, suture the cut end of the duodenum to the pancreas.'*



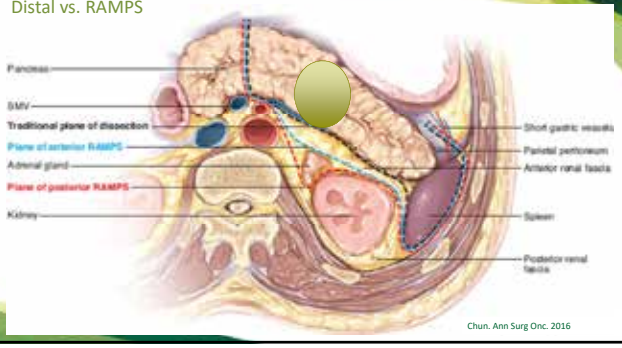
Whipple Procedure

Presents 3 patient series in 1935



Are. HPB. 2011

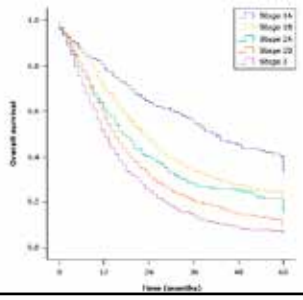
Distal vs. RAMPS



Chun. Ann Surg Onc. 2016

Outcomes

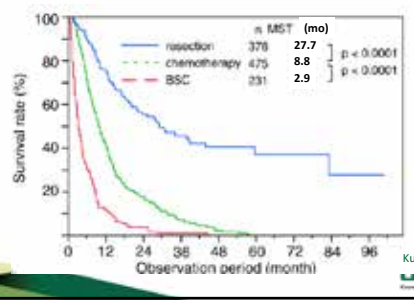
Outcomes by Stage



Number at risk						
Time (months)	0	12	24	36	48	60
Stage 1A	681	462	314	213	135	61
Stage 1B	1348	1044	588	356	227	99
Stage 2A	381	306	179	105	75	35
Stage 2B	2001	1110	991	518	309	133
Stage 3	2968	1040	421	196	87	40

Kamarajah. Ann Surg Onc. 2017

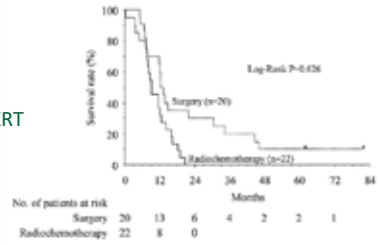
Does resection add benefit?



Kuroda. BMC GI. 2013

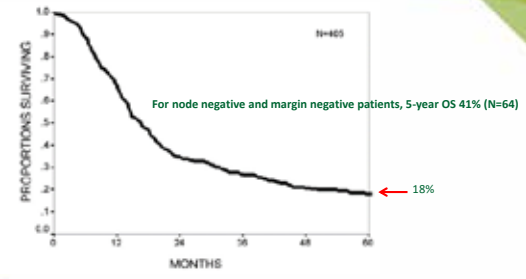
Even more evidence?

- 42 Patients in Japan
- Laparotomy
- Randomized: Resect vs XRT
- Chemo if progressed



Doi. Surg Today. 2008

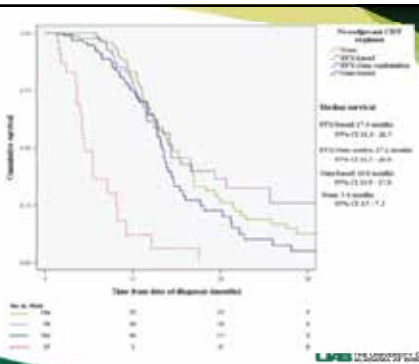
Oncologic Results



Cameron. Ann Surg. 2006

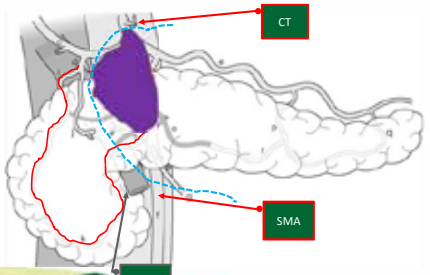
Locally Advanced

20% resection rate
All had CRT

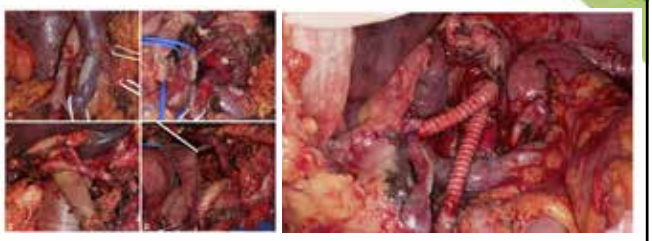


Gemenetzis. Ann Surg Onc. 2018

Modified Appleby Procedure (DP-CAR)

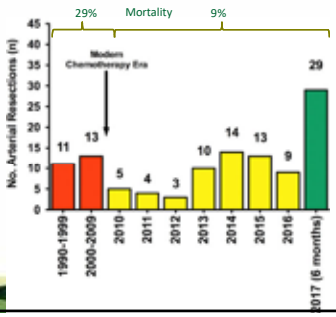


Arterial Resection for LAPC



Tee. JACS. 2018

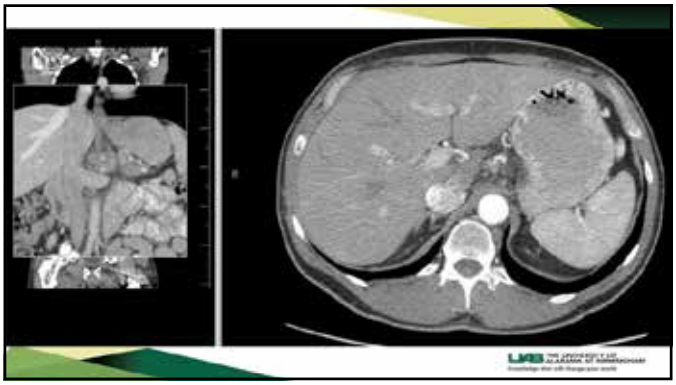
Post-op outcomes with arterial resections

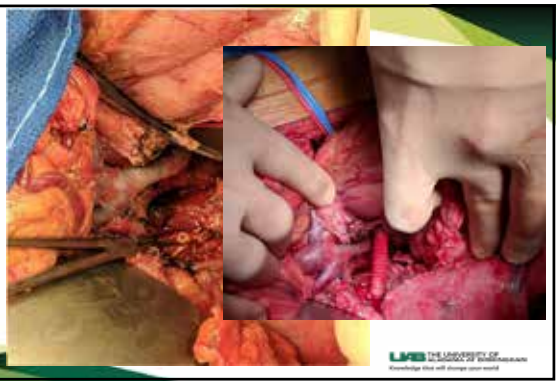


13% 90-day Mortality
54% Major morbidity
16% Reoperation
36% Readmission
41% ICU admission

MOS 28.5mo

Tee. JACS. 2018



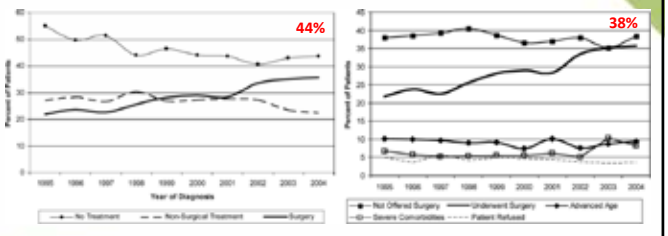


What about vein resection?

- Generally accepted to be beneficial if allows for negative margin
- Major morbidity if develops thrombosis
- Recent series of 120 patients found 28% thrombosis rate
  - 7% early (<90 days)
  - 21% late (76% with concurrent local recurrence)
  - Associated with worse OS (HR 2.2)

Synder. J Surg Onc. 2018

Are patients getting maximal therapy



Bilimoria. Ann Surg. 2007

Are we doing any better?

Table 1

	Locoregional resectable pancreatic cancer
Treatment Rate %(n/N)	resection[9]
Mean of 1X	41 %(275/671)
Median	Beaumont 40 %(8/20)
	95 % CI 36 % to 48 %
Minimum	San Antonio 22 %(15/67)
Maximum	San Angelo 75 %(3/4)

Ho. BMC Health Services Research. 2016

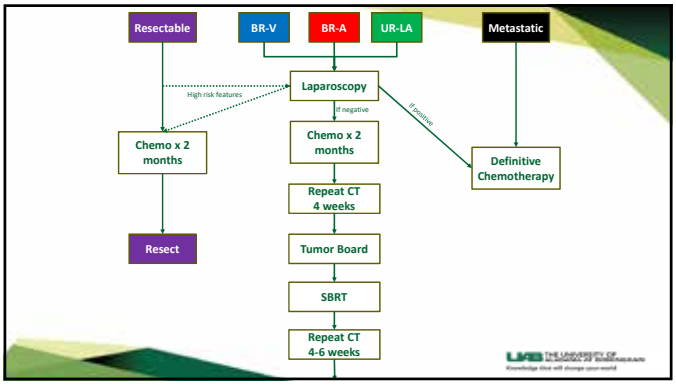
How do we move the needle?

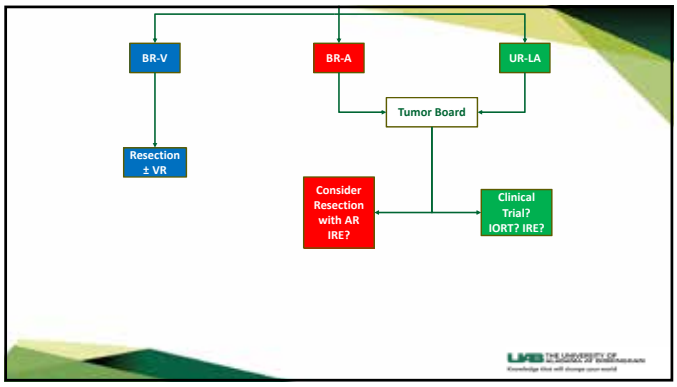
- Reduction in metastatic disease
  - Better systemic treatment
  - Early detection
- Resect everyone with local only disease
  - Identify who they are (?Circulating tumor cells)
  - 80% resected recur distant dz, so 20% room for improvement
  - More aggressive resections?
  - Make sure patients have best information

So how is UAB handling this?

UAB MEDICINE
PANCREATOBILIARY DISEASE CENTER

(833) UAB-4PDC




BR-V
BR-A
UR-LA
Tumor Board
Resection ± VR
Consider Resection with AR IRE?
Clinical Trial? IORT? IRE?


Thank you

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"Complex polypectomy: strategies for polyp resection"

Disclosures: **None**

Learning Objectives:

- Understand the importance of CRC screening/surveillance
- What is impact of colon polyp removal?
- Recognize difficult polyps
- Avoid pitfalls of attempting polypectomy
- Know when to refer to expert endoscopist
- Understand new techniques for management of complex colon polyps

Suggested readings:

1. Raju G S, Lum P J, Ross W A et al.Outcome of EMR as an alternative to surgery in patients with complex colon polyps. Gastrointest Endosc. 2016;84:315–325
2. Shaukat A, Kaltenbach T, Dominitz JA, Robertson DJ, Anderson JC, Cruise M, Burke CA, Gupta S, Lieberman D, Syngal S, Rex DK. Endoscopic Recognition and Management Strategies for Malignant Colorectal Polyps: Recommendations of the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2020 Nov;159(5):1916-1934.e2. doi: 10.1053/j.gastro.2020.08.050. Epub 2020 Nov 4. PMID: 33159840.
3. Kaltenbach T, Anderson JC, Burke CA, Dominitz JA, Gupta S, Lieberman D, Robertson DJ, Shaukat A, Syngal S, Rex DK. Endoscopic Removal of Colorectal Lesions-Recommendations by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2020 Mar;158(4):1095-1129. doi: 10.1053/j.gastro.2019.12.018. Epub 2020 Feb 11. PMID: 32122632.
4. Gupta S, Lieberman D, Anderson JC, Burke CA, Dominitz JA, Kaltenbach T, Robertson DJ, Shaukat A, Syngal S, Rex DK. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2020 Mar;158(4):1131-1153.e5. doi: 10.1053/j.gastro.2019.10.026. Epub 2020 Feb 7. PMID: 32044092; PMCID: PMC7672705.
5. Jideh B, Bourke MJ. How to Perform Wide-Field Endoscopic Mucosal Resection and Follow-up Examinations. Gastrointest Endosc Clin N Am. 2019 Oct;29(4):629-646. doi: 10.1016/j.giec.2019.05.002. Epub 2019 Jul 22. PMID: 31445687

Complex Colon Polyps – Endoscopic Mucosal Resection (EMR)

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Objectives

- Understand the importance of CRC screening/surveil
- What is impact of colon polyp removal?
- Recognize difficult polyps
- Avoid pitfalls of attempting polypectomy
- Know when to refer to expert endoscopist
- Understand new techniques

What makes a polyp difficult

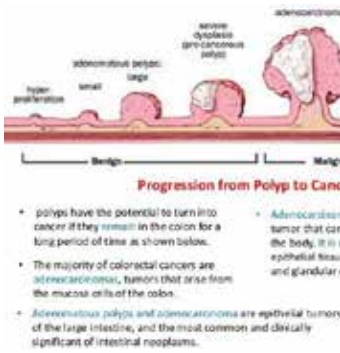
- Size
- Location
- Orientation
- Other factors—diverticuli, anastomosis etc
- Prior instrumentation
- Patient factors
- Operator (physician/nurse/tech) expertise
- Equipment/Facility

CRC screening

- Impact: The effect of screening with fecal occult-bloo
  mortality persists after 30 years but does not influenc
  sustained reduction in colorectal-cancer mortality su
  polypectomy. (Shaukat et al).

Impact/Importance of colon polyp removal

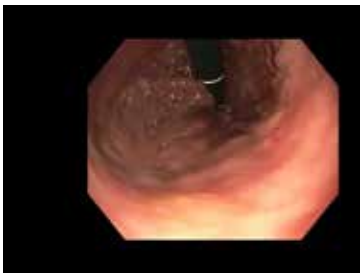
- The International Agency for Research on Cancer concluded that screening for colorectal cancer with stool-based tests and with lower endoscopy (either colonoscopy or sigmoidoscopy) saves lives.
- The proximate cause for the above effect is polypectomy.
- IARC perspective on CRC screening.



Difficult polyps--Size

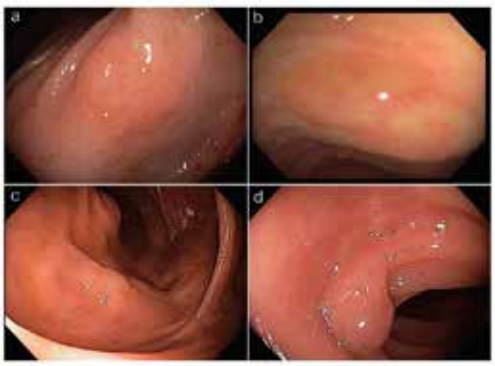
- Size in and of itself does not make a polyp difficult
- Risk of cancer increases with size in non-laterally spreading tumors
- Laterally spreading tumors are rarely malignant

Laterally spreading tum



Non-polypoid lesions > 10mmin diameter are referred to as late
LSTs : granular type (LST-G) -nodular surface, nongranular type (

SSPs

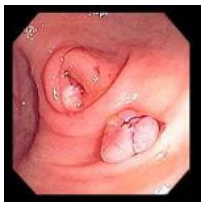


Location

- Difficult locations have a significant impact:
- hepatic flexure,
- splenic flexure,
- sigmoid colon,
- ascending colon,
- appendix
- Cecum/IC valve

Structural issues

- Anastomosis
- Diverticuli

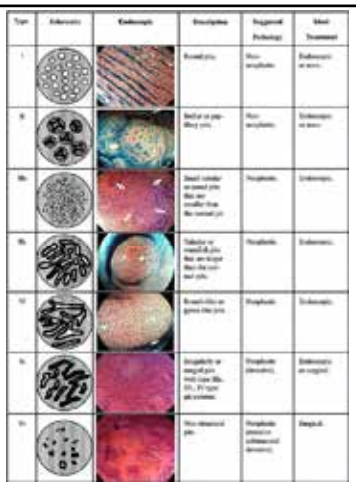


Other factors

- Prior instrumentation---
- site of remote polypectomy/EMR,
- recent partial removal,
- biopsy,
- Tattoo
  - tattoo at 2–3 separate sites
  - located 3–5 cm anatomically distal to the lesion (anal side)

Understanding a polyp—next level

- Optical biopsy
- Chromoendoscopy
- Narrow band imaging
- Kudo and Sano classifications

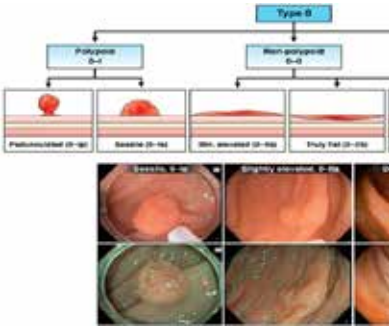


Kudo's

Paris classification

- Consensus classification of gastrointestinal neoplasia
- Robust tool to estimate the risk of invasion and metastases
- Should not be used as a surrogate to predict outcomes

Paris classificatio



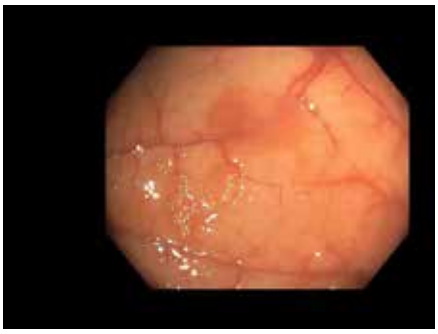
Optics - NICE classification

	Type 1	Type 2	Type 3
Color	Same or lighter than background	Browner relative to background (rarely color arises from vessels)	Brown to dark brown relative to background; sometimes patchy whiter areas
Vessels	None, or isolated lacy vessels may be present coursing across the lesion	Brown vessels surrounding white structures**	Has area(s) of disrupted or missing vessels
Surface pattern	Dark or white spots of uniform size, or homogeneous absence of pattern	Oval, tubular, or branched white structures** surrounded by brown vessels	Amorphous or absent surface pattern
Most likely pathology	Hyperplastic and sessile serrated lesions***	Adenoma****	Deep submucosal invasive cancer
			

How to recogniz

- 1.Careful endoscopic examination
- 2. Digital imaging—NBI
- 3. Chromoendoscopy if feasible
- Understand the pretest probability that the lesion is a
- Recognize need for referral before any instrumentatio

Inspection – Inspection – Inspection !!!



When to refer

- Advanced adenoma beyond local expertise
- Risk of incomplete removal
- High risk lesion for invasion/metastasis
- Complex lesion with prior instrumentation/scar/biops
- High risk for complications

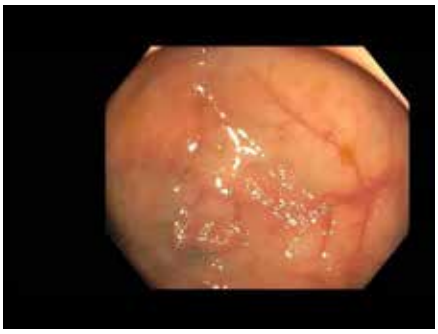
Advanced techniques

- Strong recommendation for referral
  - Endoscopic mucosal resection
  - Endoscopic submucosal dissection
  - Endoscopic full thickness resection

Tool box

- Cold snare
- Underwater EMR
- EMR with Avulsion
- FTRD
- ESD

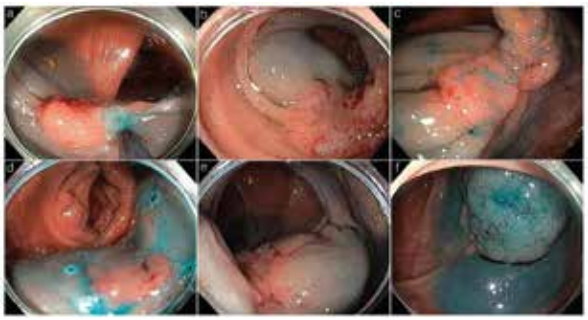
- Increasing time, cost of tools, technical complexity
- Is the extra time, tool cost and complexity useful or necessary?



Submucosal injection -

Epinephrine – no effect in preventing delayed bleed

Non-lifting sign -SMI



High-risk features suggestive of submucosal invasion include NICE classification type 3, Kudo classification type V (VN and VI), and non-lifting sign.

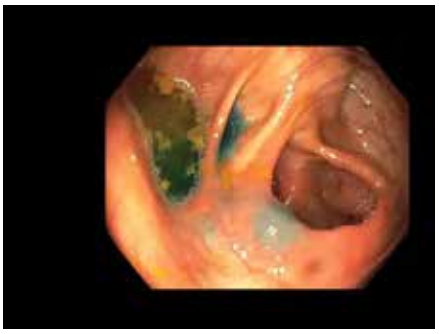
LMB MEDICINE

Cautery setting

Method	Mode	Effect	Cut dura
Inject-and-cut EMR	Endocut Q	2/3	1
Snare tip soft coagulation	Soft Coag	5	–
Hot forceps avulsion	Endocut I	1	4
Underwater EMR	Autocut, Drycut	5	–

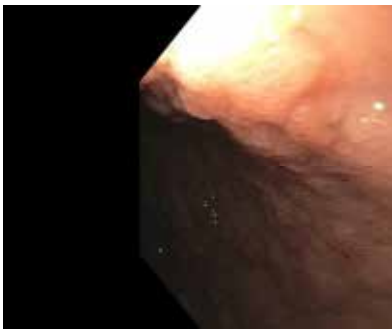
*For users of for users of other units would consult representative to identify settings that would approxima

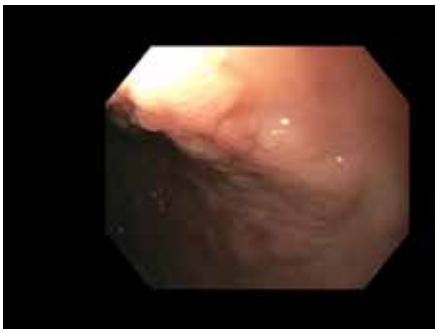
No statistically significant difference in the rate of severe adverse events betwe

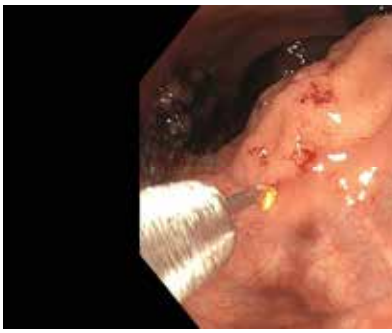


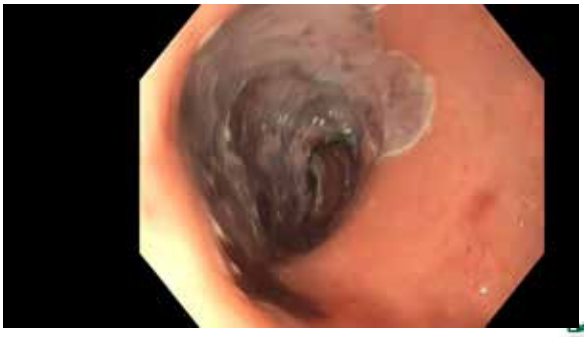
LMB MEDICINE

Piecemeal resect

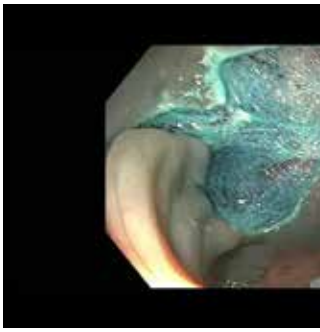


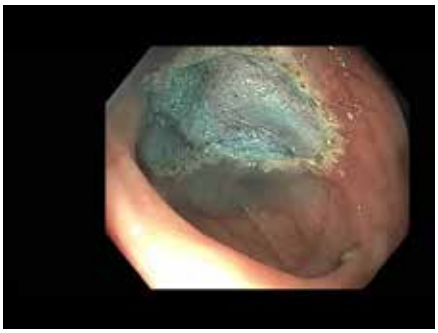




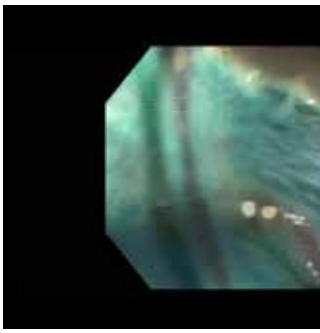


Avulsion

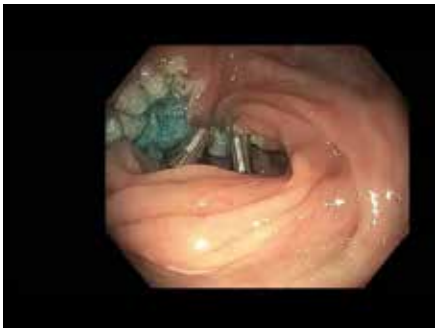




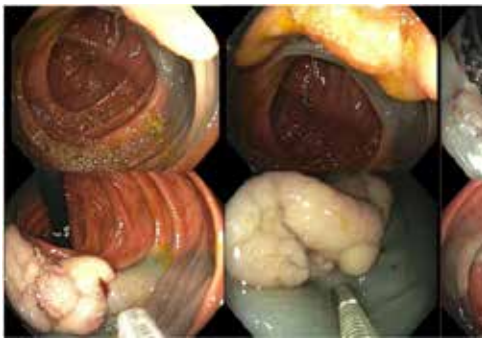
Clip closure



Retreival

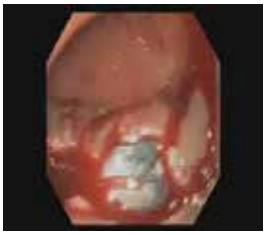


Use of retroflexion/



Adverse Events

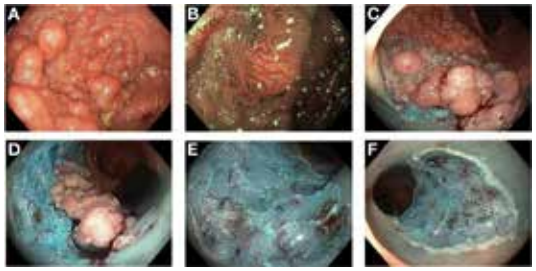
- Bleeding
- Post Polypectomy Syndrome
  - CO2
- Perforation
  - 1.5% (95% CI, 1.2%–1.7%)



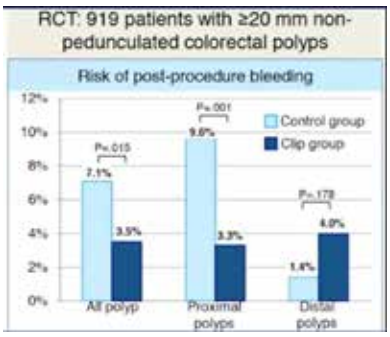
Video

- https://www.youtube.com/watch?v=4l0d8dOKxA0&list=PLkl2Xvob79od&index=22

Sequential steps



Risk of post procedural bleeding - clips



LRS MEDICINE

Piecemeal cold sn

- Increasingly used for serrated lesions and sometimes f adenomas
- Very quick (~10min). Can be done with or without subm
- If it works pretty well for initial resection, why not use it
- In one of the reports authors treated 7/9 recurrences or snare/cold biopsy/combination and did not observe rec report 5 of the lesions were previously attempted by ref
- Advantage: very safe, probably usually effective. Inject treating recurrences- usually won't lift anyway. Clipping can be discharged immediately after procedure
- Disadvantage: very fragmented specimens that are diff malignancy so not a good solution when there is clinica possible cancer. Sparse data

Underwater EMR

LRS MEDICINE

EMR for Fibrotic Po

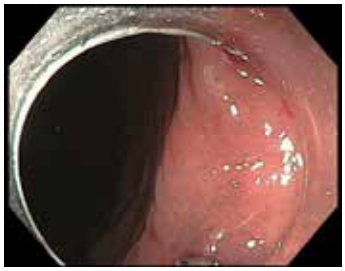
- Repeat piecemeal EMR: Typically the parts of t previously manipulated will lift with submucosa that were affected by cautery/manipulation will
- Deflation of the lumen during snare closure hel underwater EMR)
- Resection of any portions of polyp that lift with first to allow better access to nonlifting areas
- Avulsion often necessary to remove poorly liftir grasped by the snare

Convergence of methods

- Snares grasp tissue best when the lumen is nearly deflated- often easier underwater but can be similarly effective with gas
- Including some normal mucosa at the margin will often help in getting a good piece, dissipate injection fluid on that side of the polyp and makes it easier to grasp the next piece with the snare
- Remove all dysplastic tissue if at all possible- ablate residual visible adenoma only as a last resort because efficacy is marginal
- Avulsion is very useful for recalcitrant pieces of visible residual
- Inspect site carefully for muscle injury and ensure that you clip any injured areas (may wish to close entire wound if feasible also)

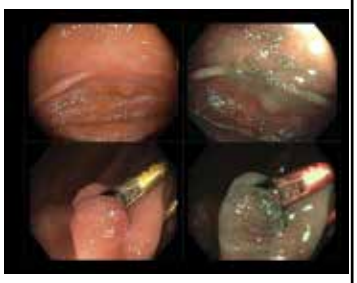
LMB MEDICINE

Endorotor salvag



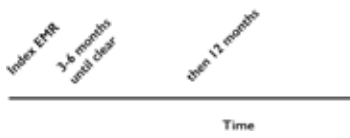
Predictors for recurrence

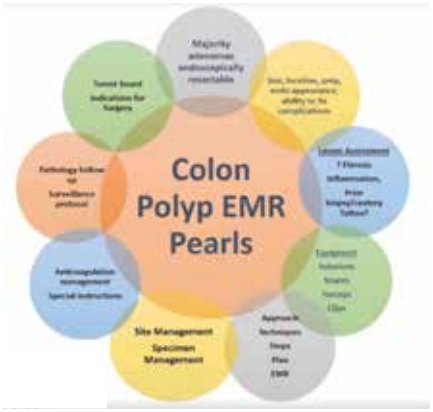
Predictor	OR	95% CI	P value
Size			
21-30mm	2.1	0.99-4.6	0.073
31-40mm	3.5	1.6-7.6	0.002
>40mm	8.2	3.9-17.3	<0.001
Previous Intervention	3.8	1.77-7.94	0.001
Ablation of Tissue	2.4	1.6-3.8	<0.001
Intra-procedure Bleeding	1.7	1.0-2.7	0.038



LMB MEDICINE

Surveillance interv





Take home messa

When referring:

- DO NOT BIOPSY
- DO NOT TATTOO NEAR LESION
- DO NOT ATTEMPT SNARE FOR SAMPLING

- DO PHOTO-DOCUMENT—SEND ACTUAL PROCEDURE
- DO DESCRIBE ACCURATELY WHAT YOU SAW AND DID

- Completely resect large lesions in one session
- Large >4 cm lesions, use of APC, intraprocedural bleeding highest risk for recurrence
- Surveillance intervals should be stressed

ACG guidelines 20

- EMR as the preferred treatment method of large (>20 mm) non-peduncula
- Endoscopist experienced in advanced polypectomy to manage large (>20 m
- Snare resection of all grossly visible tissue of a lesion in a single colonoscop number of pieces)
- Use of a contrast agent, such as indigo carmine or methylene blue, in the s recognition of thesubmucosa from the mucosa and muscularis propria laye
- Recommend against the use of tattoo, using sterile carbon particle suspens The carbon particle suspension may
- result in submucosal fibrosis, and can thus reduce the technical success of recurrent lesion
- Use of a viscous injection solution (eg, hydroxyethyl starch, Eleview, ORISE
- Recommend against the use of ablative techniques (eg, APC, snare tip soft residual tissue of a lesion as they have been associated with an increased r
- Suggest the use of adjuvant thermal ablation of the post-EMR margin, whe remains despite meticulous inspection (ie, APC, snare tip soft coagulation)
- Recommend detailed inspection of the post-resection mucosal defect to id perforation risk, and perform endoscopic clip closure, accordingly.

ACG guidelines 2020

- Suggest prophylactic closure of resection defects >20 mm in size in the right colon, when closure is feasible.
- Suggest treatment of intra-procedure bleeding using endoscopic coagulation (e.g., coagulation forceps or snare-tip soft coagulation) or mechanical therapy(eg, clip), with or without the combined use of dilute epinephrine injection.
- Suggest that patients on anti-thrombotics receive individualized assessment, balancing the risks of interrupting anticoagulation for colonoscopic polypectomy or mucosal resection against the risks of significant bleeding during and after the procedure.

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"Updates in the treatment of patients with pancreatic ducal adenocarcinoma"

Disclosure:

Grants: Bristol Myers Squibb, ERASCA, G1 Therapeutics
Consulting fee: Astra Zeneca, Taiho
Stock/shareholder: Moderna, Regenron, Cardiff
Payment for lectures, including service on speakers bureaus: AstraZeneca, Pfizer

Learning Objective:

1) **Review treatment options for pancreatic ducal adenocarcinoma**
2) **Recognize impact of new therapies on pancreatic cancer**

Updates in the treatment of pancreatic Cancer

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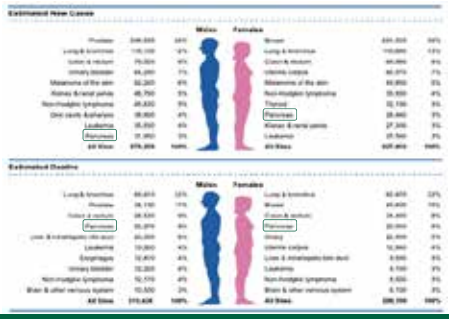
The University of Alabama at Birmingham
O'Neal Comprehensive Cancer Center

O'NEAL COMPREHENSIVE CANCER CENTER
THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

NCI Comprehensive Cancer Center

NCCN National Comprehensive Cancer Network

Epidemiology



CA CANCER J CLIN 2021;71:7-33

5-year Survival Rates by Stage at Diagnosis

SEER Stage	%	5-year Relative Survival Rate
Localized	10%	37%
Regional	37%	12%
Distant	53%	3%
All SEER stages combined		9%

American Cancer Society

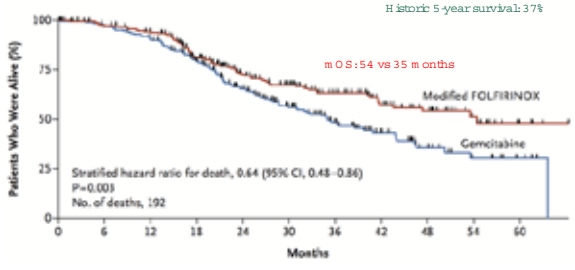
Based on patients diagnosed with pancreatic cancer between 2009 and 2015

- Numbers apply only to the stage of the cancer at time of diagnosis.
- Numbers don't take everything into account.
- Patients diagnosed now may have a better outcomes

Cancer Facts & Figures 2020

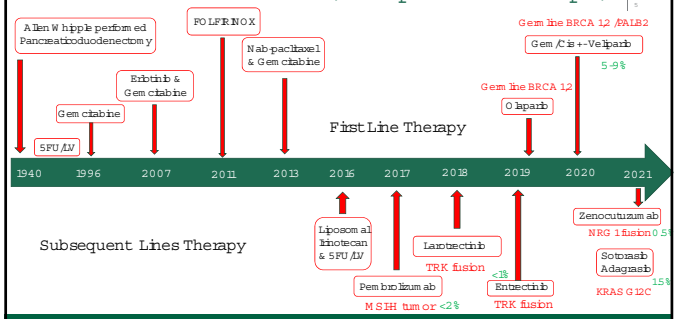
Resectable Pancreatic Cancer (Adjuvant mFOLFIRINOX)

Historic 5-year survival: 37%



n engl j med 379;25

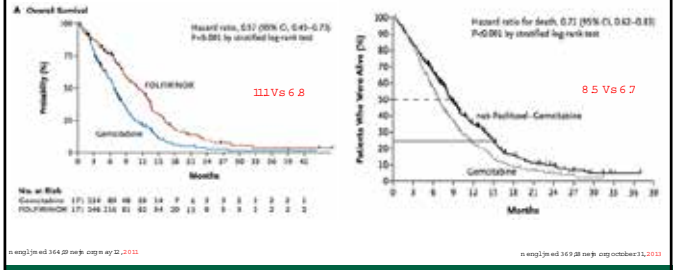
Treatment Milestones (Therapeutic Landscape)



First Line Therapy

FOLFIRINOX

Nab Paclitaxel plus Gemcitabine



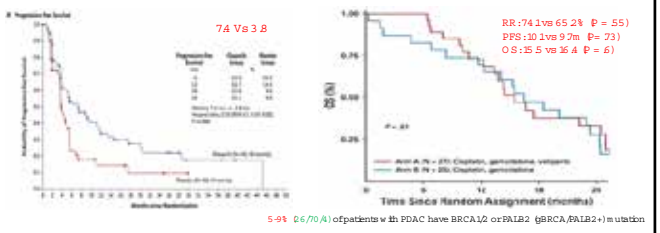
n engl j med 364;19 nejm.org may 12, 2011

n engl j med 369;18 nejm.org october 31, 2013

First Line Therapy (BRCA1,2 and PALB2)

Olaparib maintenance

Cisplatin plus Gemcitabine +- Veliparib



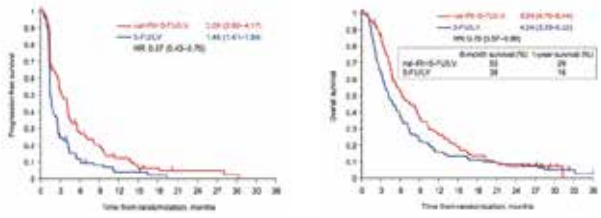
5-9% (26/704) of patients with PDAC have BRCA1,2 or PALB2 (gBRCA/PALB2+) mutation

n engl j med 381;4 nejm.org july 25, 2019

J Clin Oncol 38:1378-1388

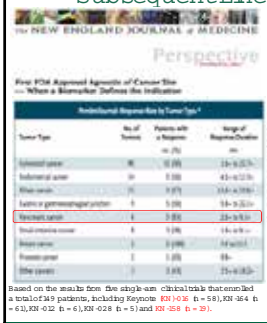
Second Line Therapy

Liposomal Irinotecan and 5-Fluorouracil



European Journal of Cancer 106 (2019) 78–87

Subsequent Line Therapy (Immunotherapy)



Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/ Mismatch Repair–Deficient Cancer: Results From the Phase II KEYNOTE-158 Study

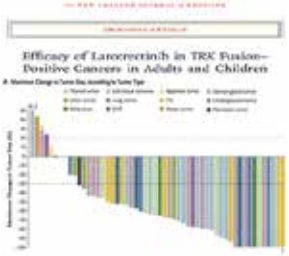
Based on the results from five single-arm clinical trials that enrolled a total of 149 patients, including Keynote 158 (n = 58), KN-164 (n = 61), KN-012 (n = 6), KN-028 (n = 5) and KN-158 (n = 19).

Unfortunately, 2 percent of advanced pancreatic cancers have dMMR

PD-L1 inhibitor (durvalumab) with or without CTLA4 inhibitor (tremelimumab): did not work!

JCO Clin Oncol 38:1-10

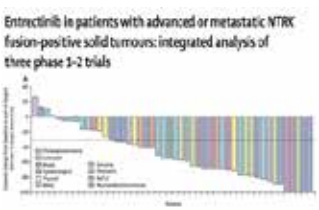
Subsequent Line Therapy targeting Tropomyosin receptor kinase (TRK)



Efficacy of Larotrectinib in TRK Fusion–Positive Cancers in Adults and Children

3 Protocols: Phase 1, Phase 1-2 and Phase 2. N: 1/55)
CR: 13%, PR: 62%, 13% SD, DOR NR

n engl j med 378;8 nejm.org February 22, 2018

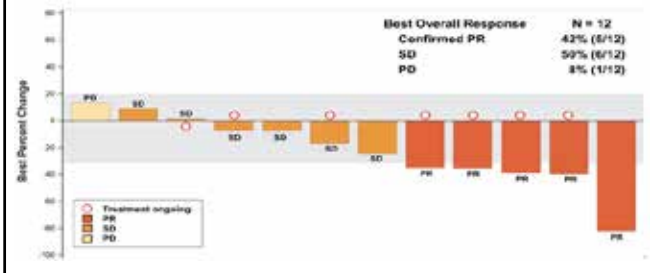


Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1–2 trials

integrated database comprised the pivotal datasets of three, ongoing phase 1 or 2 clinical trials (ALKA-372-001, STARTRK-1, and STARTRK-2) (N: 3/54)
CR: 7%, PR: 50%, 17% SD, DOR 10m
Entrectinib crosses the blood-brain-barrier

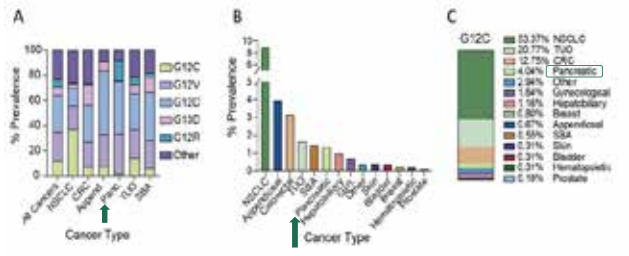
Lancet Oncol 2020; 21:271–82

Subsequent Line Therapy targeting Neuregulin 1 (NRG1) fusions



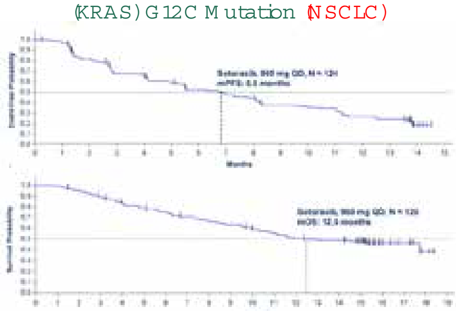
ASCO 2021 annual Meeting

Subsequent Line Therapy targeting Kristen Rat Sarcoma (KRAS) G12C Mutation



ASCO 2021 annual Meeting

Subsequent Line Therapy targeting Kristen Rat Sarcoma (KRAS) G12C Mutation (NSCLC)



Clinical trials are ongoing in patients with pancreatic cancer

ASCO 2021 annual Meeting

Progress In the Treatment of Pancreatic Cancer

NTRK (< 1%)

NRG1 (0.5%)

MSIH (1-2%)

KRAS G12C (1.5%)

BRCA1/2 +PALP2 (5-9%)

10-15%

Molecular Profiling

- Tumor tissue remains the "gold standard" for genetic analysis in cancer patients
- ctDNA can be detected and quantified in the blood of cancer patients and used for detection of tumor-specific genetic alterations
- One advantage of "liquid biopsy" is the potential for reducing data turnaround time

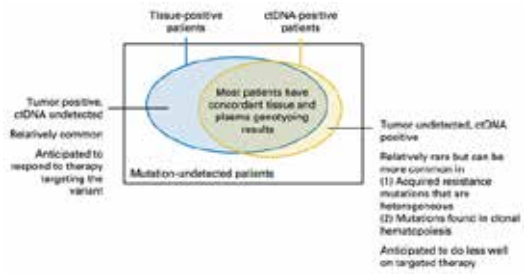
Molecular Profiling

First author	Year	Country	Patients	TNM	Tissue	Blood	Collection	Method	Codon	Sensitivity	Specificity	TP	FN	FP	TN
Bettegowda et al	2014	Multi	206	Advanced	NA	Plasma	NA	dPCR	12, 13	[illegible]	[illegible]	68	10	1	[illegible]
Dono et al	2015	Italy	[illegible]	I–IV	Frozen	Plasma	Before	ARMS-qPCR	12, 13	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Kim et al	2015	Korea	[illegible]	Advanced	FFPE	Serum	NA	[illegible]	12, 13	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Kopreski et al	2000	USA	[illegible]	NA	FFPE	Plasma	Before	[illegible]	12	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	China	[illegible]	[illegible]	NA	Plasma	NA	[illegible]	12, 13	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	France	[illegible]	IV	NA	Serum	NA	Real-time PCR	12, 13	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Liu et al	[illegible]	China	[illegible]	I–IV	Frozen	Plasma	Before	[illegible]	12, 13	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Liu et al	[illegible]	China	[illegible]	NA	Frozen	Plasma	Before	[illegible]	12	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	Japan	[illegible]	I–IV	FFPE	Plasma	Before	[illegible]	12, 13	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Morgan et al	[illegible]	USA	[illegible]	IV	FFPE	Plasma	Before	ARMS-qPCR	12, 13	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Morgan et al	[illegible]	USA	[illegible]	IV	FFPE	Serum	Before	ARMS-qPCR	12, 13	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	Switzerland	[illegible]	NA	NA	Plasma	Before	MASA-PCR	12	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	Italy	[illegible]	NA	FFPE	Plasma	Before	[illegible]	12, 13	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	China	[illegible]	I–IV	FFPE	Serum	Before	Nested PCR	12, 13	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	the Netherlands	[illegible]	I–IV	FFPE	Serum	Before	[illegible]	12, 13	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	Japan	[illegible]	NA	FFPE	Plasma	NA	[illegible]	12, 13	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	France	[illegible]	IV	FFPE	Plasma	Before	dPCR	12, 13	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Spindler et al	[illegible]	Denmark	[illegible]	IV	FFPE	Plasma	Before	ARMS-qPCR	12, 13	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Taly et al	[illegible]	France	[illegible]	IV	Frozen	Plasma	NA	dPCR	12, 13	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Thierry et al	[illegible]	France	[illegible]	IV	NA	Plasma	NA	qPCR	12, 13	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Xu et al	[illegible]	China	[illegible]	IV	FFPE	Plasma	Before	[illegible]	12, 13	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Meta-analysis of 21 studies evaluating the effectiveness of ctDNA for detection of KRAS mutations concluded that sensitivity and specificity rates were 67 (95% CI 55-78) and 96 (95% CI 95-98) percent, respectively

OncoTargets and Therapy 2017:10 945–953

Molecular Profiling (Tissue Vs ctDNA)



JCO Oncol Pract 2021;17:641-649

Conclusion

- There has been a progress in the treatment of patients with pancreatic cancer
- Modified FOLFIRINOX is the adjuvant chemotherapy of choice in patients with resectable pancreatic cancer
- The advances in the treatment of advanced/metastatic pancreatic cancer over the last 5 years have been limited to 10-15% of the patients with unique molecular alterations.
- Each patients with advanced/metastatic pancreatic cancer should undergo molecular profiling looking for BRCA1/2, PALB2, NTRK fusions, NRG1 fusions, Microsatellite instability and KRAS G12C mutation
- Tumor tissue remains the "gold standard" for genetic analysis in cancer patients. Please obtain generous biopsies

2021
NURSING SYMPOSIUM

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"Approach to dysphagia"

Disclosures: **None**

Learning objectives:

- Review the evaluation of patients with dysphagia
- Understand common pathology and causes for dysphagia
- approach to diagnostic testing for dysphagia
- Outline endoscopic strategies for management of patients with dysphagia

Suggested readings:

1. American gastroenterological association medical position statement on treatment of patients with dysphagia caused by benign disorders of the distal esophagus.
2. ASGE Standards of Practice Committee, Pasha SF, Acosta RD, Chandrasekhara V, Chathadi KV, Decker GA, Early DS, Evans JA, Fanelli RD, Fisher DA, Foley KQ, Fonkalsrud L, Hwang JH, Jue TL, Khashab MA, Lightdale JR, Muthusamy VR, Sharaf R, Saltzman JR, Shergill AK, Cash B. The role of endoscopy in the evaluation and management of dysphagia. Gastrointest Endosc. 2014 Feb;79(2):191-201. doi: 10.1016/j.gie.2013.07.042. Epub 2013 Dec 12. PMID: 24332405.
3. Gyawali CP, Carlson DA, Chen JW, Patel A, Wong RJ, Yadlapati RH. ACG Clinical Guidelines: Clinical Use of Esophageal Physiologic Testing. Am J Gastroenterol. 2020 Sep;115(9):1412-1428. doi: 10.14309/ajg.0000000000000734. PMID: 32769426.

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"Management of Inflammatory Bowel Disease"

Disclosures: **None**

Learning Objectives

1. Understand history and causes of inflammatory Bowel Disease
2. Be able to differentiate between Crohn's Disease and Ulcerative Colitis
3. Be able to manage clinical patients with proper work up
4. Recognize health maintenance needed

History of Inflammatory Bowel Disease

1. Ulcerative Colitis
2. Crohn's Disease

Causes of Inflammatory Bowel Disease

1. Pathophysiology
2. Genetics'
3. Environmental Factors
4. Evidence for Bacterial origin of Disease

Crohn's Disease

1. Location
2. Clinical presentation of symptoms
3. Perianal disease
4. Natural history

Ulcerative Colitis

1. Location
2. Clinical presentation of symptoms
3. Natural history

Medical Therapeutic Strategy

1. Oral and topical agents
2. Biologic agents
3. Immunomodulators
4. Steroids

Clinical Management

1. Patient history of disease
2. Labs
3. Imaging
4. Timing for colonoscopy

Extraintestinal Manifestations

1. Joint symptoms
2. Uveitis
3. Certain skin rashes
4. Aphthous ulcers

Health Maintenance

1. Vaccines
2. Cancer prevention
3. Bone health
4. Therapy Related Testing
5. Miscellaneous

Diet and Exercise

1. Mediterranean diet

Pregnancy in Inflammatory Bowel Disease

1. Medications
    a. Live vaccines for baby
2. Breastfeeding
3. Overall risk of mother and baby
4. C-section vs Vaginal delivery

COVID-19 in Immunosuppressed Patients

1. Secure IBD registry
2. Efficacy of vaccine

Bibliography

1. Burke, K, Kochar, B, Allegretti, J, Winter, R, Lochhead, P, Khalili, H, Colizzo, F, Hamilton, M, Chan, W, Ananthakrishnan, A. (2021). Immunosuppressive therapy and risk of COVID-19 in patients with IBD. *Inflammatory Bowel Disease*, 27(2), 155-161.
2. Clark, WT & Feuerstein, JD (2014). Colorectal cancer surveillance in IBD: Practice guidelines and recent developments. *World Journal of Gastroenterology*, 25(30). 4148-4157. doi:10.3748/wjg.v25.i30.4148
3. Ho, S, Lewis, JD, Mayer, EA, Bernstein, CN, Plevy, SE, Chuang, E, Rappaport, SM, Croitoru, K, Korzenik, JR, Krischer, J, Hyams, JS, Judson, R, Kellis, M, Jerrett, M, Miller, GW, Grant, ML, Shraizent, N, Honig, G, Hurtado-Lorzenzo, A, Wu, GD (2019). Challenges in IBD research: Environmental triggers. *Inflammatory Bowel Disease,* 25(2). 513-523. https://doi/org/10.1093/ibd/izz076

Management of Inflammatory Bowel Disease

Emily Roberson CRNP

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Knowledge that will change your world

Objectives

- Understand history and causes of Inflammatory Bowel Disease
- Be able to differentiate between Crohn's Disease and Ulcerative Colitis
- Be able to manage clinical patients with proper work up
- Recognize health maintenance needed

History of Inflammatory Bowel Disease

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Knowledge that will change your world

Alfred the Great

- 1st King of England (849-899 CE)
- May have had Crohn's disease
- "young Alfred was unable to abstain from carnal desires and as Alfred thought that these activities would incur God's disfavor he prayed to the Almighty for some kind of minor illness….after the passage of some time Alfred developed an externally visible peri-anal condition"

  Asser. Life of Alfred.

Ulcerative Colitis

- Samuel Wilks, British physician (1824-1911)
- Credited with recognizing ulcerative colitis in 1859
- Autopsy of 42 year old female patient who died after several months of diarrhea and fever demonstrated transmural ulcerative inflammation of colon and terminal ileum

Crohn's Disease

- Dr. Burrill Crohn (1884-1983)
- Dr. Leon Ginzburg
- Dr. Gordon Oppenheimer
- Columbia University
- Regional enteritis – A Pathologic and Clinical Entity. JAMA. 1932

Causes of Inflammatory Bowel Disease

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

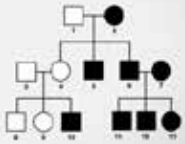
Knowledge that will change your world

Pathophysiology

- 2020: "Idiopathic"
- IBD results from an unusual and continuing immune response to the gut bacteria, caused by the genetic susceptibility of the individual. Although the cause of IBD remains largely unknown, it is believed to involve a complex interaction between the genetic, environmental or microbial factors and the immune responses.

Genetics

- Up to 1 in 4 w/ IBD have 1 affected relative w/ CD or UC
- Concordance rate for monozygotic twins: 50% CD, 15% UC
- One parent w/ IBD – risk ~3%
- Both parents w/ IBD – risk ~30%



Environmental Factors

Crohn's Disease

What is it?

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Crohn's Disease

- Can affect any part of the GI tract, from mouth to anus
- Often discontinuous and symmetric with skipped segments of normal mucosa, especially in early disease
- Often the rectum is spared
- Approximately 75% cases ileum is involved
- Depth of inflammation is mucosal, submucosal, and transmural
- Strictures often present
- Fistulas-perianal, enterocutaneous, rectovaginal, enterovesicular

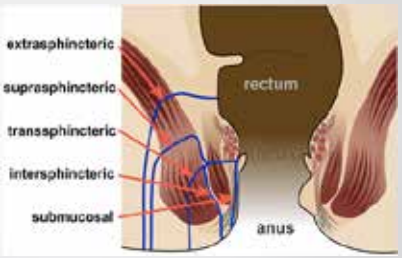
Clinical presentation of Crohn's Disease

- Ileal (30%)--Colicky RLQ abdominal pain +/- N/V, small bowel obstruction, diarrhea, weight loss, fever, anorexia, fatigue, malaise
- Colonic (20%); Ileocolonic (45%)--Diarrhea +/- blood, abdominal pain, systemic symptoms
- Upper GI (10-15%)--Esophageal ulcers/strictures, gastric or duodenal ulcers, isolated jejunal disease
- Perianal involvement--Fistulas, abscess, fissures, ulcers, skin tags, anal canal stenosis, cutaneous Crohn's
- Pediatrics--Growth Delay

Perianal Disease

- Simple:
  - Single track
  - Superficial, low inter- or transsphincteric
  - No abscess, stricture, RV fistula
- Complex
  - Everything else

Park Classification



Classification of Crohn's Disease

	Montreal Classification
Age at Diagnosis	A1: ≤16 A2: 17-40 A3: ≥ 40
Location (CD)	L1: ileal L2: colonic L3 ileocolonic L4 isolated upper digestive
Behavior (CD)	B1: non structuring, non penetrating B2: structuring B3 penetrating P: perianal disease
Extent (UC)	E1: Ulcerative proctitis E2: Left-sided UC E3: Extensive UC (pancolitis)

Ulcerative Colitis

What is it?

Ulcerative Colitis

- Micro ulcers more common; pseudopolyps more common
- Continuous, diffuse, granularity or ulceration found in entire involved segments
- Rectum always involved
- Ileum not involved, except with backwash ileitis
- Mucosal, transmural in fulminant disease
- Strictures rarely present, may suggest adenocarcinoma
- Fistula absent

ER1

Clinical presentation of Ulcerative Colitis

- **Rectal bleeding**
- **Diarrhea**
- **Abdominal pain**
- Passage of mucous
- Tenesmus
- Urgency
- Typically insidious onset, can present acutely

Clinical Management

What is needed for work up

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Knowledge that will change your world

Clinical Management

- Good history is very important
- Questions to ask
- Monitoring Labs—CBC w/ diff, CMP, CRP, ESR, iron studies, Vitamin B12, Vitamin D, fecal calprotectin, therapeutic drug monitoring
  - Labs prior to starting biologic-Hep B, T-spot
  - TPMT activity and TPMT metabolites (thioprine)
  - Prometheus panel
- Imaging-MR enterography, CT enterography (mostly for Crohn's disease)
  - For perianal disease—MR pelvis, antibiotics, surgery referral
- Timing for colonoscopy; Crohn's disease will need ileocolonoscopy

Extraintestinal Manifestations

Symptoms outside of GI tract

- Bone/Joints: arthritis, arthropathy, growth delay (children), osteoporosis
- Eye: Uveitis, iritis, episcleritis
- Skin: Aphthous stomatitis, Erythema nodosum, pyoderma gangrenosum
- Liver: gallstones, Primary sclerosing cholangitis
- Kidney: nephrolithiasis
- Vascular: thromboembolic events

Medical Therapeutic Strategy

- Steroids—Prednisone vs Budesonide
- 5-ASA
- Antibiotics
- Immunomodulators
  - Methotrexate
  - Azathioprine, 6-Mercaptopurine
- Biologics
  - Anti-TNFα: Infliximab, Adalimumab, Certolizumab Pegol, Golimumab
  - Anti-Integrin: Vedolizumab, Natalizumab
  - Anti-IL12/23: Ustekinumab
- Small Molecules
  - Tofacitinib (JAK1/3 inhibitor)
- Supportive agents
  - Antidiarrheals
  - Bile acid binders
  - Antidepressants

Medical Therapeutic Strategy

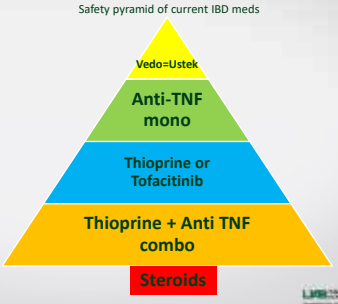
- Step-Up Approach UC (Mild-moderate)
- Top-Down Approach UC (Mod-severe): Crohn's disease

Figure: Aloi M, et. al. Nature Reviews Gastroenterology & Hepatology. 2014

Safety Pyramid

Safest

Safety pyramid of current IBD meds



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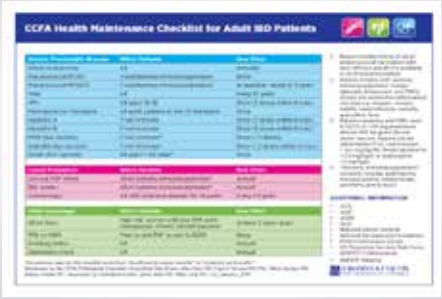
Health Maintenance



Pregnancy in IBD

- Medication safety
- Breastfeeding
- Risk of flare during pregnancy
- Mode of delivery

COVID-19 in IBD patients

- COVID in immunosuppressed patients
- Secure IBD registry
- Efficacy of vaccine in IBD patients

QUESTIONS???

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"Management of pain in chronic pancreatitis (CP)"

Disclosures: Grants: Olympus, AMBU

Learning Objectives:

1) **Understand management of pain and treatment in chronic pancreatitis**

Chronic pancreatitis is a chronic inflammatory condition of the pancreas that is difficult to identify, diagnose, and treat. Pain is a cardinal symptom and is also the most common symptom. Abdominal pain related to chronic pancreatitis can be severe, debilitating, and has a significant impact on the quality of life. Management of pain related to chronic pancreatitis can be challenging and often requires a multidisciplinary approach with multimodality treatment approaches which include medications, endoscopic interventions, surgery, and psychotherapy.

Abdominal pain due to other cause concurrent to CP:

1. PUD
2. Esophagitis
3. Gastroparesis

Pain related to Complications of CP

1. Pseudocyst
2. Acute pancreatitis
3. Biliary obstruction
4. Duodenal obstruction

Anatomic considerations:

1. Dilated PD with stricture
2. Ductal stones
3. Parenchymal stones

MANAGEMENT

Medications

1. Narcotics—lowest dose and mildest potency
2. Supplement with adjunct agents such acetaminophen and NSAIDS
3. WHO analgesic ladder

Adjunct medications
1. Tricyclic anti-depressants
2. SSRIs

Antioxidants
Endoscopic interventions
1. EUS—celiac block
2. ERCP for strictures and stones

Surgery
Multidisciplinary approach

Suggested readings:

1. Mullady DK, Yadav D, Amann ST, et al. Type of pain, pain-associated complications, quality of life, disability and resource utilisation in chronic pancreatitis: a prospective cohort study. Gut 2011; 60:77.
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THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Management of Pain in Chronic Pancreatitis

Kondal Kyanam
Director of Endoscopy
Associate Professor
UAB

Disclosure

- Olympus institutional grant recipient
- Ambu institutional grant recipient

CP symptoms

- Pain is the most common symptom
- Most common reason for intervention
- Has the most negative impact on quality of life

Challenges

- Diagnosis in the early stages of chronic pancreatitis can be very difficult
- Abdominal pain may be significant
- But characteristic and diagnostic imaging features may be absent

Systematic approach

- Detailed history
- Baseline characteristics
- Nature of pain
- Risk factors for other causes of abdominal pain

Typical pattern

- Epigastric
- Boring with radiation to the back
- Alleviated by leaning forward
- Pain is worse within 5 to 10 minutes of eating
- Initially episodic and then more continuous and chronic

CP complications

- Acute pancreatitis
- Pancreatic pseudocyst
- Bile duct obstruction
- Duodenal obstruction
- Visceral artery pseudoaneurysm
- Pancreatic ascites and pancreatic pleural effusions
- Gastric varices due to thrombosis of the splenic vein
- Pancreatic malignancy (2X)

Imaging

- Anatomy of the duct
- Anatomy of the gland
- Complications of CP
- Other causes of pain

Non-invasive approach

- Narcotics
- Acetaminophen
- NSAIDS
- Minimum possible narcotic dose
- Lowest potency class

Adjunctive agents

- Tricyclic antidepressants
- Serotonin reuptake inhibitors (SSRIs)
- Combined serotonin and norepinephrine reuptake inhibitors (eg, duloxetine)
- Gabapentoids (pregabalin or gabapentin)

- Use for weeks to months
- Pain management referral
- WHO pain ladder

Pancreas enzyme supplements

- Improves symptoms of exocrine insufficiency
- Modest effect on pain by decreasing cramping and diarrhea

Antiacid therapy

- Decreased alkalization from pancreas
- Neutralizes acid

Antioxidants

- Vitamin E (200 international units [IU])
- Vitamin C (500 mg)
- Beta-carotene (5000 IU), selenium (500 mg)
- Methionine (1000 mg)

Endoscopic interventions

- Celiac plexus block (neurolysis?)
- ERCP for structures/stones
- EUS guided therapy

Surgical

- Peaustow
- Frye
- Whipple
- Pylorus preserving Whipple
- TPIAT

- Psychological support
- Behavior modification
- Addiction medicine
- CBT
- Complex pain management approach

Take home

- Very difficulty to manage
- Multidisciplinary approach

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"Biologics in IBD: A Pharmacist's Perspective"

Disclosures: None

Learning Objectives:

- Describe current biologic medications used to treat Inflammatory Bowel Disease
- Identify barriers between patient and treatment plan
- Understand importance of patient education on biologic medications

Inflammatory Bowel Disease (IBD) is a group of chronic, idiopathic disorders of the digestive tract that is categorized into ulcerative colitis (UC) or Crohn's disease (CD). Common symptoms of IBD include abdominal pain, diarrhea, fever, rectal bleeding, weight loss, etc. The main goals of therapy are symptom control, improving quality of life, mucosal healing, decreasing hospitalizations, avoiding surgery if possible, and getting patients their medication. Treatment of IBD includes conventional agents and biologics. Biologics for IBD include adalimumab, certolizumab, golimumab, infliximab, natalizumab, ozanimod, tofacitinib, ustekinumab, and vedolizumab. Zeposia, an oral medication, was recently approved for UC and acts as an S1P receptor modulator.

Several barriers exist between providers prescribing the medication and the patient actually getting the medication in their hand. Barriers include fear of self-injecting, insurance denials, expensive copays, etc. Pharmacist's role in an IBD clinic is to help improve medication access, educate on proper administration, appeal with insurances, improve adherence, assist with coordination of care, etc. It is very important that patients know how to inject properly, store medication correctly, and have the necessary supplies. Understanding insurance and the available resources to assist patients can help alleviate obstacles and expedite patients starting therapy. Taking a team approach to treat IBD can eliminate patients' barriers to medication access, thus the patients start treatment sooner and ideally decrease surgery and hospitalizations and improve overall disease management.

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Biologics in IBD: A Pharmacist's Perspective

Lindsey Deloach Flynn, PharmD
Hibah Missoum, PharmD, BCPS

UAB MEDICINE

Disclosure

Presenters have no financial relatio
commercial supporters or providers

Objectives

At the completion of this presentation, participants will be able to:

- Describe current biologic medications used to treat Inflammatory Bowel Disease
- Identify barriers between patient and treatment plan
- Understand importance of patient education on biologic medications

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Overview

- Inflammatory Bowel Disease (IBD
  chronic, idiopathic inflammatory c
  digestive tract
- Two forms of IBD:
  - Ulcerative Colitis (UC)
  - Crohn's Disease (CD)

Clinical Features

Clinical Findings	Ulcerative Colitis	Crohn's Disease
Bowel involvement	Confined to colon and rectum	May be anywhere from mouth to anus (66% of cases in ileum)
Perianal involvement	Unlikely	More common
Depth of ulceration	Superficial	May extend to submucosa or deeper
Continuous inflammatio n	Very common	Rarely, patchy inflammation

5

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Clinical Features

- Symptoms common to both UC and
  - Abdominal pain
  - Diarrhea
  - Fever
  - Rectal bleeding
  - Weight loss
- Patients with IBD experience perio exacerbations and remissions

6

Complications

- Extraintestinal Manifestation of disease
  - Joint
  - Ocular
  - Dermatologic
  - Hepatobiliary
  - Hematologic
- Other:
  - Anemia
  - Calcium and vitamin D deficiency

7

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Goals of Therapy

- Symptom control, improve quality o healing, decrease hospitalizations, possible, sustain disease control, g medication

8

MEDICATIONS

Conventional IBD Treatments

- Aminosalicylates
  - Sulfasalazine, Mesalamine, Balsa
- Corticosteroids
  - Prednisone, Budesonide
- Immunomodulators
  - Methotrexate
  - Thiopurines (Azathioprine, 6-merc
  - Cyclosporine, Tacrolimus

Biologic Medications

	Brand	Generic	Route	IBD indication
TNF Inhibitors	Cimzia®	Certolizumab	SQ	CD
	Humira®	Adalimumab	SQ	CD or UC
	Remicade® Renflexis® Inflectra® Avsola®	Infliximab Infliximab-abda Infliximab-dyyb Infliximab-axxq	IV	CD or UC
	Simponi®	Golimumab	SQ	UC
	Entyvio®	Vedolizumab	IV	CD or UC
	Stelara®	Ustekinumab	IV then SQ	CD or UC
	Tysabri®	Natalizumab	IV	CD
	Xeljanz® Xeljanz XR®	Tofacitinib	Oral	UC
	Zeposia®	Ozanimod	Oral	UC

IBD=inflammatory bowel disease
CD= Crohn's disease
UC=Ulcerative colitis

Biosimilars

- Per the FDA, a biosimilar is highly no clinically meaningful difference FDA-approved reference product
- Biosimilars are NOT generics
- Biosimilars are NOT identical to re
- Random 4 letters after non-proprie
- See "purple book" for FDA's classif biosimilars and interchangeability

Zeposia (Ozanimod)

- MOA: S1PR1 and S1PR5 modulator, traps lymphocytes in lymph nodes thereby reducing circulating lymphocytes and minimizing access to sites of inflammation
- Oral Administration
- Indication: Moderately to severely active ulcerative colitis
- Approved: May 28, 2021

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Zeposia (Ozanimod)

- True North: pivotal phase 3 trial in adults w severe UC
  - Induction and maintenance ozanimod vs.
  - Significantly higher clinical remission rate (79/429) vs 6% (13/216) at week 10 (p<0. vs 19% (42/227)at week 52 (p<0.0001)
  - Met secondary endpoints for endoscopic i and week 52
- Currently undergoing clinical trial for Crohn
  - YELLOWSTONE- Estimated completion d

Biologics Place in Therapy

- Moderate to Severe disease: Biologics are considered first line to achieve remission

Moderate to Severe UC	Moderate to Severe CD
• Immunomodulators (azathioprine/ 6-mercaptopurine) • Anti-TNF +/- immunomodulator • Vedolizumab +/- immunomodulator • Ustekinumab • Tofacitinib • Zeposia	• Anti-TNF +/- immunomodulator • Vedolizumab +/- immunodulator • Ustekinumab

UAB HEALTH SYSTEM

Disease Burden and Barriers

Fear of self-administration/ IV infusions

Medication and healthcare costs

Emergen departme utilization hospitaliza

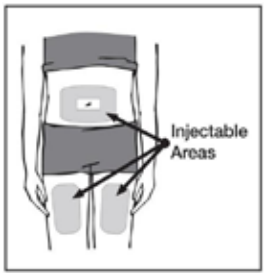
BRIDGING THE GAP

Pharmacist Role

- Improve medication access
- Educate on proper injection admin
- Appeal insurance authorization de
- Improve adherence
- Monitor medication
- Coordination of care
- Provide accessibility to the patient
- Follow up between clinic appointm

Patient Education

- Inform patients of potential risks, potential side effects, black box warnings, etc.
- Storage
- Stability
- Injection locations
- Injection technique
- Necessary supplies



Patient Concerns

- “I saw the commercial…”
- “I read on the internet…”
- “Am I going to be on this forever?”
- “I have to inject myself?”
- “I can’t take off work for infusion ap
- Cost
- Lack of insurance
- Side effects/risks

Considerations

- Administration route
- Cost
- Urgency (appeal w/ insurance or try preferred agent?)
- Infusion location/frequency of infusions
- Understanding insurance issues before they are a problem

Understanding Insurance

Issue	Resolution
Medicare Part A & B	Only covers things under MEDI 80% leaving patient responsible supplemental plan, that will take
Medicare part D	Can't use a copay card w/ Medic into Medicare "coverage gap"
Insurance denials (quantity limits, dose limitations, not on formulary)	Don't give up - - - submit appeal for off-label dosing/frequency. S & letter of medical necessity
Expensive infusion	Two ways to bill infusions - if exp benefits, try pharmacy benefits a also apply this to *some* self injec have patient get it injected at an
No insurance	Patient assistance programs offe apply for grants, etc.

Understanding Resources Available

- Manufacturer copay assistance cards
  - Private insurance only
  - Max benefit per year
  - Patient or provider can sign up
- Patient assistance programs
  - Income based
  - Patient can have insurance (private or government funded) and still qualify if copay is unaffordable
  - Decision can be appealed
  - Needymeds.org for links to applications
- GoodRX
  - Used for patients with no insurance or patients with very poor coverage
  - If patient has insurance, the amount he/she spends on that medication will not go towards deductible/ out of pocket expense

Issues/Challenges = Delay in Treatme

- Medicare coverage gap or Medica
- Non-preferred agents or no prior fa
- Lab test requirements prior to start
- Specific pharmacy required by insu
- Dose limitations under insurance a
- Prior authorization, pre-certificatio
- Failed communication with patient

Team Interventions

- Get labs drawn at appointment (TB, hepB, etc)
- Encourage smoking cessation
- Keep vaccines up to date & yearly flu vaccine
- Bone density assessment
- Colorectal cancer surveillance
- Annual dermatology exams
- Lab monitoring
- Vitamin D levels, iron levels, etc.

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Tysabri (natalizumab) [package insert]. Cambridge, MA. Biogen Inc. Revised 201

Xeljanz (tofacitinib) [package insert]. New York, NY. Pfizer Labs. Revised 2019.

Zeposia (ozanimod) [package insert]. New York, NY. Bristol-Myers Squibb Co. Re

Questions?

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"Post liver transplant hepatitis C treatment: utilizing hepatitis C viremic donors in uninfected transplant recipients"

Disclosures: None

Learning Objectives:

1. Describe current hepatitis C treatment regimens
2. Understand how hepatitis C viremic organs can be utilized in the transplant population

In the United States, hepatitis C virus (HCV) infection is a leading cause of liver-related deaths, cirrhosis, and hepatocellular carcinoma. Rapid improvements in HCV therapy have led to the approval of multiple oral direct-acting antiviral (DAA) regimens by the U.S. Food and Drug Administration (FDA). These new DAA regimens are all oral, highly effective, well-tolerated and typically require only 8–12 weeks of therapy for the majority of HCV-infected patients including those with history of previous HCV treatment, decompensated cirrhosis, end stage renal disease, HIV/HCV co-infection, and recurrent HCV infection post-liver transplantation.

With highly curative hepatitis C treatment options available, transplant centers are now evaluating opportunities to utilize HCV infected organs to increase the transplant donor pool and potentially decrease transplant waitlist time. The University of Alabama Hospital initiated a hepatitis C donor positive, recipient negative transplant protocol in 2019. A summary of the institutional protocol will be provided and outcome results will be discussed.

Suggested readings:

· AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. [July 30, 2021].
·Harvoni ®(ledipasvir and sofosbuvir) [package insert]. Foster City, CA. Gilead Sciences, Inc. Revised 2020.
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· Vosevi® (sofosbuvir, velpatasvir, and voxilaprevir) [package insert]. Foster City, CA. Gilead Sciences, Inc. Revised 2019.
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Hepatitis C treatment update: utilizing hepatitis C viremic donors in uninfected transplant recipients

DeAnn Jones, PharmD, BCPS

UAB MEDICINE

Disclosure Statement

I do not have any financial interest or affiliation with any organizations that could be perceived as a potential conflict of interest concerning the subject of this presentation

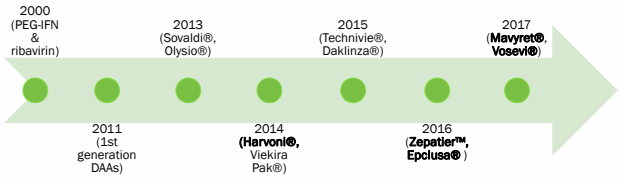
UAB MEDICINE

Learning Objective

- Summarize current Hepatitis C treatment regimens
- Review published literature supporting the use of hepatitis C (HCV) donor positive organs into HCV negative recipients
- Discuss AASLD/IDSA guideline recommendations for the treatment of HCV uninfected transplant recipients receiving organs from HCV viremic donors
- Describe UAB's experience with glecaprevir/pibrentasvir (G/P) in HCV donor positive, recipient negative (D+/R-) abdominal transplant recipients

UAB MEDICINE

Road to Hepatitis C Cure



UAB MEDICINE

Sofosbuvir/ledipasvir (Harvoni®)

- NS5B polymerase inhibitor / NS5A inhibitor
- HCV genotype 1,4,5,6
- Dosing: 1 tablet PO daily (400 mg SOF/ 90 mg LDV) x 8-24 weeks
- Pediatric (>3 yo): 200 mg SOF/ 45 mg LDV, 150 mg SOF/ 33.75 mg LDV
- Side effects: fatigue, headache, nausea
- Drug Interactions: amiodarone, warfarin, digoxin, acid reducing agents (antacids, PPIs, H2 blockers), anticonvulsants (carbamazepine, oxcarbazepine, phenytoin, phenobarbital), rifampin, St. John's wort, statins (rosuvastatin not recommended)

5 UAB MEDICINE

Sofosbuvir/velpatasivr (Epclusa®)

- NS5B polymerase inhibitor / NS5A inhibitor
- Pan-genotypic
- Dosing: 1 tablet PO daily (400 mg SOF/ 100 mg VEL) x 12-24 weeks
- Pediatric (>3 yo): 200 mg SOF/ 50 mg LDV, 150 mg SOF/ 37.5 mg LDV
- Side effects: fatigue, headache, nausea
- Drug Interactions: amiodarone, warfarin, digoxin, acid reducing agents (antacids, PPIs, H2 blockers), anticonvulsants (carbamazepine, oxcarbazepine, phenytoin, phenobarbital), rifampin, St. John's wort, statins (rosuvastatin 10 mg max)

6 UAB MEDICINE

Sofosbuvir/velpatasivr/voxilaprevir (Vosevi®)

- NS5B polymerase inhibitor / NS5A inhibitor / NS3/4A protease inhibitor
- Pan-genotypic
  - genotype 1,2,3,4,5,6 who have previously been treated with NS5A
  - genotype 1a or 3 previously treated with sofosbuvir without NS5A
- Dosing: 1 tablet PO daily (400 mg SOF/ 100 mg VEL/ 100 mg VOX) x 12 weeks
- Administer WITH FOOD
- Do not use in decompensated cirrhosis (Child-Pugh B/C)
- Side effects: fatigue, headache, nausea, diarrhea
- Drug Interactions: amiodarone, warfarin, digoxin, acid reducers (antacids, PPIs – not recommended, H2 blockers), anticonvulsants (carbamazepine, oxcarbazepine, phenytoin, phenobarbital), rifampin, statins (rosuvastatin, pitavastatin not recommended, pravastatin 40 mg max), cyclosporine, dabigatran, antiretrovirals

7 UAB MEDICINE

Elbasvir/Grazoprevir (Zepatier®)

- NS5A inhibitor / NS3/4A protease inhibitor
- HCV genotype 1,4 (1a – NS5A resistance testing recommended)
- Dosing: 1 tablet PO daily (50 mg ELB/ 100 mg GRZ) x 12-16 weeks
- Contraindicated in moderate/ severe hepatic impairment (Child-Pugh B/C)
- Side effects: fatigue, headache, nausea, elevated bilirubin and ALT
- Drug Interactions: anticonvulsants (carbamazepine, oxcarbazepine, phenytoin, phenobarbital), rifampin, St. John's wort, statins (rosuvastatin 10 mg & atorvastatin 20 mg max), cyclosporine, antiretrovirals

8 UAB MEDICINE

Glecaprevir/pibrentasvir (Mavyret®)

- NS3/4A protease inhibitor/ NS5A inhibitor
- Pan-genotypic
- Dosing: 3 tablets PO daily (100 mg GLE/ 40 mg PIB) WITH FOOD x 8-16 weeks
- Pediatric (>3 yo): 50 mg GLE/ 20 mg PIB
- Contraindicated in severe hepatic impairment (Child-Pugh B/C)
- Side effects: fatigue, headache, nausea, diarrhea, elevated bilirubin & ALT
- Drug Interactions: rifampin, warfarin, digoxin, anticonvulsants (carbamazepine, oxcarbazepine, phenytoin, phenobarbital), St. John's wort, statins (rosuvastatin 10 mg max, pravastatin 50% dose reduction), dabigatran, cyclosporine (>100 mg/day), ethinyl estradiol, antiretrovirals

Simplified HCV treatment approach

No Cirrhosis	Compensated Cirrhosis	Decompensated Cirrhosis
• PPI DDI • Statin DDI • Treatment duration • Treatment naïve: G/P x 8 weeks or SOF/VEL x 12 weeks	• PPI DDI • Statin DDI • Treatment duration • Treatment naïve: G/P x 8 weeks or SOF/VEL x 12 weeks • Genotype 3 – requires resistance testing for SOF/VEL	• Refer to transplant center • No protease inhibitor • SOF/VEL + ribavirin x 12 weeks • SOF/VEL x 24 weeks

G/P=Glecaprevir/pibrentasivr
SOF/VEL=sofosbuvir/velpatasvir

Treatment Guidelines

Background: Recent Literature

	Franco et al	Sise et al	Bethea et al
Design	Prospective, observational, multicenter	Prospective	Open-label, unblended single-center trial
Inclusion	N = 11 HCV D+/R- renal transplant recipients	N = 30 HCV D+/R- renal transplant recipients	N = 14 HCV D+/R- liver transplant recipients
Intervention	Prophylactic G/P for 8 weeks	Preemptive G/P for 8 weeks	Preemptive G/P for 12 weeks
Results	• All recipients from NAT positive donors achieved SVR12 • No patients became viremic at 6 months • One incidence of graft loss in a NAT negative donor recipient	• All patients achieved SVR12 • Three patients developed acute cellular rejection • No ADRs attributed to G/P	• All patients achieved SVR12 • Survival in NAT+ recipients 100% at median follow up of 46 weeks • One of 9 NAT+ patients experienced BPAR

BPAR=Biopsy Proven Acute Rejection
ADR=Adverse Drug Reaction
SVR=Sustained Virologic Response

Franco A. *Transplant International*. 2019; 32: 710–716
Sise ME. *J Am Soc Nephrol*. 2020 Nov;31(11):2678-2687
Bethea E. *Am J Transplant*. 2020;20:1619–1628

AASLD/IDSA Guidelines: HCV-Viremic Donors

- Early treatment with a pangenotypic DAA regimen for D+/R- liver transplant patients
  - Glecaprevir/pibrentasvir x 12 weeks
  - Sofosbuvir/velpatasvir x 12 weeks
- Prophylactic/preemptive treatment with a pangenotypic DAA regimen for D+/R- non-liver transplants
  - Glecaprevir/pibrentasvir x 8 weeks
  - Sofosbuvir/velpatasvir x 12 weeks
- Transplant programs should have a strategy to assure access to HCV treatment

13 AASLD=American Association for the Study of Liver Diseases, IDSA=Infectious Diseases Society of America
https://www.hcvguidelines.org/unique-populations/organs-from-hcv-viremic-donors

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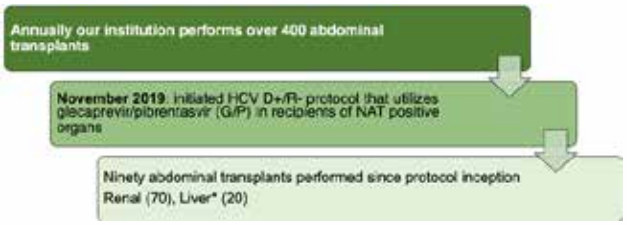

HCV=Hepatitis C virus, D+/R-=donor positive/recipient negative, NAT=nucleic acid testing, *One simultaneous liver kidney

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UAB D+/R- Abdominal Transplant Protocol

Patients are initiated on G/P on post operative (post-op) day three and receive therapy for 12 weeks

	Viral Load	LFTs
HCV NAT Positive	• Post-op day 3 and weekly through SVR12 and once at SVR24	• Post-op day 3, 7, 14, 21, 28, once in month 2, and once in month 3
HCV NAT Negative	• Post-op day 3, and weekly for up to 12 weeks or until detectable; final viral load at 6 months post transplant	

SVR=Sustained Virologic Response
LFTs=Liver Function Tests

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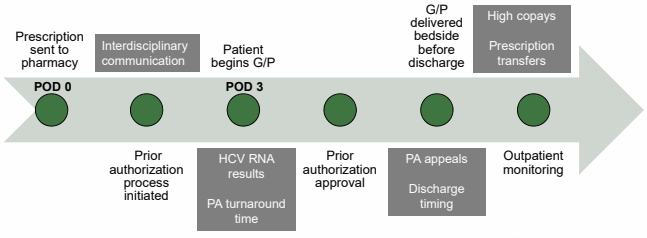
Medication Acquisition Process



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Primary Objective

- To determine the rate of SVR at 12 weeks post treatment in HCV D+/R- transplant patients

Secondary Objectives

- Describe G/P cost and prior authorization (PA) process
- Report side effects with G/P
- Assess interaction between tacrolimus and G/P
- Assess adherence to HCV D+/R- transplant institution protocol
- Assess graft function and patient survival in study patients

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Patient Population

All transplants, per protocol, between November 2019 – June 2020

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Baseline Characteristics

	N = 40 (%)
Gender	
Male	29 (73)
Race	
African American	16 (40)
Caucasian	14 (35)
Other	10 (25)
Organ	
Renal	25 (63)
Liver	14 (35)
Simultaneous Liver Kidney	1 (2)

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Baseline Characteristics

Induction	N = 40 (%)
Anti-thymocyte globulin	23 (56)
Basiliximab	11 (28)
Steroids	6 (16)
Genotype	**N = 31* (%)**
1a	10 (25)
3	5 (13)
2	3 (7)
Not analyzable+	13 (33)

*NAT positive recipients only
+Viral load <1000 IU/mL

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SVR12 Results

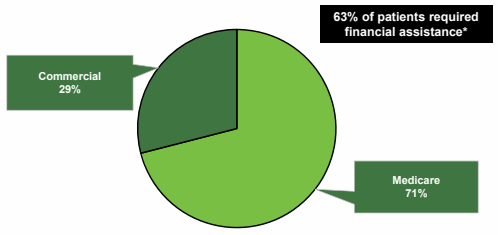
- All HCV NAT positive organ recipients completed 12 weeks of treatment
- All treated patients achieved SVR12
- Sixteen of 31 patients have documented SVR24
- No HCV NAT negative organ recipient became viremic precluding the need for G/P treatment

Prior Authorization (PA) Analysis

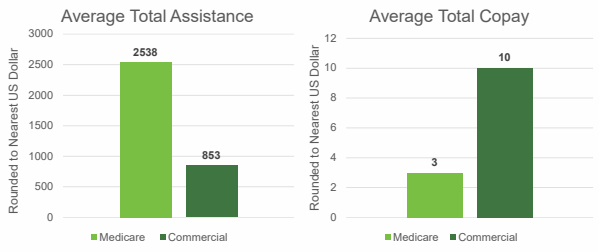
	N = 31*
Average Days to PA Approval (range)	3.39 (1-12)
Average Business Days to PA Approval (range)	2.15 (1-8)
Average Length of Stay Days (range)	9 (4-26)
PA required (%)	31 (100)
PA Appeal Required (%)	
0	6 (20)
1	19 (61)
>1	6 (19)

*NAT positive recipients only

Prescription Insurance Payor



Pharmacy Financial Data for Treatment Course+



Adverse Drug Reactions

- Nausea (2)
- Increased LFTs (1)
- Headache (1)
- Light headedness (1)

Concomitant Interacting Medications

- Tacrolimus (31)
- Statin (7)
- Apixaban (1)
- Warfarin (1)

25 (N)=instances of adverse drug reaction or concomitant interacting medications
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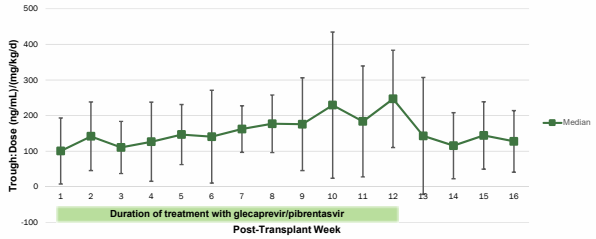
Weekly Tacrolimus Concentration-to-Dose Ratio



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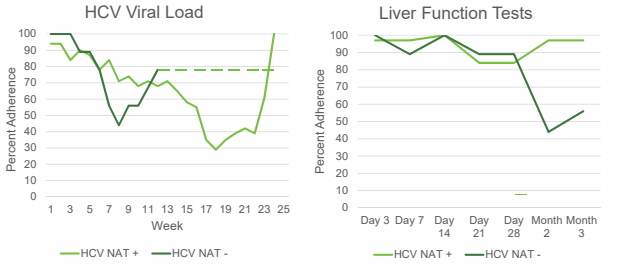
Protocol Laboratory Results: Adherence



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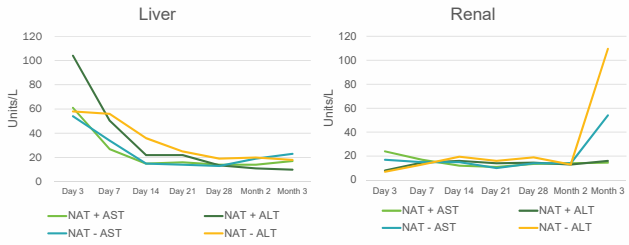
Protocol Laboratory Results: LFTs



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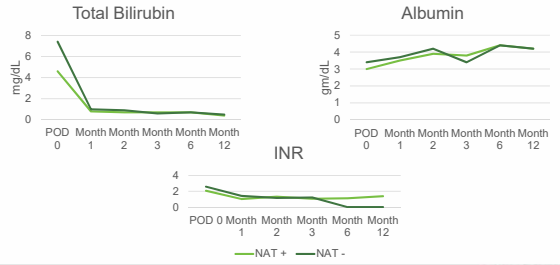
Liver Transplant Graft Function



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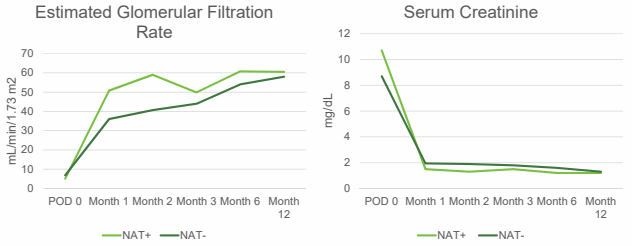
Renal Transplant Graft Function



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Transplant Outcomes

- Graft Rejection
  - One NAT positive liver and one NAT positive kidney experienced BPAR through end of follow up
  - No NAT negative patients experienced BPAR
- Patient Survival
  - 96% survival at one year (N=23)
  - Two deaths since end of follow up

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Conclusion

- The HCV D+/R- protocol appears safe and effective
- Pharmacy involvement ensured patients were able to attain timely DAA treatment to facilitate hospital discharge
- Although multifactorial, utilizing Hepatitis C positive donors appears to decrease transplant waitlist times and improve patient access to transplantation

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Questions?

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"Pre liver transplant evaluation and post liver transplant care"

Disclosures: NONE

Learning Objectives:

1. Gain understanding of the pre-liver transplant process
2. Review MELD scores
3. Understand signs & symptoms of post liver transplant rejection
4. Recognize & reduce complications
5. Understand collaborative management of and nursing contribution in the post liver transplant patient

Pre-Liver Transplant

1) Referral
2) MELD Score
3) Testing and consultations
4) Listing for transplant
5) Patients not listed
6) Contact information

Post-Liver Transplant

1) Maintain healthy liver post transplant
2) Signs & symptoms of infection/possible rejection
3) Importance of lab testing
4) Things to avoid!
5) Health maintenance
6) Contact information

Liver Transplant Evaluation Process

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Important Referral Records

- Demographics
- Insurance Information
- History and Physical
- Labs- including total bilirubin, creatinine, sodium, PT/INR
  - * serologies, drug, nicotine and alcohol screens if available
- CT or MRI scans of abdomen and pelvis
- Health Maintenance Items- (must be received before a patient can be listed)
  - Endoscopy
  - Colonoscopy
  - Mammogram
  - Pap Smear
- Echocardiogram if previously completed
- Cardiac Stress Test or Heart Cath if previously completed

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What is a MELD Score?

- **M**odel for **E**nd-Stage **L**iver **D**isease
- An allocation system created by UNOS to ensure the sickest patients are given the highest priority.
- MELD Score determines the patients place on the waitlist for their blood type.
- Scores range from 6 to 40 with larger numbers assigned to sickest patients.
- Scoring is based on total bilirubin (liver function), creatinine (kidney function), sodium, and INR (clotting time).
- Scores can be calculated on www.unos.org

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How Often Will MELD Score Be Updated Once Listed?

Recertification of MELD Scores

MELD SCORE	LABS are needed	Labs must be entered
25 or more	Every 7 Days	Within 48 Hours
19-24	Every 30 Days	Within 7 Days
11-18	Every 90 Days	Within 14 Days
10 or less	Every Year	Within 30 Days

**** If labs are not recertified by the appropriate time, MELD score will drop to 6 points ****

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Tests and Consultations

- Labs- including HIV, drug, nicotine and alcohol screens
- CT or MRI Scans of abdomen
- Echocardiogram with bubble study
- Cardiac Stress Test or Heart Cath
- EKG
- Pulmonary function tests and ABGs
- Consults:
  - Surgeon
  - Hepatology
  - Social Work
  - Financial
  - Pharmacy
  - Dietary
  - Coordinator
  - Addiction Medicine(if appropriate)

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How Does A Patient Get On The List?

- Complete the evaluation process including having up to date colonoscopy, mammogram and pap smear.
- Transplant Team reviews evaluation results at weekly meeting.
- Accepted as transplant candidate.
- Approval for surgery from the insurance company.
- Placement on the UNOS Waitlist.
- Notification of official placement and MELD Score.

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Communication While On The Waiting List

- Update the coordinator with any changes/additions to contact information.
- Notify the coordinator with any insurance changes or cancellations.
- Any hospitalizations, serious illnesses or complications must be communicated to transplant coordinator.

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"Not Listed" Patients

Reasons for not being listed may include…

- Early for transplant
- Psychosocial concerns
- Not being abstinent for illegal drugs, alcohol, or tobacco
- Medical conditions that put the patient at increased risk for transplant surgery
- Morbid obesity
- Tumor size outside UNOS criteria
- Cancer outside the liver

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Important Contact Information

- **Transplant Coordinator Office**
  - 1-866-305-5691 or 205-975-5691 Fax:205-975-2298
- **Liver/Tumor Office**(ablation or resection of tumors)
  - 205-996-5970
- **Hepatology/Liver Center**
  - 205-996-4744

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LIVER TRANSPLANT REFERRAL FORM

Thank you for your interest in the UAB Comprehensive Transplant Institute. Your completion of all the fields below and attachment of medical records will ensure that there are no unnecessary delays in the evaluation of your patient. This form and other helpful information is available at uabmedicine.org/refertransplant

REQUIRED INFORMATION:

☐ Patient demographics page from your data system ☐ Copy of front and back of all insurance cards

☐ H&P from past 12 months ☐ Tobacco & alcohol history ☐ Total Bilirubin, Creatinine, INR within 12 months

☐ Records from all hospitalizations in last 6 months ☐ Compliance concerns _____

Patient Full Name: _____

Date of Birth: _____ SSN: _____

Gender: ☐ Male ☐ Female Marital Status: ☐ S ☐ M ☐ D ☐ W

Height: _____ Weight: _____

Check One: ☐ US Citizen ☐ Non-Citizen Resident

☐ Non-Citizen, Non-Resident in country for reason other than transplant; Year of entry: _____

Person Completing This Form: _____ Phone: _____

Referring MD Name: _____ Phone: _____

Fax: _____

Referring MD NPI (for first referral): _____

Diagnosis? ☐ ETOH ☐ NASH ☐ HCV ☐ PBC ☐ PSC

Other: _____ HCC (Hepatocellular Carcinoma)? ☐ YES ☐ NO

Please also send the following clinical information from the past 12 months if available:
Liver biopsy, radiology tests, EGD/colonoscopy reports, serology testing, AFP, mammogram, & pap smear

PLEASE MAIL OR FAX THIS INFORMATION TO UAB LIVER TRANSPLANT OFFICE:
1120 Jefferson Towers • 619 19th Street South • Birmingham, Alabama 35249
Phone: 205.975.5691 • Toll-Free: 866.305.5691 • Fax: 205.975.2298

Patient will receive letter with details of their appointment, maps, and an informational brochure.
Please notify us of changes in patient's condition or contact information.

Post Liver Transplant Care

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Disclosures

- I have no relevant financial or nonfinancial relationships to disclose.

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Background

DONATE LIFE

mcagle@uabmc.edu

JSU

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UAB SCHOOL OF NURSING

Objectives

The participant will be able to:

- Verbalize the signs and symptoms of post-liver transplant rejection.
- Evaluate the need for close follow-up, to recognize and reduce complications, and treat the patient promptly.
- Describe the collaborative management of and nursing contribution to the care of the post-liver transplant patient.

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Statistics

- The liver is the largest organ in the human body.
- UAB is the only transplant center in Alabama.

- UAB is one of only 20 transplant centers in the US that average 100 or more liver transplants per year.

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How to Maintain a Healthy Liver After Transplant

- Maintain an overall active and healthy lifestyle including a balanced diet and routine check-ups.
- Know all your transplant medications: doses, times, and why you are taking them.
- Follow your transplant medication schedule daily and make changes ONLY as ordered by your transplant physician!
- Keep all of your scheduled medical appointments.
- Have blood tests drawn as required

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Signs & Symptoms of Infection/Possible Rejection

- **Fever of 101.5 or higher**
- **Pain that is severe and/or constant**
- **Incision that is painful, red, warm, and/or yellow/green/red/white drainage**
- **Yellowing of the eyes or tea colored/dark urine, clay colored stool**
- **Vomiting or diarrhea that lasts greater than 24 hours**
- **Cough that produces a yellowish or greenish substance**
- **Dry cough that lasts greater than one week**
- **Rash or any other skin changes**
- **Vaginal or penile discharge or itching**
- **Burning or discomfort with urination**

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Importance of Lab Tests

- Please do **NOT** eat, drink, or take your medications until **AFTER** labs are drawn.
- Labs will be drawn more frequently in the early weeks or months after transplant (and specifically with certain types of transplants, i.e. Risk Criteria, Hepatitis C donor + to recipient -) and then less often over time.
- You may be asked to have labs repeated or more frequently if you are sick or experiencing any complications.
- Results show how your body is recovering and how well your new liver and other body systems are functioning.
- Medications may be changed or added based on results.
- Reports important levels of anti-rejection medication in the body
  - Levels too high show that your immune system has been suppressed too much putting you at more risk of infection
  - Levels too low can trigger the rejection process

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Routine Lab Tests

- Our routine lab tests that the patient may have drawn locally include:
  - **Basic Metabolic Profile** (including Sodium, Potassium, Creatinine, BUN, Glucose)
  - **Complete Blood Count with Differential** (including White Blood Cell Count, Red Blood Cell Count, Hematocrit, Hemoglobin, Platelet Count)
  - **Hepatic Function Profile** (including Total Bilirubin, Direct Bilirubin, Indirect Bilirubin, AST, ALT, Alkaline Phosphatase)
  - **GGT** (gamma-glutamyl transferase)
  - **Immunosuppressive Drug Levels** (could include more than one of the following: Cyclosporine, Tacrolimus (Prograf), Everolimus (Zortress), Sirolimus (Rapamune)

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Things to Avoid

- **Do not get pregnant while on Cellcept or Myfortic**; should always use 2 forms of birth control; speak with your transplant provider prior to getting pregnant or **notify your coordinator immediately if you become pregnant**
- **No Live Virus vaccines ever** (i.e. MMR, Zostavax, Polio, Nasal Flu Mist);
  - Shingrix, Flu, Pneumonia, and COVID vaccines are ok
- **No dental cleanings or procedures for the first 6 months following transplant** (strongly recommended to have antibiotic prophylaxis prior to first routine dental cleaning following transplant)
- **NO NSAIDS** (i.e. Advil, Motrin, Aleve, Ibuprofen, Midol, Mobic); it is best to list as an allergy to avoid any issues
- Raw, uncooked, or undercooked foods or unpasteurized dairy products
- Extended sun exposure; use SPF 30 or greater or wear long sleeves/hat when out in the sun
- Bath tubs, swimming in any body of water for 6 months post transplant
- Driving for 4 weeks following surgery or while taking prescription pain medications
- Straining, stretching, or lifting anything over 20 pounds for at least 3 months following surgery
- No new pets for the first 6 months following surgery; preferably never any birds indoors
- No alcohol, drugs, or smoking

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Dental or Surgical Prophylaxis

- Notify your coordinator with any planned or unplanned hospitalizations, outpatient procedures/surgeries, serious illnesses, or complications.
  - Your transplant team may need to follow your labs more frequently, make adjustments to your medications to assist with healing/decrease risk of infections, or hold medications prior to a surgery/procedure
- **No dental cleanings or procedures for the first 6 months following transplant ;** it is strongly recommended to have antibiotic prophylaxis prior to first routine dental cleaning following transplant; we follow the American Heart Association Dental Prophylaxis guidelines.
- Our office does not provide medical clearance for surgeries/procedures; we will only provide clearance from a liver transplant care perspective.

- **UAB MIST Operator (MD to MD): 800-UAB-MIST (800-822-6478)**
- **Local Number: 205-975-5691**
- **Toll Free Number: 1-866-305-5691**
- **Fax Number: 205-975-2298**
- **Email: livertransplant@uabmc.edu**

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Health Maintenance

It is strongly recommended that patients maintain routine health care visits with a PCP, updated health screenings, and immunizations…

- Dental exam annually
- Ophthalmology annually
- Gynecological exam annually
- Mammogram for females based on the latest recommendations from www.ACOG.org
- PSA and exam for males based on the latest recommendations from the American Cancer Society
- Dermatology exam annually
- Stool for hemoccult annually if >50 years old
- Colonoscopy, alternating with Flexible Sigmoidoscopy, every 3 years
- Influenza vaccine annually
- Pneumococcal vaccine based on recommendations from www.cdc.gov
- Urine hCG annually (for all females on Cellcept or Myfortic)

These can all be performed locally if the patient prefers.

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Important Contact Information

- **For all life threatening emergencies, call 911**
- **UAB MIST Operator (MD to MD): 800-UAB-MIST (800-822-6478)**
- **Local Number: 205-975-5691**
- **Toll Free Number: 1-866-305-5691**
  *If you happen to get a voice mail, please leave a message that includes your name, date of birth, telephone number (with area code), and reason for calling. Someone from the office will call you back.
- **Fax Number: 205-975-2298**
- **UAB Paging Operator: 205-934-3411**
- **Email: livertransplant@uabmc.edu**

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Potential Drug Interactions with Immunosuppressive Medications

It has been reported that the following medications have been involved in drug interactions with immunosuppressive medications or have adverse side effects in liver transplant patients.

***Please note: This is not an all inclusive list. Significant drug interactions occur with patients taking either Prograf or cyclosporine. Both of these drugs are cleared by the liver via the cytochrome *P450 3A4 pathway*. The following drugs are not recommended because they are also cleared by the cytochrome P450 3A4 pathway and *can cause renal failure* when combined with either Prograf or Cyclosporine.**

Avoid the following medications and/or substances

►ALL NSAIDs (including OTC ibuprofen/motrin):

Aleve, Anaprox, Naprelan, Naprosyn (naproxen)
Arthrotec (diclofenac/misoprostol)
Cataflam, Voltaren (diclofenac)
Clinoril (sulindac)
Dolobid (diflunisal)
Indocin (indometheacin)
Mobic (meloxicam)
Prevacid NapraPC (lansoprazole/naproxen)
Relafen (nabumetone)
Ansaid (flurbiprofen)
Bextra (valdecoxib)
Celebrex (celecoxib)
Daypro (oxaprozin)
Feldene (piroxicam)
Lodine (etodolac)
Orudis (ketoprofen)
Ponstel (mefenamic acid)
Tolectin (tolmetin)

►Anti-Convulsants:

Dilantin, Phenytek (phenytoin),
Tegretol, Carbatrol (carbamazepine),
Cerebyx (fosphenytoin)
Phenobarbitol

►Calcium Channel Blockers:

Calan, Covera-HS, Isoptin, Verelan (verapamil)
Cardizem, Cartia, Dilacor XR, Dilt-CD, Diltia XT, Taxtia XT, Tiazac (diltiazem)
Tarka (trandolapril/verapamil)

►Gout:

Zyloprim (allopurinol) – avoid if pt. on Imuran (azathioprine) for immunosuppression

►Anti- Platelet:

Pletal (cilostazol)

►Anti-arrhythmic:

Rythmol (propafenone)

►Migraine Headaches:

Axert (almotriptan)

►Sedative /Hypnotic:

Lunesta (Eszopiclone)

►Live vaccines – MMR can be given ≥ six months post transplant

►Grapefruits and grapefruit juice products

Also, satsumas and Seville oranges-bitter orange from Spain used in marmalades

►All herbal remedies & products

►Alcohol, tobacco products, and illegal drugs

ANTI-MICROBIALS TO AVOID**

►**Macrolide antibiotics – all macrolide antibiotics should be avoided:**

Biaxin (clarithromycin) Dynabac (dirithromycin)
E-Mycin, E.E.S., Ery-Tab, Eryc, EryPed, Erythrocin, Ilosone, Pediazole (erythromycin)
Zithromax, Z-pak (azithromycin) – **can be especially harmful in pediatric patients**

►**Tetracyclines - all tetracyclines should be avoided:**

Achromycin, Sumycin (tetracycline) Adoxa, Doryx, Periostat
Declomycin (demeclocycline) Minocin, Vectrin (minocycline)

►**Anti-Fungals:**

Diflucan (fluconazole) Vfend (voriconazole)
Sporanox (itraconazole) Lamisil (terbinafine)
Nizoral (ketoconazole) Cancidas (caspofungin)
Monistat IV (miconzole) Mycelex (cotrimazole)
Ancobon (flucytosine) Gifulvin V, Gris-PEG (griseofulvin)
Fungizone, Abelcet, Ambisome, Amphocin, Amphotec (amphotericin)

►**Anti-Tuberculars: Rifadin, Rimactane (rifampin)**

►**Anti-Virals:** Famvir (famciclovir)

****Please contact the transplant center if there is no other choice than to prescribe one of the aforementioned anti-microbials.**

ANTI-MICROBIALS TO PRESCRIBE

►**Penicillins: If PCN allergy:** Cleocin (clindamycin)**:**

Amoxil, Trimox, Disper Mox (amoxicillin) Augmentin (amoxicillin/clavulanate)
Principne, Omnipen (ampicillin) Dynapen (dicloxacillin)
Pen-Vee K, Veetids (penicillin VK)

►**Cephalosporins:**

Duricef (cefadroxil) Keflex, Panixine DisperDose (cephalexin)
Velocef (cephradine) Ceclor (cefaclor)
Ceftin (cefuroxime) Cefzil (cefprozil)
Lorabid (loracarbef) Cedax (ceftibuten)
Omnicef (cefdinir) Spectracef (cefditoren)
Suprax (cefixime) Vantin (cefpodorime)

►**Quinolones:**

Avelox (moxifloxacin) Cipro (ciprofloxacin)
Factive (gemifloxacin) Floxin (ofloxaxin)
Levaquin (levofloxacin) Maxaquin (lomefloxacin)
Noroxin (norfloxacin) Penetrex (enoxacin)
Tequin (gatifloxacin) Trovan (trovafloxacin)

►**Sulfonamides:**

Bactrim, Septra, Cotrim (trimethoprim/sulfamethoxazole), Gantanol (sulfamethoxazole), Gantrisin (sulfisoxazole),Sulfadiazine

►**Topical Anti-Fungals**

►**Statins:** Pravachol is recommended as the first statin to try.

Dear Dentist:

I have had a liver transplant. My surgeons, Dr. Cannon, Dr. Locke, Dr. Orandi, and Dr. Sheikh would like for me to take antibiotics before any dental procedure for the first year after transplant. They recommend that you use the American Heart Association Dental Prophylaxis. Also, please avoid all NSAIDS.

DENTAL PROPHYLAXIS FOR LIVER TRANSPLANT PATIENTS

SITUATION	AGENT	REGIMEN*
Standard general Prophylaxis	Amoxicillin	Adults: 2.0 g Children: 50mg/kg orally 1 hour before procedure
Unable to take oral Medications	Ampicillin	Adults: 2.0 g Children: 50 mg/kg IM or IV within 30 min. before procedure
Allergic to penicillin	Clindamycin	Adults: 600 mg Children: 20 mg/kg orally 1 hour before procedure
	or	
	Cephalexin# or cefadroxil#	Adults: 2.0 g Children: 50 mg/kg orally 1 Hour before procedure
	or	
	Azithromycin or clarithromycin	Adults: 500 mg Children: 15 mg/kg orally 1 hour before procedure
Allergic to penicillin And unable to take Oral medications	Clindamycin	Adults: 600 mg Children: 20 mg/kg IV within 30 minutes before procedure
	or	
	Cefazolin	Adults: 1.0g Children: 25 mg/kg IM or IV Within 30 minutes before procedu

*Total children's dose should not exceed adult dose
#Cephalosporins should not be used in individuals with immediate-type hypersensitivity reaction (urticaria, angioedema, or anaphylaxis) to penicillins

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"Hepatic Encephalopathy"

Disclosures: **None**

Learning Objectives:

1. Discuss pathology
2. Increase confidence in assessment and diagnosis
3. Identify appropriate pharmacological treatment
4. Pinpoint reasons for treatment failure

Outline:

1. Definition of hepatic encephalopathy
2. Assessments and Diagnosis
3. Treatment
4. What happens when treatment fails?

HEPATIC ENCEPHALOPATHY

The Good, The Bad, and the Very Confused

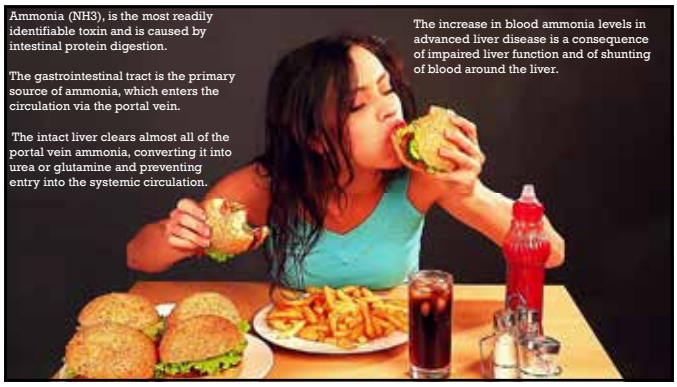
NO DISCLOSURES ☺

OBJECTIVES

- Discuss pathology
- Increase confidence in assessment and diagnosis
- Identify appropriate pharmacological treatment
- Pinpoint reasons for treatment failure

DEFINITION

- A potentially reversible impairment of neuropsychiatric function associated with impaired hepatic function (Up to Date 6/4/18)
- A state of disordered central nervous system function resulting from failure of the liver to detoxify noxious agents of gut origin because of hepatocellular dysfunction and portosystemic shunting (Current Medical Diagnosis and Treatment 2015)
- A brain dysfunction cause by liver insufficiency and/or PSS; it manifests as a wide spectrum of neurological or psychiatric abnormalities (AASLD)



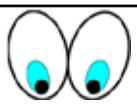
Overt hepatic encephalopathy develops in 30 to 45 percent of patients with cirrhosis and in 10 to 50 percent of patients with transjugular portal-systemic shunts (Up to Date)

ASSESSMENT AND DIAGNOSIS

LOOK FOR IMPAIRMENT IN

- Attention
- Reaction time
- Memory

LOOKS LIKE...



Grade 1: Subtle changes in personality

Memory loss

Irritability

Sleep disturbances

Grade 2: Lethargy

Grade 3: Stupor

Incoherent speech

Convulsions

Grade 4: Coma

ASK ABOUT RECENT FALLS OR TRAUMA

- If positive for a recent fall or traumatic head injury, get a CT to rule out cerebral edema or subdural hematoma
- The risk of intracerebral hemorrhage is 5-fold increased in this patient group. A brain scan should usually be a part of the diagnostic work up (AASLD)

ENCEPHALOPATHY IS NOT ...

- Bipolar disorder or schizophrenia
- Dementia or Alzheimer's disease
- Assess for hallucinations, delusions of grandeur, suicidal or homicidal ideations in addition to treating disease
- It may be necessary to involve psych and neurology to care for patient as you are treating encephalopathy
- Think of encephalopathy as a diagnosis of exclusion

TREATMENT

LACTULOSE

- A laxative-warn your patients
- A non-absorbable disaccharide syrup. This is digested by bacteria in the colon to short chain fatty acids resulting in the acidification of colon contents. This acidification favors the formation of ammonium ions which are NOT absorbable rather than NH3 which IS absorbable and thought to be neurotoxic (Current Diagnosis and Treatment).
- Oral: Dose initially to have 3-4BMs daily. Maintenance dose should be 2-3 BMs daily.
- Enema: 300mL of lactulose in 700mL of saline or sorbitol retention enema for 30-60minutes. Good luck.
- Patient titrated. Excessive BMs =/= less encephalopathy!

RIFAXIMIN

- Oral antibiotic
- 1 550mg tab BID
- Non absorbable agent, proven to reduce hospital admissions in patients that ALSO take lactulose (CMDT)
- Usually very well tolerated
- No solid data that supports using xifaxan alone

Side effects

- Cardiovascular: Peripheral edema (15%)
- Central nervous system: Dizziness (13%), fatigue (12%)
- Hepatic: Ascites (11%)
- Gastrointestinal: Nausea (14%; irritable bowel syndrome with diarrhea 2% to 3%)

(up to date)

METRONIDAZOLE

- Oral
- 250mg TID
- Mild to equal benefit as Xifaxan (Up to Date)
- Only should be prescribed for SHORT TERM use
- Side effects: ototoxicity, nephrotoxicity, neurotoxicity

NEOMYCIN

- Oral antibiotic
- Glutaminase inhibitor
- 0.5-1gm every 6-12 hours
- Side effects: diarrhea, malabsorption, superinfection, ototoxicity and nephrotoxicity ☹ . These have been noticed FREQUENTLY, especially after prolonged use. (CMDT)
- • Nephrotoxicity: **[US Boxed Warning]: May cause nephrotoxicity;** usual risk factors include preexisting renal impairment, concomitant nephrotoxic medications, advanced age and dehydration. Discontinue treatment if signs of nephrotoxicity occur; renal damage is usually reversible.
- • Neuromuscular blockade and respiratory paralysis: **[US Boxed Warning]: May cause neuromuscular blockade and respiratory paralysis;** especially when given soon after anesthesia or muscle relaxants.
- • Neurotoxicity: **[US Boxed Warning]: May cause neurotoxicity;** symptoms also include numbness, skin tingling, muscle twitching and seizures. Usual risk factors include preexisting renal impairment and concomitant neuro-/nephrotoxic medications. Discontinue treatment if signs of ototoxicity occur; risk of hearing loss continues after drug withdrawal.
- • Superinfection: Prolonged use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.

LESS STUDIED MEDS

- PEG (poly ethylene glycol) / MiraLAX- may help treat hepatic encephalopathy by increasing excretion of ammonia in the stool. PEG was compared with lactulose in a trial tha t included patients with cirrhosis who were admitted to the hospital with hepatic encephalopathy [58]. Patients were randomly assigned to receive four liters of PEG over four hours or lactulose (three or more doses of 20 to 30 g over 24 hours). After 24 hours, patients who received PEG had more improvement in their hepatic encephalopathy scoring algorithm (HESA) score compared with those who received lactulose (from a mean of 2.3 to 0.9 compared with 2.3 to 1.6). In addition, the median time to resolution of the hepatic encephalopathy was shorter with PEG (one versus two days).
- Sodium benzoate- reduces ammonia levels by reacting with glycine to form hippurate, which is renally excreted. For each mole of benzoate used, one mole of waste nitrogen is excreted into the urine.
- BCAA (branched chain amino acids)-
- Zinc- Zinc has been suggested as having potential value in some patients with chronic or recurrent hepatic encephalopathy, but little evidence exists to document its effectiveness
- Melatonin — One of the most frequently described symptoms of subclinical forms of hepatic encephalopathy is sleep disturbances or, more generally, alterations in the sleep/wake cycle. The alterations in the sleep/wake cycle may be disabling for some patients. Unsatisfactory sleep is also characteristic of patients with cirrhosis who do not have encephalopathy (40 percent of patients in one study [78]).The abnormalities in sleep may be due in part to alterations in the 24-hour rhythm of the hormone melatonin, which is considered to be the output signal of the biological "clock." In one series of patients with cirrhosis, the onset of the rise in plasma concentrations of melatonin and occurrence of the melatonin peak during the night were delayed by hours [77]. Furthermore, plasma melatonin levels in patients with cirrhosis were significantly higher during daylight hours, a time when melatonin is normally very low or absent. (See "Physiology and available preparations of melatonin".)

*AVOID RESTRICTING PROTEIN

There is consensus that low-protein nutrition should be avoided for patients with HE.

Substitution of milk based or vegetable protein is preferable to reduction of total protein intake.

Q: IF A PATIENT WITH CIRRHOSIS AND ENCEPHALOPATHY TAKES LACTULOSE AS PRESCRIBED WILL THEIR AMMONIA LEVEL DECREASE?

A. MAYBE. IF YOU RELY ONLY ON SERUM AMMONIA LEVELS, BEWARE….
."CORRELATION BETWEEN PLASMA AMMONIA AND THE DEGREE OF ENCEPHALOPATHY CAN BE ERRATIC"
-QUEST DIAGNOSTICS

HIGH BLOOD AMMONIA LEVELS ALONE DO NOT ADD ANY DIAGNOSTIC, STAGING, OR PROGNOSTIC VALUE IN HE PATIENTS WITH CLD.

QUESTION: IF A PATIENT WITH CIRRHOSIS TAKES LACTULOSE AS PRESCRIBED, SHOULD THEIR LEVEL OF CONSCIOUSNESS IMPROVE?

YES! IT SHOULD.

COGNITIVE ABILITY > LAB WORK.

LACK OF EFFECT OF LACTULOSE SHOULD PROMPT A CLINIC SEARCH FOR UNRECOGNIZED PRECIPITATING FACTORS AND COMPETING CAUSES FOR BRAIN IMPAIRMENT.

WHAT HAPPENS WHEN TREATMENT FAILS?

Think "C.C.C. L.I.V.E.R.R."

Compliance
Constipation
Cancer

Librium- think all benzos alprazolam, lorazepam, temazepam, clonazepam, diazepam

Infection-rule out SBP (spontaneous bacterial peritonitis) and sepsis!

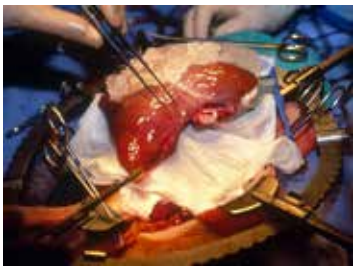
Volume status-dehydration. No fluid restriction for Na >125!

Electrolytes- routinely assess with lab work, watch for hyponatremia. correction of hypokalemia, if present, is an essential component of therapy for hepatic encephalopathy, since hypokalemia increases renal ammonia production

Rectal bleeding- upper or lower bleeding. **R**enal impairment

FINALLY

Refer for liver transplant!



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"Nutrition recommendations in NAFLD/NASH patients"

Disclosures: **None**

Learning Objectives:

1) Learn causes and populations
2) Understand nutrition recommendations in NALFD patients
3) Become aware of nutrition recommendations in managing NALFD comorbidities, including obesity, diabetes, hypertension and dyslipidemia
4) Recognize importance of a healthy lifestyle as the cornerstone for prevention and management of fatty liver

Nutrition Therapy in NAFLD and NASH

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Objectives

- States causes and populations
- Nutrition recommendations in NAFLD patients
- Enhance awareness of nutrition recommendations for managing NAFLD comorbidities, including obesity, diabetes, hypertension and dyslipidemia
- Underline the importance of a healthy lifestyle as the cornerstone for the prevention and management of NAFLD

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NAFLD cirrhosis[1]

- Main cause of Liver Transplant now
  - 25% of worldwide population

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1. Gastroenterology, 2021-02-01, Volume 160, Issue 3, Pages 912-918

NAFLD[1]

- Develop other cancers
- Subsequent CVD, HCC, Met syndrome, Ov/Ob
- Greater death risk with CVD,DM,OSA

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1. Gastroenterology, 2021-02-01, Volume 160, Issue 3, Pages 912-918

Healthy weight and NAFLD[1]

- Up to 10% of general population
  - Almost ½ NAFLD patients are healthy weight
- Greater morbidity and mortality compared to overweight NAFLD

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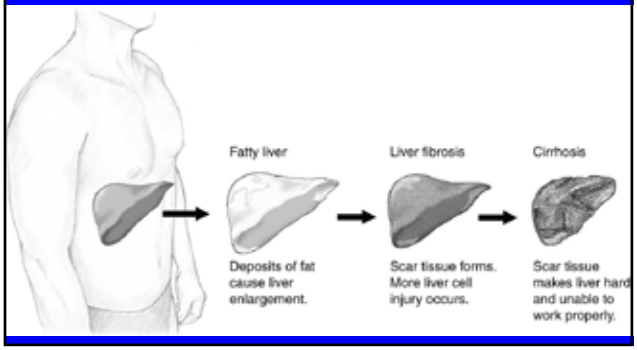
1. Gastroenterology, 2021-02-01, Volume 160, Issue 3, Pages 912-918

NAFLD Risk
Non-alcoholic fatty liver disease



AGA Clinical Practice Recommendations 2021[1]

- "Lifestyle modification to achieve weight loss remains a first-line intervention in patients with NAFLD."
- Weight loss reduces liver fat
- May lead to recuperation of liver

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AAG weight management recommendations[1]

- Assessment
- Intensive weight-loss intervention
- Weight stabilization and re-intensification prn
- Prevent regain
- Diet, PA, Bariatrics

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AGA recommendations

- Best practices
- Team approach for optimal outcomes
  - RDN
  - PT or Exercise Specialist
  - Culturally competent
  - SMART(ER) goals

AGA recommendations[1]

1. Weight loss with diet and exercise
2. Weight loss percent
   - 5% improves fatty liver
   - 7% resolves NASH
   - 10% stable or resolved fibrosis
3. Kcal goal
   - 500-1,000 ⇩ kcals/d
4. Med/Heart healthy and limit added fructose
   - DO NOT restrict fruit
   - Avoid SSB, sweets, desserts

1 Gastroenterology, 2021-02-01, Volume 160, Issue 3, Pages 912-918

4. Mediterranean Diet

- 2021 RCT with n - 294[2]
  - Green tea, walnuts, 2 x loss intra-hepatic fat vs. std Med diet
  - No red, processed meats
- Med has most research for NAFLD[1]
  - Nutraceuticals
    - Phytochemicals
    - Antixodiants
    - MUFA, Omega 3
    - Polyphenols

1. Gastroenterology, 2021-02-01, Volume 160, Issue 3, Pages 912-918
2. Gut. 2021 Jan 18;gutjnl-2020-323106. doi: 10.1136/gutjnl-2020-323106

AGA recommendations[1]

5. Lean NAFLD patient
   - 3 - 5% weight loss resolves ½ NAFLD
   - 7-10% loss resolves 70% NAFLD patients
6. Specific "diets" and supplements
   - Limited data for LCHF, IF, Meal replacement
   - Vit E, Vit C
     - Some benefits
     - Potential risks and harm

RCT n-74 Nordic diet for 12 weeks[3]

- 5:2
  - 2 non-consec days 500 to 700 kcals/d
  - Other 5 days 2000 to 2400 kcals/d
  - Mean of 1600-1700 kcals/d
- LCHF
  - 1600 to 1900 kcals
  - CHO 5-10%
  - PRO < 15%
  - Fat 50 to 80%

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3. JHEP Reports. Volume 3, Issue 3, June 2021, 100256. Treatment of NAFLD with intermittent calorie restriction or low-carb high-fat diet – a randomised controlled trial

RCT n-74 Nordic diet for 12 weeks[3]

- Std of Care
  - Hepatologist Rx Diet
  - 3 meals daily
  - Low sat fat
  - Low sweets
  - Avoid large portions
- 5:2 and LCHF best
  - Lowered steatosis
  - Lowered LDL
  - Reduced weight
  - Tolerated well

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AGA recommendations[1]

7. Physical activity

- 150-300 mins mod intensity/wk
- 75 to 150 mins vigorous/wk
- Resistance add'l, NOT a substitute

- PA improves weight loss
- PA + Med Diet = most benefits
  - Lower VAT
  - ↓ intrahepatic fat

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Systematic review and meta-analysis[4]

- Exercise beneficial for NAFLD
- Even without weight loss improves NAFLD
- Most beneficial from HIIT
- May prevent hepatic lipogenesis
- Calorie expenditure

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4. Battista, F, Ermolao, A, van Baak, MA, et al. Effect of exercise on cardiometabolic health of adults with overweight or obesity: Focus on blood pressure, insulin resistance, and intrahepatic fat—A systematic review and meta-analysis. Obesity Reviews. 2021; 22(S4):e13269

AGA recommendations[1]

8. Evaluate for comorbid conditions

- 20 to 83% have DM, CVD, HTN, OSA, Dyslipidemia
- CVD leading cause of death

- Risk eval recoms
- ACC/AHA risk stratification
- Weight mgmt strategies
  - Practice guide on obesity and weight management

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AGA recommendations[1]

9. Avoid ETOH

- Controversial
  - Cross-sect study
    - Mod intake ↓ NAFLD, NASH risk
  - Large prospective study
    - Low to mod intake = 2 x hepatic risk
  - Never smokers
    - ETOH intake = NO CV risk

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AGA recommendations[1]

- Sarcopenia
  - Over ½ awaiting liver had sarcopenia
    - Age, obesity independently associated
    - NASH also indep associated
      - 6 x risk sarcopenic obesity

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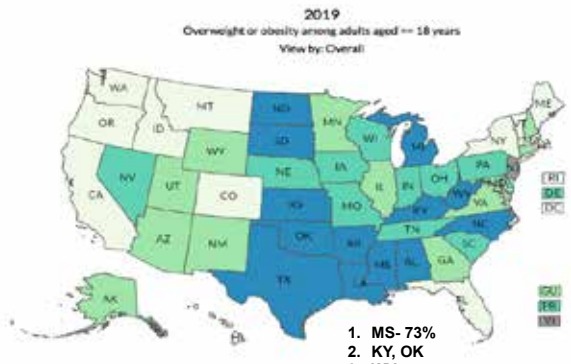

1. MS- 73%
2. KY, OK
3. WV
4. ND
5. LA, AK
6. SD
7. AL- 70.1%

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Food insecurity and Liver disease[5]

- Retrospecitive cohort NHANES 1999-2014
  - 4,800 NAFLD and 28% food insecure
  - 1650 Advanced fibrosis with 21% food insecure
- Poverty
- Diabetes and obesity
- Uninsured
  - No public, nor private
- Non-Hispanic
- Non-white

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5. Kardashian A, et al "Food insecurity is associated with all-cause mortality in U.S. adults with non-alcoholic fatty liver disease and advanced fibrosis" EASL 2021; Abstract GS-1072.

Food insecure outcomes[5]

- ~ 7 years follow-up
- All-cause mortality higher
- Higher Mortality risk
  - NAFLD 46%
  - Adv Fibrosis 37%
  - Smoking history
  - Public insured

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Food insecurity and Liver disease[5]

- Up to 22% deaths in NAFLD prevented if poverty and food insecurity abated
- Researcher recommendations
  - Screenings
  - Referrals
  - Linkages needed
- AL at 25% is 2nd highest food hardship rate[6]
  - Adults 32.6 million (14.2% of all adults)
  - Kids 16.2 million (21.6 % all children)

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6. alfba.org/hunger-in-alabama

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1. Gastroenterology, 2021-02-01, Volume 160, Issue 3, Pages 912-918.
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3. JHEP Reports. Volume 3, Issue 3, June 2021, 100256. Treatment of NAFLD with intermittent calorie restriction or low-carb high-fat diet – a randomised controlled trial
4. Battista, F, Ermolao, A, van Baak, MA, et al. Effect of exercise on cardiometabolic health of adults with overweight or obesity: Focus on blood pressure, insulin resistance, and intrahepatic fat—A systematic review and meta-analysis. Obesity Reviews. 2021; 22(S4):e13269
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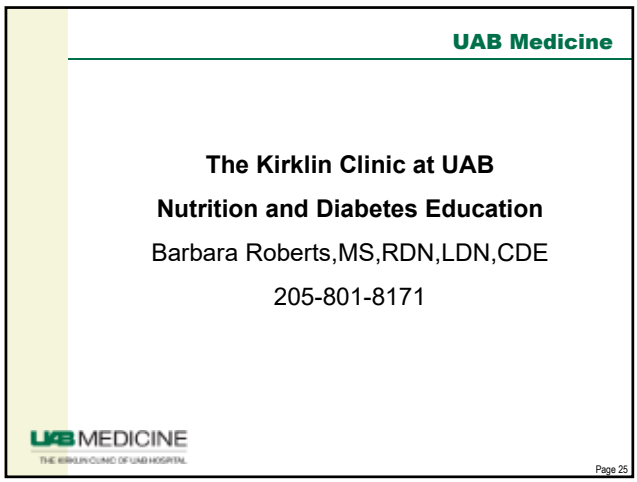
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"Palliative Care for End-Stage Liver Disease"

Disclosures: Grant: PCORI-Pal Liver Study

Learning Objectives:

1) Gain understanding of benefits of palliative care in ESLD

Palliative care (PC) is an integral part in the management of patients with chronic disease especially those with high symptom burden. Patients with end-stage liver disease (ESLD) experience a poor quality of life (QOL) related to a fluctuating clinical course with episodes of high symptom burden, however, patients with ESLD are rarely referred for PC and when they are it is often very late in the disease course. Several major barriers have been identified in providing PC to patients with ESLD including inadequate access to PC providers, discomfort with end of life discussions, preferential focus on life saving interventions, and clinical time constraints of providers. As the prevalence of ESLD continues to increase, providing optimal care for these patients, which includes components of PC, continues to be a challenge. In addition to patients, family caregivers (FCGs) –an integral part of the ESLD management team – have supportive care needs that are also under-recognized and poorly understood. The AGA recently provided a clinical practice update for PC in the care of patients with ESLD, highlighting 10 best practices regarding palliative care integration into practices. Currently, multiple ongoing studies are hoping to provide evidence-based guidance for PC in patients with ESLD. UAB is part of a larger national-effort to determine how to integrate PC into ESLD management through the PAL Liver study, a multi-institution cluster-randomized comparative effectiveness trial comparing hepatologist *vs* PC specialist-delivered PC. As a member of the PAL Liver network, UAB is aiming to define optimal PC delivery for patients with ESLD and their FCGs and to guide providers in ways to integrate PC into their clinical practice.

Suggested readings:

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Hepatocellular Carcinoma: A Rapid Review of Literature. J Palliat Med. 2018 Aug;21(8):1177-1184. doi: 10.1089/jpm.2017.0656. Epub 2018 Apr 26. PMID: 29698124; PMCID: PMC6104656.

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THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Palliative Care for End-Stage Liver Disease

Nicholas Hoppmann
Transplant Hepatology

Objectives

- End-Stage Liver Disease in the US
- Palliative Care in End-Stage Liver Disease – Current state of affairs
- Palliative Care in End-Stage Liver Disease – What's on the horizon
- PAL-LIVER Study
- Integration of PC – What can we do now?

End-Stage Liver Disease: Increasing in the US

Prevalence

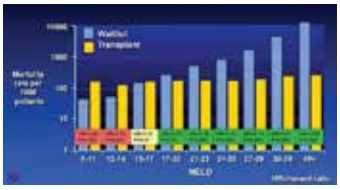
- 600,000 patients w/ cirrhosis in US
- ESLD doubled from 2001- 2013
- Younger (25-34 years)
  - Men increase 7.9%
  - Women increase 11.4%

Mortality

- 36,427 deaths in 2013
  - 66,000 deaths per year
- 12th leading cause of death
  - 7th for aged 25-64 years
  - Mortality rate increased 65% from 1999- 2016

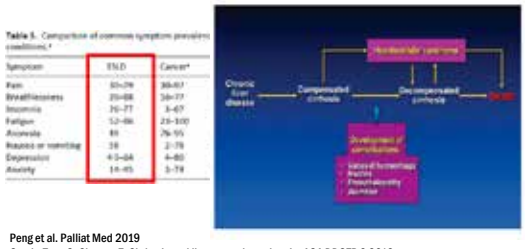
Scaglione et al. J Clin Gastroenterol 2015
Asrani SK et al. Gastroenterology 2013
Tapper EB, Parikh ND. BMJ 2018
U.S. Department of Health and Human Services; CDC; National Center for Health Statistics, 2019.

End-Stage Liver Disease: A Unique Position



Garcia-Tsao G. Chapter 7: Cirrhosis and liver transplantation. In: AGA DDSEP 9 2019

End-Stage Liver Disease: A Unique Position



Peng et al. Palliat Med 2019
Garcia-Tsao G. Chapter 7: Cirrhosis and liver transplantation. In: AGA DDSEP 9 2019

End-Stage Liver Disease: A Unique Position

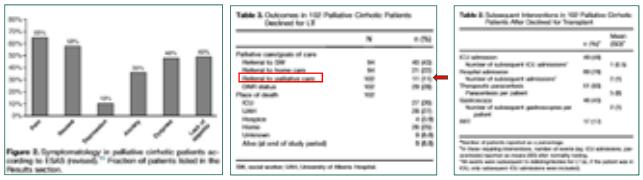
SUPPORT Study (2000)

- Similar symptoms to patients with lung and colorectal cancer
- Pain, dyspnea, confusion, depressed mood, anxiety
- Perceived QOL – fair or poor > 70%
- Understanding Prognosis: 160 (27%) patient who died during index hospitalization predicted their likelihood of 2-month survival at 75% or greater

Roth et al. J Am Geriatr Soc. 2000

End-Stage Liver Disease: A Unique Position

- Retrospective EMR review of 102 adult patients
  - Removed from LT or declined from 2005-2010 at their institution



Poonja et al. Clin Gastroenterol Hepatol. 2014

End-Stage Liver Disease: A Unique Position

- Family Caregivers (88% had FCG at home)
  - 15% quit work to care for patient
  - 37% loss major source of family income
  - 32% exhausted savings
  - 9% gave up or deferred education
  - 10% answered yes to “Has anyone else in the family become ill or unable to function normally in part because of stress and strain” of the illness

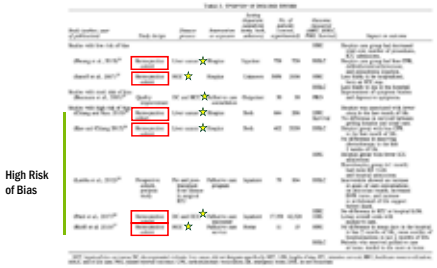
Roth et al. J Am Geriatr Soc. 2000

ESLD & Palliative Care

- Infrequent
- Delayed until the very end of life
- Stigmatized

- Major barriers
  - Inadequate access to PC providers
  - Episodes of decompensation occur with increased frequency over time
  - Discomfort with end of life care discussions
  - Preferential focus on life saving interventions
  - Time and training for palliative care

Palliative Care in ESLD: Rapid Review



High Risk of Bias

3 Main Outcome Groups

Healthcare Resource Utilization (HRU)
End-of-life Care (EOLC)
Patient-reported outcomes

Mudumbi SK et al. J Palliat Med. 2018

Palliative Care in ESLD: Prospective Studies

Verma M et al. Hepatology. 2020

Aren't PC providers better?

- Depends!
  - No standard model for integrating PC services within hepatology
- *Numbers game?*
  - PC providers: overburdened, not enough
- *"Who is this?"*
  - Another specialist may "unintentionally undermine existing therapeutic relationships"
- *"Talk to your [insert: Liver or Palliative Care] doctor?"*

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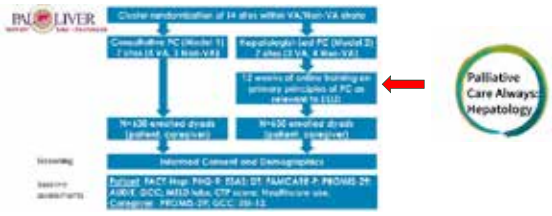
PAL LIVER
SUPPORT · CARE · COMPASSION

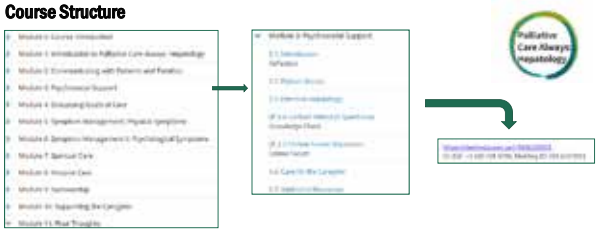
Introducing Palliative Care (PC) within the Treatment of End Stage Liver Disease: A Cluster Randomized Controlled Trial

Enrolling Protocol



Hepatology-Palliative Care Training

Course Structure



Intervention & Follow-Up

Evaluating Patients & Caregivers Experiences with Each Model: Qualitative Sub-Study
Patient-Caregiver Experiences

What can we do now?

AGA Clinical Practice Update – 10 Best Practice Advice (BPA)

1. Care with palliative care principles should be provided to any patient with advanced serious chronic illness or life-limiting illness such as cirrhosis, irrespective of transplant candidacy; this care should be based on needs assessment instead of prognosis alone, delivered concurrently with curative or life-prolonging treatments, and tailored to stage of disease.
2. Care inclusive of palliative care principles may be delivered by healthcare providers from any specialty within any healthcare setting.
3. Providers caring for persons with cirrhosis should assess for the presence and severity of symptoms within physical, psychological, social, and spiritual domains related to their liver disease, its treatment, and prognosis.
4. Across the spectrum of cirrhosis, excellence in communication is integral to high quality advance care planning, goals of care conversations, and the cultivation of prognostic awareness with patients and caregivers.
5. Routine care for patients with cirrhosis, and particularly those with decompensated disease, should include assessment of caregiver support and screening for caregiver needs.
6. Prognosis should be evaluated by gastroenterology/hepatology providers during routine care visits and at sentinel events.
7. Goals of care discussions in patients with cirrhosis should be repeated at sentinel events including hospital or intensive care admission, before initiation of lifesupporting therapies, before surgery, on new onset of cirrhosis-related complications, and after determination of transplant eligibility.
8. Because lack of time is one of the major barriers to administering palliative care, healthcare providers should consider how they can optimize efficiencies in palliative care delivery (identifying local billing codes, prescreening surveys carried out by ancillary staff, development of multidisciplinary teams).
9. Dedicated specialist palliative care services are often a limited resource. As such, healthcare providers should work together with local specialist palliative care teams to establish clear triggers and pathways for referral.
10. Healthcare providers caring for patients with cirrhosis should provide timely referral to hospice for patients who have comfort-oriented goals and prognosis of 6 months or less.

Tandon P, Walling A, Patton H, Taddei T. Clin Gastroenterol Hepatol. 2021

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Palliative Care: Anyone, anywhere.

AGA: PC in ESLD Best Practice Advice

1. Care with palliative care principles should be provided to any patient with advanced serious chronic illness or life-limiting illness such as cirrhosis, irrespective of transplant candidacy; this care should be based on needs assessment instead of prognosis alone, delivered concurrently with curative or life-prolonging treatments, and tailored to stage of disease.
2. Care inclusive of palliative care principles may be delivered by healthcare providers from any specialty within any healthcare setting.

Consider the palliative care measures you can provide for your patients with cirrhosis at any time.

Tandon P, Walling A, Patton H, Taddei T. Clin Gastroenterol Hepatol. 2021

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Beyond Decompensation Management

AGA: PC in ESLD Best Practice Advice

3. Providers caring for persons with cirrhosis should assess for the presence and severity of symptoms within physical, psychological, social, and spiritual domains related to their liver disease, its treatment, and prognosis.

Consider incorporating new symptom assessment and management into your practice.

Tandon P, Walling A, Patton H, Taddei T. Clin Gastroenterol Hepatol. 2021

Communication is Key

AGA: PC in ESLD Best Practice Advice

4. Across the spectrum of cirrhosis, excellence in communication is integral to high quality advance care planning, goals of care conversations, and the cultivation of prognostic awareness with patients and caregivers.

6. Prognosis should be evaluated by gastroenterology/hepatology providers during routine care visits and at sentinel events.

7. Goals of care discussions in patients with cirrhosis should be repeated at sentinel events including hospital or intensive care admission, before initiation of life supporting therapies, before surgery, on new onset of cirrhosis-related complications, and after determination of transplant eligibility.

Find resources to improve communication about goal of care, advanced care planning, prognosis.

The Conversation Project

Your Conversation Starter Guide
What Matter to Me Workbook
Your Guide to Choosing a Heath Care Proxy
Your Guide to Being a Health Care Proxy

Tandon P, Walling A, Patton H, Taddei T. Clin Gastroenterol Hepatol. 2021

Caregivers are critical

AGA: PC in ESLD Best Practice Advice

5. Routine care for patients with cirrhosis, and particularly those with decompensated disease, should include assessment of caregiver support and screening for caregiver needs.

Consider caregiver needs and establish resources to provide.

https://www.liver.ca/patients-caregivers/for-caregivers/

https://liverfoundation.org/caregivers/caregiver-support/

http://www.cirrhosis-caregivers.com/

https://www.caregiving.org/resources/

Tandon P, Walling A, Patton H, Taddei T. Clin Gastroenterol Hepatol. 2021

Plan for Palliative Care

AGA: PC in ESLD Best Practice Advice

8. Because lack of time is one of the major barriers to administering palliative care, healthcare providers should consider how they can optimize efficiencies in palliative care delivery (identifying local billing codes, prescreening surveys carried out by ancillary staff, development of multidisciplinary teams).

9. Dedicated specialist palliative care services are often a limited resource. As such, healthcare providers should work together with local specialist palliative care teams to establish clear triggers and pathways for referral.

10. Healthcare providers caring for patients with cirrhosis should provide timely referral to hospice for patients who have comfort-oriented goals and prognosis of 6 months or less.

Take time to plan incorporation of PC into your practice and establish easy avenues for referral.

Tandon P, Walling A, Patton H, Taddei T. Clin Gastroenterol Hepatol. 2021

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Thank you!

Nicholas Hoppmann
NHoppmann@uabmc.edu

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- Tandon P, Walling A, Patton H, Taddei T. AGA Clinical Practice Update on Palliative Care Management in Cirrhosis: Expert Review. Clin Gastroenterol Hepatol. 2021 Apr;19(4):646-656.e3. doi: 10.1016/j.cgh.2020.11.027. Epub 2020 Nov 19. PMID: 33221550.

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"Evaluation and treatment of liver lesions"

Disclosures: None

Learning objectives:

1. Identify the most important features of common benign liver tumors
2. Know the risk factors, diagnosis and management of hepatocellular carcinoma (HCC)

Classify liver lesions, benign vs. malignant:

Benign: hemangioma, focal nodular hyperplasia, adenoma, and liver cysts
Malignant: Primary liver cancers – HCC, Fibro lamellar carcinoma, Hepatoblastoma; Metastases

Will discuss clinical features of the benign liver lesions as well as diagnosis and management. Will review imaging findings.

Will discuss HCC incidence, risk factors, clinical features, sites of metastases, laboratory findings, diagnosis, imaging findings and prognosis. Will discuss treatment modalities.

Will discuss Fibro-Lamellar Carcinoma and Secondary Liver Metastases

References:

1. Bonder A, Afdhal N. Evaluation of liver lesions. Clin Liver Dis 2012; 16:271.
2. Tsung A, Geller DA. Workup of the incidental liver lesion. Adv Surg 2005; 39:331.
3. Heimbach J, Kulik LM, Finn R, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 2017.
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5. English K, Brodin NP, Shankar V, et al. Association of Addition of Ablative Therapy Following Transarterial Chemoembolization With Survival Rates in Patients With Hepatocellular Carcinoma. JAMA Netw Open 2020; 3:e2023942.

Evaluation and Management of Liver Lesions

Dana Scott, CRNP
UAB Department of Liver Transplant and Hepatobiliary Surgery

UAB MEDICINE

Objectives

1. Identify the most important features of common benign liver tumors

2. Know the risk factors, diagnosis, and management of hepatocellular carcinoma (Primary Liver cancer)

UAB MEDICINE

Classification

Benign

- Hemangioma
- Focal nodular hyperplasia
- Adenoma
- Liver cysts

Malignant

- Primary liver cancers
  -Hepatocellular carcinoma
  -Fibrolamellar carcinoma

- Metastases

UAB MEDICINE

Benign Liver Lesions

- Hemangioma
- Focal nodular hyperplasia
- Adenoma
- Cysts

UAB MEDICINE

Hemangioma
Clinical Features

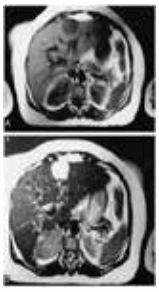
- The most common benign liver tumor
- Typically found incidentally
- 60-80% are diagnosed in ages 30-50, more frequent in women with a ratio ~ 3:1
- Often solitary but multiple lesions may be present
- Usually asymptomatic, symptoms more likely with large lesions ie, > 10cm

Hemangioma Diagnosis and Management

Diagnosis
- US: echogenic spot, well demarcated
- CT: venous enhancement from periphery to center
- MRI: homogenous and hyperintense on T2
- No need for FNA or biopsy, radiographic diagnosis

Treatment
- No need for treatment in most cases
- Large symptomatic lesions – surgical resection; may require transcatheter arterial embolization prior to resection

CT/Hemangioma



Focal Nodular Hyperplasia (FNH)
Clinical Features

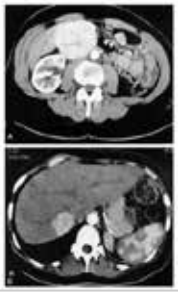
- Benign nodule formation of normal liver tissue (proliferation of hyperplastic hepatocytes)
- Most common in young and middle age women
- No relation with sex hormones
- Usually asymptomatic
- Painful lesions may require intervention
  -surgical resection, transarterial embolization, radiofrequency ablation

Focal Nodular Hyperplasia (FNH) Diagnosis and Management

Diagnosis:
- US: Nodule with varying echogenicity
- CT: Hypervascular mass with central scar
- MRI: iso or hyperintense mass

Treatment:
- No treatment necessary
- Pregnancy and hormones OK

CT/FNH



Hepatic Adenoma

Clinical features

- Uncommon, solid, benign liver lesion
- Typically seen in young women
- Associated with use of estrogen-containing medications, glycogen storage disease, metabolic syndrome, obesity
- Usually asymptomatic but may have RUQ pain
- May present with rupture, hemorrhage, or malignant transformation (very rare)

Hepatic Adenoma Diagnosis and Management

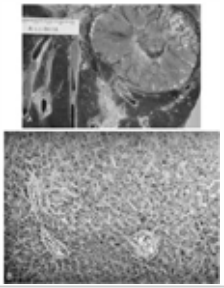
DX
- US: filling defect
- CT: Diffuse arterial enhancement
- MRI: hypo or hyper intense lesion
- Core bx/FNA: may be indicated but frequently insufficient tissue

Hepatic Adenoma Diagnosis and Management (con't)

Treatment

- Stop hormones
- Asymptomatic </= 5cm q 6mo MRI, annually when stable
- Symptoms or >5cm surgical resection d/t bleeding risk
- Men – resection irrespective of size d/t malignant transformation risk
- Pregnant women – follow by high risk OB, surveillance with US q 6-12 weeks

Adenoma



Liver Cysts
Clinical Features

- Most are incidental finding
- May be single or multiple
- May be part of polycystic kidney disease or polycystic liver disease (less common)
- Patients often asymptomatic, no treatment required
- Large and symptomatic – laproscopic wide unroofing (procedure of choice)
- Important to distinguish from more concerning lesions such as mucinous cystic neoplasm

Malignant Liver Lesions

Malignant Liver Tumors

1. Hepatocellular carcinoma (HCC)
2. Fibro-lamellar carcinoma of the liver
3. Hepatoblastoma
4. Intrahepatic cholangiocarcinoma
5. Others

HCC: Incidence

- The most common primary liver cancer
- 6th most frequently dx'd cancer worldwide and 4th leading cause of cancer-related mortality worldwide
- Typically develops in setting of chronic liver disease, particularly cirrhosis and chronic Hep B
- More frequent in men than women 3:1
- NASH increasingly common risk factor in Western Countries

HCC: Risk Factors

The most important risk factor is cirrhosis from any cause:

1. Hepatitis B (integrates in DNA)
2. Hepatitis C
3. Alcohol
4. Environmental toxins (work synergistically with other risk factors such as HBV infection)
5. NASH

HCC: Clinical Features

- Asymptomatic
- Wt loss and RUQ pain
- Worsening of pre-existing chronic liver disease
- Acute liver failure

O/E:
- Signs of cirrhosis
- Hard enlarged mass

HCC: Metastases

- Rest of the liver
- Portal vein
- Lymph nodes
- Lung
- Bone
- Brain

HCC: Systemic Features

- Hypercalcemia
- Hypoglycemia
- Obstructive jaundice
- Erythrocytosis

HCC: labs

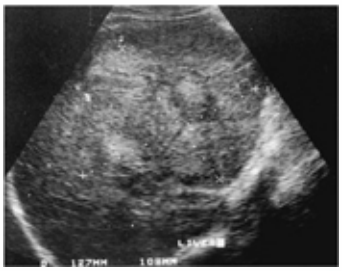
- Labs of liver cirrhosis

AFP (Alfa-fetoprotein)
- Tumor marker for HCC
- ~ 60% sensitivity and 80% specificity for HCC detection
- Typically higher for advanced HCC
- Serum AFP levels > 400ng/mL in a high-risk patient are nearly diagnostic of HCC (specificity > 95%)

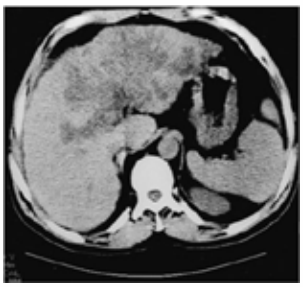
HCC: Diagnosis

- Clinical presentation
- Elevated AFP
- US
- Diagnosis can be made radiographically with MRI or CT, obviating the need for biopsy
- Biopsy

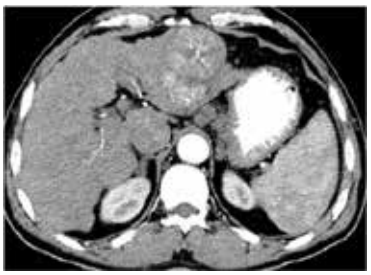
US: HCC



CT: Venous Phase



CT: Arterial Phase



HCC: Prognosis

- Severity of underlying liver disease
- Tumor size
- Extension of tumor into adjacent structures
- Presence or absence of metastases

HCC: Liver Transplantation

- Potentially curative option for selected patients with HCC
- Overall survival and disease recurrence following OLT for HCC similar to or slightly worse than for non-malig causes
- Criteria: single lesion</= 5cm, up to 3 separate lesions none >3cm, no evidence of VI, no regional nodal or extrahepatic distant metastases/ Downstaging

HCC: Resection

- Preferred therapy (potentially curative) for localized HCC
- Majority of pt's not eligible d/t tumor extent, underlying liver dysfunction
- Ideal: solitary HCC w/o VI, no portal HTN, well-preserved hepatic function
- Long-term relapse-free survival rates 40%+, 5 yr survival rates as high as 90%

HCC: Local Ablation

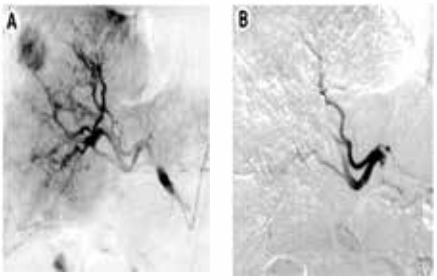
- For non resectable pt w/o extrahepatic mets
- 1 or 2 tumors < 4cm
- Radiofrequency ablation/microwave ablation
- Not curative/can be bridge to transplant

Radio Frequency Ablation

HCC: Chemoembolization (TACE)

- Treatment of large unresectable HCCs
- Inject chemotherapy selectivity in hepatic artery
- Then inject an embolic agent
- Only in pt with early cirrhosis
- No role for systemic chemotherapy
- Radioembolization (Y-90) – combines embolization and radiation therapy to treat HCC

Chemoembolization



Fibrolamellar Carcinoma

- Rare
- Affects younger individuals (5-35)
- Not related to cirrhosis
- AFP is normal
- Does not have a male predominance
- CT shows large, sharply defined, heterogeneously enhancing mass, +/- calcifications

Secondary Liver Cancer (metastases)

- The most common site for metastasis
- Common primaries: colon, breast, esophageal, lung, stomach, pancreas, and melanoma
- Diagnostic imaging and/or biopsy
- Treatment depends on the primary cancer

Summary

Benign

- Hemangioma
- Focal nodular hyperplasia
- Adenoma
- Liver cysts

Malignant

1. Primary liver cancers
   - Hepatocellular carcinoma
   - Fibrolamellar carcinoma
2. Metastases

Thank you!

UAB Liver Tumor Clinic
(205)996-5970

UAB Digestive Health & Liver Center

Mailing Address:
1720 2nd Avenue South, BDB 3rd Floor
Birmingham, Alabama 35294
Telephone: 205-966-4744

"Referring a patient to UAB Gastroenterology & Hepatology"

- **Digestive Health and Liver Center (form attached for Liver Center Referrals)**
  - Appointment scheduling — 205-996-4744, option 1
  - GI/HEP Call Center (Nurses) — 205-996-4744, option 2
  - Incoming Fax for referrals — 205-801-8668

- **Liver Transplant Evaluations**
  (see attached referral form) — 205-975-5691
  Toll-free 1-866-305-5691
  Fax: 205-975-2298

- **Liver Tumor Clinic**
  (See attached form) — 205-996-5970
  Fax: 205-996-9037

- **Basil I Hirschowitz Endoscopic Center of Excellence** — 205-934-6895
  - RFA and Cryotherapy for Barrett's
  - Endoscopic mucosal resection of GI polyps
  - Diagnosis and therapeutic endoscopic ultrasound
  - Advanced and routine hepatobiliary procedures including ERCP, spyglass, biliary rendezvous
  - Endoscopic removal of early cancer of esophagus, stomach and colon using procedures such as endoscopic mucosal resection and endoscopic submucosal dissection
  - EUS guided biliary and pancreatic access and therapy
  - EUS guided celiac plexus neurolysis

After hours/weekends and/or for emergencies or hospital transfers – please call the GI Fellow or Hepatology attending on call through the UAB Paging Operator: **1-800-UAB-MIST (800-822-6478)**

For more information on how to refer to UAB:
https://www.uabmedicine.org/web/medicalprofessionals/refer-a-patient

Thank you for your interest in the UAB Liver Center. We are pleased that you are allowing us to aid the care of your patients. Your completion of the all the fields below and attachment of medical records will ensure that there are no unnecessary delays in the evaluation of your patient.

Required Information:

- Patient demographics page from your data system
- Clinic notes, labs, procedure reports, and imaging for the past 12 months
- Copy of insurance cards or insurance information

Patient Full Name:	Patient Contact Number:
Date of Birth:	Office Contact Name:
Referring MD Name:	Referring MD NPI: (first referral only)
Referring MD Address:	Referring MD Phone:
Indication/Clinical Concern:	Referring MD Fax:

Reason for Visit: Please check box below

	Liver Mass (Please refer to Hepatobiliary/Liver Mass Clinic Form)
	Transplant Evaluation
	General Hepatology (please list diagnosis/concern above)
	Viral Hepatitis / ABC Clinic

Requested Provider and fax number to fax records:

	Brendan McGuire, MD	205-975-9777
	Meagan Gray, MD	205-975-9777
	Mohamed Shoreibah, MD	205-975-9393
	Nicholas Hoppmann, MD	205-975-9393
	David Fettig, MD	866-728-9320
	Sujan Ravi, MD	866-728-9320
	Viral Hepatitis / ABC Clinic	866-408-1445

UAB Department of Gastroenterology & Hepatology
NAFLD Clinic

UAB's NAFLD clinic is a comprehensive resource for patients with nonalcoholic fatty liver disease (NAFLD). NAFLD is currently the most common cause of chronic liver disease globally, and affects approximately 30% of adults in the United States. Patients with NAFLD are often asymptomatic until the disease becomes advanced. Risk factors include obesity, type 2 diabetes mellitus, high blood pressure and high cholesterol. NAFLD is quickly becoming the most common cause of cirrhosis, liver cancer and the most common indication for liver transplantation. It is grossly under diagnosed, under recognized and under treated. There are currently no FDA approved medications to treat NAFLD, although there are many drugs in clinical trials. We know that weight loss of 5-10 percent of total body weight leads to improvement in liver fat content, as well as liver scarring, which is the main focus of the clinic.

Our Approach

Our team approach includes individualized care by a trained hepatologist who specializes in the care of patients with liver disease and a registered dietician.

Services include:

- Basic metabolic rate (BMR) testing: All patients will receive complimentary BMR testing that estimates energy expenditure at rest that can help determine daily calorie needs necessary for successful weight loss.
- Ultrasound elastography: Elastography provides a quick, noninvasive, accurate estimate of how much damage (or fibrosis) has been done to the liver from fat.
- Registered Dietician: Patients will receive a complimentary session with a registered dietician on their initial visit to help tailor a food plan for weight loss success.
- Research: A hepatology research coordinator is available to talk with patients about options for NAFLD clinical trials if they are interested.
- UAB Weight Loss Medicine: Patients will also have the option to follow up with the UAB Weight Loss Medicine clinic, which can provide additional services to aid in patient's weight loss journey and provide the appropriate pre- and post-operative care for patients interested in bariatric surgery.

UAB's NAFLD Clinic is conveniently located in the UAB Weight Loss Medicine clinic at UAB Hospital-Highlands, Suite 515, 1201 11th Avenue South, Birmingham, AL 35205.

Patients may be self- or physician-referred by calling 205.996.4744. For physician-to-physician consultation, please call UAB MIST at 205-934-6478 or 800-UAB-MIST (800-822-6478).

Our Specialist

Meagan Gray, M.D.
Assistant Professor

LIVER TREATMENT SERVICES

Medical and surgical care for liver disorders at UAB is administered by a team of highly skilled and dedicated physicians and surgeons. At UAB, patients benefit from collaboration between the UAB Division of Gastroenterology and the Comprehensive Transplant Institute (CTI), both of which are staffed by nationally recognized leaders in the treatment of all aspects of liver disease.

LIVER DISEASE MANAGEMENT

The UAB Liver Center is a clinical and research facility dedicated to advancing knowledge and medical treatment of liver disease. Some of the diseases and conditions treated include:

- Alcoholic liver disease
- Alpha-1-antitrypsin deficiency
- Amyloidosis
- Ascites
- Autoimmune liver disease
- Caroli's disease
- Cholestatic liver diseases
- Cirrhosis
- Cystic liver diseases
- Drug-induced liver diseases
- Esophageal varices
- Fatty liver disease (NAFLD/NASH)
- Fulminant hepatic failure
- Granulomatous liver disease
- Hemochromatosis
- Hepatic encephalopathy
- Primary biliary cirrhosis
- Primary and secondary sclerosing cholangitis
- Viral hepatitis A,B,C,D, and E
- Wilson's disease

LIVER TRANSPLANTATION

The UAB Liver Transplant Program is the only transplant center in Alabama and one of only 20 in the country that averages 100 or more liver transplants annually. Our program is one of the nation's most experienced, having performed more than 2,700 liver transplants to date, with outcomes among the best in the United States. Due to the wide geographic area we serve, UAB developed a streamlined transplant evaluation process for the convenience of patients. The state-of-the-art, multidisciplinary care continues throughout the transplant process, from the advanced operating suites at UAB Hospital to comprehensive post-transplant management in both inpatient and outpatient settings. Liver transplantation is the preferred therapy for those patients who have end-stage liver disease and need a transplant to survive. To refer a patient for a liver transplant evaluation, please call 833.UAB.CTI1 (833.822.2841). For more information, visit uabmedicine.org/referlivertransplant.

LIVER TUMOR CLINIC

The Hepatobiliary Surgery Clinic, also referred to as The Liver Tumor Clinic, is a multidisciplinary clinic staffed by the Liver Transplant surgeons and advanced practice providers, and supported via the Liver Tumor Board by Radiology, Hepatology, Medical and Radiation Oncology, Interventional Radiology and Pathology. This team provides a collaborative effort to diagnose and treat patients with focal hepatic lesions (such as adenoma and focal nodular hyperplasia), hepatocellular carcinoma (HCC), hepatic metastases and cholangiocarcinoma. We are a high volume center offering open and laparoscopic procedures as well as loco-regional therapies including chemoembolization/radioembolization, ablation, irreversible electroporation and external beam radiotherapy for treatment of primary and metastatic hepatobiliary malignancies. Furthermore, we offer the full range of services listed above for HCC, as well as the possibility of liver transplant for tumor burden that is within Milan or UCSF criteria.

- To refer a patient for a liver transplant evaluation, please call 833.UAB.CTI1 (833.822.2841). or visit uabmedicine.org/referlivertransplant.
- To refer a patient to the UAB Liver Center, call 205.996.4744 or visit uabmedicine.org/referlivertransplant.

UAB MEDICINE TRANSPLANT APP

The UAB Medicine Transplant app gives referring physicians 24/7 access to the UAB Comprehensive Transplant Institute (CTI) team. It includes quick references to our selection criteria and secure access to patient records, plus contact information for all CTI doctors and surgeons. A built-in form allows physicians to easily start the referral process from their iOS or Android device. Scan the QR code here for more information.

FOR REFERRING PHYSICIANS

Our faculty is committed to providing immediate consultations and care for your patients. For physician-to-physician consultations, please call UAB MIST at 800.UAB.MIST (800.822.6478).

800.UAB.MIST (800.822.6478)
uabmedicine.org/physician

UAB MEDICINE
The University of Alabama at Birmingham

UAB MEDICINE
PHYSICIAN SERVICES

UAB Ambassador Program

The Ambassador Program allows practitioners to have complete access to their patients' UAB records, including admission and discharge summaries, clinical notes, activities and lab results through a secure web portal. This innovative tool improves communication between UAB Medicine and referring practitioners, enhancing continuity of care. There is no charge to participate in this program.

To request access to the program, please complete and fax the attached form to Physician Services at 205-996-9107. A secure token, user ID and password will then be created for you. A physician liaison will visit your office to provide training on the use of the program.

As a practitioner who will be granted access to the protected health information (PHI) provided within Ambassador, you acknowledge and agree to the following UAB Health System Security Policies:

- The PHI you access is for the continuation of patient care of your patients only.
- Your logon and token cannot be shared with additional personnel other than the Designee User listed on your request form
- You are responsible for all activity and usage associated with your logon. Logon activities are regularly monitored.
- When viewing PHI via Ambassador, you will not leave the computer terminal unattended and will log off once you have completed your task.
- This privilege will be terminated immediately in the event you view data or medical information of individuals who are not your patients.
- UAB cannot guarantee that Ambassador will be accessible during a medical emergency.
- UAB cannot guarantee the accuracy, completeness or timeliness of the information within Ambassador.
- To be connected with other physicians within the practice, the Consent to Link Physician Practice section must be completed and on file with UAB Physician Services.

If you have any questions or need additional information regarding Ambassador or UAB Medicine, please feel free to contact Physician Services at 205-934-6890 or Ambassador@uabmc.edu.

Disclaimer:
UAB Medicine seeks to enhance the continuity of care for our patients. Physician Services, through UAB Ambassador, aims to provide enhanced communication between UAB and referring physicians throughout the Region. UAB Physician Services will continue to follow the protocol and procedures outlined above, and will modify if necessary to remain in accordance with privacy and safety measures. Questions or concerns should be directed to: UAB Physician Services, 500 22nd Street S., Birmingham, AL 35294. 205-934-6890.

Updated Feb 2021

UAB MEDICINE
PHYSICIAN SERVICES

For Questions, Please Contact Physician Services
205-934-6890 (Phone)
205-996-9107 (FAX)
Ambassador@uabmc.edu

Request for UAB Ambassador Token Access

Please circle one: **Physician** **Nurse Practitioner** **Physician Assistant**

Physicians have two token options: Hard token ___ or Smart Phone app token ___ (Android ___ or iPhone ____)

NP & PA: Tokens are available via an app on smart phones only. Circle one: Android iPhone

First Name _____ Middle Initial ____ Last Name_____

Physician NPI #_____Practice Name _____

Street Address_____

City _____ State _____ Zip Code_____

Phone _____ Fax _____ County _____

Specialty _____ Email _____

Designated User(s) _____

Consent To Link Physician Practice

Practitioners within the same office may be linked to one another's Ambassador Portal. Once linked, each practitioner will be able to view patients of the others within the practice. For access to this feature, UAB Physician Services must have the consent of each practitioner wishing to participate. UAB Physician Services will only connect those who agree to share their patient lists. Should a practitioner choose not to participate in the practice connection, he or she will not appear in the practice group, and the patient list can only be accessed by their individual Ambassador token. A practitioner can be removed from a practice group at any time, and if a practitioner leaves or relocates to another practice, Physician Services must be notified.

_____ I authorize my patient list to be linked to these practitioners' within the practice _____

_____

_____ I do not wish to link my patient list with the practitioners within our practice at this time.

I have read and understand the terms and conditions (attached) for use of the UAB Ambassador Program. I agree to abide by these terms and conditions.

Signature _____ Date _____

Acknowledgement: I acknowledge that I have received my Ambassador Token, Liaison Training and UAB Ambassador User Guide.

Received Signature _____Delivery Date_____

Disclaimer: UAB Medicine seeks to enhance the continuity of care for our patients. Physician Services, through UAB Ambassador, aims to provide enhanced communication between UAB and referring physicians throughout the Region. UAB Physician Services will continue to follow the protocol and procedures outlined above, and will modify if necessary to remain in accordance with privacy and safety measures. Questions or concerns should be directed to: UAB Physician Services, 500 22nd Street S., Birmingham, AL 35294. 205-934-6890.

Updated Feb 2021

RESOURCES FOR REFERRING PHYSICIANS

UAB Physician Services
Physician Services seeks to improve communication between UAB Medicine and referring physicians, while also providing support that will enhance continuity of care. Physician Services is available to assist physicians by facilitating the referral process, communicating timely and pertinent information regarding a patent's visit to UAB, and providing up-to-date information regarding the programs and services available within UAB Medicine. To reach our office directly, you may call 205.934.6890 Monday-Friday 8:00 am-4:30pm, or email *physicianservices@uabmc.edu.*

Physician Liaisons
Our physician liaisons travel throughout Alabama, and into surrounding areas visiting referring physicians and their office staff. As licensed, registered nurses, the liaisons are able to discuss clinical issues with physicians and assist in the referral process. The liaisons' goal is to maintain an open line of communication between the referring community and the health system, providing referring physicians with the most up-to-date information on research, technologies, physicians, and services at UAB. Our liaisons are assigned geographically and are available to discuss any concerns or issues that you may have. Contact the Physician Services office to connect or schedule a visit with the physician liaison in your area.

UAB Ambassador
UAB Ambassador is a secure, Web-based tool providing referring physicians with access to their patients' electronic medical record. Ambassador enhances continuity of care by giving physicians the ability to follow patients throughout UAB Medicine for both inpatient and outpatient visits, including consultation notes, labs, procedure reports and discharge summaries. UAB Ambassador improves communication between UAB Medicine and referring physicians, by removing barriers to timely access of patient records. To register for Ambassador, or for additional information, please contact Physician Services at 205.934.6890 or email *physicianservices@uabmc.edu.*

UAB MIST (Medical Information Service via Telephone)
UAB MIST is a toll-free 24-hour service which gives physicians and healthcare professionals immediate access to UAB faculty, staff, and services regarding inpatient referrals, outpatient appointments, consults and patient follow-up.

The MIST service:
- Triages consultation and referral calls to the appropriate UAB physician and service
- Facilitates the patient transfer process with the UAB Center for Patient Flow
- Provides the appropriate routing of patient follow-up, outpatient appointment and health related calls including documentation and call data

In addition, referring physicians may also call MIST to:
- Return calls from UAB or provide follow-up information
- Make arrangements for Critical Care Transport
- Contact UAB Physician Services, the UAB Center for Patient Flow or other UAB administrative offices

Contact MIST by phone at 1.800.UAB.MIST (1.800.822.6478) or via email to *mist@uabmc.edu.*

UAB Digestive Health & Liver Center
Mailing Address:
1720 2nd Avenue South, BDB 3rd Floor
Birmingham, Alabama 35294
Telephone: 205-966-4744

Thank you for attending our 2021 Update in Gastroenterology & Hepatology!

Please do not forget to turn your evaluation forms in by placing in box at the door or box at the registration table as you leave. This helps us in our planning for next year.

Stay safe and call us if you need us!