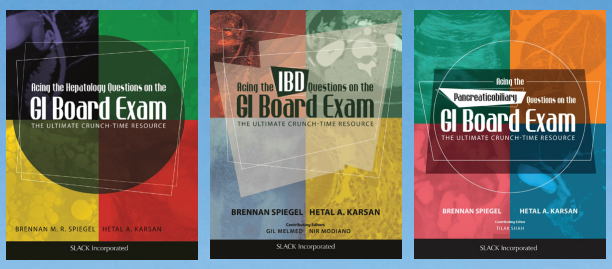
OFFERING CME & MOC CREDITS!

AT THE FOREFRONT
UChicago Medicine
Digestive Diseases Center

ANNUAL GI AND LIVER UPDATES MEETS "ACING THE BOARDS"



SEPT. 20–21 2019

CONFERENCE CO-DIRECTORS
Sonia Kupfer, MD—UChicago Medicine
David T. Rubin, MD—UChicago Medicine
Brennan Spiegel, MD, MSHS—Cedars-Sinai
Hetal A. Karsan, MD—Atlanta Gastroenterology Associates & Emory University

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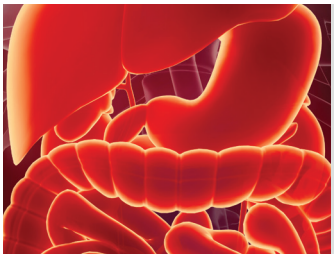
221 N Columbus Drive

Course credit: **https://cme.uchicago.edu/DigestiveDiseases2019**
Syllabus/Slides: **https://cme.uchicago.edu/DigestiveDiseasesSyllabus19**



ANNUAL GI AND LIVER UPDATES MEETS "ACING THE BOARDS"

Radisson Blu Aqua Hotel Chicago

September 20-21, 2019

DESCRIPTION

The overall goal of this activity is to provide up-to-date evidence-based education in diagnosis and management of gastrointestinal and liver diseases as well as to provide high-yield board examination preparation that will lead to highly trained healthcare professionals who provide the highest level of patient care.

TARGET AUDIENCE

This activity is designed for physicians and other healthcare professionals dedicated to the prevention and treatment of gastrointestinal diseases.

LEARNING OBJECTIVES

At the conclusion of this education activity, participants will be able to:

- *Describe how to implement evidence-based medicine in the diagnosis and management of gastrointestinal and liver diseases;*
- *State the role of emerging technologies for medical and surgical management of gastrointestinal diseases;*
- *Discuss how to apply high-yield clinical pearls to diagnose complex gastrointestinal diseases;*
- *Evaluate different views in controversial areas of the management of gastrointestinal and liver diseases;*
- *Outline new guidelines for the therapeutic monitoring and management of gastrointestinal diseases.*

ACCREDITATION AND CREDIT DESIGNATION

PHYSICIAN CREDIT

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

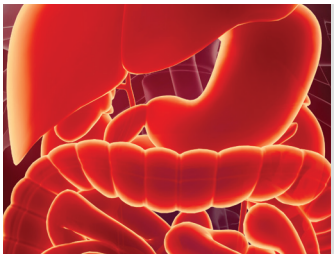
The University of Chicago Pritzker School of Medicine designates this live activity for a maximum of 12 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

AMERICAN BOARD OF INTERNAL MEDICINE MOC PART II CREDIT

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 12 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

OTHER HEALTHCARE PROFESSIONS CREDIT

Nurses and other healthcare professionals will receive a Certificate of Participation. For information on the applicability and acceptance of Certificates of Participation for educational activities certified for *AMA PRA Category 1 Credit*™ from organizations accredited by the ACCME, please consult your professional licensing board.



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EDUCATIONAL GRANTS/COMMERCIAL SUPPORT

Educational grant funding has been generously provided by:

Biocompatibles Inc.

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Prometheus Labratories, Inc.

Takeda Pharmaceuticals U.S.A., Inc.

Supported by an educational grant from:

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We would also like to thank our exhibitors:

AbbVie, Inc.
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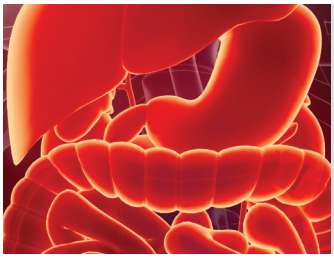
Takeda



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DISCLOSURE DECLARATIONS

As a provider accredited by the ACCME, The University of Chicago Pritzker School of Medicine asks everyone who is in a position to control the content of an education activity to disclose all relevant financial relationships with any commercial interest. This includes any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients. The ACCME defines "relevant financial relationships" as financial relationships in any amount, occurring within the past 12 months, including financial relationships of a spouse or life partner that could create a conflict of interest. Mechanisms are in place to identify and resolve any potential conflict of interest prior to the start of the activity.

Additionally, The University of Chicago Pritzker School of Medicine requires Authors to identify investigational products or off-label uses of products regulated by the US Food and Drug Administration at first mention and where appropriate in the content.

COURSE FACULTY

The following individuals have disclosed no relevant financial relationships:

Talia B. Baker, MD
Nina Gupta, MD
Sonia Kupfer, MD
Edwin K. McDonald IV, MD
Charles Muller, MD
Sajan J. Nagpal, MD
Sonali Paul, MD, MS
Carol E. Semrad, MD
Jessica Stoll, MS, CGC
Kiran K. Turaga, MD, MPH

Christopher Chapman, MD has served as a consultant for Apollo Endosurgery and Neurotronic, Inc.

Michael R. Charlton, MBBS has served as a consultant for Gilead, Terns, Mylan, Celgene, Metacrine, BMS, Novartis, and Intercept.

Russell D. Cohen, MD has served on the speaker's bureau for Abbvie and Takeda. Dr. Cohen has served as a consultant, advisor, and scientific advisory board member for Abbvie Laboratories, Celgene, Entera Health, Hospira, Janssen, Pfizer, Sandoz Biopharmaceuticals, Takeda, and UCB Pharma. Dr. Cohen has received research funding from Astra Zeneca, Celgene, Gilead Sciences, Medimmune, Mesoblast Ltd., Osiris Therapeutics, Pfizer, Receptos, RedHill Biopharma, Sanofi-Aventis, and UCB Pharma.

Sushila Dalal, MD has received research funding from Pfizer.

Mustafa Hussain, MD has served as a speaker for W.L. Gore and as a teacher for Intuitive.

Hetal Karsan, MD has served on the advisory board for Takeda and Gilead and on the speakers bureau for Abbvie.

Joel Pekow, MD has served as a consultant for Verastem and an advisory board member for Janssen and Pfizer. Dr. Pekow has received grant funding from Abbvie and Takeda.

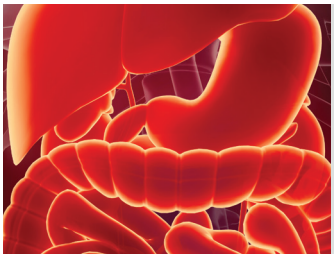
David T. Rubin, MD has served as a consultant for Abbvie, Abgenomics, Allergan, Inc., Arena Pharmaceuticals, Biomica, Bristol-Myers Squibb, Dizal Pharmaceuticals, Ferring Pharmaceuticals, Inc., Genentech/Roche, Janssen Pharmaceuticals, Lilly, Merck & Co., Inc., Medtronic, Napo Pharmaceuticals, Pfizer, Shire, Takeda, and Target PharmaSolutions, Inc. Dr. Rubin has received grant funding from Prometheus Laboratories, Abbvie, Genentech/Roche, Janssen Pharmaceuticals, Shire, and Takeda.

Uzma D. Siddiqui, MD has served as a consultant and speaker for Boston Scientific, Medtronic, and Olympus.

Brennan Spiegel, MD has received grant funding from Alnylum, Shire, Takeda, and Samsung.

Irving Waxman, MD has served as a consultant for BSCI, Medtronic, and Cook Medical.

The staff of the Center for Continuing Medical Education have no relevant financial relationships to disclose.



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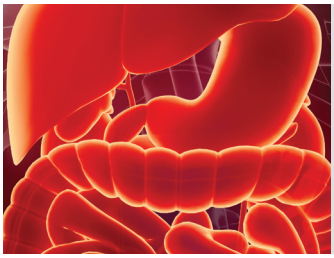
DISCLAIMER

The views expressed in this activity are those of the individual speaker. It should not be inferred or assumed that they are expressing the views of any pharmaceutical or product/device manufacturer, provider of commercial services, or The University of Chicago. The drug selection and dosage information presented in this activity are believed to be accurate. However, participants are urged to consult the full prescribing information on any agent(s) presented in this activity for recommended dosage, indications, contraindications, warnings, precautions, and adverse effects before prescribing any medication. This is particularly important when a drug is new or infrequently prescribed.

Please Note: Requests to claim *AMA PRA Category 1 Credit*™ after three months will be subject to additional fees.



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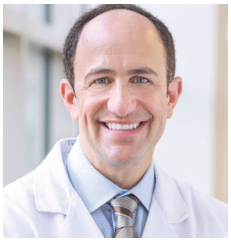
CONFERENCE FACULTY

Course Directors

Sonia Kupfer, MD
Associate Professor of Medicine
Director, Gastrointestinal Cancer Risk and Prevention Clinic



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Joseph B. Kirsner Professor of Medicine
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Adjunct Professor of Medicine
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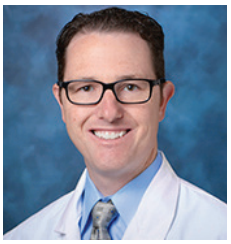

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Director of Health Services Research, Cedars-Sinai Health System
Director, Center for Outcomes Research and Education (CORE)
Professor of Medicine Cedars-Sinai, Los Angeles, CA

University of Chicago Speakers

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Program and Surgical Director, Liver Transplant
Director, Living Donor Liver Transplant Program
Liver Transplantation and Hepatobiliary Surgery

Christopher Chapman, MD
Assistant Professor of Medicine
Director, Bariatric and Metabolic Endoscopy

Michael Charlton, MD, FRCP
Professor of Medicine
Co-Director, Transplantation Institute
Director, Center for Liver Diseases

Russell D. Cohen, MD
Professor of Medicine
Director, Inflammatory Bowel Disease Center
Co-Director, Advanced IBD Fellowship Program

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Assistant Professor of Medicine

Mustafa Hussain, MD
Assistant Professor of Surgery
Director, Center for the Surgical Treatment of Obesity
Associate Program Director, General Surgery

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Sonali Paul, MD, MS
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Director, Regional Therapeutics Program

Irving Waxman, MD
Sara and Harold Lincoln Thompson Professor of Medicine and Surgery
Director, Center for Endoscopic Research and Therapeutics (CERT)

CONFERENCE AGENDA

FRIDAY, SEPTEMBER 20, 2019

12:30 p.m.	**REGISTRATION**
12:55	**Welcome** Conference Co-Directors: Sonia Kupfer, MD; David T. Rubin, MD; Brennan Spiegel, MD, MSHS; and Hetal A. Karsan, MD
	Liver Diseases Moderator: Michael Charlton
1:00	**Overview of Hepatology Programs** Michael Charlton
1:05	**Updates in NAFLD Evaluation and Treatment** Michael Charlton
1:25	**Prevention of Hepatitis B Reactivation** Sonali Paul
1:45	**Living Donor Liver Transplantation** Talia Baker
2:05	**Panel Discussion**
2:20	**Acing the Boards: Liver** Hetal A. Karsan
3:20	**BREAK**
	Small Bowel, Diarrheal Illnesses & Obesity Moderator: Carol Semrad
3:30	**Overview of the Small Bowel & Nutrition Programs** Carol Semrad
3:35	**What's New in Bariatric Surgery?** Mustafa Hussain
3:55	**Updates in Medical Management of Obesity** Edwin McDonald
4:15	**Diarrhea and Enteropathies: Other Suspects** Carol Semrad
4:35	**Panel Discussion**
4:45	**Acing the Boards: Foregut** Brennan Spiegel
5:45	**WELCOME RECEPTION**

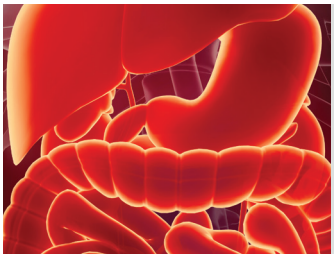
Agenda and speaker selection subject to change.

CONFERENCE AGENDA

SATURDAY, SEPTEMBER 21, 2019

7:30 a.m.	**CONTINENTAL BREAKFAST**
	Gastrointestinal Cancers Moderator: Sonia Kupfer
8:00	**Pancreatic Cancer Screening** Sonia Kupfer
8:20	**Genetic Testing for GI Cancers and Pancreatitis in 2019** Jessica Stoll
8:40	**Robotic Surgery for GI Cancers** Kiran Turaga
9:00	**Panel Discussion**
9:15	**Acing the Boards: Lower GI** Brennan Spiegel
10:15	**BREAK**
	Advanced Endoscopy Moderator: Uzma Siddiqui
10:25	**Overview of Center for Endoscopic Research and Therapeutics** Irving Waxman
10:35	**Endoscopic Submucosal Dissection: Where are We Now & Where Are We Going?** Irving Waxman
10:55	**To Drain or Not to Drain: Management of Pancreatic Fluid Collections** Uzma Siddiqui
11:15	**Endoscopic Obesity Treatments** Christopher Chapman
11:35	**Panel Discussion**
11:50	**Acing the Boards: Pancreaticobiliary** Hetal A. Karsan
12:50 p.m.	**LUNCH with Challenging Cases** University of Chicago GI Fellows and Faculty
2:00	**Acing the Boards: Rapid Fire Review** Hetal A. Karsan and Brennan Spiegel
	Inflammatory Bowel Diseases Moderator: Russell Cohen
2:45	**Overview of the IBD Programs** Russell Cohen
2:50	**Updates on the New IBD Guidelines** David Rubin
3:10	**Approaches to Managing Loss of Response to IBD Therapy** Joel Pekow
3:30	**State-of-the-art in Pouchitis** Sushila Dalal
3:50	**Panel Discussion & Wrap-up**
4:15	**ADJOURN**

Agenda and speaker selection subject to change.

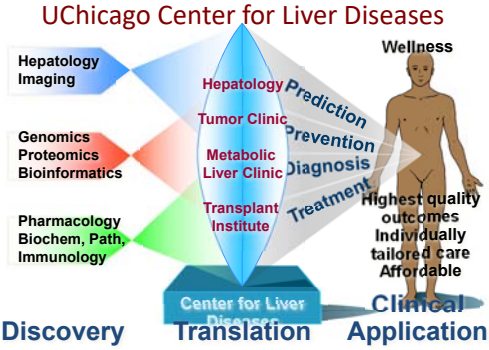


Overview of Hepatology Programs

Michael Charlton, MD, FRCP

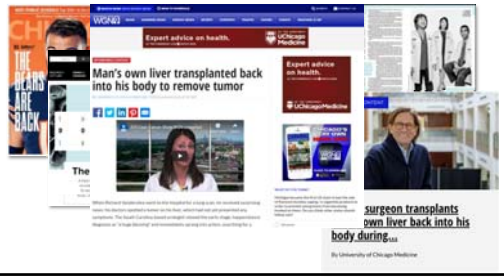
UChicago Center for Liver Diseases

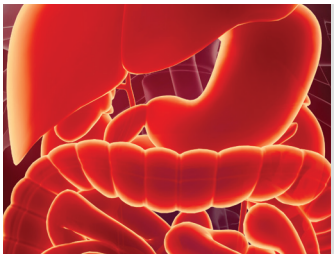
UChicago Center for Liver Diseases



UChicago Center for Liver Diseases

Chicago Magazine covered the triple transplant in an 8-page, 6,000 word story in the September issue of the magazine as well as on their website. Also covered in every major news outlet nationally.





Updates in NAFLD Evaluation and Treatment

Michael Charlton, MD, FRCP

AT THE FOREFRONT
UChicago Medicine

NASH State of the Art and Science in 2019

Michael Charlton, MD, FRCP
Professor of Medicine
Director, Transplant Institute,
Director, Center for Liver Diseases
University of Chicago

Agenda

- Update on epidemiology
- Phase 2b and 3 study results
- Therapeutic and Evaluation advances
- Liver Transplant and NASH

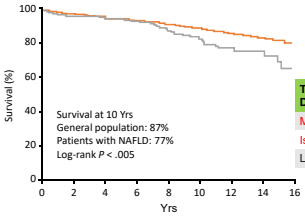
The scale of the problem

NAFLD	Estimated number of NAFLD patients in the USA and EU: 155.4 million[1, 2]
NASH	Estimated number of NASH patients in the USA and EU: 28.9 million[1,2]
F3/F4 fibrosis due to NASH	Estimated number of F3/F4 fibrosis patients due to NASH in the USA and EU: 5.8 million[1,2]

1. Estes C, et al. Hepatology 2018;67:123–33 ;
2. Razavi H, et al. Disease Burden Report for Europe 2017 (http://www.elpa.eu/sites/default/files/documents/NAFLD%20Disease%20Burden%20by%20Dr.%20H.%20Razavi_NASH%20NAFLD%20Summit.pdf (Accessed January 2018)

Causes of Mortality in NAFLD

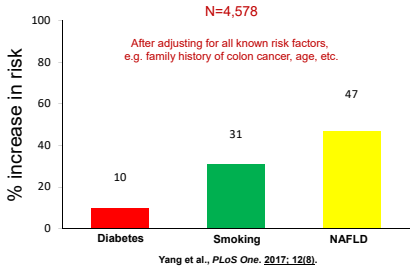
- Patients with NAFLD (N = 420) matched by age and sex to general population in Minnesota, followed for 7.6 ± 4.0 yrs



Top 3 Causes of Death in NAFLD, %	Patients (n = 53)
Malignancy	28
Ischemic heart disease	25
Liver disease	13

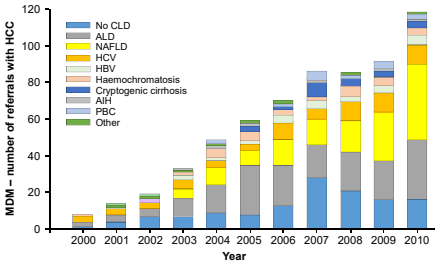
Adams LA, et al. Gastroenterology. 2005;129:113-121.

NAFLD as a Risk Factor for Colon Cancer on Follow-Up Colonoscopy



Yang et al., *PLoS One*. 2017; 12(8).

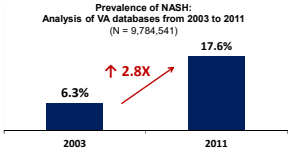
NAFLD is becoming the leading cause of HCC



Dyson J, et al. J Hepatol 2014;60:110–7

AIH: autoimmune hepatitis; ALD: alcoholic liver disease; CLD: chronic liver disease; MDM: multidisciplinary meeting; PBC: primary biliary cirrhosis

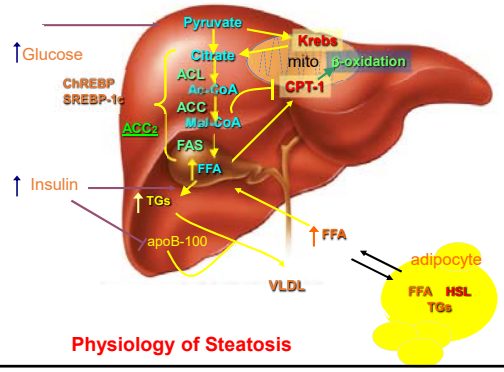
Rising Prevalence But Lack of Weight Loss Interventions in NAFLD



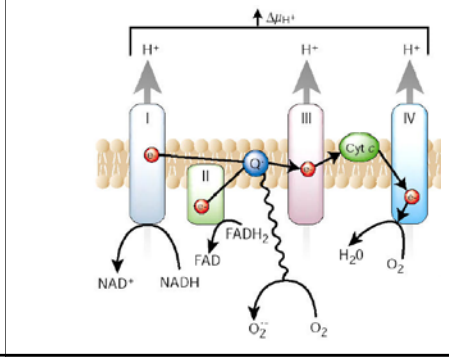
- Prevalence of NASH increased at significantly greater rates in patients **<45 years** vs older patients
- Only **20% patients** enroll in diet/exercise programs
- Only **2% patients** undergo bariatric surgery

Patel YA, et al. *Aliment Pharmacol Ther*. 2018;47(2):268-278.

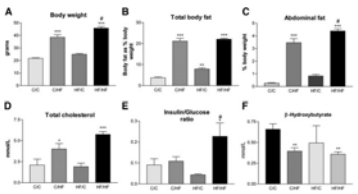
Pathophysiology



Physiology of Steatosis



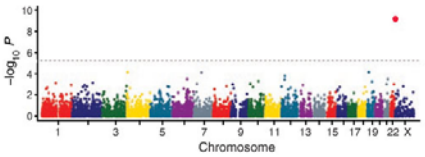
Effects of Maternal Diet / *In Utero* Conditioning



Bruce et al, *Hepatology* 2009

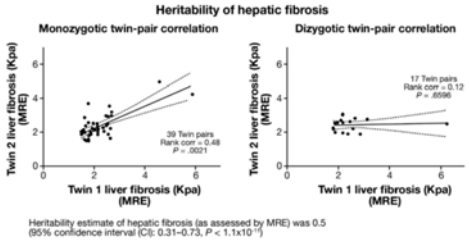
Genetic Susceptibility to NASH

PNPLA3



***Nature Genetics* 40**, 1461 - 1465 (2008)

Heritability of hepatic fibrosis content
Twin Study



Heritability estimate of hepatic fibrosis (as assessed by MRE) was 0.5 (95% confidence interval (CI): 0.31–0.73, $P < 1.1 \times 10^{-5}$)

Loomba et al. Gastroenterology 2015

Fast food diet mouse: novel small animal model of NASH with ballooning, progressive fibrosis, and high physiological fidelity to the human condition

Michael Charlton,[1] Anuradha Krishnan,[1] Kimberly Viker,[1] Schuyler Sanderson,[2] Sophie Cazanave,[1] Andrea McConico,[1] Howard Masuoka,[1] and Gregory Gores[1]

Divisions of [1]Gastroenterology and Hepatology and [2]Anatomic Pathology, Mayo Clinic and Foundation, Rochester, Minnesota

Submitted 12 April 2011; accepted in final form 3 August 2011

Modifiers of Nonalcoholic Fatty Liver Disease

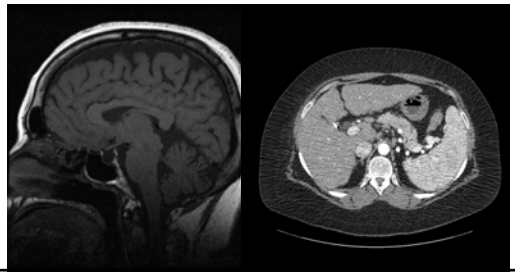
Comorbidities	Genetic	Microbiome products	Environmental
Obesity **Metabolic Syndrome** **Insulin Resistance** **Type 2 DM** Dyslipidemia Hypertension OSA PCOS Hypopituitarism **Low GH** **Low testosterone** Thyroid disease LAL-D Iron overload CVD CKD Alstrom's syndrome Wilson's disease Inflammatory bowel disease	**PNPLA3** **TM6SF2** **A1AT** HSD17B13 LYPLAL1 GCKR APOB MTTP IL28B KLF6 SOD2 UCP2 LPIN1 MERTK Irisin MBOAT **DNA methylation** **Chromatin remodelling** **Non-coding RNAs**	ETOH Lipopolysaccharide Reactive oxygen species Cholesterol oxidation products Butyrate Acetate Phenylacetate Secondary bile acids Choline deficiency	**Alcohol** **Cholesterol** **Fructose** Coffee Triazine Bendiocarb PCBs Endocrine disrupting compounds Tamoxifen Amiodarone Methotrexate Valproate Mipomersen Lomatapide NRTIs Corticosteroids 5-FU regimens Estrogens Nifedipine Tetracycline Vitamin A 5-ASA Diltiazem

Red = major impact
Green = protective
Bold = common and major impact

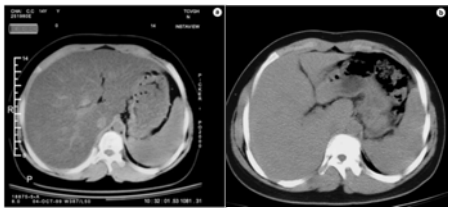
Case

- 48 yr old pediatric cardiologist
- Treated for nasopharyngeal carcinoma 11 yrs ago, hypopituitarism subsequently
- Persistent elevation in AST and ALT 2-5x normal
- Now obese (BMI 41.7 kg/m2), no ascites
- Develops hematemesis
- INR 1.8, bili 3-4x normal, Cr normal, MELD 18

Case

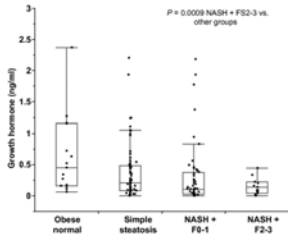


Growth Hormone and Metabolic Syndrome – Clues from Treatment of Alstroms Syndrome



Horm Res 2003;60:297–301

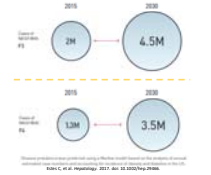
Growth hormone, DHEA and adiponectin levels in NASH: an endocrine signature for advanced fibrosis in obese patients



Growth hormone, dehydroepiandrosterone and adiponectin levels in non-alcoholic steatohepatitis: an endocrine signature for advanced fibrosis in obese patients, *Liver Intl* Vol: 32, Issue: 2, Pages: 279-286, 2011.

Prevalence trends of NASH with advanced fibrosis and patients at high risk

Prevalence of NASH with advanced fibrosis is expected to increase



Kim C, et al. Hepatology. 2017. doi: 10.1002/hep.29386.

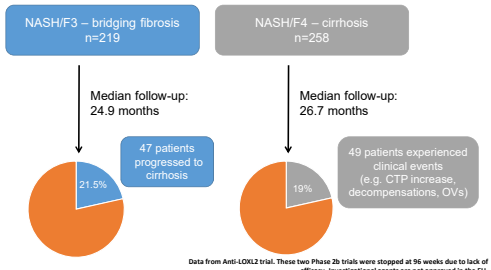
Patients at high risk for NASH with advanced fibrosis

Metabolic syndrome requires 3/5 of the following:
1. Waist circumference: ≥ 102 cm (male), ≥ 88 cm (female); 2. TG ≥150 mg/dL; 3. HDL-C <40 mg/dL (men), <50 mg/dL (women); 4. SBP ≥130 mm Hg or DBP ≥85 mm Hg; 5. FPG ≥100 mg/dL

1. Kim C, et al. Hepatology. 2017. doi: 10.1002/hep.29386.
2. Dayyeh et al. Aliment Pharmacol Ther. 2016;43:95–95.

Advanced fibrosis exponentially increases all-cause and liver-related mortality and morbidity

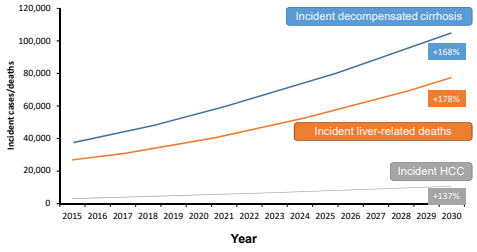
Risk of liver disease progression in NASH patients with advanced fibrosis



Data from Anti-LOXL2 trial. These two Phase 2b trials were stopped at 96 weeks due to lack of efficacy. Investigational agents are not approved in the EU.
CTP: Child–Turcotte–Pugh; EMA: European Medicines Agency; LOXL2: lysyl oxidase homolog 2; OV: oesophageal varices

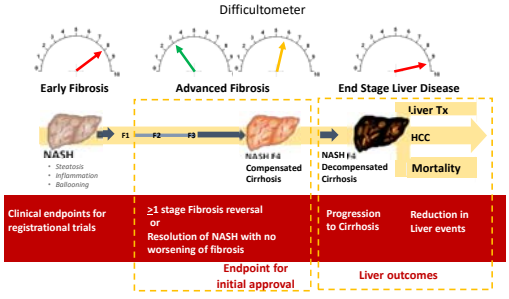
Sanyal A, et al. ILC 2017; Abstract #GS-004

Incident decompensated cirrhosis, HCC and liver-related deaths among the NAFLD population in the USA for 2015–2030



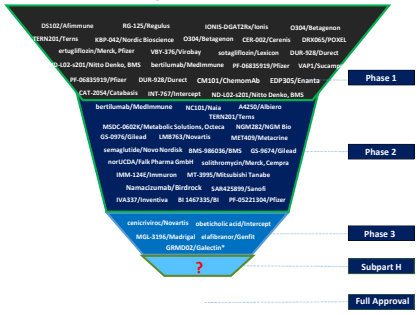
Estes C, et al. Hepatology 2018;67:123–33

Regulatory pathway for NASH treatments



Adapted from: Younossi et al. Hepatology 2015; Sanyal et al. Hepatology 2006

Global Pipeline for NASH



NASH agents in phase 3 clinical development

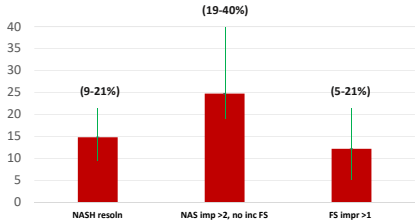
Agent	Target (mechanism)	Trial, patients and primary endpoint(s)
Cenicriviroc	Inflammation/ immune activation (CCR2/5 antagonist)	**AURORA (n=2000*, fibrosis stage 2–3)** • Fibrosis improvement ≥1 stage without NASH worsening • Composite of progression to cirrhosis, liver-related clinical outcomes and all-cause mortality
Elafibranor	Lipotoxicity/ oxidative stress (PPARα/δ agonist)	**RESOLVE-IT (n=2000*, fibrosis stage 1–3)** • NASH resolution without worsening of fibrosis • Long-term composite of all-cause mortality, cirrhosis and liver-related events
Obeticholic acid	Lipotoxicity/oxidative stress (FXR agonist)	**REGENERATE (n=2965*, fibrosis stage 1–3)** • Fibrosis improvement ≥1 stage without NASH worsening • NASH resolution without fibrosis worsening • All-cause mortality and liver-related events **REVERSE (n=540*, compensated cirrhosis)** • Fibrosis improvement ≥1 stage without NASH worsening
Selonsertib	Apoptosis/necrosis (ASK1 inhibitor)	**STELLAR-4 (n=883, compensated cirrhosis)** • Fibrosis improvement ≥1 stage without NASH worsening • Event-free survival **STELLAR-3 (n=808, fibrosis stage 3)** • Fibrosis improvement ≥1 stage without NASH worsening • Event-free survival
Resmetirom (MGL-3196)	Lipotoxicity (TRß agonist)	**MAESTRO Phase 3 study (n=2000*, fibrosis stage 2–3)** • NASH resolution without worsening of fibrosis

Estimated readout: REGENERATE Feb 2019; STELLAR-4 Feb 2019; STELLAR-3 Q2 2019 — 2019; RESOLVE-IT Q1 2020; REVERSE Jul 2020 — 2020; MAESTRO 2021? — 2021

*planned. ASK, apoptosis signal-regulating kinase; CCR, CC chemokine receptor; PPAR, peroxisome proliferator-activated receptor; FXR, farnesoid X receptor; TR, thyroid hormone. ClinicalTrials.gov. NCT03028740;ClinicalTrials.gov. NCT02704403; ClinicalTrials.gov. NCT02548351; ClinicalTrials.gov. NCT03449054; ClinicalTrials.gov. NCT03053050; ClinicalTrials.gov. NCT03053062. Madrigal press release: Madrigal Pharmaceuticals. 2018. https://www.madrigalpharma.com/wp-content/uploads/2018/05/Madrigal-Pharmaceuticals-Initiates-Phase-3-NASH-Study-ENDS_-final.pdf. Accessed April 2018.

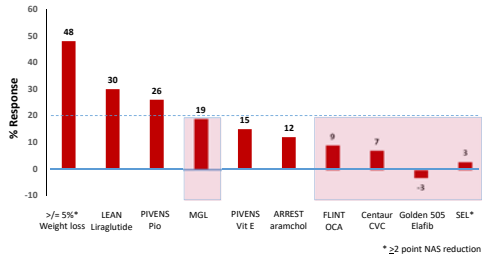
Frontrunner Efficacy

Placebo Response Rates by Endpoint



Gastro 2015;149:367–78; AASLD #104; AASLD #LB4; Lawitz et al. EASL 2018 ; AASLD #14; Sanyal et al. *Lancet*, accepted; Petit et al. *Clin Endocrinol Metab*, February 2017; AASLD #736; AASLD #LB23; AAASLD #LB5; Loomba et al. *Hepatology* 2018

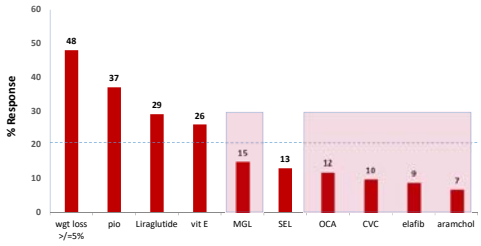
NASH Resolution – Margin over Placebo



* ≥2 point NAS reduction

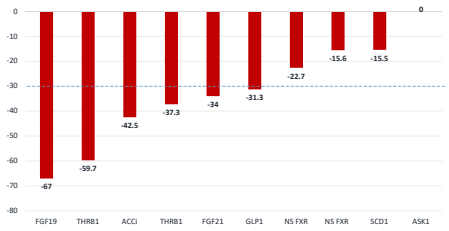
Gastro 2015;149:367–78; AASLD #104; AASLD #LB4; Lawitz et al. EASL 2018 ; AASLD #14; Sanyal et al. *Lancet*, accepted; Petit et al. *Clin Endocrinol Metab*, February 2017; AASLD #736; AASLD #LB23; AAASLD #LB5; Loomba et al. *Hepatology* 2018

NASH Resolution – vs. 10% Standard Placebo (equivalent to 0-5% weight loss*)



Gastro 2015;149:367–78; AASLD #104; AASLD #LB4; Lawitz et al. EASL 2018 ; AASLD #14; Sanyal et al. *Lancet*, accepted; Petit et al. *Clin Endocrinol Metab*, February 2017; AASLD #736; AASLD #LB23; AAASLD #LB5; Loomba et al. *Hepatology* 2018

Relative Change (%) in PDFF at Highest Dose



1. #104; 2. #LB4; 3. Lawitz et al. EASL 2018 ;4. #14; 5. Sanyal et al. Lancet, accepted; 6. Petit et al. Clin Endocrinol Metab, February 2017; 7. #736; 8. #LB23; 9. #LB5; 10. Loomba et al. Hepatology 2018

STELLAR 3/4: Selonsertib

- DBRCT 877 patients with stage 3 or compensated NASH cirrhosis
- **Primary endpoint:** ≥1 stage improvement in fibrosis *without worsening of NASH after 48 weeks*

	STELLAR-4		STELLAR-3		Phase 2 (open label)*	
Group	% response	P value vs. placebo	% response	P value vs. placebo	% response	P value vs. SIM
SEL 18 mg					**43% (13/30)**	?
SEL 6 mg					**30% (8/27)**	
Placebo					**SIM: 20% (2/10)**	

Gilead Press release Feb 11, April 2019

STELLAR 3/4: Selonsertib

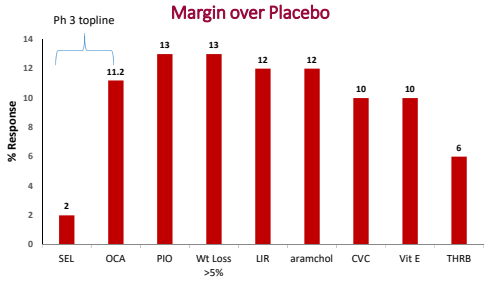
- DBRCT 877 patients with stage 3 or compensated NASH cirrhosis
- **Primary endpoint:** ≥1 stage improvement in fibrosis *without worsening of NASH after 48 weeks*

	STELLAR-4		STELLAR-3		Phase 2 (open label)*	
Group	% response	P value vs. placebo	% response	P value vs. placebo	% response	P value vs. SIM
SEL 18 mg	**14.4%**	0.56	**9.3%**	0.42	**43% (13/30)**	?
SEL 6 mg	**12.5%**	1.0	**12.1%**	0.93	**30% (8/27)**	
Placebo	**12.8%**		**13.2**		**SIM: 20% (2/10)**	

*** Caveats:**
- No placebo
- Small numbers
- No worsening of NASH not specified

Gilead Press release Feb 11, April 2019

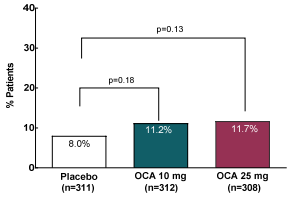
Fibrosis Improvement ≥1 Stage – Margin over Placebo



Gastro 2015;149:367–78; AASLD #104; AASLD #LB4; Lawitz et al. EASL 2018 ; AASLD #14; Sanyal et al. *Lancet*, accepted; Petit et al. *Clin Endocrinol Metab*, February 2017; AASLD #736; AASLD #LB23; AASLD #LB5; Loomba et al. *Hepatology* 2018
SHG = second harmonic generation digital image analysis

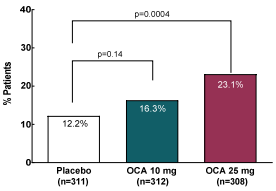
Focus on Obeticholic Acid

NASH Resolution With No Worsening of Fibrosis by criteria



Primary endpoint definition: (i) pathologist overall histopathologic assessment of "no fatty liver disease" or "fatty liver disease (simple or isolated steatosis) without steatohepatitis"; (ii) NAFLD Activity Score (NAS): hepatocellular ballooning = 0 and lobular inflammation = 0 or 1; and (iii) no increase in fibrosis stage from baseline

Gestalt: Resolution of Definite NASH With No Worsening of Fibrosis

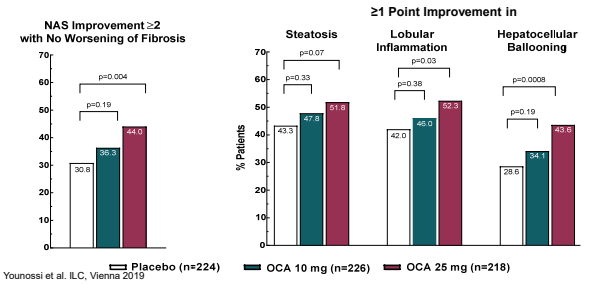


Endpoint defined as (i) resolution of definite NASH (i.e., absence of steatohepatitis) based on pathologist overall diagnostic assessment and (ii) no worsening of fibrosis stage from baseline. P values are nominal.
ITT population (N=931).

Younossi et al. ILC, Vienna 2019

Presented at EASL, April 10-14, 2019; Vienna, Austria

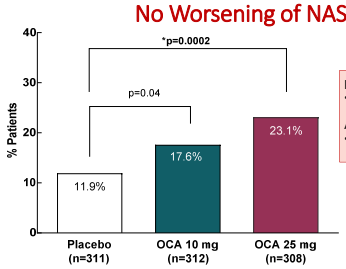
Improvement by NAS ≥2 and individual components



Younossi et al. ILC, Vienna 2019

P values are nominal.
Per protocol population (N=668).

Fibrosis Improvement by ≥1 Stage with No Worsening of NASH (ITT, F2/3)



Primary endpoint definition:
- Improvement in fibrosis by ≥1 stage (NASH CRN)

AND
- no worsening of lobular inflammation, hepatocellular ballooning **or steatosis**

Younossi et al. ILC, Vienna 2019

OCA: Adverse Events

Most Frequent Treatment-Emergent Adverse Events

Safety Population: Events Occurring in ≥10% of Patients in Any Treatment Group

n (%)	Placebo (n=657)	OCA 10 mg (n=653)	OCA 25 mg (n=658)
Pruritus (all pooled terms)	123 (19)	183 (28)	336 (51)
LDL increased	47 (7)	109 (17)	115 (17)
Nausea	77 (12)	72 (11)	83 (13)
Fatigue	88 (13)	78 (12)	71 (11)
Constipation	36 (5)	65 (10)	70 (11)
Abdominal pain	62 (9)	66 (10)	67 (10)
Diarrhea	79 (12)	44 (7)	49 (7)

Most frequent TEAEs were mild to moderate in severity and consistent with the known profile of OCA

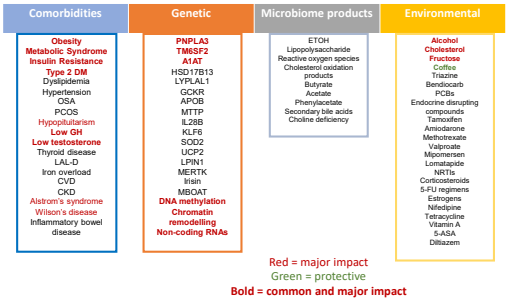
Presented by Younoussi at EASL 2019.

Why have the clinical trials been so disappointing?

NASH Therapeutics and Incentive Compatibility

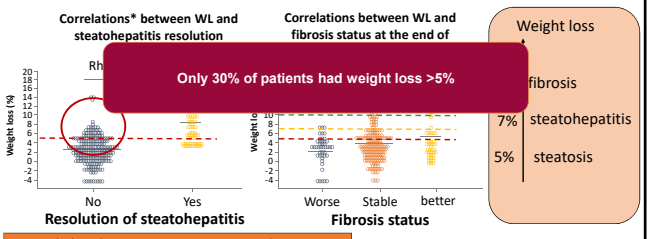
- Every participant can achieve the best outcome to themselves just by acting according to their true preferences
- You fare best, or at least not worse, by being truthful, *regardless* of what the others do.

Modifiers of Nonalcoholic Fatty Liver Disease



Weight Loss

Impact of Weight Loss (WL) on Histology

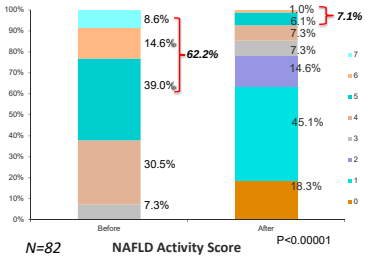


- Weight loss does not guarantee NASH resolution
- Fibrosis improvement can occur with less than 10% weight loss

Vilar Gomez et al, Gastroenterology. 2015 Aug;149(2):367-78

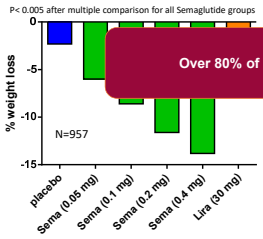
Impact of Bariatric Surgery on Histology

- Prospective study of bariatric surgery in pts with biopsy-validated NASH, ≥ 1 comorbidity factor for
  > 5 yrs, no other chronic liver disease (N = 109)

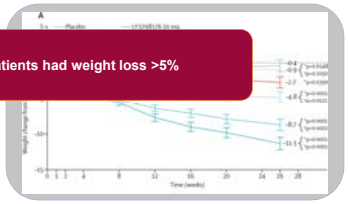


Lassailly et al. Gastroenterology 2015

Pharmacological-weight loss therapy is Improving



Over 80% of patients had weight loss >5%

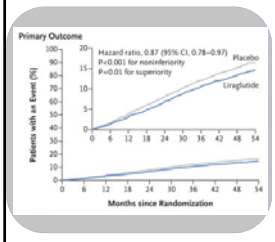


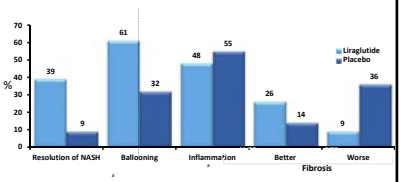
GLP-1/GIP agonist (terzepatide)

O'Neill et al, Lancet. 2018 Aug 25;392(10148):637-649.

Frias et al, Lancet, in press 2018
https://doi.org/10.1016/S0140-6736

GLP-1 receptor agonists have the potential for cardio-metabolic as well as liver-benefits

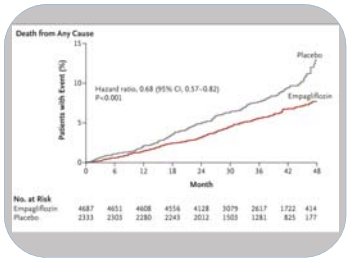




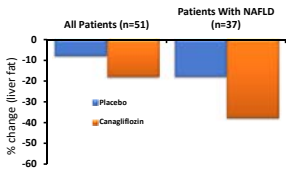
Marso et al, N Engl J Med. 2016 Jul 28;375(4):311-22

Armstrong MJ, et al. *Lancet* 2016;387(10019):679-690.

SGLT2 inhibitors also have the potential for improved cardiac-metabolic-renal-liver outcome improvement

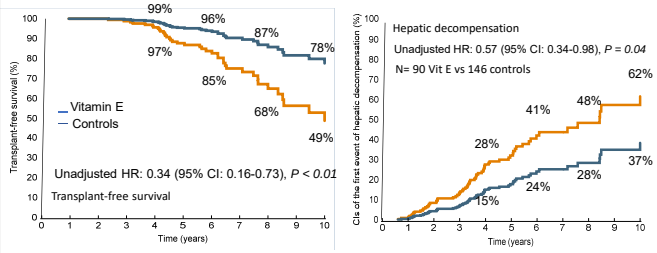


Zinman et al, N Engl J Med. 2015 Nov 26;373(22):2117-28



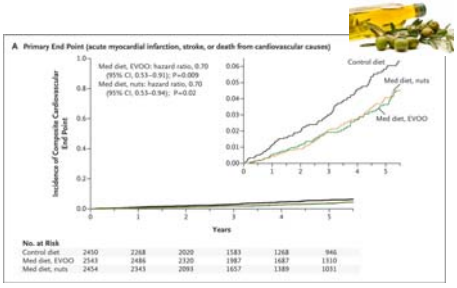
Cusi K, et al. Endocrine Society. 2018; Abstract OR05-3

Vitamin E improves transplant free survival and decompensation rates in NASH with stage 3 or 4 fibrosis



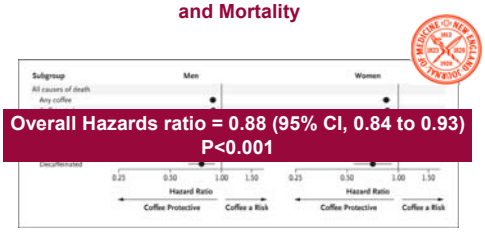
Vilar Gomez et al, 2018 Hepatology, EPUB ahead of print.

Impact of Olive Oil on Mortality, Stroke and MI



Estruch R et al. N Engl J Med 2013;368:1279-1290.

Associations between Coffee Consumption and Mortality



Overall Hazards ratio = 0.88 (95% CI, 0.84 to 0.93) P<0.001

N=617,000 follow up 5,148,000 person years

Evolving Medical Therapy for Fibrosing NASH

T2DM F2-3	GLP1 resistant	Low testost	Low GH	Wt loss resistant	F4 (CPT-A)
GLP-1 Vs. SGLT	DAAN Combo Vs. DAAN mono Vs. DAAN +GLP1	Testost-orone	GH	DAAN Combo Vs. DAAN mono Vs. DAAN +GLP1	DAAN +GLP1 Vs. DAAN mono

Nutritional Approach to Fatty Liver Disease

- Lifestyle
  - Mediterranean diet –
    - Foods without labels
    - 60mls of extra virgin olive per day + nuts
    - Avoid animal fats, red meats
  - Exercise – 4,000 to 10,000 steps per day (give away pedometers)
  - Coffee >/=3 cups caffeinated, filtered

Summary of Efficacy of NASH Therapies

- Comparative efficacy varies substantially with endpoint and with reference placebo.
- The reported efficacy for the current key endpoints, NAS resolution and fibrosis reduction >/=1 stage, is modest for all single agents in phase 2b and 3 studies.
- Strong phase 2 efficacy signals, have not translated into Phase 3 results.
- Obeticholic acid has met its primary endpoint for fibrosis improvement without worsening of NASH.
- We already have good, FDA approved tools for achieving weight loss >5%, an excellent therapy in itself.

Challenges in NASH Management – Defining Disease in Individual Patients

Current invasive tools available for staging fibrosis

Current standard: Liver Biopsy

According to the AASLD guidelines, liver biopsy remains the most reliable tool to identify steatohepatitis and fibrosis but it presents many challenges[1]

Liver biopsy evaluates histology

Biopsy allows evaluation of the defining histological features of NASH (steatosis, inflammation, cellular ballooning) and also evaluation of fibrosis stage

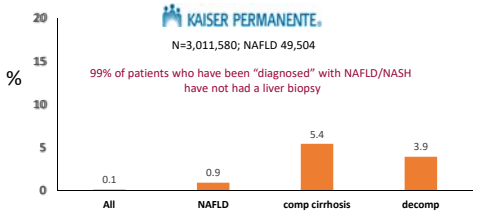
The procedure can cost from $1k to $3k[2]

Mis-staging fibrosis in up to 41% of cases[3]

0.35% risk of serious bleeding and 0.14% risk of death[4]

Sources: 1. Chalasani N, et al. Hepatology. 2017. doi:10.1002/hep.29487. 2. Francisco A. Hepatitis C Support Project 2016. 3. Ratziu V, et al. Gastroenterology. 2005;128:1898-1906. 4. Myers RP, et al. Liver Int. 2003;23:707-712.

Frequency of Liver Biopsies in Large Community-Based Healthcare System



- Included patients ≥18 yrs with ICD-10 code for NAFLD, NASH, or cryptogenic cirrhosis between 1/2015 – 12/2016, absent other liver disease/alcohol abuse

Source: Patton H, et al, Clinical Characteristics and Epidemiology of Patients with Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic Steatohepatitis (NASH) in a Large Community-based Healthcare Delivery System in the U.S.

What do the AASLD guidelines say about non-invasive tools?

Noninvasive Tools

VCTE	Assesses liver stiffness via measurement of shear wave velocity. Approved by the FDA in 2013 for use in adults and children with liver disease
MRE	Stiffness measurement through modified phase-contrast pulse sequence using magnetic resonance technology
FIB-4 Index	Noninvasive scoring system based on several routine laboratory tests that help to estimate the amount of liver fibrosis
NAFLD Fibrosis Score (NFS)	Based on 6 readily available variables and is calculated using a published formula
ELF Test	An algorithm combining specific serum markers. Approved for commercial use in Europe but not available for clinical use in the US

VCTE: Vibration controlled transient elastography
MRE: Magnetic resonance elastography
ELF: Enhanced liver fibrosis test

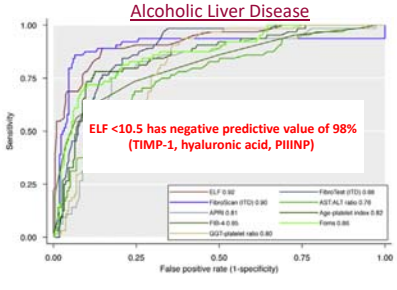
AASLD Guidance Statements[1]

- **NFS** or **FIB-4** Index are clinically useful tools for identifying NAFLD patients with higher likelihood of having bridging fibrosis (F3) or cirrhosis (F4)
- **Vibration controlled transient elastography (VCTE)** or Magnetic resonance elastography (**MRE**) are clinically useful tools for identifying advanced fibrosis in patients with NAFLD

Sources: 1. Chalasani N, et al. *Hepatology*. 2017. doi:10.1002/hep.29367. 2. Francisscus A. Hepatitis C Support Project 2014. 3. Ratziu V, et al. *Gastroenterology*. 2005;128:1898-1906. 4. Myers RP, et al. *Liver Int*. 2008;28:705-712.

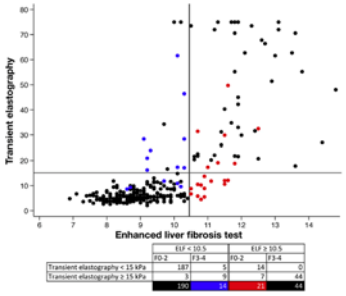
Biomarker Performance F0-2 vs. F3-4

Alcoholic Liver Disease



Thiele et al., *Gastroenterology* 2018;154:1369–1379

Biomarker Performance F0-2 vs. F3-4



Thiele et al., *Gastroenterology* 2018;154:1369–1379

Distinguishing NASH Stages 0-2 vs. 3-4 Using Simple Tests

Comparison of the Diagnostic Performance of Simple Tests for Advanced Fibrosis

Test	AUC (95% CI)	Cutoff	Sens, %	Spec, %	PPV, %	NPV, %
AST/ALT ratio	0.83 (0.74-0.91)	0.8	74	78	44	93
		1	52	90	55	89
APRI	0.67 (0.54-0.8)	1	27	89	37	84
BARD score	0.77 (0.68-0.87)	2	89	44	27	95
FIB-4 score	0.86 (0.78-0.94)	1.30	85	65	36	95
		3.25	26	98	75	85
NFS	0.81 (0.71-0.91)	-1.455	78	58	30	92
		0.676	33	98	79	86

- Strength of noninvasive fibrosis predictive tests is in their ability to exclude advanced disease (F3-F4)
- Least accurate in identifying middle ranges of fibrosis

Slide courtesy of Michael Charlton, MBBS

BARD: scoring system that incorporates BMI, AST/ALT ratio, presence of T2DM; APRI: AST to platelet ratio; PPV: positive predictive value; NPV: negative predictive value.

McPherson S, et al. *Gut* 2010;59:1265-1269; McPherson S, et al. *Am J Gastroenterol* 2017;112:740-751.

Imaging

Imaging to Assess NASH Fibrosis: Elastography

- **VCTE**
  - Accurate in detecting advanced fibrosis
  - Predicts risk of decompensation and complications
  - Correlates well with portal pressure
  - Most reliable in ruling out advanced disease
  - Most widely used

MRE

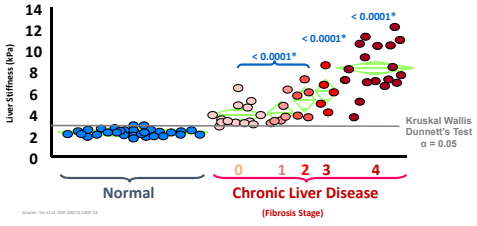
- Most accurate of the imaging modalities
- Costly, no point of care access

Elastography Point Quantification

- Emerging ultrasound-based system
- Measures real-time liver stiffness during an ultrasound scan
- Non-inferior level of accuracy compared to TE

Corbi F, et al. *Clin Gastroenterol Hepatol*. 2018. Epub ahead of print

Liver stiffness correlates with fibrosis stage

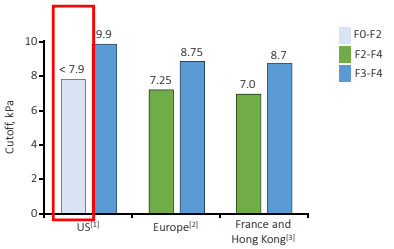


Source: Yin et al. Gastroenterology 2013;144:1300-1309

The FibroScan Report PDF

Reassuring VCTE:
IQR≤30% and
kPa≤7.9
(CAP≤290)

Vibration-Controlled Transient Elastography: Cutoffs for Fibrosis



1. Tapper EB, et al. Am J Gastroenterol. 2016;111:677-684.
2. Petta S, et al. Aliment Pharmacol Ther. 2011;33:1350-1360.
3. Wong VW, et al. Hepatology. 2010;51:454-462.

Can I predict bridging fibrosis and cirrhosis without a biopsy?

Moderately well.

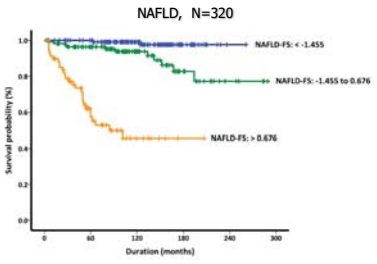
Should I care about liver histology?

Should I care about liver histology?

"Yes" but I should care more about predicting *clinical events*.

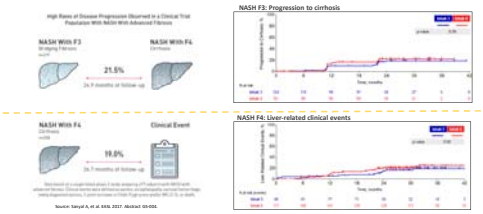
Can I predict *clinical events* without a biopsy?

NFS Predicts Mortality



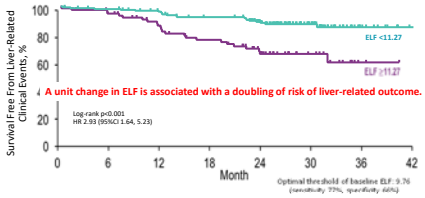
Angulo, *Gastroenterology* 2015.

Fibrosis is a weak determinant of Progression



ELF Score Clinical Events and Fibrosis Progression *More Accurately* than Biopsy

Liver-Related Clinical Events According to Baseline ELF



A unit change in ELF is associated with a doubling of risk of liver-related outcome.

Parameter	Adjusted HR (95% CI)	*P*-value
Baseline ELF	2.40 (1.70, 3.38)	<0.001
Change in ELF	1.53 (1.09, 2.14)	0.01
Ishak stage 6 vs 5	0.89 (0.47, 1.68)	0.71

Harrison, AASLD 2017, Poster 2122
Parkes et al., Gut 2010;59:1245-1251.

Bringing it all together…

Clinical Decision Making in Chronic Liver Disease

	VCTE <7.9 kPa Or FIB-4 ≤1.3 Or ELF ≤10.5 ETOH/viral hep, 9.3 NAFLD	VCTE ≥7.9 kPa Or FIB-4 >1.3 Or ELF >10.5 ETOH/viral hep, 9.3 NAFLD
High Clinical Suspicion of advanced disease	Further testing (e.g. MRE or Bx)	Treat as high risk
Low Clinical Suspicion of advanced disease	Treat as low risk Re-eval in 3-5 yrs	Further testing (e.g. MRE or Bx)

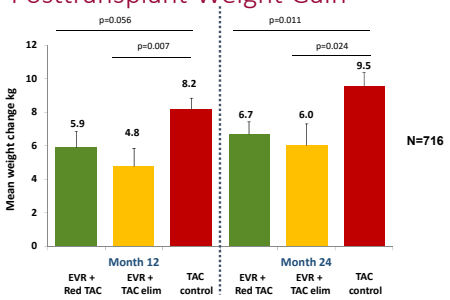
You will be correct ≥95% of the time
and
Nothing is likely to happen when you are wrong

Gastric Sleeve vs. Roux-en-Y Gastric Bypass in Liver Transplantation

- Tacrolimus and mTORis are primarily absorbed in duodenum.
- Intestinal cytochrome P450 is an important component of tac and mTORi metabolism.
- Mycophenolate is absorbed in the stomach.
- Cyclosporine is substantially bile salt dependent for absorption.
- AUC is reduced by 40-50% for tac, MMF and mTORi's in RYGB.
- MMF only affected by sleeve gastrectomy.
- Impact is highly variable between patients.

Clin Transplantation 22(3): 281-291, 2008

Posttransplant Weight Gain



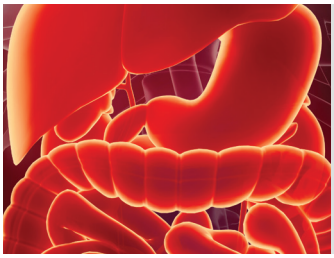
Charlton et al., *Transplantation* 101(12): 2873-2882.

Metabolic Effects of Immunosuppression

Outcome	corticosteroids	tacrolimus	cyclosporine	mTOR i
Obesity	+	⬌	⬌	⬇
New Onset DM	+++	+	+	⬌
Dyslipidemia	+	+	++	+++
Hypertension	+	++	++	⬌

Liver Transpl 2010;16:431-439.
Transplantation 2011;91:684-689.
Liver Transpl 2001;7:363-373.
Am J Gastroenterol 2010;105:613-620
Liver Transpl 2007;13:844-847.

Thank you!



Prevention of Hepatitis B Reactivation

Sonali Paul, MD, MS

AT THE FOREFRONT UChicago Medicine

Hepatitis B Reactivation

Sonali Paul, MD MS
Assistant Professor of Medicine
Center for Liver Diseases

Disclosures

- Research / grant funding from: Intercept, GENFIT, TARGET PharmaSolutions
- I will not discuss off label use or investigational use in my presentation

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High Worldwide HBV Prevalence

- 350 millions persons worldwide
- 2 billion with past or present infection
- Country of origin MAJOR risk factor
- United States
  - 0.3% chronic HBV
  - 5% + core antibody

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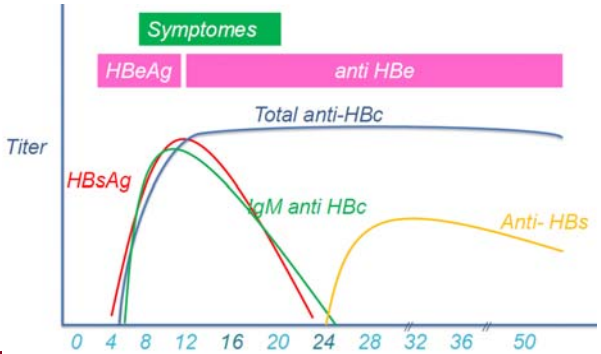
WHO. HBV Fact Sheet. CDC. 2012.

Acute HBV Serology



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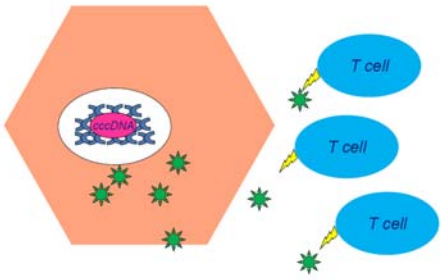
Is HBV Ever Curable?

- Immune control, not clearance
- "Resolved HBV" misnomer
- HBV persists in liver as cccDNA, reservoir for HBV reactivation



Werle-Lapostolle et al. Gastroenterology. 2004.

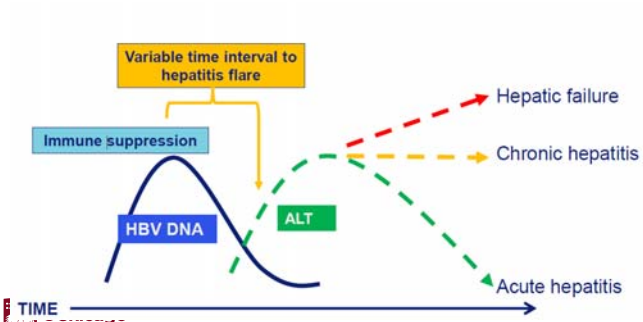
Is HBV Ever Curable?

- Immune control can be lost
- Immune mediated liver damage with immune reconstitution

Immunosuppression
HIV
Steroids

Werle-Lapostolle et al. Gastroenterology. 2004.

HBV Reactivation



Hoofnagle JH. Hepatology. 2009.

HBV Reactivation

- **Definition**
  - Loss of HBV immune control in patient with inactive ("resolved") HBV infection
  - Increase in viral replication with liver damage around immune reconstitution
- **Clinically**
  - Subclinical to severe / fatal hepatitis
  - ↑ HBV DNA +/- return of HBeAg
  - ↑ ALT
  - Progress to liver failure / death

Hoofnagle JH. Hepatology. 2009.

HBV Reactivation

Component	Criteria
Reactivation: HBsAg+ anti-HBc+	At least 1 of the following: • ≥100-fold (≥ 2 $\log_{10}$ IU/mL) increase in HBV DNA compared to baseline level • HBV DNA ≥ 3 log (1,000) IU/ml with previously undetectable level • HBV DNA ≥ 4 log (10,000) IU/ml if baseline not available
Reactivation: HBsAg- anti-HBc+	• HBV DNA is detectable • Reverse HBsAg seroconversion occurs (reappearance of HBsAg)

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Terrault N et al. Hepatology. 2018.

Risk of Reactivation (15 – 80%)

Patient

- Male
- Young age

Virus

- HBsAg +
- HBeAg +
- Baseline HBV DNA
- Precore-core mutation

Therapy

- Intensity of immunosuppression
  - BMT, Rituximab
  - Solid tumor chemo
- High dose steroids
- Timing of antiviral therapy

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Hwang JP et al. Suppor Care Cancer. 2012.

Risk of Reactivation

Classification of Reactivation Risk by Anti-Cancer Types Lacks Rigor

"Although many immunosuppressive and immune-modulating drugs have been associated with HBV reactivation, it is difficult to discern the risk caused by specific drugs or drug regimens because of the lack of systemically collected data."

Terrault, Hepatology, 2018.

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Hwang et al. Nat Rev Gastroenterol Hepatol. 2013.

Risk of Reactivation

Gastroenterology 2015;148:215–219

AGA SECTION

American Gastroenterological Association Institute Guideline on the Prevention and Treatment of Hepatitis B Virus Reactivation During Immunosuppressive Drug Therapy

K. Rajender Reddy,[1] Kimberly L. Beavers,[2] Sarah P. Hammond,[3] Joseph K. Lim,[4] and Yngve T. Falck-Ytter[5]

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High Risk Agents

Risk of Reactivation > 10%

B-cel supressive therapy (Rituximab, Ofatumab)
- HBsAg +/ anti HBc +: 30-60 %
- HBsAg -/ anti HBc +: >10%

Antracyclin (Doxorubicin, Epirubicin)
- HBsAg +/ anti HBc +: 15-30 %

Antiviral prophylaxis for at least 6 - 12 months after discontinuation of immunosuppression.

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Reddy et al. Gastroenterology. 2015.

Rituximab

- Monoclonal antibodies against CD20
- **Both HBsAg positive**
- **AND HBsAg negative / anti-HBc +**
- Effects persist long after treatment cessation

- **FDA Review**
  - 109 cases fatal HBV acute liver failure (1997 to 2012)
  - > 50% had not been screened (or screened with only HBsAg)
  - Boxed Warning: screening and antiviral therapy

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Hui et al. Gastroenterology. 2016.

Rituximab

- **In those with occult HBV (HBsAg- / anti-HBc +) + lymphoma**
- 20% of 224 patients developed fulminant hepatitis B

Cox proportional hazard analysis

Variable	Hazard Ratio	95% CI	P-value
Rituximab containing regimen	16.84	2.1-137.4	0.008
Steroid containing regimen	5.01	0.61-40.88	0.21

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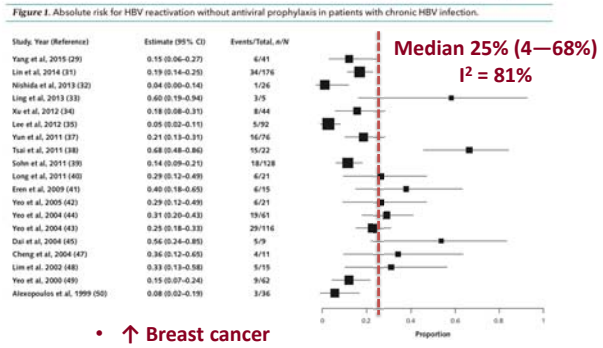
Hui et al. Gastroenterology. 2016.

Solid Tumor Chemotherapy, HBsAg+



Median 25% (4—68%)
I^2 = 81%

- **↑ Breast cancer**
- **↑ Anthracycline regimens**

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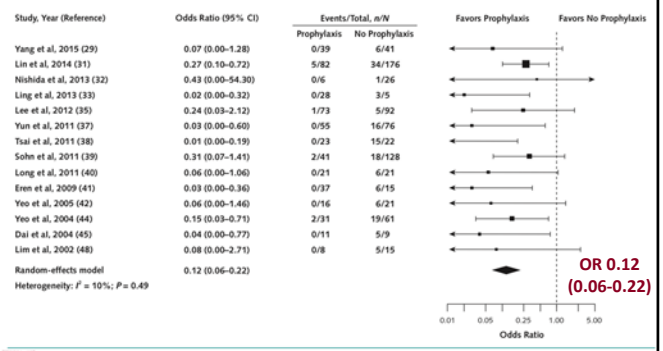
Paul et al. Ann Intern Med. 2015.

Solid Tumor Chemotherapy, HBsAG+

Figure 3. Odds ratio for HBV reactivation with and without antiviral prophylaxis in patients with chronic HBV infection.



Medicine

Paul et al. Ann Intern Med. 2015.

Intermediate Risk Agents

Risk of Reactivation 1 - 10%

TNF-α inhibitors (Etanercept, Adalumimab, Infliximab)
- HBsAg +/ anti HBc +: 1-10%
- HBsAg -/ anti HBc +: 1%

Other cytokine and integrin inhibitors (Abatacept, Ustekinumab)
- HBsAg +/ anti HBc +: 15-30 %

Tyrosine kinase inhibitors (Imatinib, Nilotinib)
- HBsAg +/ anti HBc +: 1-10%
- HBsAg -/ anti HBc +: 1%

Anthracyclines: Doxorubicine en Epirubicine
- HBsAg- / anti-HBc+:1-10%

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Antiviral prophylaxis (or can monitor)

Reddy et al. Gastroenterology. 2015.

TNF-Alpha Inhibitors (Infliximab)

- **89 HBsAg+ patients**
  - 39% had HBVr (35 patients) → 5 ALF → 1 Death
- **168 occult HBV (HBsAg- / anti-HBc +) patients**
  - 5% had HBVr (9 patients) → 1 ALF → 1 Death
- **↑ risk with**
  - Infliximab
  - Concomitant use of other immunosuppression

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Perez-Alvarez R et al. Medicine. 2011.

Low Risk Agents

Risk of Reactivation <1%

Traditional immunosuppressive agents
- HBsAg +/ anti HBc +: < 1%
- HBsAg -/ anti HBc +: << 1%

No antiviral prophylaxis

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Reddy et al. Gastroenterology. 2015.

Corticosteroids

- **Stimulates glucocorticoid element in HBV genome**
  - Unregulated HBV expression
  - Depressed cytotoxic T cell function
- **HBsAg+ receive long term prednisone (10mg)**
  - Delay in biochemical remission
  - Earlier relapse after discontinuation
  - Increase in complications (death)

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Lam et al. NEJM. 1981.

Corticosteroids & HBVr

High Risk

Corticosteroid treatment > 4 weeks, high dose *
- HBsAg +/ anti HBc +: > 10%

Intermediate Risk

Corticosteroid treatment ≥ 4 weeks, low dose *
- HBsAg+ / anti-HBc+: 1-10%

Corticosteroiden ≥ 4 weeks, intermediate/high dose*
- HBsAg - / anti-HBc+:1-10%

Low Risk

Corticosteroid treatment < 1 week
- HBsAg +/ anti HBc +: < 1%
- HBsAg -/ anti HBc +: << 1%

Corticosteroid treatment ≥ 4 weeks in a low dose*
- HBsAg +/ anti HBc +: < 1%

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*Prednisone high dose > 20mg; intermediate 10-20 mg; low < 10mg daily

Reddy et al. Gastroenterology. 2015.

HBV, HCV, & DAA Therapy

- HBV replication suppressed due to HCV infection
  - Inverse relationship of viral levels
- HCV clears → HBV reactivates
- **Implications**
  - All patients should be screened for HBV prior to DAA therapy
  - Treatment of those with active infection
  - Monitor HBV DNA levels during DAA therapy

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Algorithm for HBV-HCV Infection + DAAs

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Ma AT and Feld JJ. Gastroenterology. 2018.

A Word on Immunotherapy

- **Enhances** immune system to fight disease
- HBV reactivation should not occur
- ?immune activation leading to HBVr
- Used in combination with other therapies

Table 1. Immune Checkpoint–Blocking Antibodies Approved by the Food and Drug Administration.[a]

Drug	Target	Indication
Ipilimumab	CTLA-4	Melanoma
Nivolumab	PD-1	Melanoma, non–small-cell lung cancer, renal-cell carcinoma, hepatocellular carcinoma, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer with high microsatellite instability or mismatch-repair deficiency
Pembrolizumab	PD-1	Melanoma, non–small-cell lung cancer, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, gastric cancer, solid tumors with high microsatellite instability or mismatch-repair deficiency
Atezolizumab	PD-L1	Non–small-cell lung cancer, urothelial carcinoma
Avelumab	PD-L1	Merkel-cell carcinoma, urothelial carcinoma
Durvalumab	PD-L1	Urothelial carcinoma

[a] CTLA-4 denotes cytotoxic T-lymphocyte antigen 4, PD-1 programmed cell death 1, and PD-L1 programmed cell death ligand 1.

Postow et al. NEJM. 2018.

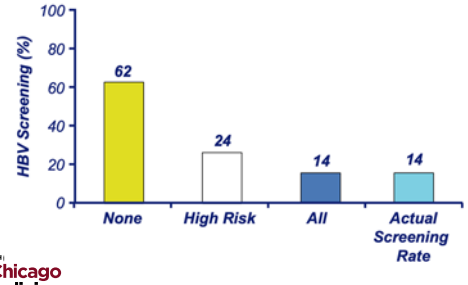
Who Should Be Screened?

Organization	Population to be screened	Screening tests*
ASCO[1]	Therapies associated with high risk of reactivation (SCT, anti-CD20); risk of HBV infection	HBsAg, anti-HBc
NCCN[2]	B cell lymphoid malignancies, risk of HBV infection, intense immunosuppression, anti-CD20	HBsAg, anti-HBc, anti-HBs
AASLD[3]	All patients before immunosuppression	HBsAg, anti-HBc
CDC[4]	All patients before immunosuppression	HBsAg, anti-HBc, anti-HBs
EASL[5]	All patients before immunosuppression	HBsAg, anti-HBc
APASL[6]	All patients before immunosuppression	HBsAg; anti-HBc if anti-CD20 mabs or anti-TNF

[1]**ASCO** (American Society of Clinical Oncology):Hwang, 2015; [2]**NCCN** (National Comprehensive Cancer Network): Prevention and Treatment of Cancer-Related Infections (Version 2.2014), http://www.nccn.org/professionals/physician_gls/pdf/infections.pdf, 2014; [3]**AASLD** (American Association for the Study of Liver Diseases):Terrault, Hepatology, 2018; [4]**CDC** (Centers for Disease Control and Prevention):Weinbaum, MMWR, 2008; [5]**EASL** (European Association for the Study of the Liver), J Hepatol. 2012; [6]**APASL** (Asian Pacific Association for the Study of the Liver), Hepatol Int, 2012.

High Risk Screening is Difficult

- Few oncologists routinely screen all or high risk patients



Khokhar et al. Chemotherapy. 2009.

Optimal Screening Strategy

- Universal screening is easiest
- Found to be cost effective in breast cancer patients
- Optimal test unclear
  - EASL: HBsAg and anti HBc
  - AASLD: HBsAg and anti HBc
  - CDC: HBsAg and anti HBc and anti- HBs
  - ASCO: HBsAg

Unless anti-CD20 treatment, then anti HBc

Treatment or Prophylaxis for HBVr

- **Antiviral prophylaxis ↓ ↓ ↓ reactivation risk**
- **# reactivations prevented / 1000 patients**
  - **High risk agents: n = 435 (!!)**
  - Intermediate risk agents (HbSAg): n = 44
  - Low risk agents: n = 1

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Reddy et al. Gastroenterology. 2015.

Which Antiviral Treatment is Best

- **Determined by HBV DNA level**
  - HBV DNA < 2000 IU/mL: any therapy (including lamivudine)
  - HBV DNA > 2000 IU/mL: entecavir or tenofovir
- **Affected by duration of therapy**
  - > 12 months: entecavir or tenofovir
- **HBV DNA and ALT monitored every 3 months**

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EASL. J Hepatol. 2009.

Antiviral Therapy Timing

- **Not necessary to delay start of chemotherapy**
  - Unless HBV DNA > 10,000 IU/mL
- **When to stop**
  - Baseline DNA > 2000 IU/mL: high risk withdrawal
    - Continue as for chronic HBV infection
  - Baseline DNA < 2000 IU/mL
    - 6-12 months after end of chemotherapy
    - 12 months for CD-20 antibodies
- **Monitor for flares with HBV DNA and ALT**

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EASL. J Hepatol. 2009.

Take Home Points

- HBV can reactivate
- Risk depends on immunosuppression, HBV serology

	Therapy	HBsAg +	HBsAg – anti-HBc +
High Risk	- Anti-CD20 - HSCT	High risk	Moderate risk[a]
Moderate Risk	- Cytotoxic chemotherapy (anthracycline containing regimen) - Anti-CD 52 - Mod* to high† dose corticosteroids (prednisone ≥ 10 mg or equivalent for ≥ 4 weeks) - **Anti-TNF** - **Cytokine inhibitors/ integrin inhibitors** - **Anti-rejection medication for non-liver solid organ transplant**	High risk	Low[b] to moderate risk[c]
Low Risk	- Methotrexate - Azathioprine	Low risk	Rare

*moderate dose : prednisone 10- 20 mg for ≥ 4 wks
† high dose : prednisone >20mg for ≥ 4 wks

Take Home Points

- Monitor for HBV reactivation when treating HCV
- Universal screening is likely more effective
- Antiviral prophylaxis is beneficial

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Thanks for your attention!

spaul@medicine.bsd.uchicago.edu

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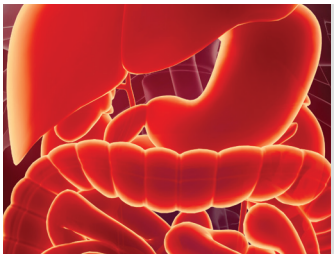


Living Donor Liver Transplantation

Talia Baker, MD, FACS

THE UNIVERSITY OF CHICAGO MEDICINE

Living Donor Liver Transplant and the Adult-to-Adult Living Liver Transplantation (A2ALL) Consortium

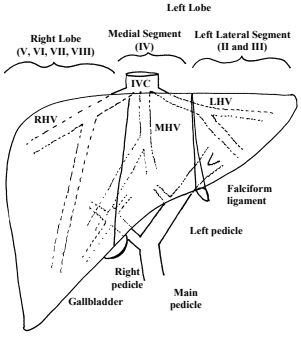
Talia B Baker, MD
Surgical and Program Director, Liver Transplant
Transplantation Institute
University of Chicago Medicine

Liver regeneration and Greek mythology

Prometheus, a Titan Hero, credited for creation of man from clay and for the theft of fire for mankind's use.

Sentenced by Zeus to eternal torment by being bound to a rock where each day an eagle was sent to feed on his liver only to have it grow back and be eaten again the next day.

Surgical Anatomy of the Liver

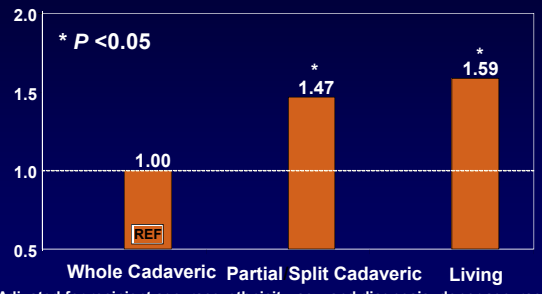


Living donor liver transplant

- Historically, LDLT began as a means for parents of children with severe liver disease to donate a portion of their healthy liver to replace their child's entire damaged liver.
- The first report of successful LDLT was by Dr. Christoph Broelsch at the University of Chicago Medical Center in November 1989, when two-year-old Alyssa Smith received a portion of her mother's liver

Adjusted† Relative Risk of Graft Failure for Living Donor Recipients

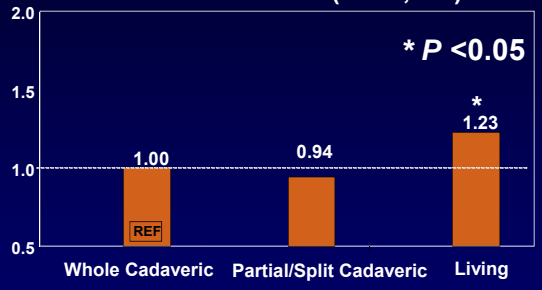
UNOS - 1998-2001 (N=16,595)



†Adjusted for recipient age, race, ethnicity, sex, and diagnosis; donor age, race, and sex; recipient medical urgency status, creatinine, bilirubin, medical condition, on life support, on dialysis, on ventilator, and NYHA functional status at transplant; ABO compatibility

Adjusted† Relative Mortality Risk for Living Donor Recipients

UNOS - 1998-2001 (N=15,158)



†Adjusted for recipient age, race, ethnicity, sex, and diagnosis; donor age, race, and sex; recipient medical urgency status, creatinine, bilirubin, medical condition, on life support, on dialysis, on ventilator, and NYHA functional status at transplant; ABO compatibility

The Ultimate Sacrifice

A healthy man gives his brother half his liver—and dies. Should this kind of transplant be allowed?

By CHRISTINE GORMAN

MIKE AND ADAM HUREWITZ GREW UP together on Long Island, in the suburbs of New York City. They were very close, even for brothers. So when Adam's liver started failing, Mike offered to give him half of his. The operation saved Adam's life. But Mike, who went into the hospital in seemingly excellent health, developed a complication—perhaps a blood clot—and died last week. He was 57.

Mike Hurewitz's death has prompted a

like bad odds, but there's more to this ethical dilemma than a simple ratio. The first and most sacred rule of medicine is to do no harm. "For a normal healthy person, a mortality rate of 1% is hard to justify," says Dr. John Fung, chief of transplantation at the University of Pittsburgh Medical Center. "If the rate stays at 1%, it's just not going to be accepted."

On the other hand, there's an acute shortage of traditional donor organs from people who have died in accidents or suffered fatal heart attacks. If family members fully understand the risks and are willing to

Participating A2ALL Centers

www.nih-a2all.org

A2ALL

- The first 7 years (2003-2009)
  - Achievements
  - Failures
- The following 5 years (2010-2014)
  - The expectations
  - The conclusions

A2ALL Prospective Cohort Study
Primary Aims

1. To characterize the differences between LDLT and DDLT in terms of post-transplant outcomes. To quantify the impact of choosing LDLT on the candidate for transplantation.
2. To assess LD outcomes (complications)
3. To determine short and long-term impact on QOL after donation compared to a control population
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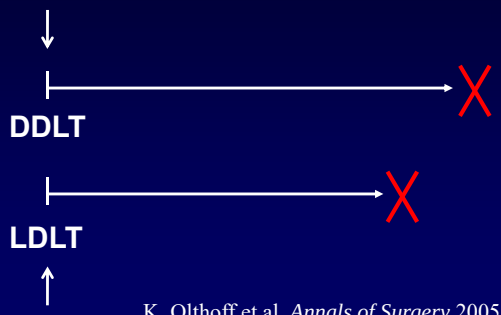
Analysis of Time from Transplant to Death or Graft failure

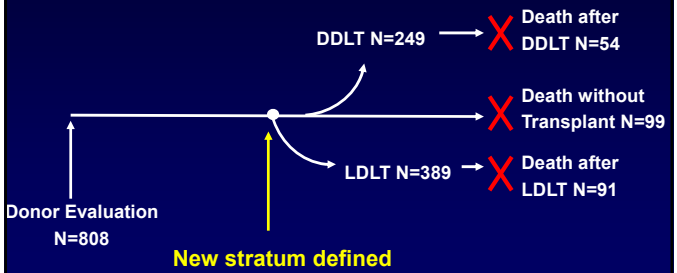


K. Olthoff et al, *Annals of Surgery* 2005

Study Population – Retrospective Cohort

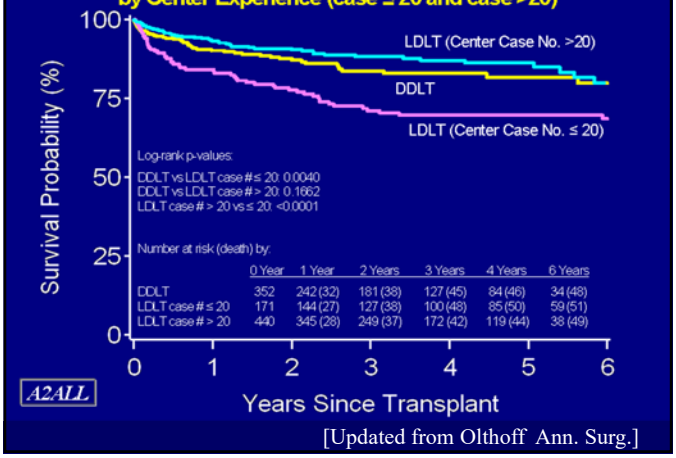
- 808 patients who had a potential living donor evaluated between 1998 and 2003 in one of the 9 A2ALL Cohort Study centers
- Follow-up data for these patients came from A2ALL centers and SRTR
- Median follow-up 4.3 years

Analysis of Time from Evaluation of Potential Living Donor to Death: Sequential Stratification Approach



C. Berg et al, *Gastroenterology 2007*

Retro/Bridge/Cohort Patient Survival from Transplant by Center Experience (case ≤ 20 and case >20)



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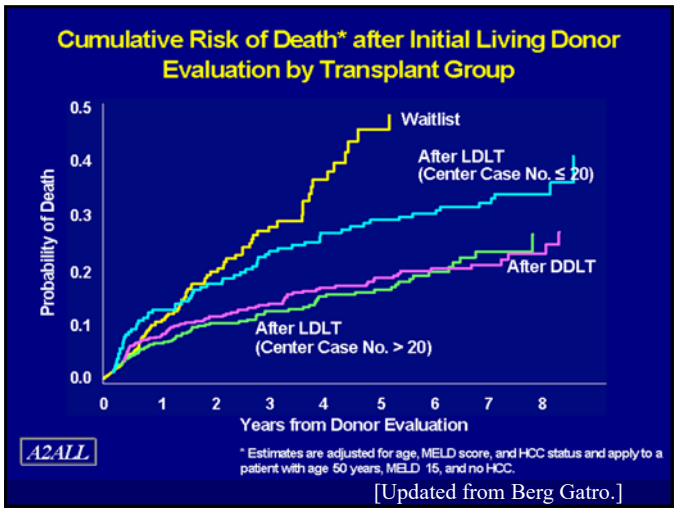
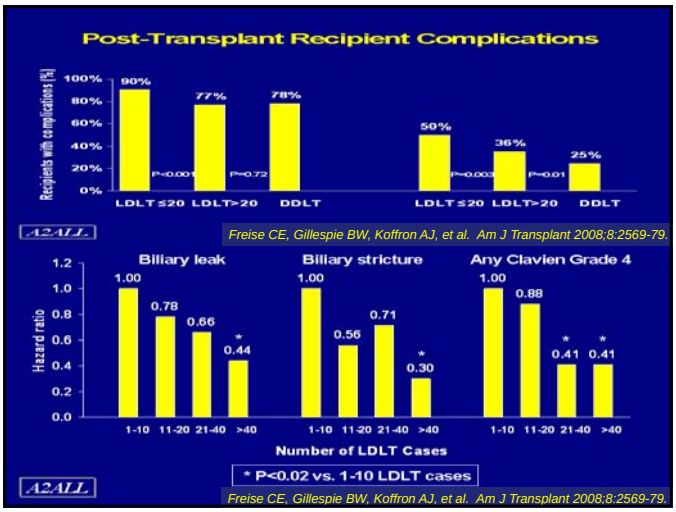


[Updated from Berg Gatro.]



Conclusions

- Post-transplant survival after LDLT and DDLT in experienced centers is equivalent
- Adult LDLT is associated with lower candidate mortality compared with waiting for DDLT
  - Effect is magnified in experienced centers
- Lower mortality in LDLT recipients is associated with reduced exposure to wait list mortality
- Recipient complications decrease with experience

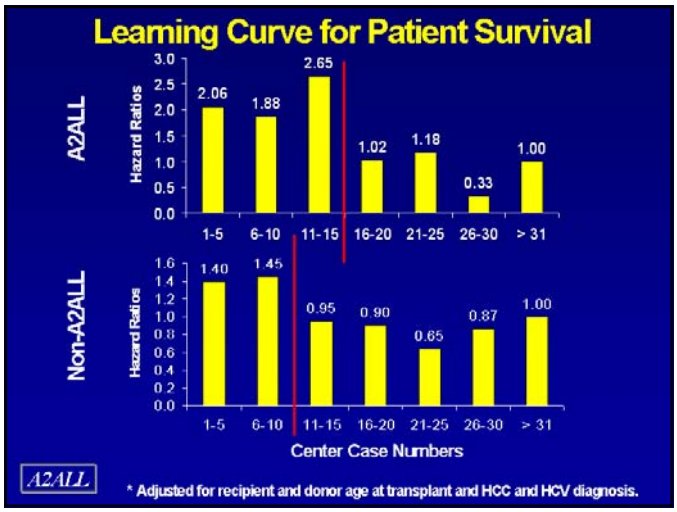
K. Olthoff et al. *Annals of Surgery* 2005
C. Berg et al. *Gastroenterology* 2007
C. Friese et al. *Am. J. Transplantation* 2008

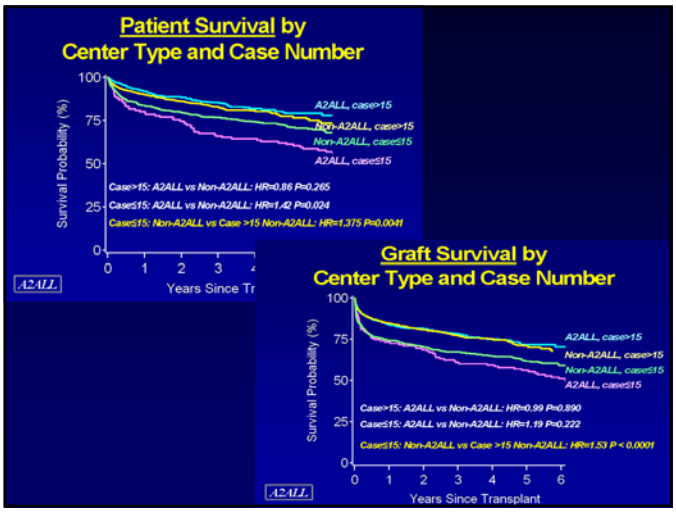
A2ALL Adult to Adult Living Donor Liver Transplantation Cohort Study

Comparison of National AALDLT Outcomes to A2ALL Centers: Analysis of Learning Curve and Risk Factors for Graft Loss

Kim M. Olthoff, Michael M. Abecassis, Jean C. Emond, Robert M. Merion, Brenda W. Gillespie, Lan Tong, Abraham Shaked and the A2ALL Study Group

NIDDK National Institutes of Health (NIH) Bethesda, Maryland 20892
Department of Health and Human Services HRSA Health Resources and Services Administration
The FOUNDATION of the ASTS American Society of Transplant Surgeons





Risk factors associated with mortality

Predictor	A2ALL Only		Non-A2ALL Only		A2ALL Non-A2ALL Interaction
	HR	P	HR	P	P
Donor age per 10 yr	1.22	0.02	1.11	0.05	0.27
Recipient age per 10 yr	1.41	<0.0001	1.19	0.001	0.18
Recipient case ≤ 15	2.24	<0.0001	1.38	0.004	0.01
Diagnosis of HCV	1.32	0.10	1.16	0.19	0.40
Diagnosis of HCC	1.49	0.28	2.24	<0.0001	0.24
Cold ischemia time >4.5 hours*	2.53	0.005	1.54	0.11	0.095

A2ALL *Note: Results for CIT are based on separate models because of 34% missing CIT values.

Conclusions

- After 15 first cases, outcomes in A2ALL centers similar to non-A2ALL centers
- Similar risk factors identified (Donor age, Recipient age and Center experience)
- Separate models yield consistent results of similar magnitude
- CIT seems more important in A2ALL and HCC in non-A2ALL
- Incomplete data collection and lack of granularity in SRTR vs A2ALL may explain discrepancies

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A2ALL Adult to Adult Living Donor Liver Transplantation Cohort Study

Complications After Living Liver Donation: A Prospective, Multi-center Report

Michael M. Abecassis, Kim M. Olthoff, James F. Trotter, Robert A. Fisher, Robert M. Merion, Lan Tong, Benjamin Samstein, Ronald W. Busuttil, Christopher E. Freise, Paul H. Hayashi, Carl L. Berg, and the A2ALL Study Group

NIDDK National Institutes of Health (NIH) Bethesda, Maryland 20892 | Department of Health and Human Services HRSA Health Resources and Services Administration | The FOUNDATION of the ASTS American Society of Transplant Surgeons

Background

- We previously reported a 38% incidence of living liver donor complications in a retrospective cohort (n=405).*
- However, prospectively collected, standardized, multi-center data on living liver donor complications have not been presented.

* M. Ghobrial et al. *Gastroenterology* 2008

Number of Complications

Complications (#)	Retrospective N (%)*	Prospective N (%)**
0	245 (62%)	165 (71%)
1	82 (21%)	39 (17%)
2	40 (10%)	13 (6%)
3	16 (4%)	6 (3%)
4	5 (1%)	5 (2%)
5 - 9	5 (1%)	3 (1%)
Total	393 (100%)	231 (100%)

Chi-square test for any complication P=0.04
Mantel-Haenszel trend test for number of complications P=0.14

*** Ghobrial et al. Gastroenterology 2008; 135: 468-476.**
**** Includes 6 aborted donations**

Methods – Clavien Severity Grading System

Grade 1. Any alteration from ideal postoperative course with complete recovery, not requiring significant intervention

Grade 2. Requiring significant intervention or potentially life-threatening, but without residual disability or persistent disease

Grade 3. Any complication with residual or lasting functional disability or development of malignant disease

Grade 4. Complications that lead to transplantation or death

Comparison of Graded Complications (Retrospective vs. Prospective)

Grade	Retrospective N (%)	Prospective N (%)
1	106 (48%)	46 (39%)
2	103 (47%)	68 (58%)
3	8 (4%)	4 (3%)
4	3 (1%)	0 (0%)
Total # Graded Complications	220 (100%)	118 (100%)

Chi-square test for grade 1 vs. grades 2, 3, and 4
P=0.13

Summary

- 231 living liver donors with prospectively collected data using a standardized classification (up to 5-year follow-up)
- 3% incidence of aborted donations
- 29% of patients undergoing living liver donation had at least one complication
- Vast majority of biliary and infectious complications occurred within 30 days
- 4 Grade 3, 0 Grade 4 complications

Conclusions

- These prospective data demonstrate that complications after living liver donation remain common and confirm our previous retrospective observations
- “Surgical complications” in this prospective cohort occurred significantly less frequently than in the retrospective cohort

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QOL Measurement

- Subjects respond to a variety of QOL questionnaires, presented on a tablet PC.
- Questionnaires include validated instruments to measure pain, health symptoms, depression score, suicidality, alcohol and drug dependence and anxiety.
- The QOL assessments also include an extensive instrument developed by project investigators that queries subjects on a variety of issues, including:
  - Relationship with partner and recipient candidate
  - Concerns about body image
  - Sexual satisfaction

A2ALL

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Measuring Informed Consent

- MacArthur Competency Assessment – subject views a video educational presentation and then answers several questions about the content.
- Structured assessment tool
- Provides a structured opportunity to inform and educate potential living donors
- Provides the opportunity to increase the objectivity by which physicians and health care providers assess donor competency to consent to evaluation and potential donation
- Four areas of ability derived from comprehensive reviews of definitions of legal competence
  - Understanding, appreciation, reasoning, expressing a choice

A2ALL

Results (n = 30)

Element (Max score)	Range	Mean	SD	%Correct
Understanding				
Evaluation (8 pts)	2.5 - 8.0	6.0	1.8	75.0
Purpose (6 pts)	2.0 - 6.0	4.9	1.2	81.7
Risks/Benefits (4 pts)	1.0 - 4.0	2.9	0.8	72.5
Right to Refuse (4 pts)	4.0	4.0	0.0	*100.0*
Appreciation (6 pts)	2.0 – 6.0	4.8	1.0	80.0
Reasoning (4 pts)	1.5 - 4.0	3.02	0.7	75.0
Expression of choice (4 pts)	2.0 – 4.0	3.8	0.6	*93.8*
Total Score (36 maximum)	**20.0 - 35.5**	**29.2**	**3.9**	**81.1**

A2ALL

Conclusions

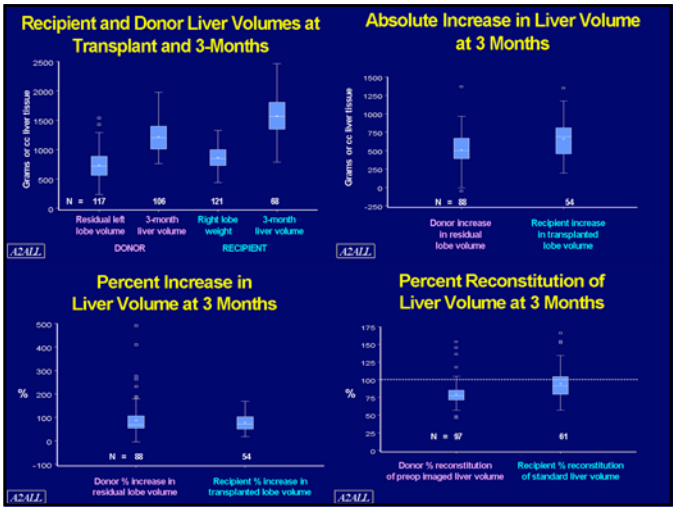
- The psychologist "sniff" test concluded that these potential donors would be scored as competent in the usual sense
- The adapted MacArthur Competency Assessment Tool-Clinical Research (aMCAT-CR) showed that potential liver donors
  - knew they could withdraw from the process at any time
  - demonstrated the expression of choice
  - demonstrated considerable heterogeneity of understanding and appreciation
- The aMCAT-CR has strong promise as a reliable tool to assess donor competence for consent

A2ALL

A2ALL Prospective Cohort Study

Secondary Aims

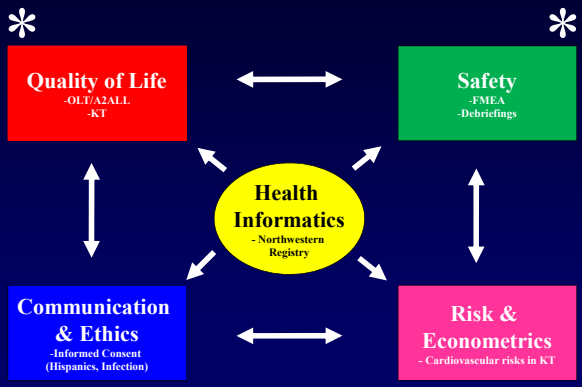
1. Severity of recurrent HCV
2. Recurrence of HCC for LD versus DD
3. Systematically characterize liver regeneration and function in donors and recipients
4. Evaluate differences in immune response to LDLT and DDLT
5. Establish a robust data and sample repository that will be used to study clinical and biological questions with emerging technologies



Summary

- A2ALL met its primary and secondary objectives
- Remaining questions mostly in the prospective domain (LADR, HCC genomics, Regeneration genomics, QOL, IC)
- A2ALL RFA for renewal mainly focused on long-term donor health outcomes

The Second 5 Years



QOL – Preliminary data

- Validated versus non-validated instruments
  - Disease specific
  - Liver transplant specific
  - Living donor liver transplant specific (donors and recipients)
- Psychometric properties
  - Health status
  - Well being
  - Disfigurement
  - Social function
  - Sexual function
- Comprehensive
  - Insurance issues
  - Other financial considerations

Informed Consent – Preliminary data

- Health information
- Health literacy
  - Numeracy
- Cultural and ethnic differences
- Impact of IC on outcomes
  - Expectations
  - Perceived versus Real

Safety

- Failure Modes Effects Analysis (FMEA) for LDLT
  - Debriefing
  - Chart review
  - "Near misses"
- Standardized Safety Protocols
  - Checklists
  - Generalizability
- Effect on outcomes
  - Direct and Indirect
  - Pre-, Peri- and Post-transplant

Summary and Future Directions

- ALDLT is safe (donor and recipient)
- Outcomes improve with experience
- Donor complications persist
- Health status, safety and other healthcare outcomes need further assessment
- ?Left lobe – transferring risk donor -> recipient
- Laparoscopic approach safe and effective

Living Liver Donation

- Why should we do living donors?
  - Organ shortages
  - Decrease wait times and wait list drop outs
- Why shouldn't we do living donors?
  - Ethical concerns
  - Donor complications
  - Unlike living kidney donation – no proven improved outcomes over DD grafts

Living Liver Donation

- Who should be a LD recipient:
  - Low MELD?
  - High MELD?
  - HCC
  - Complications of ESLD?
    - Ascites
    - HE
    - Portal hypertension

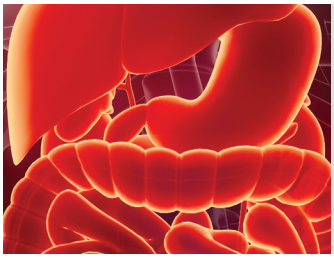
Living Liver Donation

- Living Donor Requirements:
  - Blood type compatible
  - 18-55 years old
  - Healthy!
  - Able to comprehend informed consent
  - Motivated by altruistic reasons

Living Liver Donation

- Improving the living donor process – why aren't we doing more living donors?
  - perceptions
  - Barriers
  - Surgical Approaches
  - Anonymous directed and non directed donors

Thank You



Acing: Liver Vignettes

Hetal A. Karsan, MD

Arthritis

A 59 year-old Caucasian ♂ has bilateral discomfort of his 2nd and 3rd metacarpophalangeal joints, symptomatic idiopathic congestive cardiomyopathy, mild hepatomegaly, darkening of his skin and mildly elevated aminotransferases. Further evaluation reveals an elevated serum ferritin and transferrin saturation, normal platelet count, and an HFE mutation analysis with C282Y homozygosity. Which of the following is most likely to persist after therapeutic phlebotomies?

A. Skin bronzing
B. Arthralgias
C. Hepatomegaly
D. Congestive heart failure
E. Elevated aminotransferases

Phlebotomy in Hemochromatosis

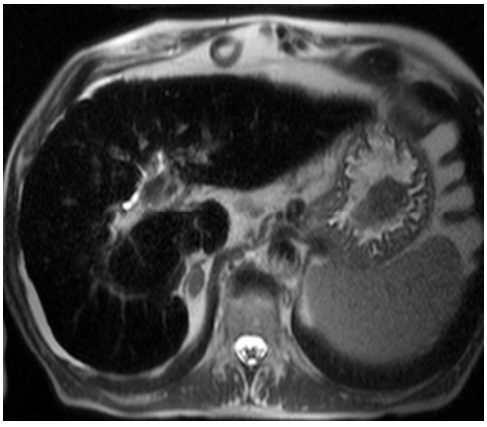
Things that can improve

- Skin hyperpigmentation
- Hepatomegaly
- Elevated liver tests
- Heart failure
- Fatigue

Things unlikely to improve

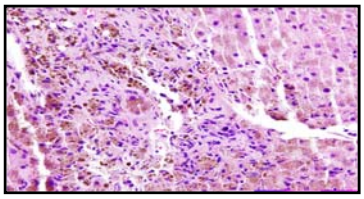
- Hypogonadism
- Arthralgias
- Cirrhosis

"HHC HACs your body"



Hemochromatosis

- Liver biopsy to evaluate for cirrhosis if:
  - Ferritin > 1000 ng/mL
  - Abnormal ALT, AST
  - Possible coexisting liver disease (NASH, EtOH, HCV, HBV, …)
- Life expectancy unchanged if no advanced fibrosis
- Avoid vitamin C



Beach Vacation

54 year-old ♂ with compensated cirrhosis (MELD=7) was vacationing in the Louisiana Gulf and presents to the ED with watery diarrhea, vomiting, lethargy and fever.

In ED: BP 78/46 → Started on IVF, pressors, antibiotics, admitted to ICU…

Dies 3 hours later…

What happened?

Bloating with IBS

43 year-old ♀ has progressive abdominal bloating over several months without abdominal pain or change in bowel habits.

She shows you that she "looks pregnant."

She gets diagnosed with IBS and told to take over the counter laxatives.

Bloating with IBS

Laxatives don't help (she was not constipated).

Unfortunately, her bloating persists.

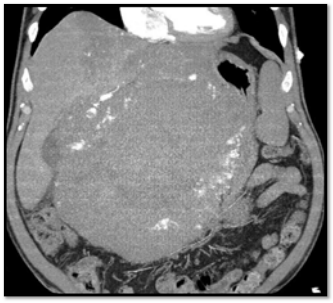
She suddenly gets more fatigued and notices bruises on her extremities and a bloody mouth due to bleeding gums.

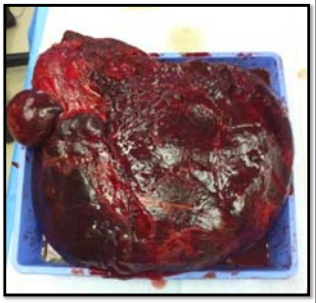
Finally, she goes to the ED…

Bloating with IBS

TB 4.9, ALT 51, AST 62, Hgb 7.2, Plat 40K, LDH 487, INR 2.7, Fibrinogen→low, Fibrin degrad products→ high, aPTT→ high

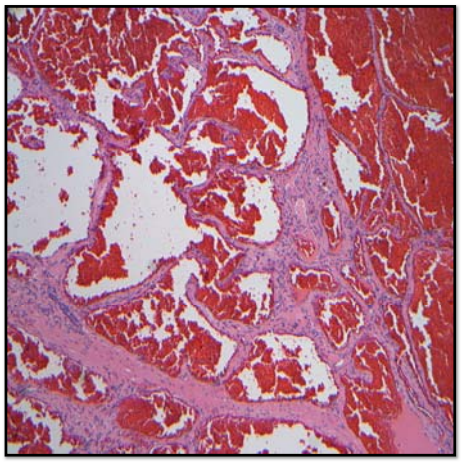
Abdominal CT shows something… It's removed by surgery





Bloating with IBS

1. What is this tumor?
2. What process explains the lab results?
3. What is the name of this syndrome?



Another Bloater

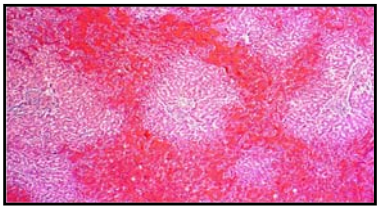
A 34 year-old ♀ has bloating and intermittent RUQ pain x 6 months. Prior studies were negative: EGD, colonoscopy, SBFT and HIDA.

No EtOH use. Smokes ½ pack daily. No family history of liver disease.

Meds: OCP and occasional acetaminophen.

Labs: AST 50, ALT 70, ALP 125, GGT 285, TB 1.3, Ferritin 240, HBc Ab +, HBsAg – , HBsAb +, HCV Ab – . Ultrasound: Hepatomegaly with fluid.

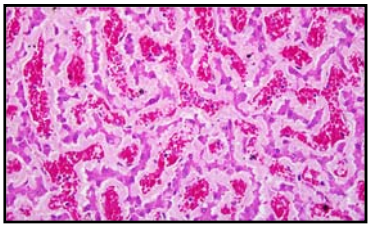
What is the diagnosis?



Yet Another Bloater

44 year-old ♂ with RA complains of bloating with weight loss, anorexia. Exam remarkable for anasarca and hepatomegaly. Labs show elevated alkaline phosphatase and proteinuria. Liver biopsy is shown below:

What is the diagnosis?



Cirrhosis One-Liner Potpourri

Clinically significant portal HTN begins at this pressure →

Minimal MELD score to qualify for OLT for cirrhosis →

Most common cirrhotic decompensation →

OLT One-Liner Potpourri

Largest size single HCC within Milan criteria →

Highest weighted variable in MELD scoring system →

Most common type of cancer after OLT →

Recurrence rate for α-1 AT cirrhosis after OLT →

Minimal Information

28 year-old ♀ presents to the ED with malaise.

Labs: ALT 1940, AST 1360, LDH 580

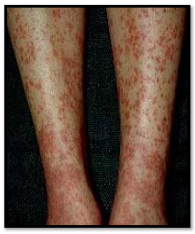
Which of the following is most likely?

A. Herbal drug-induced liver injury
B. Acute alcoholic hepatitis
C. Ischemic hepatopathy
D. Viral hepatitis
E. Acetaminophen hepatoxicity

A Rash of Problems

54 year-old ♂ with stage 1 HCV geno 1a, treatment naïve, develops increasing edema, joint aches with this new rash.

Cr 2.1, Alb 2.4, AST 55, ALT 62, Alk Phos 70, T Bili 1.3, INR 1.0; 24-hour urine protein 4g; Complement levels low.



What is the diagnosis?

Concerned Mother

Which of the following should you advise?

A. Avoid fetal scalp monitoring

B. Very small risk of vertical transmission (like a needle stick)

C. Start HCV therapy now

D. Plan for C-section to decrease risk for vertical transmission

E. Check the newborn antibody at 6 months

F. Avoid breastfeeding

Excused Abscess

Amebic and Pyogenic Abscess: TRUE or FALSE?

Amebic usually have worse prognosis

Pyogenic usually due to 1˚ abdominal infection

Amebic more often multiple in number

Pyogenic often right elevated hemidiaphragm

Amebic should be aspirated initially

Variceal Bleed with Eosinophilia

40 year-old adventurer returned from Africa this summer and now presents with variceal hemorrhage.

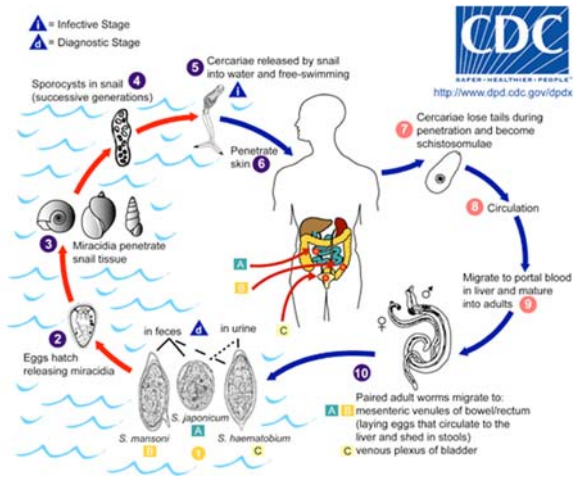
Admission labs: Eosinophilia with normal bilirubin, albumin, INR. Platelets are low. Transaminases are mildly elevated.

Exam significant for hepatosplenomegaly.

Liver biopsy reveals portal fibrosis with granuloma formation.

What is the diagnosis?

What is the treatment?



GI Bleeder

43 year-old ♂ with long history of alcoholism presents with sudden hematemesis. He was diagnosed with cirrhosis last year but has no prior history of previous GI bleeding, ascites or encephalopathy. Multiple supportive family member are present and confirm recent binge drinking.

WBC 4.0, Hgb 7.2, plt 108, INR 1.8, creat 0.9, alb 2.9, T Bili 2.2, Na 139, K 4.0, AST 132, ALT 70.

IVF, PPI and octreotide started in ED

EGD in ED → Mild portal hypertensive gastropathy, no varices, small clean-based duodenal ulcer without stigmata

What would you do?

A. Assist with alcohol rehab and discharge home with family
B. Discharge home after blood transfusion in ED
C. Admit for inpatient blood transfusion; stop octreotide
D. Admit for inpatient FFP; stop octreotide
E. Admit for inpatient observation and antibiotics
F. Transfer to liver transplant center immediately

Rave

20 year-old student is brought in by friends to the ED with nausea, vomiting, and anxiety. There is no PMH, no recent travel, and no unusual food consumption. He denies alcohol use but his friends mention that he frequently goes to "raves." He is anxious and diaphoretic with a temperature of 104 F. On exam he is jaundiced and has tender hepatomegaly. His jaw is tightly closed and clenched. Emergent lumbar puncture is negative.

Labs: INR 1.5, ALT 1790, AST 1640, TB 3.9, Cr 1.0, WBC 8.1, Hgb 14.2, platelets 190, CK 50, pH 7.40; blood cultures are pending.

What is the most likely diagnosis?

Rave

Check out http://livertox.nih.gov

Acute Liver Failure Mini Vignettes

Alcoholic + chronic pain + super high ALT and AST + jaundice + coagulopathy + confusion + pH 7.26

Nature enthusiast + Western Europe foraging + gastroenteritis + super high ALT and AST + jaundice + coagulopathy + confusion

Acute Liver Failure Mini Vignettes

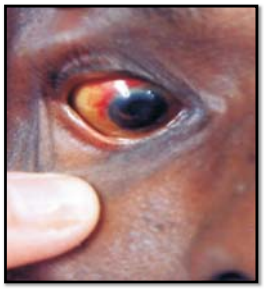
Most common cause of ALF in the US

Most common cause of DILI (non-ALF) in the US

Leading two causes of death in ALF patients

Red eye

48 year-old Indian farmer with fever, rigors, myalgias and deep jaundice. ALT 70. Malaria screen negative.



Third Trimester Jaundice

26 year-old ♀ presents with jaundice at week 31 of pregnancy. She has nausea, diarrhea, muscle aches, and progressive fatigue. Labs include:

AST 672, ALT 840, T Bili 1.7, Alb 3.2

In general, what is the most likely cause of her jaundice?

Which specific diagnosis needs urgent treatment here?

Pregnancy Liver Problems #1

A 36 year-old Chilean ♀ who is expecting twins via in vitro fertilization has insomnia due to pruritis at 28 weeks gestation. You note excoriations all over her body. Positive "fork" sign.

Labs: ALT 56, AST 51, T Bili 1.4, WBC 6.1, Hgb 12.9, platelets 204, glucose 90, INR 1.6, creat 0.8

What is most likely diagnosis?

What test should you order?

Intrahepatic Cholestasis of Pregnancy (ICP)

- Pruritis starts on palms and soles
- Elevated serum bile acids (up to 100x)
- Late 2nd or early 3rd trimester most common
- Older age, multiple pregnancies and gestations
- Bolivian and Chilean descent at increased risk
- Maternal prognosis good; but, ↑ fetal risk (4% death)
- Treatment with UDCA and early delivery
- Can recur with future pregnancies

Pregnancy Liver Problems #2

28 year-old primigravid ♀ with twins develops anorexia and nausea during week 38, which is promptly followed by jaundice and confusion 1 week later. Labs:

T Bili 8.3, Plt 142, INR 2.3, Cr 2.1, Gluc 60

What is the most likely diagnosis?

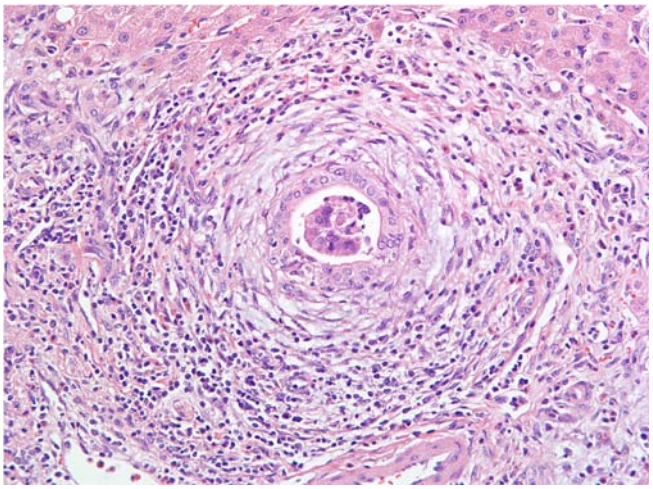
What does the biopsy show?

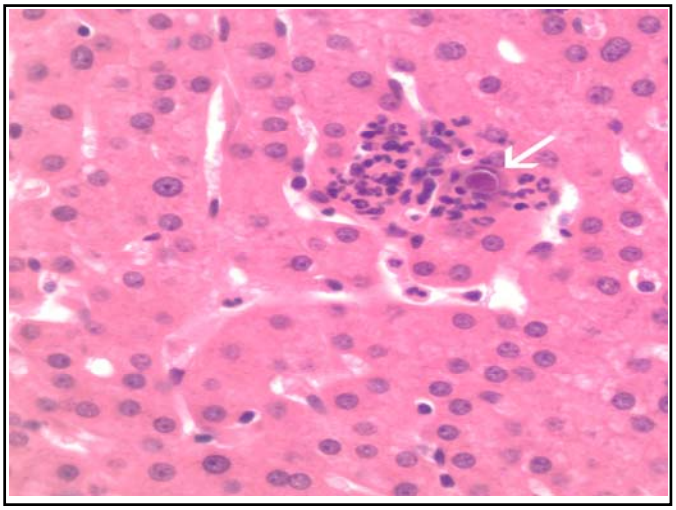
What is the treatment?

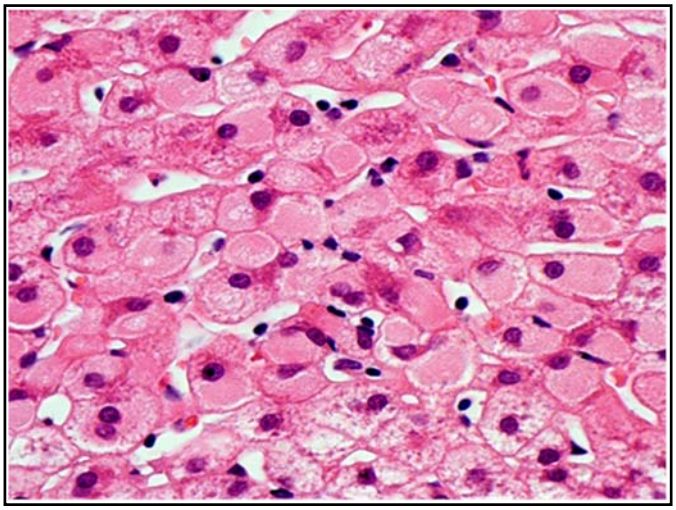
AFLP vs. HELLP

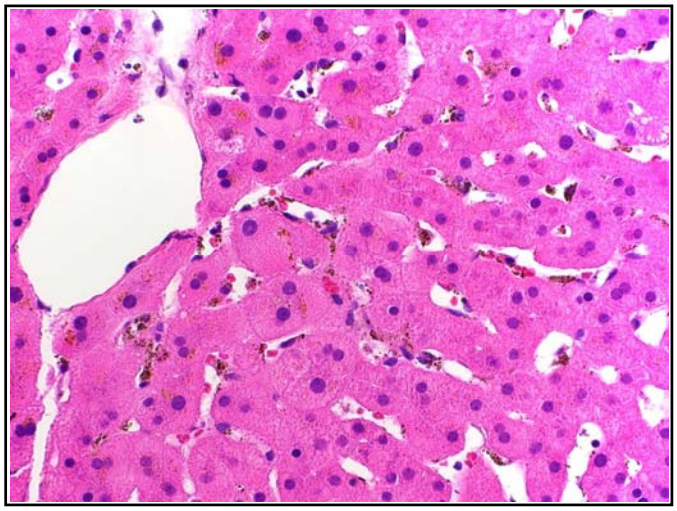
Characteristic	AFLP	HELLP
Period of pregnancy	Third TM	Late 2nd + 3rd TM
Parity	Nulliparous, twins	Multiparous
Mean TB	8	2
Encephalopathy	+	-
Platelets	Low Normal	Low
Creatinine	Elevated	Elevated
Glucose	Low	Normal
INR	Elevated	Normal
Treatment	Delivery	Delivery

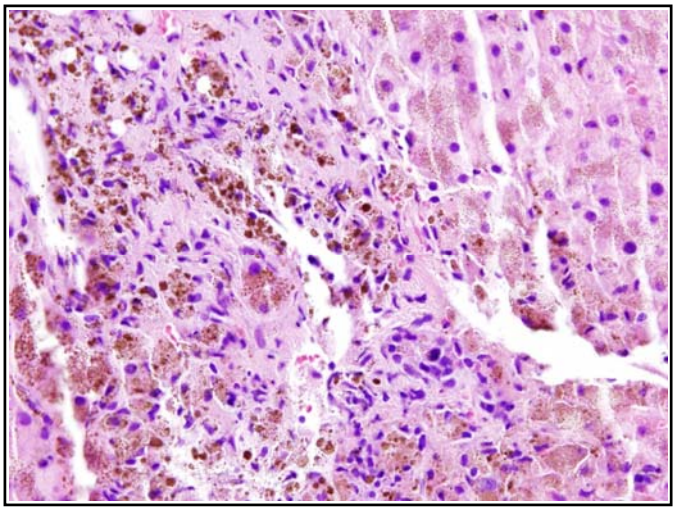
Hufti Ar, Reau N. *Clin Liver Dis* 2012;16:247-269.
Hay JE. *Hepatology* 2008;47:1067-1076.

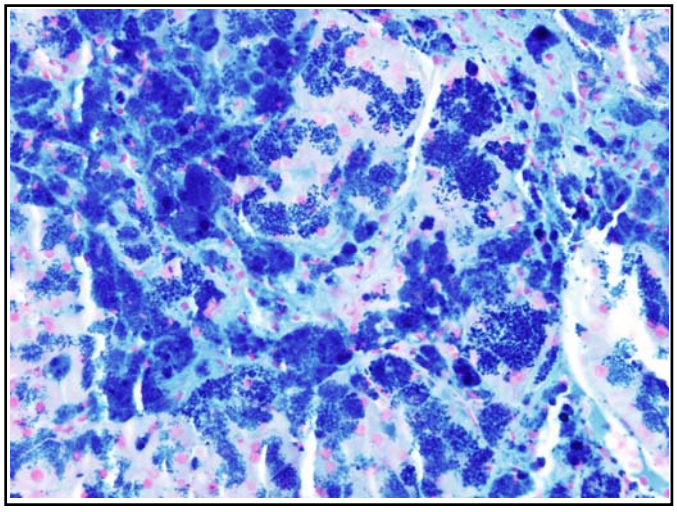


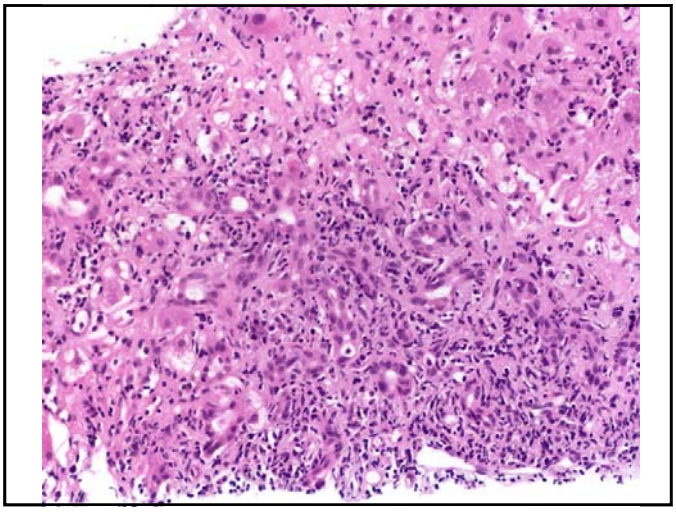


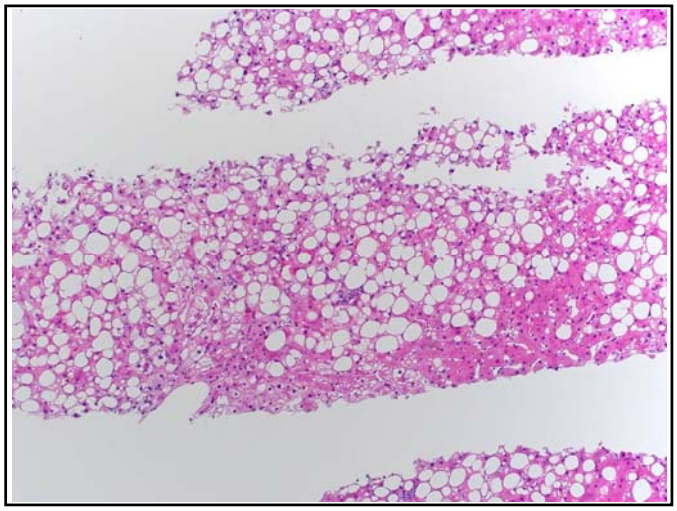


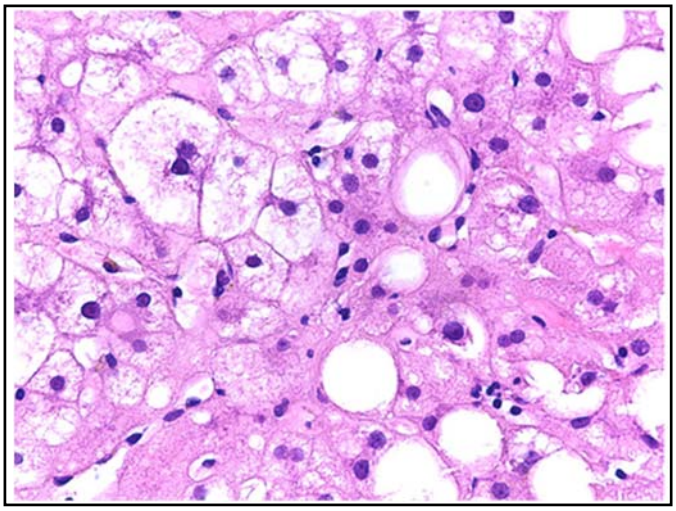


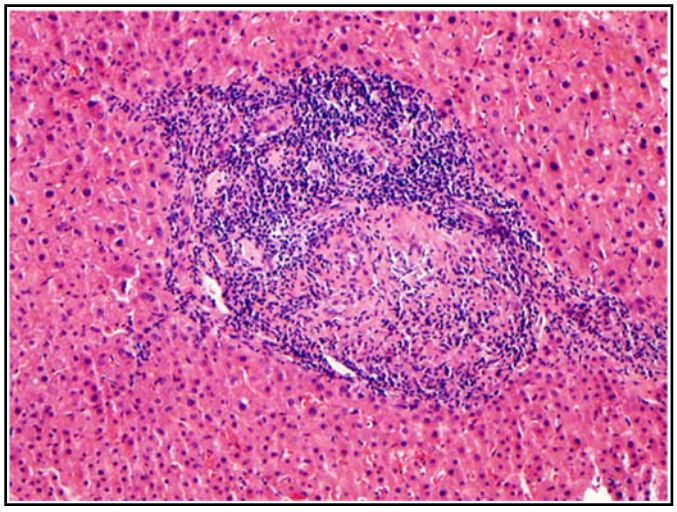


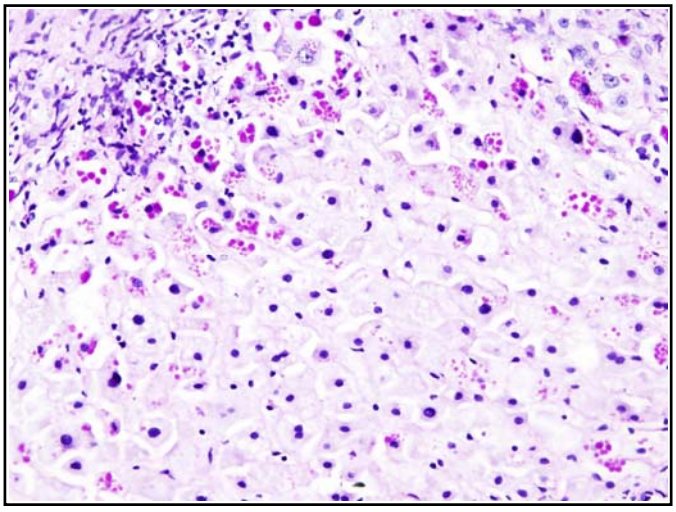


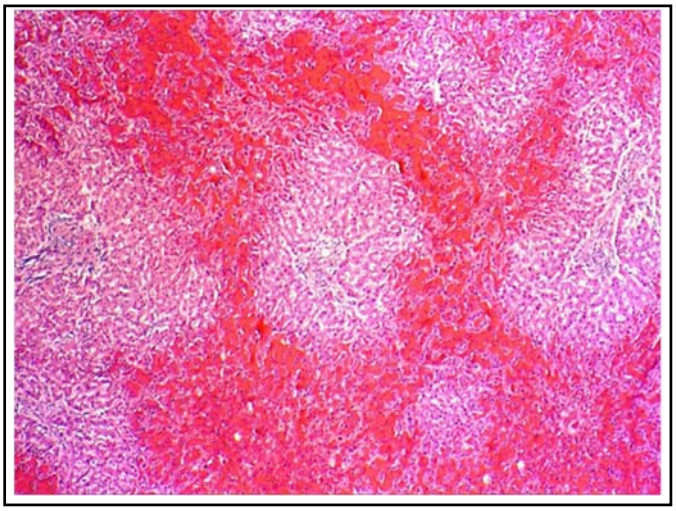


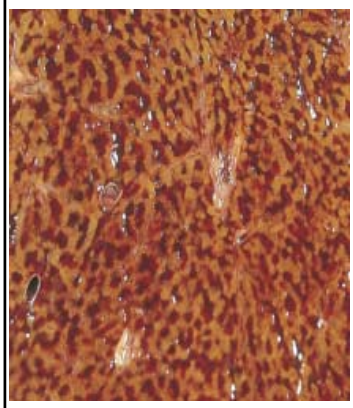












Rapid Fire Hepatology Review

Most common cause of jaundice in pregnancy

Cirrhosis + oysters + septic shock

"Rave" party + bruxism + high AST/ALT

Acute flare of hepatitis + HBV carrier + IVDU

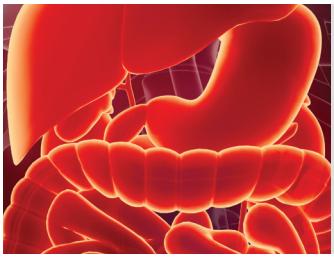
Elevated alk phos + liver granulomas + positive AMA

Most common cause of ALF in USA

Pregnant + low platelets + proteinuria + hepatic rupture

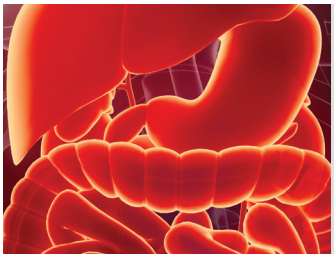
Mean survival for refractory ascites

Mortality rate for: new medication + jaundice + 3X ALT



Overview of the Small Bowel & Nutrition Programs

Carol Semrad, MD



What's New in Bariatric Surgery?

Mustafa Hussain, MD

THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

Acing the Boards: Bariatric Surgery

Mustafa Hussain MD FACS
Associate Professor
Director of Bariatric Surgery
University of Chicago MEDICINE

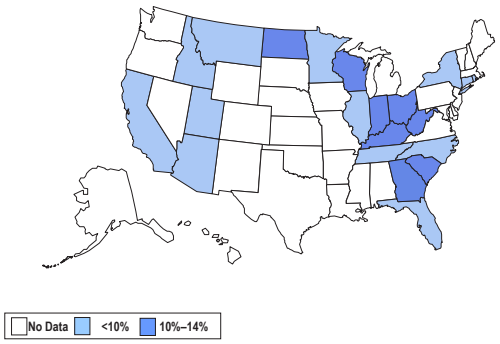
Disclosures

- W.L. Gore
  - Speaker Honorarium
- Intuitive
  - Teaching Expenses
- No off-label discussion

Obesity Trends* Among U.S. Adults

BRFSS, 1985

(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)



Obesity Trends* Among U.S. Adults

BRFSS, 1990

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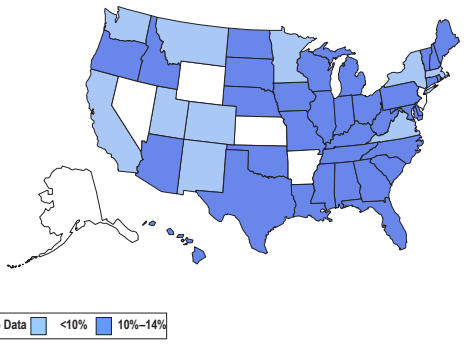
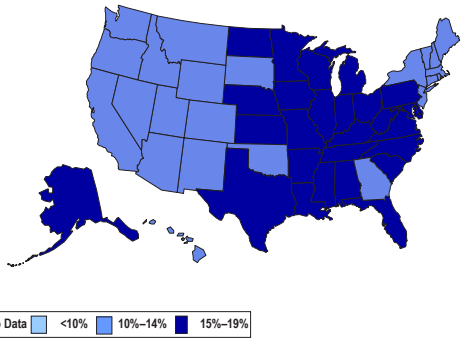
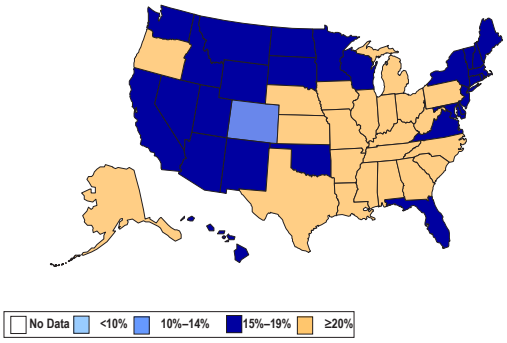


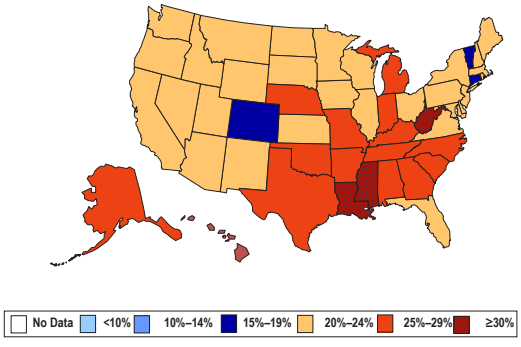
Obesity Trends* Among U.S. Adults
BRFSS, 1995
(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)



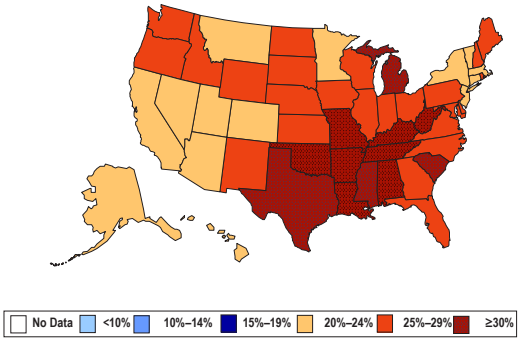
Obesity Trends* Among U.S. Adults
BRFSS, 2000
(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)



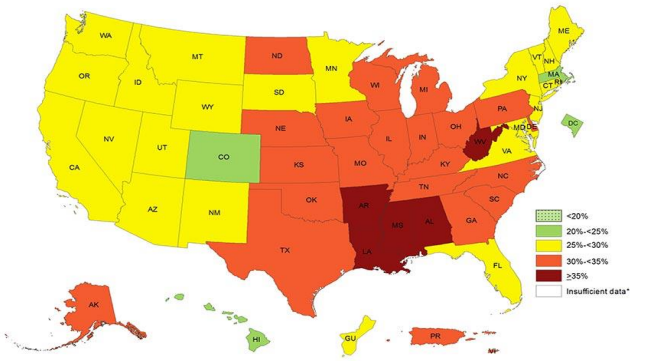
Obesity Trends* Among U.S. Adults
BRFSS, 2005
(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)



Obesity Trends* Among U.S. Adults
BRFSS, 2010
(*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)



Prevalence¶ of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2016¶



*Sample size <50 or the relative standard error (dividing the standard error by the prevalence) ≥ 30%.

Why do we care?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Body-Mass Index and Mortality among 1.46 Million White Adults

- **Pooled analysis of 19 prospective studies, examining all cause mortality.**

	22.5–25 kg/m^2	30–35 kg/m^2	35–40 kg/m^2	40–45 kg/m^2
White women	1.0	1.44	1.88	2.51
White men	1.0	1.44	2.06	2.93

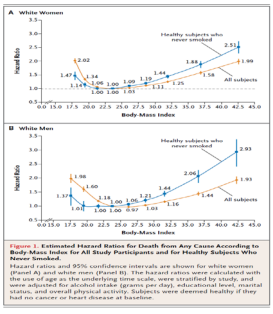
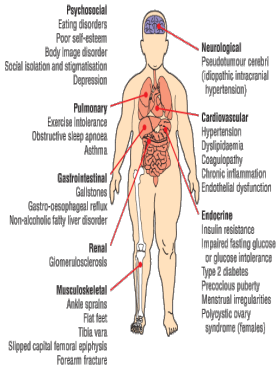


Figure 1. Estimated Hazard Ratios for Death from Any Cause According to Body-Mass Index for All Study Participants and for Healthy Subjects Who Never Smoked.

Hazard ratios and 95% confidence intervals are shown for white women (Panel A) and white men (Panel B). The hazard ratios were calculated with the use of age as the underlying time scale, were stratified by study, and were adjusted for alcohol intake (grams per day), educational level, marital status, and overall physical activity. Subjects were deemed healthy if they had no cancer or heart disease at baseline.



So what are we doing?

ORIGINAL ARTICLE

A Two-Year Randomized Trial of Obesity Treatment in Primary Care Practice

Thomas A. Wadden, Ph.D., Sheri Volger, R.D., M.S., David B. Sarwer, Ph.D., Marion L. Vetter, M.D., R.D., Adam G. Tsai, M.D., Robert I. Berkowitz, M.D., Shiriki Kumanyika, Ph.D., M.P.H., Kathryn H. Schmitz, Ph.D., M.P.H., Lisa K. Diewald, R.D., M.S., Ronald Barg, M.D., Jesse Chittams, M.S., and Reneé H. Moore, Ph.D.

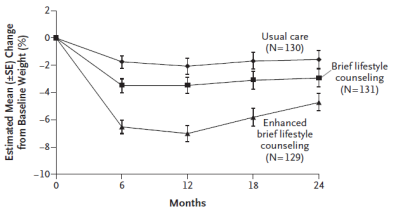
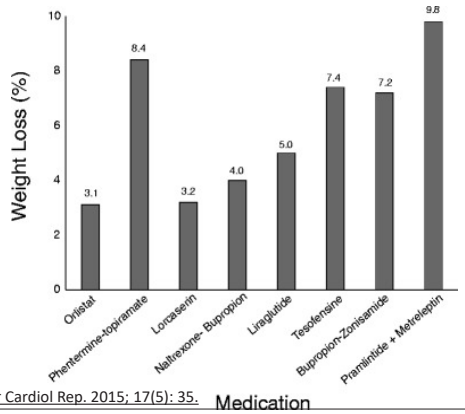


Figure 2. Estimated Percent Reduction in Baseline Weight over a 24-Month Period in the Intention-to-Treat Population.

11lbs!

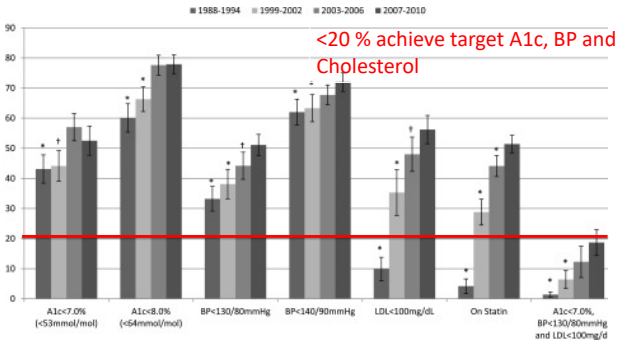
Medications for Weight Loss



10-30 lbs. Often discontinued due to side effects.

Curr Cardiol Rep. 2015; 17(5): 35.

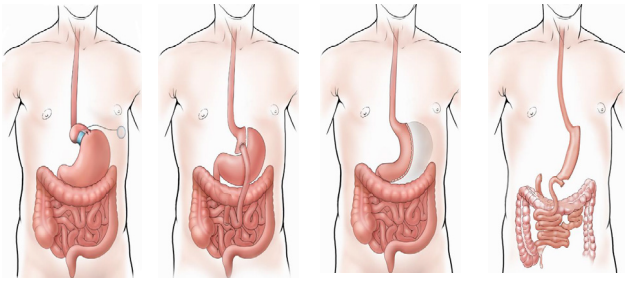
The Prevalence of Meeting A1C, Blood Pressure, and LDL Goals Among People With Diabetes, 1988–2010



<20 % achieve target A1c, BP and Cholesterol

Diabetes Care. 2013 Aug; 36(8): 2271–2279.

Surgery Works Better!



LAGB	Gastric Bypass	Sleeve	BPD-DS
45% EWL	70%EWL	60%EWL	>80%EWL

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 AUGUST 23, 2007 VOL. 357 NO. 8

Effects of Bariatric Surgery on Mortality in Swedish Obese Subjects

Lars Sjöström, M.D., Ph.D., Kristina Narbro, Ph.D., C. David Sjöström, M.D., Ph.D., Kristjan Karason, M.D., Ph.D., Bo Larsson, M.D., Ph.D., Hans Wedel, Ph.D., Ted Lystig, Ph.D., Marianne Sullivan, Ph.D., Claude Bouchard, Ph.D., Björn Carlsson, M.D., Ph.D., Calle Bengtsson, M.D., Ph.D., Sven Dahlgren, M.D., Ph.D., Anders Gummesson, M.D., Peter Jacobson, M.D., Ph.D., Jan Karlsson, Ph.D., Anna-Karin Lindroos, Ph.D., Hans Lönroth, M.D., Ph.D., Ingmar Näslund, M.D., Ph.D., Torsten Olbers, M.D., Ph.D., Kaj Stenlöf, M.D., Ph.D., Jarl Torgerson, M.D., Ph.D., Göran Ågren, M.D., and Lena M.S. Carlsson, M.D., Ph.D., for the Swedish Obese Subjects Study

Prospective nonrandomized study of greater than 4000 patients with **> 15 year** follow-up comparing surgery vs. non-surgical therapy for weight loss.

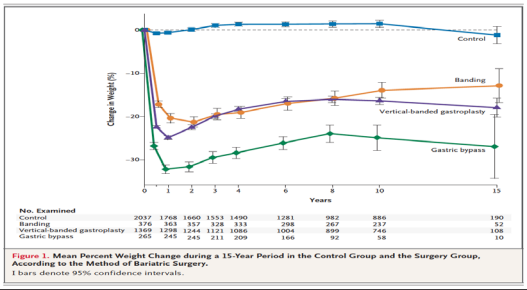
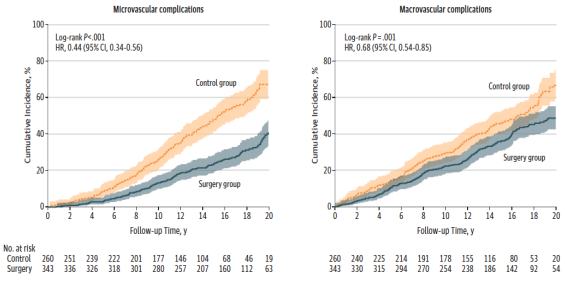


Figure 1. **Mean Percent Weight Change during a 15-Year Period in the Control Group and the Surgery Group, According to the Method of Bariatric Surgery.**
I bars denote 95% confidence intervals.

Fewer vascular events in patients who have undergone surgery.

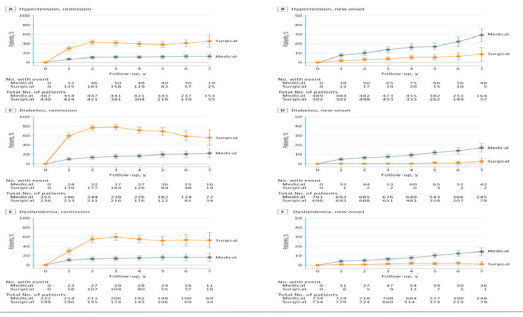
Figure 3. Cumulative Incidence of Microvascular and Macrovascular Diabetes Complications in the Surgery and Control Groups



From: **Association of Bariatric Surgery vs Medical Obesity Treatment With Long-term Medical Complications and Obesity-Related Comorbidities**

JAMA. 2018;319(3):291-301. doi:10.1001/jama.2017.21055

930 Gastric bypass patients vs 950 medically managed patients

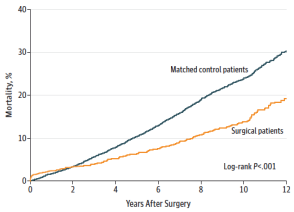


Original Investigation

Association Between Bariatric Surgery and Long-term Survival

David E. Arterburn, MD, MPH; Maren K. Olsen, PhD; Valerie A. Smith, MS; Edward H. Livingston, MD, MS; Lynn Van Scoyoc; William S. Yancy Jr, MD, MHSc; George Eid, MD; Hollis Weidenbacher, PhD; Matthew L. Maciejewski, PhD

Figure. Kaplan-Meier Estimated Mortality Curves for Surgical Patients and Matched Control Patients



No. at risk

Matched control patients	7462	7114	5306	3878	2641	1407	472
Surgical patients	2500	2416	1868	1412	1004	552	185

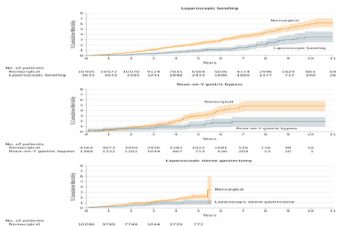
2500 Veteran Surgical patients matched with 7500 observation group.

Surgical patients were twice as likely to be alive at 5 and 10 years.

The JAMA Network

From: **Association of Bariatric Surgery Using Laparoscopic Banding, Roux-en-Y Gastric Bypass, or Laparoscopic Sleeve Gastrectomy vs Usual Care Obesity Management With All-Cause Mortality**

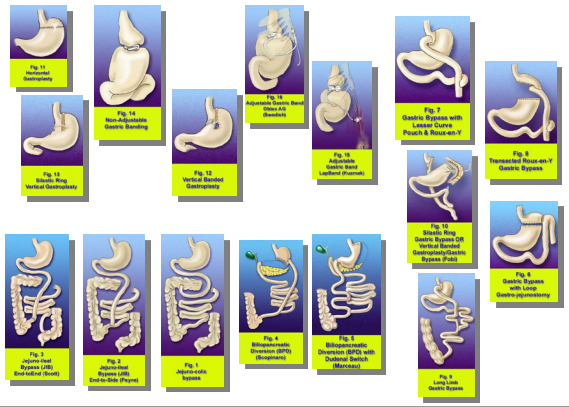
JAMA. 2018;319(3):279-290. doi:10.1001/jama.2017.20513



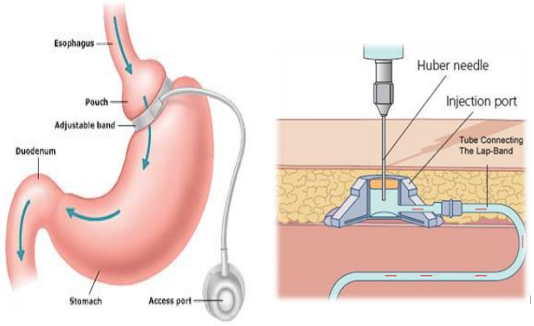
Adjusted hazard ratios (HRs) for mortality among nonsurgical vs surgical patients were 2.02 (95% CI, 1.63-2.52) for the entire study population; by surgical type, HRs were 2.01 (95% CI, 1.50-2.69) for laparoscopic banding, 2.65 (95% CI, 1.55-4.52) for gastric bypass, and 1.60 (95% CI, 1.02-2.51) for laparoscopic sleeve gastrectomy.

Retrospective cohort study including 33,000 patients (9000 surgical) with mean f/u of 5 years.

Obesity Surgery Through the Years…



LAGB

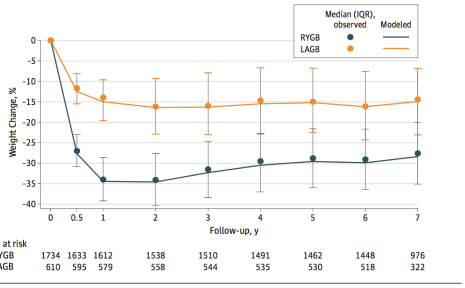


LAGB

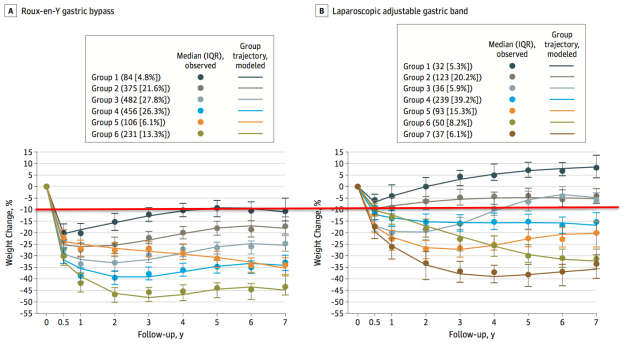
- Pros:
  - Lowest *perioperative* complication rate
  - "Adjustable"
  - "Reversible"
  - Anatomy not altered
- Cons:
  - "Modest" results→ 47% EWL
  - 25% Inadequate weight loss
  - Device –**20-30 % reoperation rate**
    - "Slip"
    - Tubing/port failure
    - Erosion
  - Very long term data demonstrates **nearly half removed.**

Seven-Year Weight Trajectories and Health Outcomes in the Longitudinal Assessment of Bariatric Surgery (LABS) Study

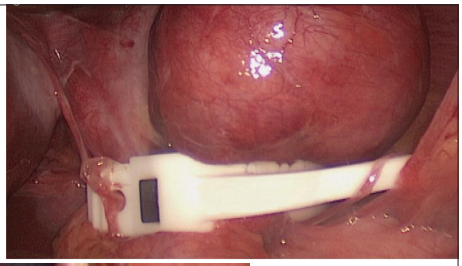
Figure 1. Observed and Modeled Percentage of Weight Change Following Bariatric Surgery

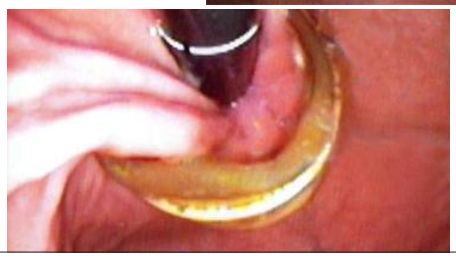


JAMA Surgery Published online December 6, 2017



"Slip"





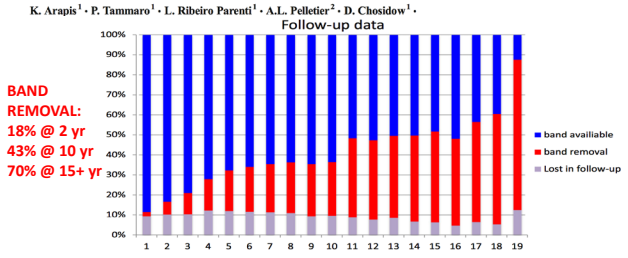
Erosion

ORIGINAL CONTRIBUTIONS

Long-Term Results After Laparoscopic Adjustable Gastric Banding for Morbid Obesity: 18-Year Follow-Up in a Single University Unit

K. Arapis[1] · P. Tammaro[1] · L. Ribeiro Parenti[1] · A.L. Pelletier[2] · D. Chosidow[1] ·

BAND REMOVAL:
18% @ 2 yr
43% @ 10 yr
70% @ 15+ yr



Eligible patients	897	897	897	897	897	897	897	897	813	794	723	668	552	376	257	150	78	38	8
Patients losti n follow-up	75	85	90	97	95	92	90	87	75	69	59	52	44	28	16	11	7	2	1
Available patients (number)	822	812	807	800	802	805	807	810	738	718	664	616	508	348	241	139	71	36	7
Available patients (percentage)	91.6	90.5	89.9	89.1	89.4	89.7	89.9	90.3	90.7	90.4	91.8	92.2	92.0	92.5	93.7	92.6	91	94.7	87.5

OBES SURG (2017) 27:630–640
DOI 10.1007/s11695-016-2309-7

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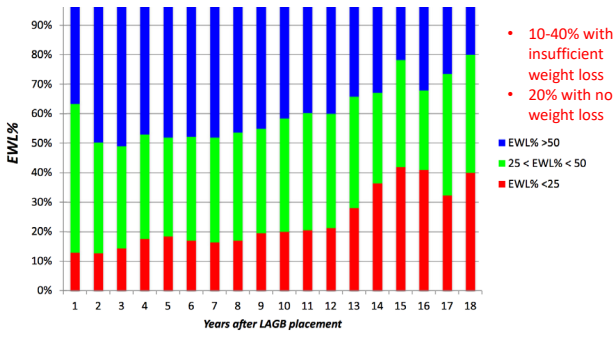
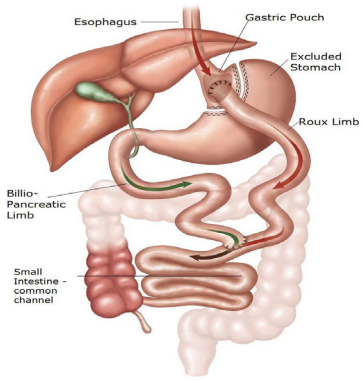


- 10-40% with insufficient weight loss
- 20% with no weight loss

Gastric Bypass



Bypass

- **Pros**:
  - Mason and Ito 1966
    - Longest data
  - **Consistent and durable** weight loss
    - **-70-60%** excess weight loss
  - Generally *eliminates reflux*
  - **Multifactorial Mechanism --Superior for Diabetes**
    - **84% have significantly improved or in remission**
  - "Reversible"

- **Cons**:
  - Rearranged anatomy
    - Malnutrition
    - Bowel obstruction
    - Stricture
    - Ulcer
  - Excluded stomach and duodenum
    - Consideration for endoscopic interventions
  - Leak "(1%)"
    - (0/5-0.1%)
  - **Limited options for inadequate weight loss**

Sleeve Gastrectomy

- 2/3-3/4 of Stomach removed.

Sleeve

- **Pros:**
  - No intestinal rearrangement
    - Less nutritional concerns
    - Fewer long term complications
  - Preferred for higher risk patients
  - Consistent weight loss
    - 60% excess weight loss
  - Can be readily converted to other procedures
- **Cons**:
  - Permanent
  - Leak "(1%)"
  - Stricture/obstruction (5%)
  - Reflux
    - 20-30%
  - Limited long term results (8 years)

Laparoscopic Sleeve Gastrectomy and GERD: A Systematic Review and Meta-analysis

- 33 articles
- 28 studies reported on prevalence of GERD after SG
  - 16 increase in GERD up to 57.1%
  - 12 decrease in GERD up to 56%
- 24 studies reported on new onset GERD 0-34.9% incidence
- Conclusion: the exact effect of laparoscopic SG on the prevalence of GERD remains unanswered

Oor J et al. *Am J Surg* 2016; 2: 250-67

Laparoscopic Sleeve Gastrectomy and GERD: A Systematic Review and Meta-analysis

Table 3 Included studies reporting on 24-hour pH results

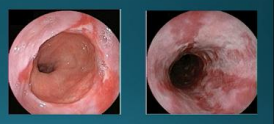
Study	N	Preoperative total acid exposure, mean (SD)*	Postoperative total acid exposure, mean (SD)†	Relative difference of effect (%)	Preoperative DeMeester score, mean (SD)	Postoperative DeMeester score, mean (SD)	Relative difference of effect (%)	De novo pathologic pH results (%)	Excess weight loss (%)	Follow-up (months)	Bougie size (Fr)
Gonzalez et al (2015)[14]	14	3.8 (3.1)	7.7 (5.4)	102.6 (I), $P \leq .06$	12.6 (10.1)	28.4 (19)	125.4 (I), $P \leq .05$	36	74	12	36
Burgerhart et al (2014)[15]	20	4.1 (3.5)	12 (10.4)	193 (I), $P = .004$	NA	NA	NA	NA	19	3	34
Rebecchi et al (2014)[16]	37/65	3.2 (1.2)	3.5 (1.1)	9.4 (I)	11.9 (2.1)	12 (2.3)	.8 (I)	10.8	56	24	36
	28/65	10.2 (3.7)	4.2 (2.6)	58.8 (D), $P < .001$	39.5 (16.5)	10.6 (5.8)	73.2 (D)	NA	54	24	36

D = decrease; Fr = French; I = increase; NA = not answered; SD = standard deviation.
*Preoperative pathologic results from 24-hour pH study, defined as the total acid exposure with pH less than 4.
†Postoperative pathologic results from 24-hour pH study defined as total acid exposure with pH less than 4.

Oor J et al. *Am J Surg* 2016; 2: 250-67

Upper Endoscopy

- Esophagitis
- Strictures
- Barrett's esophagus
- Hiatal Hernia
- 6-63% incidence of new onset esophagitis



Tai CM et al. *Surg Endos* 2013; 27: 1260-6
Sharma A, et al. Surg Obes Relat Dis 2014;10:600-5

Exacerbation of GERD after sleeve

- Increased intraluminal pressure
- Decreased gastric compliance
- Decreased lower esophageal sphincter pressure
- Disruption of sling fibers
- Contour of the sleeve gastrectomy

Yehoshua RT , et al. *Obes Surg* 2008; 18: 1083-8
Reynolds J, et al. *Surg Endosc* 2016; 30:4904-09
Himpens J, et al. *Obes Surg* 2006; 16: 1450-6

- 47 pts 2013-2015
- APM preop and 1 year after SG (30 also had HRM)
- Group 1: 31 pts no preop GERD; Group 2: 16 with preop GERD
- At 1 yr, group 1 had increased time pH<4 but not group 2
- Group 1 also had 52% pts de novo GERD
- Group 2: 62% improvement or resolution, 38% worsened

Coupaye et al. *Obes Surg* 2018; 28: 838-45

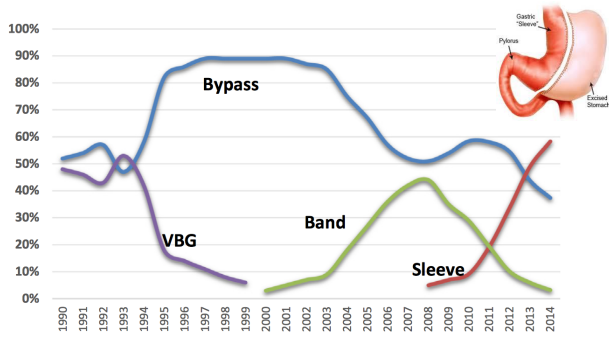
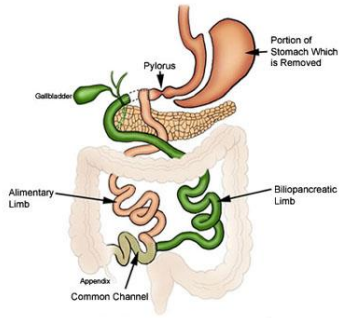
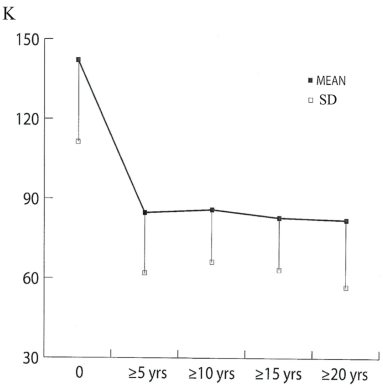


Fig. 4. Combined analysis of available literature data on utilization of bariatric surgery since 1990. Source: Pope [13] (1990–1997), Trus [14] (1990–2000), Santry [15] (1998–2002), Nguyen [16] (2003–2008), Nguyen [2] (2008–2010), present study (2010–2014).

Biliopancreatic Diversion with Duodenal Switch



Body weight change at 5-year intervals (± 3 months)



Operated patients n	2615	2117	901	383	29
Last weight n	2615	1974	847	313	25
% of patients n	100%	93%	94%	82%	86%

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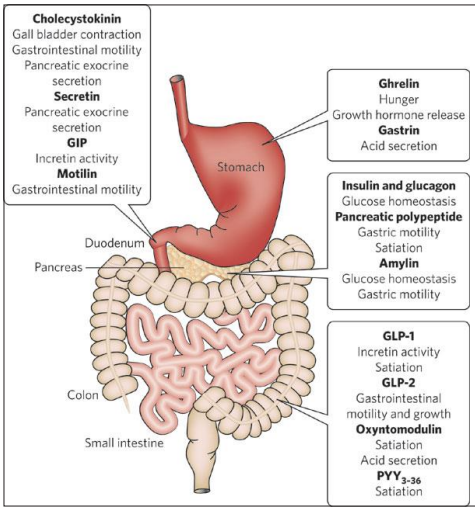
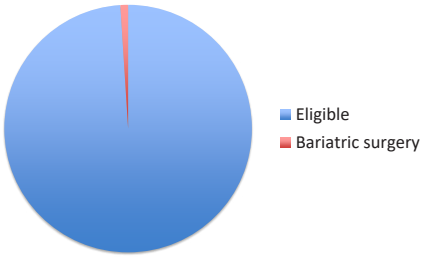
How Does it work?



BRAVE: bile flow alteration, reduction of gastric size, anatomical rearrangement, vagal manipulation, and enteric gut hormone modulation

Minority of obese subjects elect to have bariatric surgery



Not safe/Too Invasive?

DIET & EXERCISE

Diets can be successful in the short-term, but often fail for many reasons[1]

Growing number of pharmaceutical options with modest weight loss

PHARMACEUTICAL

SURGERY

Most effective approach for long-term weight loss[1] but rejected by most patients as too invasive

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 30, 2009 VOL. 361 NO. 5

Perioperative Safety in the Longitudinal Assessment of Bariatric Surgery

The Longitudinal Assessment of Bariatric Surgery (LABS) Consortium

Table 2. Adverse Outcomes within 30 Days after Surgery, According to Surgical Procedure.

Outcome	Total (N=4610)*	Laparoscopic Adjustable Gastric Banding (N=1198)	Laparoscopic Roux-en-Y Gastric Bypass (N=2975)	Open Roux-en-Y Gastric Bypass (N=437)	P Value†
Death	15 (0.3)	0	6 (0.2)	9 (2.1)	<0.001
Deep-vein thrombosis or venous thromboembolism	20 (0.4)	3 (0.3)	12 (0.4)	5 (1.1)	0.05
Tracheal reintubation					0.004
Endoscopy					<0.001
Operation					
Tracheostomy					0.001
Placement of percutaneous drain	16 (0.3)	0	13 (0.4)	3 (0.7)	0.48
Abdominal operation	118 (2.6)	9 (0.8)	94 (3.2)	15 (3.4)	<0.001
Failure to be discharged by day 30	17 (0.4)	0	13 (0.4)	4 (0.9)	0.02
Composite end point‡	189 (4.1)	12 (1.0)	143 (4.8)	34 (7.8)	<0.0001

- **4.1% Overall Peri-op Complication rate.**
- **0.3% Death rate**

* The total excludes 166 procedures, including 117 sleeve gastrectomies, 47 biliopancreatic diversions with or without a duodenal switch, 1 vertical banded gastroplasty, and 1 open adjustable gastric banding.
† P values are for the comparison between treatment groups. Values were calculated with the use of the chi-square test.
‡ This end point is a composite of death; deep-vein thrombosis or venous thromboembolism; reintervention with the use of a percutaneous, endoscopic, or operative technique; or failure to be discharged from the hospital within 30 days after surgery.

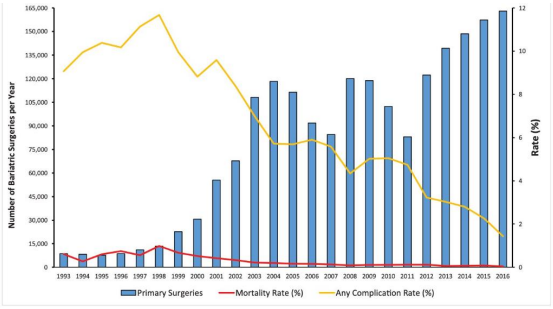


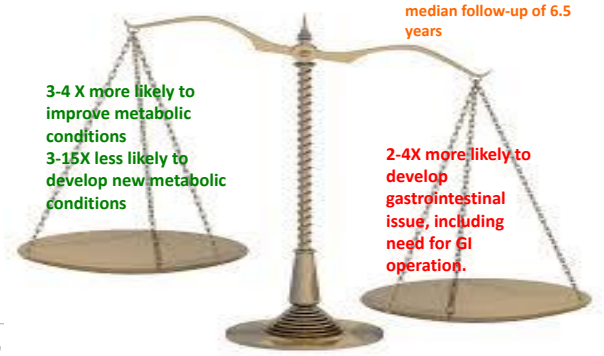
FIGURE 2. Number of inpatient primary bariatric surgery procedures and initial admission complication and mortality rates in the United States from 1993 to 2016.

The JAMA Network

From: **Association of Bariatric Surgery vs Medical Obesity Treatment With Long-term Medical Complications and Obesity-Related Comorbidities**

JAMA. 2018;319(3):291-301. doi:10.1001/jama.2017.21055

900 Bypass vs. 900 Medical, median follow-up of 6.5 years



3-4 X more likely to improve metabolic conditions
3-15X less likely to develop new metabolic conditions

2-4X more likely to develop gastrointestinal issue, including need for GI operation.

Date

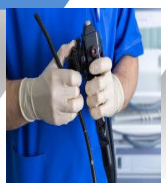
Bridging the divide

DIET & EXERCISE

Diets can be successful in the short-term, but often fail for many reasons[1]

PHARMACEUTICAL

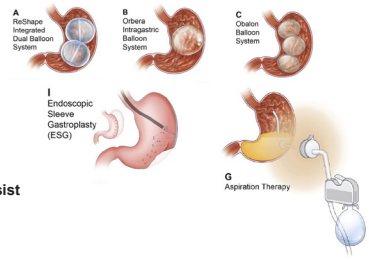
Growing number of pharmaceutical options with modest weight loss



SURGERY

Most effective approach for long-term weight loss[1] but rejected by most patients as too invasive

- **GASTRIC INTERVENTIONS**
  - Space Occupying Device
    - **Intragastric Balloons**
      - **Orbera**
      - **Reshape Duo**
      - **Obalon**
      - Spatz3 Adjustable
      - Ellipse
    - Transpyloric shuttle
    - Full Sense
  - **Gastric volume reduction**
    - POSE
    - Endomina
    - **Endoscopic Sleeve Gastroplasty**
  - **Aspiration therapy: Aspire Assist**
- **SMALL BOWEL INTERVENTIONS**
  - EndoBarrier
  - Revita Duodenal Mucosal Resurfacing
  - Self-Assembling Magnets – GI Windows



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- **GASTRIC INTERVENTIONS**
  - Space Occupying Device
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      - Orbera
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      - Spatz3 Adjustable
      - Ellipse
    - ***Transpyloric shuttle****
    - ***Full Sense****
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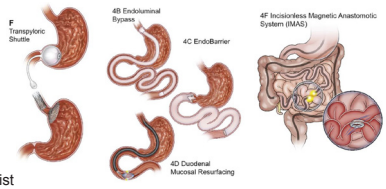

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- THANK YOU

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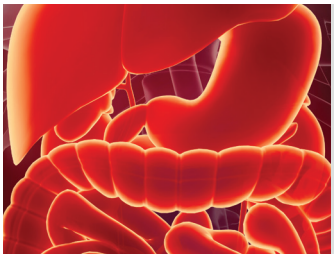
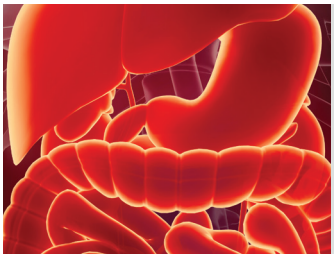


Updates in Medical Management of Obesity

Edwin McDonald, MD



Diarrhea and Enteropathies: Other Suspects

Carol Semrad, MD

THE UNIVERSITY OF CHICAGO MEDICINE
Digestive Diseases Center

Diarrhea and Enteropathies: Other Suspects

Carol E. Semrad, M.D.
Professor of Medicine
Director, Small Bowel Disease and Nutrition

Disclosure

- None

Diarrhea

- Due to many causes: Infection, Drug, Diet, Disease
- History most important for diagnosis
- Diarrhea, Gas/bloating, Weight loss, vit/min deficiencies
  - Think Small Bowel Enteropathy = villous atrophy

Diseases Associated with Villous Atrophy

Examples	Mechanism	Biopsy Specific?
Infections Giardia, Whipple, crypto	various organisms	yes
Celiac Disease	gluten	no
Tropical Sprue	? coliform bacteria	no
Agammaglobulinemia	lack of plasma cells	yes
Autoimmune GVHD	crypt apoptosis, no goblets crypt apoptosis	maybe
Drugs - olmesartan - mycophenolate - methotrexate - check point inhibitors	various	no

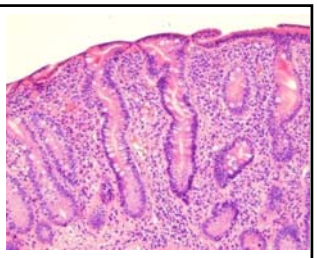
Case 1

- 59 y.o. Caucasian woman
- 6 mo watery diarrhea, bloating, nausea, vomiting
- 60 pound weight loss
- PMH: Obesity, no travel
- Medications: loperamide
- Laboratory Studies:
  - Hgb 10.9 g/dl
  - Alb 2.8, TP 5.2 g/dl
  - ALT 80 AST 60
  - Low folate, Fe, vitamin A, E, D
- Stool Studies for Infection: negative

Diagnosis and management

- Admitted to hospital for rapid evaluation
- Suspected Enteropathy
- Differential Diagnosis
  - Celiac Disease

- EGD: duodenal scalloping
  Duodenal Biopsy (4-5)
  - total villous atrophy
  - crypt hyperplasia
  - increased IELs
  - lymphoplasmacytic infiltrate



- TTG IgA >100 EMA Positive
- Diagnosis: Celiac Disease with Crisis
- Management
  - strict gluten-free diet
  - consider bridge with budesonide 9 mg OD
- Recovered

When to think about mimics of Celiac Disease?

- > 50 years of age
- Transplant
- Chemotherapy/checkpoint inhibitors
- Unusual histologic feature(s):
  - atrophy without increase IELs
  - crypt cell apoptosis
  - no plasma cells
- Poor response to a Gluten Free Diet

Case 2

- 74 y.o. Caucasian man
- 2 yrs of diarrhea with wt loss, dehydration
- EGD with duodenal scalloping
- Duodenal Bx: villous atrophy, increased IELs
- Told he had celiac disease
- No response to gluten free diet

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Review of Data

- Elderly man
- Diarrhea and weight loss to suggest enteropathy
- No celiac serologies sent prior to GFD
- Review of Medications: Olmesartan for HTN

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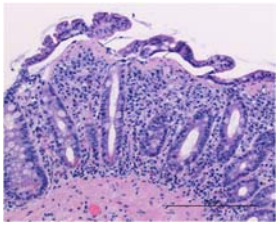
Digestive Diseases Center

Diagnosis and Management

- HLA D[illegible] negative

NOT CELIAC DISEASE

- Review of Duodenal biopsy:
  - villous atrophy
  - subepithelial collagen membrane
- Discontinued Olmesartan
- Diarrhea resolved, regained weight
- Gluten re-introduced into diet and tolerated



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Olmesartan Enteropathy

- Angiotensin II receptor antagonist (ARB)
- Older age group
- Presents as diarrhea, wt loss, 1-2 yrs after drug start
- Biopsy looks like CeD or Collagenous Sprue
- Negative Celiac Serologies
- Unresponsive to a gluten-free diet
- Accounts for 30% non-celiac villous atrophy
  - in retrospect called seronegative CeD
- Associated lymphocytic gastritis or colitis
- Resolves with drug removal

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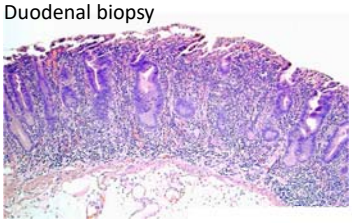
Digestive Diseases Center

Rubio-Tapia et al. Mayo Clin Proc 2012;87:732
DeGaetani et al. Am J Gastroenterol 2013;108:647
Marietta et al Dig Dis 2015;33:215

Case 3

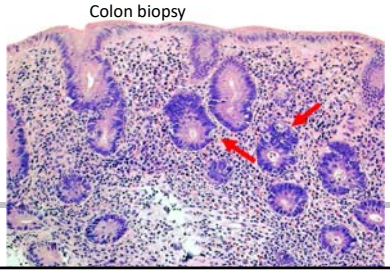
- 72 y.o. South American woman
- 2 yrs nausea, vomiting, diarrhea, wt loss
- PMH: Autoimmune hemolytic anemia
- Low Hgb, Alb, Total Protein
- EGD/Colonoscopy: villous atrophy, erosions TI
- TTG IgA negative, Total IgA normal.

Duodenal biopsy



Biopsy Findings:
- Villous atrophy
- Lack of goblet cells
- Crypt apoptosis

Colon biopsy



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Digestive Diseases Center

Autoimmune Enteropathy

- Rare
- Infants, elderly
- History other autoimmune diseases
- Diarrhea, weight loss
- Autoantibodies
  - Anti-Enterocyte
  - Anti-Goblet Cell
- May involve stomach and colon as well
- No response to a gluten free diet
- Usually requires immunosuppression
  - corticosteroids (budesonide, prednisone)
  - azathioprine, tacrolimus, cyclosporine
  - inflixamab
  - may require PN

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Digestive Diseases Center

Montalto et al. Scan J Gastroenterol 2009;44:1029

Case 4

- 39 y.o. Caucasian woman
- Chronic diarrhea, gas/bloating, wt loss
- PMH:
  - bronchitis
  - recurrent Sinusitis
- TTG IgA, EMA Negative; Total IgA < 5
- HLA DQ 2.5 Positive
- Stool O&P, Giardia/Crypto Ag Negative
- Started on a GFD for ? Celiac Disease without improvement
- Further wt loss

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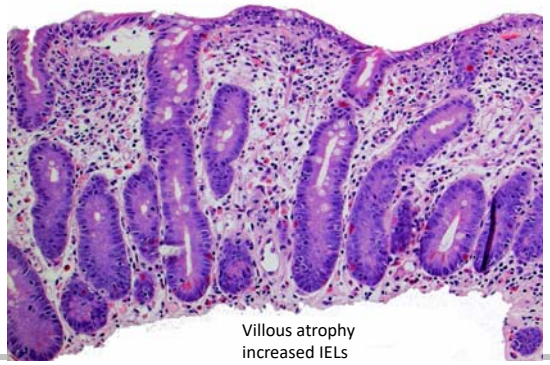
Review of Data

- Quantitative Immunoglobulins
  - IgG 359 (800-1700 mg/dl)
  - IgA < 5 undetectable
  - IgM 35 (60-370 mg/dl)

Duodenal Biopsy



Villous atrophy
increased IELs
no plasma cells

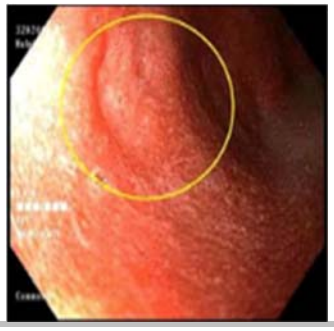
- Treatment: Started on PN and IVIG
- Decreased bronchitis, no improvement in diarrhea
- Failed:
  - oral bovine-derived Ig
  - budesonide, prednisone
- Currently on vedolizumab
  - maintaining weight off PN
  - decreased nocturnal diarrhea

When to think about mimics of IBD?

- > 60 years of age
- Stem cell or solid organ transplant patient
- Patient on chemotherapy/ checkpoint inhibitors
- Patient with proctitis only
- Unusual histologic feature(s)
  - crypt withering
  - crypt cell apoptosis
  - poorly developed chronic features
- Poor response to therapy for IBD (?)

John Hart, Pathology

65 yr old man with chronic diarrhea
On ipilimumab for metastatic melanoma



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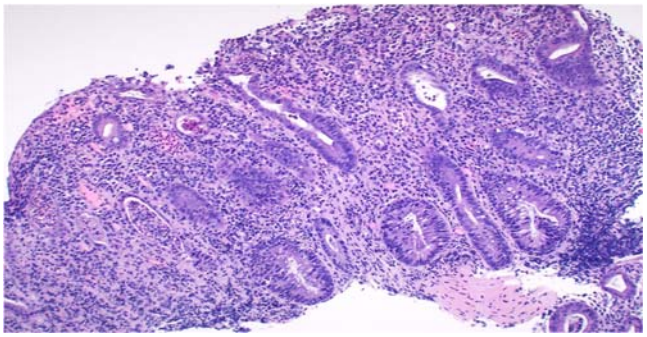

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Immune Checkpoint Inhibitors

- Augments immune response to tumor
  - Cytotoxic T-lymphocyte antigen-4 antibody (CTLA-4 inhibitor)
  - Programmed cell death protein antibody (anti-PD1)
- Side effect is impaired self-tolerance (autoimmune inflammation)
- GI toxicity common, up to 50% with diarrhea on dual therapy
- Occurs 5-10 weeks after therapy or months after stopping
- Loose stools to left-sided Colitis
  - Diagnosis by sigmoidoscopy
  - IBD like pathology
- Enteropathy less common
- Treatment
  - Grade 1 (mild diarrhea) consider drug hold, conservative care
  - Grade 2 (4-6 BMs) hold drug, steroid
  - Grade 3-4 (> 7 BMs, severe sxs) admit, stop drug, steroid

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Thompson et al. J Natl Compr Canc Netw 2019;17:255
Brahmer et al. J Clin Oncol 2018;17:1714
Spain et al Cancer Treat Rev 2016;44:51

Treatment Immune Check Point Inhibitor Related Colitis

Grade	Diarrhea	Hold Drug?	Treatment
1	Mild (< 4 BM/day)	consider	loperamide hydration
2	Moderate (4-6 BM/day)	yes	steroid Infliximab*
3-4	Severe symptoms (> 7 BM/day)	stop admit	IV steroid Infliximab* Vedolizumab#

*if no response 2-3 day
#if refractory to infliximab

Thompson et al. J Natl Compr Canc Netw 2019;17:255

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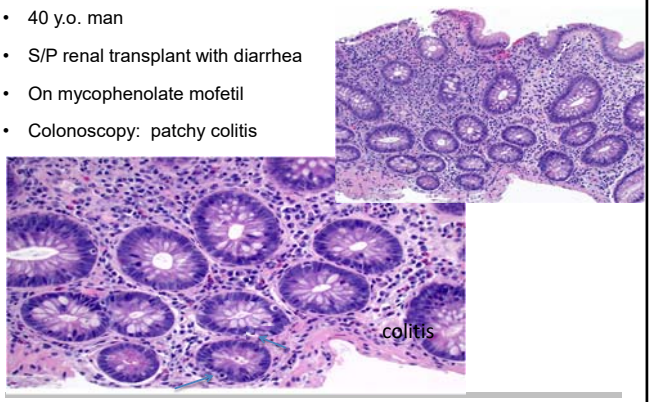
- 40 y.o. man
- S/P renal transplant with diarrhea
- On mycophenolate mofetil
- Colonoscopy: patchy colitis



Mycophenolate Mofetil

- Immunosuppressant used in solid organ transplant
- Diarrhea, nausea, vomiting
- GI Toxicity in up to 45% of renal transplant patients
- Usually occurs at doses 1-2 g/day
- Colitis most common with crypt apoptosis
- Enteropathy characterized by villous atrophy
  - without increase in IELs
  - crypt apoptosis
- Treatment is to decrease or stop drug

Filiopoulos et al Transplantation 2018;4e375
Karamchandani J Clin Pathol 2018;71:1033

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Enteropathies - Summary

- Presents with diarrhea, weight loss, vit/min deficiencies
- Many diseases and drugs cause villous atrophy
- Gastritis and colitis can be associated
- Celiac disease common
  - positive tTG IgA, EMA serology supports diagnosis
  - positive DGP IgG in those with IgA deficiency
- In elderly, think drug (olmesartan), autoimmune
- In transplant and cancer patients, think drug or GVHD
- Colitis common with check point inhibitor therapy
- When severe treat with steroids and stop drug

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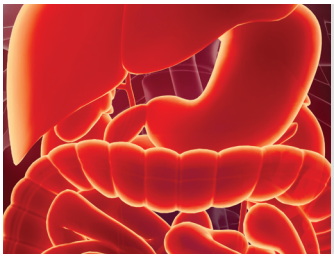


Acing the Boards: Foregut

Brennan Spiegel, MD, MSHS

Acing the GI Board Exam: Upper GI Vignettes

Brennan Spiegel, MD, MSHS

Cedars-Sinai Medical Center
Cedars-Sinai Center for Outcomes Research and Education (CS-CORE)

Disclosure Information

- I have the following financial relationships to disclose:
  - Advisory Board: Alnylum, Arena, Ferring, Ironwood, Salix, Shire, Takeda
  - Speaker's Bureau: None
  - Grants: appliedVR, Commonwealth Diagnostics, Alnylum, Ironwood, Samsung Electronics, Shire, Takeda, Traveler's Insurance
  - Royalties: SLACK Publishing
- I will not discuss off label use or investigational use in my presentation

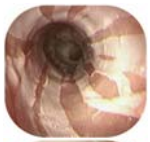
"Lizard Tongue"

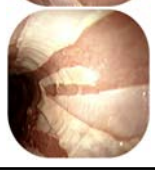
A 32-year-old male presents with history of recurrent vomiting. Describes a column of "fleshy tissue" that "snaps out of his mouth like a lizard's tongue" after vomiting, and then "snaps back in."

→ What is the diagnosis?

Weird Esophagus

A 52-year-old man with pemphigus vulgaris presents with chest pain and vomiting. He reports vomiting a long "white tube" of tissue. Upper endoscopy is performed. Representative images are shown.





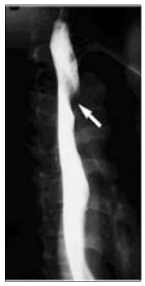
→What the heck is this?

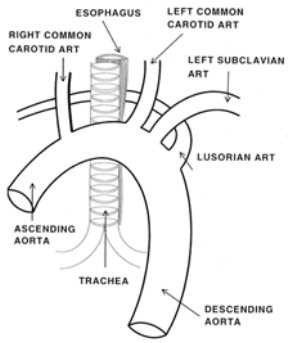
MOC Q#11

More Dysphagia

A 36-year-old, otherwise-healthy woman with a 6-year history of progressive dysphagia is referred to you for evaluation. Barium esophagram reveals an oblique defect at the upper thoracic level just above the aortic arch.

→ What is the most likely diagnosis?





Other GI Vascular Mini-Vignettes

Rapid weight loss, then nausea + vomiting + abrupt cutoff across third part of duodenum?

Sitophobia + postprandial epigastric pain + epigastric bruit + weight loss?

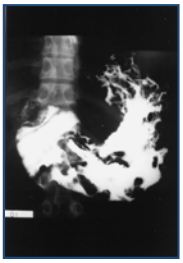
Pregnant cirrhotic patient has LUQ discomfort + bruit?

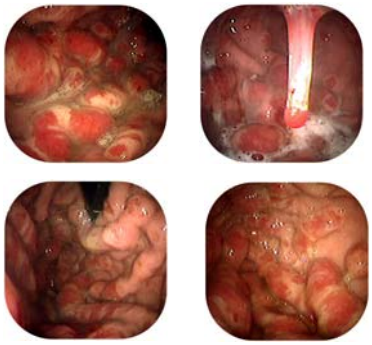
Weird Stomach

22 yo with dyspepsia, recurrent nausea and vomiting, progressive weight loss, and lower extremity edema. No fevers or LAD. Gastrin is 230, and increases to 300 with secretin stimulation test. Albumin is 2.7. UGIS is abnormal (pictured).

→ What is the diagnosis?

→ What specific abnormality may be seen on biopsy of the gastric body?





Images courtesy of Fred Weinstein

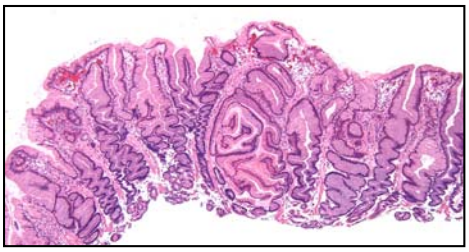
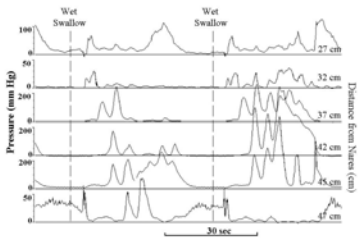
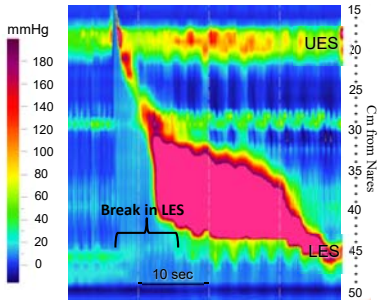


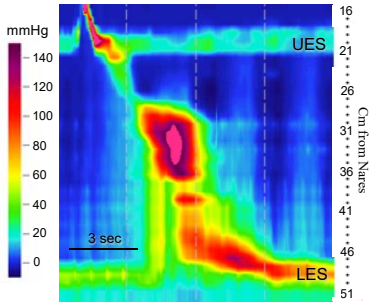
Image courtesy of Fred Weinstein

Old School Manometry



→ What is the diagnosis?

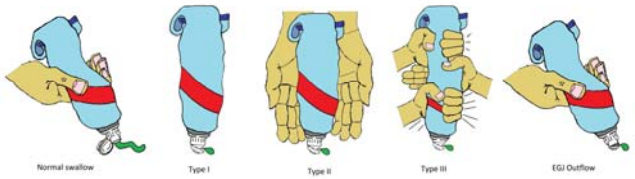




Chicago Classification of Achalasia

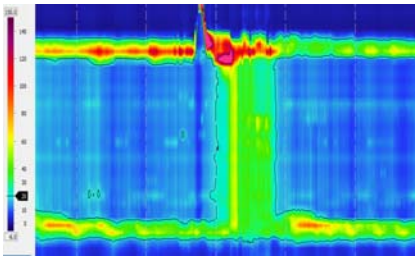
New Name	Old Name	Manometric Features	Treatment Notes
Type I	Classic achalasia	No esophageal pressurization	Intermediate chance of responding to treatment (44%)
Type II	N/A	Simultaneous isobaric pressurization across entire esophagus	Most likely to respond to treatments (80%); "early form" of achalasia
Type III	Vigorous / spastic achalasia	Lumen-obliterating contractions or spasms	Least likely to respond to treatments (9%)

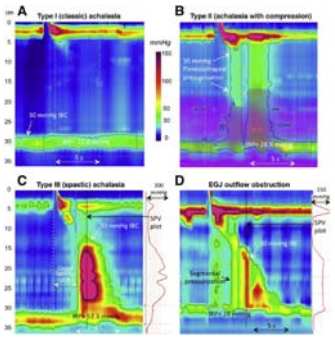
Types of Achalasia and EGJ Outflow



Courtesy of Jonathan Gotfried, MD

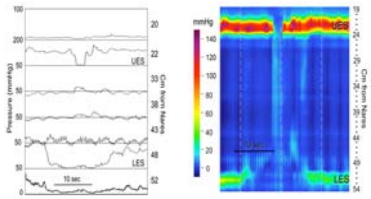
What Type is This?





More Manometry

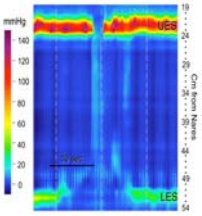
A 38 yo man with no significant PMH presents for evaluation of heartburn and regurgitation. He was managed with high-dose PPIs which helped the heartburn symptoms, but he continued to experience regurgitation of liquid and food into his throat multiple times per day. Esophageal manometry was performed to further evaluate the symptoms. A motor event occurred during the manometry, as pictured on both low-resolution (left panel) and high-resolution (right panel) tracings:



Continued…

In addition to continuing proton pump inhibitors for heartburn, which of the following additional medications may effectively treat this clinical and manometric presentation?

A. Nitroglycerin
B. Diltiazem
C. Ranitidine
D. Peppermint oil
E. Baclofen



"Thatched Roof Hut"

A 17-year-old girl, who is a recent immigrant from Mexico, presents with dysphagia for solids and liquids. The symptoms began three months ago. She recalls swelling around her left eye prior to the onset of symptoms. She had been living in a "thatched roof hut" in Mexico.

Which of the following is most likely to be seen on esophageal manometry:

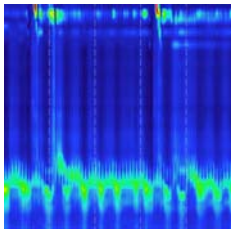
A. Hypertonic upper esophageal sphincter
B. Cricopharyngeal bar
C. Diffuse esophageal spasm
D. Inability of lower esophageal sphincter to relax with swallowing
E. Tonically elevated lower esophageal sphincter pressure

"Shawl Sign"

A 50-year-old woman presents with progressive dysphagia for solids and liquids. She has difficulty standing from a seated position, and describes a violaceous rash, like a "shawl," at the nape of her neck.

Which of the following is most likely to be seen on esophageal manometry?

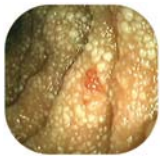
A. Hypertonic upper esophageal sphincter
B. Hypertensive peristalsis
C. Diffuse esophageal spasm
D. Inability LES to relax with swallowing
E. Diminished peristalsis of the proximal one-third of the esophagus

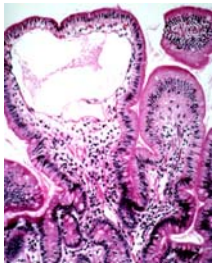


CHF and Duodenal Spots

A 72-year-old with Class III CHF referred for diarrhea. Symptoms began 6 months ago and coincided with worsening of heart failure. Over the last two months has intermittent nausea, vomiting, and diffuse abdominal fullness. Exam reveals bibasilar crackles, enlarged yet soft liver, hepatojugular reflux, and shifting dullness. There is 3+ LE pitting edema. No stigmata of chronic liver disease. Labs: Albumin=2.4; serum carotene=8; ALP=190; AST=99; ALT=85; INR=1.1. Enteroscopy reveals focal white spots throughout the visualized duodenum and jejunum.

→ What is the diagnosis?
→ What will biopsies show?





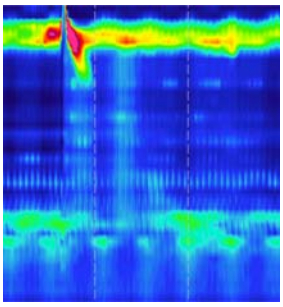
Courtesy of Fred Weinstein

"Megaduodenum"

A 32-year-old woman presents with progressive dysphagia, first for solids, then for solids and liquids. She has a "megaduodenum" on small bowel follow-through, and has recurrent bouts of small intestinal bacterial overgrowth.

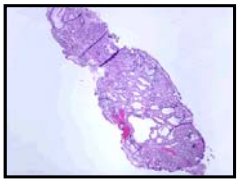
→ What is the diagnosis?

→ What will be seen on manometry?



Gastric Polyps

50-year-old man receiving chronic PPI therapy for GERD undergoes endoscopy for recurrent reflux symptoms. There are 5 polyps in the mid-body, greater curve, but no polyps in the antrum. Biopsy of the polyps reveals the histology pictured below.

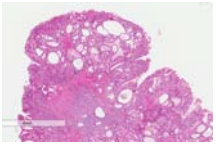


→ What is the diagnosis?

Gastric Polyps

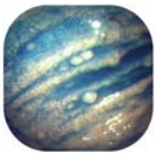
20 yo has dyspepsia. You perform an EGD which reveals ~30 diminutive polyps in the gastric cardia, body, and antrum. A few similar lesions are found in the proximal duodenum. You biopsy many of these lesions and the histology is shown in the figure. What would you recommend at this point?

A. Discontinue the omeprazole and EGD in 6 months.
B. Annual gastric surveillance
C. Colonoscopy
D. Repeat EGD with removal of any lesion greater than 5 mm in size.



Bumps in the Stomach

A 52-year-old woman with Hashimoto's thyroiditis, now with dyspepsia, is referred to rule out Zollinger Ellison Syndrome because her gastrin is 1450. Endoscopy reveals no ulcers, and identifies these lesions in gastric body upon staining with indigo carmine.



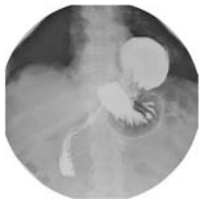
→ What are these lesions?
→ What is her underlying diagnosis?

Gastric Disastric

A 63 yo woman presents to the ED with severe abdominal pain. She reports 4 days of recurrent vomiting prior to finally presenting for care, culminating in 3 hours of intense pain and retching, but an inability to vomit. An NGT is placed through the nares but cannot be advanced beyond 30 cm. Vital signs: RR=18, HR=110, Temp=99.3, BP=132/88. Exam reveals epigastric tenderness but no rebound or guarding. The liver and spleen are not enlarged. Labs reveal WBC=14.2, Hgb=12.9, Platelet=321. Electrolytes are unremarkable.

Continued…

Review of the patient's medical record reveals she had recurrent nausea and vomiting 6 months prior, and a barium upper gastrointestinal series was performed as an outpatient, as pictured. What is the most appropriate next step to manage this patient's current presentation?



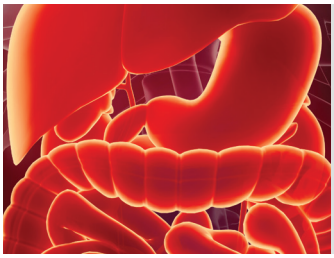
A. Upper endoscopy with attempted decompression
B. Re-attempt placement of a nasogastric tube
C. Admit for close observation and intravenous fluids
D. Surgical consultation
E. Percutaneous endoscopic gastrostomy (PEG) tube for gastric fixation

Rapid Buzzword Review

Dysphagia + thatched roof hut → ?
Weird white strips in esophagus → ?
Dysphagia + "megaduodenum" → ?
Dysphagia + oblique defect across esophagus → ?
What medicine inhibits TLESRs? → ?
Dysphagia + Gottron nodules? → ?
Crazy lizard tongue → ?

Rapid Buzzword Review

NET missed by scintigraphy → ?
High gastrin and Hashimoto's → ?
High gastrin and foveolar hyperplasia → ?
Fundic gland polyposis without PPIs → ?
CHF and white spots in SI → ?
Antral mass with central umbilication → ?
Retching, no vomiting, can't pass NGT → ?



Pancreatic Cancer Screening

Sonia Kupfer, MD

AT THE FOREFRONT
UChicago Medicine

Pancreatic Cancer Screening

Sonia Kupfer, MD
Director, GI Cancer Risk & Prevention Clinic

September 21, 2019

1

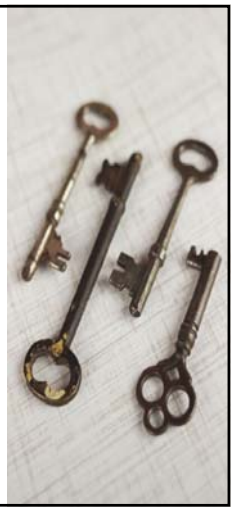
Disclosures

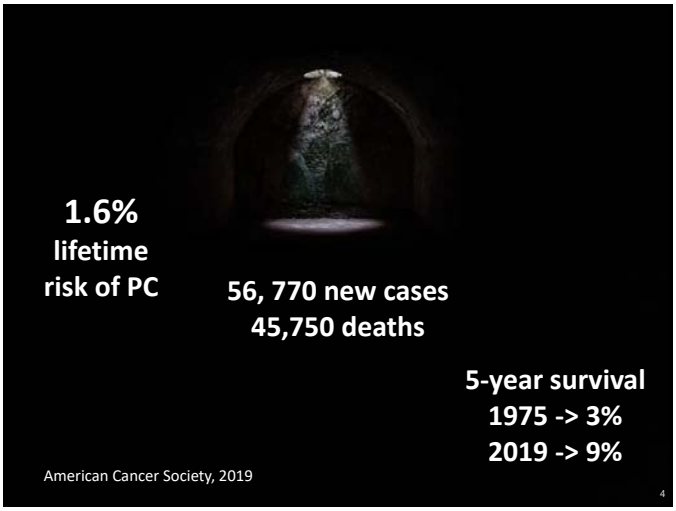
Clinical trial with Immunovia

2

Key points

- ✓ Deadly disease
- ✓ High-risk populations
- ✓ Screening outcomes good





U.S. Preventive Services TASK FORCE

Recommends <u>against</u> PC screening in asymptomatic individuals at average risk

JAMA, August 6, 2019

High-risk populations

- Peutz-Jeghers
- Hereditary pancreatitis
- FAMMM
- Familial pancreatic cancer
- Lynch syndrome
- Familial breast & ovarian cancer
- Familial adenomatous polyposis

Risk estimates

Syndrome	Gene	Relative risk
Peutz-Jeghers	*STK11*	132x
Hereditary pancreatitis	*PRSS1*	53x
Familial atypical multiple mole & melanoma (FAMMM)	*CDKN2A*	13-40x

Syngal et al *Am J Gastro* 2015

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Familial pancreatic cancer	Unknown	4-7x (2 FDR) 17-32x (> 2 FDR)

Syngal et al *Am J Gastro* 2015

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Familial pancreatic cancer	Unknown	4-7x (2 FDR) 17-32x (> 2 FDR)
Lynch syndrome	*MLH1, MSH2, MSH6*	9-11x
Familial breast & ovarian cancer	*BRCA1, BRCA2, PALB2, ATM*	2-9x
Familial adenomatous polyposis (FAP)	*APC*	5x

Syngal et al *Am J Gastro* 2015

When to start screening?

- Peutz-Jeghers syndrome — age 35*
- FAMMM — age 50*
- Familial pancreatic cancer — age 50*

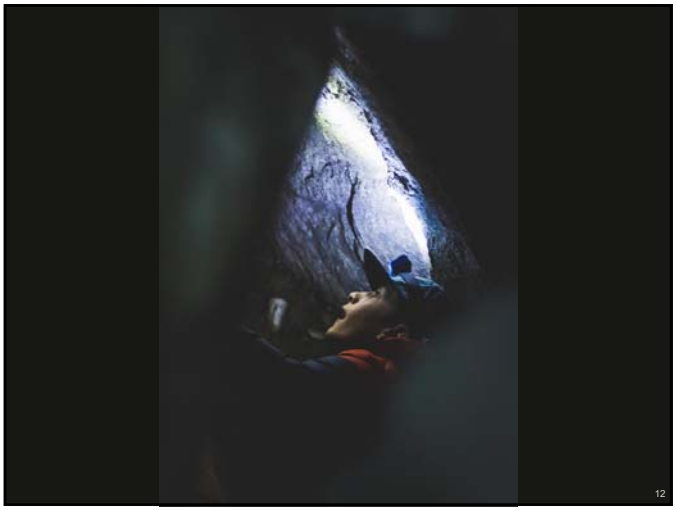
With 1 first-degree relative w/ PC:

- Lynch, breast/ovarian, FAP — age 50*
- Hereditary pancreatitis** — age 40*

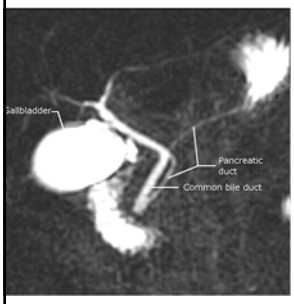
*or 10 years earlier than youngest PC in family
** with history of pancreatitis

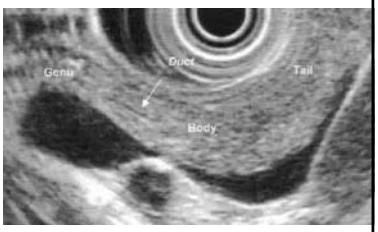
Canto M et al *Gut* 2013

New in 2019:
Genetic testing of <u>all</u> pancreatic cancer patients



Screening modalities





Harinck et al *Gut* 2016
Canto M et al *Gut* 2013

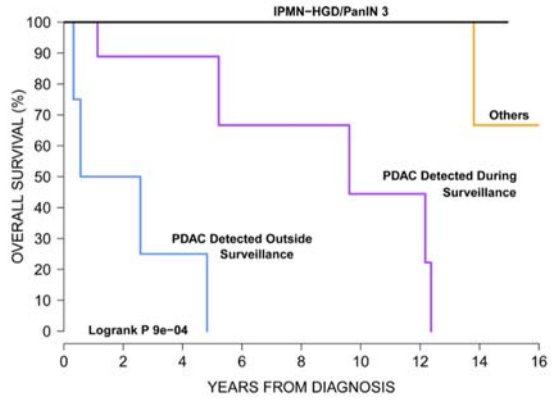
Screening studies

- 411 high-risk individuals
  - 178 *CDKN2A* carriers
- 7% of *CDKN2A* carriers w/ PC
- 75% resection rate
- 24% 5-year survival

Vasen H et al *J Clin Onc* 2016

- 354 high-risk individuals
  - Mostly familial, some mutations
- 3.4% w/ PC
- 3% w/ IPMN-HGD or PanIN-3
- 90% resection rate
- 85% 3-year survival

Canto M et al *Gastroenterol* 2018



Canto M et al *Gastroenterol* 2018

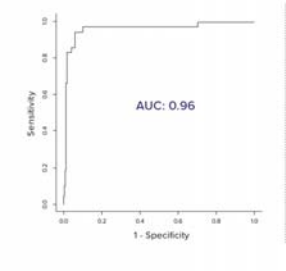
Encouraging outcomes for screening

Screen a lot of people; find a few cancers & a lot of low risk cysts

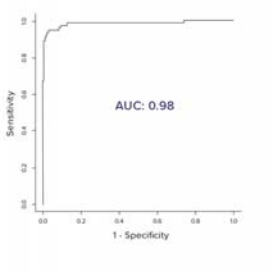
Better risk stratification needed

New immune-based biomarkers

STAGE I/II



STAGE III/IV

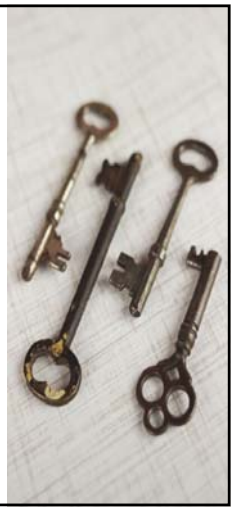


Mellby L et al *J Clin Onc* 2018

immunovia

Key points

- ✓ Deadly disease
- ✓ High-risk populations
- ✓ Screening outcomes good
  *but we have to screen a lot of people to find high-risk lesions
- ✓ *Current clinical trial at UCM to test immune-based biomarkers*



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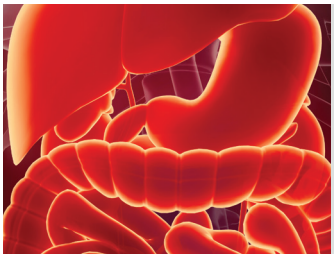
Thank You

skupfer@medicine.bsd.uchicago.edu



Genetic Testing for GI Cancers and Pancreatitis in 2019

Jessica Stoll, MS, CGC

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Genetic Testing for GI Cancers and Pancreatitis: 2019 Update

Jessica Stoll, MS, CGC
Certified Genetic Counselor
Associate Director, GI Cancer Risk and Prevention Clinic

September 21st, 2019

Disclosure Information

- I have the following relationships to disclose:
  - Genetic Counselor Advisory Board for Invitae
- I will not discuss off label use or investigational use in my presentation

Outline

- Hereditary GI cancer syndromes
- Approach to genetic testing for GI cancer syndromes
- Interpretation of genetic testing results

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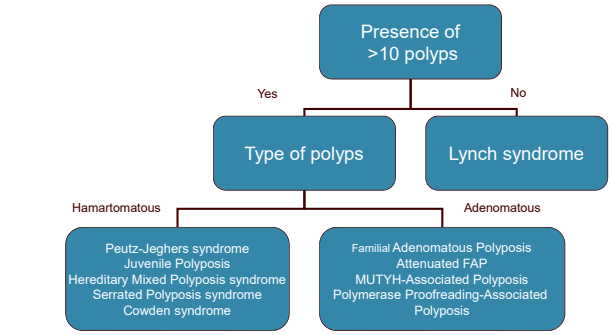
Genetics of Hereditary Gastrointestinal Cancers and Pancreatitis

Hereditary Colorectal Cancer/Polyposis



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Hereditary Gastric Cancer

- 1-3% of gastric cancer is familial/hereditary
  - Intestinal vs. diffuse type
- Genetics of gastric cancer:
  - Hereditary diffuse gastric cancer (HDGC)
    - *CDH1*: accounts for 30-50% of all HDGC cases
    - *CTNNA1:* few families identified; exact risk unknown
  - Lynch syndrome
    - *MLH1, MSH2, MSH6, PMS2, EPCAM*
  - Polyposis
    - Familial adenomatous polyposis: *APC, MUTYH*
    - Juvenile polyposis syndrome: *SMAD4, BMPR1A*
  - Hereditary breast and ovarian cancer syndrome
    - *BRCA1/2*
  - Others

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Hereditary Pancreatic Cancer

- ~10% of pancreatic cancer is hereditary
  - **Genetic testing for all pancreatic cancers (NCCN 2.2019)**
- Common syndromes associated with pancreatic cancer:
  - Hereditary breast and ovarian cancer syndrome (HBOC)
    - Mutations in *BRCA1/2*
    - Up to 7% risk of pancreatic cancer (w/ *BRCA2*)
  - *PALB2*
    - Breast and pancreatic cancer
    - Exact risk estimates unknown
  - Familial atypical multiple mole melanoma (FAMMM)
    - Mutations in *CDKN2A*
    - High risk of melanoma (~90%), up to 17% risk of pancreatic cancer
  - Others: Peutz-Jeghers syndrome, Lynch syndrome, FAP, *ATM*

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Hereditary Pancreatitis

- Two or more individuals with pancreatitis in two or more generations of a family OR
- Pancreatitis due to a gene mutation
  - *PRSS1*
  - *SPINK1*
  - *CTRC*
  - *CFTR* (also causes cystic fibrosis)
  - *CASR*
- Usually begins in childhood
- Autosomal dominant inheritance
- Increased risk of pancreatic cancer:
  - 50x increased risk
  - 40% by age 70

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Indications for Genetic Testing or Genetics Referral

- Personal history of early onset cancer diagnosis (<50 years)
- Personal history of bilateral or multiple cancers
- Abnormal tumor testing
  - Immunohistochemistry or MSI for MMR deficiency
  - Tumor gene sequencing
- GI polyposis (10+ colon polyps)

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Indications for Genetic Testing or Genetics Referral (continued)

- Family history of cancer
  - Early onset
  - Multiple or bilateral cancers
  - Related cancers (i.e. colorectal and endometrial, pancreatic and breast)
  - Multiple generations with cancer
- Pancreatitis
  - Idiopathic chronic or recurrent acute pancreatitis (particularly if early onset)
  - Family history of pancreatitis +/- pancreatic cancer
  - Personal or family history of cystic fibrosis, male infertility, chronic sinusitis, nasal polyps, diabetes, and/or exocrine insufficiency

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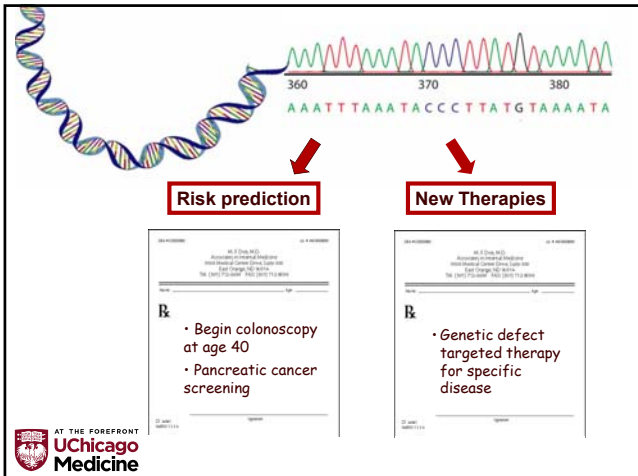
Approach to Testing for Gastrointestinal Cancers



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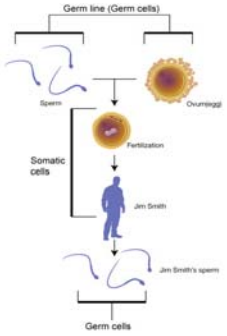
Somatic vs. Germline Genetics

Germline Mutations	Somatic Mutations
• Germ cells (egg or sperm) • Inherited • Present at conception • Present in every cell in the body • Can be passed from generation to generation	• Acquired • Arise by chance in any cell of the body • Cannot be passed from generation to generation



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Germline Genetic Testing Options

Testing Option	Description
Multigene panel	• Tests multiple genes simultaneously • Tests for multiple hereditary cancer syndromes at once
Single Gene(s)	• Tests 1-2 genes • Tests for a single hereditary cancer syndrome
Single Site (Known familial mutation)	• Tests for specific mutation identified in another family member
Founder Mutation Panel	• Tests for specific sites commonly mutated in certain high-risk populations (ex. Ashkenazi Jewish 3-site BRCA1/2 panel)

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Multigene Panel Testing

- Next-generation sequencing (NGS):
  High-throughput sequencing technology that allows for rapid analysis of multiple genes at once
  - Benefits:
    - Cost-effective
    - Time-saving
  - Challenges:
    - Variants of uncertain significance
    - Moderate penetrance genes/genes with limited information
    - Multiple pathogenic mutations in different genes
- Types of multigene panels:
  - Pan-cancer panels (25-80 genes)
  - Cancer site specific panels (ex. Breast cancer panel)
  - Guidelines-based panels
  - High/moderate risk panels

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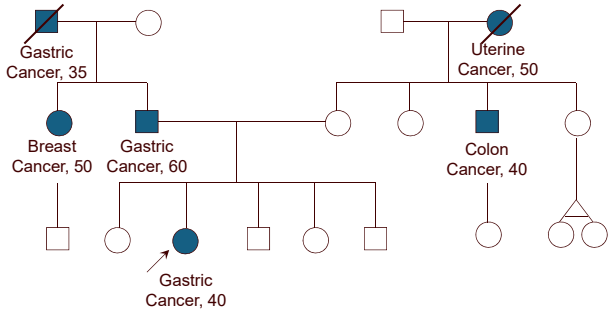
Gene Panel Testing



- Multiple types of cancers
- Multiple possible syndromes
- Cancer on both sides of the family

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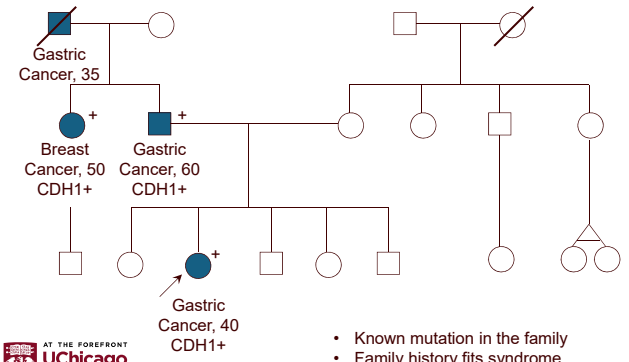
Single Site Testing – Familial Mutation

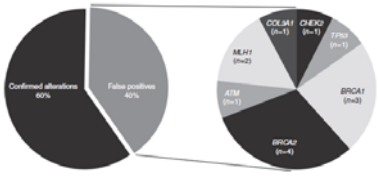


- Known mutation in the family
- Family history fits syndrome
- No cancer on opposite side of family

Direct to Consumer Testing

- Different technology than clinical testing
- May or may not identify all genetic mutations associated with disease
- Possibility of false positive and false negative results

False Positive Calls from DTC Testing



40% false positive calls in clinically actionable genes

8 "increased risk" alterations classified as "benign" by Ambry

Table 3 Classification discrepancies

Gene	Variant	DTC/third party[a]	Ambry[b]	ClinVar[c]
ATM	p.M1040V (c.3118A>G)	Increased risk	Benign	Benign
BRCA1	p.Q356R (c.1067A>G)	Increased risk	Benign	Benign
BRCA2	p.N372H (c.1114A>C)	Increased risk	Benign	Benign
COL3A1	p.A698T (c.2092G>A)	Increased risk	Benign	Benign
COL5A1	c.655-8689C>T	Increased risk	Deep intronic—benign	N/A
COL5A1	c.654+2749A>G	Increased risk	Deep intronic—benign	N/A
COL5A1	c.1827+399C>T	Increased risk	Deep intronic—VUS	N/A
COL5A1	c.1827+1142T>C	Increased risk	Deep intronic—benign	N/A

Tandy-Conner S, *et al* Genet Med 2018

DTC Testing: Take Home Points

- Variability in DTC genetic testing methods/technology
- Raw data/third party interpretation limitations:
  - Lots of information, but not diagnostic
  - Not comprehensive
  - False positive calls/inaccurate interpretations
- Clinical confirmatory testing of DTC raw data alterations strongly recommended
  - Patients should be seen by a qualified HCP

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Interpretation of Genetic Testing Results

Possible Germline Genetic Test Results

Positive —*Pathogenic mutation identified*→ Increased cancer risk

Negative —*No mutations identified (benign variants/polymorphisms typically not reported)*→ Cancer risk based on personal/family history

VUS —*VUS*→ Cancer risk not yet known
(Variant of Uncertain Significance)

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Positive: Pathogenic Mutation

- Harmful mutation identified
- Increased risk for one or more types of cancer
- Allows for family member testing

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Negative: No mutations detected

- Does not eliminate increased risk for family members
- Based on currently available information about cancer genetics

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VUS: Variant of Uncertain Significance

- Unclear if variant is associated with increased risk for cancer
- Typically do NOT offer family members testing
- Family members may still be at increased risk of cancer
- May be eligible for family variant studies

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Benefits of Genetic Testing

- May provide a more specific cancer risk
- May provide an "answer" for families
- May decrease cancer anxiety
- Impact on family

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Limitations/Risks of Genetic Testing

- Interpretation of results
- Implications for family members
- Cost/insurance coverage
- Increase in anxiety
- Concerns about genetic discrimination

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GINA: Genetic Information Nondiscrimination Act

- Prohibits discrimination by **health insurance companies** and **employers** based on "genetic information"
- Does NOT apply to life, disability, or long-term care insurance

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Conclusions

- Genetic testing may help define risk of cancer in families
- Many genes/syndromes that involve gastrointestinal cancer risk
- Multiple approaches to genetic testing
- Results of genetic testing must be interpreted carefully

Thank you!

Questions?

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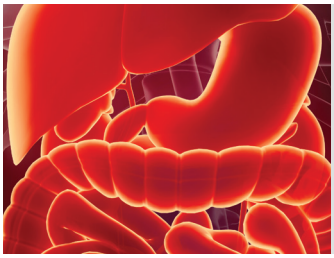

Robotic Surgery for GI Cancers

Kiran Turaga, MD, MPH

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Robotic Surgery for GI Cancers

Kiran K. Turaga MD MPH FACS

Vice Chief of General Surgery and Surgical Oncology

Program Director, Complex General Surgical Oncology Fellowship

1

Disclosures

- None
- I will not discuss off label use or investigational use in my presentation. But…

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2

U.S. FOOD & DRUG ADMINISTRATION

Home / Medical Devices / Medical Device Safety / Safety Communications / Caution When Using Robotically-Assisted Surgical Devices in Women's Health including Mastectomy and Other Cancer-Related Surgeries: FDA Safety Communication

Caution When Using Robotically-Assisted Surgical Devices in Women's Health including Mastectomy and Other Cancer-Related Surgeries: FDA Safety Communication

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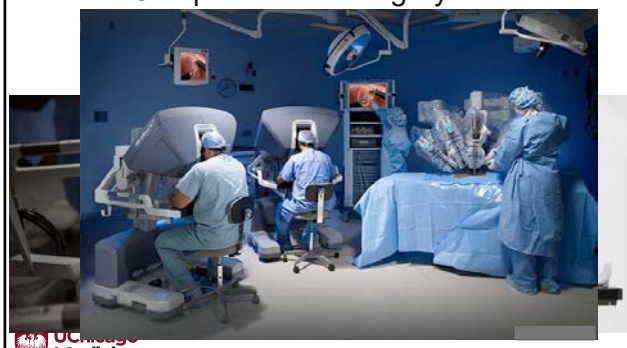
3

What is robotic surgery?

- Computer aided surgery



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www.aarp.org

www.intuitive.com

4

Robotic Surgery

PROS	CONS
Flexibility of instruments/Articulation	Lack of haptic feedback
Intuitive adoption	Expensive
Extends ability to perform MIS surgery	Technical Proficiency
Reduces tremors	Limited Data
Ergonomic	Initial experience for complex surgery requires two proficient surgeons*
Magnification	Long Learning curve
Precision	Not widely available/Large footprint
Allows for learning/reproduction/standardization	Industry monopoly*

Questions in 2019

- How is it better than laparoscopic surgery?
- How does it compare to open surgery for oncological outcomes?

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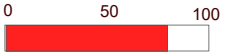
Site	Technical Advantage Over Laparoscopic	Short Term/ Patient Reported Superiority over Open	Oncological Non-inferiority	Cost
Esophagus	-Thoracic anastomosis -Three field lymphadenectomy	Yes	Yes	More
Stomach	-Lymphadenectomy -Anastomosis	Shorter LOS	Weak evidence	More
Liver	-Biliary visualization -Better retraction	Yes but weak data	Absent data	More
Pancreaticoduodenectomy	-Anastomosis -SMV dissection	Partially	Weak evidence Sooner Adjuvant	Equivalent or cheaper with ERAS

Site	Technical Advantage Over Laparoscopic	Short Term/ Patient Reported Superiority over Open	Oncological Non-inferiority	Cost
Distal Pancreas	-Splenic Preservation	Partially	Not Proven	More
Colectomy	-Complete mesocolic excision	Partially	Not Proven	More
Rectal Resection	-Transanal approaches -Complete excision	Partially	2 trials suggest yes, 2 suggest no	More

8

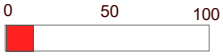
Esophagus



RCT, Single center, proctors

Outcome Measure (N=112)	Robotic Esophagectomy (N=56)	Open Esophagectomy (N=56)
Post Operative Complications	59%	80%
Pulmonary	RR 0.54 (0.34-0.85)	
Quality of Life at 6 weeks	Mean difference 11.1(1,0-21.1)	
Operating Time	349 minutes	296 minutes
Overall Survival	Not reached, but similar at 40 months	
DFS	26 months	28 months

Esophagus



Multiple centers

Outcome Measure (N=207)	Hybrid Esophagectomy (N=103)	Open Esophagectomy (N=104)
Post Operative Complications	36%	64%
Pulmonary	18%	30%
Quality of Life at 6 weeks		
Operating Time	327 minutes	330 minutes
Overall Survival	52.2 months	47.6 months
DFS	57% at 3 years	48% at 3 years

Esophagus

RCT, Multiple centers

Outcome Measure (N=115)	Minimally Invasive Esophagectomy (N=59)	Open Esophagectomy (N=56)
Post Operative Complications		
Pulmonary	12%	34%
Quality of Life at 6 weeks	Better	
Operating Time	326 minutes	295 minutes
Overall Survival	42.9% at 3 years	41.2% at 3 years
DFS	42.9% at 3 years	37.3% at 3 years

Esophagus Learning Curve

Outcome	Cases
Lymph Node Retrieval	30
Vocal Cord Palsy	60
Anastomotic Leak	80

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Esophagus Summary

- Robotic surgery is equivalent to open surgery for oncological and superior for short term post operative outcomes.
- MIE vs Robotic Esophagectomy benefit unknown.

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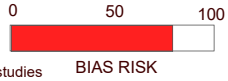
Gastric



Meta-analysis, 37 observational studies

Outcome Measure (N=5953)	Robotic Gastrectomy (N=1830)	Laparoscopic Gastrectomy (N=4123)
Post Operative Complications	RR=0.96(0.82-1.13)	
Cost	$ 3944(4943, 2946)	
Operating Time	49 minutes(58, 39.9)	
Overall Survival* (largest study)	85% at 3 years	78% at 3 years
DFS	No difference but poorly reported	

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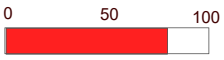
Chen Ke BMC Surgery 93:2017

Gastric



Meta-analysis, 13 trials

Outcome Measure (N=2794)	Laparoscopic Gastrectomy (N=1288)	Open Gastrectomy (N=1244)
Post Operative Complications	16.1% at 3 months	20.7% at 3 months
Number of Lymph Nodes	MD 0.63 (-1.5, 0.25)	
Length of Hospital Stay	-1.82 days (-3.72, 0.07)	
Overall Survival* (largest study)	HR 0.94(0.70-1.25)	
DFS	HR 0.95 (0.7-1.30)	

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Best LM Cochrane Database Syst Rev 2016 Mar 31;3

Gastric Learning Curve

Outcome	Cases
Proficiency	25
Mastery	48

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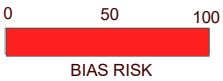
Kim MS Ann Surg 2019 Sep 9

Gastric Summary

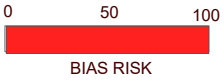
- Robotic gastrectomy appears equivalent to laparoscopic gastrectomy and superior to open gastrectomy in short term outcomes.
- Oncological outcomes have not been adequately studied but appear similar.

Hepatic Resection



- INTERNATIONAL CONSENSUS STATEMENT ON ROBOTIC HEPATIC SURGERY IN 2018
- Recommendation 1: Robotic hepatectomy is as safe and feasible as traditional open hepatectomy.
- Robotic hepatectomy has longer operative time, less intraoperative blood loss, less length of hospital stays, lower complication rate and lower severe complication rate.
- The intraoperative blood loss of robotic hepatectomy is comparable to that of open hepatectomy.
- ***The level of evidence: low. Level of recommendation: Weak (Grade 2C)***

Hepatic Resection



- Recommendation 2: Robotic hepatectomy has similar effectiveness for liver malignancy lesion compared to open hepatectomy. Regarding the oncological outcome there is no significant difference in the radical resection rate, overall survival rate and recurrence rate between robotic hepatectomy and open hepatectomy.
- ***Level of recommendation: Very low.***
- ***Level of recommendation: Weak (Grade 2D)***

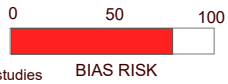
Hepatectomy Learning Curve

Outcome	Cases
Initial	15
Intermediate	25
Mature	52

Hepatectomy Summary

- Too little good quality data to recommend for or against a robotic hepatectomy.

Pancreaticoduodenectomy

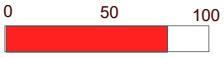


Meta-analysis, 44 observational studies

Outcome Measure (N=3462)	Robotic PD (N=1025)	Laparoscopic PD (N=2437)
Post Operative Complications	48%	47%
All Pancreatic fistula Rates	19%	19%
Operating Time	465(413-518)	417(389-445)
Overall Survival* (largest study)	Not Studied	
DFS	Not Studied	

Kamarajah S EJSO Aug 2019

Pancreaticoduodenectomy



Multi-institutional Observational

Outcome Measure (N=1028)	Robotic PD (N=211)	Open PD (N=817)
Post Operative Complications	23.7	23.87
Pancreatic B/C fistula Rates	13.7%	9%
Operating Time	75.4 minutes Longer (17.5-133)	
R1 margins	50%	31%
Lymph Node harvest	27.5	19
Time to Adjuvant Chemotherapy	Sooner	
LOS	Shorter	
Costs with ERAS Protocol		OR High Cost 1.53 (0.68-3.4)

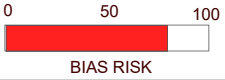
Zureikat Ann Surg 264(4): 640-649

Pancreaticoduodenectomy Learning Curve

Outcome	Cases
Conversions and Blood Loss	20
Pancreatic Fistula	40
Operative Time	80

Boone BA JAMA Surg 2015 May; 150(5): 416-22

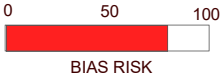
Distal Pancreatectomy



Multi-institutional Observational

Outcome Measure (N=1212)	Minimally Invasive DP (N=340)	Open DP (N=340, propensity matched)
Conversion rate	19%	
Hospital LOS	8 (6-12)	9(7-14)
Complications	18%	21%
Operating Time	239 min	240 min
Lymph Node harvest	14 (8-22)	18(11-28)
R0 resection	67%	60%
Adjuvant Chemotherapy	74%	73%
Time to starting chemotherapy	54 days	57 days
Overall Survival	28 (22-34 months)	31(26-36 months)

Distal Pancreatectomy



NETWORK META-ANALYSIS

The results of the present study demonstrate that reduced blood losses and shorter length of stay are the advantages of RDP and LDP compared to ODP. However, demographic discrepancies, underpowered RDP sample and differences in oncological burden do not permit certain conclusions regarding the oncological safety of RDP and LDP for pancreatic adenocarcinoma.

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Distal Pancreatectomy

Minimally invasive distal pancreatectomy reduces LOS, blood loss. Oncological equivalence is yet to be proven. Robotic DP form a small percentage of MIDP but may have technical superiority in splenic preservation.

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Distal Pancreatectomy Learning Curve

Outcome	Cases
Operative Time reduction	20
Readmission reduction	40

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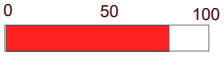
Colon Resection



Premier Perspective Database

Outcome Measure (N=36,701)	Robotic Colo-Rectal (N=3918)	Laparoscopic Colorectal (N=32783)
Conversion to Open	4.7%	3.7%
Hospital LOS	6	5 (NS)
Wound Infection	2.3	4.7
Cost	$1402-2698	

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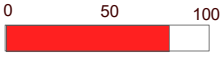
Al-Mazrou J Gastr Surg 2018 22 (6): 1043-51

Colon Resection



NSQIP Database

Outcome Measure (N=17774)	Robotic Colectomy (N=653)	Laparoscopic Colectomy (N=11267)
Conversion to Open	10.3	12.2
Hospital LOS	5	6
Anastomotic Leak	3.4	3.1

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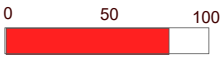
Miller PE J Am Coll Surg 2016 Aug 223 (2): 369-73

Colon Resection



Systematic Review

Outcome Measure (N=4072)	Robotic Right Hemicolectomy (N=831)	Laparoscopic Right Hemicolectomy (N=3241)
Conversion to Open	0-3.9%	0-18%
Positive Margin	0	0.9%
LOS	4-8.5	4.5-9
Incisional Hernia	0-17%	2.5-22%
Complications	10-32%	7-36%

Medicine

Waters PS Colorectal Dis 2019 Aug 10

Robotic Colon Resection Learning Curve

Outcome	Cases
Phase I	44
Phase II	90
Proficiency	>90

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Parisi A Surg Oncol 2017 Mar 26 (1): 28-36

Rectal Resection

Multicenter RCT

Outcome Measure (N=462)	Laparoscopic Rectal (N=240)	Open Rectal (N=222)
Successful resection	81.7% (76.8-86.6)	86.9%(82.5-91.4)
Hospital LOS	7.3	7
Complications	22.5%	22.1%
Operating Time	266 min	220 min
Negative Circumferential Margin	87.9%	92.3%

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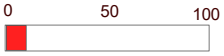
Rectal Resection



Multicenter RCT

Outcome Measure (N=1044)	Laparoscopic Rectal (N=699)	Open Rectal (N=345)
Locoregional Recurrence	5.0%	5.0%
DFS	74.8% at 3 years	70.8% at 3 years
OS	86.7% at 3 years	83.6% at 3 years

Similar Inference from COREAN Trial

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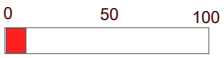
Rectal Resection



Multicenter RCT

Outcome Measure (N=471)	Robotic Rectal (N=237)	Laparoscopic Rectal (N=234)
Conversion to laparotomy	8.1%	12.2%
Circumferential Margin +	5.1	6.3
Intra and Post op Complications, plane of surgery, bladder and sexual dysfunction	NO DIFFERENCE	
Cost	$13688	$12556

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Robotic Rectal Resection Learning Curve

Outcome	Cases
Phase I	<20
Phase II	20-78
Proficiency	>78

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Robotic Rectal Resection Summary

Robotic surgery is no different from laparoscopic surgery which may be equivalent in oncological outcomes to open surgery.

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Site	Technical Advantage Over Laparoscopic	Short Term/ Patient Reported Superiority over Open	Oncological Non-inferiority	Cost
Esophagus	-Thoracic anastomosis -Three field lymphadenectomy	Yes	Yes	More
Stomach	-Lymphadenectomy -Anastomosis	Shorter LOS	Weak evidence	More
Liver	-Biliary visualization -Better retraction	Yes but weak data	Absent data	More
Pancreaticoduodenectomy	-Anastomosis -SMV dissection	Partially	Weak evidence Sooner Adjuvant	Equivalent or cheaper with ERAS

Site	Technical Advantage Over Laparoscopic	Short Term/ Patient Reported Superiority over Open	Oncological Non-inferiority	Cost
Distal Pancreas	-Splenic Preservation	Partially	Not Proven	More
Colectomy	-Complete mesocolic excision	Partially	Not Proven	More
Rectal Resection	-Transanal approaches -Complete excision	Partially	2 trials suggest yes, 2 suggest no	More

Comment

Adoption of new technology offers surgeons and patients an opportunity for improving short and long term outcomes.

Rigorous study of these technologies remain critically important.

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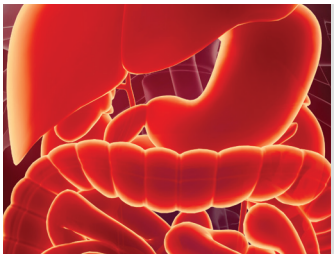


Acing the Boards: Lower GI

Brennan Spiegel, MD, MSHS

Acing the GI Board Exam: Midgut and Hindgut Vignettes

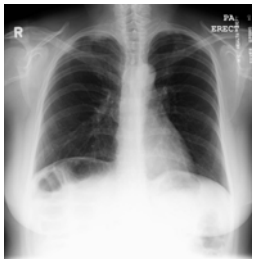
Brennan Spiegel, MD, MSHS

Cedars-Sinai Medical Center
Cedars-Sinai Center for Outcomes Research and Education (CS-CORE)

Disclosure Information

- I have the following financial relationships to disclose:
  - Advisory Board: Alnylum, Arena, Ferring, Ironwood, Salix, Shire, Takeda
  - Speaker's Bureau: None
  - Grants: appliedVR, Commonwealth Diagnostics, Alnylum, Ironwood, Samsung Electronics, Shire, Takeda, Traveler's Insurance
  - Royalties: SLACK Publishing
- I will not discuss off label use or investigational use in my presentation

A patient with COPD and three months of right upper quadrant abdominal pain has this finding on XR:

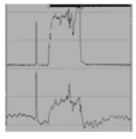


Which of the following is the most appropriate next step in management?

A. Surgical consultation
B. ERCP
C. MRCP
D. Conservative management
E. Colonoscopic decompression

Constipation

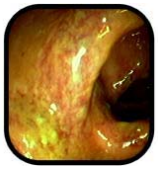
A 38-year-old woman presents with a 15-year history of constipation and rectal spasm. Bowels move once or twice a week and after excess straining or use of enemas. She has incomplete evacuation. A colonic transit study showed retention of 20/24 markers on a plain abdomen X-ray taken at 120 hours after ingestion of Sitzmark capsule. Anorectal manometry showed the following manometric pattern in a rectal sensor (top) and anal sensor (below) during attempted defecation.



→What is the diagnosis?
→What is the treatment?

Acute Colitis

21-year-old student develops abdominal pain and vomiting after returning from Mexico. Labs include: BUN=38; Cr=1.6; Plat=216; WBC=12K. No fever. Admitted for IV fluids. Next day develops bloody diarrhea. Colonoscopy is performed. Biopsy reveals colitis without architectural distortion.

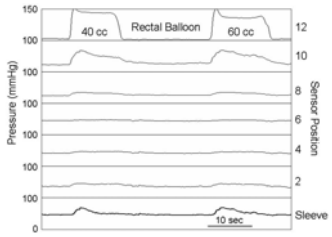


→ What is most likely diagnosis?

→ What treatment should be avoided?

More Constipation

18 yo woman with chronic constipation requiring laxatives. Complains of excessive straining and occasional rectal digital manipulation to help in evacuation of stool



→ What is the diagnosis? → What is treatment?

Strawberries in the Colon?

A 62-year-old patient is referred after multiple polyps found on flexsig. Review of systems reveals progressive hair loss and patches of hyperpigmented skin. Has recurrent loose stools, but no abdominal pain. On exam is found to have alopecia and dystrophic fingernails. Albumin is 2.8. Patient undergoes colonoscopy, which reveals scattered polyps along with a bizarre appearance of subepithelial speckled hemorrhages and lymphedema. Biopsies are pending.

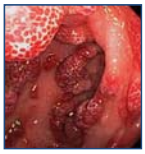


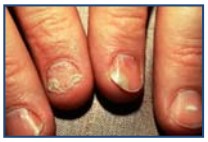
Image courtesy Binh Pham, MD

→ What is the diagnosis?

→ Is this inherited?

Cronkhite-Canada Syndrome

- Non-inherited condition characterized by gastric, enteric, and colonic hamartomatous polyps
- Associated with protein-losing enteropathy and associated malabsorptive diarrhea
- May have integument abnormalities, including alopecia and dystrophic fingernails
- Unknown etiology



Bumps on Face and Bowels

A 59-year-old woman presents with a 20-year history of papules on the hands, feet and face. Screening colonoscopy reveals multiple hamartomas. Physical exam reveals "cobblestoned" tongue and goiter.

→ What is the diagnosis?

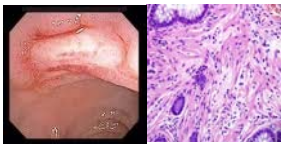
→ What are these bumps?

Hematochezia

A 26 yo man has recurrent rectal bleeding and tenesmus in the setting of chronic constipation. Colon reveals a lesion in the rectum, as pictured, and an otherwise normal sigmoid. The rest of the exam is normal. Biopsy reveals no crypt distortion or organisms, but evidence of granulation tissue and a fibrinopurulent exudate. There is no history of anal intercourse or foreign bodies. He is diagnosed with ulcerative proctitis and receives mesalamine suppositories and enemas, although this does not improve the symptoms. He then receives intra-rectal steroids foam applications, which also do not improve the bleeding and tenesmus.

Which of the following therapies is most appropriate?

A. Infliximab
B. Increase dose of mesalamine
C. Corticosteroid enemas
D. Antibiotics
E. Polyethylene glycol (PEG) 3350



Surveillance in Lynch Syndrome

Patients with Lynch syndrome are at risk of developing extra-colonic malignancy. In addition to performing guideline-recommended colorectal cancer screening, which of the following is also a recommended screening approach?

A. Mammography once per year, starting at age 25 to 30
B. Pelvic examination with endometrial sampling annually beginning at age 30 to 35
C. Ultrasonography of the thyroid every two years, starting at age 35 to 40
D. Radiograph of the chest every two years, beginning at age 35 to 40
E. Abdominal computerized tomography every 3 years, beginning at age 40

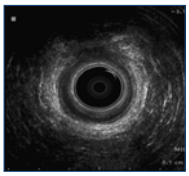
Guidelines for Screening in Lynch Syndrome

Intervention	Recommendation	Strength of recommendation
Colonoscopy	Every 1 – 2 y beginning at age 20 – 25 y or 2 – 5 y younger than youngest age at diagnosis of CRC in family if diagnosis before age 25 y Considerations: Start at age 30 y in MSH6 and 35 in PMS2 families Annual colonoscopy in MMR mutation carriers	Strong recommendation: Level of evidence (II): well-designed and conducted cohort or case-controlled studies from more than 1 group with cancer GRADE rating: moderate
Pelvic examination with endometrial sampling	Annually beginning at age 30 – 35 y	Offer to patient: Level of evidence (V): expert consensus GRADE rating: low
Transvaginal ultrasound	Annually beginning at age 30 – 35 y	Offer to patient: Level of evidence (V): expert consensus GRADE rating: low
EGD with biopsy of the gastric antrum	Beginning at age 30 – 35 y and subsequent surveillance every 2 – 3 y can be considered based on patient risk factors	Offer to patient: Level of evidence (V): expert consensus GRADE rating: low
Urinalysis	Annually beginning at age 30 – 35 y	Consideration: Level of evidence (V): expert consensus GRADE rating: low

Multi-Society Task Force Guidelines

Fecal Urgency

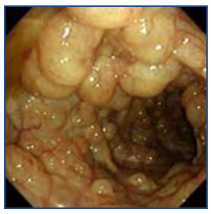
A 72 year-old woman presents with fecal urgency. She reluctantly admits to fecal incontinence of soft stool. Her past history is notable for osteoarthritis and four vaginal deliveries although there were no obstetric tears. You order anorectal manomety and anal EUS (pictured). Based on the EUS image, what findings would you expect on anorectal manometry?



A) Absent recto-anal inhibitory reflex
B) Diminished rectal compliance
C) Diminished pressure at rest
D) Paradoxical increased pressure on straining
E) Diminished squeeze pressure

Lots of Blebs

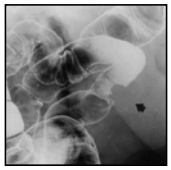
A 41-year-old woman with systemic sclerosis and constipation undergoes colonoscopy, which reveals innumerable sub-mucosal rounded masses. Biopsy causes masses to collapse.



→ What is the name of this consequence of scleroderma?
→ Name 1 other condition associated with this lesion.

Abdominal Cramping in a Young Woman

24-year-old woman with monthly left-sided cramping. IBS is considered. PCP later performs barium enema between symptom flares and it is normal. Subsequent BE during flare is shown. Follow-up colonoscopy is normal.



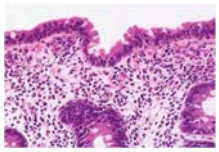
→ What diagnosis is likely?

Hereditary CRC and Polyposis Syndrome Matching Quiz

Buzzword	Syndrome
Glioblastoma	Muir-Torre variant of LS
Trichilemmomas	Cowden's syndrome
Mandibular osteoma	Gardner's syndrome
Sebaceous adenoma	FAP
Retinal pigment hypertrophy	Tuberous sclerosis
Facial angiofibromas	Turcot's syndrome
Sertoli cell tumor	Peutz-Jeghers Syndrome

Anemia and Diarrhea

A 52-year-old male recently traveled to Puerto Rico for 3 months. Developed fatigue, malaise, and abdominal cramps one week after returning, followed by diarrhea and dyspepsia. Labs revealed macrocytic anemia. Endoscopy revealed scalloping in the duodenum. Biopsy is pictured.

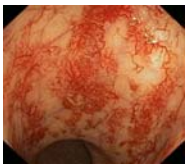


→ What is the most likely diagnosis?

→ What is the treatment?

More Hematochezia

69 yo man presents with urgency, tenesmus, and hematochezia. Evaluation is notable for a Hgb of 8.4 gm/dl. His PMH includes gouty arthritis, CAD and prostate cancer treated with XRT 2 years prior to his current presentation. His past surgical history is notable for a 4 vessel CABG 10 years ago. He takes a lipid lowering agent, ACEI, allopurinol, and ASA 325 mg per day. Rectum is shown.



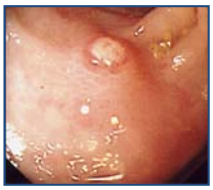
Which of the following interventions should be performed next to best treat this condition?

A. Discontinue ASA
B. Biopsy the rectum to confirm the diagnosis
C. Begin oral mesalamine 2,400 mg BID
D. Begin twice daily hydrocortisone retention enemas
E. Perform argon plasma coagulation of visible lesions

MOC Q#9

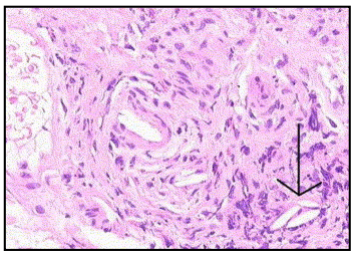
Raised Nodules and Anemia

A 78-year-old is referred for microcytic anemia. Has history of ischemic heart disease, renovascular disease and AAA repair. Exam reveals bruits over carotid and femoral arteries. Labs reveal eosinophilia and ESR of 66. Colonoscopy revealed multiple small, raised, focal nodules.



→ What is the diagnosis?

Gaya D et al. *Gastro* 2006;130:631



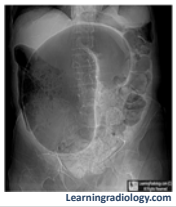
Gaya D et al. *Gastro* 2006;130:631

Bent Inner Tube

65 yo is transferred to the ED from a retirement home with a short history of abdominal distension, periumbilical pain, obstipation, nausea and vomiting. Exam reveals a distended abdomen with tinkle sounds on auscultation and hyper-resonance on percussion. Past medical and surgical history unremarkable. Plain abdominal x-ray is shown. There is no evidence of air in the rectum.

What is the next step?

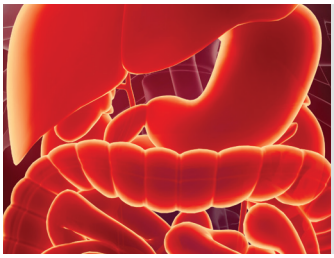
A. Barium enema
B. Flexible sigmoidoscopy
C. CT scan
D. Laparotomy



Learningradiology.com

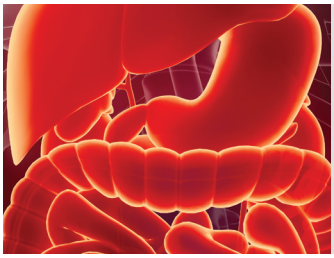
Rapid Buzzword Review

- Anal retentive and constipation → ?
- Colitis + HUS-TTP → ?
- Aganglionic rectum → ?
- Rectal bleeding + fibromuscular obliteration → ?
- Mandibular osteoma → ?
- Cyclic rectal bleeding in a women → ?
- Anemia + needle-shaped clefts on rectal biopsy → ?
- Bent inner tube → ?
- Name of XRT Proctopathy Lesion → ?
- COPD + colon stuck under diaphragm → ?
- Scleroderma + lots of intestinal blebs → ?
- Diarrhea + Missionary + High MCV Anemia → ?



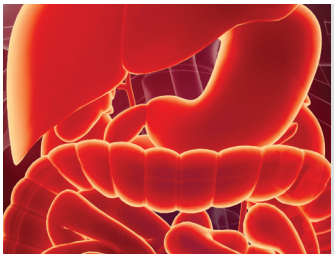
Overview of Center for Endoscopic Research and Therapeutics

Irving Waxman, MD



Endoscopic Submucosal Dissection: Where are We Now & Where Are We Going?

Irving Waxman, MD



To Drain or Not to Drain: Management of Pancreatic Fluid Collections

Uzma Siddiqui, MD

AT THE FOREFRONT UChicago Medicine

To Drain or Not to Drain: Management of Pancreatic Fluid Collections

Uzma D. Siddiqui, MD, FASGE
Associate Professor of Medicine
Associate Director, CERT
Director, EUS and Advanced Endoscopy Training

Relevant Disclosures

- Consultant for Boston Scientific, Olympus and Medtronic

OUTLINE

- Define pancreatic fluid collections (PFCs)
- Overview of endoscopic techniques used for PFC drainage
  - Evolution of devices
  - Lumen apposing metal stents (LAMS)
- Outcomes and complications related to endoscopic therapy
- Cases

CASE

PANCREATIC FLUID COLLECTIONS (PFC): DEFINITIONS

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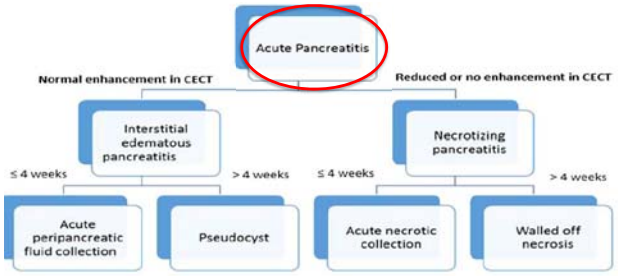
Types of Pancreatic Fluid Collections (PFC): Revised Atlanta Criteria



Banks P, et al. Gut 2013

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Indications for intervention→ **SYMPTOMS**

- Suspected or proven infection
- Obstructive symptoms
- Failure to thrive/chronic abdominal pain/unable to tolerate PO intake

Endoscopic therapy tailored to type of collection

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Options for Drainage

- Approaches
  - Endoscopic
  - Surgical
  - IR
  - Combined approaches
- Management should be performed in multidisciplinary fashion
  - Consider endoscopic first, assess for need for hybrid, support for complications or lack of response

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Planning Endoscopic Management

- Multidisciplinary team
  - Surgical, IR, ICU, Nursing
- Intubate patient
- CO2 insufflation
- Have equipment ready

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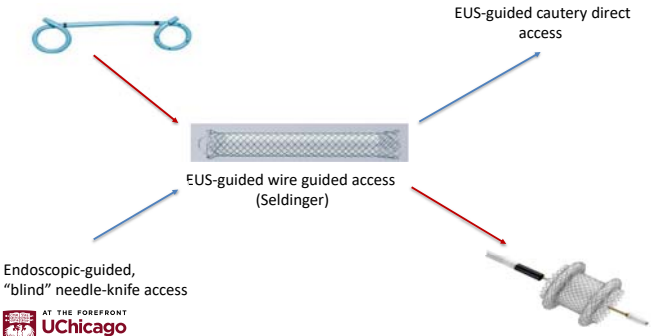
Evolution of Techniques and Tools



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Endoscopic-Guided

- ERCP scope, needle knif/cystotome blindly into collection, place wire under fluoroscopy and place plastic stents
- Limitations: Suspected varices, non-bulging PPC (40%)

  –>EUS guided drainage

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Advantages of EUS-guided Drainage

- Doppler → avoid intervening vessels
- Assess degree of necrosis
- Determine maturity of cyst wall
- Sampling to rule out mucinous neoplasm
- Visible bulge not necessary for drainage
- Compared to prior endoscopic drainage techniques
  - Higher technical success (95 vs. 33-66 %)
  - Lower adverse event rates (0-4 vs. 13-15 %)

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Bruno, A et al. J Clinc Gastro 2011

Lumen Apposing Metal Stents (LAMS)

- In the past, EUS-guided drainage with plastic and metal stents used in ERCP
  - **PROBLEMS**
    - Too long→no lumen apposition, risk of separation
    - Migration
    - Need for dilation and fluoroscopy
    - Time needed to deploy multiple plastic stents
- LAMS designed specifically for transluminal drainage
  - **ADVANTAGES**
    - Easy deployment
    - Good lumen apposition
    - Tract maintenance→allows direct endoscopic debridement
    - Low rates of migration

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FDA approved indication → Pseudocyst drainage

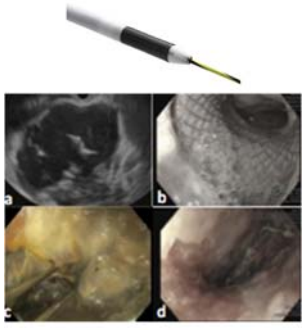
Lumen Apposing Metal Stents (LAMS)

STENT	DIAMETER	IMAGE
AXIOS (Boston Scientific, Marlborough, MA) - Cold (non-cautery enhanced) - Hot (cautery enhanced)	10mm 15mm 20mm $$$$$$$$	
SPAXUS (Taewoong Medical, Gimpo, S. Korea)	8mm 10mm 16mm	
NAGI (Taewoong Medical, Gimpo, S. Korea)	10mm 12mm 14mm 16mm	

Siddiqui UD and Levy M, et al. Gastro 2018

Cautery Enhanced LAMS (CE-LAMS) Advantages

- Allows for direct puncture without guidewire
- No dilation needed
- No fluoroscopy needed



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Complications of Endoscopic Therapy

- Complications: 15-30%
  - Bleeding
  - Perforation/tract separation of lumens
  - Pneumoperitoneum
  - Air embolism
  - Pseudoanuerysm
  - Tract occlusion with further infection
  - Stent migration
- Mortality 5%

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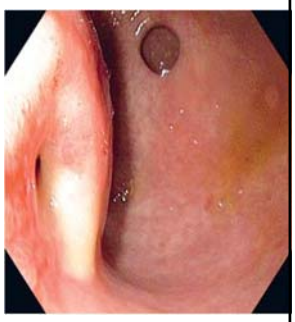
LAMS: Reported Adverse Events

- Delayed bleeding
- Tissue overgrowth
- Stent occlusion by food
- Large distance between collection and GI tract
  - Peritonitis
  - Perforation



Seerden T, et al. Endoscopy 2016
Bang JY, et al. Gut 2016
Fabbri C, et al. GIE 2015
Shah R, et al. CGH 2015

VIDEO: LAMS Pseudocyst Drainage

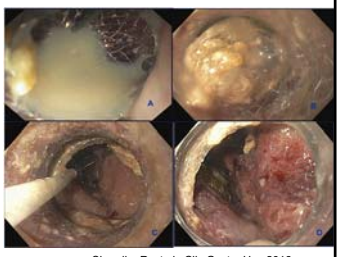
LAMS Drainage: Pancreatic Pseudocysts

- **Itoi et al., GIE 2012**
  - 15 patients
  - All stents successfully deployed (med removal 15 days) with 1 stent migration
  - All with complete resolution of PFCs following initial procedure and no recurrence at 1 yr
  - Safety and feasibility of performing pancreatic necrosectomy through Axios stent demonstrated
- **Gornal**
  - Co
  - Te
  - 10
  - Co
    - Similar technical and clinical success
    - Lower rates of complications, recurrences, and stent migrations
- **Shah et al., Clin Gastro Hep 2015**
  - Prospective, multicenter study in 33 patients
  - Axios 91% successfully placed in PFCs with a 93% resolution rate
  - Complications 5 patients (15%)
    - Abdominal/back pain (n = 2), stent migration (n = 1), fever (n = 1), access-site infection (n = 1)

High technical success rate >89%
High resolution rate >93%
Low adverse event rates

Pancreatic Necrosis

- Incidence: 20% of acute pancreatitis
- Associated with 8-39% mortality
- Major causes of death: Infected necrosis→ Sepsis→MOF→Death
- Walled-off necrosis (WON)
  - Necrotic tissue with reactive tissue wall, >4wks



Sharaiha R, et al., Clin Gastro Hep 2016

Banks P, et al. Gut 2013

VIDEO: Endoscopic Necrosectomy

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LAMS: Outcomes

- Several multicenter, prospective studies reported high rates of technical success (91-98%), and resolution rates (93% for pseudocysts versus 81% for WON)
- 52 patients with WON, reported technical success in 99% and clinical success in 93% of patients, with 5.6% developing an AE including infection, pneumoperitoneum, stent displacement, perforation, or massive bleeding.
- Multicenter, retrospective study of 124 patients examined LAMS use for WON
  - 100% technical success and 86% clinical success over the 3 months follow-up
  - Median of 2 endoscopic interventions
  - Early (< 30 days) and late AEs were reported in 14% and 7.2% of patients, respectively.

WON and LAMS:
-High technical success rate >91%
-High resolution rate >86%
-Low adverse event rates <14%

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Shah R, et al. CGH 2015
Itoi T, et al. GIE 2012
Sharaiha R, et al. CGH 2016
Walter D, et al. Endoscopy 2015
Rinella E, et al. GIE 2015

CASES

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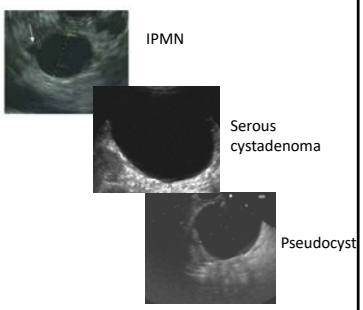
EUS morphology alone→ Unreliable!

- Morphologic criteria for mucinous cysts vs non-mucinous cysts NOT that useful
  - Accuracy 51%, Sensitivity 56%, Specificity 45%
- US multicenter study, 12 centers, 341 patients



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Brugge et al., Gastroenterology 2004

CASE

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CASE

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Take Home Points

- Need significant hx of pancreatitis
- Do NOT drain unless confirmed PFC
- Do NOT intervene on pancreatic collections UNLESS the patient is symptomatic
- If collection is accessible from the GI tract, endoscopic drainage is first line therapy *at expert centers*
- Multi-disciplinary approach

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CONTACT US:
773-702-1459 uchospitals.edu/cert

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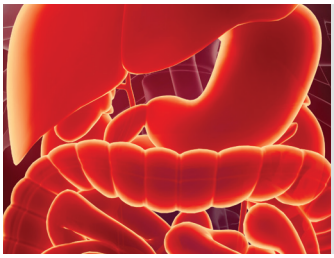
Center for Endoscopic Research & Therapeutics (CERT)



Endoscopic Obesity Treatments

Christopher Chapman, MD

SEPT 21, 2019
ANNUAL GI AND LIVER UPDATES MEETS ACING THE BOARDS

FRONTIERS IN ENDOSCOPIC OBESITY MANAGEMENT

Christopher Chapman, MD

Director of Bariatric
and Metabolic Endoscopy

AT THE FOREFRONT
UChicago Medicine

DISCLOSURES

CONSULTANT FOR

Apollo Endosurgery
Boston Scientific

THE FOLLPOWING INVESTIGATIONAL DEVICES WILL BE DISCUSSED:
SPATZ3, DUODENAL MUCOSAL RESURFACING, ENDOBARRIER, SELF-ASSEMBLING MAGNETS

FIG. 1

OBESITY TRENDS AMONG U.S. ADULTS

1993 - 1995 COMBINED DATA

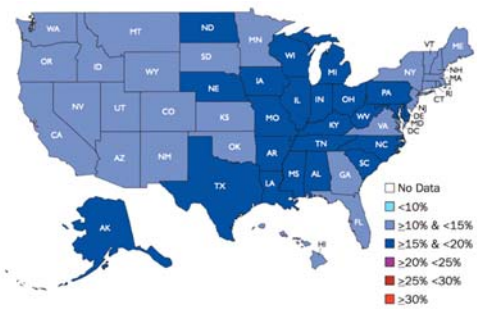
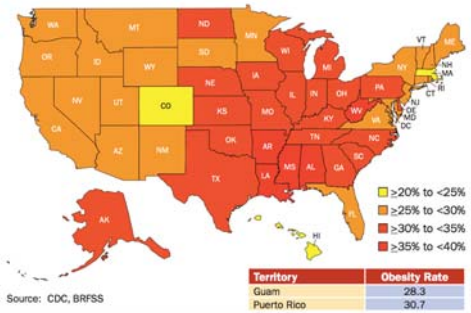


FIG. 2

OBESITY TRENDS AMONG U.S. ADULTS

2016 DATA



Territory	Obesity Rate
Guam	28.3
Puerto Rico	30.7

Source: CDC, BRFSS

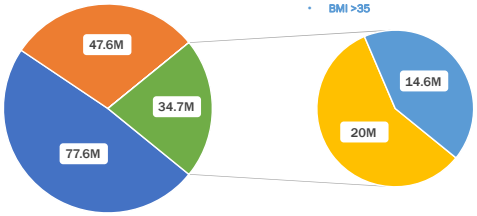
FIG. 3

THE SCOPE OF THE PROBLEM

U.S. CENSUS, 230 MILLION, AGE >20, 2012

BMI 30-35
- Obese: Do not qualify for surgery, failed diet and exercise.

SURGICAL CANDIDATES
- Class II or III
  - BMI >40
  - BMI >35



BMI 25-30
- Overweight: At risk for metabolic disorders (NASH, DM II).

Ponce, et al. Surg Obes Rel Dis(2015)
http://www.infoplease.com/science-health/health/age-adjusted-percent-distributions-body-mass-index-bmi-among-persons-20-years

SOCIAL & ECONOMIC EFFECTS

1 In 3 *U.S. adults are obese.*[3]

SOCIAL
- Social bias or discrimination[1]
- Dealing with judgmental behavior[2]
- Compromised health and premature aging[2]

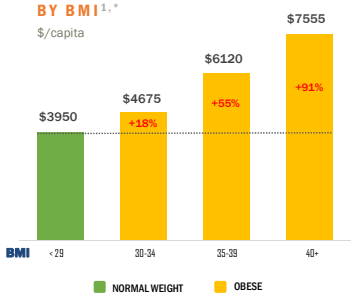
ECONOMIC
Obesity has a direct impact on the U.S. healthcare system.[3]
- In 2008, an estimated $147 billion was spent in medical costs for obesity.[4]
- If obesity trends continue, it's estimated that related medical costs could rise an additional $43 to $66 billion each year in the U.S. by 2030.

1. NHLBI clinical guidelines. NIH publication No. 98-4083. 1998:1-262.
2. Sturm R. Health Aff. 2002;21:245-253. http://www.rand.org/publications/RB/RB4548. Accessed July 14, 2010.
3. http://obesitycampaign.org/obesity_facts.asp
4. http://www.cdc.gov/obesity/adult/causes/index.html

FIG. 4

PERSONAL ECONOMIC COSTS

HEALTHCARE COSTS BY BMI[1,*]
$/capita



COST OF DIET PROGRAMS

Jenny Craig
+$2,500/year[2]

Nutrisystem®
+$3,000/year[3]

*For the US adult population (aged 20-64)

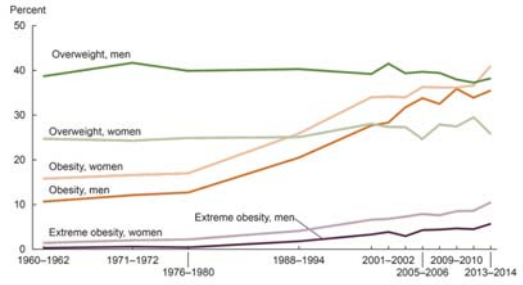
1. Algozy et al. Health Interol. 2010.
2. http://globalhealth.duke.edu/media/news/research-compares-cost-effectiveness-weight-loss-programs-drugs
3. http://money.usnews.com/money/personal-finance/articles/2003/01/02/the-heavy-price-of-losing-weight

EVERY POINT OF BMI ABOVE 30 ADDS ≈ $300 IN PER CAPITA ANNUAL HEALTHCARE COSTS

FIG. 5

TRENDS IN ADULT OVERWEIGHT, OBESITY, & EXTREME OBESITY

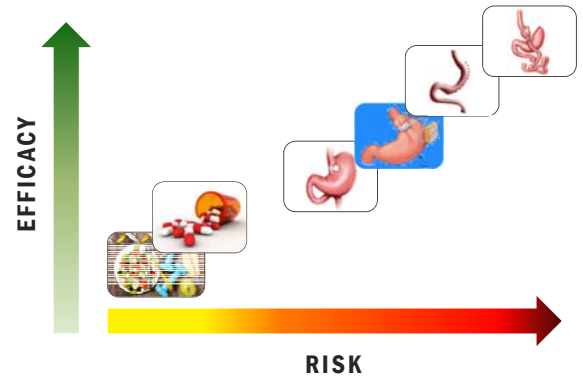
U.S. MEN & WOMEN, 20-74, 1960-62 TO 2013-14



NOTES: Age-adjusted by the direct method to the year 2000 U.S. Census Bureau estimates using age groups 20-39, 40-59, and 60-74. Overweight is body mass index (BMI) of 25 kg/m² or greater but less than 30 kg/m²; obesity is BMI greater than or equal to 30; and extreme obesity is BMI greater than or equal to 40. Pregnant females were excluded from the analysis.

SOURCES: NCHS, National Health Examination Survey and National Health and Nutrition Examination Surveys.

TREATMENTS FOR OBESITY



Courtesy of Abu Dayyeh

FIG. 6

ESTIMATE OF BARIATRIC SURGERY NUMBERS

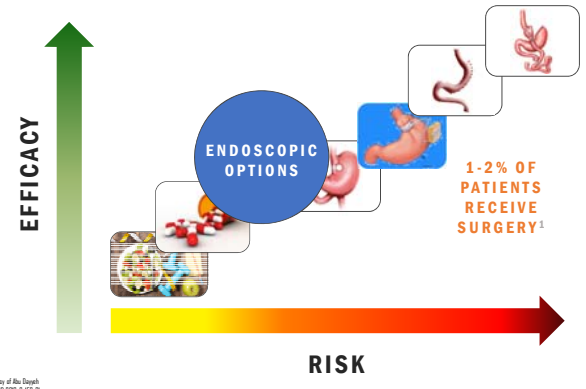
2011-2017

	2011	2012	2013	2014	2015	2016	2017
TOTAL	**158,000**	**173,000**	**179,000**	**193,000**	**196,000**	**216,000**	**228,000**
Sleeve	17.80%	33.00%	42.10%	51.70%	53.61%	58.11%	53.39%
RYGB	36.70%	37.50%	34.20%	26.80%	23.02%	18.69%	17.80%
Band	35.40%	20.20%	14.00%	9.50%	5.68%	3.39%	2.77%
BPD-DS	0.90%	1.00%	1.00%	0.40%	0.60%	0.57%	0.70%
Revision	6.00%	6.00%	6.00%	11.50%	13.55%	13.95%	14.14%
Other	3.20%	2.30%	2.70%	0.10%	3.19%	2.63%	2.46%
Balloons	–	–	–	–	0.36%	2.66%	2.75%

Published June 2018

The ASMBS total bariatric procedure numbers are based on the best estimates from available data (BOLD: ACS/MBSAQIP, National Inpatient Sample Data and outpatient estimations).

TREATMENTS FOR OBESITY



Courtesy of Abu Dayyeh
1. SSWHO 2018; 9:158-91

BARIATRIC SURGERY RECEPTIVITY

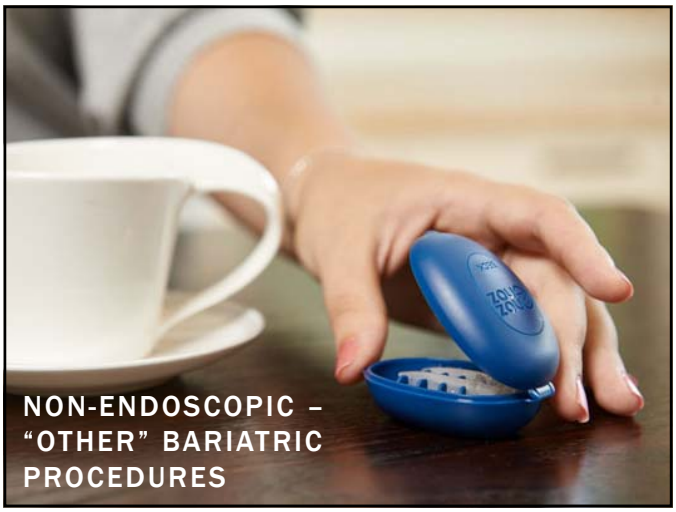
2019

NOT INTERESTED IN BARIATRIC SURGERY (n=284)

Fear of other complications from surgery	145 (51%)
Do not need surgery to lose weight	91 (32%)
Fear of dying	70 (24.6%)
Fear of surgery in general	68 (23.9%)
Cost	58 (20.4%)
Pain	39 (13.7%)
Do not believe it will work	22 (7.7%)
Fear of judgment	9 (3.2%)
Religious or cultural reasons	2 (0.7%)

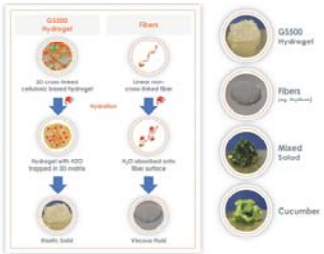
Fang, M et al. Receptivity to Bariatric Surgery in Qualified Patients. J Obes 2016

FIG. 7

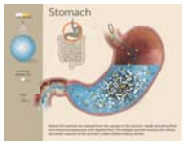


NON-ENDOSCOPIC - "OTHER" BARIATRIC PROCEDURES

Three-dimensional structure generates an elastic response similar to vegetables and orders of magnitude greater than fibers

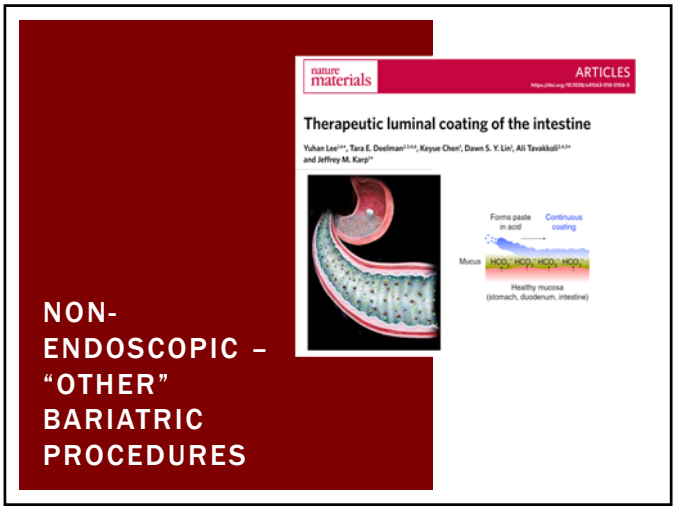


Images showing samples after hydration in simulated gastric fluids with water (1/3 ratio). Vegetables were masticated to stimulate normal digestion by blender and by human volunteers. Elastic response was measured by validated and repeated rheological tests.



- Cellulose based
- TID dosing
- FDA approved in 4/2019
- BMI 25-40
- Rx: 6.4% vs. placebo 4.4%, p = 0.0007
- 59% adults achieved 5% TBWL, 26% achieved 10%

FIG. 8



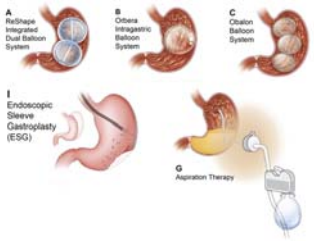
TYPES OF ENDOSCOPIC BARIATRIC DEVICS

GASTRIC INTERVENTIONS

- **SPACE OCCUPYING DEVICE**
  - **Intragastric Balloons**
    - **Orbera**
    - **Reshape Duo**
    - **Obalon**
    - Spatz3 Adjustable
    - Ellipse
  - Transpyloric Shuttle
  - Full Sense
- Gastric Volume Reduction
  - POSE
  - Endomina
  - **Endoscopic Sleeve Gastroplasty**
- **Aspiration Therapy: Aspire Assist**

SMALL BOWEL INTERVENTIONS

- EndoBarrier
- Revita Duodenal Mucosal Resurfacing
- Self-Assembling Magnets – GI Windows



Courtesy of Abu Dayyeh
I. SOARD 2013; 9: 159-91

TYPES OF ENDOSCOPIC BARIATRIC DEVICS

GASTRIC INTERVENTIONS

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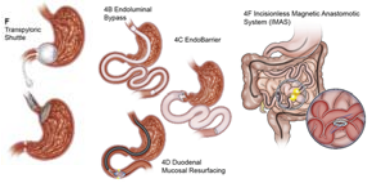
    - Ellipse
  - Transpyloric Shuttle
  - ***Full Sense***®
- Gastric Volume Reduction
  - POSE
  - Endomina
  - Endoscopic Sleeve Gastroplasty
- Aspiration Therapy: Aspire Assist

SMALL BOWEL INTERVENTIONS

- ***EndoBarrier***®
- ***Revita Duodenal Mucosal Resurfacing***®
- ***Self-Assembling Magnets – GI Windows***®



Courtesy of Abu Dayyeh
I. SOARD 2013; 9: 159-91

ENDOSCOPIC THERAPY: PROS & CONS

Durability

Amount of Weight Loss

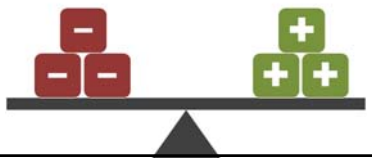
Outpatient

Less Cost*

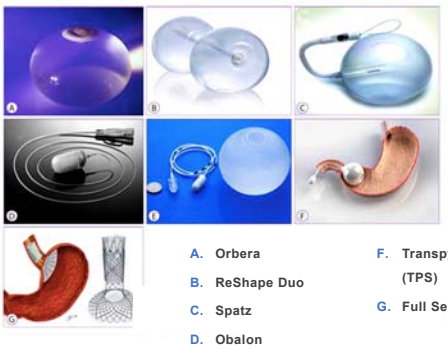
Less Complications

Reversible – No Permanent Anatomy Alteration

Repeatable



SPACE OCCUPYING DEVICES



A. Orbera
B. ReShape Duo
C. Spatz
D. Obalon
E. Elipse
F. Transpyloric Shuttle (TPS)
G. Full Sense

FIG. 9

EFFICACY OF IGBs – PIVOTAL TRIAL DATA

DEVICE	STUDY DESIGN	NUMBER OF SUBJECTS		BMI		% TOTAL BODY WEIGHT LOSS (TBWL)		ACTIVE GROUP RESPONDER RATE (% OF SUBJECTS WITH >5 % TBWL OR /25% EBWL)	SERIOUS ADVERSE EVENT RATE
		CONTROL GROUP	ACTIVE GROUP	CONTROL GROUP	ACTIVE GROUP	CONTROL GROUP	ACTIVE GROUP		
Orbera	Randomized, open label, BMI 30 to 40, moderate intensity lifestyle intervention.	130	125	35.4 +/- 2.7	35.2 +/- 3.2	3.3. +/- 5.0%	10.2 +/1 6.6%	79.2%	10%
Reshape Duo	Randomized, sham controlled, BMI 30 to 40, moderate intensity lifestyle intervention.	139	34.20%	35.4 +/- 2.8	35.3 +/- 2.8	3.3%	6.8%	48.8%	10.6%
Obalon	Randomized, sham controlled, BMI 30 to 40, moderate intensity lifestyle intervention.	189	14.00%	35.4 +/- 2.7	35.1 +/- 2.7	3.4 +/- 5.0%	6.6% +/- 5.1%	62.1%	0.5%

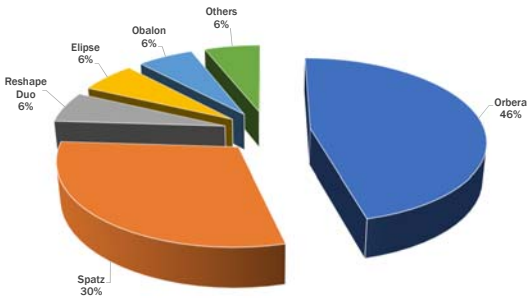
2019

FIG. 10

MARKET & PENETRANCE*

2019

>330,000 IGB IMPLATED TO DATE
>2,000 ACTIVE USERS
40,000 IGB PER YEAR GLOBALLY



*Adapted from. B. Abu Dayyeh

SPATZ3 - VIDEO

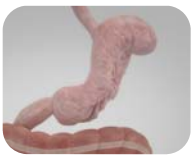
IGB: SAFETY

- **RCTs (n=866 patients from 15 RCTs)**
  - Mortality 0%
  - Perforation 2 (0.002%)
  - Bleeding 3 (0.003%)
  - Migration 11 (0.01%) (All Helioscope)
  - Obstruction 1 (0.002)
  - Aspiration 2 (0.002%)
- **Post-FDA Approval Consecutive Patients in US (n=321)**
  - Mortality 0%
  - Perforation 0%
  - Bleeding 0%
  - Migration Needing Surgery 0%
  - Pancreatitis 0%
  - Hyperinflation 0%
  - Aspiration 1 (1%)
  - Hospital Admission 11 (4%)
    - *Vargas et al. CGH 2018*
- **Meta-analysis (n=6,800 patients from 68 studies)**
  - Mortality 0.08%
  - Perforation 0.1% (half in patients with previous surgery)
  - Migration 1.4%
  - Bowel Obstruction 0.3%
  - Gastric ulcer 2%
    - *Abu Dayyeh et al. Gastrointestinal Endoscopy 2015;82:425*
- **Brazilian Consensus (n=41,863)**
  - Mortality with Balloon in 12 (0.03%) only 3 balloon related (0.007%)
  - Hyperinflation (0.9%)
  - Deflation (0.8%)
  - Migration needing surgery 24 (0.05% – air filled older balloons)
    - *Neto MG. et al Surg Obes Relat Dis 2017*

IGB: SAFETY

ENDOSCOPIC SLEEVE GASTROPLASTY

- Based on a cap-based flexible endoscopic suturing system (Overstitch, Apollo Endosurgery)
- Mounted onto a double channel endoscope (Olympus GIF-2T180)
- Placed through an esophageal overtube
- General anesthesia



CONSTRUCTION OF THE GASTROPLASTY

ESG

Clinical Gastroenterology and Hepatology 2017;15:504–510

Endoscopic Sleeve Gastroplasty Significantly Reduces Body Mass Index and Metabolic Complications in Obese Patients

Reem Z. Sharaiha,* Nikhil A. Kumta,* Monica Saumoy,* Amit P. Desai,* Alex M. Sarkisian,* Andrea Benevenuto,* Amy Tyberg,* Rekha Kumar,‡ Leon Igel,‡ Elizabeth C. Verna,§ Robert Schwartz,* Christina Frissora,* Alpana Shukla,‡ Louis J. Aronne,‡ and Michel Kahaleh*

*Department of Gastroenterology and ‡Department of Endocrinology, Weill Cornell Medicine, New York, New York; and §Department of Gastroenterology, Columbia University Medical Center, New York, New York

- 91 Consecutive Patients
- August 2013 to March 2016
- Mean Age: 43.9 +/- 11.3 years
- Gender:
  - % M = 32%
  - % F = 68%
- Baseline BMI: 40.7 +/- 7.0 kg/m^2

ESG

Clinical Gastroenterology and Hepatology 2017;15:504–510

Endoscopic Sleeve Gastroplasty Significantly Reduces Body Mass Index and Metabolic Complications in Obese Patients

Reem Z. Sharaiha,* Nikhil A. Kumta,* Monica Saumoy,* Amit P. Desai,* Alex M. Sarkisian,* Andrea Benevenuto,* Amy Tyberg,* Rekha Kumar,‡ Leon Igel,‡ Elizabeth C. Verna,§ Robert Schwartz,* Christina Frissora,* Alpana Shukla,‡ Louis J. Aronne,‡ and Michel Kahaleh*

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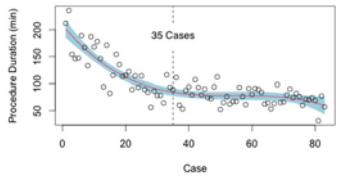

ESG

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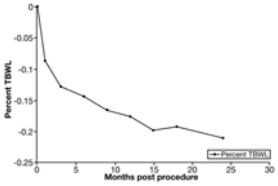


FIG. 11

IMPACT ON COMORBITIES

	Prior To ESG, Mean (SD)	12 Months After ESG, Mean (SD)	p=value
HgbA1c, % (all patients)	6.1 (1.1)	5.5 (0.48)	0.05
HgbA1c, % (only diabetics and prediabetics)	6.6(1.2)	5.6 (0.51)	0.02
Waist circumference, cm	119.66 (14.05)	92.75 (5.85)	<0.001
Systolic blood pressure, mmHg	129.02 (13.44)	122.23 (11.69)	0.023
LDL, mg/dL	121.62 (38.61)	124.27 (27.82)	0.786
TG, mg/dL	131.84 (83.19)	92.36 (39.43)	0.017
ALT (mg/dL)	32.28 (16.43)	20.68 (11.44)	<0.001

Sharaiha et al. CGH 2016

ESG

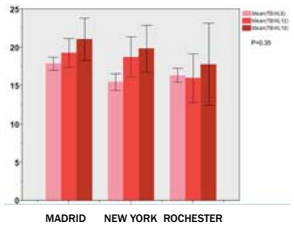
- Consecutive patients (n = 248)
- At least 6 months follow-up
- Age: 44.5 +/- 10 years
- Gender:
  - % M = 27%
  - % F = 73%
- Baseline BMI: 37.8 +/- 5.6 kg/m^2

FIG. 12

ESG

N total	*N* lost to follow-up	%TBWL Madrid	%TBWL Rochester	%TBWL New York	%TBWL All	p-value
6 months						
248	33	15.8 (14.6-16)	14 (11.5-16.3)	14.2 (12.2-16.25)	15.17 (14.2-16.25)	0.25
24 months (18-24)						
92	35	19.3 (15.1-23.5)	16.8 (11.5-22.1)	19.5 (13.5-25.6)	18.6 (15.7-21.5)	0.7

95% confidence intervals shown.



Comparison of %TBWL between the three centers in the study at 6 and 24 months.

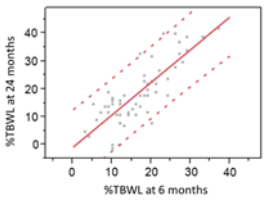
FIG. 13

Multivariate Linear Regression Model
Predicting % TBWL at 24 Months

ESG

	Univariable ß	p-value	Multivariable ß	p-value
Age	-0.22	0.11	0.105	0.25
Gender	0.16	0.44	0.07	0.59
BMI	1.5	0.66	0.2	0.93
%TBWL at 6 months	1.17	<0.001	1.21	<0.001

95% confidence intervals shown.



Odds of achieving >10% TBWL at 24 months if a patient achieved ≤10% TBWL at 6 months is 0.18 [0.034–0.84]

ESG: ADVERSE EVENTS

MINOR (CORNELL EXPERIENCE)

- 35 patients (38.4%) experienced self-limited nausea that lasted <48 hours
- 25 patients (27.4%) experienced mild to moderate abdominal pain that was cramping in nature, again lasting <48 hours

SERIOUS (2%)

- (N=2) – Perigastric inflammatory serous fluid collection that resolved with percutaneous drainage
- (N=1) – Sub-massive pulmonary embolism 72 hours after procedure
- (N=1) – Self limited hemorrhage after splenic laceration
- (N=1) – Pneumoperitoneum and pneumothroax requiring chest tube placement with no further need for any surgical intervention and full recovery

Clinical Gastroenterology and Hepatology 2017;15:37–43

ALIMENTARY TRACT

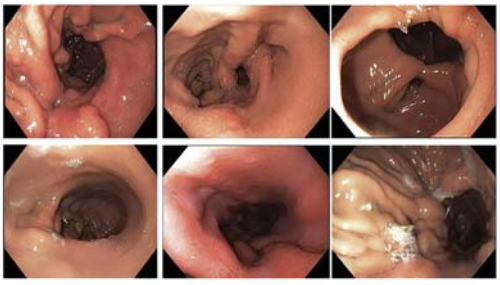
Endoscopic Sleeve Gastroplasty Alters Gastric Physiology and Induces Loss of Body Weight in Obese Individuals

Barham K. Abu Dayyeh,[*,‡] Andres Acosta,[‡] Michael Camilleri,[‡] Manpreet S. Mundi,[§] Elizabeth Rajan,[*] Mark D. Topazian,[*] and Christopher J. Gostout[*]

[*]Developmental Endoscopy Unit, Division of Gastroenterology and Hepatology, Department of Medicine; [‡]Clinical Enteric Neuroscience Translational and Epidemiological Research, Division of Gastroenterology and Hepatology, Department of Medicine; and [§]Division of Endocrinology, Department of Medicine, Mayo Clinic, Rochester, Minnesota

- 25 consecutive patients
- September 2012 to March 2015
- Mean Age: 47.6 +/- 10 years
- Baseline BMI: 35.5 +/- 2.6 kg/m^2

ESG DURATION



Fully Intact ESG at 3 Months (6/9 Patients)

Partially Intact ESG at 3 Months (3/9 Patients)

CLINICAL DISCUSSION: MECHANISM

PRE-GASTROPLASTY

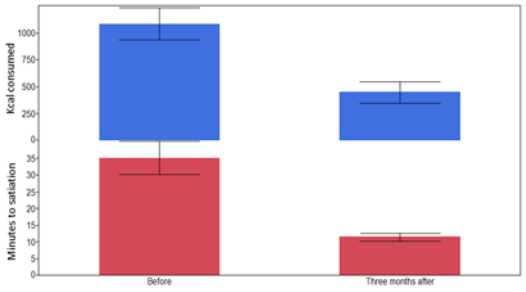
3-MONTHS POST-GASTROPLASTY

FIG. 14

PHYSIOLOGY OF ESG

CHANGES IN SATIATION ON MEAL TOLERANCE TEST

- 3 months after ESG, active fasting and postprandial ghrelin levels decreased by 29.4% (p=.1)
- No statistically significant changes in leptin, GLP-1, and PYY levels



Abu Dayyeh, Gastrost. et al. CGH (2016)

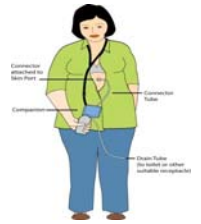
ESG

1. Weight loss from ESG is reproducible (among different centers).
2. Weight loss from ESG is durable at two years (steps ahead of other non-surgical interventions).
3. The procedure appears to be safe with very low rates of adverse events. No surgeries required for complications and no mortalities.

ASPIRATION THERAPY

GASTRIC INTERVENTIONS

- Patient drains (aspirates) stomach contents through customized gastrostomy (A-Tube) ~ 20 minutes after ~ 3 meals /day (less for maintenance)
- Aspiration removes ~ 30% consumed calories
- Aspiration takes ~ 5-10 minutes
- Aspiration Therapy done in connection with Lifestyle Modification Program
- Feature on AspireAssist prevents patient from aspirating >115 times (~4-6 weeks) without getting "refill order" from physician
- FDA approved for BMI 35 to 55



ASPIRATION THERAPY - VIDEO

ASPIRATION THERAPY: DUAL MECHANISMS OF ACTION

Lifestyle Therapy and AspireAssist reinforce one-another:

1

CALORIC DIVERSION

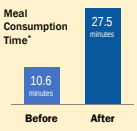
≤30% of calories drained by AspireAssist

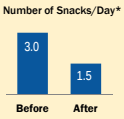
***Responsible for 50-80% of weight loss**

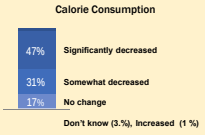
2

IMPROVED EATING BEHAVIOR

Through chewing/slower eating
Increased water consumption
Less snacking
Mindful eating
Meal planning







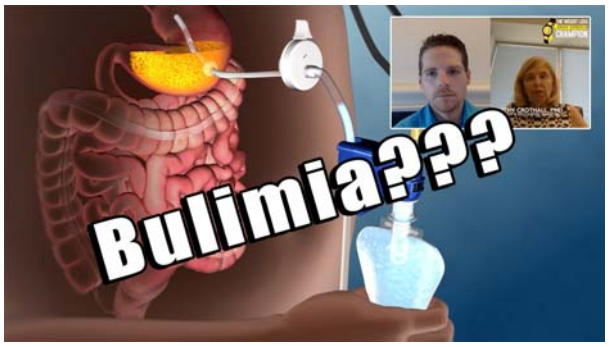
*Sullivan et al. Gastroenterology 2008; 145-1252

ASPIRATION THERAPY

Percutatneous Gastrostomy Device For The Treatment Of Class II & Class III Obesity: Results Of Randomized Controlled Trial

- US pivotal multi-center randomized open-label clinical trial
- 111 patients were enrolled to undergo AT in addition to a lifestyle intervention for 12 months.
- Intervention TBWL of 14.2% ± 9.8% compared to control TBWL of 4.9% ± 7%.
- Adverse events:
  - Stoma granulation tissue formation (40.5%)
  - Stoma infection (14.4%)
  - Peritonitis (0.9%)
  - Gastric ulcer (0.9%).

nature.com/ajg March 2007 Volume 102



EATING BEHAVIORS

Subjects assessed for binge-eating, bulimia, & night-eating syndrome

- Eating Behavior Assessment: Questionnaire on Eating and Weight Patterns-Revised (QWEPR) and the Eating Disorder Examination)
- Assessments at Baseline, Week 14 (AT subjects only), Week 28, and Week 52
- 1 Control subject developed binge-eating syndrome at Week 28 and was removed from study
- No AT subject showed any evidence of worsening eating behaviors

Frequency of aspiration monitored by Connector counts

- No evidence of any subject excessively aspirating

Self-reported data show an improvement in ea… che… sna… eati…

- C… b…

NO EVIDENCE OF ANY PATIENT SHOWING A DETERIORATION IN EATING BEHAVIORS

ASPIRATION THERAPY: SUPER OBESE

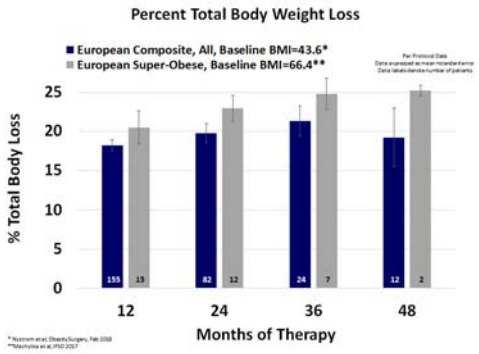


FIG. 18

SMALL BOWEL THERAPIES: NOT FDA APPROVED

ENDOBARRIER

REVITA DUODENAL MUCOSAL RESURFACING PROCEDURES (FRACTYL)

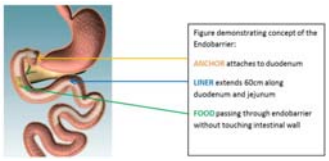
SELF-ASSEMBLING MAGNETS (GI WINDOWS)

SMALL BOWEL THERAPIES: ENDOBARRIER

- 65-cm long Teflon-coated duodenal jejunal bypass sleeve (DJBS)
- Allows undigested food to reach the jejunum, where it mixes with pancreaticobiliary juices.
- Anchored to the duodenal bulb through a nitinol crown with barbs.
- The device (sleeve and anchor) comes in a capsule that is placed under general anesthesia with fluoroscopic guidance.
    - Once the capsule reaches the duodenal bulb, the sleeve is advanced 65 cm into the small bowel.
    - The anchor is then deployed 5 cm distal to the pylorus.

SMALL BOWEL THERAPIES: ENDOBARRIER

- Meta-analysis showed that at 12 months, patients achieved 35.3% (95% CI, 24.6%–46.1%) EWL.
- US pivotal multicenter double-blinded sham control trial was terminated early after enrolment of 325/500 patients owing to a 3.5% incidence of hepatic abscess formation.
- With two-third enrollment, compared to the sham group, subjects who received the DJBS lost significantly more weight at 12 months (TBWL 7.7%±9.6% vs. 2.1%±5.4%, p<0.0001) and had more significant improvement in HgbA1c (−1.1±1.5 vs. −0.3±1.6).



SMALL BOWEL THERAPIES: DUEDONAL RESURFACING

- Hydrothermal ablation of 10 cm of superficial duodenal mucosa is achieved with the aid of a special catheter that delivers hot water after a sub-mucosal lift.
- Mucosal remodeling may hypothetically reset the diseased duodenal enteroendocrine cells, thus restoring signaling, which can improve diabetes control through an incretin effect, with minimal transient decrease in body weight.

	Sample Size	Baseline A1c	A1c Change	Outcome	Country
FIH Fractyl	28	9.50%	1.4 ± 0.3%	6 months	Chile
FIH Fractyl	8	9%	1.8 ± 0.5%	6 months	Chile
FIH Fractyl	15	8.50%	1.30%	12 months	Chile
Revita 1	37	8.60%	1 ± 0.2%	12 months	EU + Brazil
Revita 2	24 (open label cohort only)	8.40%	1%	3 months	EU
Digma	18	9.40%	1.30%	6 months	Czech

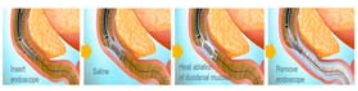


FIG. 19

SMALL BOWEL THERAPIES: SELF-ASSEMBLING MAGNETS

Two standard endoscopes are used to access the small bowel.

Self-forming magnets are deployed from the working channel of each endoscope.

The devices are connected to create a compression anastomosis.

When the anastomosis is fully formed, the devices are passed.

A treatment path is created, bypassing a portion of the small intestine.

SMALL BOWEL THERAPIES: SELF-ASSEMBLING MAGNETS - VIDEO

ANASTOMOTIC/POUCH REDUCTION- VIDEO

ORIGINAL ARTICLE: Clinical Endoscopy

Transoral outlet reduction for weight regain after gastric bypass: long-term follow-up (CME)

Nitin Kumar, MD,[1] Christopher C. Thompson, MD[2]
Boston, Massachusetts, USA

ANASTOMOTIC/POUCH REDUCTION: LONG-TERM FOLLOW UP

ANASTOMOTIC/POUCH REDUCTION: LONG-TERM FOLLOW UP

- Consecutive post-RYGB patients with weight regain and a gastrojejunal anastomosis aperture greater than 15 mm.
- 150 patients who had regained 49.9% +/- 3.6% of the weight lost after gastric bypass

WEIGHT RESULTS

	3 Months	6 Months	12 Months	24 Months	36 Months
No. (no. lost to follow-up)	146 (4)	144 (2)	109 (2)	63 (1)	40 (3)
Weight loss, kg.	9.6 ± 0.6	10.6 ± 0.7	10.5 ± 1.2	9.0 ± 1.7	9.5 ± 2.1
BMI loss, kg/m²	3.5 ± 0.2	3.8 ± 0.2	3.8 ± 0.4	3.3 ± 0.6	3.4 ± 0.8
EWL, %	25.0 ± 1.9	28.8 ± 2.7	24.9 ± 2.6	20.0 ± 6.4	19.2 ± 4.6
TWL, %	8.7± 0.5	9.6 ± 0.6	9.5 ± 0.9	8.1 ± 1.4	8.6 ± 1.5

BMI, body mass index; EWL, excess weight loss; TWL, total weight loss.

- Conclusion: TORe safely and effectively arrested weight regain and provided durable weight loss with a low number needed to treat.

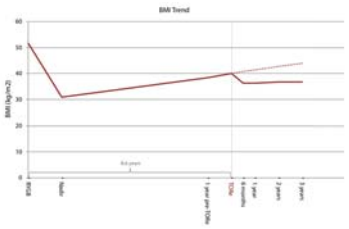
FIG. 20

ANASTOMOTIC/ POUCH REDUCTION: LONG-TERM FOLLOW UP

ORIGINAL ARTICLE: Clinical Endoscopy

Transoral outlet reduction for weight regain after gastric bypass: long-term follow-up (CME)

Nitin Kumar, MD,[1] Christopher C. Thompson, MD[2]
Boston, Massachusetts, USA



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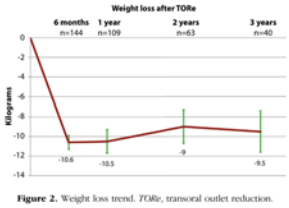


Figure 2. Weight loss trend. *TORe*, transoral outlet reduction.

NOVEL ENDOSCOPIC APPROACHES

ENDOSCOPIC MANAGEMENT OF WEIGHT REGAIN AFTER RYGB

Dose Response for APC in the Treatment of Weight Regain following RYGB

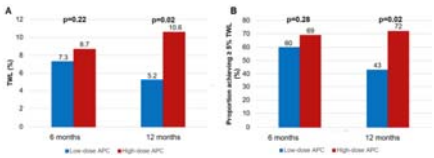
- *Jirapinyo et al. DDW 2019 Tu1900*
- Single center, APC for RYGB 2014-2018
  - Low dose (45-55 W) vs. High dose (70-80 W)
  - Repeat sessions q10-12 weeks until target weight or GJA <10 mm

FIG. 21

ENDOSCOPIC MANAGEMENT OF WEIGHT REGAIN AFTER RYGB

Dose Response for APC in the Treatment of Weight Regain following RYGB

Characteristics	All (N=204)	Low-dose APC (N=114)	High-dose APC (N=90)
Age (years)	48 ± 10	50 ± 10	45 ± 10
Sex (F, %)	183 (90)	102 (89)	81 (90)
BMI (kg/m²)	36.4 ± 8.0	35.2 ± 6.6	37.9 ± 9.3
Weight Regain (% from maximal weight loss)	40.8 ± 31.0	34.7 ± 23.3	48.6 ± 37.5
GJA Size (mm)	18.8 ± 6.4	16.9 ± 4.2	21.2 ± 7.7
Number of APC Sessions	2.4 ± 1.8	3.0 ± 1.9	1.0 ± 0.6



Jirapinyo et al. GIW 2019 Ta1000

ENDOSCOPIC MANAGEMENT OF WEIGHT REGAIN AFTER RYGB

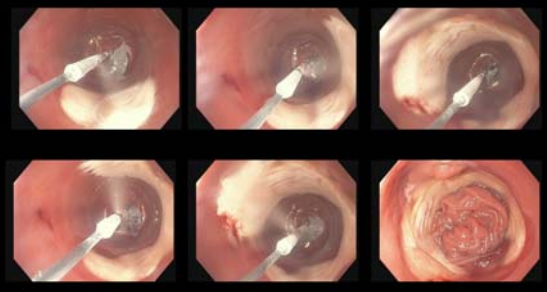
Combination of Submucosal Dissection and Suturing for the Treatment of Weight Regain after RYGB: Outcomes and Comparison to Traditional TORe

Characteristics	All (n=60)	Modified ESD TORe (n=15)	APC TORe (n=45)	P-value
Unmatched Parameters				
Age (years)	50 ± 11	45 ± 9	52 ± 11	0.04
Sex (F, %)	53 (88)	15 (100)	38 (84)	–
Years from RYGB (years)	9 ± 4	10 ± 5	8 ± 4	0.26
BMI (kg/m²)	37.3 ± 6.8	36.0 ± 7.1	37.8 ± 6.7	0.40
Weight Regain (% of maximal weight loss)	44.9 ± 32.8	42.5 ± 19.3	45.4 ± 36.9	0.78
Matched Paramaeers				
Pre-TORe GJA size (mm)	24.0 ± 6.4	24.0 ± 6.6	24.0 ± 6.4	0.95
Pre-TORe Pouch size (cm)	4.4 ± 1.5	4.6 ± 1.8	4.3 ± 1.4	0.55
Outcomes				
TWL at 3 months (%)	8.3 ± 4.0	9.5 ± 5.0	7.1 ± 2.3	0.13
TWL at 6 months (%)	10.0 ± 4.9	12.1 ± 5.4	8.0 ± 3.4	0.03
Post-TORe GJA size at 6 months (mm)	14.6 ± 5.8	11.5 ± 4.1	15.8 ± 6.0	0.04

Jirapinyo et al. GIW 2019 Ta1065

ENDOSCOPIC MANAGEMENT OF WEIGHT REGAIN AFTER RYGB

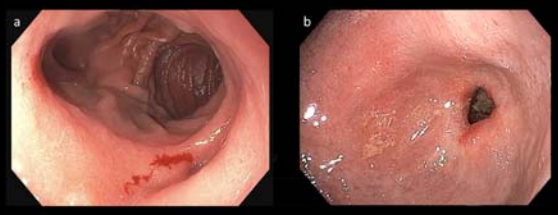
Cryoballoon Ablation for Gastric Pouch And/Or Outlet Reduction in Patients with Weight Regain Post Roux-En-Y Gastric Bypass



Fayad et al. GIW 2019 Su0993

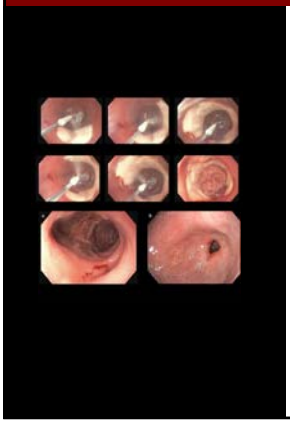
Endoscopic Management of Weight Regain after RYGB

Cryoballoon Ablation for Gastric Pouch And/Or Outlet Reduction in Patients with Weight Regain Post Roux-En-Y Gastric Bypass



Fayad et al. GIW 2019 Su0993

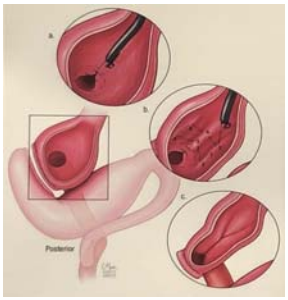
ENDOSCOPIC MANAGEMENT OF WEIGHT REGAIN AFTER RYGB



Cryoballoon Ablation for Gastric Pouch and/or Outlet Reduction in Patients with Weight Regain Post Roux-En-Y Gastric Bypass

- *Fayad et al. DDW 2019 Sa1993*
- 2 centers: 22 patients
- Outlet size reduction @ 8weeks –
  - From 24.1 mm to 17.1 mm (p <0.001)
- %TBWL was 8.1 +/- 12.8 at 8 weeks

WEIGHT REGAIN AFTER RYGB: POUCH REDUCTION



tTORe

Endoscopic Tubular Outlet Reduction (tTORe) for the Treatment of Weight Regain Enhances Weight Loss and Improves Quality of Life

- *Vargas et al. DDW 2019 Sa1985*
- 80 patients
  - tTORe n=34; TORe n=46
  - % TBWL
    - 3 mos: 9.6% vs 7%, p=0.036
    - 12 mos: 14.3% vs 6.8%, p=0.06

Sa2003

Comparison of Transoral Outlet Reduction (TORE) Alone Versus Tore With Gastroplasty (Tore-G): A Matched Cohort Analysis

Rabindra R. Watson*[1], Brian L. Huang[1], Deepinder Goyal[3], Neela Easwar[1], Shayan S. Irani[2], Michael C. Larsen[2]

[1]Gastroenterology, UCLA, Los Angeles, CA; [2]Digestive Disease Institute, Virginia Mason Medical Center, Seattle, WA; [3]Gastroenterology, University of Texas at Houston, Houston, CA

WEIGHT REGAIN AFTER RYGB: POUCH REDUCTION

SMALL BOWEL THERAPIES: DUEDONAL RESURFACING

- *DDW 2017 Sa2003*
- 30 patients
- TORe, n=15 ; TORe-G, n=15
- No significant difference in weight loss
- TORe 16.1 +/- 11.4 kg vs. TORe-G 16.5 +/- 7.3 kg)

BASELINE CHARACTERISTICS

	TORe group	TORe-G group	P value
Sex, no,	1 M/14 F	4M/11F	.1606
Age, y	46.3 ± 9.1	51.3 ± 10.5	.7877
Weight regained, kg	36..6 ± 16.6	34.4 ± 16.4	.9015
Pre TORe BMI	43.7 ± 9.4	44.0 ± 9.2	.9302
Pre TORe stoma, mm	26.3 ± 2.3	28 ± 3.1	.1032
Pre TORe pouch, mm	4.6 ± 1	7.86 ± 2.6	.0001

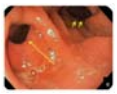
FIG. 22

COMPARISON OF ENDOSCOPIC AND SURGICAL REVISIONS IN THE TREATMENT OF WEIGHT REGAIN FOLLOWING RYGB

Comparison of Endoscopic and Surgical Revisions in the Treatment of Weight Regain Following RYGB

- *Jirapinyo et al. DDW 2019. Sa1979*
- 1:1 matched cohort study
  - Endo (TORe), n=18 vs. Surgical (GJA revision + revised JJ), n=18
  - Weight loss:
    - 6 mo: Endo 11.2% +/- 11.6 vs. Surg 10.3 +/- 7.8, p=0.45
    - 12 mo: Endo 13.9% +/- 11.3 vs. Surg 12.6 +/- 13.2, p=0.82
  - SAE
    - Endo 5.6% (1/18) vs. Surg 38.9% (7/18), p=0.02

WEIGHT REGAIN AFTER RYGB WITH GASTROGASTRIC FISTULA



Sleeve through Fistula Remodeling of the Remnant Stomach: a Novel Treatment Option for Weight Regain in RYGB with GG Fistula

- *Jirapinyo et al. DDW 2019. Sa*
- 17 RYGB with GG Fistula
  - 8 Endoscopic suturing and 9 with endoscopic plication
  - Outlet revision to divert to endoscopic sleeve
  - 6 mo TBWL:
    - Endo sleeve: 7.3% +/- 4.9 vs. Endo-GGF repair: 0.4% +/- 13.8 (p=0.045)
    - Endo sleeve: 7.3% +/- 4.9 vs. Surgical-GGF repair: 8.0% +/- 11.2 (p=0.80)

BARIATRIC SURGERY TRENDS

2011-2017

ACS: 1271 bariatric surgeons
MBSAQIP: 1300 bariatric surgeons
ASMBS: 1810 active surgeon members*

	2011	2012	2013	2014	2015	2016	2017
TOTAL	158,000	173,000	179,000	193,000	196,000	216,000	228,000
Sleeve	17.80%	33.00%	42.10%	51.70%	53.61%	58.11%	53.39%
RYGB	36.70%	37.50%	34.20%	26.80%	23.02%	18.69%	17.80%
Band	35.40%	20.20%	14.00%	9.50%	5.68%	3.39%	2.77%
BPD-DS	0.90%	1.00%	1.00%	0.40%	0.60%	0.57%	0.70%
Revision	6.00%	6.00%	6.00%	11.50%	13.55%	13.95%	14.14%
Other	3.20%	2.30%	2.70%	0.10%	3.19%	2.63%	2.46%
Balloons	–	–	–	–	0.36%	2.66%	2.75%

Published June 2018

ASMBS

The ASMBS total bariatric procedure numbers are based on the best estimates from available data (BRUO, ACS/MBSAQIP, National Inpatient Sample Data and outpatient estimations).

*Ponce, et al. Surgery for Obesity and Related Diseases 12 (2016) 1637–1639

FIG. 23

ENDOSCOPIC MANAGEMENT OF WEIGHT REGAIN AFTER SG - VIDEO

ENDOSCOPIC MANAGEMENT OF WEIGHT REGAIN AFTER LSG

Endoscopic suturing for Weight Regain After Sleeve Gastrectomy: Multicenter Series

- *Vargas et al. DDW 2019 Sa1992*
- Multi-center retrospective
- 9 patients – 1/2018-7/2018
- Median 5 years post-SG
  - Mean 27% weight regain
  - 73% weight loss regained
- 6 month weight loss: 12.7% +/- 4.8% TBWL

Variable	Mean ± s.d.
Age	52.8 ± 10.7
Sex	78% female (n=7)
Time from sleeve gastrectomy	Median: 5 years (range 4-7)
Weight	315.8 ± 53.8 lbs.
Weight regained from nadir	27% (95% CI 13.8-41.5%)
Weight loss regained	73% (95% CI: 42-103%)
Procedural time	69.5 minutes (range 48-86)
Sutures used	Median 5 (range 5-7)
Adverse events	N=1 dilation
1 month %TBWL n=8	5.8% ± 2.5%
2 month %TBWL n=8	9.9% ± 5.8%
3 month %TBWL n=7	10.2% ± 4.2%
6 month %TBWL n=6	12.7% ± 4.8%
9 month %TBWL n=3	18.5% ± 10.3%

ENDOSCOPIC MANAGEMENT OF WEIGHT REGAIN AFTER SG - VIDEO

CONCLUSIONS

- A full spectrum of care is essential to optimally treat obesity
- Endoscopic therapy will have a role, likely in early obesity (likely not a FAD).
- The Future of Endoscopic bariatric therapy is:
  - Repeatable
  - Combinable
  - Sequential
  - Enhanced
  - Personalized

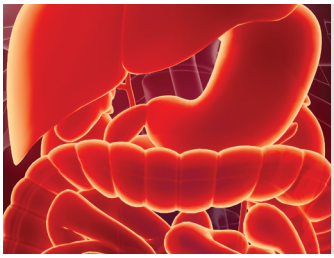
SEPT 21, 2019
ANNUAL GI AND LIVER UPDATES MEETS ACING THE BOARDS

THANK YOU

Christopher Chapman, MD

Director of Bariatric
and Metabolic Endoscopy

AT THE FOREFRONT
UChicago Medicine



Pancreaticobiliary Vignettes

Hetal A. Karsan, MD

Oozing Oil

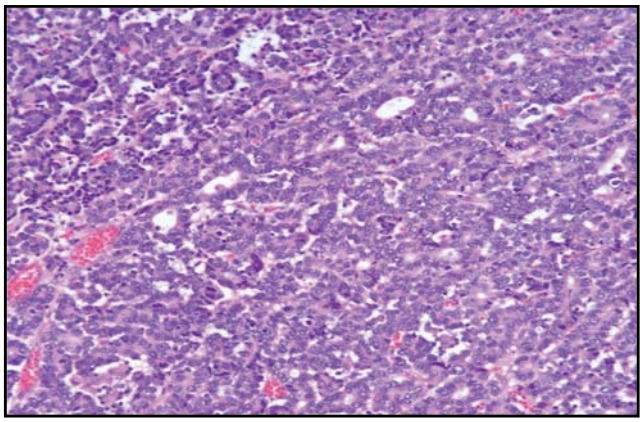
60-year-old ♀ has had painful skin nodules x 6 months with no improvement on prednisone prescribed by her dermatologist for presumed erythema nodosum.

Now with brownish oily discharge from some skin lesions.

No abdominal pain or nausea or vomiting but has 30 pound unintentional weight loss.

Lipase = 10,600 U/L. Abd CT scan → 9-cm mass in tail.

CT-guided biopsy of the pancreatic mass is performed…



What's the diagnosis?

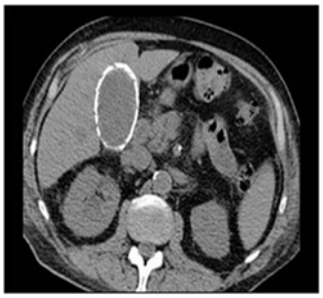
Scooter Mishap

33 year-old ♂ presents to the ED with a leg injury after a collision on his electric scooter.

He denies abdominal pain but does mention that he had bouts of intermittent epigastric pain last year which had spontaneously resolved. Even though he has no abdominal pain now…

Since he is the ED, an obligatory CT scan is performed …

Scooter Mishap

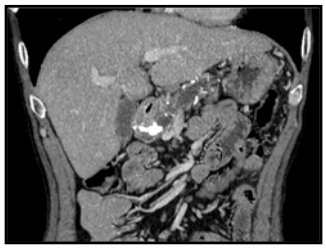


What's the diagnosis?

What should you recommend?

Chronic Pancreatitis Pain

A 60 year-old ♂ with chronic pain due to chronic pancreatitis currently on methadone requests the most definitive therapy for his pain. No gallstones and no alcohol use. TG and IgG4 levels are normal. A CT scan is performed:



Chronic Pancreatitis Pain

What is the best *long-term* treatment for his pain?

A. EUS with celiac plexus neurolysis
B. Pancreatic enzymes with PPI
C. ERCP with pancreatic sphincterotomy and stone removal
D. Pancreaticojejunostomy
E. Increased dosing of methadone

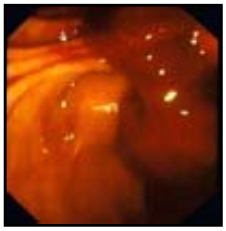
Chronic Calcific Pancreatitis Pain Treatment

- Lateral Pancreaticojejunostomy (Puestow procedure)
  - Most durable therapy for appropriate indications
  - Most cost-effective
- ERCP with panc sphincterotomy, dilation, stone removal (usually does not provide long-term relief)
  - Almost 70% eventually need surgery
- Celiac plexus block and medications/enzymes
  - Not as durable as surgery

Ahmed Ali, et al. *Cochrane Database Syst Rev* 2012; Jan 18;1
Cahen DL, et al. *Gastroenterology* 2011 Nov;141(5):1690-5.
Laramee P, et al. *BMJ Open* 2013; Sept 23;3(9).

Mahogany Mess

A 68-year-old ♂ with chronic pancreatitis presents with acute mahogany-colored stools and hypotension. Emergent EGD → Normal mucosa, there is no blood in the stomach, but this is a view of the 2nd duodenum:



What is the most likely diagnosis?

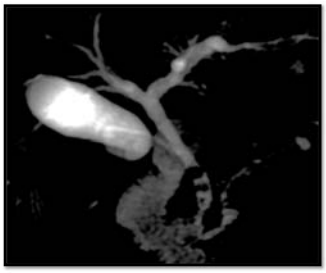
(HINT: Coolest name in GI)

What should you do now?

Between a Rock and a Hard Place

58 year-old ♀ presents with fever, RUQ pain and jaundice. PMHx: MVR on warfarin. Temp 103.1°, HR 118, BP 90/62.

LABS: WBC 19.3, Hgb 14.7, Plt 308, ALT 162, AST 151, Total Bili 5.9, Direct Bili 4.8, Alk Phos 428, INR 3.1.



IVF and IV antibiotics given.

MRCP is obtained.

The nurse reports lethargy.

What should be done now?

Ascending Cholangitis

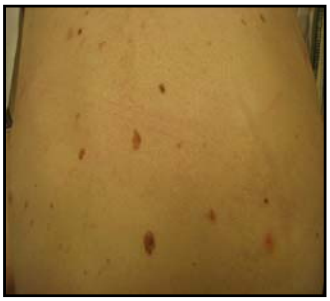
- Charcot's triad – pain, fever, jaundice
- Reynold's pentad – hypotension, Δ mental status
- Need to drain the infected bile duct ASAP
- ERCP with plastic stent now!
- Sphincterotomy has high bleeding risk here
- Don't acutely reverse coagulopathy in MVR due to risk of thrombosis

Fammmily Vacation

A 58 year-old ♀ returns from an European vacation with painless jaundice, weight loss and fatigue. Her family noted that her eyes and skin "looked yellow" and she was urged her to see you. She has no history of alcohol, smoking or drug use. She has not taken any prescribed medications, OTC or herbal medications in over 5 years. While on vacation she learns that she has multiple first and second degree family members with melanoma and pancreatic cancer.

Numerous nevi

Exam: Soft, nontender abdomen. Scleral and cutaneous icterus and multiple nevi throughout her body.



Labs: TB 6, Alk Phos 405, AST 61, ALT 73

CT: 3.5-cm heterogeneous mass in pancreatic head

EUS w/ FNA → adenoCA

Why did she develop pancreatic cancer?

Genetics Association Mini-Quiz

Name the related genetic association

SPINK 1 mutation

CFTR mutation

PRSS1 mutation

STK11 mutation

CDKN2A mutation

ATP7B mutation

ERCP Consult

A 40 year-old ♀ colleague asks you for ERCP for SOD

- Recurrent epigastric pain after CCY 2 years ago for symptomatic biliary colic
- ED x 5 for acute biliary pain with ↑ ALT and ↑AST
- Ultrasound → CBD 12 mm during pain in ED
- Now pain-free in clinic with normal liver tests and negative MRCP with CBD = 6 mm
- Wants sphincterotomy for relief

ERCP Consult

What should you do?

A. Prescribe narcotics prn for recurrence of pain

B. EUS to examine for retained CBD stone

C. Laparoscopic transduodenal surgical sphincterotomy

D. ERCP with sphincterotomy with rectal NSAID

E. Refer for another opinion at a lower volume center so they can spend more time

Post-ERCP Pancreatitis Risk Factors

- Suspected SOD (normal bili)
- Female
- Young (< 50 years old)
- Difficult cannulation
- PD injection(s) – acinarization
- Pancreatic sphincterotomy or PD therapy
- Precut, ampullectomy, balloon bil sphincter
- Inexperienced endoscopist
- History of acute pancreatitis w/o chronic pancreatitis

ERCP Potpourri – TRUE or FALSE

When initial biliary cannulation is difficult, then EUS-guided biliary cannulation with a ***small*** CBD is preferable to precut biliary sphincterotomy

Try to avoid precut biliary sphincterotomy on the rim of a diverticulum due to risk of perforation

Thoughtful patient selection is the most important criterion for prevention of post ERCP pancreatitis

ERCP Potpourri – TRUE or FALSE

Early use of alternative cannulation techniques such as precut or double wire technique is preferred

PD stent should be considered after double wire technique for biliary cannulation

Sphincter of Oddi disorder occurs in those with an intact gallbladder

A Perfect Storm

A 41 year-old obese Caucasian ♀ has been hospitalized and is currently in the SICU after surgical complications following surgical resection of a somatostatinoma. She has remained on IV ceftriaxone and TPN.

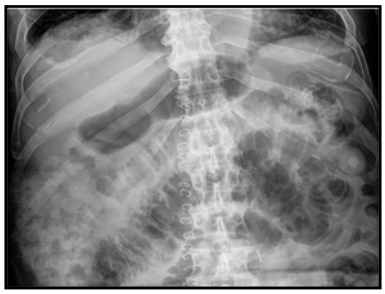
You are seeing her today since she has just suddenly developed severe abdominal pain with total bilirubin 3.2, AST 301, ALT 286, lipase 1049.

What happened?

Name some risk factors for today's event (perfect storm).

Abdominal Pain

62 year-old ♀ presents to ED with severe and increasing abdominal pain and distention with N/V. No recent flatus or BM.
PMH: C-Section x 3; TAH; chronic back pain → taking NSAIDS.
Abdominal X-ray in ED:

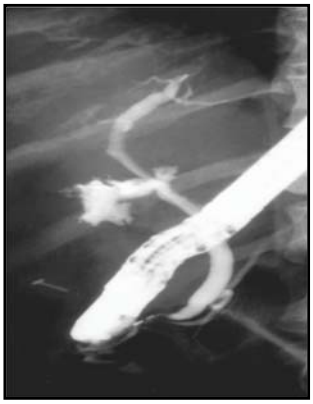


Abdominal Pain

Which of the following is the most likely diagnosis?

A. Abdominal pain due to NSAID-induced PUD
B. Small bowel obstruction from adhesions
C. Gallstone ileus
D. Gastric outlet obstruction from PUD
E. Irritable Bowel Syndrome

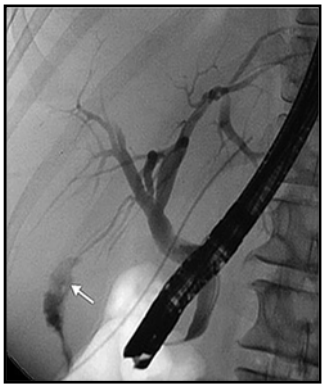
Post-CCY Pain #1



What is the diagnosis?

What should be done?

Post-CCY Pain #2

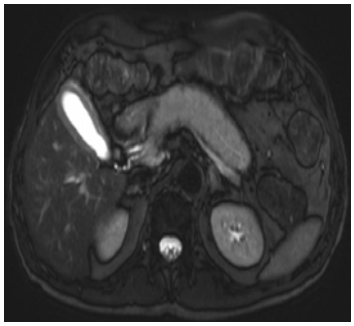


What is the diagnosis?

What should be done?

Image is Everything #1

A 53 year-old ♂ is admitted with acute pancreatitis.

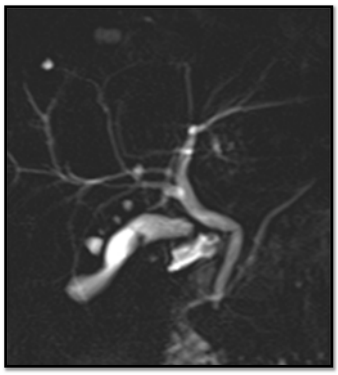


What is the diagnosis?

Which lab test helps you?

Image is Everything #2

A 53 year-old ♂ is admitted with recurrent acute pancreatitis.



What is the diagnosis?

Napping Archeologist

A 28 year-old ♀ archeologist has been doing fieldwork at Olduvai Gorge, Tanzania. One sunny afternoon, she decides to take a nap on the ground. Later that day, she develops acute epigastric abdominal pain radiating to the back with vomiting. She is rushed to a hospital in Arusha where labs show lipase = 3100, normal TG with normal GB on ultrasound. She takes no medications, no herbals, no alcohol and no drugs.

What happened?

Meds → Acute Pancreatitis

	P entamidine
	A zathioprine
Metro	**N** idazole
	C imetidine
Valp	**R**oic acid
	E strogens
5-	**A** SA
	T etracycline
Dd	**I**
HC	**T** Z
	I
La	**S** ix-MP; **S**ulfonamides

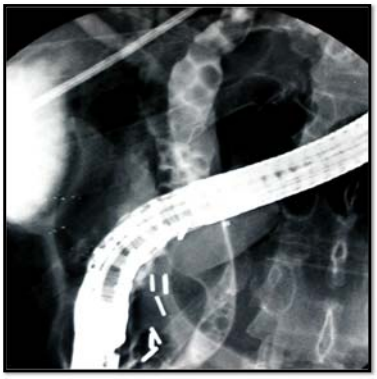
Stone Quarry

26 year-old ♂ recent immigrant from Hong Kong presents to ED with acute RUQ pain, fever and jaundice. He has had multiple similar episodes for 3 years.

Exam: Temp 101.4°, BP 114/70. Icteric with no other stigmata of chronic liver disease. Tender in RUQ with negative Murphy's sign and GB is not palpable.

Labs: T Bili 8.5 (Direct Bili 7.1), AST 60, ALT 72, INR 1.1, Alb 3.4, Alk Phos 360, WBC 16.2K (90% PMNs), Cr 1.2

ERCP is performed…

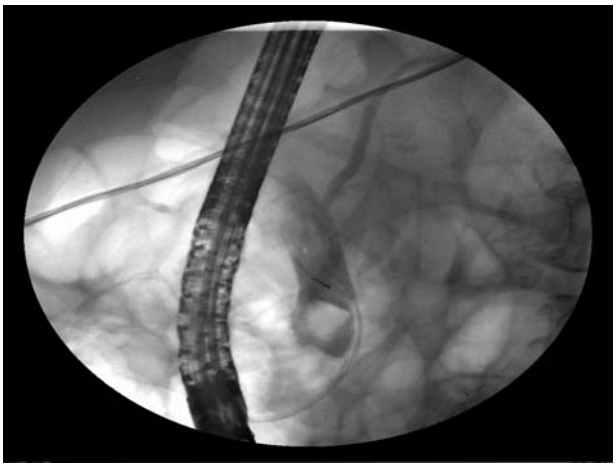


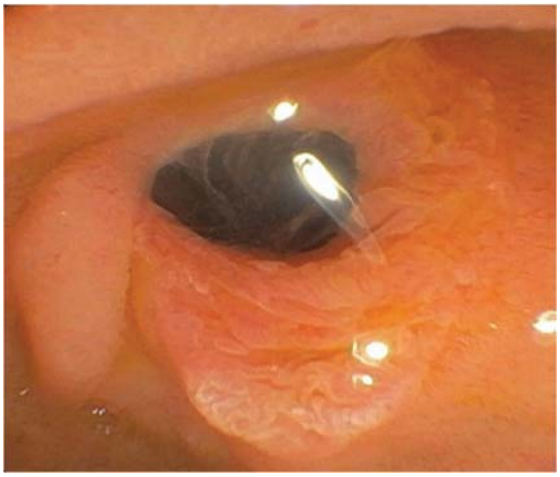
What is the diagnosis?

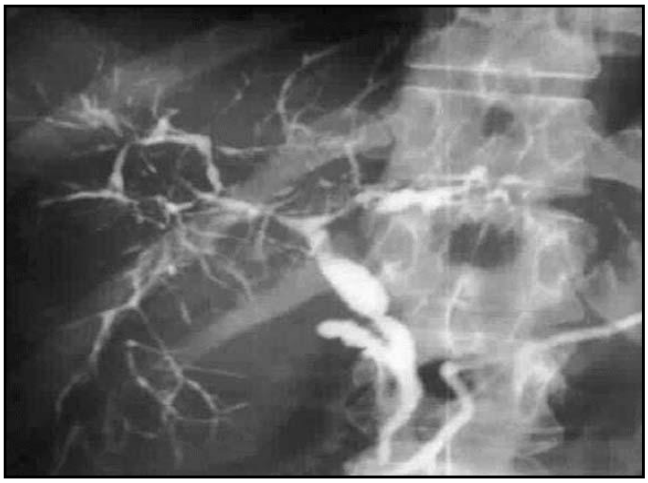
What *kind* of stones are these?

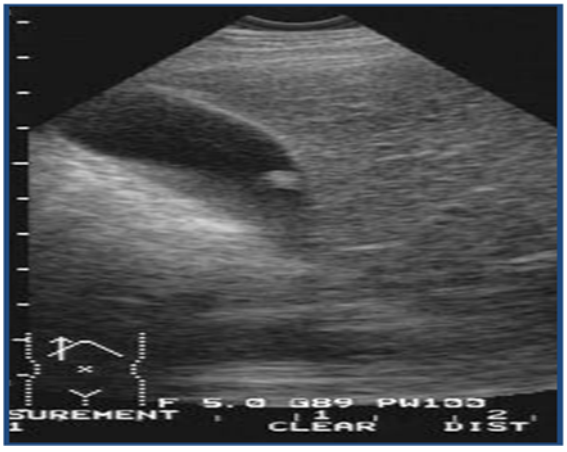
Stoned

Clinical Scenario	TYPE of Stone Cholesterol, Brown, Black
Somatostatinoma	
Obese on a 'crash' diet	
Sickle cell anemia	
Recurrent pyogenic cholangitis	
Longstanding TPN use	
Cirrhotic with portal hypertension	
Pregnant	
Septic on ceftriaxone	





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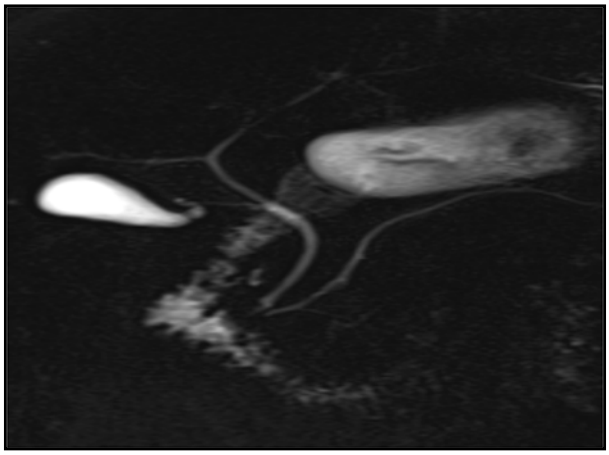

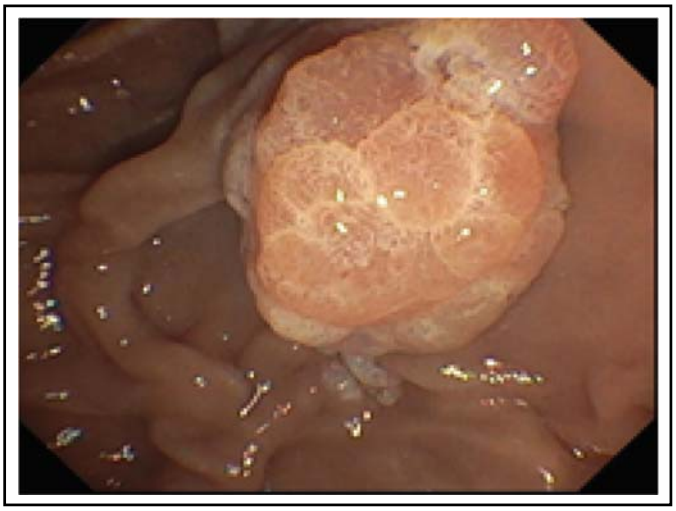

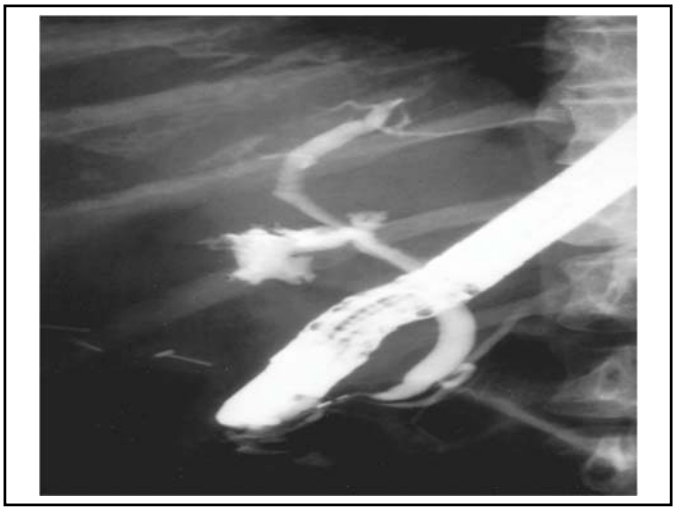

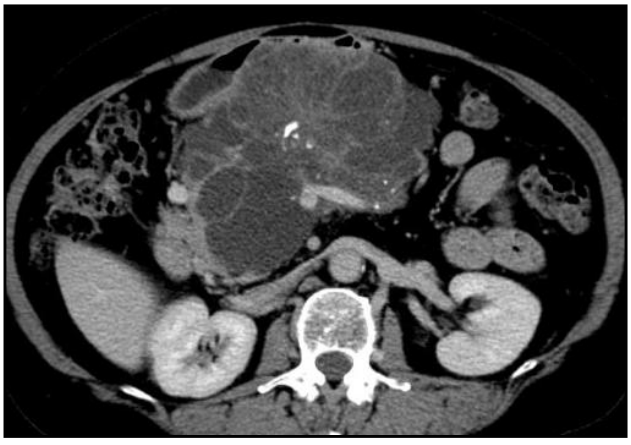

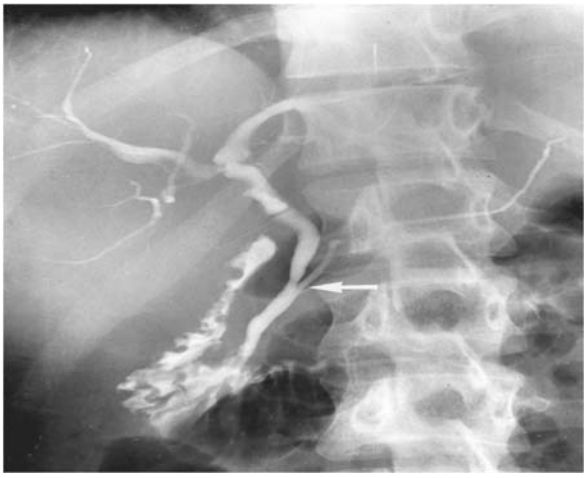

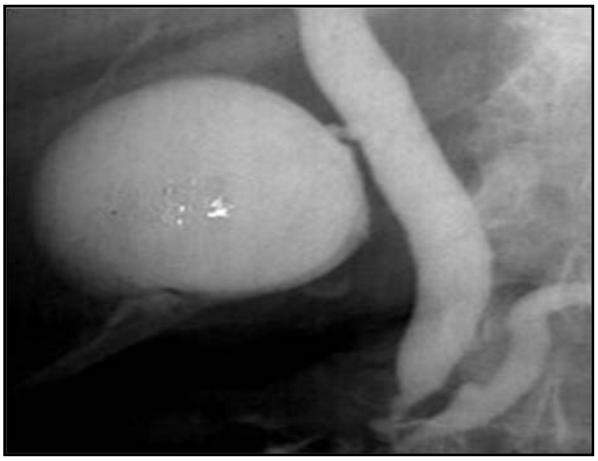

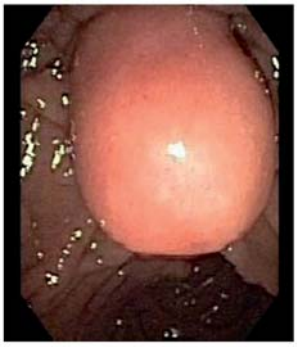

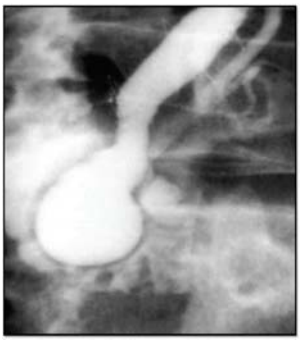

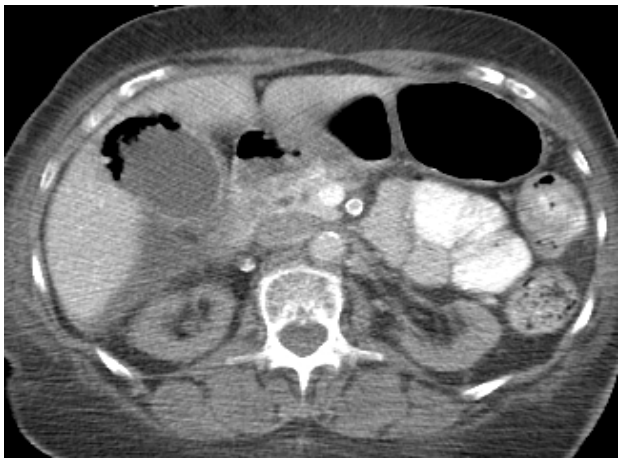

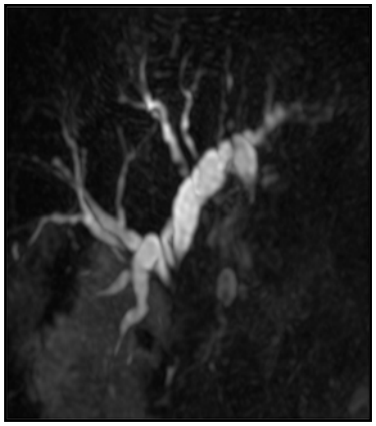

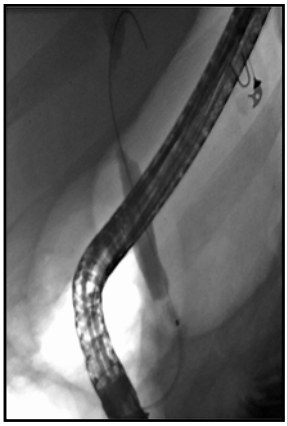

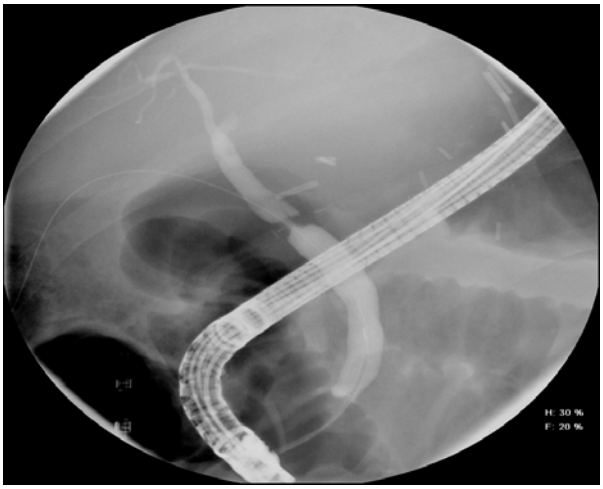
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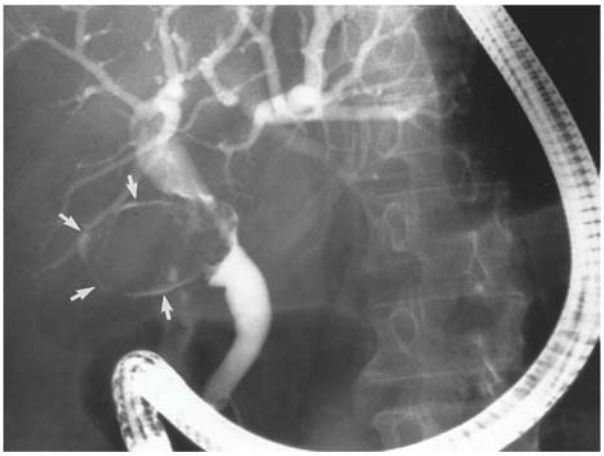
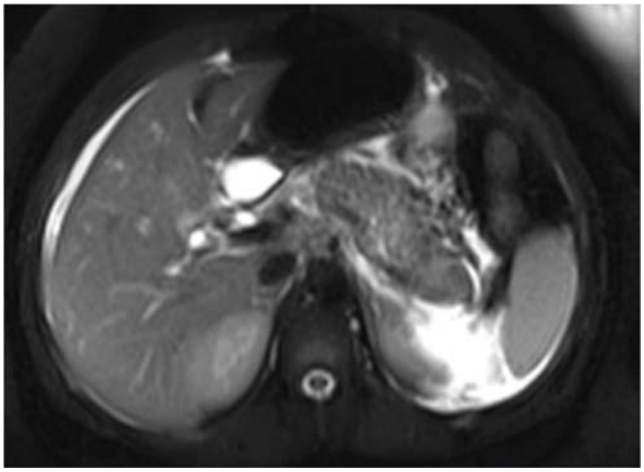
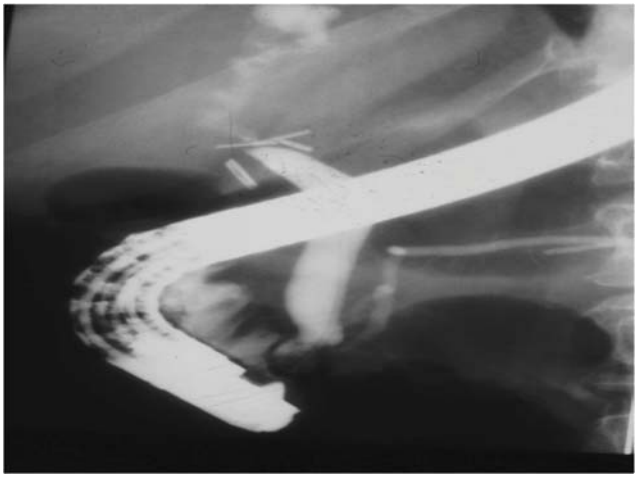
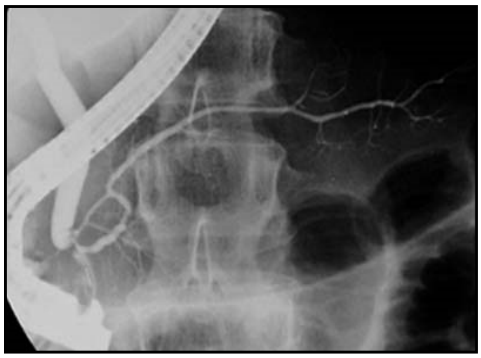








Name this gallbladder condition

Pancreaticobiliary One-Liners

Blood in duo w/ nml mucosa + pancreatitis

Fishmouth ampulla with cluster of grapes in pancreas

Pancreatic tumor + peripheral fat necrosis

Most common mutation in autosomal dom hereditary panc

Most common type of pancreatic cancer

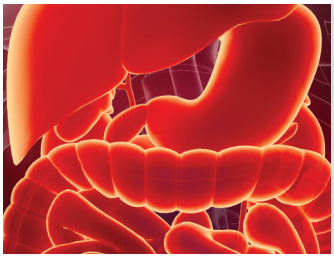
Elderly ♀ + "honeycomb" panc cyst

Most common congenital pancreatic ductal variant

Risk of malignant transformation of pseudocyst

Most common cause of pancreatitis in children

Pancreatic tumor + weight gain



Acing the Boards: Rapid Fire Review

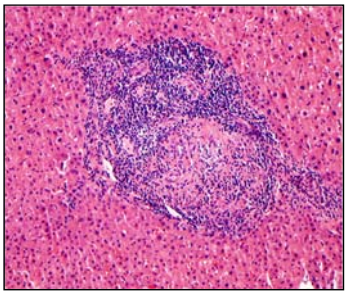
Hetal A. Karsan, MD; and Brennan Spiegel, MD, MSHS

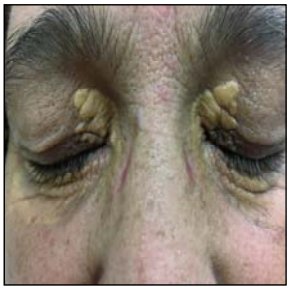
GI Boards: Rapid Fire Review Test

Brennan Spiegel, MD, MSHS, FACG, AGAF
Hetal A. Karsan, MD, FACG, FASGE, FAASLD, FACP

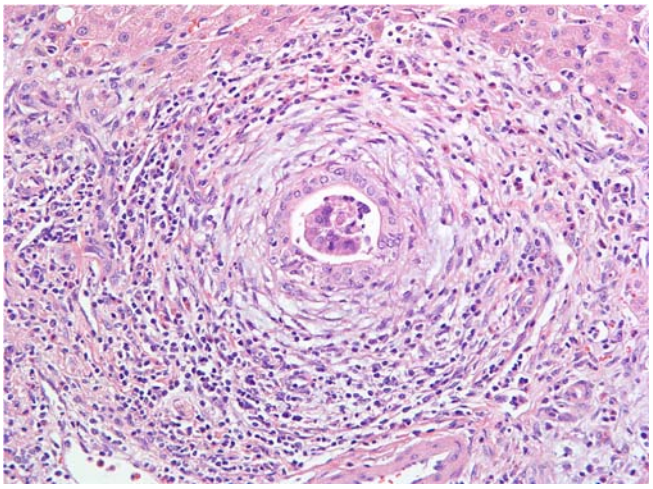
CEDARS-SINAI · ATLANTA Gastroenterology Associates · GRE · EMORY UNIVERSITY

Liver

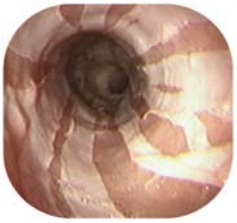




"Fork" sign



Esophagus



→ What's the diagnosis?

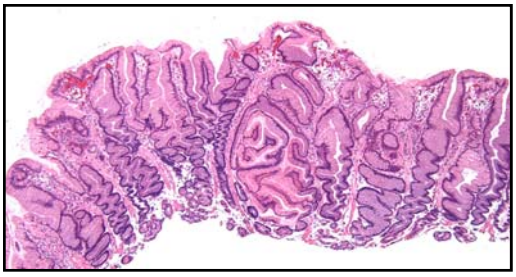
Esophagus

Dysphagia + thatched roof hut

Crazy lizard tongue shoots out of mouth

Smoker gets dysphagia and constipation

Stomach & Duodenum



And hypergastrinemia

Stomach & Duodenum

High gastrin, dyspepsia, history of Hashimoto's

Fundic gland polyposis without PPIs

CHF + diarrhea + white spots in duodenum

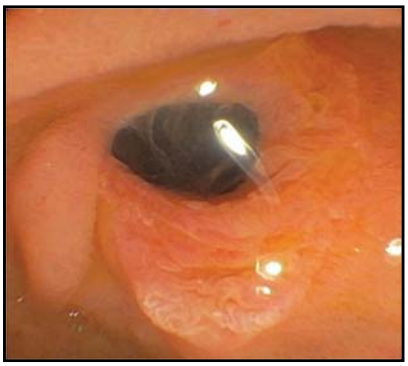
Pancreaticobiliary

Pancreatitis + UGIB + blood in duodenum without mucosal lesions

Cluster of grapes seen on pancreatic imaging

Two malignancies associated with APBJ

Pancreaticobiliary



Pancreaticobiliary

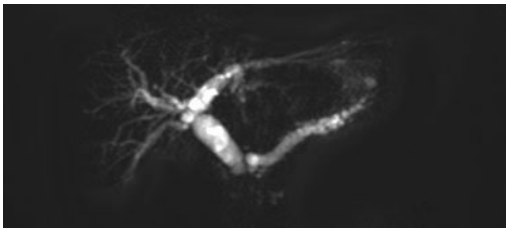
Pancreatic tumor with peripheral fat necrosis

Chronic pancreatitis + gastric varices

Epigastric pain + succussion splash + calcification near pylorus

Name of syndrome and cause of syndrome

Elderly patient with weight loss



What is the name of this finding?

What causes this finding?

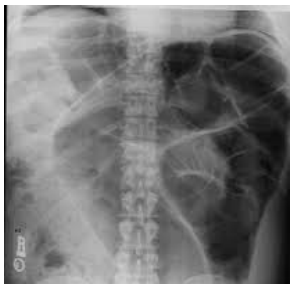
Colon

Acute colitis + HUS-TTP

Rectal bleeding + fibromuscular obliteration

Cyclical rectal bleeding in a woman with submucosal nodule on colonoscopy

Colon



Bent inner tube

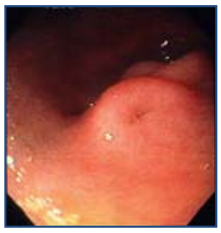
Esophagus

Dysphagia + oblique defect across esophagus

Dysphagia + “Shawl Sign”

Dysphagia + “Megaduodenum”

Stomach & Duodenum



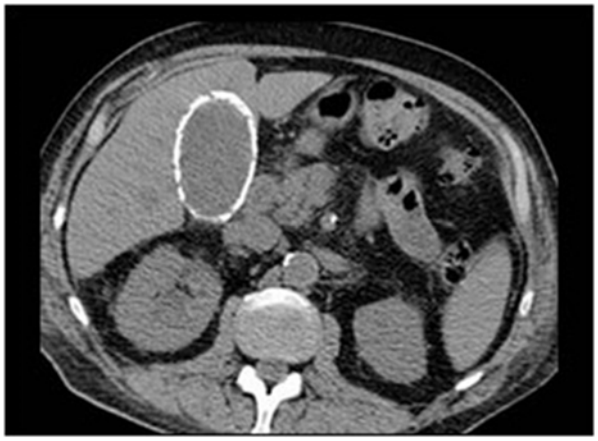
→ What’s the diagnosis?

Pancreaticobiliary

Decreased bicarb secretion leads to viscous secretions + ductular plugs and obstruction

Tropical pancreatitis related to this mutation

Scorpion sting + abdominal pain



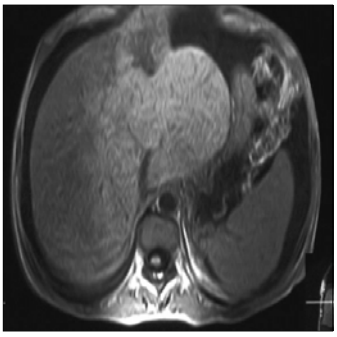
Liver

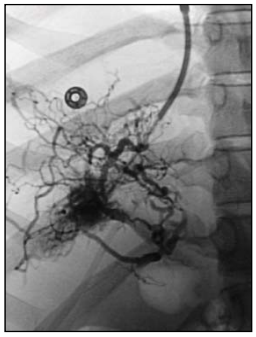
Health freak develops elevated liver tests and has lipid-filled stellate cells on liver biopsy

Liver lesion aspiration with anchovy paste

Caudate lobe hypertrophy

Liver





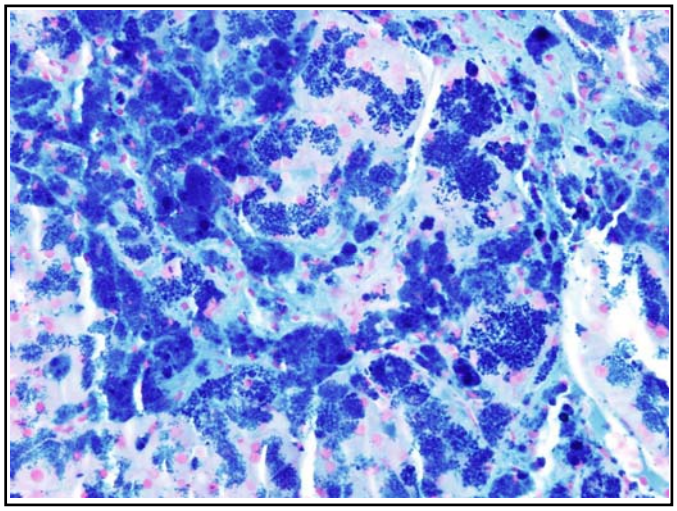
Polycythemia vera + ascites

Liver

Young + micrographia + acute liver failure + hemolytic anemia

Amazon traveler + acute hepatitis + fever + jaundice

Percentage of liver disease in null genotype A1AT deficiency



Liver

Most common hepatic decompensation

Two diseases caused by ATP7 mutation

Sunflower cataracts

Functional GI & Motility

Bloating + low B12 + high folate

"Anal retentive" with chronic constipation

Aganglionic rectum and constipation

Functional GI & Motility

Effortless regurgitation without alarm features

Recurrent vomiting in setting of THC usage

Mechanism of linaclotide

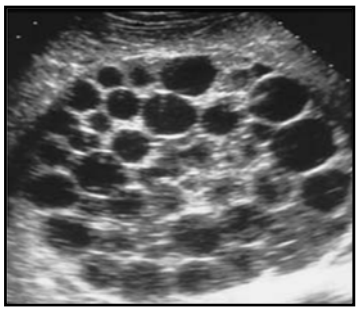
Esophagus

Vomiting and left pleural effusion

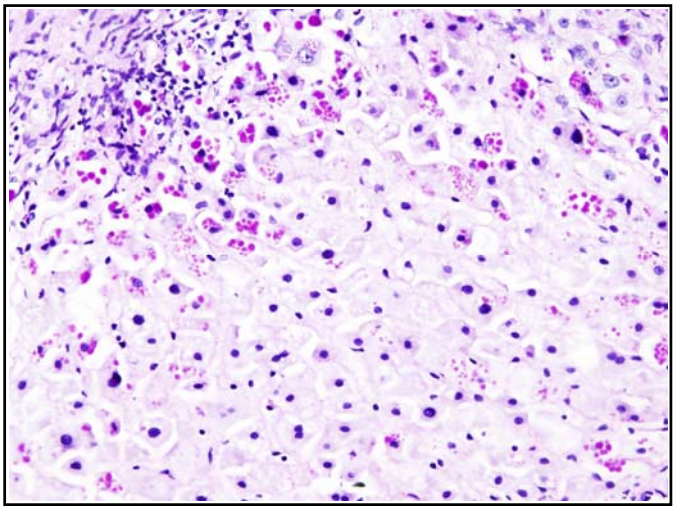
High amplitude *propagating* esophageal contractions

Multiple “volcano ulcers” in esophagus with odynophagia

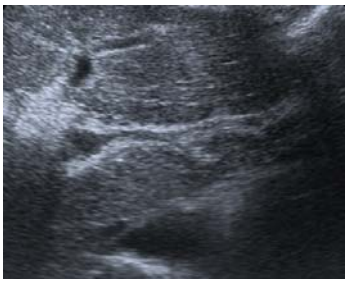
Liver



Shepherd + anaphylaxis with “sand” aspiration



Liver



Serum sickness after swimming in a lake

Liver

HCV genotype associated with steatohepatitis

Most common cause of ALF in USA

"Rave" party + bruxism + super high ALT

Lake swim + red eye + fever + ↑↑↑TB + ↑ALT

Liver

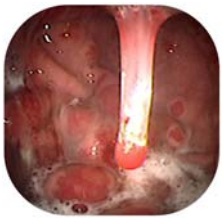
Most common genotype of Hepatitis E in USA

T or F: Hepatitis E can cause chronic liver disease

T or F: Coffee is good for the liver

Three iron-loving bacteria

Stomach & Duodenum



And protein-losing enteropathy

Stomach & Duodenum

Retching without vomiting + acute epigastric pain + inability to pass NGT

Premature graying + vitiligo + positive Rhomberg sign

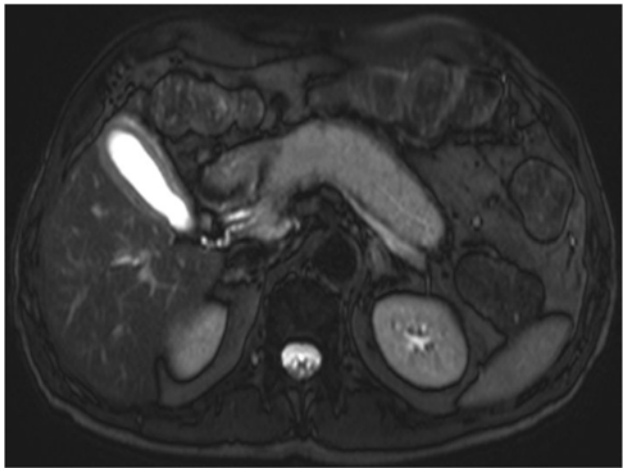
Gastric nodules in patient with pernicious anemia

Pancreaticobiliary

#1 environment risk factor for pancreatic cancer

Liver tumor causing capsular retraction instead of bulge

Portal vein thrombosis + collaterals + biliary obstruction



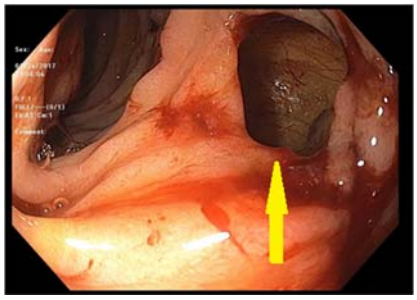
Pancreaticobiliary

Most common extrapancreatic manifestation of type 1 autoimmune pancreatitis

Most common extrapancreatic manifestation of type 2 autoimmune pancreatitis

Jaundice after CCY + ERCP shows no opacification of proximal bile duct and surgical clip near bile duct

Pancreaticobiliary



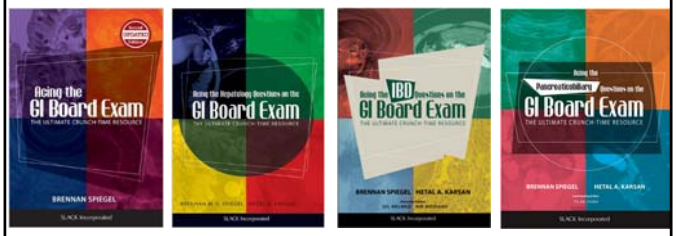
Long position ERCP + abd pain + normal lipase

Pancreaticobiliary

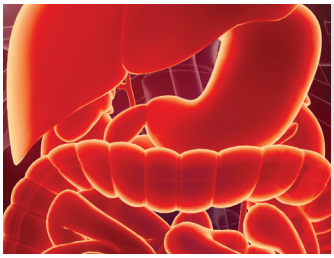
Most common cause of pancreatitis in children

Most common cause of *viral* pancreatitis in children

Pancreatic tumor with weight gain

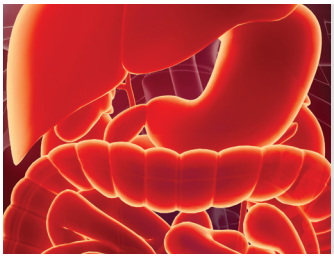


Thank You!



Overview of the IBD Programs

Russell Cohen, MD

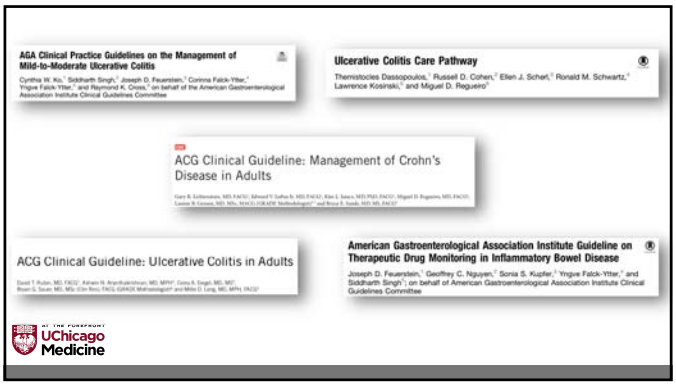


Updates on the New IBD Guidelines

David Rubin, MD

Updates on the New IBD Guidelines

David T. Rubin, MD, FACG, AGAF, FACP, FASGE
Joseph B. Kirsner Professor of Medicine
Chief, Section of Gastroenterology, Hepatology and Nutrition
University of Chicago
@IBDMD



How Are Guidelines Developed?

ACG[1]

- Conference call with the Practice Parameters Committee
- Systematic reviews of the evidence
- Recommendations by the "nominal group technique"
- Statements GRADEd for strength of evidence and recommendation
- Final review: Board of Trustees, Practice Parameters Committee and the AJG

AGA[2]

- AGA Institute's Clinical Guidelines Committee and approved by the AGA Institute Governing Board
- Members selected by the AGA Clinical Guidelines Committee
- Participants develop focused clinical questions→ approved by the AGA Governing Board
- Technical reviews AND using GRADE

ECCO

- Open call for participants → ECCO participants selected by the Guidelines' Committee of ECCO (GuiCom)
- Provisional guideline statements are written following a comprehensive literature review→ two voting rounds
- Level of evidence is graded
- Statements finalized by the authors and represent consensus with agreement of at least 80% of the participants

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[1]ACG. https://gi.org/clinical-guidelines/guideline-development-policies/ Accessed February 5 2019.
[2]Singh S, et al. *Gastroenterology*. 2019;156(3):769-808.e29.

Mucosal Healing as a Target in UC

- Treat UC to achieve MH in order to increase sustained steroid-free remission, and prevent hospitalizations and surgery[1,2]
- Fecal calprotectin as surrogate for endoscopy when endoscopy not feasible to assess for mucosal healing and disease activity[1,2]
- Histological healing is distinct from endoscopic mucosal healing[3]

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[1]Rubin DT, et al. *Am J Gastroenterol*. 2019;114(3):384-413.
[2]Wei CS, et al. *Intest Res*. 2017;15(3):266–284.
[3]Magro F, et al. *J Crohns Colitis*. 2017;11(6):649-670.

Monitoring Disease Activity: Treat to Target

- Fecal **calprotectin** → adjunctive role in monitoring activity, response to therapy
  - Levels > 100 µg/g → indicates endoscopic recurrence (89% sensitivity)
  - Fecal calprotectin > 160 µg/g → predicted relapse for infliximab-induced remission (92% sensitivity, 83% specificity)
- **C-reactive protein** → baseline values >15 mg/L predicted primary non-response to infliximab (67% sensitivity, 65% specificity)
  - Normalization of CRP at week 14 → greater chance of continued response during maintenance
- **Mucosal healing → ABSENCE** of ulceration
  - Predicts sustained remission, decreased surgery, decreased hospitalization

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ACG Clinical Guidelines: Management of Crohn's disease in adults. *Am J Gastroenterol*. 2018;113:481-517.

New UC Activity Index

	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

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Modified from Truelove SC, Witts LJ. *Br Med J*. 1955;2:1041-8.

Crohn's Disease Activity Index (CDAI)

Clinical or Laboratory Variable	Weighting Factor
Number of liquid or soft stools each day for seven days	x2
Abdominal pain (graded from 0-3 on severity) each of the seven days)	x5
General well being, subjectively assessed from 0 (well) to 4(terrible) each day for seven days	x7
Presence of complications	x20
Taking Lomotil or opiates for diarrhea	x30
Presence of abdominal mass (0 as none, 2 as questionable, 5 as definite)	x10
Hematocrit of <0.47 in men and <0.42 in women	x6
Percentage deviation from standard weight	x1

- One point is added for each of the following complications
  - Arthralgias/Arthritis
  - Iritis/Uveitis
  - Erythema nodosum/pyoderma gangrenosum, aphthous ulcers, anal fissures, fistulae, or abscesses
  - Other fistulae
  - Fever during the previous week
- CDAI score classification
  - Remission: <150
  - Mild: 150-220
  - Moderate: 220-450
  - Severe: >450

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ACG Clinical Guidelines: Management of Crohn's disease in adults. *Am J Gastroenterol*.2018;113:481-517.

Poor Prognostic Factors in Ulcerative Colitis Disease Severity

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

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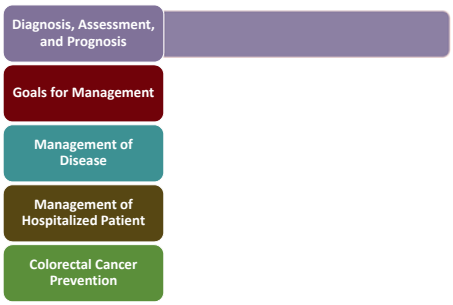
Poor Prognostic Factors in Crohn's Disease Severity

Poor Prognostic Factors
Young age of diagnosis
Extensive colitis
Ileal/ileocolonic involvement
Perianal/severe rectal disease
Penetrating or stenosis disease phenotype

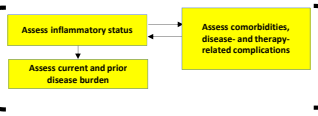


Diagnosis, Assessment, and Prognosis of UC

- Recommendations:
  - Against serologic antibody testing to establish or rule out diagnosis of UC
  - Against serologic antibody testing to determine the prognosis of UC
- Key Concept Statements:
  - Disease severity should be based on:
    - Patient reported outcomes (bleeding and normalization of bowel habits)
    - Inflammatory burden (endoscopic assessment including extent and severity, and markers of inflammation)
    - Disease course (need for hospitalization, need for steroids, failure to respond to medications)
    - Disease impact (functionality, QoL)

Crohn's Disease: Diagnosis and Risk Stratification Are Used to Guide Treatment

- **Location**
- **Extent**
- **Severity**
- **EIMs**



- **Infections**
- **Strictures**
- **Surgical hx**
- **Adverse rxns**
- **Fistulas**

ACG 2018 statement: **IBD type, location, and disease activity should be documented in the medical record.**

ACG Clinical Guidelines: Management of Crohn's disease in adults. *Am J Gastroenterol*.2018;113:481-517.
Sandborn WJ. *Gastroenterology*. 2014;147(3):702-705.

Crohn's Disease Guidelines: Disease Modifiers

- Non-steroidal anti-inflammatory drugs → May exacerbate disease activity and should be avoided when possible
- Cigarette smoking → exacerbates disease activity and accelerates disease recurrence and should be avoided
- Antibiotic usage → should not be restricted in order to prevent disease flares
- Stress, depression, anxiety → common in IBD, associated with decreased quality of life, lower adherence
  - Psychosocial assessments and management part of comprehensive IBD care

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Diagnosing Crohn's Disease: Assessing Inflammatory Status

Assess inflammatory status

Assess symptoms/signs
- Fever
- Abdominal pain
- GI bleeding
- Localized tenderness
- Weight loss
- Extra-intestinal manifestations

Perform clinical lab testing
- CBC
- CRP
- CMP
- **Fecal calprotectin**
- C.difficile
- Enteric pathogens

ACG 2018 guideline: Fecal calprotectin → differentiate IBD vs IBS

ACG 2018 statement: IBD serologies, IBD genetics *NOT* indicated

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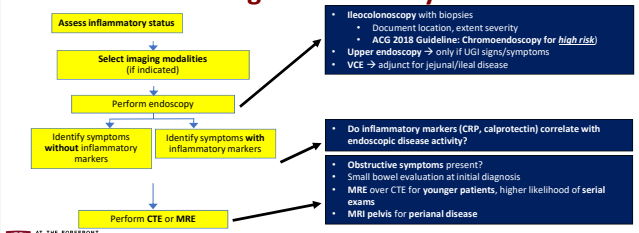
Sandborn WJ. *Gastroenterology*. 2014;147(3):702-705.
ACG Clinical Guidelines: Management of Crohn's disease in adults. *Am J Gastroenterol*.2018;113:481-517.

Diagnosing Crohn's Disease: Assessing Inflammatory Status



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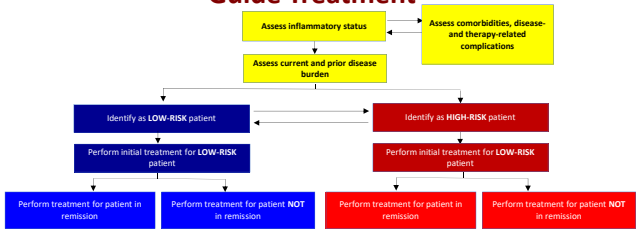
Crohn's Disease: Risk Stratification Used to Guide Treatment



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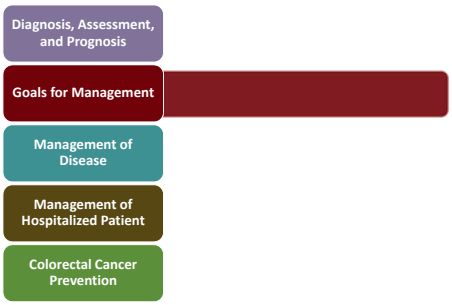
Sandborn WJ. *Gastroenterology*. 2014;147(3):702-705.



Goals for Managing Patients with UC

- Recommendations:
  - Treat patients with UC to achieve mucosal healing in order to increase the likelihood of sustained steroid-free remission, and prevent hospitalizations and surgery
  - Fecal calprotectin as surrogate for endoscopy for when endoscopy is not feasible or available, to assess for mucosal healing

Goals for Managing Patients with UC

- Key Concept Statements:
  - Therapeutic decisions should be categorized into those for a) induction and b) maintenance; with a goal of obtaining and maintaining a steroid-free remission
  - Control of mucosal inflammation may reduce dysplasia risk
  - Screen for co-existent anxiety and depressive disorders and, when identified, provide resources to address these conditions
  - In general, favor topical/organ selective treatments before systemic ones

Management of CD: Goals of therapy

- Induce and maintain remission
- Objective evaluation should be performed to confirm subjective improvement
- Define timeframe for response to initial or change in treatment
  - Clinical evidence of improvement within 2-4 weeks
  - Maximal improvement should occur within 12-16 weeks
- Continued symptoms → Diagnostic evaluation, Dose adjustment or Change in therapy

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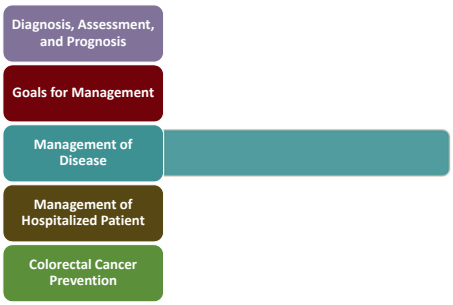

Induction of Remission in Mildly Active UC

- Recommendations:
  - For proctitis → rectal 5-ASA therapies at a dose of 1 g/day
  - For left-sided UC→ rectal 5-ASA enemas at a dose of at least 1 g/day preferred over rectal steroids
  - For left-sided UC who are intolerant or non-responsive to oral and rectal 5-ASA at appropriate doses (oral at least 2.0 g daily and rectal at least 1 g daily) → use oral budesonide MMX 9 mg/day
  - For extensive UC → oral 5-ASA at a dose of at least 2.0 g daily
  - For UC of any extent who fail to respond to 5-ASA therapy → oral systemic corticosteroids
  - For UC of any extent → low dose (2.0-2.4g) of 5-ASA, in comparison to a higher dose (4.8g), as there is no difference in remission rate

Induction of Remission in Mildly Active UC

- Key Concept Statements:
  - Patients with mildly active UC and a number of prognostic factors associated with an increased risk of hospitalization or surgery should be treated with therapies for moderate-to-severe disease
  - Reassessment of response to induction therapy within 6 weeks
  - Fecal microbiota transplantation requires more study and clarification of treatment prior to use as a therapy for UC
  - Complementary therapies such as probiotics and curcumin require further study with adequate power and clarification of endpoints

Options for INDUCTION Therapy : Mild to Moderate Disease activity/LOW-RISK CD

- Sulfasalazine → ***COLONIC*** disease only
- Mesalamines should ***NOT*** be used to treat Crohn's disease
- Controlled ileal release budesonide 9mg daily → mild to moderate ***ILEAL*** or ***ILEOCECAL*** disease
- Antibiotics: ciprofloxacin, metronidazole, anti-mycobacterial therapy → should ***NOT*** be used for primary treatment of luminal Crohn's disease

Potentially acceptable strategies for patients with ***low risk of progression***:
- anti-diarrheals
- "other non-specific" medications
- dietary manipulation

With these strategies:
- observation for symptom relief or worsening
- Routine assessments to identify disease progression

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Maintenance of Remission in Patients with Previously Mildly Active UC

- Recommendations:
  - For proctitis → rectal 5-ASA at a dose of 1 g daily
  - For left-sided or extensive UC → oral 5-ASA therapy (at least 2 g/day)
  - Against systemic corticosteroids

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Options for MAINTENANCE Therapy : Mild to Moderate Disease activity/LOW-RISK CD

- **Sulfasalazine** → "data lacking", no role for maintenance treatment
- **Oral mesalamines** → no role for maintenance treatment
- **Oral budesonide** → no role for maintenance treatment

ACG 2018 statement:
- **NO MAINTENANCE TREATMENT** may be an option for **ASYMPTOMATIC** or **MILD** disease
- **SURGERY** may be considered for **SYMPTOMATIC SHORT SEGMENT** disease
- Monitor for disease progression or recurrence

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Induction of Remission in Moderately-to-Severely Active UC

- Recommendations:
  - For moderately active UC → oral budesonide MMX
  - For moderately-to-severely active UC:
    - Oral systemic corticosteroids
    - Anti-TNF therapy using adalimumab, golimumab or infliximab
    - When IFX is used as induction therapy, combine therapy with a thiopurine
    - Vedolizumab
    - If previously failed anti-TNF therapy → vedolizumab
    - Tofacitinib 10 mg orally twice daily for 8 weeks
    - If previously failed anti-TNF therapy → tofacitinib
    - If now losing response to anti-TNF therapy, suggest measuring serum drug levels and antibodies (if there is not a therapeutic level) to assess reason for loss of response

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Induction of Remission in Moderately-to-Severely Active UC

- Key Concept Statements:
  - If lost efficacy to one anti-TNF therapy → alternative anti-TNF therapy (but not the biosimilar to the original brand) as compared to no treatment for induction of remission
  - If non-response or loss of response to therapy → assess with TDM to identify the reason for lack of response and whether to optimize the existing therapy or to select an alternate therapy
  - Obtain consultation with a surgeon and consider colectomy in patients who are refractory or intolerant to medical therapy

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Options for INDUCTION Therapy: Moderate to Severe Disease activity/HIGH-RISK CD

- **Oral steroids** → only for short term induction agents for inflammatory Crohn's disease
- **Thiopurines** → no role for induction, only for maintenance of remission
  - TPMT testing prior to initiation
- **Methotrexate** → no role for induction, only maintenance of remission in steroid-dependent disease
  - Consider family planning when using for both men and women
- **Anti-TNF agents** → steroid resistant or thiopurine or methotrexate refractory disease

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Options for INDUCTION Therapy: Moderate to Severe Disease activity/HIGH-RISK CD

- **Combination therapy with infliximab** → more effective than monotherapy with thiopurines or infliximab for ***NAÏVE*** patients
- **Anti-integrin** therapy → vedolizumab with or without immunomodulator
- **Natalizumab** → induction of response/remission
  - Risk of progressive multi-focal leukoencephalopathy
    - JC virus antibody positive → 1:100 risk if positive, check every 6 months
    - Prior history of immunosuppressive use
    - Treatment duration > 2+ years

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Options for INDUCTION Therapy: Moderate to Severe Disease activity/HIGH-RISK CD

- **Ustekinumab** → for patients who failed steroids, thiopurines, methotrexate, anti-TNFs, or anti-TNF naïve
- Cyclosporine, mycophenolate mofetil, tacrolimus → should ***NOT*** be used
- **Biosimilars** → same indications as originator anti-TNFs for de novo induction
  - *"Insufficient data… to support safety and efficacy of switching patients in stable disease maintenance"*

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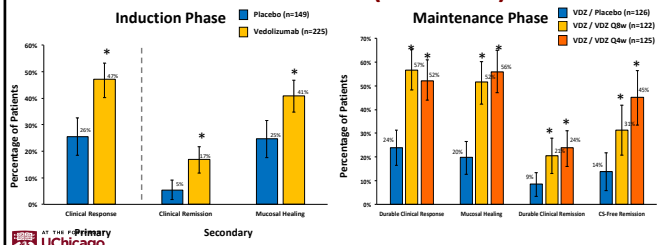
Vedolizumab for Induction and Maintenance of Remission in UC (GEMINI 1)



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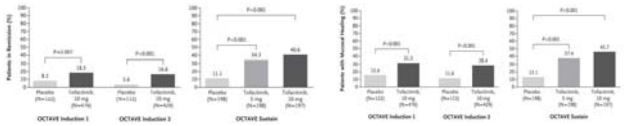
Feagan B, et al. *N Engl J Med*. 2013;369(8):699-710.

Tofacitinib is Safe and Effective as Induction and Maintenance Therapy for Moderately-to-Severely Active UC

Clinical Remission **Mucosal Healing**



Sandborn W, et al. *N Engl J Med*. 2017;376(18):1723-1736.

Maintenance of Remission in Patients with Previously Moderately-to-Severely Active UC

- Recommendations:
  - Thiopurines
  - Against methotrexate
  - Continuing anti-TNF therapy using adalimumab, golimumab or infliximab to maintain remission after anti-TNF induction
  - Continuing vedolizumab to maintain remission after vedolizumab induction
- Key Concept Statements:
  - Elective proctocolectomy in patients failing maximal management

Management of the Hospitalized Patient with Acute Severe UC

- Recommendations:
  - DVT prophylaxis as compared to no prophylaxis to prevent VTE
  - Testing for *C. diff*
  - If concomitant *C. diff*, treat with vancomycin instead of metronidazole
  - Against total parenteral nutrition for the purpose of bowel rest
  - A total of 60 mg/day of methylprednisolone or hydrocortisone 100 mg 3-4x per day
  - If failing to adequately respond to IVCS by 3-5 days→ medical rescue therapy with infliximab or cyclosporine
  - For those who achieve remission with cyclosporine, maintain remission with:
    - Thiopurines
    - Vedolizumab

Options for MAINTENANCE Therapy: Moderate to Severe Disease activity/HIGH-RISK CD

- **Thiopurines/Methotrexate** → steroid-induced remission
  - **STEROID-DEPENDENT → consider thiopurines/MTX with anti-TNFs**
- **Anti-TNFs** → maintain anti-TNF-induced remission
  - **COMBINATION therapy** recommended with thiopurines or methotrexate due to **IMMUNOGENICITY** and **LOSS OF RESPONSE**
- **Vedolizumab** → maintain vedolizumab-induced remission
- **Natalizumab** → maintain natalizumab-induced remission in JC-virus negative patients only
- **Ustekinumab** → maintain ustekinumab-induced response

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Management of the Hospitalized Patient with Acute Severe UC

- Key Concept Statements:
  - Have stool test to rule out *C. diff*
  - Patients should undergo flexible sigmoidoscopy within 72 hours (preferably 24 hrs) of admission
  - Assess for the presence of toxic megacolon
  - Response in patients with ASC should be monitored using stool frequency, rectal bleeding, physical examination, vital signs, and serial CRP measurements
  - NSAIDs, narcotics, and medications with anticholinergic side effects should be avoided
  - Infliximab and cyclosporine do not increase post-op complications and surgery must not be deferred

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Indications for Surgery in CD

- Required to treat enteric complications
- Bowel resection of diseased segment → obstruction or fistula
- Indications:
  - Intractable hemorrhage
  - Perforation
  - Abscess → treat with antibiotics and drainage (radiology or surgery)
  - Obstruction
  - Dysplasia/Cancer
  - Refractory disease
- **CD patients with ***abdominal abscess*** should have surgical resection**

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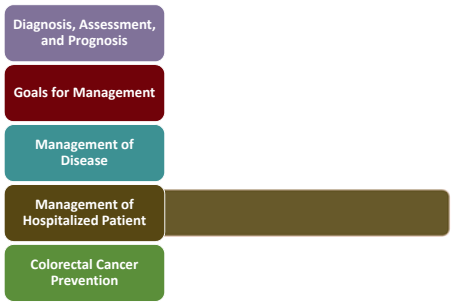

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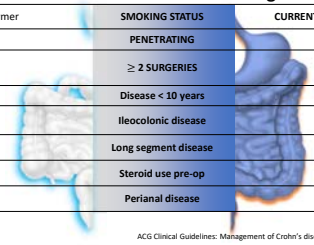
Post-operative Crohn's disease management → risk stratification determines choice

Low-Risk	SMOKING STATUS	High-Risk
Never/Former		CURRENT/RECENT
No	PENETRATING	YES
No	≥ 2 SURGERIES	Yes
No	Disease < 10 years	Yes
No	Ileocolonic disease	Yes
No	Long segment disease	Yes
No	Steroid use pre-op	Yes
No	Perianal disease	Yes



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Post-operative Crohn's disease management → risk stratification determines choice

- **Smoking cessation** recommended for ***ALL*** surgical patients
- **Mesalamine** → **low-risk** patients only
  - no risk factors for recurrence – mesalamines vs no treatment
- **Imidazole antibiotics** → 1-2 grams daily, **low-risk** patients
- **Thiopurines** → more effective than mesalamines or no treatment
  - Not effective to prevent severe endoscopic recurrence
  - **NOT** for high-risk patients
- **Anti-TNFs** → **HIGH-RISK** patients
  - Start within 4 weeks post-op
  - Combination therapy with immunomodulators recommended

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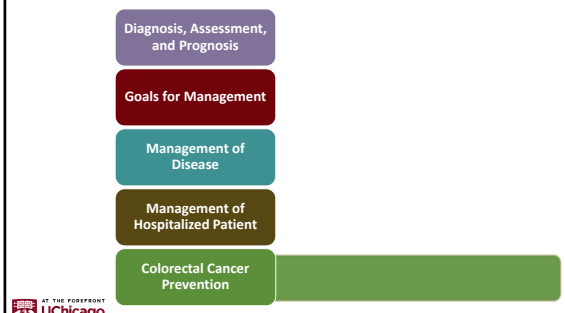

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Colorectal Cancer Prevention in UC

- Recommendations:
  - Colonoscopic screening and surveillance to identify neoplasia in patients with UC of any extent beyond the rectum
  - Using standard definition colonoscopes → dye spray chromoendoscopy with methylene blue or indigo carmine to identify dysplasia
  - Using high definition colonoscopes → white light endoscopy with NBI or dye spray chromoendoscopy with methylene blue or indigo carmine to identify dysplasia

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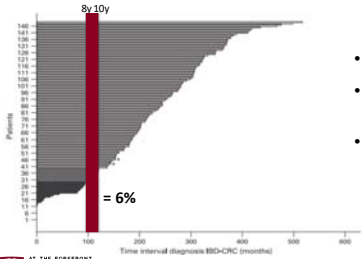
Start CRC Screening 8 Years Post Diagnosis



- N=149
- Diagnosis of IBD to CRC varied from 0 to 45 years
- Earlier surveillance at 8 years instead of 10 years captures an additional 6% of patients developing CRC

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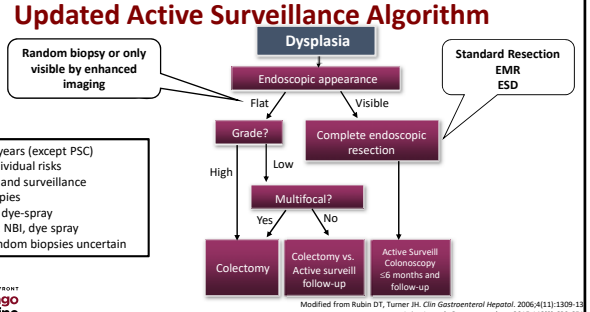
Lutgens MW, et al. *Gut*. 2008;16:1106-1113.e3.

Updated Active Surveillance Algorithm



- Start at 8 years (except PSC)
- Assess individual risks
- Screening and surveillance colonoscopies
  - If SD: dye-spray
  - If HD: NBI, dye spray
- Role of random biopsies uncertain

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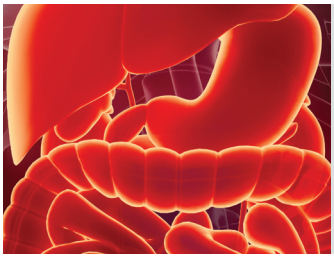
Modified from Rubin DT, Turner JH. *Clin Gastroenterol Hepatol*. 2006;4(11):1309-13
Laine L, et al. *Gastroenterology*. 2015;148(3):639-651
Rubin DT, et al. *Am J Gastroenterol*. 2019;114(3):384-413



Approaches to Managing Loss of Response to IBD Therapy

Joel Pekow, MD

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Approaching Loss of Response to IBD Therapy

Joel Pekow, MD

9/21/2019

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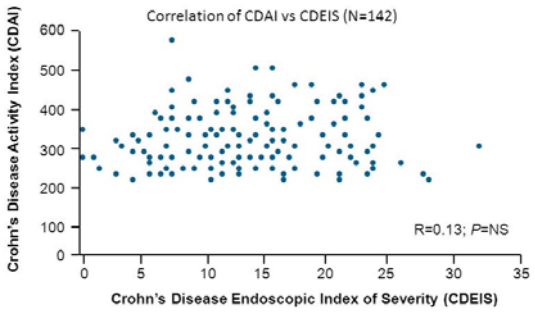
1. In symptomatic patients, confirm that the patient has active disease

Poor Correlation Between Symptoms and Mucosal Inflammation in Crohn's disease



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Modigliani et al. Gastroenterology 1990; 98:811-818

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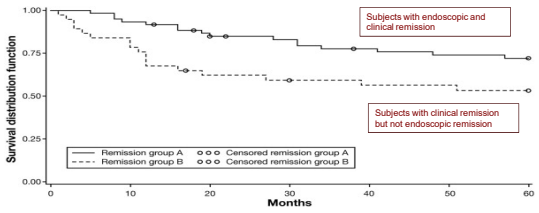
2. In patients without clinical symptoms, objectively assess for subclinical inflammation

25% of patients with UC achieve clinical remission without endoscopic remission



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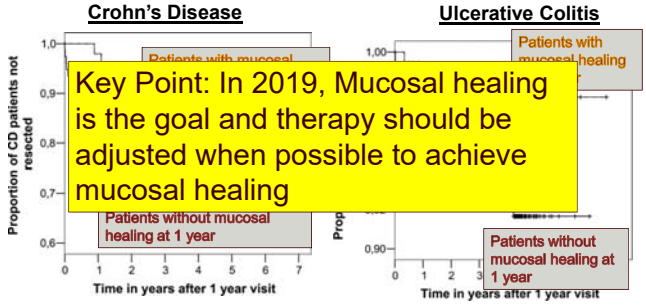
Ardizzone et al. Clin Gastro Hepatol 2011;9:483-89.

Mucosal Healing on Treatment Improves Long Term Outcomes



Key Point: In 2019, Mucosal healing is the goal and therapy should be adjusted when possible to achieve mucosal healing

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Objective measures of active inflammation

- Endoscopic evaluation
- Small bowel imaging in patients with Crohn's disease
- CRP
- Fecal Calprotectin

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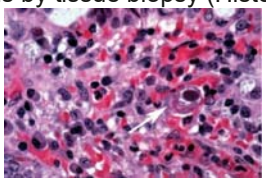
3. Evaluate for a co-infection

C.Diff and IBD

- Symptoms may be indistinguishable from IBD flares:
  - Diarrhea with or without overt bleeding
  - Abdominal pain
  - Leukocytosis
  - Uncommon for IBD patients to have pseudomembranes

CMV and IBD

- More commonly seen in patients with severe ulcerative colitis (often require escalation of medical therapy)
- Can present as acute colitis/enteritis in a patient previously in remission on immunosuppression.
- Diagnosis by tissue biopsy (Histology, IHC, or PCR)



Kandiel A, AM J Gastroenterol 2006

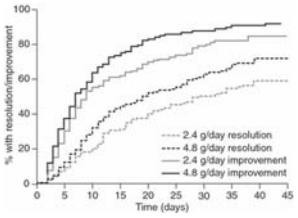
4. Managing loss of response to mesalamine

4.8gm/day is more effective than 2.4gm/day at inducing remission

- Data from two RCTs
- Symptom relief at week 14

associated with week 6 outcomes

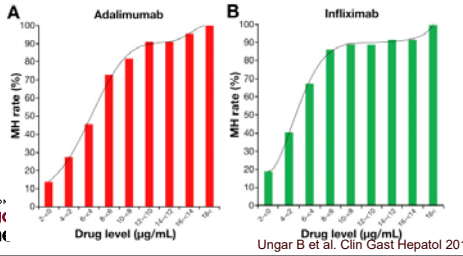
Other studies have not shown a clear benefit



Orchard TR. Aliment Pharmacol Ther 2011 May;33(9)1028-35.
Safdi AV and Cohen RD. Aliment Pharmacol Ther 2007 Nov;26(9)1179.

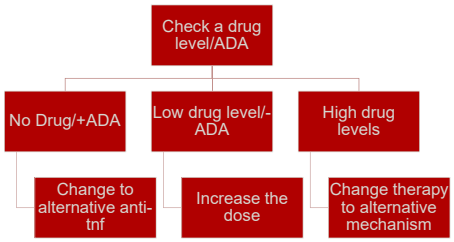
Therapeutic drug monitoring and dose escalation is an important strategy to improve response.

- Significant variation across studies. In most studies response is associated with a trough level during maintenance around 5-7ug/ml (several studies show even lower levels in responders to infliximab).
- There may be benefit and maintaining higher levels:



Ungar B et al. Clin Gast Hepatol 2016;14:550-7.

Managing loss of response to anti-tnf inhibitors



Infliximab dose escalation in loss of response

- Multicenter retrospective study: 97 patients. 10mg/kg q8 weeks vs. 5mg/kg q6 weeks (67% vs. 69%)[1]
- Retrospective: 309 patients with loss of response. 41% dose escalated, 56% achieved remission.[2]
- Multicenter retrospective cohort: 168 patients, 47% regained response with dose escalation.[3]
- Retrospective cohort of 157 UC patients - >50% achieved a clinical response to dose doubling.[4]

1. Kopylov et al. Aliment Pharm Ther 2011.
2. Chapparo et al. J Clin Gastroenterol 2011.
3. Katz L et al. Inflamm Bowel Dis 2012.
4. Dumitrescu. Aliment Pharm Ther 2015.

Adalimumab Loss of Response and Dose Escalation

Primary Responders with loss of Response

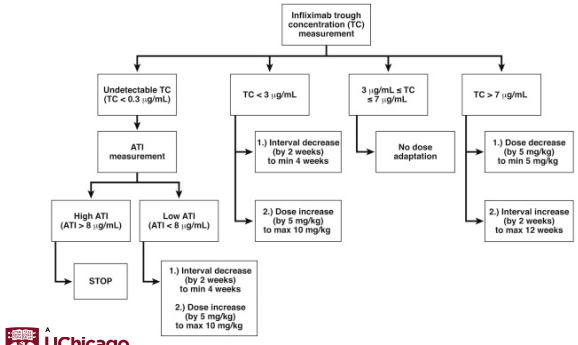
- 39 Studies
- 37% of primary responders required dose escalation
  - Response to be gained in 71.4%
  - Remission in 39.9%

Classic II:

- Primary non-responders to loading and initial maintenance
  - 40% who increased to weekly were in remission at one year.

Billioud et al. Am J Gastroenterol 2011; 17:152-9
Sandborn WJ et al. Gut 2007;56:1232-9.

Is prospective adjustment of infliximab useful?



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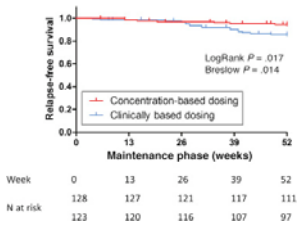
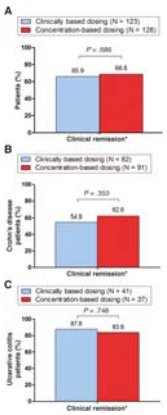
Vande Casteele N et al. Gastroenterology;2015;148:1320-9

TAXIT Study – is prospective adjustment of infliximab useful





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Vande Casteele N et al. Gastroenterology;2015;148:1320-9.

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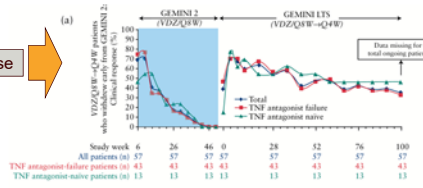
7. Managing Loss of Response to Vedolizumab

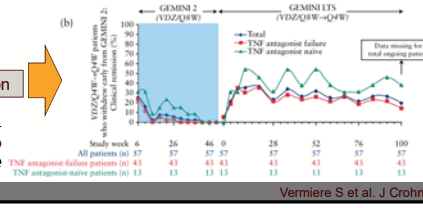
Dose escalation of vedolizumab in patients who lose response

Clinical Response



47%

Clinical Remission



32%

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Vermiere S et al. J Crohn's Colitis. 2016

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8. Managing loss of response to ustekinumab

Is dose escalation effective in patients with no response or a loss of response?

- McGill cohort:
  - - Dose escalation was successful in 11/18 patients with loss of response (variable dosing and intervals)
- British Columbia Cohort:
  - -3/16 patients responded after loss of response
- Canadian multicenter retrospective cohort:
  - Dose escalation for loss of response in 17 patients with 9 achieving response (q4 or q6 week dosing)
  - Reinduction with dose escalation in 7 patients with 4 achieving response.

Ma C. et al. Inflamm Bowel Dis 2017;23: 833-9.
Kopylov U et al. J Crohns Colitis 2014; 8: 1516-22.
Greenup AS et al. Scand J Gastreonterol 2017; 52:1354-1359.
Sam et al. Inflamm Bowel Dis 2016; 22:1662-9.

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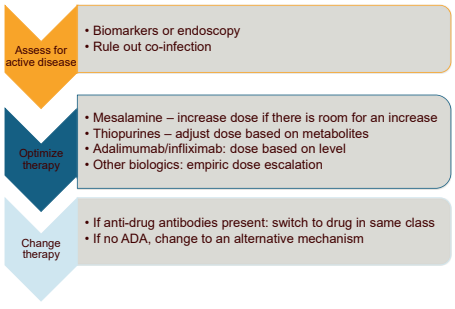
Summary: how to manage loss of response



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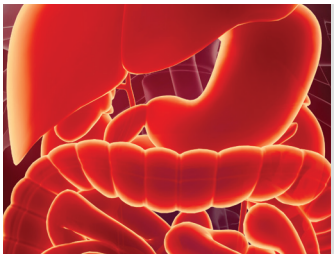

State-of-the-art in Pouchitis

Sushila Dalal, MD

AT THE FOREFRONT UChicago Medicine

State of the Art in Pouchitis

Sushila Dalal, M.D.

September 21, 2019

Disclosure information

- I have the following financial relationship to disclose:
  - Grant/Research support from: Pfizer
- I will not discuss off label use or investigational use in my presentation

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High percentage of pouch patients report symptoms

TABLE 3. Odds of Experiencing Worse Outcomes as Defined by PROMIS Measures Among Patients from CCFA Partners with a History of Pouch-Related Symptoms Within 6 Months of Survey Compared with Those with No History of Pouch-Related Symptoms[a]

	Unadjusted Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio (95% Confidence Interval)[b]
Pain interference	4.15 (1.61–10.72)	3.99 (0.153–10.41)
Depression	2.27 (0.92–5.60)	2.07 (0.83–5.16)
Anxiety	2.19 (0.95–5.08)	2.09 (0.90–4.90)
Satisfaction with social role	0.24 (0.09–0.62)	0.24 (0.09–0.63)
Fatigue	4.79 (2.00–11.45)	4.52 (2.88–10.90)
Sleep disturbance	0.82 (0.36–1.83)	0.82 (0.36–1.87)

[a]For categorical analysis, PROMIS measures were divided at the point of clinically meaningful difference (>52 for pain interference, depression, anxiety, and fatigue; <48 for satisfaction with social role).
[b]Multivariable analysis adjusted for age and sex.

-Crohn's and Colitis Foundation partners internet based cohort of IBD patients

-243 patients with IPAA included

-82% reported a history of pouch symptoms

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Inflamm Bowel Dis 2017;23:1218–1224

Can we predict pouch outcomes?

- Recent Israeli study following 253 pouch patients found that only 28.1% had a sustained normal pouch over time
- Factors associated with favorable outcomes:
  - Older age at UC diagnosis
  - Long UC duration at surgery
  - Surgery indication was dysplasia/cancer instead of refractory disease
- Previously reported predictors include extensive UC, PSC, backwash ileitis, smoking, NSAID use

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Aliment Pharmacol Ther. 2017;46:508–515
Inflamm Bowel Dis. 2017 Jul;23(7):1195-1201
Inflamm Bowel Dis. 2016 Apr;22(4):902-11

Pouch Symptom Differential Diagnosis

- Infection
- Pouchitis
- Cuffitis
- Anastomotic stricture
- Long efferent limb
- Pelvic floor dysfunction
- Stricture
- Crohn's disease

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Inflamm Bowel Dis 2009; 15: 1424-1431

How should we evaluate the pouch?

- Recent study with poor inter-viewer variability except for ulcerations and ulcerated surface area
- Review of pouchoscopy reports reveals that multiple components of the pouch (pre pouch ileum, inlet, efferent limb, cuff, anastomosis) are not explicitly reported upon
- Most endoscopic indices are not validated or are partially validated

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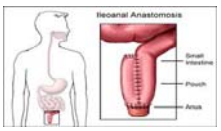
Samaan et al. *Gastrointestinal Endoscopy* 2018; 88: 360-9
Van er Ploegu et al. *Frontline Gastroenterology* 2018; 9: 309-314

Pouch Endoscopic evaluation

- Areas to describe (with representative pictures):
  - Afferent limb (distinguish 10cm proximal to the pouch)
  - Pouch inlet
  - Efferent limb
  - Proximal and distal portions of pouch
  - Cuff, with length estimate
  - Description of ileal-anal anastomosis
  - Perianal exam
- Features to include
  - Distinguish whether ulcerations on suture line
  - Terms such as edema, granularity, vascular pattern, mucus, ulcers
  - Include clinical symptoms at time of procedure



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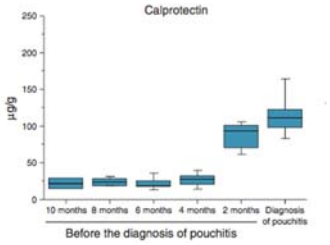
Fecal Calprotectin in Pouchitis Diagnosis



-ROC identified a cutoff of 56ug/g to predict pouchitis

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Am J Gastroenterol 2015; 110:881–887

Pouch Disease Activity Index ≥ 7 indicates pouchitis

Clinical:	
Stool Frequency	
Baseline	0
Additional 1-2 stools	1
Additional 3 stools	2
Rectal Bleeding	
None	0
Present Daily	1
Fecal Urgency or Abdominal Cramps	
None	0
Occasional	1
Usual	2
Fever	
Absent	0
Present	1

Endoscopic:	
Edema	1
Granularity	1
Friability	1
Loss of vascular pattern	1
Mucoid exudate	1
Ulceration	1
Histologic:	
PMN infiltration	
Mild	1
Moderate+crypt abscess	2
Severe+crypt abscess	3
Ulceration per low power field	
<25%	1
25-50%	2
>50%	3

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Shen, B et al. *Dis Colon Rectum* 2003. 46:748-53

Categories

- Acute pouchitis
  - Symptoms less than 4 weeks
- Chronic pouchitis
  - Symptoms more than 4 weeks
- Crohn's disease of the pouch
  - Inflammation in the afferent limb
  - Perianal disease, not related to surgery
  - Stricture
- Cuffitis (Ulcerative proctitis)

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Antibiotics for Acute Pouchitis

- Randomized trial of Cipro 1000mg/day x 2 weeks vs Metronidazole 20mg/kg/day x 2 weeks
  - Both decreased PDAI, though Cipro did to greater extent
  - Cipro had fewer adverse reactions
- Rifaximin has been studied in a small placebo controlled trial, and was not significantly better than placebo

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Inflamm Bowel Dis 2001, 7:301-305
Inflamm Bowel Dis 2007, 13:1250-1255

VSL#3 and Pouchitis

- VSL#3 is a mixture of Lactobacilli, Bifidobacteria, and Streptrococci strains
- Maintenance of remission
  - One study showed 15% relapse vs 100% in placebo group at 9mths (Gionchetti et al)
  - 2nd study showed 15% relapse with VSL#3 in a year vs 94% in placebo group (Mimura et al)
  - American open label study only 6 of 31 patients remained on VSL after 8 mths, 23 quit due to relapses and 2 due to adverse effects (Shen et al)
- Prophylaxis of pouchitis
  - 10% incidence of pouchitis in VSL#3 group vs 40% in placebo

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Gastroenterology 2000; 19: 305-309
Gut 2004; 53: 108-14
Gastroenterology 2003; 124: 1202-1209
Aliment Pharmacol Ther 2005; 22:721-728

Treatment of Chronic Pouchitis: Antibiotics

- Amongst patients who have had symptoms despite 4 weeks of antibiotic therapy, some response seen to combination antibiotic therapy
  - Ciprofloxacin 500mg BID and Metronidazole 500mg BID
  - Ciprofloxacin 500mg BID and Rifaximin 1gm BID
  - Ciprofloxacin 500mg BID and Tinidazole 15mg/kg

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Aliment Pharmacol Ther 2017;45: 581-592

Can we define the microbial triggers of pouchitis?

- Study of pre colectomy stool samples in 19 patients suggested that presence of *R. gnavus*, *B. vulgatus*, and *C. perfringens* and absence of *Blautia* and *Roseburia* predicted pouchitis in the first year
- Longitudinal study of pouch patients at UChicago found increase in *Bacteroides* during pouchitis
  - Though the bacteria strains these patients had were similar to commonly found strains they had some unique genes for a part of the cell wall (capsular polysaccharide-CPS)
  - Transfer of gene elements that make bacteria more "virulent" may occur in the pouch

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Machiels K. et al *Gut* 2017; 66: 79-88
Vineis J et al *MBio* 2016; 7: e01713-16.

Fecal transplant for chronic pouchitis?

- What is the best delivery mechanism?
- Small studies of single FMT delivered by pouchoscopy have yet failed to show efficacy on engraftment of the donor microbiota, as measure by 16S sequencing
- When is the right time in the disease course to do FMT?

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Selvig D et al. *Dig Dis Sci* 2019 July 13 Epub ahead of print
Herfarth H et al. *Inflamm Intest Dis* 2019 May; 4(1): 1-6.

Controlled Ileal release Budesonide

- Eight week treatment with budesonide 9mg daily induced remission in 75% patients in 20 person open label study

PDAI score	Before antibiotic treatment	Baseline	8 weeks	After budesonide cessation (16 weeks)
Total	15 (8–16)	14 (9–16)	3 (2–10)**	3 (2–11)
Clinical	3 (2–5)	3 (2–4)	1 (0–3)*	1 (0–3)
Endoscopic	5 (2–6)	5 (3–6)	1 (1–3)*	1 (1–3)
Histologic	5 (3–6)	5 (3–6)	1 (1–4)*	1 (1–4)

Results expressed as median (range).
PDAI, Pouchitis Disease Activity Index.
**$P < 0.001$, *$P < 0.002$.

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Aliment Pharmacol Ther 2007 25, 1231–1236

Efficacy of Anti-TNF treatment

- Observational studies have shown some benefit for infliximab and adalimumab
- Recent systematic review and meta-analysis suggests that anti-TNFs more effective for CD like inflammation rather than chronic pouchitis
  - Long term remission rates in the meta-analysis was 0.57 with (95% CI 0.43-0.71) for CD like disease vs 0.37 (95% CI 0.14-0.62) for chronic pouchitis
- Prospective clinical trials needed

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Inflamm Bowel Dis 2018; 24: 261-268

Clinical and endoscopic efficacy of vedolizumab

- Retrospective multicenter cohort of 83 patients with chronic pouchitis and CD had 71.1% clinical response
  - 19.3% clinical remission
- Of the 74 patients with follow up pouchoscopy, endoscopic response in 54.1%
  - Mucosal healing in 17.6%
- Ongoing multicenter double blind placebo controlled trial for chronic pouchitis

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Inflamm Bowel Dis 2019 Aug 20; 25(9): 1569-1576.

Ustekinumab for chronic pouchitis and CD of pouch

- Retrospective single center cohort of 24 patients with chronic pouchitis had 50% clinical response rate
  - 13 patients with pouchoscopies had improvement in mean endoscopic score
- Retrospective multi-center study of 56 patient with CD of pouch (47) and chronic pouchitis (9) had 83% clinical response rate

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Dig Dis Sci 2019 Jun 11 Epub ahead of print
Inflamm Bowel Dis 2019 Mar 14; 25 (4): 767-774

Alicaforsen under study for chronic pouchitis

- Human ICAM-1 antisense oligonucleotide
  - ICAM-1 is on surface of epithelial cells and vascular endothelial cells
    - Contributes to leukocyte adhesion, migration
- 13 patient Swedish cases series of nightly enema for 6 weeks showed clinical response in 11/13 (84.6%)
- Randomized placebo controlled trial now ongoing

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United European Gastroenterology Journal 2016, Vol. 4(1) 97–104

How often dose pouch dysplasia or cancer occur?

- Recent UK retrospective cohort of 272 patients with median follow up 10.5 years at 5 centers found 2 cases of adenocarcinoma of the rectal cuff
- Danish Cancer Registry Study of 1723 patients with IPAA with median follow up of 12.9 years found 2 cancers (0.12%)
- Cleveland clinic study of 3203 patients found pouch neoplasia at 5, 10, 15, 20, 25 years was 0.9%, 1.3%, 1.9%, 4.2%, and 5.1%
  - Neoplasia included pouch or cuff adenocarcinoma, dysplasia, anal squamous cell cancer, pouch lymphoma

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Samaan M et al. *J Crohn's Colitis* 2019; 735-743
Mark-Christensen A et al. *J Crohn's Colitis* 2018; 12(1): 57-62
Kariv R et al *Gastroenterology* 2010; 139 (2): 806-812.

How often should we survey the pouch?

Table 1. Overview of pouch surveillance guidelines.

Guideline	Year of publication	Risk stratification		Surveillance strategy
		Yes/no	Risk categories	
AGA[3]	2010	N/A	N/A	No recommendations
BSG[2]	2010	Yes	High risk: previous rectal dysplasia, dysplasia/cancer at the time of pouch surgery, primary sclerosing cholangitis, type C pouch mucosa[a]	Yearly
			Low risk: absence of high-risk factors	5-yearly
ASGE[4]	2015	Yes	Highest risk: - History of dysplasia or cancer.	Yearly surveillance should be considered
			High risk: primary sclerosing cholangitis, type C pouch mucosa,[a] refractory pouchitis	Yearly surveillance may be considered
			Other patients	No recommendations
ECCO[5]	2015	Yes	High risk: dysplasia/cancer at the time of pouch surgery, primary sclerosing cholangitis, type C pouch mucosa[a] unremitting pouchitis	Yearly
			Absence of high-risk factors	No evidence that supports routine surveillance

AGA, American Gastroenterology Association; BSG, British Society of Gastroenterology; ASGE, American Society for Gastrointestinal Endoscopy; ECCO, European Crohn's and Colitis Organisation; N/A, not available.
[a]Type C pouch mucosa is defined as exhibiting permanent persistent atrophy and severe inflammation.

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Samaan M et al. *J Crohn's Colitis* 2019; 735-743

Summary

- Incidence of pouch related symptoms may be high over time
- More aggressive disease course prior to colectomy may predict outcomes
- For acute pouchitis, 2 week course of Cipro considered first line
- Chronic pouchitis (sx greater than 4 week despite antibiotics) may require use of "IBD meds", though prospective, controlled data is lacking
- Ideal pouch surveillance interval is unknown, but reasonable to survey given low risk, quick procedure

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