CLINICAL HEPATOLOGY UPDATE

June 14–15, 2019

Hyatt Regency Bellevue | Bellevue, WA

Program Chairs:

Marcelo Kugelmas, MD, FAASLD
Elizabeth K. Goacher, PA-C, MHS
Janice Jou, MD, MHS
Lisa Catalli, MSN, NP-BC

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

Schedule-at-a-Glance and Meeting Locations

Wi-Fi Network: AASLD

Wi-Fi Password: AASLD19

Friday, June 14

6:30 AM – 5:30 PM	Registration	Evergreen Foyer
7 AM – 8 AM	Breakfast	Evergreen ABC
8 AM – 5:30 PM	General Session	Evergreen DEFGH
9:50 AM – 10:20 AM	Break	Evergreen Foyer
12:30 PM – 1:30 PM	**Breakout Sessions (Lunch Served)** *Breakout #1*: Lifestyle Modifications: Making it Really Happen - A Clinician's Guide for the 15 Minute Return Visit	Evergreen ABC
	Breakout #2: Meet the Professor: An Extension of the Conversation on Palliative Interventions for Portal Hypertension	Evergreen DEFGH
3:20 PM – 3:40 PM	Break	Evergreen Foyer

Saturday, June 15

7 AM – 12:30 PM	Registration	Evergreen Foyer
7 AM – 8 AM	Breakfast	Evergreen ABC
8 AM – 12:30 PM	General Session	Evergreen DEFGH
9:50 AM – 10:10 AM	Break	Evergreen Foyer

– Notice –

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Clinical Hepatology Update
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Hilton Regency Bellevue
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Program Chairs: Marcelo Kugelmas, MD, FAASLD, Elizabeth K. Goacher, PA-C, MHS, Janice Jou, MD, MHS and Lisa Catalli, MSN, NP-BC

Continuing Education Information
Upon completion of this activity, participants will be able to:

- To understand and describe the current standard of care for the diagnosis and management of non-alcoholic fatty liver disease
- Manage patients with complications of portal hypertension
- Recognize when decompensated cirrhosis patients are appropriate candidates for palliative care and hospice referral

This activity was planned in the context of the following ACGME/IOM/IPEC competencies: Patient Care and Procedural Skills, Provide Patient-centered Care, Values/Ethics for Interprofessional Practice, Medical Knowledge, Work in Interdisciplinary Teams, Roles/Responsibilities, Practice-based Learning and Improvement, Employ Evidence-based Practice, Interprofessional Communication, Interpersonal and Communication Skills, Apply Quality Improvement, Teams and Teamwork, Systems-based Practice

Accreditation and Designation Statements
Continuing Medical Education (CME)
The American Association for the Study of Liver Diseases (AASLD) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. AASLD designates this live activity for a maximum of 13.00 *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 Maintenance of Certification (MOC)
Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 13.00 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 points.

Continuing Education (Nurse Credits)
JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

In support of improving patient care, this activity has been planned and implemented by Amedco LLC and the American Association for the Study of Livver Diseases. Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team. Credit Designation Statement – Amedco LLC designates this live activity for a maximum of 13.00 contact hours for nurses. Learners should claim only the credit commensurate with the extent of their participation in the activity.

Nurse Pharmacology Credits
The following presentations are also eligible for 1.25 pharmacotherapeutic hours:

- The Other Side of the Triad: Non-Cirrhotic Portal Hypertension
- Anticoagulation in Portal Hypertension
- Back to the Basics: Hepatitis B Management
- AIH: When to Change and If/When to Stop Therapy

Please note onsite documentation for identification of sessions eligible for pharmacotherapeutic hours and self-submit those to your board. Keep the agenda as a reference in case they have questions.

Claiming CME Credits
Physicians and other health care professionals seeking 13.00 *AMA PRA Category 1 Credits*™for this live continuing medical education activity must complete an evaluation by **Monday, July 15**. A link to the CME evaluation will be emailed to attendees after the conference.

Claiming CE Credits
Satisfactory completion
Participants must complete an evaluation form to receive a certificate of completion by **Monday, July 15**. Learners must complete an evaluation form to receive a certificate of completion. Your chosen sessions must be attended in their entirety. Partial credit of individual sessions is not available. If you are seeking continuing education credit for a specialty not listed, it is your responsibility to contact your licensing/certification board to determine course eligibility for your licensing/certification requirement. A link to the CE evaluation will be emailed to attendees after the meeting.

Claiming MOC Points
Physicians seeking ABIM MOC points must complete the CME and MOC evaluation by **Monday, July 15**. Requests for MOC after this date will not be honored. The MOC evaluation is included in the CME evaluation.

MOC Points will be reported to the ABIM by the end of July 2019 for attendees who successfully complete the MOC evaluation.

Disclosures
This live educational activity has been planned in accordance with AASLD and ACCME Standards of Commercial Support by members of the Clinical Hepatology Update faculty and Clinical Research Committee.

As an accredited provider, AASLD requires individuals involved in the planning of continuing medical education (CME) activities to disclose all financial relationships, including those of their spouse or partner, with a commercial interest within the past 12 months. A commercial interest is defined as any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients. All conflicts of interest are resolved prior to participation.

Statement on off-label and investigational use: Speakers are asked to make a reasonable effort to identify during their presentation any discussion of off-label or investigative use or application of a product or device.

Financial disclosures will appear at the beginning of each session and are provided below.

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Conference Agenda

**eligible for 1.25 Pharmacology Hours*

Friday, June 14, 2019

7 am	**Breakfast**
Session I: NASH *Moderators: Robert G. Gish, MD, FAASLD and Kathleen E. Corey, MD, MPH, MMSc*	
8 am – 8:20 am	Liver Biopsies for Everyone? Diagnostic Dilemma in the Epidemic - Fibrosis Assessment and Risk Stratification *Kathleen E. Corey, MD, MPH, MMSc*
8:20 am – 8:40 am	Nonalcoholic Fatty Liver Disease: Current State of Care Management *Sonali Paul, MD, MS*
8:40 am – 9 am	NASH as a Team Sport: Multidisciplinary Management, Successful Examples/Best Practices *Michael F. Chang, MD, MSc, MBA, FAASLD*
9 am – 9:20 am	NASH is More than BMI: Prevalence and Impact of Lean NASH *Anne M. Larson, MD, FAASLD*
9:20 am – 9:50 am	Q&A
9:50 am – 10:20 am	**Break**
Session II: Portal Hypertension *Moderators: Janice Jou, MD, MHS and Punetta Tandon, MD, FRCPC*	
10:20 am – 10:40 am	Non-cirrhotic Portal Hypertension *Willscott E. Naugler, MD, FAASLD*
10:40 am – 11 am	The Expanding Role of TIPS *Khashayar Farsad, MD, PhD*
11 am – 11:20 am	Gastric Variceal Bleed Management: BRTO Primer, Glue *Bryan L. Balmadrid, MD*
11:20 am – 11:40 am	Anticoagulation in Portal Hypertension: Who, When, How, and for How Long? *Stephen H. Caldwell, MD, FAASLD*
11:40 am – Noon	Palliative Interventions: Who, How, What? *Jody C. Olson, MD*
Noon – 12:30 pm	Q&A
12:30 pm – 1:30 pm	**Lunch** **Two options for breakouts** **1.** Lifestyle Modifications: Making it Really Happen - A Clinician's Guide for the 15 Minute Return Visit *Elizabeth K. Goacher, PA-C, MHS* **2.** Meet the Professor: An Extension of the Conversation on Palliative Interventions for Portal Hypertension *Jody C. Olson, MD*
Session III: Lumps and Bumps in the Road *Moderators: Cynthia Levy, MD, FAASLD and Marcelo Kugelmas, MD, FAASLD*	

1:30 pm – 1:50 pm	Liver Adenomas, Management According to Size, Location, Symptoms and Genetics *K. Rajender Reddy, MD, FAASLD*
1:50 pm – 2:10 pm	Immunotherapies for HCC: What the Hepatologist Needs to Know *Catherine T. Frenette, MD*
2:10 pm – 2:30 pm	The Changing Landscape of HCC Management *Janice Jou, MD, MHS*
2:30 pm – 2:50 pm	Clinical Pearls for Less Common Liver Diseases *Michael F. Chang, MD, MSc, MBA, FAASLD*
2:50 pm – 3:20 pm	Q&A
3:20 pm – 3:40 pm	**Break**
Session IV: Everything But NASH *Moderators: Lisa Catalli, MSN, NP-BC and K. Rajender Reddy, MD, FAASLD*	
3:40 pm – 4 pm	HBV Diagnostics: Anything New *Robert G. Gish, MD, FAASLD*
4 pm – 4:20 pm	Autoimmune Hepatitis: When to Change and When/IF to Stop Therapy *Marcelo Kugelmas, MD, FAASLD*
4:20 pm – 4:40 pm	Pearls in the Management of PBC and PSC *Cynthia Levy, MD, FAASLD*
4:40 pm – 5 pm	It's All About the Microbiome: A State-of-the-Art Lecture *Jasmojan S. Bajaj, MD, FAASLD*
5 pm – 5:30 pm	Q&A

Saturday, June 15, 2019

7 am	**Breakfast**
Session V: Nutrition, Frailty and Palliative Care *Moderators: Elizabeth K. Goacher, PA-C, MHS and Jasmohan S. Bajaj, MD, FAASLD*	
8 am – 8:20 am	Quality of Care in Cirrhosis *Elliot B.Tapper, MD*
8:20 am – 8:40 am	Frailty: Impact of Sarcopenia and Overcoming Management Challenges *Jennifer C. Lai, MD, MBA*
8:40 am – 9 am	Practical Tips for Closing the "Know-Do Gap" to Enhance Nutrition in the Lives of Patients with Cirrhosis *Punetta Tandon, MD, FRCPC*
9 am – 9:20 am	Palliative Care: When to Refer *Arpan Patel, MD*
9:20 am – 9:50 am	Q&A
9:50 am – 10:10 am	**Break**
Session VI: **Hepatology Practice Outside of the Hepatology Clinic** *Moderators: Jennifer C. Lai, MD, MBA and Elliot B.Tapper, MD*	
10:10 am – 10:30 am	Liver Disease in the Pregnant Patient *Jackie F. Fleckenstein, MD, FAASLD*

10:30 am – 10:50 am	Hepatology in and Around the OR: Pre-op Risk Assessment and Perioperative Management *Jody C. Olson, MD*
10:50 am – 11:10 am	Behavioral Therapy in Liver Disease *Robert M. Weinrieb, MD*
11:10 am – 11:30 am	Transplant Medicine Back Home: Pearls for the Non-Transplant Provider *Michael D. Leise, MD*
11:30 am – 11:50 am	Controversies to Consider When Treating HCV Before or After Liver and/or Kidney Transplant *Richard Gilroy, MD*
11:50 am – 12:10 pm	Q&A
12:10 pm – 12:30 pm	Conference Summary and Wrap-Up
12:30 pm	**Adjourn**

Financial Commercial support and In-Kind Commercial support was not provided for this activity.

SPEAKER SUMMARIES AND PRESENTATIONS

Kathleen E. Corey, MD, MPH, MMSc
Massachusetts General Hospital
Cambridge, MA
Email: kcorey@partners.org

Liver Biopsies for Everyone? Diagnostic Dilemma in the Epidemic - Fibrosis Assessment and Risk Stratification

Nonalcoholic fatty liver disease (NAFLD) is a significant cause of liver disease worldwide and a threat to public health. NAFLD, a spectrum ranging from steatosis and non-alcoholic steatohepatitis (NASH) to NASH cirrhosis, affects 25% of the global population.[12] In the United States, NAFLD is the leading cause of liver disease impacting 22% of adults in the general population, 40% of individuals with type 2 diabetes and 45% with obesity.[22] NASH, the progressive form of NAFLD, can lead to cirrhosis, decompensated liver disease and hepatocellular carcinoma (HCC).[23,24] NASH is the second leading indication for liver transplantation in the United States and is predicted to be the leading indication within the next decade.[13]

The gold standard for the diagnosis and staging of NAFLD is liver biopsy. Liver biopsy can confirm the diagnosis of NAFLD, evaluate for other etiologies of liver disease, quantify lobular inflammation, hepatocyte ballooning and steatosis, distinguish steatosis from NASH and stage fibrosis. However, biopsy is an invasive procedure that has associated risks including clinically significantly bleeding, organ perforation and pain. Biopsy is also limited by variation in sampling and in interpretation and by variable uptake by both clinicians and patients. While still an essential tool in the diagnosis and staging of patients at high risk of NASH and fibrosis, it is not a reasonable screening tool for NAFLD in the general population.

Non-invasive testing in NAFLD includes circulating biomarkers, fibrosis scores and elastography that are best suited to identify patients at low risk of advanced fibrosis. The use of fibrosis scores, such as the NAFLD Fibrosis Score (NFS) and Fibrosis-4 score (FIB-4_ in combination with elastography can identify patients who are at low risk of fibrosis and not in need of liver biopsy. Patients found to have elevated NFS or FIB-4 scores and elevated elastographic scores can either have confirmatory biopsy, especially if pharmacotherapy or clinical trial participation is desired, or be managed and screened as a patient with NASH cirrhosis. Discordant results between fibrosis score and elastography also warrant a biopsy to determine the fibrosis stage and next steps in management. Use of fibrosis score and elastography can prevent unnecessary biopsies in low risk patients while allowing a focus on patients who are at high risk and in need of more aggressive management.

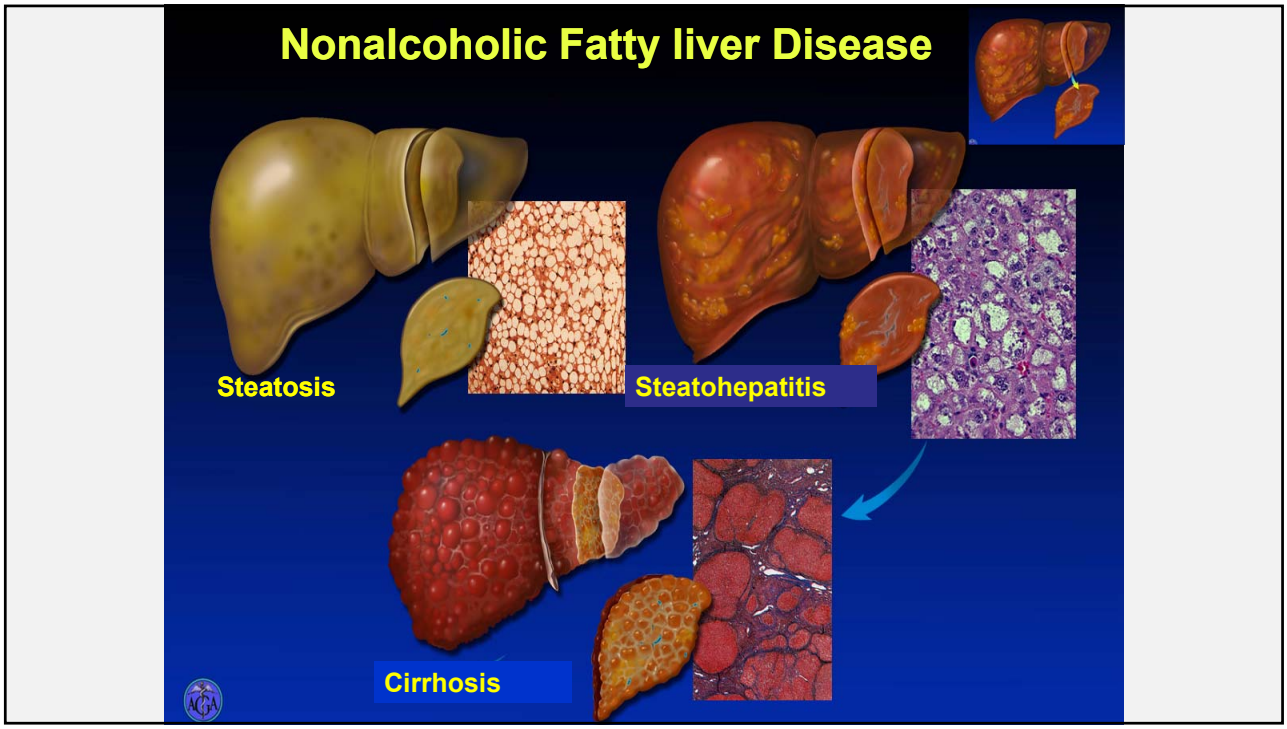
LIVER BIOPSIES FOR EVERYONE?

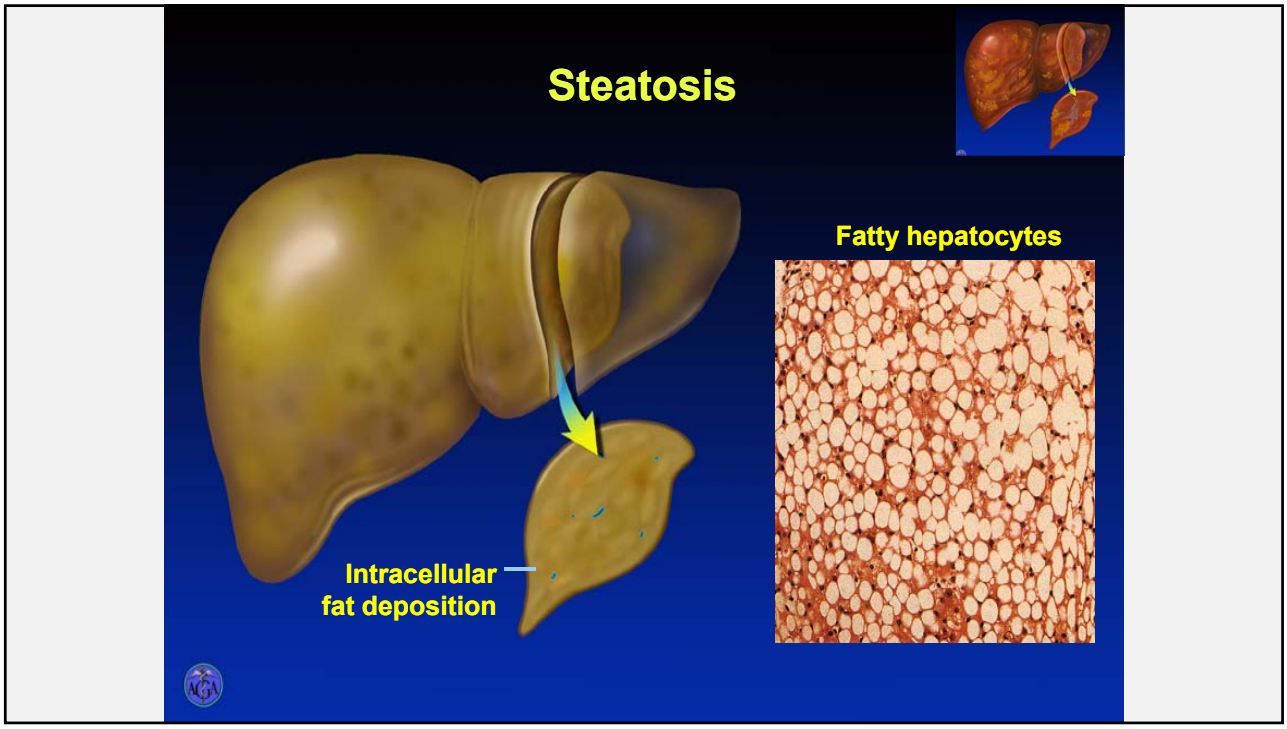
Kathleen E Corey, MD, MPH, MMSc

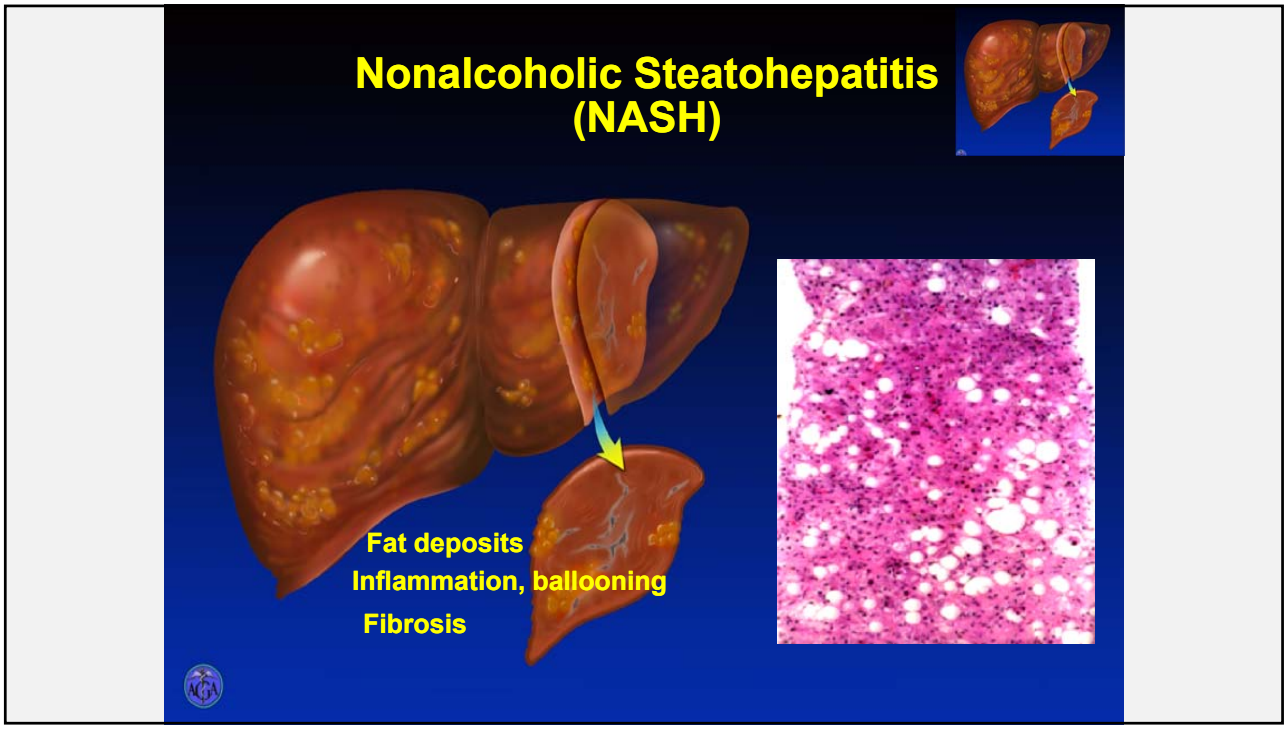
WHAT IS NAFLD?

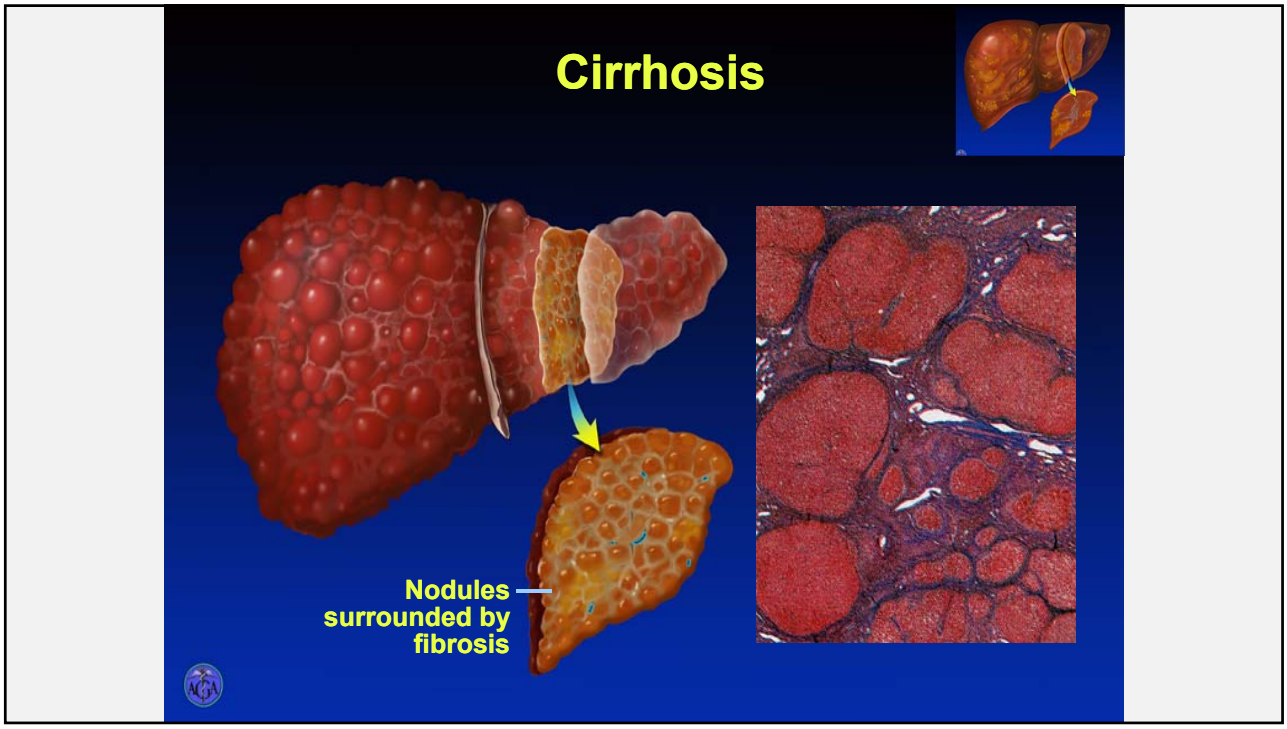
Chronic liver disease characterized by excess storage of fat within the liver in the absence of significant alcohol use

Major Comorbidities	Emerging Associations
• Type 2 Diabetes • Obesity • Dyslipidemia • Metabolic syndrome	• Obstructive sleep apnea • Hypothyroidism • Polycystic ovary syndrome


Nonalcoholic Fatty liver Disease
Steatosis
Steatohepatitis
Cirrhosis


Steatosis
Fatty hepatocytes
Intracellular
fat deposition


Nonalcoholic Steatohepatitis (NASH)
Fat deposits
Inflammation, ballooning
Fibrosis


Cirrhosis
Nodules surrounded by fibrosis

NAFLD GLOBAL PREVALENCE: 25%

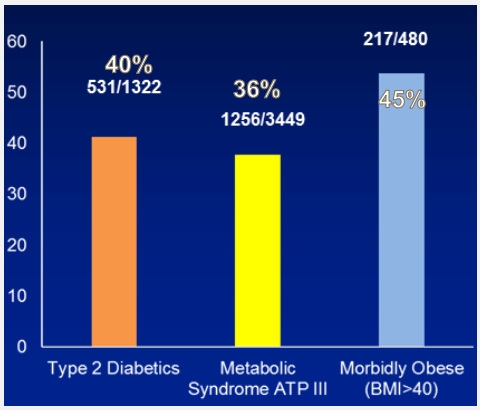
Region	N	Prevalence (%)
Africa	2	13.48
Asia	14	27.37
Europe	11	23.71
Middle East	3	31.79
North America	13	24.13
South America	2	30.45
Overall	45	25.24

NASH Prevalence: 1.5-6.6%

Z. Younossi et, Hep 2016

PREVALENCE OF NAFLD IN HIGH RISK POPULATIONS

Prevalence by Ultrasound from NHANES III



NAFLD not confined to high-risk populations

Prevalence in lean: 7%

- Women
- Young age
- Normal ALT

Slide Adapted and Courtesy of Z. Younossi
Z. Younossi et, Hep 2016
Z. Younossi et al. Medicine 2012

NAFLD PREVALENCE IN UNITED STATES

NAFLD Prevalence in US Adults		
Phenotype	**Percentage**	**Number**
NAFLD	21.9%	51.6 million
NAFLD Stage ≥ 2	23.8% (of NAFLD)	12.2 million
NAFLD Stage ≥ 3	2.3% - 9.7% (of NAFLD)	Up to 5 million

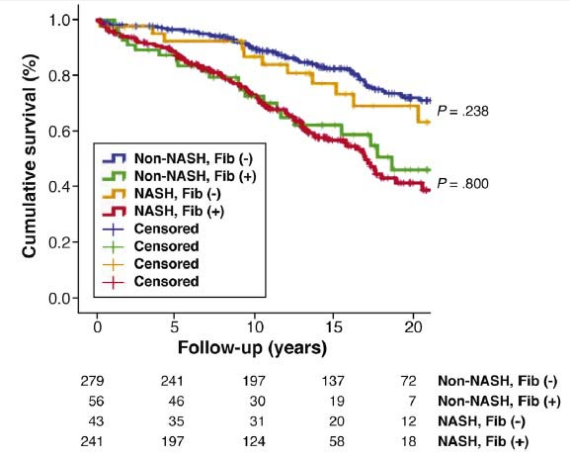
R. Wong et al., APT 2017

FIBROSIS STAGE PREDICTS DEATH/LIVER TRANSPLANT

	Hazard ratio	95% CI of HR	*P* value
Model 1			
Fibrosis, stage 0	1 (reference)		
Fibrosis, stage 1	2.07	1.40–3.08	<.001
Fibrosis, stage 2	3.02	2.0–4.56	<.001
Fibrosis, stage 3	3.97	2.50–6.30	<.001
Fibrosis, stage 4	11.97	6.47–22.12	<.001
Model 2			
Fibrosis, stage 0	1 (reference)		
Fibrosis, stage 1	1.82	1.18–2.81	.007
Fibrosis, stage 2	1.91	1.20–3.03	.007
Fibrosis, stage 3	1.90	1.16–3.12	.01
Fibrosis, stage 4	6.35	3.35–12.04	<.001
Age, *y*	1.07	1.05–1.08	<.001
Diabetes, yes	1.60	1.11–2.30	.01
Smoking			
Never	1 (reference)		
Former	1.11	0.71–1.73	.640
Current	2.62	1.67–4.10	<.001
Statin use, yes	0.32	0.15–0.71	.005

P Angulo et al. Gastro 2016

FIBROSIS PREDICTS DEATH AND LIVER TRANSPLANTATION



Treatment should target those with fibrosis, diabetes, tobacco use.

P Angulo et al. Gastro 2016

HOW TO IDENTIFY FIBROSIS: GOLD STANDARD IS LIVER BIOPSY

- **Benefits of Liver Biopsy**
  - Evaluate for secondary conditions
  - Confirmation of NAFLD
  - Distinguishes between steatosis and NASH by grading
    - Lobular Inflammation
    - Hepatocyte ballooning
  - Stages fibrosis 0-4
- **Limitations of Liver Biopsy**
  - Complications (next slide)
  - Sampling error (1/50,000th of liver) and interpretation variation
  - Cost: ~$1,500

HOW TO IDENTIFY FIBROSIS: GOLD STANDARD IS LIVER BIOPSY

- **Benefits of Liver Biopsy**
  - Evaluate for secondary conditions
  - Confirmation of NAFLD
  - Distinguishes between steatosis and NASH by grading
    - Lobular Inflammation
    - Hepatocyte ballooning
  - Stages fibrosis 0-4
- **How Will This Change Management?**
  - Allow treatment of distinct or concurrent disease (Ex. AIH, HHC)
  - Allow for pharmacotherapy
    - Vitamin E and Pioglitazone only recommended in biopsy-proven NASH
    - Allow consideration for clinical trials
  - Initiate HCC screening, monitoring for decompensation, etc

COMPLICATIONS OF LIVER BIOPSY

Complication	Percutaneous Liver Biopsy	Colonoscopy
Pain	30-50%	
Clinical significant bleeding	0.05-0.6%	0.08%
Other organ injury	0.08%	Perforation: 0.02-0.3%
Death	0.01- 0.1%	29.2 per1,000 perforation (30 d)

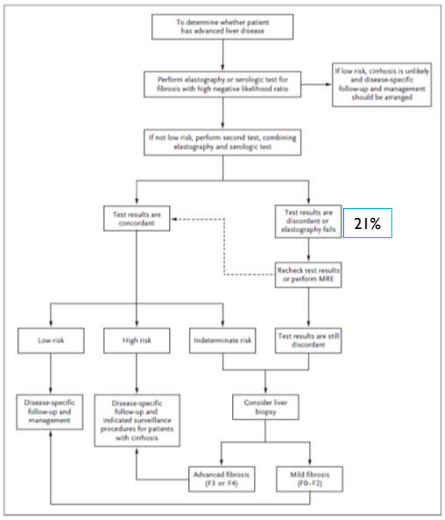
Modality	Performance Characteristics for Advanced Fibrosis	Advantages	Disadvantages	Limitations
Fibrosis Scores				
NAFLD Fibrosis Score (NFS)	NPV 93% PPV 90% AUROC 0.85	Calculate with basic clinic info and labs	Detect advanced fibrosis only	Age> 65 Has “indeterminant” group (28%)
Fibrosis-4 Score (FIB-4)	NPV 90% PPV 80%	Calculate with basic clinic info and labs	Detect advanced fibrosis only	Age> 65 Has “indeterminant” group (28%)
ELF Panel (3 matrix turnover proteins)	AUROC 0.90	Blood test only	Send out; Commercial use only in Europe	CKD, chronic inflammation
Elastography				
Vibration Controlled Transient Elastography (FibroScan)	NPV 90% PPV 65% AUROC 0.83	Point of care testing	No imaging; Detect advanced fibrosis only	Congestion, postprandial hyperemia, inflammation, steatosis Failure rate 2.6-10%
Sheer wave Elastography	AUROC 0.8-0.91	Provides imaging	Detect advanced fibrosis only	
MR Elastography	NPV 0.97% PPV 0.68% AUROC 0.89-0.924	+ imaging; high AUROC lower F stage, **No impact obesity, inflammation**	Reimbursement issues,	Hepatic iron, congestion, inflammation, limitations of MRI

NON-INVASIVE TESTING: AASLD GUIDELINES

- NFS or FIB-4 clinically useful tools for identifying stage 3-4 fibrosis
- VCTE or MRE clinically useful for advanced fibrosis
- Biopsy indications: MetS, elevated NFS, FIB-4 or liver stiffness of VCTE or MRI, need for exclusion of competing etiologies

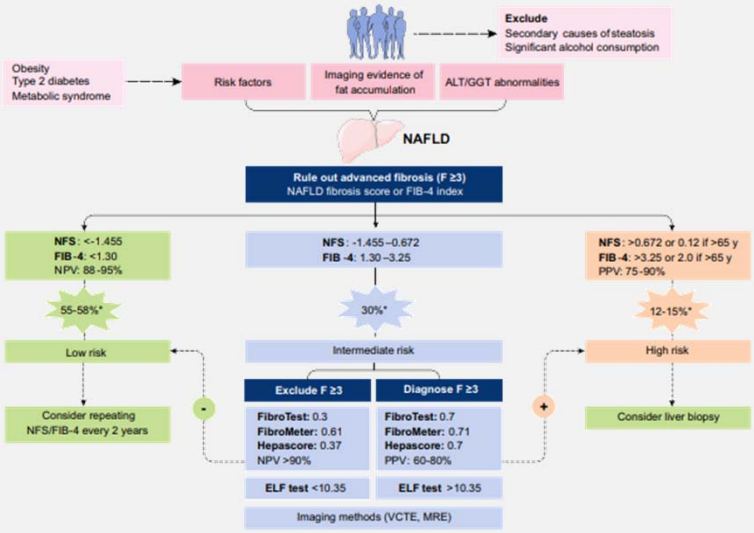
N. Chalasani et al. Hepatology 2017

NAFLD Fibrosis Staging Algorithm



E. Tapper and A S.-F Lok. NEJM 2017

POTENTIAL ALGORITHM FOR NON-INVASIVE ASSESSMENT: PREDICTION RULES AND BLOOD-BASED BIOMARKERS



*Estimated prevalence for low-, intermediate- and high-risk groups
Vilar-Gomez E, Chalasani N. J Hepatol 2018;68:305–15

CASE 1

- 45 year old woman with diabetes, BMI 41 presents with incidentally noted fatty infiltration of the liver on ultrasound
- ALT 75, AST 33, ALP 90, total bilirubin 0.8, albumin 4.0, INR 1.0, platelets 230
- Next Steps?

CASE 1

EXCLUDE OTHER CAUSES OF FATTY LIVER

- Alcohol
- Hepatitis C
- Lipid disorders
- Celiac Disease
- Hypothyroidism
- Wilson's disease when appropriate

ABNORMAL LFT EVALUATION

- + ANA 1:640
- + ASMA 1:40
- Normal SPEP

Go straight to liver biopsy when competing etiologies require evaluation

CASE 1: + ULTRASOUND, NORMAL LIVER ENZYMES

- NFS + 2.0 = indicates high risk of advanced fibrosis
- Send for Fibroscan
  - Fibroscan LSM 12 kPA, c/w advanced fibrosis
- Confirm with liver biopsy
  - Liver Biopsy: NASH with stage 4 fibrosis
- Treatment options

CASE 2

- 45 year old woman with diabetes, BMI 41 presents with incidentally noted fatty infiltration of the liver on ultrasound
- ALT 18 ,AST 16, ALP 90, total bilirubin 0.8, albumin 4.0, INR 1.0, platelets 230
- Next Steps?
- NAFLD Fibrosis Score and Elastography

CASE 2

- NAFLD Fibrosis Score + 2.0 – indicates high risk of advanced fibrosis
- Fibroscan LSM 12 kPA, c/w advanced fibrosis
- Liver Biopsy: NASH with stage 4 fibrosis
- Clinical trial vs bariatric surgery
- HCC and variceal screening (maybe)

- Fibrosis Scores and Elastography
  - Ideal to identify low risk patients and avoid biopsy
  - Use together to risk strateify
- Liver Biopsy: Not a screening tool or routine tool to risk stratify NAFLD
  - Use with competing etiologies, discordant staging, to confirm advanced fibrosis and for pharmacotherapy

THANK YOU

EXTRA SLIDES

LIVER STIFFNESS MEASUREMENTS IN CIRRHOSIS

- < 20 kPa and platelet count >150,000 per cubic millimeter: low risk esophageal varices

TAPPER NEJM 2017 ARTICLE

- Samples 1/50,000th of liver volume
- NAFLD biopsies
  - 51 patients, 2 biopsies on same day, 35% had F3 in one sample and F0-F1 in the other – REF 6
  - Single pass NPV 74% in NAFLD – REF 6
  - Intraobserver concordance for fibrosis 75% REF 3
  - Cost of perc biopsy
    - Average $1,558 (REF 14, 15)
    - 14 and 45 – biopsy first approaches

Complication	Frequency	Reference
Pain	30-50%	10
Clinical significant bleeding	0.05-0.6%	11
Other organ injury	0.08%	12
Death	0.01- 0.1%	2
Perforation rate in colonoscopy	0.02-0.3% 0.035-0.073 0.04% and major hemorrhage or 0.08% for bleed per USPTF	T Thulin United European Gastro J 2018 M Laanani CGH 2019
30 day mortality after perforation	29.2 per 1,000 perforation	M Laanani CGH 2019

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Nonalcoholic Fatty Liver Disease: Current State of Management

Nonalcoholic fatty liver disease (NAFLD) is quickly becoming the leading cause for liver transplantation. NAFLD is a spectrum of disorders, ranging from simple steatosis (or nonalcoholic fatty liver, NAFL) to steatohepatitis (NASH), and often progressing to cirrhosis. It is estimated that approximately 25-30% of the US population has some form of NAFLD, affecting approximately 83 million people.[1] And the incidence is rising at an alarming rate, especially in younger people aged 18 to 39 years.[2]

Risk factors for NAFLD include metabolic syndrome, insulin resistance and diabetes, obesity, and certain ethnicities (Hispanics for example have a ~ 45% prevalence of NAFLD), and genetic predispositions (the PNPLA3 gene for example). Given these risk factors and the rising public health crisis, there are questions over whether we should screen patients for NAFLD. Currently AASLD guidelines do not recommend universal screening, but do note that there should be a higher index of suspicion in patients with type 2 diabetes.[1]

Once diagnosed with fatty liver (seen on imaging for example), it is important to exclude other causes of fatty liver, including alcohol, hepatitis C, Wilson's disease, and certain medications (steroids, amiodarone, tamoxifen for example). If the patient has abnormal liver tests, additionally evaluation for viral hepatitis, autoimmune liver disease, hemochromatosis, and other chronic liver disease should be perused. If NAFLD is suspected, it is important to identify other key risk factors including diabetes, insulin resistance, and obesity. And finally, it is important to stage and risk stratify their liver disease. Do they have NASH (as this is a risk factor for progression to cirrhosis) or advanced fibrosis. Liver biopsy is required for the diagnosis of NASH but emerging imaging modalities such as transient elastography and MR elastography may obviate the need for biopsy.

There are currently no FDA approved therapies for NAFLD, although there are many clinical trials and emerging therapies. The cornerstone of treatment for NAFLD is lifestyle modifications in combination with addressing their metabolic comorbidities. Referring to an endocrinologist for strict glycemic control is often helpful. Weight loss has been shown to improve not only steatosis (3% body weight) but also NASH (~7% weight loss) and fibrosis (~10% weight loss).[3] The Mediterranean diet has been shown to decrease steatosis on imaging in addition to the benefits of coffee and physical activity on liver related health. Although lifestyle interventions are and should be first line, they are difficult to maintain as only 10% will achieve sustained weight loss.

There are 2 medications that have shown some promise in treating nonalcoholic fatty liver disease. Pioglitazone, an established treatment for diabetes, has shown to decrease ballooning, lobular inflammation, and steatosis.[4] However, it can cause weight gain and has been linked to an increased risk of bladder cancer so patients should be counseled on these effects. Vitamin E has also been studied in the treatment of NAFLD in the PIVENs study, comparing Vitamin E to pioglitazone to placebo.[5] Vitamin E 800 IU/day decreased histological NASH and AST/ALT with a number needed to treat of 4 patients. However, upon discontinuation of treatment, liver tests increased again. Current AASLD guidelines recommend 800 IU/day of vitamin E in non-diabetic

patients with biopsy proven NASH.[1] However, long term concerns surrounding prostate cancer, hemorrhagic stroke, and cardiovascular risk should be discussed with patients prior to starting therapy.

Bariatric surgery has been shown to induce long term weight loss and decrease long term mortality for diabetes, cardiovascular disease, and cancer with decreases in steatosis, hepatocyte ballooning, lobular inflammation, and NAFLD activity score 1 year after surgery.[6] However, currently NAFLD is not a sole indication for bariatric surgery.

Another rapidly evolving area in drug development has been with anti-obesity medications. Currently there are 6 FDA approved medications for weight loss (phentermine, phentermine / topiramate, bupriopion / naltrexone, liraglutide, lorcaserin, and orlistat). Liraglutide is the only one that has been evaluated in the treatment of NAFLD. Liraglutide is a long acting glucagon like peptide 1 (GLP-1) agonist that is secreting after eating and increases insulin secretion and satiety. Used for diabetes (at a dose of 1.8mg daily), the anti-obesity dose is 3.0mg daily. The Phase 2 LEAN trial of 52 patients showed resolution of NASH with a RR of 4.3.[7] Further studies are needed to determine if GLP-1 agonists have a rule in the treatment of NAFLD.

There are numerous emerging therapies in the pipeline for NAFLD. The first successful pivotal trial in NASH was the REGENERATE trial looking at obeticholic acid versus placebo in patients with stage 2 or 3 fibrosis.[8] They found OCA 25mg daily had fibrosis improvement (>1 stage) with no worsening of NASH (p=0.002) compared to placebo. However, they did not achieve their other endpoint of NASH resolution (without worsening fibrosis).

In summary, NAFLD is an increasing public health burden. Lifestyle interventions that lead to weight loss are currently the only available treatments. Bariatric surgery and anti-obesity medications have a promising role as well in this epidemic. Aggressively modifying risk factors is also pivotal in the treatment of NAFLD. There are many clinical trials and emerging therapies that will likely be available in the coming years, but emphasis cannot be lost on the role of lifestyle modifications in tandem with pharmacotherapy.

References

1. Chalassani et al. The diagnosis and management of Nonalcoholic fatty liver disease: Practice guideline from the American Association for the Study of Liver Diseases. Hepatology 2018; 67(1): 328-357.
2. Allen et al. Nonalcoholic fatty liver disease incidence and impact on metabolic burden and death: A 20 year community study. Hepatology 2018; 67(5): 1726-1736.
3. Vilar-Gomez et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology 2015; 149(2): 367-78.
4. Boettcher E et al. Meta-analysis: Pioglitazone improves liver histology and fibrosis in patients with non-alcoholic steatohepatitis. Aliment Pharmacol Ther 2012; 35(1): 66-75.
5. Sanyal A et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med 2010; 362(18): 1675-85.
6. Lassailly et al. Bariatric surgery reduces features of nonalcoholic steatohepatitis in morbidly obese patients. Gastroenterology 2015, (149(2): 379-88.
7. Armstrong MJ et al. Liraglutide safety and efficacy in patients with nonalcoholic steatohepatitis (LEAN): a multicenter, double blind, randomized, placebo-controlled phase 2 study. The Lancet 2016, 387(10019): 679-690.
8. Younossi et al. Interim analysis of the Phase 3 REGENRATE study. EASL 2019.

Nonalcoholic Fatty Liver Disease: Current State of Management

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Center for Liver Diseases

Disclosure Information

- Research / grant funding from: Intercept, GENFIT, TARGET PharmaSolutions

Common Case

- 45 year old Hispanic man referred for abnormal liver tests
- AST 56, ALT 90
- History of diabetes (HgA1c 8.1)
- Obesity (BMI 35)
- Ultrasound shows evidence of fatty liver

- … now what?

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Objectives

- Review NAFLD burden
- Discuss current management paradigms
- Discuss future treatments

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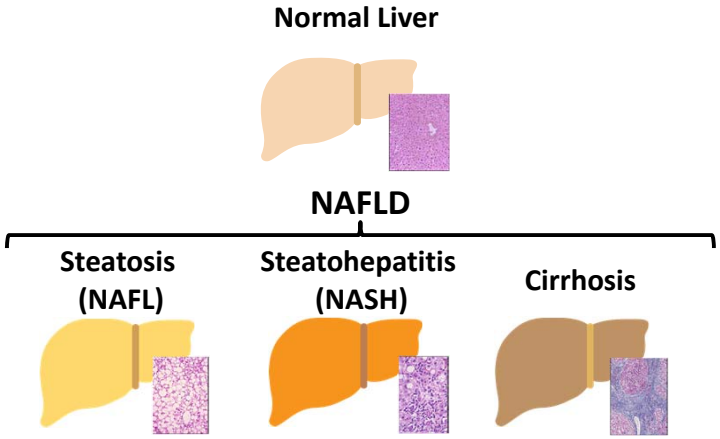
Spectrum of NAFLD



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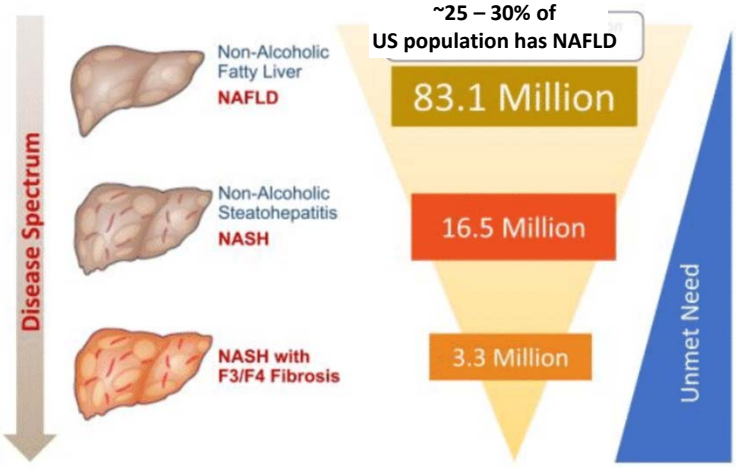
Burden of NAFLD



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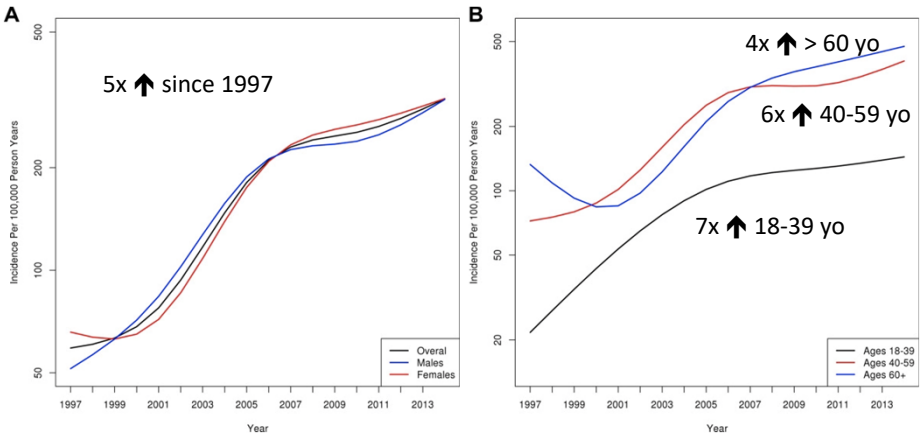
Estes C et al. Hepatology. 2018.

Rising NAFLD Incidence (Olmsted County, MN)



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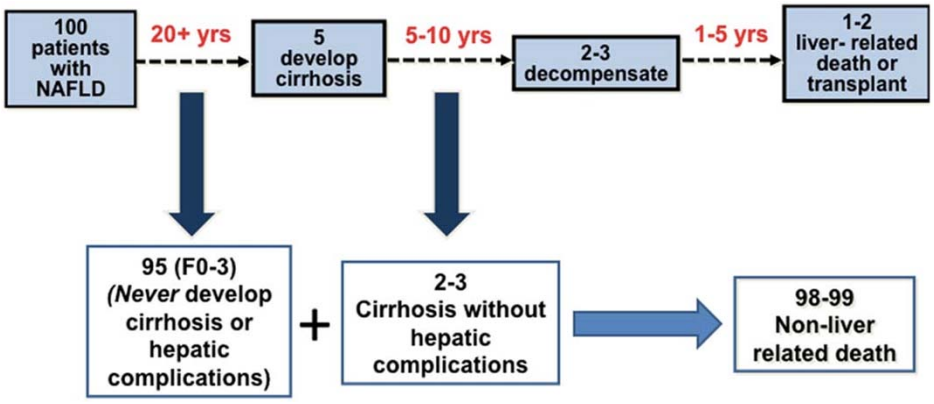
Allen et al. *Hepatology*. 2018.

Natural History of NAFLD



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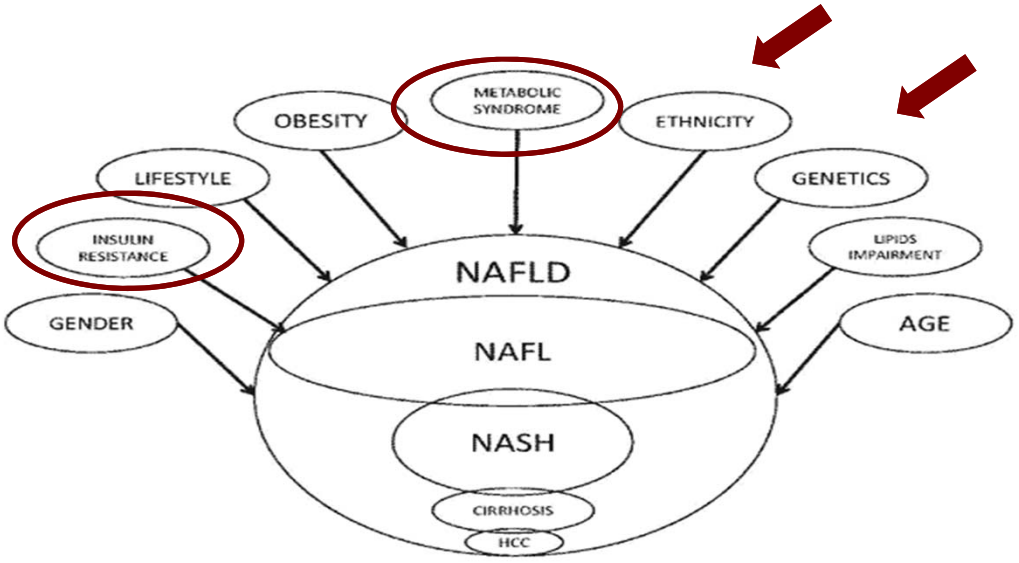
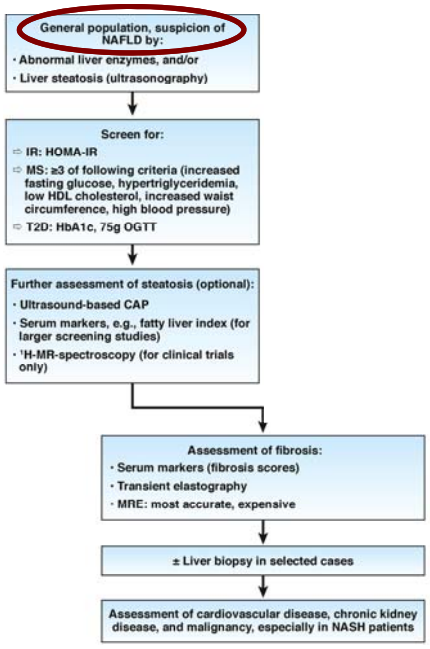
Rinella ME & Charlton M. *Hepatology. 2016.*

NAFLD Risk Factors



Should we screen patients for NAFLD?



Tilg H. Gastroenterology. 2017.

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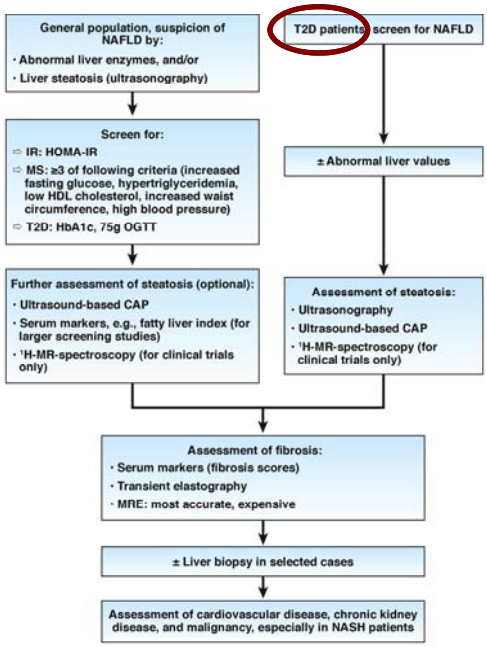
Should we screen patients for NAFLD?



Current AASLD Guidelines do not recommend screening

Have high index of suspicion in patients with T2DM.

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Tilg H. Gastroenterology. 2017.

My Patient Has Fatty Liver, Now What?

- **Exclude other causes of fatty liver / liver disease**
  - Hepatitis C, Wilson's disease, medications, alcohol
  - If abnormal liver tests, evaluate for viral hepatitis, autoimmune, iron overload, alpha 1
- **If this is NAFLD, are there other metabolic risk factors?**
  - Insulin resistance, diabetes, obesity
- **Stage & risk stratify their liver disease**

  … do they have non alcoholic steatohepatitis

  … do they have advanced fibrosis?

Requires more aggressive treatment.

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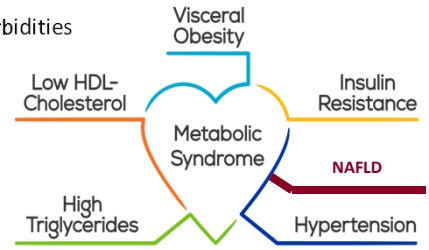
NAFLD Treatment

- No current FDA approved drug treatments
- Many clinical trials – emerging therapies

- Considerations
  - Treat liver disease + metabolic comorbidities



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Question

- Which treatment is recommended by the AASLD for the treatment of biopsy proven NASH in diabetic and non-diabetic patients?

A. Vitamin E
B. Metformin
C. Liraglutide
D. Pioglitazone

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Question

- Which treatment is recommended by the AASLD for the treatment of biopsy proven NASH in diabetic and non-diabetic patients?

A. Vitamin E
B. Metformin
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D. Pioglitazone

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NAFLD & Weight Loss

Weight Loss	Outcome Among Patients Achieving Weight Loss	Patients Sustaining Weight Loss at 1 Yr
≥ 10%	Fibrosis	< 10%
≥ 7%	NASH Resolution	18%
≥ 5%	Ballooning/Inflammation	30%
≥ 3%	Steatosis	Not reported

Vilar-Gomez et al. Gastroenterology 2015. Promrat et al. Hepatology 2010. Wong et al. J Hepatol 2013.

Dietary Advice

- Reduce sugar sweetened beverages
- Reduce simple carbohydrates
- Stop eating after a certain time
  - Allows for actual “fast” overnight
- Mediterranean diet

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Mediterranean Diet

- ↑ monounsaturated fatty acids
- ↓steatosis on MRI compared to high fat / low carbohydrate
- ↓all-cause mortality, CV disease, cancer, obesity, diabetes

Haufe et al. Hepatology. 2011.
www.mayoclinic.org

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Coffee, > 3-4 cups / day

125,580 patients

- Without liver disease
- 22 years f/u

Table 2. Adjusted* Relative Risk of Cirrhosis According to Whether an Individual Drinks Coffee or Tea

	Subjects With Cirrhosis	
Coffee or Tea, Cups per Day	Alcoholic	Nonalcoholic
Coffee		
Never or seldom	1.0	1.0
<1	0.7 (0.4-1.1)	1.2 (0.6-2.2)
1-3	0.6 (0.4-0.8)†	1.3 (0.8-2.1)
≥4	0.2 (0.1-0.4)†	0.7 (0.4-1.3)
Per cup of coffee per day‡	0.8 (0.7-0.9)†	0.9 (0.8-1.0)
Tea		
Never or seldom	1.0	1.0
<1	0.6 (0.4-1.0)§	1.0 (0.7-1.6)
≥1‖	1.0 (0.7-1.5)	1.1 (0.7-1.7)
Per cup of tea per day‡	0.9 (0.8-1.1)	1.0 (0.9-1.2)

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Klatsky et al. Arch Intern Med. 2006.

Physical Activity

- NHANES Data
- 2701 adults with NAFLD age 20 - 74 yo
- 150 minutes moderate intensity exercise / week
- ↓all cause mortality
- ↓mortality related to CV disease and diabetes

	Prevalence (n=2,701)		All Cause	Cardiovascular Disease	Diabetes
Physical Activity Status [a]	% (95% CI)	N (100,000)	aHR[b] (95% CI)	aHR[b] (95% CI)	aHR[b] (95% CI)
Inactive	15.51 (13.09 - 17.93)	45.10	Ref.	Ref.	Ref.
Insufficiently Active	36.57 (32.98 - 40.15)	106.34	0.75 (0.56 - 1.01)	**0.53 (0.30 - 0.95)**	0.54 (0.26 - 1.11)
Recommended Active	47.92 (43.84 - 52.01)	139.37	**0.64 (0.48 - 0.86)**	**0.46 (0.25 - 0.84)**	**0.40 (0.23 - 0.72)**

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Elsaid et al. AASLD 2018. Abstract 67.

Lifestyle Interventions

- Difficult to sustain
- Only ~ 10% will achieve sustained weight loss
- **Should** remain first line therapy for NASH

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Glass et al. Dig Dis Sci. 2015.
Kleiner et al. Clin Liver Dis. 2016.

Current Available Pharmacologic Therapies

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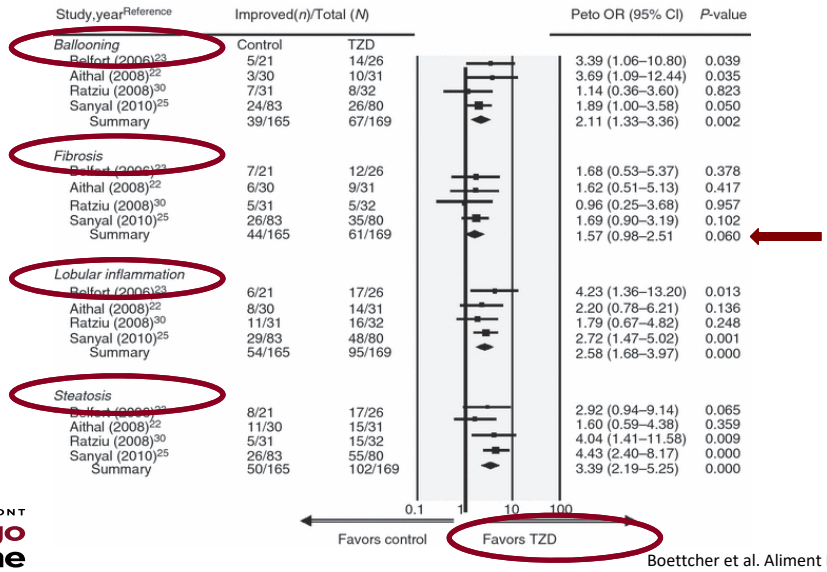
Pioglitazone (TZDs)



Boettcher et al. Aliment Pharmacol Ther. 2012.

Glitazones

AASLD Guidelines

- Pioglitazone for patients +/- Diabetes

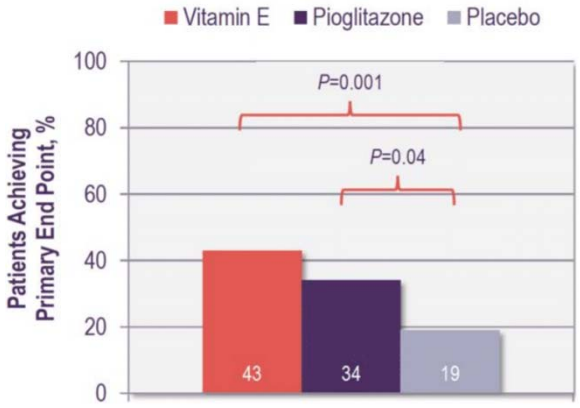
- Not sustained when discontinued / NASH returns
- Weight gain
- Bladder cancer

Sanyal et al. N Engl J. 2010.
Ratziu et al. Hepatology 2010.
Boettcher et al. Aliment Pharmacol Ther. 2012.

Vitamin E: PIVENS

Vit E 800 IU/day or Pioglitazone x 96 weeks

- ↓ histological NASH (NNT 4.2)



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Sanyal et al. N Engl j Med. 2010.

Vitamin E: PIVENS

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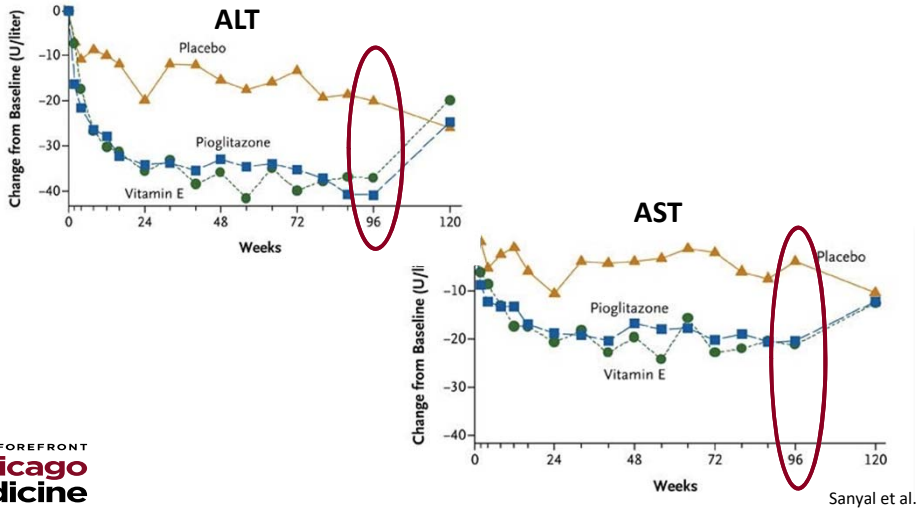

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Sanyal et al. N Engl j Med. 2010.

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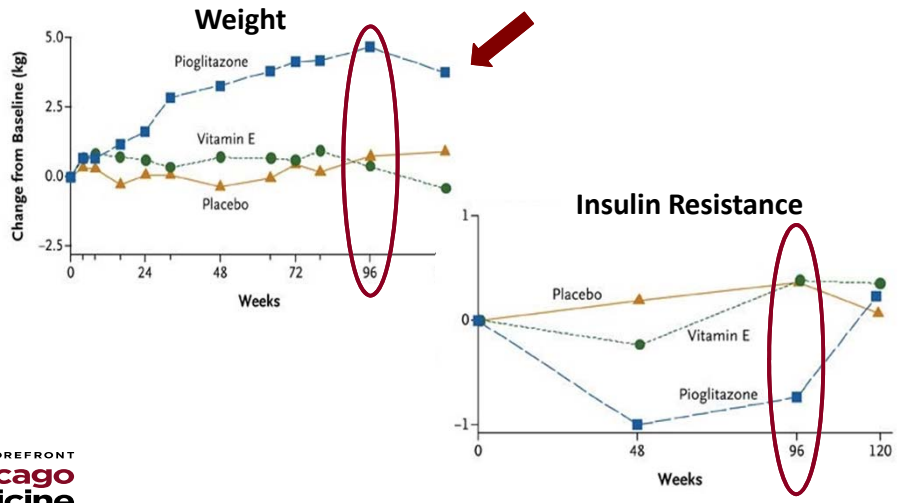
Vit E 800 IU/day or Pioglitazone x 96 weeks



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Sanyal et al. N Engl j Med. 2010.

Vitamin E: AASLD Guidelines

- 800 IU/day in **non-diabetic** patients with **biopsy** proven NASH
- **Do not Use in**
  - Diabetic patients
  - Without liver biopsy
  - Cirrhosis
- **Long terms concerns**
  - Hemorrhagic stroke
  - Prostate cancer
- No data on all-cause / liver related mortality

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Chalasani et al. N Engl j Med. 2010.
Sanyal et al. N Engl j Med. 2010.

Liraglutide

- Long acting glucagon like peptide-1 (GLP-1) agonist
- Secreted after eating
  - L cells of small bowel and proximal colon
  - ↑ insulin secretion, ↓ hepatic glucose, ↑ satiety, ↑CV protection

Phase 2 Trial (LEAN)

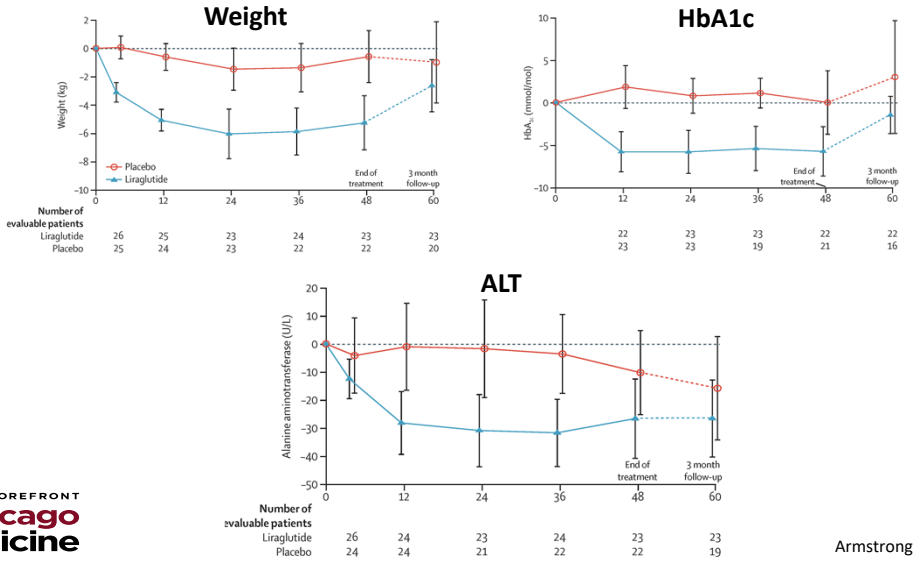
- 26 patients Liraglutide vs 26 placebo
- **Resolution of NASH** (RR 4.3, 95% CI 1.0-17.7, p = 0.019)
- Minimal side effects: diarrhea

AT THE FOREFRONT UChicago Medicine

Armstrong et al. Lancet. 2016.

Placebo ----
Liraglutide ----

Liraglutide



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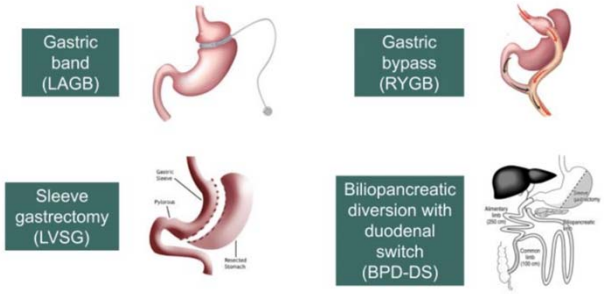
Armstrong et al. Lancet. 2016.

Bariatric Surgery



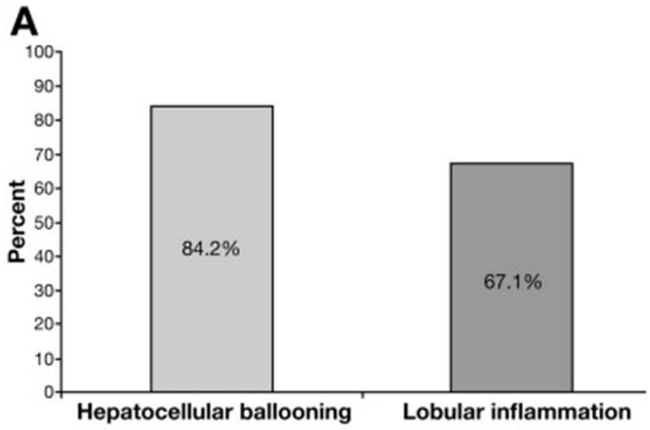
- Induce long-term weight loss
- ↓ long-term mortality T2DM, CV, cancer
- ↓ adiposity = ↓ insulin resistance
- Currently NASH not in indication for bariatric surgery alone

AT THE FOREFRONT UChicago Medicine

Lassailly et al. Gastroenterology. 2015.

Bariatric Surgery

109 patients, 1 year follow-up



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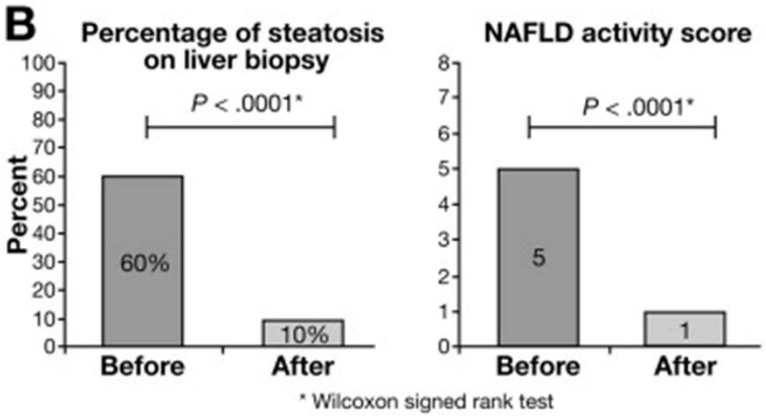
Lassailly et al. Gastroenterology. 2015.

Bariatric Surgery

109 patients, 1 year follow-up



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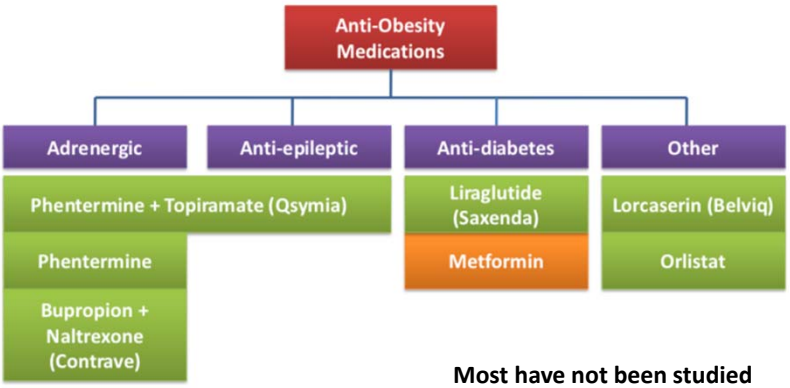
Lassailly et al. Gastroenterology. 2015.

Anti-Obesity Medications



Most have not been studied specifically for NAFLD.

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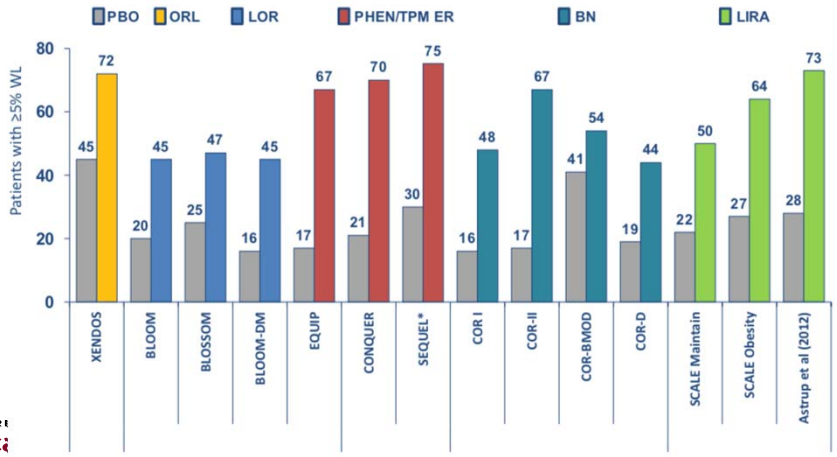
Anti-obesity Pharmacotherapy Increases Magnitude of Weight Loss



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NAFLD Treatment Paradigm

Endocrinologist

Weight loss[1-3]
- Diet
- Exercise
- Bariatric surgery
- Anti-obesity meds

Other approaches
- Metformin[7,8]
- Simvastatin[8]

(Statins are OK, decrease CV risk)

Treat metabolic syndrome[4,5]
- Hypertension
- Dyslipidemia*
- T2D

Liver-directed treatment
- Vitamin E[9]
- Pioglitazone[9,10]
- Liraglutide [11]

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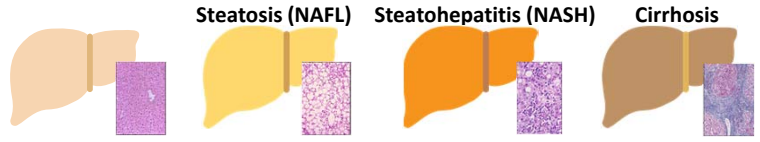
1. Promrat. Hepatology. 2010;51:121. 2. Vilar-Gomez. Gastroenterology. 2015;149:367. 3. Lassailly. Gastroenterology. 2015;149:379. 4. Musso. Hepatology. 2010;52:79. 5. Ratziu. J Hepatol. 2010;53:372. 6. Bril. J Clin Endocrinol Metab. 2017;102:2950. 7. Zhang. Scand J Gastroenterol. 2013;48:78. 8. Chen. Medicine (Baltimore). 2015;94:e1013. 9. Sanyal. NEJM. 2010;362:1675. 10. Cusi. Ann Intern Med. 2016;165:305. 11. Armstrong. Lancet. 2016;387:679.

Slide Credit: clinicaloptions.com

Emerging Therapies



Insulin Resistance / Lipid Metabolism → Lipotoxicity and oxidative stress → Inflammation and immune activation → Cell death (apoptosis and necrosis) → Fibrogenesis and collagen turnover

PPARγ: Pioglitazone
GLP-1: Liraglutide, Semaglutide
ACC: GS-0976
SCD1: Aramchol
FGF21: BMS-986036
THR-β: MGL-3196, VK 2807

PPARα/∂: Elafibranor
FXR: OCA, GS-9674, Tropifexor
FGF19: NGM282
Vitamin E

CCR2/5: Cenicriviroc
TLR4: JKB-121

ASK1: Selonsertib

Galectin: GR-MD-02

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Bold: Phase III Trials

Slide Credit: clinicaloptions.com

Ongoing NASH Phase 3 Trials

- Obeticholic Acid **REGENERATE & REVERSE**
- Elafibranor **RESOLVE-IT**
- ~~Selonsertib~~ ~~**STELLAR 3 & 4**~~
- Cenicriviroc (CVC) **AURORA**

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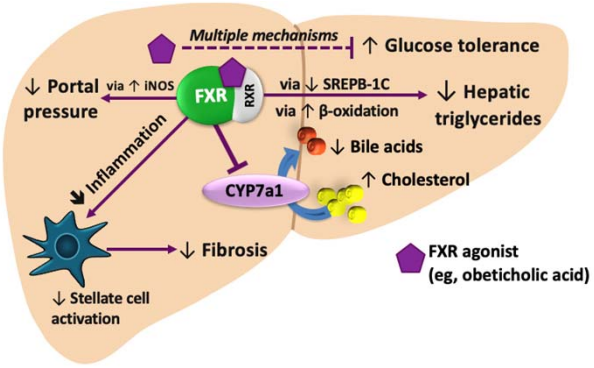
Obeticholic Acid: FXR Agonist

- FXR central to multiple key pathways in animal models



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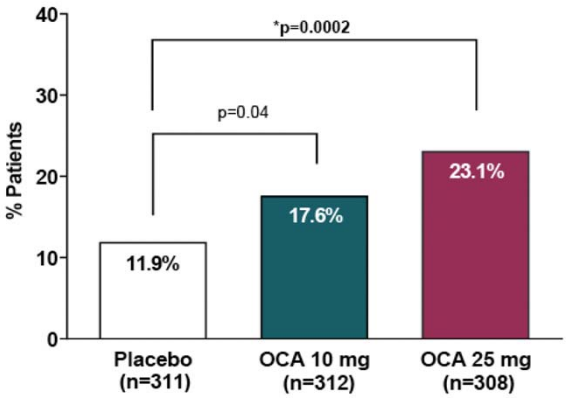
Obeticholic Acid & REGENERATE

- **First successful pivotal trial in NASH**
- RCT, double blind, placebo controlled
- Stage 2 or 3 Fibrosis

- Fibrosis improvement (≥ 1 stage) with no worsening of NASH



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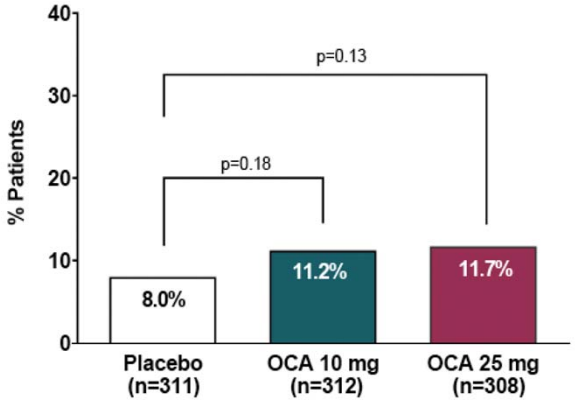
Younossi et al. EASL 2019.

Obeticholic Acid & REGENERATE

- **Did NOT achieve:**
  NASH resolution without worsening fibrosis



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Younossi et al. EASL 2019.

Conclusions

- NAFLD increasing public health burden
- Weight loss only available treatment
  - Mediterranean diet, coffee, physical activity
  - Bariatric surgery, anti-obesity medications
- Risk factor modification important
- Many emerging therapies
  - Future role for obeticholic acid

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Thanks for Your Attention!

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AT THE FOREFRONT
UChicago Medicine

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NASH as a Team Sport: Multidisciplinary Management, Successful Examples/Best Practices

Overall burden of non-alcoholic fatty liver disease (NAFLD) in the US approaches 100 million people. Natural history studies show that the key determinant of poor outcome in this group is in those individuals who develop inflammation, and more importantly, fibrosis in response to the steatosis[1]. Thankfully, only 3-5% of the population develops non-alcoholic steatohepatitis (NASH) and an even smaller fraction with fibrosis. Unfortunately, this still means upwards of 1 million people in the United States have advanced fibrosis / cirrhosis related to NAFLD/NASH. For the group with cirrhosis, 50% will not be alive in 15 years and their all cause mortality will be be nearly 7 times higher than those with just NAFLD alone [2].

Patients with NAFLD have higher risks for additional health problems. Dulai et al. have demonstrated an increased burden of co-morbid conditions, including significant increases in new onset diabetes, increased risks of heart disease, kidney disease, and even colon and breast cancer [3]. From a population health standpoint, to identify those with risk for NAFLD and better target resources, strong associations have been described with obesity, diabetes, dyslipidemia, metabolic syndrome, and also with those of Hispanic ethnicity [4]. It is important to also recognize that NAFLD is not solely a disease of obese people and that an abnormal serum alanine transaminase (ALT) is not necessary to have the condition. In fact, almost 50% of patients with NAFLD are not obese and 1 in 5 is considered LEAN (BMI<25) [5, 6].
From a provider standpoint, probably the most important aspect to recognize is that NAFLD/NASH is a reversible condition for most people! Weight loss remains the foundation of therapy for NAFLD/NASH while we await effective pharmacotherapy. Recent studies shows that 2/3 of NAFLD is reversible with as little as 3-10% weight loss and that steatohepatitis and even fibrosis can be improved with weight loss of >10% [7, 8].

So how do we begin to tackle this problem? Where and how does change begin? Cardiologists and Endocrinologists have been dealing with metabolic syndrome for decades – what can we do to change the landscape? The truth is that it will take hard work and a *different* kind of work. We must approach this from the vantage point that this is a long-term condition that is not "cured", but rather, managed. With the foundation of our interventions resting on behavior change, we need to start to become "change" specialists. What can be done in a 15 minutes visit? Turns out, there is A LOT that can be done. Motivational Interviewing (MI) has been around since the 90's. MI has been shown to be effective in even short session (called Brief Interventions) [9]. The key to MI is the approach – our frame. It begins by recognizing that change is personal! To find that personal reason why a person wants to change, it requires us to suspend judgement, acknowledge the patient's autonomy in making a choice, and then equipping the patient to make the best decision for themselves. This means it must be ok for the patient to make the "wrong" choice and then keep the conversation going. Psychology 101 – if you push, they push back. If you argue for change and find the patient arguing back, they are justifying their reasons for not changing.

With regards to building the right team for a NAFLD/NASH/Metabolic Clinic, it starts with the stakeholders. Primary Care, Endocrine/Diabetes, Pharmacy, Bariatrics, Nutrition, Physical Therapy, and Mental Health all should have a seat at the table. The truth is, we are at the

infancy of building these multidisciplinary teams. Two papers have been written about multidisciplinary NAFLD clinics [10, 11] which describe early concepts of stakeholders and process. Lacking are key analyses of long term outcomes, impact of specific stakeholders (mental health, cardiology, coaches, etc) and the frequency of visits and interventions. Individually, interventions by Clinical Pharmacists, dieticians, physical therapists, bariatric surgeons, and weight counselor have all shown some improvement in outcomes – what the right mix remains to be seen. As with colorectal cancer screening, the stance that *any* screening is better than no screening is the same stance we should take – partnered approaches offer more value to the patient and should continue to be explored.

References

1. Hagstrom, H., et al., Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. J Hepatol, 2017. 67(6): p. 1265-1273.
2. Dulai, P.S., et al., Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. Hepatology, 2017. 65(5): p. 1557-1565.
3. Estes, C., et al., Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology, 2018. 67(1): p. 123-133.
4. Chalasani, N., et al., The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology, 2018. 67(1): p. 328-357.
5. Browning, J.D., et al., Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology, 2004. 40(6): p. 1387-95.
6. Kim, D., et al., Nonalcoholic fatty liver disease is associated with coronary artery calcification. Hepatology, 2012. 56(2): p. 605-13.
7. Vilar-Gomez, E., et al., Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis. Gastroenterology, 2015. 149(2): p. 367-78 e5; quiz e14-5.
8. Wong, V.W., et al., Beneficial effects of lifestyle intervention in non-obese patients with non-alcoholic fatty liver disease. J Hepatol, 2018. 69(6): p. 1349-1356.
9. Force, U.S.P.S.T., et al., Behavioral Weight Loss Interventions to Prevent Obesity-Related Morbidity and Mortality in Adults: US Preventive Services Task Force Recommendation Statement. JAMA, 2018. 320(11): p. 1163-1171.
10. Townsend, S.A. and P.N. Newsome, The Role of a Dedicated Non-Alcoholic Fatty Liver Disease Clinic in 2016. Dig Dis, 2017. 35(4): p. 371-376.
11. Cobbold, J.F.L., et al., Piloting a multidisciplinary clinic for the management of non-alcoholic fatty liver disease: initial 5-year experience. Frontline Gastroenterol, 2013. 4(4): p. 263-269.

NASH as a Team Sport

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1

Disclosures

- **No financial disclosures**

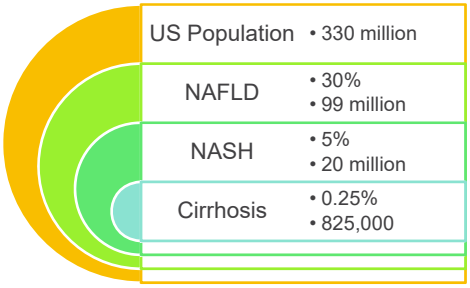
2

- Background
- Getting to behavior change?
  - Simple techniques and language for the healthcare team
- Areas to build a more integrated system
  - Primary Care
  - Pharmacy Care
  - Diabetes Clinics
  - Bariatrics Clinics
  - Individual Training
- Do we have data on Multidisciplinary NAFLD Clinics?
  - Multidisciplinary Tumor Boards

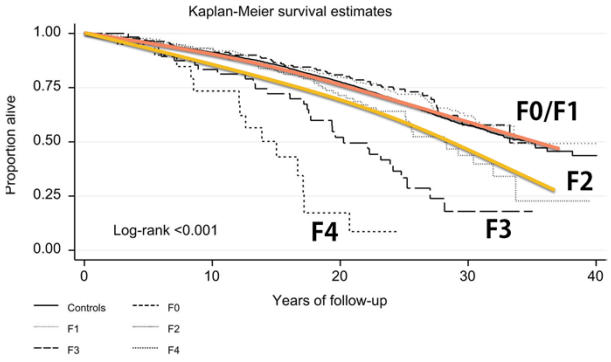
Background – The Why

Why NASH Matters

- NAFLD→ NASH→ Fibrosis
  - Fibrosis is main predictor of poor outcomes
  - Finding NASH identifies treatment candidates



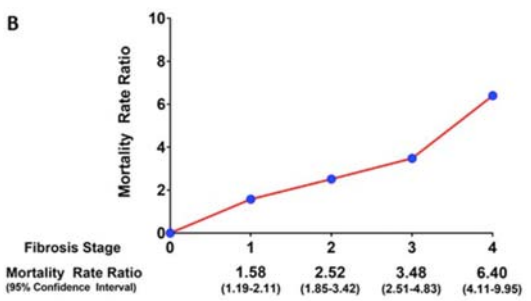
- Fibrosis associated with mortality
  - **Fibrosis ≥ F2** associated with increased mortality



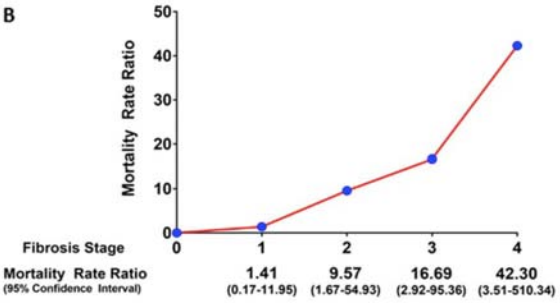
Hagström. J Hepatology. 2017;67:1265. Kim D Hepatology Int 2019

NASH: Fibrosis and Mortality

All Cause Mortality

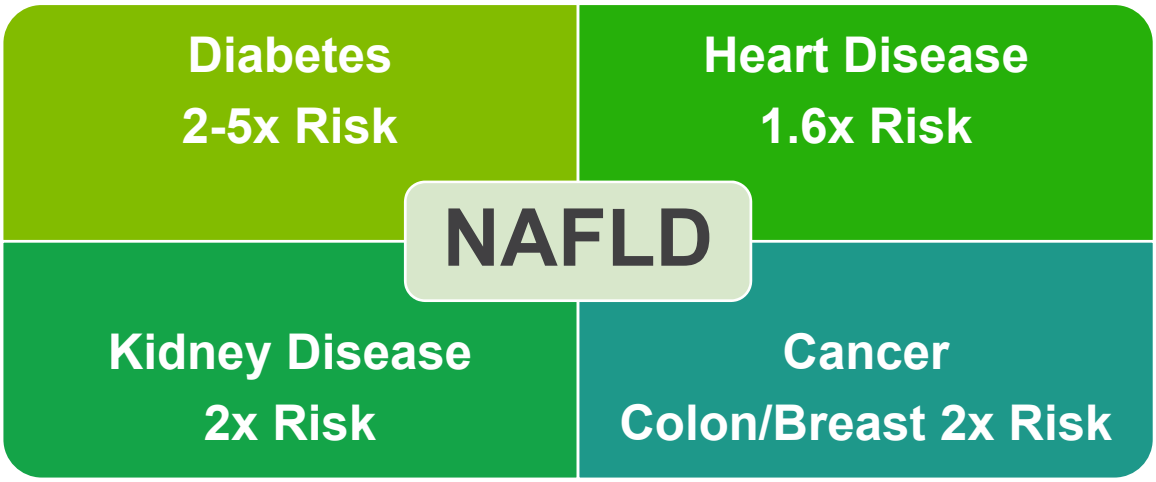


Liver Related Mortality



Dulai P. Hepatology 2017, Angulo P. Gastroenterology 2015

NAFLD: Disease Associations



Estes C. Hepatology 2018

NAFLD Risk Factors

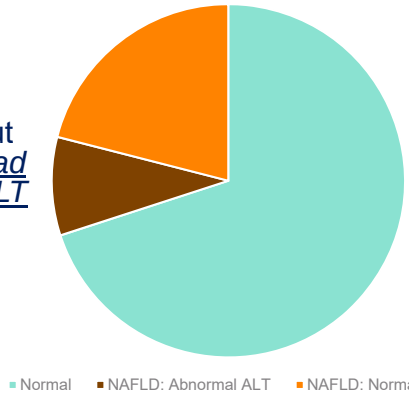
Population	NAFLD Prevalence
Morbid Obesity (BMI ≥35)	80-90% in bariatric surgery patients
Obesity	70%
T2DM	70%
Metabolic Syndrome	53%
Dyslipidemia	50%
Hispanic Ethnicity	45-50%

Chalasani N. Hepatology. 2018, Targher, G. Diabetes Care 2007, Portillo-Sanchez P. J Clin Endocrinol Metab 2015, Argo CK. Clin Liver Dis. 2009, Lonardo A. Digestive and Liver Dis. 2015

Fatty Liver: It's Not About Being Big

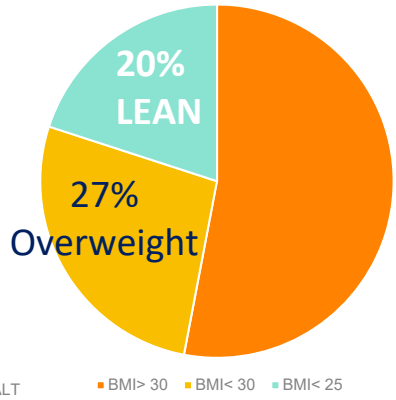
AASLD

2,287 Patients Screened for NAFLD



1/3 with NAFLD, but *only 21% had abnormal ALT*

1:5 Normal Weight



47% of patients with NAFLD were **NOT** obese

Browning. Hepatology. 2004; Kim D. Hepatology 2012

It's Not Too Late !!!

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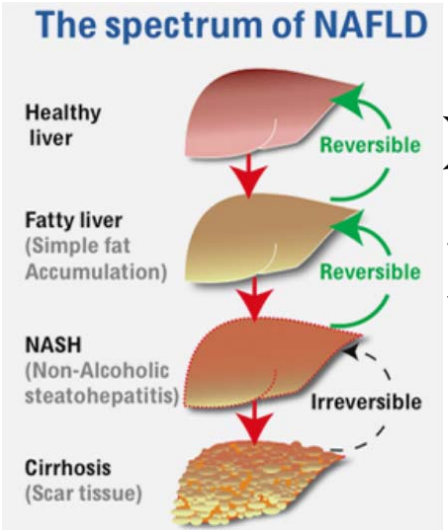

5% weight loss

10-12% weight loss

10

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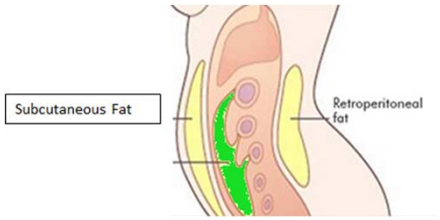
So, how do we get from here…



…or here?

…to here?

11

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We Need This

12

Simple Techniques and Language

AASLD

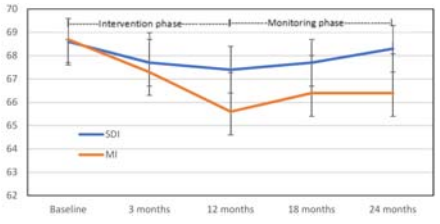
Motivational Interviewing Skills For the Whole Team

13

MI Works

AASLD

- MI Works
  - 40 Something Randomized Control Trial
    - 54 patients, 27 normal weight, enrolled in 1 year trial and then followed for an additional year
  - USPSTF Behavioral Weight Loss Interventions – Grade B
    - …behavioral counseling (ie. Motivational Interviewing)…produced clinically meaningful weight loss (4 to 7 kg).



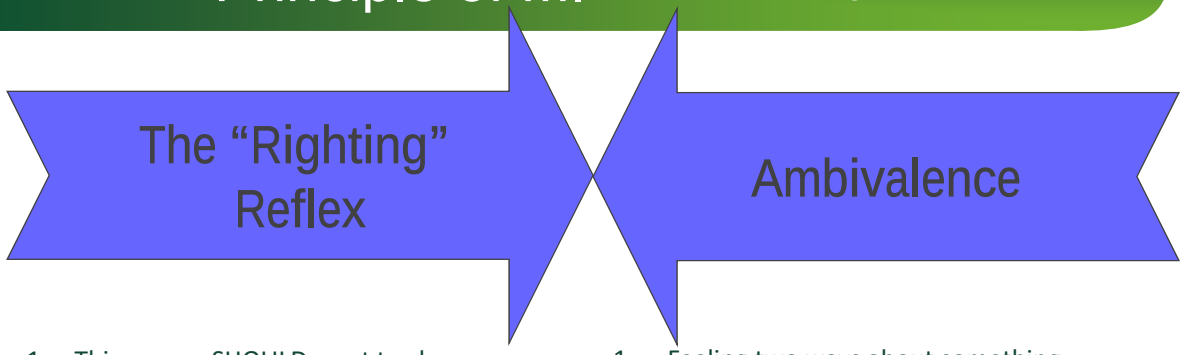
14

Williams L. et al. *Nutrients* 2019, *11*(5), 1100; Curry J. USPSTF, JAMA. 2018;320(11):1163-117

MI Defined

- " *client-centered, directive method for enhancing intrinsic motivation to change by exploring and resolving ambivalence*" (Miller and Rollnick, 2002)
- "… *a collaborative, person-centered form of guiding to elicit and strengthen motivation for change"* (Miller and Rollnick, 2009)
- A clinical "*style*"; a "*way of being with people*" (Miller and Rollnick, 2002; Rollnick and Miller, 1995)

Principle of MI



1. This person SHOULD want to change.
2. NOW is the right time to change.
3. A TOUGH/clear/honest approach is best.
4. Patient should follow my EXPERT ADVICE.
5. If patient doesn't change, the session FAILED.

1. Feeling two ways about something
2. Both sides already there
3. Ubiquitous prior to changing drinking.
4. TRAP: You argue for change, and patient defends behavior.
5. Defending status quo makes *change less likely*

One Model for Providing MI

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Feedback
- **Set the stage**
- **Give test results**

Look for reasons
- **Explore Good & "Less"**
- **Explore Importance/Confidence**

Options
- **Discuss change options**
- **Offer Advice**
- ***Close on good terms***

F Feedback

AASLD

o Ask Permission:
- *Can we take a few minutes to go over some health information that is specifically about you?*

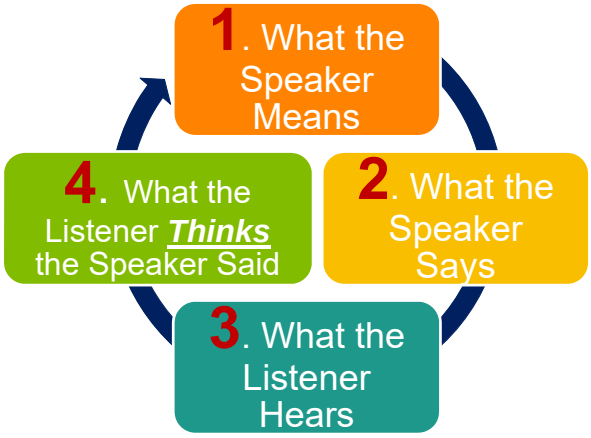
o Support Autonomy:
- *My job is just to give you the information…Your job is to decide what to do with it*

o Reduce Demands - Permission to Disagree:
- *This may or may not seem important to you….*

L Listening

AASLD

- Reflective Listening is a way of thinking !
- It is Hypothesis testing
- NEEDS PRACTICE
- Powerful for increasing readiness.



O Options

AASLD

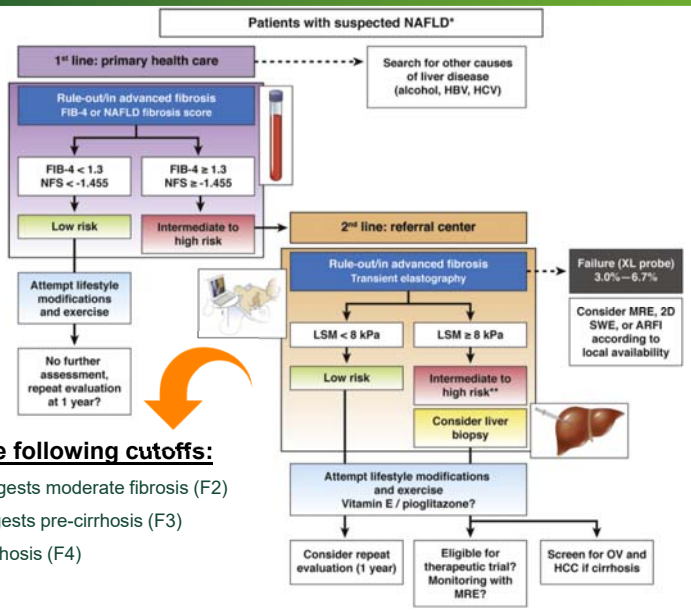
- *What do you think you will do?*
- *What changes are you thinking about making?*
- *What do you see as your options?*
- *Where do we go from here?*
- *What happens next?*

- **Conditional Statement**
  - If you wanted to…
  - If you decided to…
  - If the time were right…
- **Plan of Action**
  - How would you do it?
  - How would you go about it?
  - What would you do?

Building a More Integrated System

21

Primary Care



Studies suggest the following cutoffs:

- ≥ 7.5 to < 9.5 kPa suggests moderate fibrosis (F2)
- ≥ 9.5 to < 12 kPa suggests pre-cirrhosis (F3)
- ≥ 12 kPa suggests cirrhosis (F4)

Castera, L. Gastro 2019

Population Based Care

- Wisconsin Dept of Public Health
  - Created obesity dashboard to track outcomes in the state
- EPIC Cohort Identification Tool
  - Can help generate a cohort of high risk patients
  - Alerts to Primary Care to bring attention to patients and enter referrals
- VA Liver Disease Cube, HCC Cube, Local FIB4/NFS Registries
  - Patient level data
  - Sort whole population based on existing risk factors
  - Allows for *direct outreach* to patients
  - Letters sent to patients inviting them to participate in multidisciplinary clinic

Ryan K. WMJ. 2016 Nov; 115(5): 224–227; Lauren Beste, Liver Disease Database team

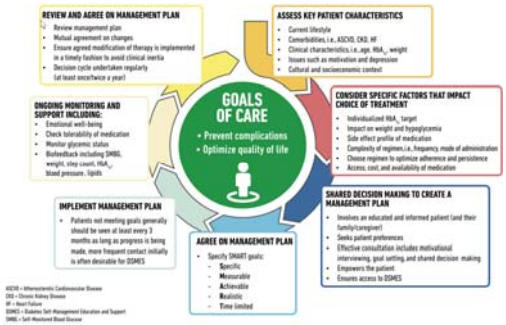
Pharmacy

- Scotland-based study
  - 314 patients, yearlong behavioral counseling at the pharmacy
  - 42% attended the 10-30 minute appointments
  - Weight loss of ≥ 5% total body weight attained at 1 year
- Maricopa County, Arizona
  - Walgreens-based intervention by Pharmacy Residents
  - Proof of concept: 6 months, 14 visits, conducted at Walgreens
  - Mean weight loss 5kg, 4.5% total body weight
- Medication based therapies – co-management model
  - GLP1 agonists (liraglutide)
  - Lorcaserin (selective 5-HT2C receptor antagonist)
  - Phentermine/Topiramate
  - Naltrexone/Buproprion

Harmon M, et al. J Am Pharm Assoc. 2014;54(3):302–307 ; Morrison D,.*BMC Public Health*. 2013;13:282

Diabetes

- ADA continues to endorse team based approach
- Newest guidelines (Jan 2019) now endorsing evaluation of NAFLD/ NASH as part of their assessment
- In depth knowledge of managing life-long condition



Nonalcoholic Fatty Liver Disease

Recommendation

4.14 Patients with type 2 diabetes or prediabetes and elevated liver enzymes (alanine aminotransferase) or fatty liver on ultrasound should be evaluated for presence of nonalcoholic steatohepatitis and liver fibrosis. **C**

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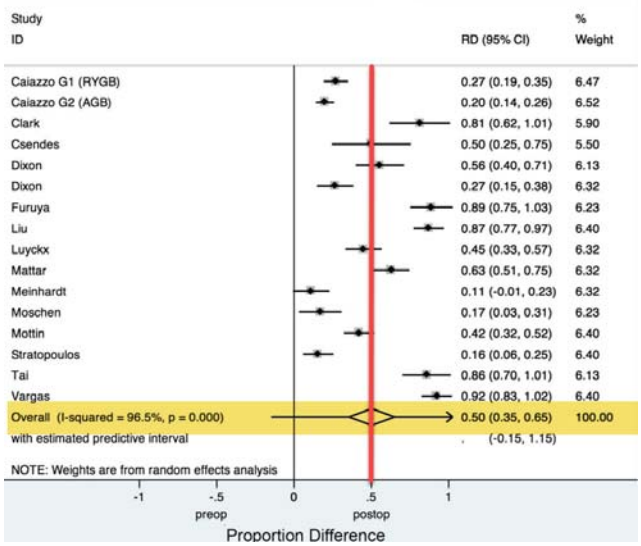
ADA - Comprehensive medical evaluation and assessment of comorbidities: Standards of Medical Care in Diabetesd 2019. Diabetes Care 2019;42(Suppl. 1):S34–S45

Bariatrics

- Cumulative data suggests significant improvement in both NAFLD and NASH in those undergoing gastric bypass surgery.
- Gastric bypass is a reasonable tool for the treatment of morbid obesity and has secondary benefits on the liver.
- Metaanalysis of 29 studies showing more then 50% reduction in steatosis and 12% reduction in fibrosis.



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Bower, G. *Obesity Surgery.* 25.12 (2015): 2280-289

Physical Therapy / Exercise

- Exercise ≠ Weight Loss
  - 198 patients given 2 “doses” of exercise, over 6 months, compared to a control group
  - No dietary counseling
  - Only 1/3 lost any weight; 1/3 did not lose weight or even gained weight
  - Compensatory changes were related to increased caloric intake, not changes in metabolism or activity outside of exercise !
- Emphasizes need to multi-prong approach with education
  - Weight loss is related to calorie restriction, not calorie burning

Martin, CK. *The American Journal of Clinical Nutrition.*: The American Journal of Clinical Nutrition. , 2019, Jun 7.

Nutrition

- Meta-analysis of RCT of nutritionist led weight loss programs
  - 14 studies
  - Modest outcomes comparing Nutrition Education alone

Weight loss (kg) – Intervention vs Comparator.

Williams LT. Healthcare **2019**, *7*(1), 20.

So – Where Do We Go From Here?

1. This is a serious problem with a large at-risk population
2. Most of the patients who are at-risk have MODIFIABLE DISEASE
3. Review of individual interventions shows that weight loss can be achieved, albeit at modest levels

The next step is integrated, multidisciplinary care

No good data, but *many* centers now engaged in developing multidisciplinary Metabolic / Liver / Fatty Liver Clinics

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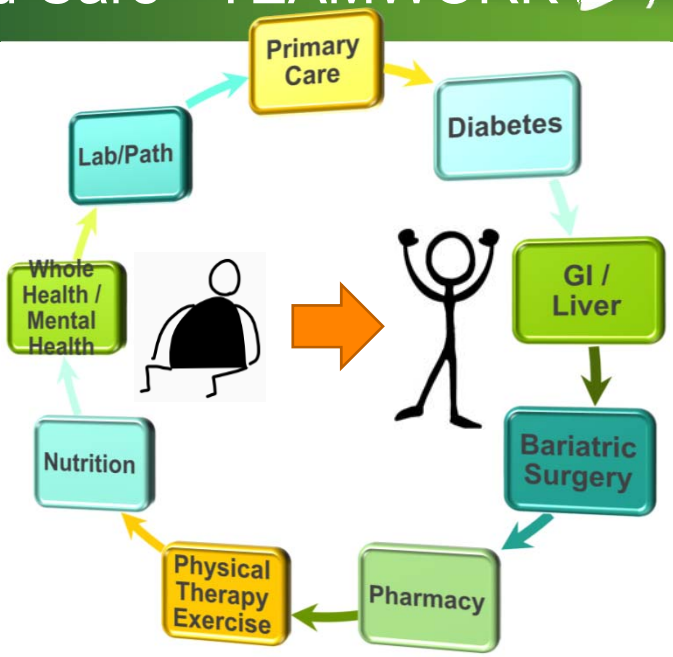
Coordinated Care - TEAMWORK



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NASH is More than BMI: Prevalence & Impact of Lean NASH

Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are emerging as a significant cause of liver disease in the world-wide population. Initially felt to be associated with obesity, it is now clear that persons with a normal body mass index (BMI) can develop NAFLD/NASH and its subsequent complications. In population-based studies, a normal BMI is generally defined as <25 kg/m^2 in Caucasians and <23 kg/m^2 in Asians.

Lean NASH has been described in multiple ethnic groups and across all age ranges, including adolescents (aged 12-18). It is reported in up to 20% in Caucasians and up to 26% in Asian populations. The pathophysiology of lean NASH remains poorly understood. Individuals with lean NASH appear to have a metabolically obese physiology, despite being normal weight (MONW). They have greater visceral adiposity and alterations are seen in adipose and muscle function, similar to that in their obese counterparts. These individuals may have genetic alterations which predispose them to fatty liver and often have a different pattern of gut microbiota.

Lean individuals have milder features of metabolic syndrome. When compared to healthy controls, however, they have a higher prevalence of dyslipidemia, hypertension, insulin resistance and diabetes. Data regarding long-term prognosis has been mixed, but many of these patients will develop severe and progressive liver disease. Treatment remains elusive.

References

1. Bellentani S, Saccoccio G, et al. Prevalence of and risk factors for hepatic steatosis in Northern Italy. Ann Intern Med 2000;132(02):112–117
2. Browning JD, Szczepaniak LS, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology 2004;40(06):1387–1395
3. Chen CH, Huang MH, et al. Prevalence and risk factors of nonalcoholic fatty liver disease in an adult population of Taiwan: metabolic significance of nonalcoholic fatty liver disease in nonobese adults. J Clin Gastroenterol 2006;40(08):745–752
4. Conjeevaram Selvakumar PK, Kabbany MN, et al. Prevalence of suspected nonalcoholic fatty liver disease in lean adolescents in the United States. J Pediatr Gastroenterol Nutr 2018;67(01):75–79
5. Cruz ACD, Bugianesi E, et al. Characteristics and long-term prognosis of lean patients with nonalcoholic fatty liver disease. Gastroenterology 2014;146(05): S-909
6. Das K, Das K, et al. Nonobese population in a developing country has a high prevalence of nonalcoholic fatty liver and significant liver disease. Hepatology 2010;51(05): 1593–1602
7. Feldman A, Eder SK, et al. Clinical and metabolic characterization of lean Caucasian subjects with non-alcoholic fatty liver. Am J Gastroenterol 2017;112(01):102–110
8. Duarte SMB, Stefano JT, et al. Gut microbiome composition in lean patients with NASH is associated with liver damage independent of caloric intake: A prospective pilot study. Nutr Metab Cardiovasc Dis 2018;28(04):369–384
9. Feng RN, Du SS, et al. Lean-non-alcoholic fatty liver disease increases risk for metabolic disorders in a normal weight Chinese population. World J Gastroenterol 2014;20(47): 17932–17940

10. Gurjal UP, Vittinghoff E, et al. Cardiometabolic abnormalities amont normal-weight persons from five racial/ethnic groups in the US: a cross-sectional analysis of two cohort studies. Ann Intern Med 2017; 166:628.
11. Hagström H, Nasr P, et al. Risk for development of severe liver disease in lean patients with nonalcoholic fatty liver disease: a long-term follow-up study. Hepatol Commun 2017;2 (01):48–57
12. Kim NH, Kim JH, et al. Clinical and metabolic factors associated with development and regression of nonalcoholic fatty liver disease in nonobese subjects. Liver Int 2014;34(04):604–611
13. Kwon YM, Oh SW, et al. Association of nonalcoholic fatty liver disease with components of metabolic syndrome according to body mass index in Korean adults. Am J Gastroenterol 2012;107(12):1852–1858
14. Leung JC, Loong TC, et al. Histological severity and clinical outcomes of nonalcoholic fatty liver disease in nonobese patients. Hepatology 2017;65(01):54–64
15. Nishioji K, Sumida Y, et al. Prevalence of and risk factors for non-alcoholic fatty liver disease in a non-obese Japanese population, 2011-2012. J Gastroenterol 2015;50(01):95–108
16. Stefan N, Schick F, et al. Causes, characteristics, and consequences of metabolically unhealthy normal weight in humans. Cell Metab 2017;26(02):292–300
17. Wei JL, Leung JC, et al. Prevalence and severity of nonalcoholic fatty liver disease in non-obese patients: a population study using proton-magnetic resonance spectroscopy. Am J Gastroenterol 2015 ;110(09): 1306–1314, quiz 1315
18. Wong VW, Wong GL, et al. Incidence of non-alcoholic fatty liver disease in Hong Kong: a population study with paired proton-magnetic resonance spectroscopy. J Hepatol 2015;62(01): 182–189
19. Xu C, Yu C, et al. Prevalence and risk factors for the development of nonalcoholic fatty liver disease in a nonobese Chinese population: the Zhejiang Zhenhai Study. Am J Gastroenterol 2013;108(08):1299–1304
20. Younes R, Bugianesi E. NASH in lean individuals. Sem Liver Dis 2019; 39:86–95
21. Younossi ZM, Stepanova M, et al. Nonalcoholic fatty liver disease in lean individuals in the United States. Medicine (Baltimore) 2012;91(06):319–327
22. Younossi Z, Anstee QM, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018;15(01):11–20
23. Younossi ZM, Blissett D, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. Hepatology 2016; 64:1577

NASH is more than BMI: Prevalence & Impact of Lean NASH

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CASE

- 38 year old man sees you for ↑ liver enzymes
  - He does not drink alcohol and is taking no medications/CAMs
  - BP 123 / 70
  - Weight 159 # Height 70" BMI 22.8 kg/m^2
  - AST 45 (0-33) ALT 55 (0-33) All others normal
  - Lipid panel – normal except LDL 204 mg/dL (normal <100)
  - Glucose 100 Hemoglobin A1c 5.9%
  - Studies negative for cause of enzyme change
  - Liver Ultrasound – diffusely increased echogenicity

DEFINITION

- NAFLD (nonalcoholic fatty liver disease)
  - Hepatic steatosis >5%
- NASH (nonalcoholic steatohepatitis)
  - Hepatic steatosis >5%
  - Mixed acinar inflammation
  - Hepatocellular ballooning

  } NAS NAFLD Activity Score
  - Pericellular or periportal fibrosis

Chalasani. *Hepatology* 2018; 67:328

DEFINITION

- Nonalcoholic fatty liver disease (NAFLD)
  - Most common cause of chronic liver disease worldwide
    - Affects 25% of the global adult population (10% in children)
  - Associated with
    - Insulin resistance / diabetes mellitus
    - Metabolic syndrome
    - BMI ≥30 kg/m^2
    - Hypertension
    - Others (race, post-menopausal, age >50 …)

Younossi. *Hepatology* 2018; 68:349
Younossi. *Hepatology* 2016; 64:1577

DEFINITION

- Lean NAFLD / NASH
  - No standard definition of Lean NAFLD
  - Occurs in absence of obesity
  - BMI definition of "Lean"
    - Caucasian studies → ≤25 kg/m^2
    - Asian studies → ≤23 kg/m^2
  - Histologically identical to Obese NASH

For a given BMI, Asians have a higher proportion of body fat than Europeans.

Younes. *Sem Liv Dis* 2019; 39:86
Kumar. *JCTH* 2017; 5:216
WHO. *Lancet* 2004; 363:157

DIAGNOSIS

- Liver Biopsy – gold standard
- Liver enzymes
  - Normal in a significant portion of patients with NAFLD
- Imaging – US / CT / MRI
  - Ultrasound
    - Operator dependent
    - Limited sensitivity (73.3%) / specificity (69.6%)
  - CT / MRI
    - More expensive; better

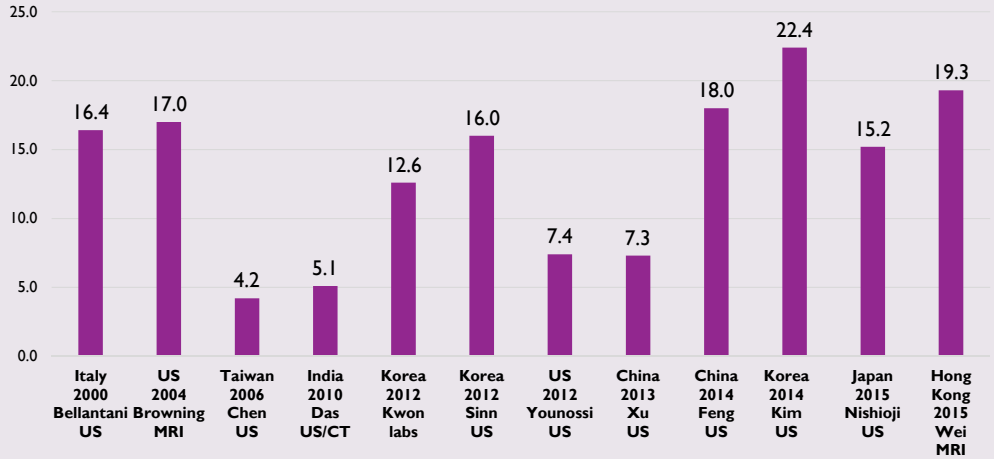
Kumar. *JCTH* 2017; 5:216
Bohte. *Eur Rad* 2011; 21:87

EPIDEMIOLOGY

- Population based
  - Data reported as far back as 2000
- Cross-sectional
  - Associations
- Longitudinal
  - Outcomes

EPIDEMIOLOGY

- Population Based Studies (lean NAFLD)



EPIDEMIOLOGIC ASSOCIATIONS

- Cross-Sectional Studies
  - Observed across all ages (8% ages 12-18 years)
  - Younger age
  - Female sex
  - Insulin resistance
  - Dyslipidemia – low HDL; elevated triglycerides
  - Lower adiponectin levels
  - More active & pro-inflammatory visceral fat
  - Greater waist circumference
- Overall
  - 5-26% in Asians 7-20% in Caucasians

Younes. *Sem Liv Dis* 2019; 39:86
C. Selvakumar. *J Pediat GI Nutr* 2018; 67: 75
Feldman. *Am J Gastro* 2017; 112: 102
Wong. *J Hepatol* 2015; 62:182
Kim. *Liver Int* 2014; 34:604
Feng. *World J Gastro* 2014; 20: 17932
Younossi. *Med (Balt)* 2012; 91:319

LIMITATIONS IN EPIDEMIOLOGIC STUDIES

- Definition of metabolic syndrome varies
- Criteria is used to define NAFLD varies
  - Liver tests – imaging – algorithms
- Lack of noninvasive markers of NAFLD/NASH
- BMI definition of "Lean" varies
  - Most studies (Caucasians) → ≤25 kg/m^2
    - Some even use BMI ≤30 kg/m^2
  - Asian studies → ≤23 kg/m^2

Younes. *Sem Liv Dis* 2019; 39:86
Consultation WHOE. *Lancet* 2004; 363:157

ETIOLOGY

- Don't Forget
  - Endocrine
    - Polycystic ovarian syndrome
    - Hypothyroidism
    - Growth hormone deficiency
  - Genetic disorders
    - Familial hypobetalipoproteinemia (FHBL)
    - Lysosomal acid lipase deficiency (LAL-D)
    - Cystic Fibrosis
    - Wilson Disease
  - Drug-related
    - Amiodarone / Methotrexate / tamoxifen / corticosteroids
  - Lipodystrophy
    - Congenital / Acquired – HAART
  - Other
    - Malnutrition / Starvation (Jejunoileal bypass) / TPN

Younes. *Sem Liv Dis* 2019; 39:86
Romeo. *Nat Genet* 2008; 40:1461
Abid. *J Hepatol* 2009; 51:918

ETIOLOGY

- Possibly associated with Lean NASH
  - High fructose intake
    - Particularly in children and adolescents
    - Fructose is an inducer of de novo lipogenesis
    - Fructose induces hepatocellular oxidative stress
    - Fructose diet increases visceral adipose in humans & animal models
    - Gut microbiome likely crucial to fructose's contribution to NAFLD/NASH
      - *Lactobacillus rhamnosus GG* products against fructose-induced NAFLD

Duarte. *Nutr Met Card Dis* 2018; 28:369
Spruss. *J Nutr Bioch* 2009; 20:657
Abid. *J Hepatol* 2009; 51:913
Thuy. *J Nutr* 2008; 138:1452

Younes. *Sem Liv Dis* 2019; 39:86
Jensen. *J Hep* 2018; 68:1063
Jegatheesan. *Nutrients*. 2017; 9:230
Ritze. *PLoS One.* 2014; 9(1):e80169

ETIOLOGY

- Possibly associated with Lean NASH
  - Genetic polymorphisms
    - PNPLA 3 (patatin-like phospholipase domain-containing protein) GG variant
      - Encodes adiponutrin – mechanism of disease not understood
      - 78.4% (nonobese NAFLD) vs 59.8% (obese NAFLD)
      - Independently associated with NAFLD and more aggressive disease
    - CETP (cholesteryl ester transfer protein)
    - SREBP (sterol regulatory element binding protein)
    - APOC3 (apolipoprotein 3)

Fracanzani. *Clin Gasto Hep* 2017; 15:1604.
Nishioji. *PLoS One*. 2015; 10:e0140427
Liu. *Nat Commun* 2014; 5:4309
Adams. *J Gastro Hep* 2012; 27:1520

Younes. *Sem Liv Dis* 2019; 39:86
Kumar. *JCTH* 2017; 5:216
Hussain. *Endo Metab Clin NA* 2016; 45:783
Singal. *Am J Gastro* 2014; 109:325
Romeo. *Nat Genet* 2008; 40:1461
Stanhope. *J Clin Invest*. 2009; 119: 1322

ETIOLOGY

- Possibly associated with Lean NASH
  - Gut Flora & dysbiosis
    - In General:
      - Lower – *Firmicutes; Ruminococcus; lactobacilli; Lachnospiraceae*
      - Higher – *Prevotella; Porphyromonas; EtOH-producing organisms*
    - Data Mixed – *Bacteroidetes*
    - Gut fructose metabolism → increase gut permeability → increased endotoxin in the portal vein/liver → ↑ inflammation in the liver

Younes. *Sem Liv Dis* 2019; 39:86
Duarte. *Nutr Metab Card Dis* 2018; 28:369
Wang. *Sci Rep* 2016; 6:32002

Houghton. *Int J Mol Sci* 2016; 17:447
Zhu. *Hep* 2013; 57:601
Soga. *Bioch Bioph Res Comm* 2005; 326; 744

PATHOPHYSIOLOGY

- Metabolic Obesity / Normal Weight (MONW)
  - Visceral Obesity
  - Insulin Resistance (IR)
    - Lean NAFLD patients are IR compared to healthy controls
    - Similar to that observed in obesity
  - Higher circulating free fatty acids
  - Proinflammatory circulating milieu
    - Decreased adiponectin

Younes. *Sem Liv Dis* 2019; 39:86
Feng. *Lipids Health Dis* 2017; 16:165
Stefan. *Cell Metab* 2017; 26:292.

Gurjal. *Ann Int Med* 2017; 166:628
Conus. *Appl Phys Nutr Met* 2007; 32:4
Bugianesi. *Diabetologia* 2005; 48: 634

PATHOPHYSIOLOGY

- Metabolic Obesity / Normal Weight (MONW)
  - Prevalence (assessed by CT; BMI <30 kg/m^2)

Group	Percent MONW	% NAFLD by CT
Caucasians	21%	9%
Chinese Americans	32%	
African Americans	31%	6%
Hispanics	38.5%	18%
South Asians	43.6%	

Younes. *Sem Liv Dis* 2019; 39:86
Gurjal. *Ann Int Med* 2017; 166:628

OUTCOMES / CLINICAL IMPLICATIONS

- Little information regarding natural history
- Lean NASH is likely not be more "benign"
  - Despite less obesity-related comorbidities
  - Clinical events & mortality similar to obese NASH
- Longitudinal Studies
  - Hypertriglyceridemia → advanced disease
  - Higher creatinine → advanced disease
  - Higher mortality
- Data remains conflicting

Dela Cruz. *Gastro* 2014; 146: S909
Younossi. *Metab* 2013; 62:352

Hagström. *Hepatol Comm* 2017; 2: 48
Leung. *Hepatology*. 2017; 65: 54

SUMMARY

- Lean NAFLD
  - Up to 26% in Asian populations
  - Up to 20% in Western populations
  - Factors other than body weight are important
    - ?genetics
    - ?microbiome / metabolome
    - ?other
  - Outcome data conflicting, but concerning
    - Lean NAFLD patients can develop severe disease
    - Long-term prognostic data lacking

QUESTION

- Lean NAFLD/NASH subjects can have all of the following features except:
  - A. Insulin resistance
  - B. Normal visceral adiposity
  - C. Dyslipidemia
  - D. Decreased muscle mass
  - E. Hypertension

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Non-cirrhotic Portal Hypertension

Portal Hypertension

- Is characterized clinically by
  - Clinical signs:
    - Splenomegaly
    - Caput Medusae
    - Thrombocytopenia
    - Anemia
  - Clinical symptoms:
    - Variceal bleeding
    - Ascites
- In Western countries is usually (~90%) caused by cirrhosis; ~10% of portal hypertension in Western countries will have a non-cirrhotic cause(*1*)
- In Sub-Saharan Africa and East Asia, the most common cause of PH is schistosomiasis(*2*)

Non-cirrhotic Portal Hypertension (NCPH)

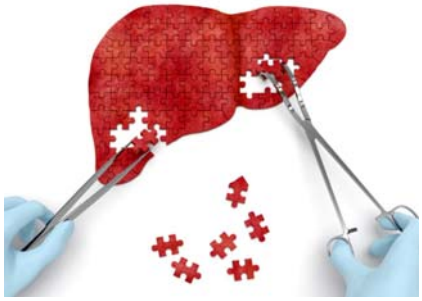
- The diagnosis of NCPH can be made by ruling out cirrhosis when there is clear evidence of portal hypertension
  - The best way to confirm portal hypertension is to perform portal pressures, where the Free Hepatic Venous Pressure (FHVP) and the Wedged Hepatic Venous Pressure (WHVP) are measured, then a calculation of WHVP – FHVP gives the Hepatic Venous Pressure Gradient (HVPG); portal hypertension is confirmed when the HVPG is > 5 mm HG
  - Liver stiffness (elastography) is usually much lower in NCPH compared to cirrhotics, but this is not in itself a reliable test to diagnose NCPH(*3*)
  - Marked splenomegaly is a common feature of NCPH, and may predict the presence of esophageal or gastric varices(*3*)
  - HVPG measurements are often much lower in NCPH compared to cirrhotic PH, which is due to an increased number of collateral formations
- The most common clinical problem arising in patients with NCPH is variceal bleeding. Though scant data supports the recommendations, most guidelines suggest treating variceal bleeding in NCPH similarly to that occurring in cirrhotics(*4*)
  - Vasoactive medications
  - Endoscopy with band ligation as indicated
  - Primary and secondary prophylaxis with non-selective beta blockers
  - TIPS when indicated
- Patients with NCPH rarely develop ascites or hepatic encephalopathy(*5*)
- Patients with NCPH have an excellent long-term prognosis, even if there is variceal bleeding. One study documented a 10 year survival rate of 82%, (*5*) and liver transplant is rarely performed for NCPH.(*6*)

- NCPH can arise from Pre-Hepatic (Portal Vein Thrombosis), Intrahepatic (Schistosomiasis and Idiopathic NCPH) and Post-Hepatic (Budd-Chiaria and right-heart failure) causes
    - For these causes, cross-sectional imaging and venography/biopsy/portal pressure measurement can usually clinch the diagnosis
- Idiopathic NCPH (INPH) is a syndrome that encompasses several different clinicopathological entities that share a common pathway of obliterative portal venopathy; the term Idiopathic NCPH is the preferred terminology, though these entities may have different presentations and clinical courses in different parts of the world
    - Nodular regenerative hyperplasia
    - Noncirrhotic portal fibrosis
    - Idiopathic portal hypertension
    - Hepatoportal sclerosis
    - Incomplete septal cirrhosis
    - Obliterative portal venopathy
    - Benign intrahepatic portal hypertension
    - Idiopathic presinusoidal portal hypertension
- Though “Idiopathic,” INPH has been associated with several underlying disorders:
    - Chronic infections
    - Immune system disturbances including HIV
    - Myelodysplastic syndromes and other malignancies
    - Medications like azathioprine and cytotoxic chemotherapies
    - Hypercoagulable states

References

1. A. Berzigotti, S. Seijo, E. Reverter, J. Bosch, Assessing portal hypertension in liver diseases. *Expert Rev Gastroenterol Hepatol* **7**, 141-155 (2013)
2. K. M. De Cock, Hepatosplenic schistosomiasis: a clinical review. *Gut* **27**, 734-745 (1986).PMC1433333
3. M. E. Cunningham, G. Parastandeh-Chehr, O. Cerocchi, D. K. Wong, K. Patel, Noninvasive Predictors of High-Risk Varices in Patients with Non-Cirrhotic Portal Hypertension. *Canadian journal of gastroenterology & hepatology* **2019**, 1808797 (2019).PMC6383430
4. S. Siramolpiwat, S. Seijo, R. Miquel, A. Berzigotti, A. Garcia-Criado, A. Darnell, F. Turon, V. Hernandez-Gea, J. Bosch, J. C. Garcia-Pagan, Idiopathic portal hypertension: natural history and long-term outcome. *Hepatology* **59**, 2276-2285 (2014)
5. R. K. Dhiman, Y. Chawla, R. K. Vasishta, N. Kakkar, J. B. Dilawari, M. S. Trehan, P. Puri, S. K. Mitra, S. Suri, Non-cirrhotic portal fibrosis (idiopathic portal hypertension): experience with 151 patients and a review of the literature. *J Gastroenterol Hepatol* **17**, 6-16 (2002)
6. B. Meijer, M. Simsek, H. Blokzijl, R. A. de Man, M. J. Coenraad, G. Dijkstra, C. M. van Nieuwkerk, C. J. Mulder, N. K. de Boer, Nodular regenerative hyperplasia rarely leads to liver transplantation: A 20-year cohort study in all Dutch liver transplant units. *United European gastroenterology journal* **5**, 658-667 (2017).PMC5548351

The other side of the triad: **Non-cirrhotic portal hypertension**



JUNE 14, 2019

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Disclosure slide

Nothing to disclose

Non-cirrhotic portal hypertension
Objectives

1. Understand classification of portal PH
2. Cirrhotic versus non-cirrhotic PH
3. Causes of non-cirrhotic PH

Signs and Symptoms of PH

Symptoms

- Variceal bleeding
- Ascites

Signs

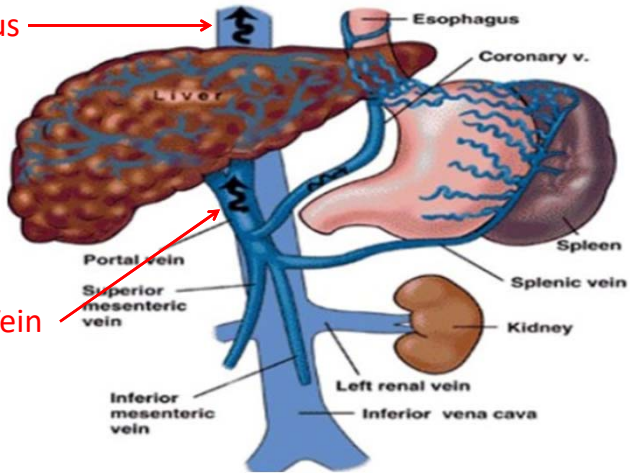
- Splenomegaly
- Thrombocytopenia
- Caput Medusae
- Anemia

Portal hypertension

PH = elevated Hepatic Venous Pressure Gradient (HVPG)
HVPG (= WHVP minus FHVP) > 5 mm Hg

Free Hepatic venous pressure (FHVP)

Wedged Hepatic Vein Pressure (WHVP)



Berzigotti, Exp Rev Gastro, 2013

Broad categories of PH

	Western
Cirrhotic	**~90%**
Non-cirrhotic	**~10%**

Berzigotti, Exp Rev Gastro, 2013
De Cock, Gut, 1986

Broad categories of PH

	India
Cirrhotic	
Non-cirrhotic	
PVT/Idiopathic	**>50%**

Berzigotti, Exp Rev Gastro, 2013
De Cock, Gut, 1986

Broad categories of PH

	Africa/SE Asia
Cirrhotic	
Non-cirrhotic	
Schistosomiasis*	**>50%**

***Most common cause of PH in the world**

Berzigotti, Exp Rev Gastro, 2013
De Cock, Gut, 1986

Broad categories of PH

	Western	India	Africa/SE Asia
Cirrhotic	~90%		
Non-cirrhotic	~10%		
PVT/Idiopathic		>50%	
Schistosomiasis*			>50%

*Most common cause of PH in the world

Berzigotti, Exp Rev Gastro, 2013
De Cock, Gut, 1986

Broad categories of PH

Pre-Hepatic

Intrahepatic

Post-Hepatic

Broad categories of PH

Pre-Hepatic

- Portal vein thrombosis

Intrahepatic

Post-Hepatic

Broad categories of PH

Pre-Hepatic

- Cirrhosis
- Schistosomiasis
- Idiopathic Non-Cirrhotic Portal Hypertension (INPH)

Intrahepatic

Post-Hepatic

Broad categories of PH

Pre-Hepatic

- Budd-Chiari Syndrome
- Right-sided heart failure
  - Constrictive pericarditis

Intrahepatic

Post-Hepatic

Broad categories of PH

Pre-Hepatic

Intrahepatic

Post-Hepatic

Clinical Caveat:

Non-cirrhotic PH may evolve to cirrhosis

Cirrhotic vs Non-cirrhotic PH

Associated clinical manifestations

Cirrhotic PH

- Variceal bleeding
- Ascites
- Encephalopathy
- HCC
- Death

Cirrhotic vs Non-cirrhotic PH

Associated clinical manifestations

Cirrhotic PH

- Variceal bleeding
- Ascites
- Encephalopathy
- HCC
- Death

Non-cirrhotic PH

- Variceal bleeding
- Ascites
- Encephalopathy
- HCC
- Death

Cirrhotic vs Non-cirrhotic PH

Associated clinical manifestations: NCPH

Number of patients	151
GI bleeding	65%
Ascites	10%
Encephalopathy	0%

Dhiman, J GI & Hepatology, 2002

Cirrhotic vs Non-cirrhotic PH

Variceal bleeding

<u>Cirrhotic PH</u>

- High mortality
- Prognosis related to cirrhosis stage

<u>Non-cirrhotic PH</u>

- Low mortality
- Prognosis related to hemostasis

Cirrhotic vs Non-cirrhotic PH

Variceal bleeding: treatments

Cirrhotic PH

- Vasoactive meds
- Antibiotics
- Band ligation
- NS beta-blockers
- TIPS

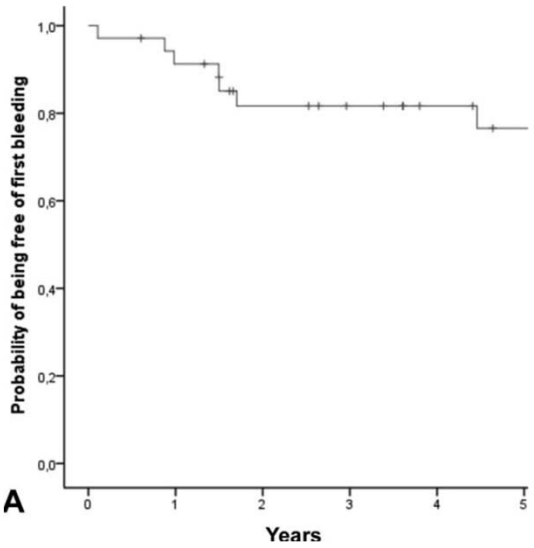
Non-cirrhotic PH

- Vasoactive meds
- Antibiotics
- Band ligation
- NS beta-blockers
- TIPS
- Surgical shunt

Siramolpiwat, Hepatology, 2014

Non-cirrhotic PH

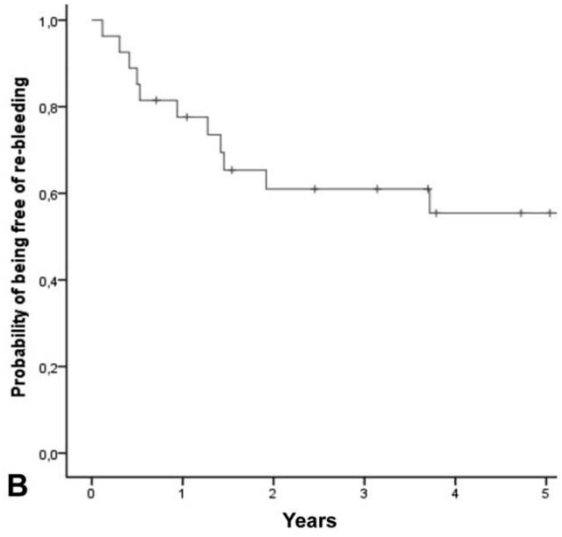
NCPH with large varices undergoing primary prophylaxis



Siramolpiwat, Hepatology, 2014

Non-cirrhotic PH

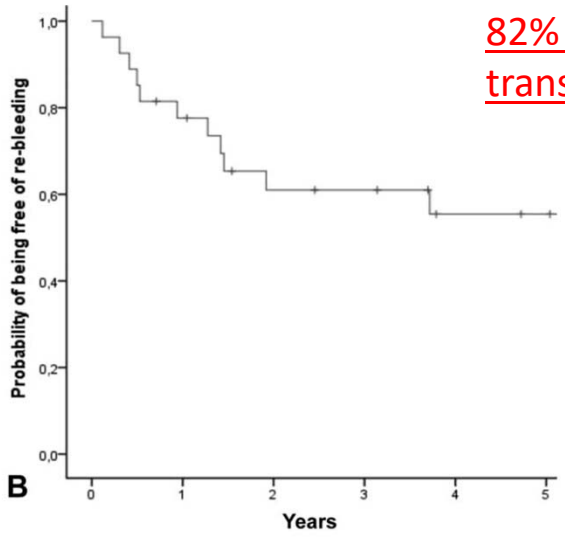
NCPH undergoing secondary prophylaxis



ramolpiwat, Hepatology, 2014

Non-cirrhotic PH

NCPH undergoing secondary prophylaxis



82% ten year transplant-free survival

ramolpiwat, Hepatology, 2014

Non-cirrhotic PH

Rarely progresses to liver failure or need for LT

11 of 1886 liver transplants over 20 years were found to be NCPH on explant

- Had been thought cirrhotic until pathology

Meijer, UE GI Journal, 2017

Non-cirrhotic PH

Screening for HCC: not recommended

Although there exist case reports of HCC developing in NCPH, these are extremely rare and there is no clear association between the two.

Heimbach, Hepatology, 2018

Non-cirrhotic PH: Diagnosis

1. Rule out cirrhosis
2. Cross-sectional imaging
3. Venography, portal pressures, biopsy
   "Hat Trick"
4. Stool O & P (if ? Schistosomiasis)

Causes of Non-cirrhotic PH

Pre-Hepatic	• Portal Vein Thrombosis
Intrahepatic	• Schistosomiasis • Idiopathic
Post-Hepatic	• Budd-Chiari Syndrome • Right-sided heart failure – Constrictive pericarditis

(Really) rare Causes of Non-cirrhotic PH

Sarcoidosis

Amyloidosis

Radiation

Mastocytosis

Gaucher Disease

Agnogenic myeloid metaplasia

Idiopathic Non-cirrhotic PH (INPH)

Many names, perhaps same entity

- Nodular regenerative hyperplasia
- Noncirrhotic portal fibrosis
- Idiopathic portal hypertension
- Hepatoportal sclerosis
- Incomplete septal cirrhosis
- Obliterative portal venopathy
- Benign intrahepatic portal hypertension
- Idiopathic presinusoidal portal hypertension

Idiopathic Non-cirrhotic PH (INPH)

Etiologic associations

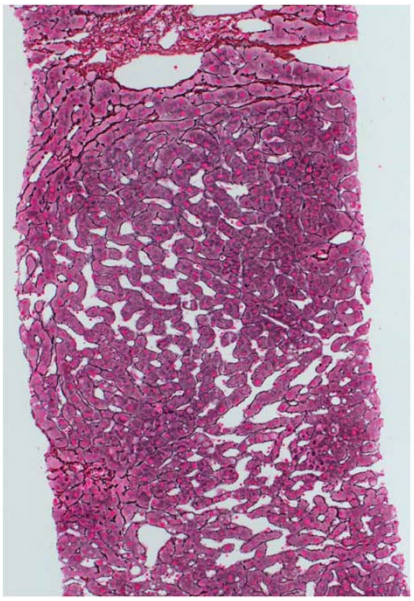
- Myelodysplastic disorders
- Chronic infections
- Immune disorders (HIV)
- Drugs (azathioprine, cytotoxic chemotherapies)
- Hypercoagulable states

Idiopathic Non-cirrhotic PH (INPH)

Pathopysiology

- Obliterative venopathy arising from inflammation or ischemic state
- May see dilated sinusoids and nodular contours without significant fibrosis
- There is often focal fibrosis around the portal triad
- May be atrophy of artery and bile duct (along with dilated portal vein radical)

Idiopathic Non-cirrhotic PH (INPH)

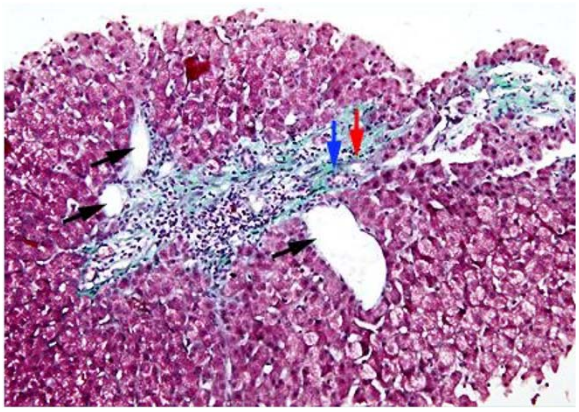


Dilated hepatic sinusoids

Semela, Clinical Liver Disease, 2015

Idiopathic Non-cirrhotic PH (INPH)

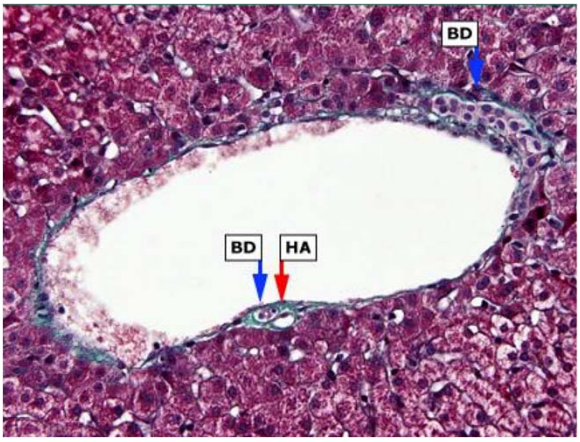
Focal portal fibrosis



Up to Date, courtesy of Rosa Miquel, MD

Idiopathic Non-cirrhotic PH (INPH)

Large PV radical, small artery and bile duct



Up to Date, courtesy of Rosa Miquel, MD

Idiopathic Non-cirrhotic PH (INPH)

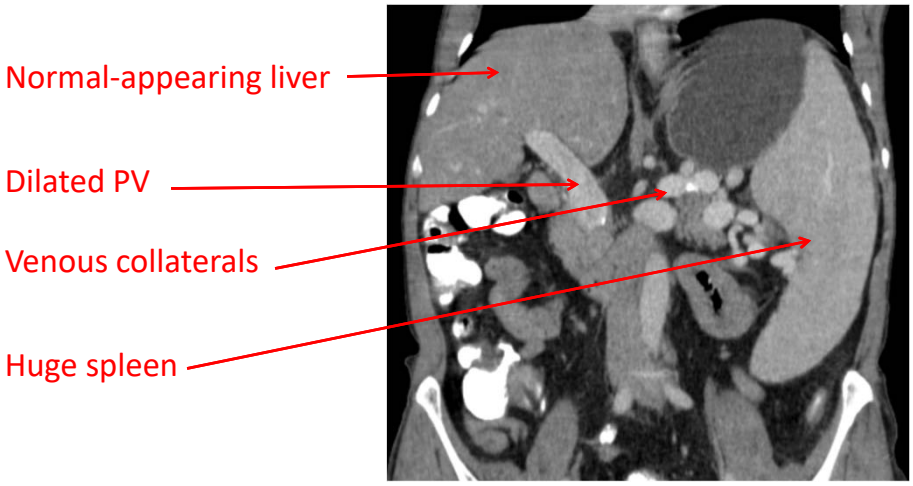
Diagnostic notes

- Though elevated, HVPG is on average much lower than seen in cirrhosis
  - Average HVPG ~ 7 mm Hg in INPH vs 17 in cirrhotics
  - HVPG may be normal despite other signs of portal hypertension (bleeding varices)
    - Due to significant collaterals decompressing system
  - Splenomegaly usually more profound than cirrhosis

Seijo, Dig Dis Liv, 2012

Idiopathic Non-cirrhotic PH (INPH)

Diagnostic notes



I found it on the Internet

Non-cirrhotic PH

Summary

- Non-cirrhotic PH makes up about 10% of all portal hypertension in Western countries
  - Cirrhosis causes 90% of PH
- Main clinical manifestation of non-cirrhotic PH is variceal bleeding (ascites, HE rare)
- Varices/bleeding in non-cirrhotic PH are treated similarly to those in cirrhosis
  - But long-term prognosis much better than cirrhosis

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The Expanding Role of TIPS

The transjugular intrahepatic portosystemic shunt (TIPS) procedure was created initially as a consequence of attempts at performing transjugular cholangiography. The first clinical use of the procedure was in 1982; however, it was not until stent technology evolved in the late 1980s-1990s, and most recently, with dedicated stent grafts in the last 15 years, that the procedure demonstrated its true efficacy. Primary indications for TIPS creation proven in prospective trials include secondary prevention of variceal bleeding and treatment of refractory cirrhotic ascites. With the evolution of experience and technical advancement, there are now increasing clinical scenarios where TIPS creation may be beneficial. These include cases of acute and chronic portal vein thrombosis, portal cavernous cholangiopathy, Budd-Chiari or polycystic liver disease, and pre-operative TIPS creation to reduce morbidity and mortality from abdominal surgery. TIPS creation for acute portomesenteric thrombosis can help mitigate acute symptoms as well as maintain patency of the portal system for potential transplant. Reconstruction of chronic portal vein thrombosis has been recently shown successful, with improvement in managing complications of portal hypertension, and also with the promise of aiding successful liver transplant. With chronic portal vein occlusion, increasing recognition of portal cavernous cholangiopathy has resulted in treatment options for this often challenging disease. In addition, anatomic challenges, including with Budd-Chiari or with polycystic liver disease, have been surmounted with improved image-guidance technology during TIPS. Finally, recent observational data are showing reversal of cirrhosis associated sarcopenia in patients after TIPS creation, a finding which may have broad implications in both management of portal hypertension and in patients awaiting transplant.

References

1. Keller et al. “The Transjugular Intrahepatic Portosystemic Shunt: Technique and Instruments.” Tech Vasc Interv Radiol 2016 19(1)2-9.
2. hornberg et al. “Pretransplantation Portal Vein Recanalization and Transjugular Intrahepatic Portosystemic Shunt Creation for Chronic Portal Vein Thrombosis: Final Analysis of a 61-Patient Cohort” J Vasc Inter Rad 2017 28:1714-21
3. Lahat et al., “Transjugular intrahepatic portosystemic shunt as a bridge to non-hepatic surgery in cirrhotic patients with severe portal hypertension: a systematic review.” HPB 2018, 20(2):101-109
4. Schlansky, Barry, et al. "Portal Biliopathy Causing Recurrent Biliary Obstruction and Hemobilia." ACG case reports journal 1.1 (2013): 44.
5. Jahangiri Y, Pathak P, Tomozawa Y, et al. “Muscle Gain after Transjugular Intrahepatic Portosystemic Shunt Creation: Time Course and Prognostic Implications for Survival in Cirrhosis.” Journal of Vascular and Interventional Radiology, 2019 in press.
6. Praktiknjo M, Book M, Luetkens J, et al. Fat-free muscle mass in magnetic resonance imaging predicts acute-on-chronic liver failure and survival in decompensated cirrhosis. Hepatology 2018; 67:1014-26.
7. Tsien C, Shah SN, McCullough AJ, Dasarathy S. Reversal of sarcopenia predicts survival after a transjugular intrahepatic portosystemic stent. Eur J Gastroenterol Hepatol 2013; 25:85-93.

8. Dasarathy J, Alkhouri N, Dasarathy S. Changes in body composition after transjugular intrahepatic portosystemic stent in cirrhosis: a critical review of literature. Liver Int 2011; 31:1250-8.
9. Nardelli S, Lattanzi B, Torrisi S, et al. Sarcopenia Is Risk Factor for Development of Hepatic Encephalopathy After Transjugular Intrahepatic Portosystemic Shunt Placement. Clin Gastroenterol Hepatol 2017; 15:934-6.
10. DiMartini A, Cruz RJ, Jr., Dew MA, et al. Muscle mass predicts outcomes following liver transplantation. Liver Transpl 2013; 19:1172-80.

The Expanding Role of TIPS

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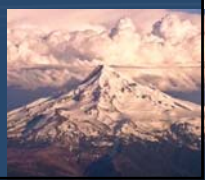

Relevant Disclosures

- Consulting: Cook Medical; Guerbet, LLC
- Research support: Guerbet, LLC; Baylis Medical;
- Advisory Board: BTG, Dova Pharmaceuticals

TIPS: Emerging indications

- Acute portomesenteric thrombosis
- Chronic portal vein thrombosis
- Portal biliopathy
- Advanced guidance techniques
- Pre-operative TIPS
- Sarcopenia

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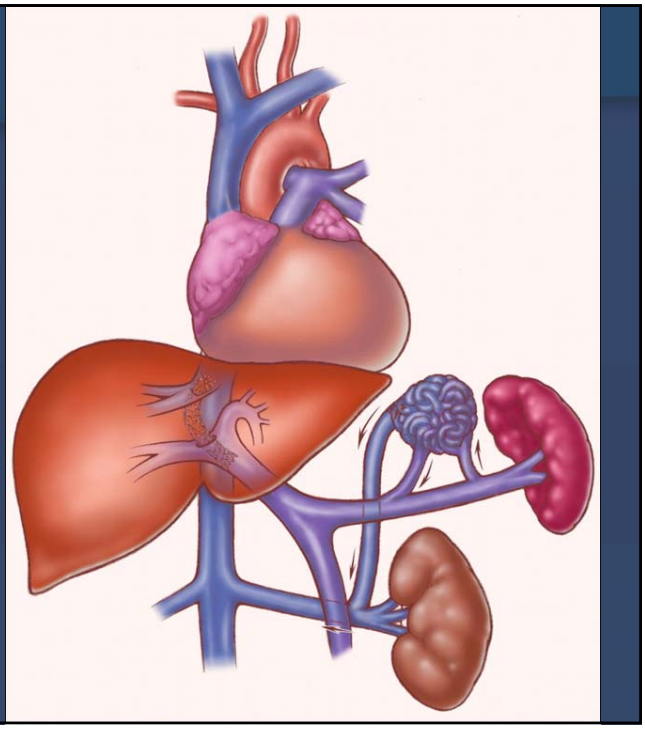
TIPS

- 1969, Josef Rosch
  - Transjugular cholangiography
- 1982, Colapinto
  - First clinical use (balloon angioplasty)
- 1988, Richter
  - Clinical TIPS with stents
- 2004, Viatorr Stentgraft
  - (Gore Medical)



TIPS Indications

- **Efficacy Determined by Prospective Trials**
  - Secondary prevention variceal bleeding
  - Refractory cirrhotic ascites
- **Efficacy Assessed in Uncontrolled Series**
  - Refractory acutely bleeding varices
  - Portal hypertensive gastropathy
  - Bleeding gastric varices
  - Refractory hepatic hydrothorax
  - Hepatorenal syndrome
  - Budd-Chiari syndrome
  - Veno-occlusive disease
  - Hepatopulmonary syndrome

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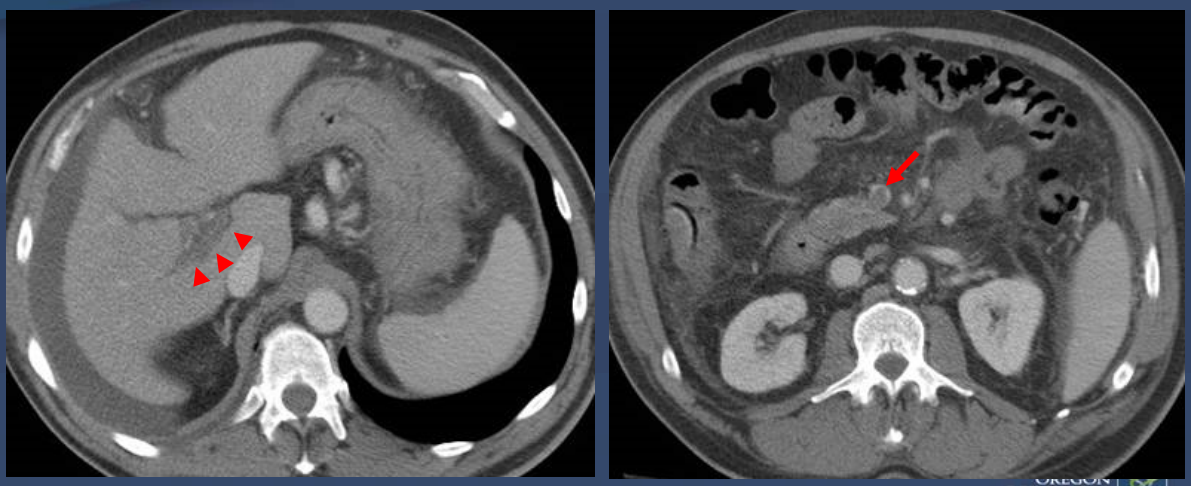
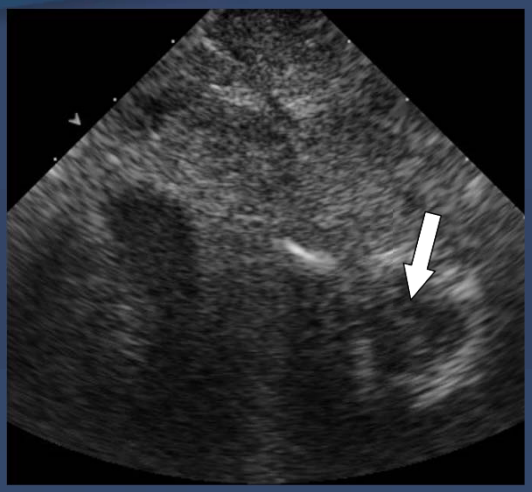
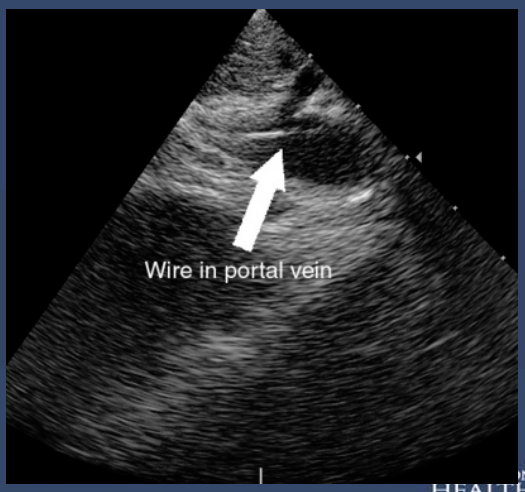
TIPS: Acute Portal Vein Thrombosis



TIPS: Acute Portal Vein Thrombosis





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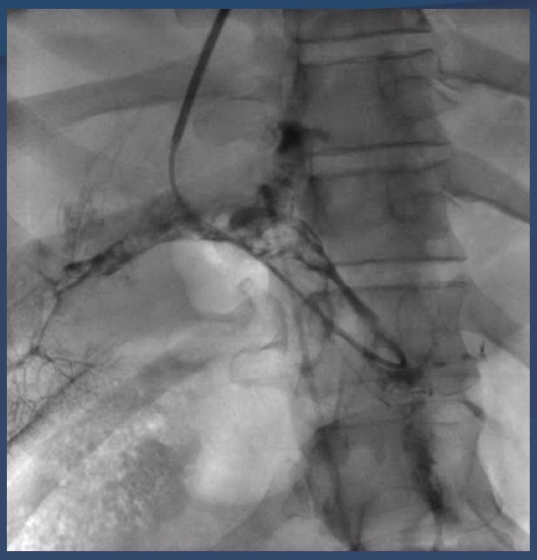
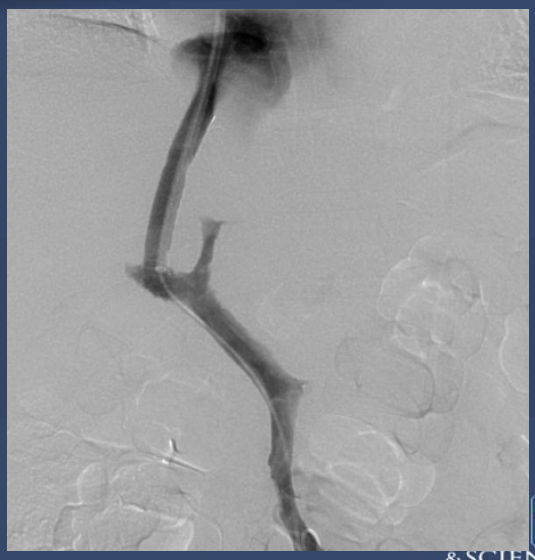
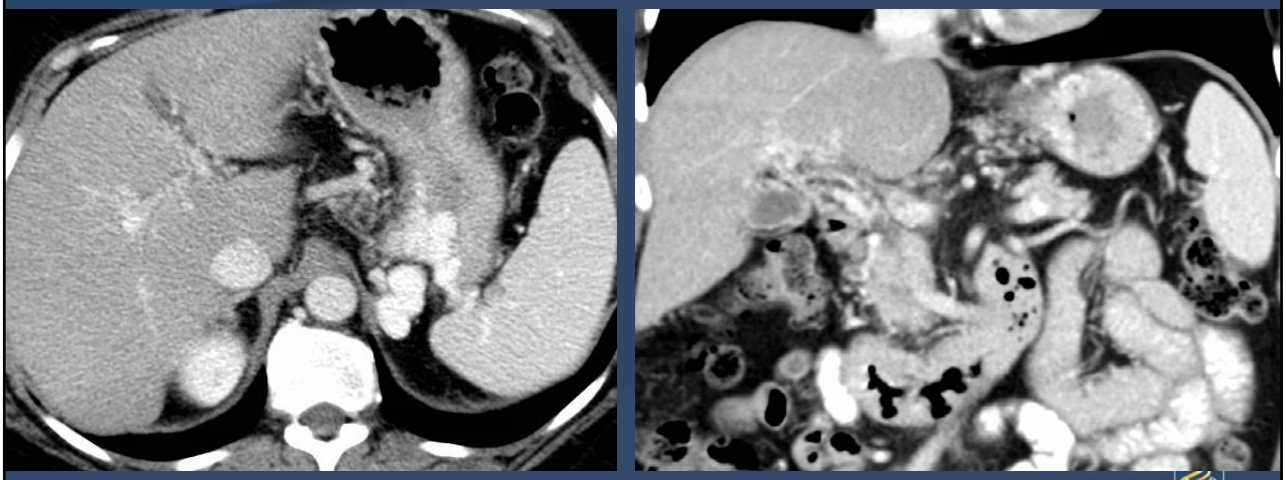




TIPS: Chronic Portal Vein Thrombosis



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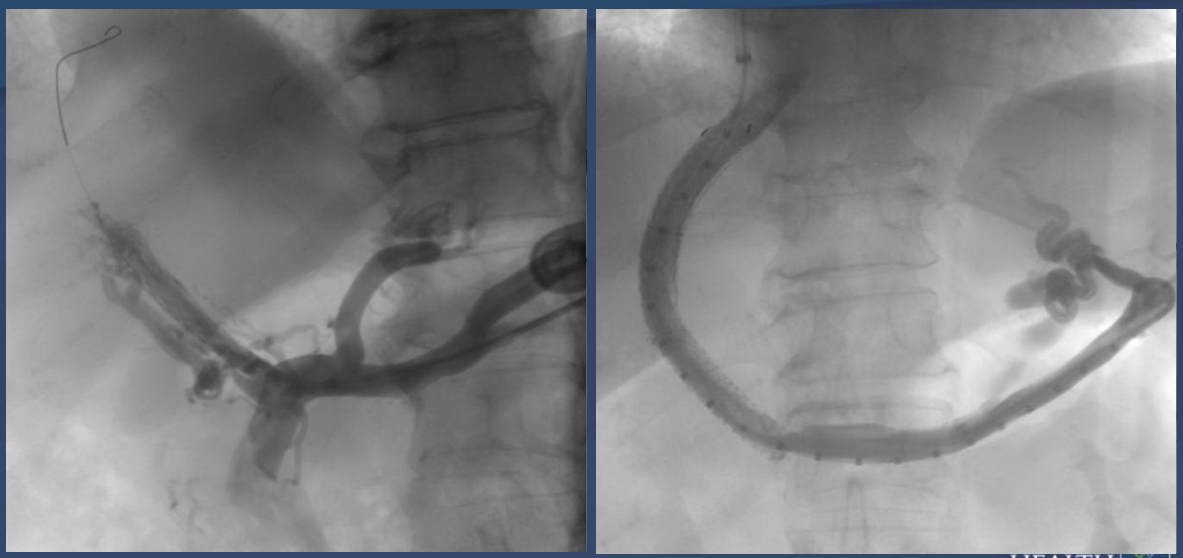
TIPS: Chronic Portal Vein Thrombosis



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Portal Vein Thrombosis: Recanalization/TIPS as Bridge to Transplant

- Thornberg et al (Northwestern U) *J Vasc Inter Rad* 2017 28:1714-21
- 61 patients, retrospective, single center
  - 44% partial PVT, 56% complete PVT. Forty-nine patients (80%)
  - 48% cavernous transformation of PV.
- 98% technical success
- 92% PV/TIPS patency (median fu 19.2 mo)
- 24 (39%) underwent transplantation, 23 with an end-to-end anastomosis.
- No recurrent PVT following transplantation (median 32.5 mo)
- 5 year OS = 82%

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TIPS: Portal Biliopathy
(Portal Cavernoma Cholangiopathy)

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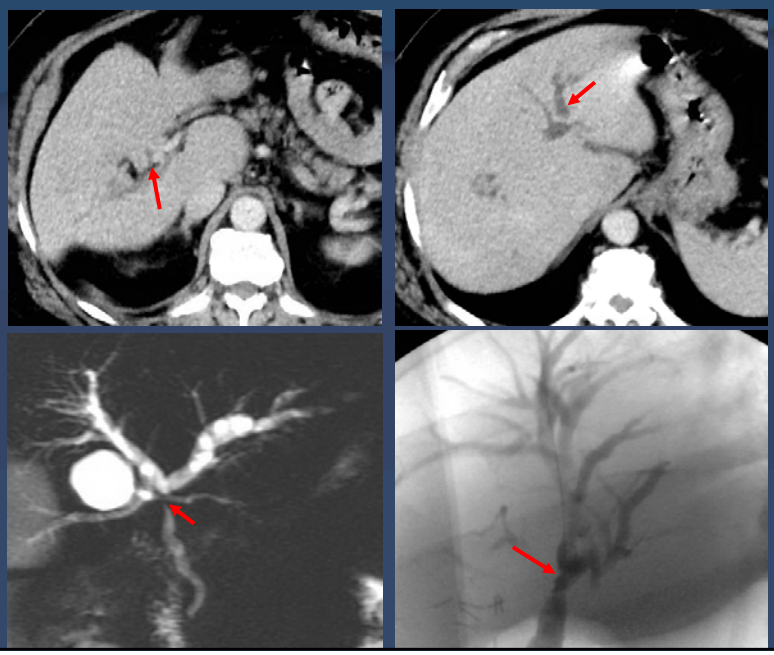
TIPS: Portal Biliopathy



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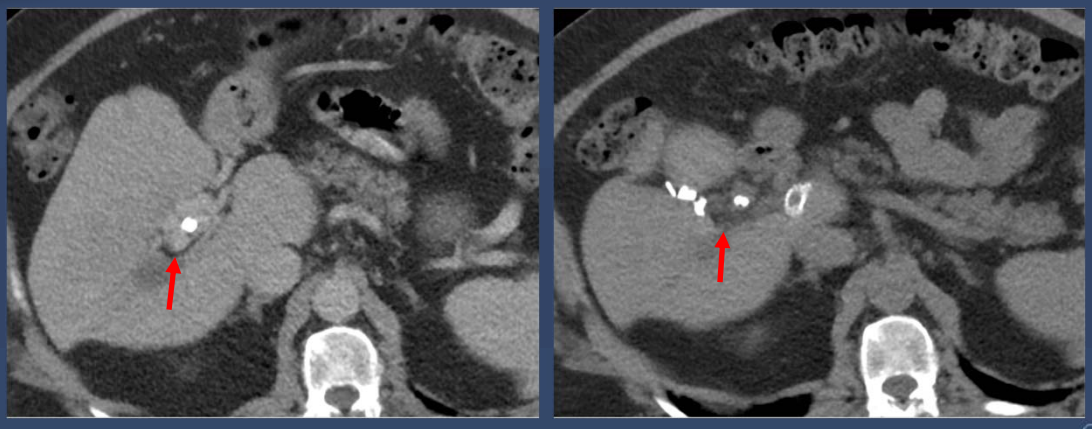
TIPS: Portal Biliopathy



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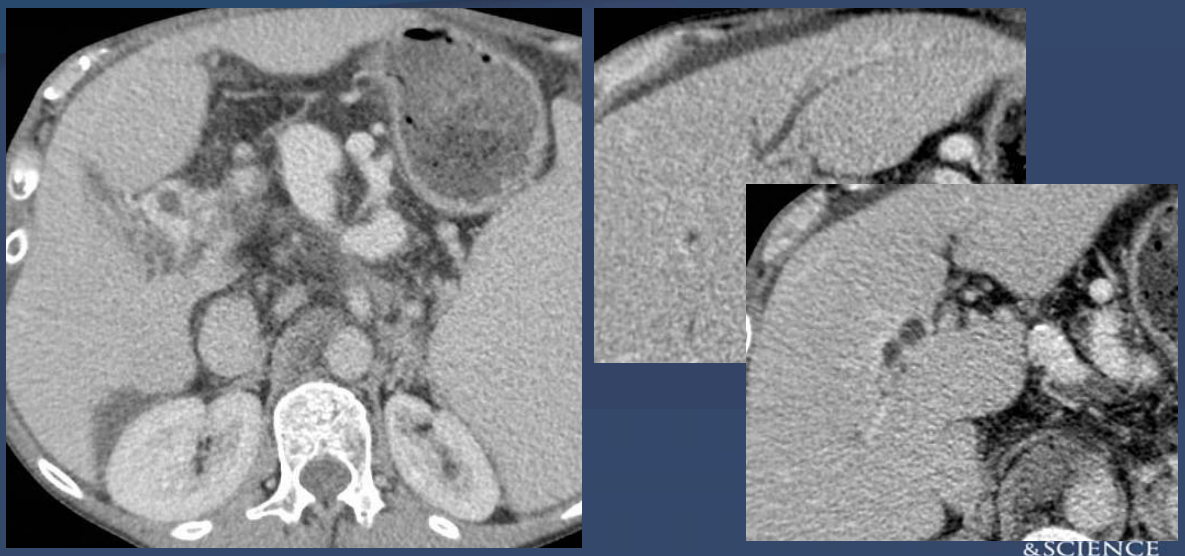
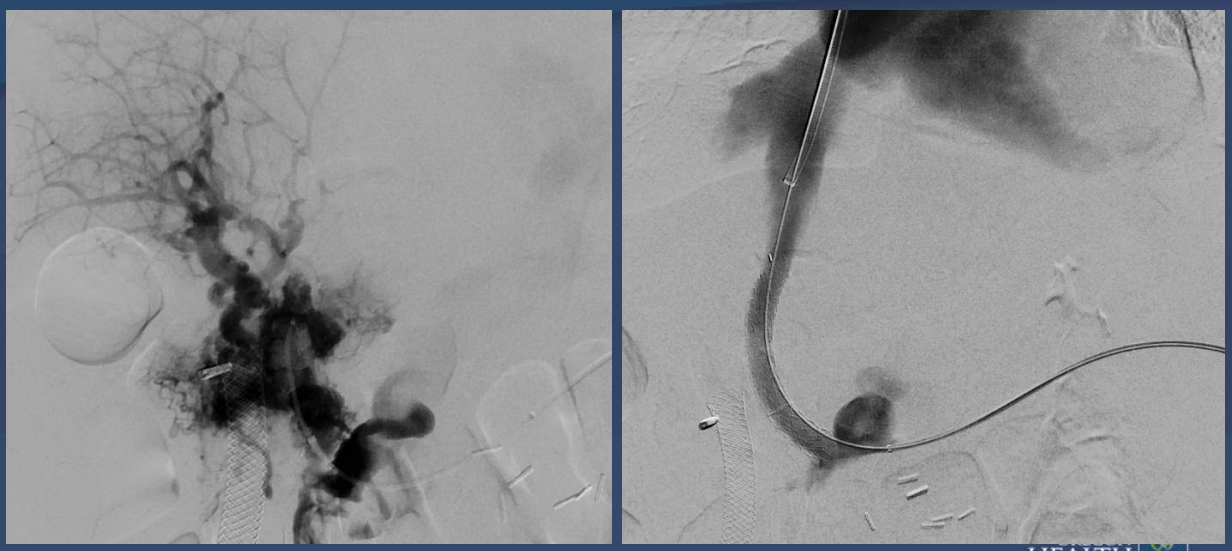
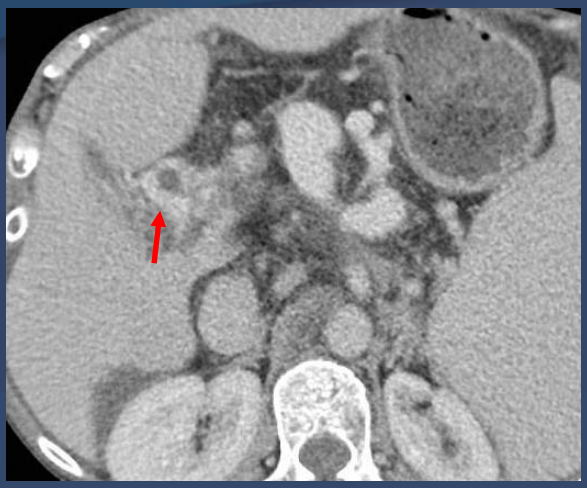
TIPS: Portal Biliopathy

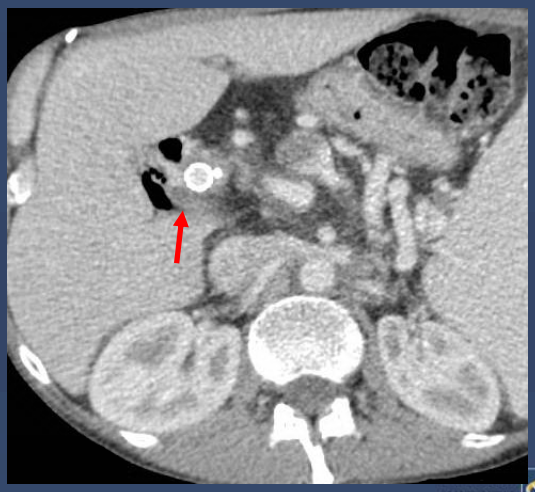


TIPS: Portal Biliopathy



TIPS: Portal Biliopathy





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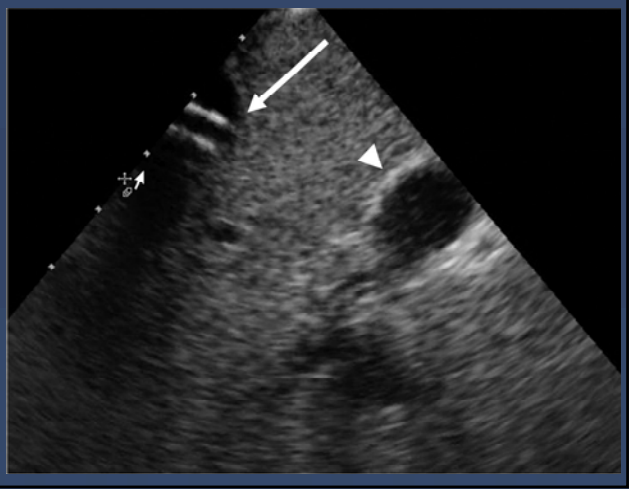
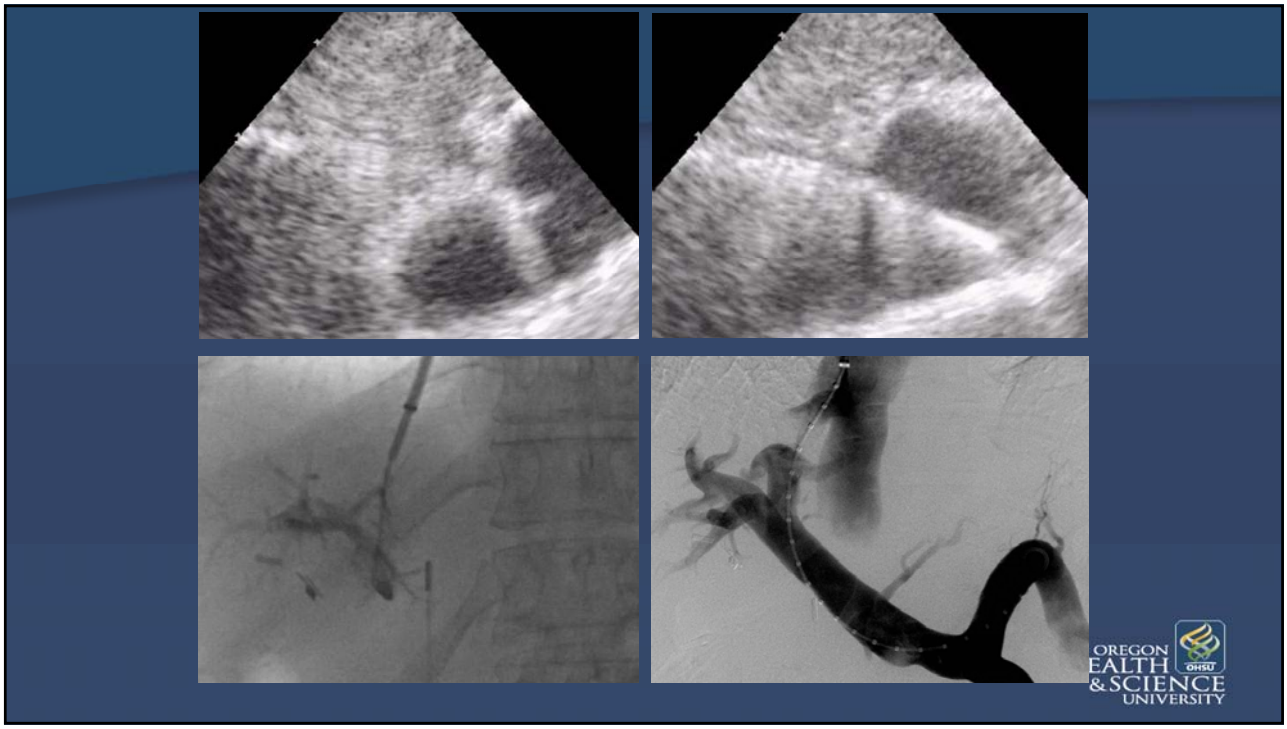
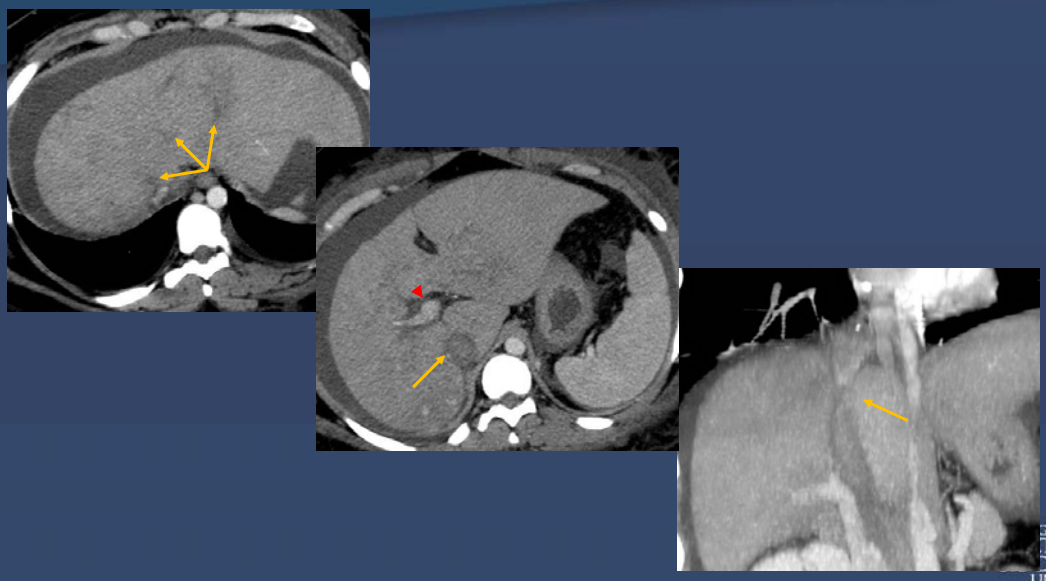
TIPS: Advanced Imaging with Intravascular Ultrasound (IVUS)

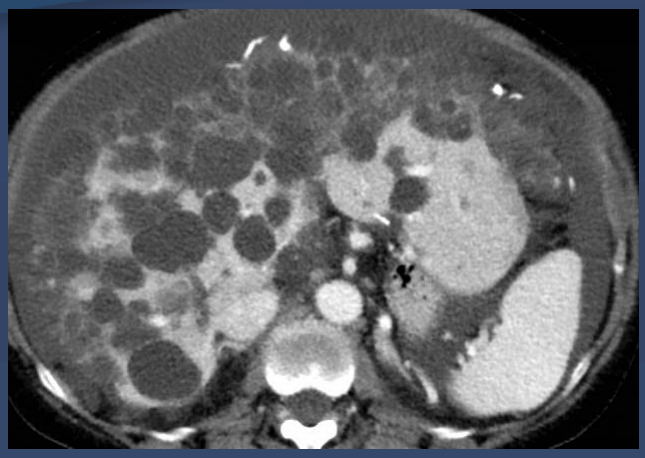


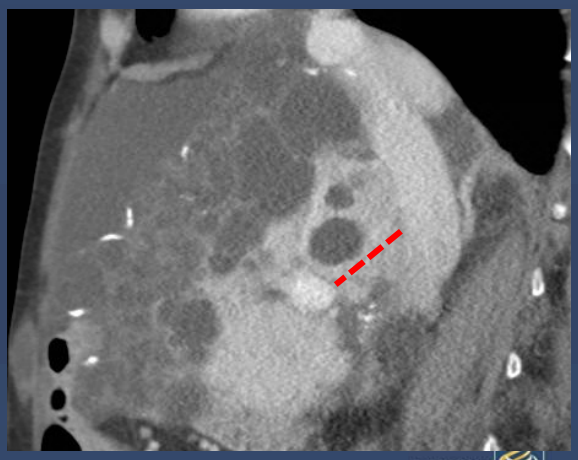


TIPS : Budd-Chiari



Advanced Guidance Techniques: Polycystic Liver





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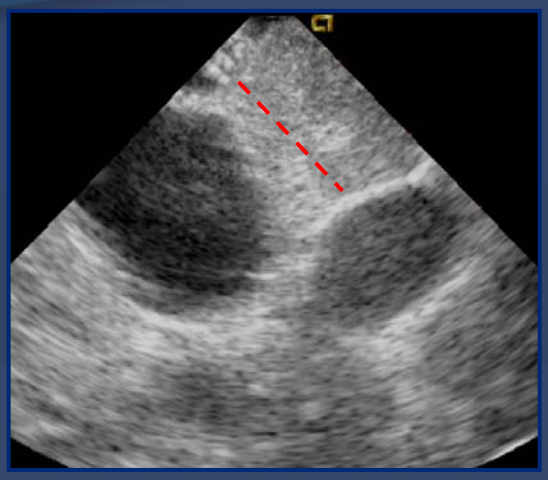
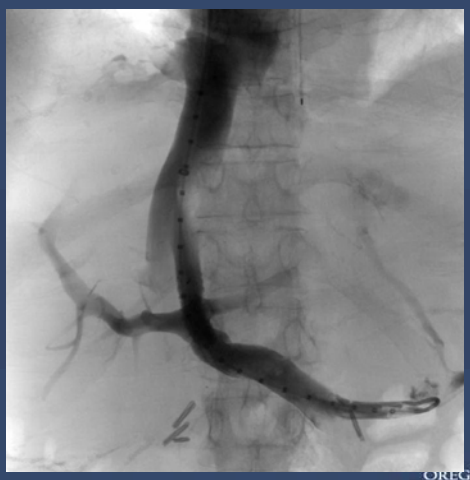
TIPS: Polycystic Liver





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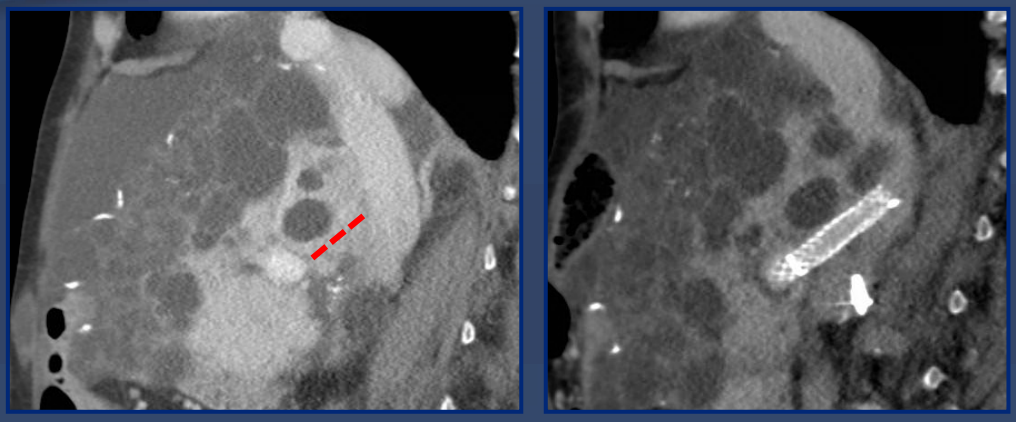
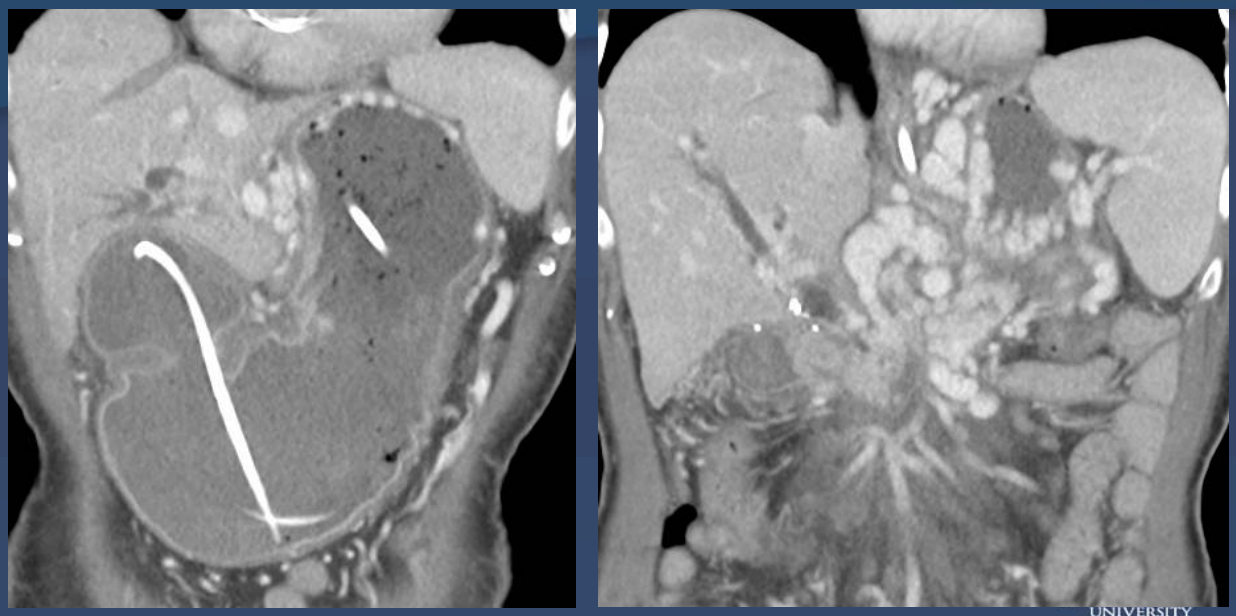
TIPS: Polycystic Liver



TIPS: Pre-Operative to Reduce Risk from Portal Hypertension

TIPS: Pre-operative gastrojejunostomy



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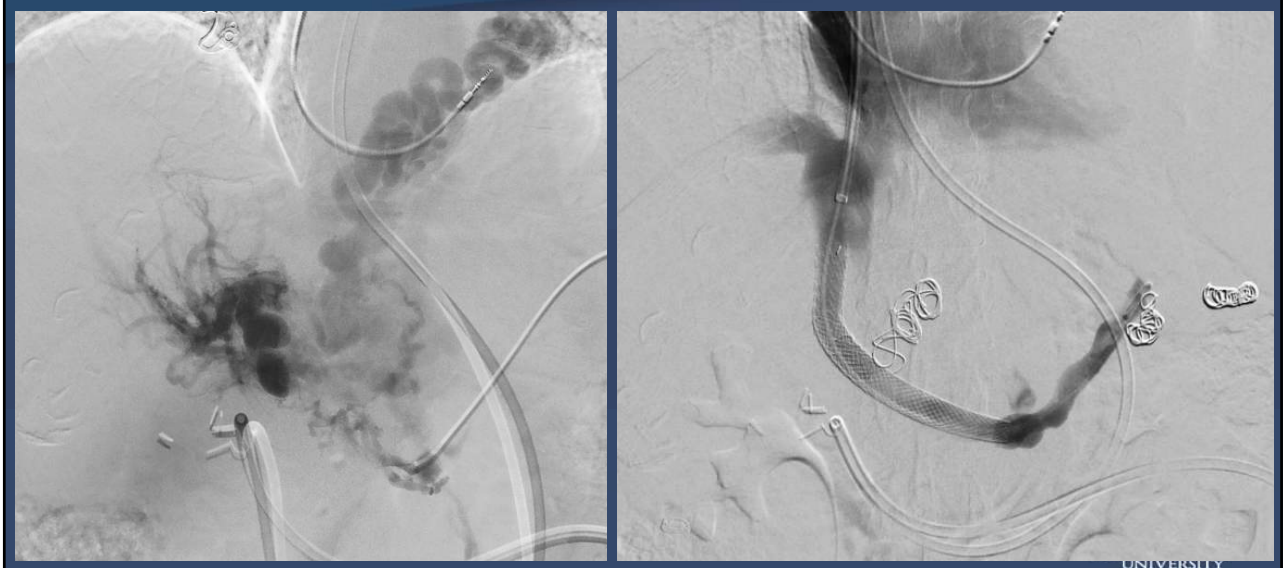
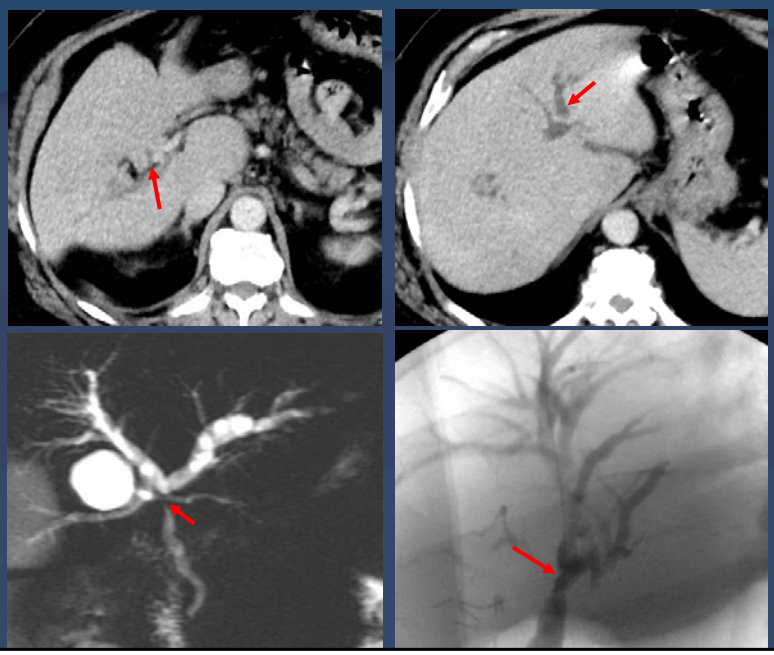


TIPS: Pre-operative hepaticojejunostomy



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Pre-operative TIPS

Lahat et al., HPB 2018, 20(2):101-109

- 19 studies, 64 patients
- GI/Pelvic surgery in 94%
- Median 30 days to OR
- Overall survival 80%
- Mortality rate 8%

Table 4. Morbidity and mortality of surgery prepared by TIPS

	N cases (%)
Complication	
None	26 (40.6)
Yes	38 (59.4)
Complications	
Ascites	8 (12.5)
Hemorrhage	4 (6.3)
Encephalopathy	8 (12.5)
Infection[a]	8 (12.5)
Intestinal leakage	5 (7.8)
Liver failure	4 (6.3)
Ileus	6 (9.4)
Miscellaneous	15 (23.4)
Mortality	5 (7.8)
Root-cause	
Intestinal leakage	2
Ascites and hemorrhage	1
Multiple organ failure	1
Acute respiratory distress syndrome	1

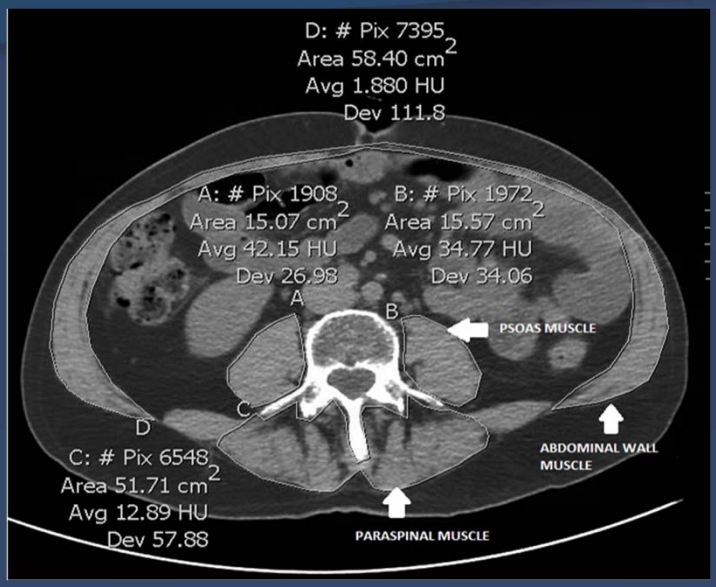
TIPS:
Muscle Gains after TIPS

Muscle Gain after TIPS

- Sarcopenia increases transplant waitlist mortality in cirrhosis
- Improved survival after TIPS observed with reversal of sarcopenia

- Single institution retrospective study (N=76)
- Association of TIPS with muscle mass in cirrhosis
- Cross-sectional truncal skeletal muscle area by CT.
- Changes in truncal muscle density were also examined.

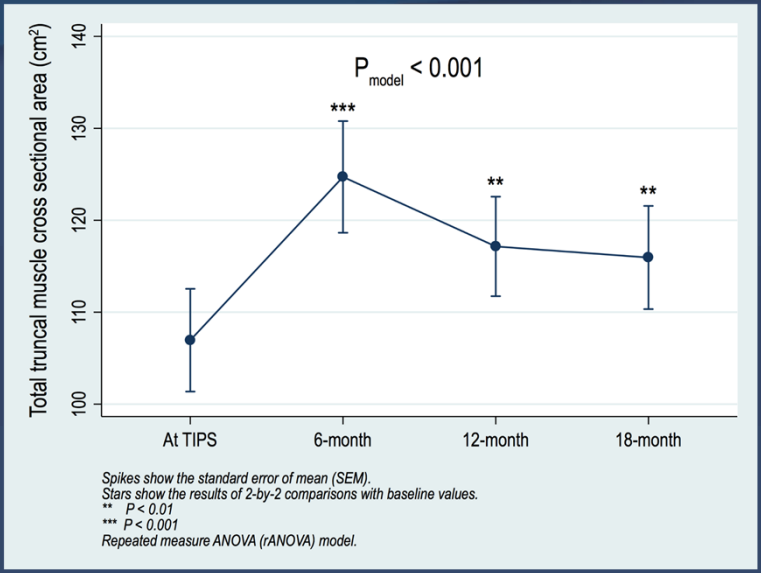
Muscle Gains after TIPS Improves Survival



Pre- Post-TIPS Change in Muscle Gain and Density

	Pre-TIPS	Post-TIPS	Mean change	P[1]
Muscle area, cm[2] ± SD				
Psoas major	20.5±6.1	22.9±7.0	2.4±4.7	**<0.001**
Paraspinal	48.4±8.2	50.3±9.4	1.9±5.5	**0.004**
Abdominal wall	63.3±18.8	65.7±20.5	2.4±11.5	0.076
Core[1]	69.0±13.0	73.3±14.7	4.2±9.1	**<0.001**
Total[2]	132.3±30.0	138.9±33.1	6.6±18.5	**0.002**
Muscle attenuation, HU ± SD				
Psoas	36.4±7.6	39.5±7.7	3.1±8.5	**0.022**
Paraspinal	23.0±13.0	24.5±17.1	1.5±15.8	0.545
Abdominal wall	-4.8±25.3	-0.1±27.8	4.7±27.8	0.275

Time Course of Muscle Gains after TIPS



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Summary

- Expanding Role of TIPS
  - Portal vein thrombosis
  - Portal biliopathy
  - Advanced techniques for challenging cases
  - Pre-operative TIPS
  - Pre-transplant
    - Portal vein thrombosis
    - Sarcopenia

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Thank You!

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Gastric Variceal Bleed Management: BRTO Primer, Glue

Gastric varices occur less often than esophageal varices but typically signify higher portal pressures and are associated with more morbidity and mortality with bleeding. It is classified by the location of the endoscopically visible varices in the stomach. The most often used is the Sarin classification which divides gastric varices between ones associated with esophageal varices (GOV's) and ones that are isolated gastric varices (IGV). Both divisions are further subdivided into two types with Type 1 being the more common and Type 2 the least of the two groups. However, it may be more important to signify fundus involvement of the gastric varices as these have higher risk for bleeding, and this also exemplifies the different pathophysiology of gastric varices versus esophageal varices. A majority of gastric varices are caused the by the formation of a splenorenal shunt, a shunt directly involving the venous system.

Historical management of bleeding gastric varices involved endoscopic variceal band ligation (EVL) and balloon tamponade (i.e. Minnesota or Blakemore) which are still appropriate to use in the correct scenario. For small varices, band ligation can be effective. Balloon tamponade is an effective temporizing measure and can be used as a bridge to more definitive treatment. Endoscopic Cyanoacrylate (glue) injections have been used more frequently and has shown good efficacy and more effective in larger varices as opposed to EVL and has started to become the standard of endoscopic treatment with its lower rebleeding rate. Because of the concern for glue emboli, there have been modifications to the standard injection of glue with a regular endoscope. One of these relatively new developments is the use of a linear echoendoscope to not only inject glue and assess for loss of Doppler flow to determine efficacy of injection, but also to inject a coil into the vessel to allow for a stratus for the glue to polymerize and to prevent glue embolization. These modalities have shown to be efficacious in stopping bleeding and also obliterating gastric varices on endoscopic follow up. They also have low rebleed rates.

Interventional radiology has offered us yet another modality that focuses on obliterating the blood supply of the gastric varices rather than treating the perforating vessels in endoscopic cyanoacrylate injections. This has shown success in stopping bleed and also has a low rebleeding rate. There may be added effects of improving hepatic encephalopathy and transiently improving liver function as more blood is redirected back into the portal circulation and through the liver. However, because of the increase flow of blood into the portal system, portal pressures can be increased which often leads to worsening esophageal varices and thus increased risk for variceal bleed. Thus, EGD surveillance with esophageal varices banding is performed after a BRTO.

There are other novel approaches such as combining endoscopic cyanoacrylate injections with an IR approach. The mainstay of treatment would be BRTO or cyanoacrylate injections because of their efficacy an lower rebleed rate. Good comparative studies are lacking between the two, but there may be less rebleed rate with the BRTO modality.

References

1. J Clin Gastroenterol 2011;45:133–148
2. Hepatogastroenterology. 2002 Jul-Aug;49(46):1180-2

3. Sarin et al Hepatology 1992;16:1343-1349.
4. Kim et al. Hepatology 1997;25:307-312.
5. AASLD 2016 Practice Guidelines. Hepatology. 2017 Jan;65(1):310-335.
6. Panes Dig Dis Sci. 1988 Apr:33(4):454-9
7. Hepatology. 2001;33:1060–1064
8. Hepatology. 2006;43:690–697
9. Cochrane Database Syst Rev 2015;(5):
10. Gastrointest Endosc 2011;74:1019-25.
11. Saad. Semin Intervent Radiol 2012;29:118-128.

Gastric Variceal Bleed Management: BRTO Primer and Glue

Bryan Balmadrid, MD

University of Washington Harborview Medical Center

Clinical Chief in the Department of Gastroenterology

Advanced Endoscopy

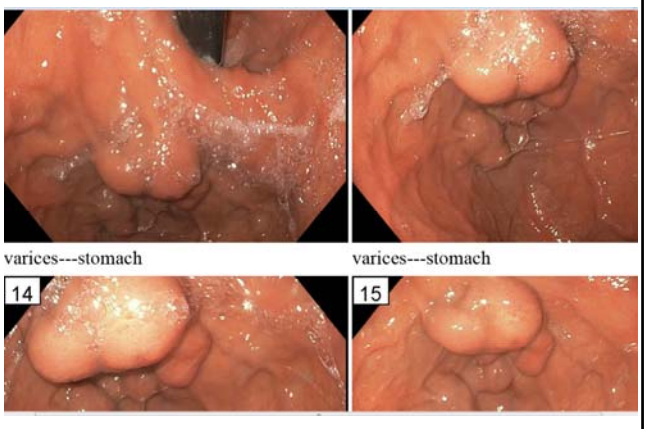
No Disclosures

Objectives

- Pathophysiology of gastric varices
- Historical and current management of high risk gastric varices
  - Band Ligation
  - Cyanoacrylate (Super Glue) injections
  - **B**alloon **R**etrograde **T**rans**R**enal Obliteration (BRTO)

Case 1

- 42 yo with Childs Pugh B, ETOH cirrhosis transferred from outside hospital for esophageal vs gastric variceal bleed.
- 5/29/15 EGD with large amount of clots and nonbleeding gastric varices
- Resuscitated and stabilized and showed no signs of continued bleeding
- Repeat EGD 2 days later showed pictures on the right



What Are Your Management Recommendations?

- Information that will affect management
  - Has this bled?
  - MELD? Is it important?
  - Other complications from cirrhosis such as:
    - Hepatic Encephalopathy
    - Ascites
    - Esophageal varices
- This has bled and should be treated. We will discuss treatment options later.

Primary Prevention of GV Hemorrhage

- Only one randomized trial of 89 patients with large (> = 10 mm) GOV2 and IGV1 randomized to:
  - Endoscopic injection of cyanoacrylate (CI)
  - Nonselective Beta Blockers (NSBBs)
  - Observation.
- Cyanoacrylate injection was associated with lower bleeding rates (10%) than NSBBs (38%) and observation (53%).
- Survival was higher in the cyanoacrylate group (93%) compared to observation (74%), but no different from those on NSBBs (83%).
- "Firm recommendations cannot be derived from this trial. The least invasive treatment is NSBBs, and this could be recommended because, as mentioned previously, they could have beneficial effects in preventing other complications of cirrhosis." (1)

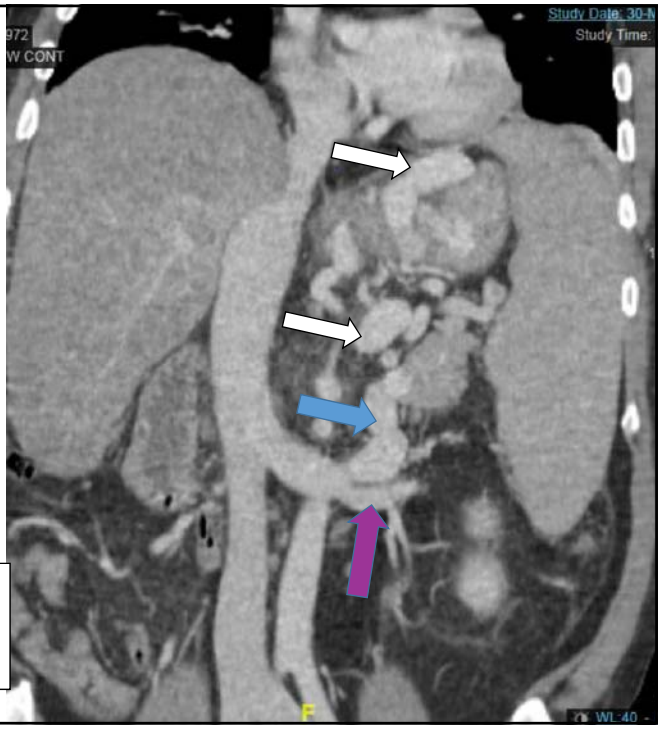
	CI	NSBBs	Observation
Bleeding Rate	10%	38%	53%
Survival	93%	83%	74%

Mishra, Sarin et al. J Hepatol 2011;54:1161-1167.

1) AASLD 2016 Practice Guidelines. Hepatology. 2017 Jan;65(1):310-335.

Case Continued

- Plan for BRTO
- CT Abdomen
  - Splenorenal shunt with significant collaterals leading to gastric varices



Renal vein = Purple
Splenorenal shunt = Blue
Gastric varices = White

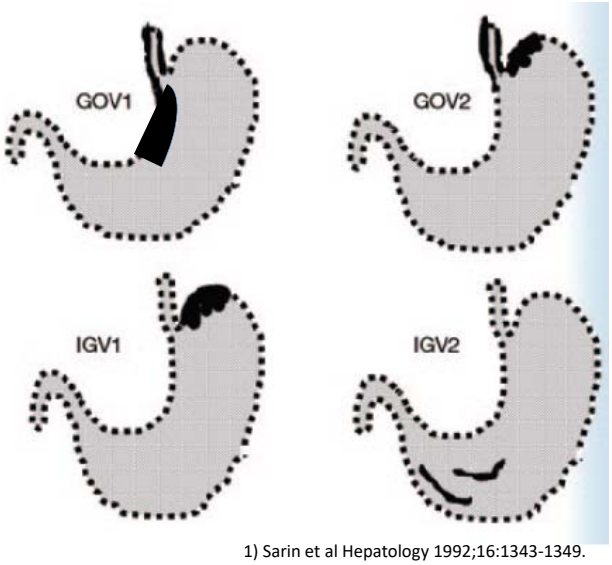
Gastric Varices: Background

- Manifestation of portal hypertension in 5 – 33% (1-3)
- Less common than esophageal varices (1)
- 20% of variceal bleeding (1)
- Poor prognosis
- Usually different pathway than esophageal varices

1) J Clin Gastroenterol 2011;45:133–148
2) Hepatogastroenterology. 2002 Jul-Aug;49(46):1180-2
3) Sarin et al Hepatology 1992;16:1343-1349.

Classification of Gastric Varices

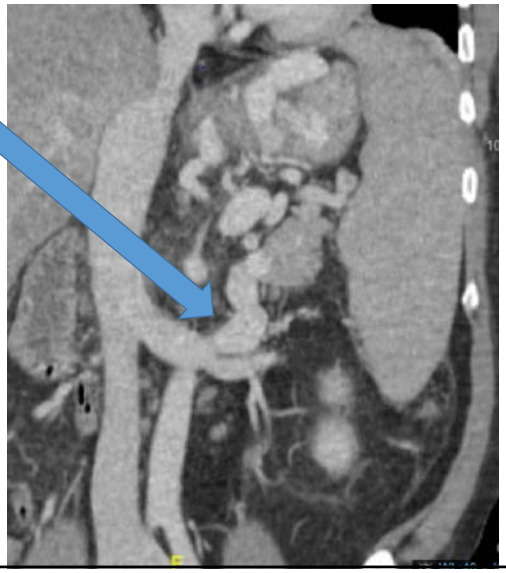
- **Sarin** endoscopic classification
  - Gastroesophageal varices: GOV (75%). Has esophageal varices.
    - Type 1 (GOV1) extends to lesser curvature.
    - Type 2 (GOV2) extends to the fundus.
  - Isolated Gastric Varices: IGV (25%)
    - Type 1 (IGV1): Fundus
    - Type 2 (IGV2): Distal involvement.



1) Sarin et al Hepatology 1992;16:1343-1349.
2) Kim et al. Hepatology 1997;25:307-312.

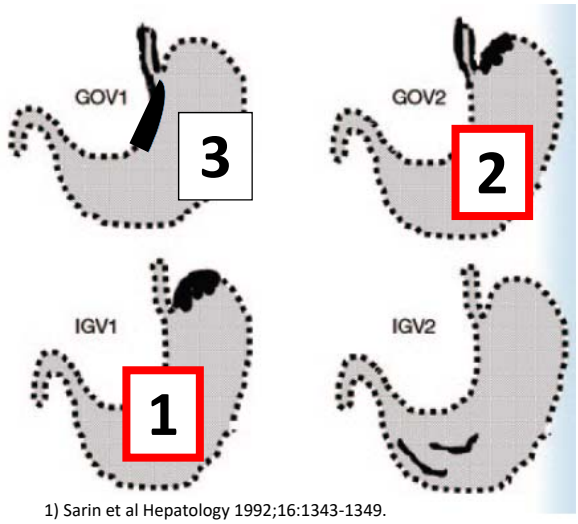
The Feeding Vessels of Gastric Varices

- 85% gastrorenal or splenorenal shunts
- 10% gastrocaval shunts
- 5% gastrocardiophrenic shunts
- The perforating gastric varices most often supplied by the left gastric, posterior gastric, or short gastric veins or a combination of these vessels.



Bleeding Risk: Risk Factors

- Location
  - IGV1 > GOV2 > GOV1
- Size
  - Large (> 10 mm)
  - Medium (5-10 mm)
  - Small (< 5 mm)
- Child class
  - C > B > A
- Endoscopic presence of variceal red spots
- Concomitant HCC
- HVPG > 20 mm Hg



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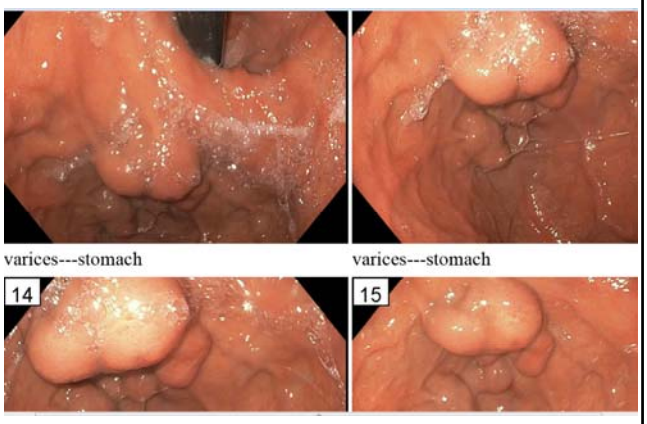


1) Sarin et al Hepatology 1992;16:1343-1349.
2) Kim et al. Hepatology 1997;25:307-312.
3) AASLD 2016 Practice Guidelines. Hepatology. 2017 Jan;65(1):310-335.

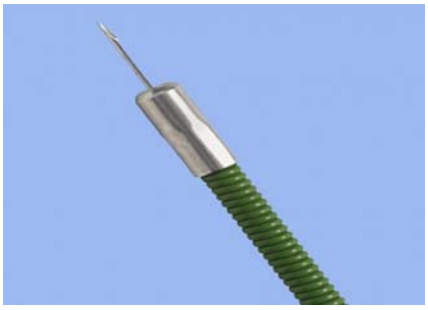
Bleeding Risk: Incidence

- Incidence to bleed variable
  - As low as 9.4% in 3 years to as high as 25% in 2 years
  - One estimation is 16%, 36%, 44% at 1, 3 and 5 years, respectively
  - Summary 9 – 36% risk of bleeding in 2-3 years.
- Difficult to treat

1) J Clin Gastroenterol 2011;45:133–148
2) Hepatogastroenterology. 2002 Jul-Aug;49(46):1180-2
3) Sarin et al Hepatology 1992;16:1343-1349.
4) *Henry. Clin Liv Dis. 2014*

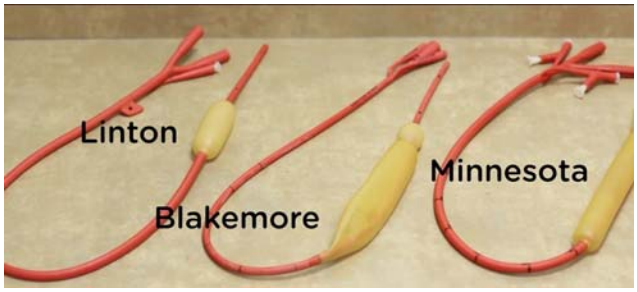
Management

- Balloon Tamponade: Minnesota, Blakemore tubes
- Band Ligation (BL)
- Cyanoacrylate injections (CI)
- BRTO



Balloon Tamponade Evidence

- 151 consecutive bleeding pt's in single center Barcelona
  - 118 SBT -> esophageal varices
  - 33 Linton-Nachlas -> gastric varices
- 24 hr hemostasis
  - 91.5% SBT
  - 88% LN
- Permanent hemostasis 47.7% of all cases
- Complications: 10% pulmonary aspiration



Panes Dig Dis Sci. 1988 Apr:33(4):454-9

How Long to Keep Balloon Inflated

- No standard
- Gastric balloon (once confirmed in the stomach) can be maintained 24-48 hours
- Esophageal balloon pressures should be monitored regularly. Recommendations for intermittent take down are not widely implemented

Endoscopic Variceal Band Ligation (EVL)

- EVL should only be performed on small GV in which both the mucosal and contralateral wall of the vessel can be suctioned into the ligator
- Effective in the appropriate setting

RCTs Comparing BL to CI: Differing Results

- Lo et al. 31 CI vs. 29 BL
  - Initial hemostasis (no bleeding within 72 hrs) 87% vs 45% BL
  - 0.5 mL CI/1.5mL Lipiodol
  - **Likely,** 1 injection given & rarely 2.

Lo et al.	CI	BL	P
Pts	31	29	
Initial hemostasis	87%	45%	.03
Rebleed	31%	54%	<.01
Post ulcer bleed	7%	28%	.03
Transfusions	2.6	4.2	<.01
Death	9	14	.05

Hepatology. 2001;33:1060–1064

- Tan et al. 49 CI vs. 48 BL
  - HCC included
  - 0.5 mL CI/0.5mL Lipiodol
  - 6 injection max

Tan et al.	CI	BL	P
Pts	49	48	
Control active bleed	14/15	14/15	
Rebleed (p 24 hrs)	44%	22%	.044
3 yr cumulative rebld	72%	27%	.014
30 d mortality	Same	Same	
1 yr mortality	42%	45%	
3 yr mortality	57%	63%	

Hepatology. 2006;43:690–697

Other Studies Comparing BL to CI

- Hong et al. Retrospective study. GOV1 acute bleed. CI 64pts vs BL 20 pts
- Fewer statistically non-significant lower complications in BL
  - 1.5% embolization in CI

Hong et al.	CI	BL	P
Pts.	64	20	
Control active bleed	97%	90%	.24
Early rebleed (< 6wks)	27.4%	16.7%	.42
Late rebleed (6wk – yr)	17%	44%	.04
Aspiration Pneumonia	7.8%	5%	
1-yr Mortality	19.4%	5.6%	.138
Median survival (days)	852	1160	.115

Ho et al. Chonnam Med J 2013;49:14-19

EVL vs. Cyanoacrylate Injections

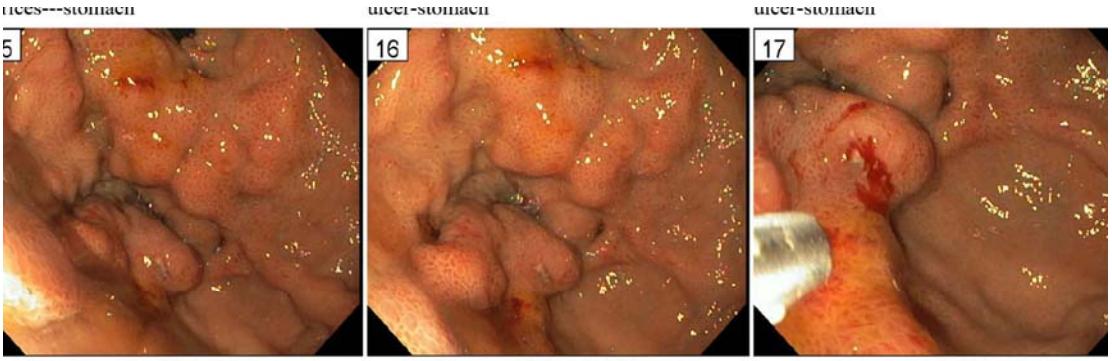
- Meta-analysis of three RCTs shows both therapies are equally effective for initial hemostasis, but cyanoacrylate injection is associated with significantly lower rebleeding rates. (1)
- The overall quality of the evidence is low given small sample sizes, and the metaanalysis was dominated by the larger study including only GOV1 varices. (2,3)

(1) Cochrane Database Syst Rev 2015;(5):
(2) Trop Gastroenterol 2010;31:279-284.
(3) AASLD 2016 Practice Guidelines. Hepatology. 2017 Jan;65(1):310-335.

Case Continued

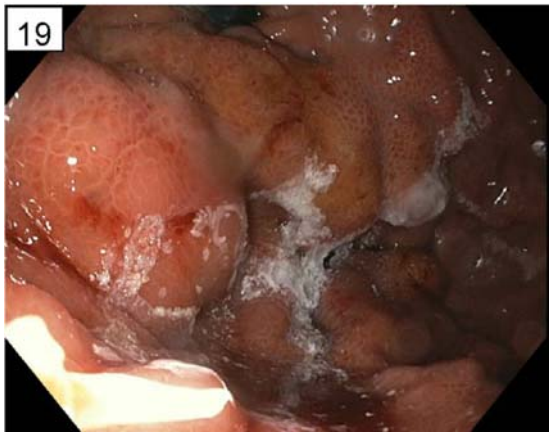
- Initially follow up EUS within 48 hours and 2 months later showed obliteration of flow in the gastric varices
- 4 months later, presented with small hematemesis
- Repeat EGD w EUS shows recurrence of flow in the gastric varices

Cyanoacrylate Injections Were Performed



Post CI

- 2 Octyl Cyanoacrylate



Cyanoacrylate Injections

- Various methods to inject CI
- Often combined with lipiodol and fluoroscopy
- Concern for emboli into the right system (lungs) and if PFO, left system emboli

Table 1. ***In vitro*** **polymerization time for various cyanoacrylates**

Cyanoacrylate [*n*]	Time to polymerization (s), mean ± s.d. (range)
Histoacryl:ethiodol (1:1) [10] *N*-Butyl-2-cyanoacrylate:oil	10 ± 0.6 (9.44–11)
Dermabond alone [10] 2-Octyl-cyanoacrylate	16.4 ± 2.9 (3–28)
Dermabond:ethiodol (1:1) [10] 2-Octyl-cyanoacrylate:oil	54.4 ± 11.7 (15–100)
Viscous Dermabond alone [8] 2-Octyl-cyanoacrylate	7.54 ± 0.95 (6.54–8.8)
Viscous Dermabond:ethiodol (1:1) [8] 2-Octyl-cyanoacrylate:oil	10.07 ± 0.65 (9.43–11.1)
TRUFILL:ethiodol (1:1) [4] *N*-Butyl-2-cyanoacrylate:oil	18.55 ± 6.85 (9.1–23.8)
Indermil alone[a] *N*-Butyl-2-cyanoacrylate	4–5 seconds consistently

Gastrointest Endosc 2011;74:1019-25.

Cyanoacrylate Injections

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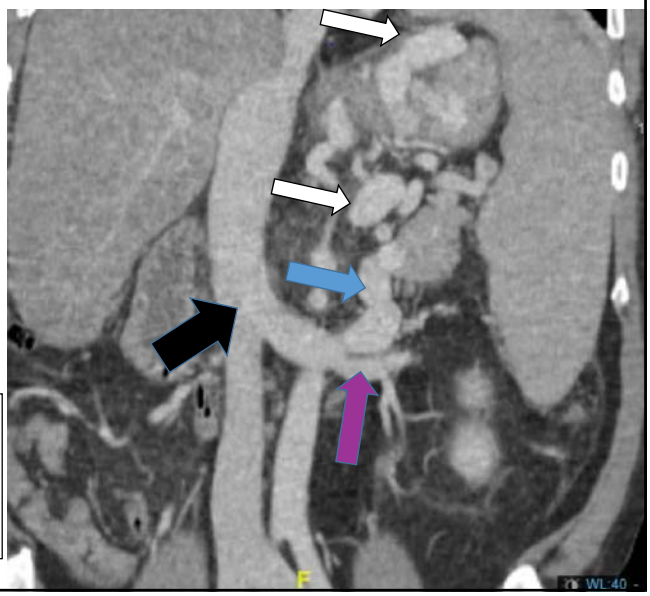
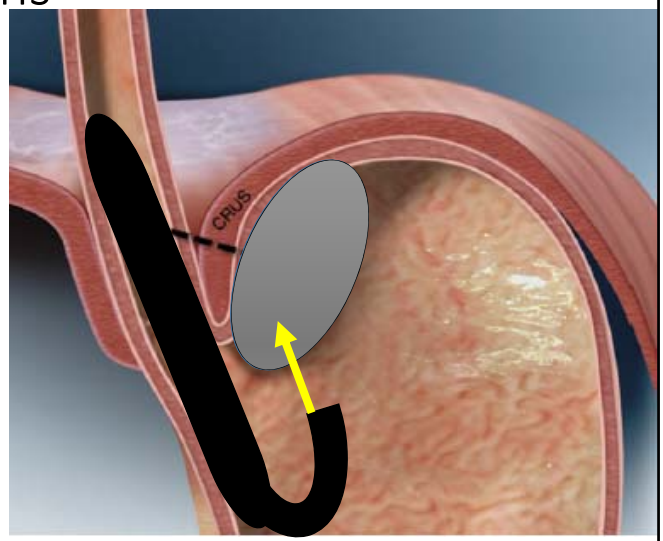
- Often combined with lipiodol and fluoroscopy
- Concern for emboli into the right system (lungs) and if PFO, left system emboli

Renal vein = Purple
Splenorenal shunt = Blue
Gastric varices = White
IVC = Black



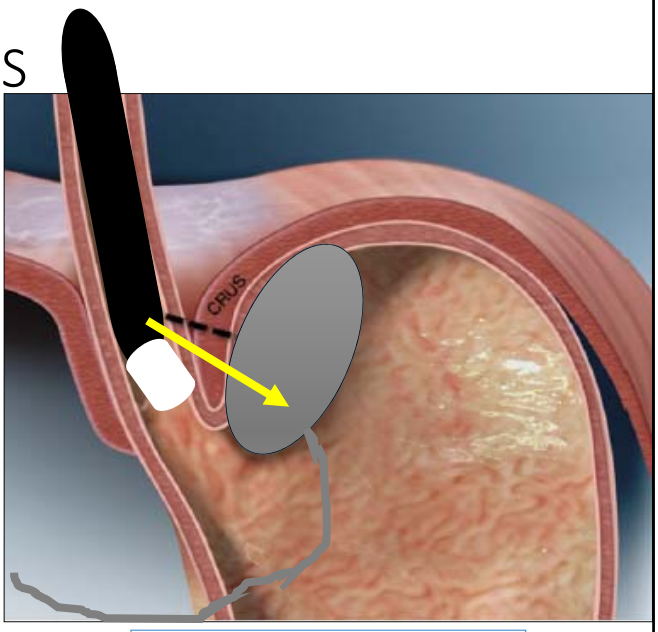
Cyanoacrylate Injections

- Prime channel and prime large gauge needle with normal saline.
- Prepare glue
  - Undiluted
  - 1:1 mixture with lipiodol
- Inject 1-2 cc at a time
- Keep needle 1 cm away from scope if possible
- Use fluoroscopy if available.



Cyanoacrylate with EUS

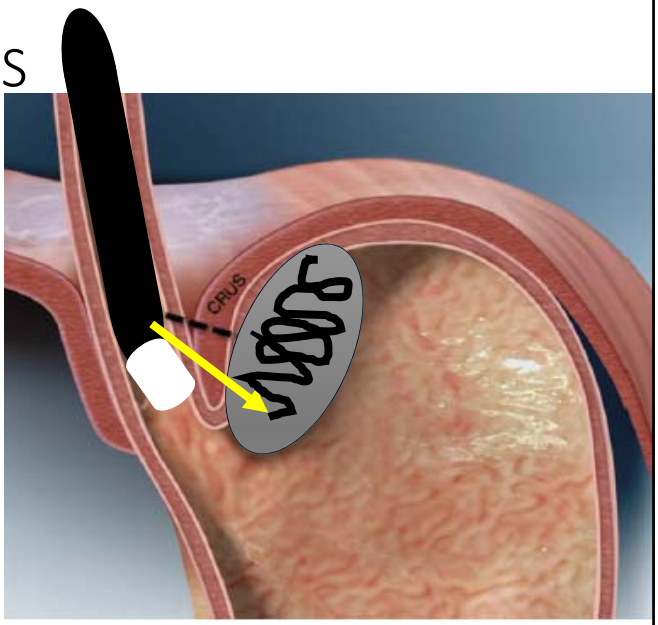
- EUS with CYA injection
- EUS + coil with CYA injection
- Allows the use of Doppler flow to assess efficacy of injections



Gastrointest Endosc 2011;74:1019-25.

Cyanoacrylate with EUS

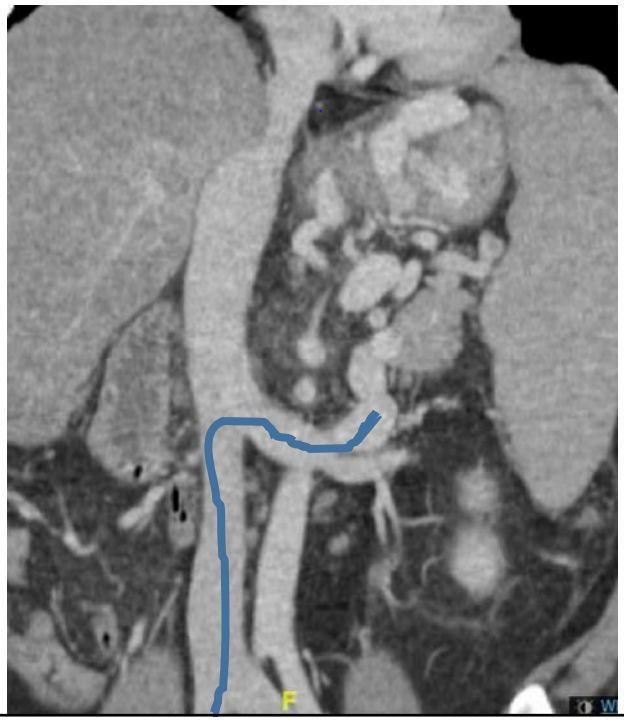
- EUS with CYA injection
- EUS + coil with CYA injection
  - 100% hemostasis in 30/30 pts
  - 23 of 24 pt with follow up had obliteration of GV in one procedure.
  - Rebleeding 4 (16.6%), none attributed to GV bleeding



Gastrointest Endosc 2011;74:1019-25.

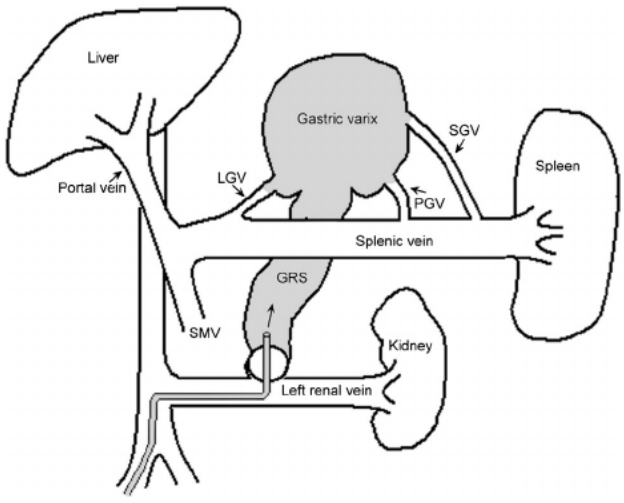
BRTO

- Access through the venous system (i.e. femoral vein) to enter the splenorenal shunt (source of the blood supply)
- Splenorenal shunt (most common anatomy) leads to IGV1 and GOV2
- **Enhances flow into liver, but may increase portal pressures**
  - Complications of esophageal varices development and bleed
- May need to measure portal pressures after BRTO and perform TIPS

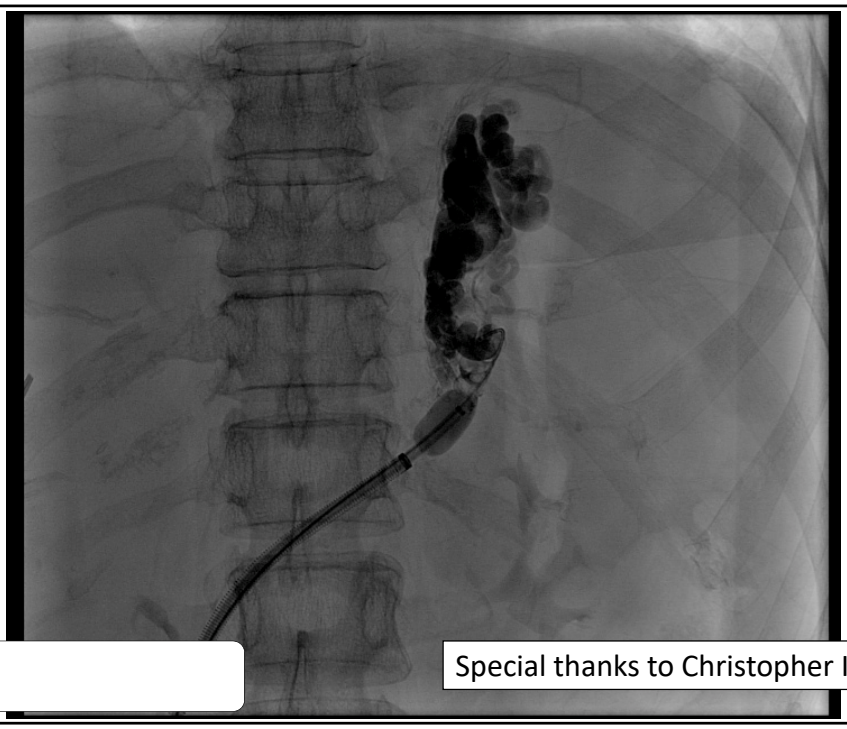


BRTO

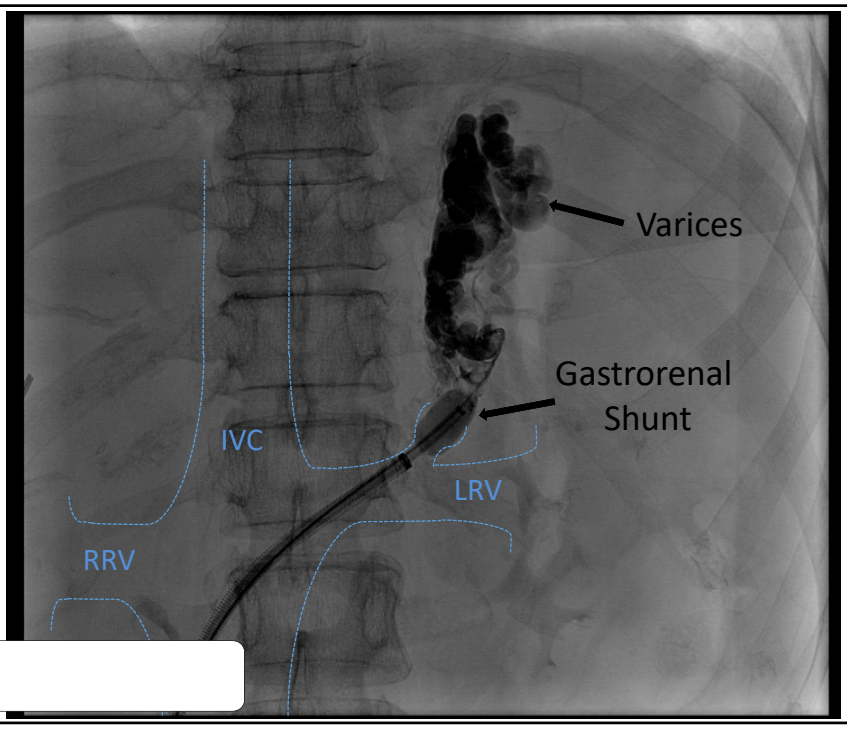
- CT abdomen/pelvis in venous phase or 3 phase liver CT
  - Serves as a baseline prior to BRTO
  - Assesses patency of splenic and portal veins
  - Allows for planning of shunt occlusion
- Echocardiogram
  - Assess for right to left shunts

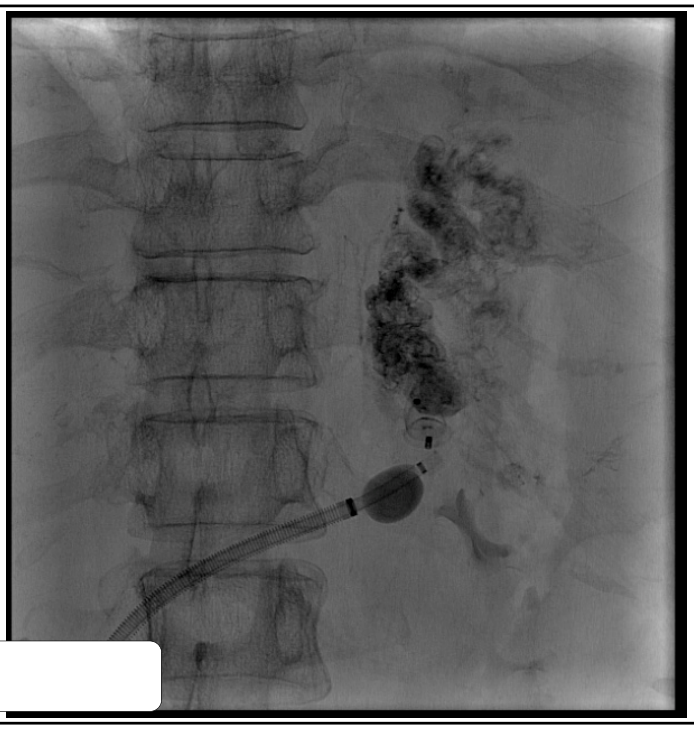


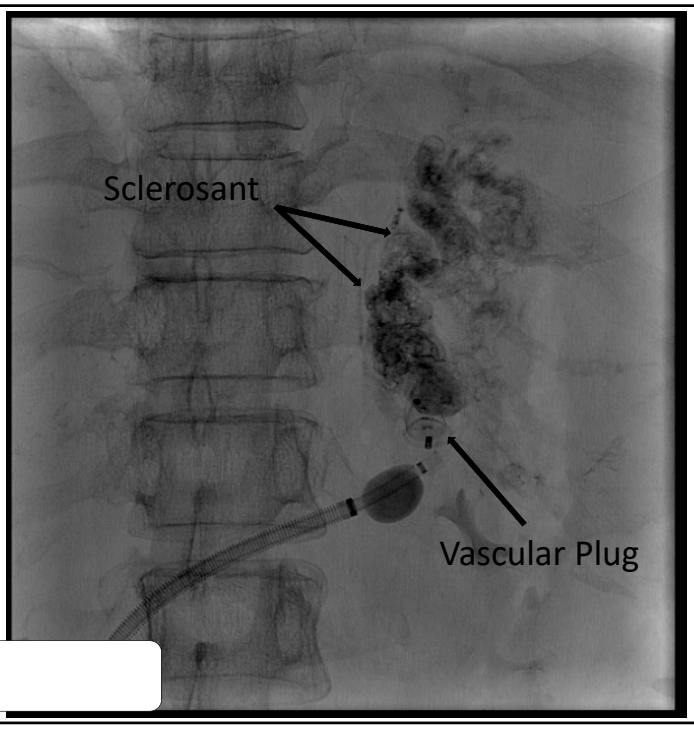
https://www.researchgate.net/profile/Shou-Dong_Lee2/publication/251568924/figure/fig2/AS:298235798278145@1448116363323/Illustration-of-balloon-occluded-retrograde-transvenous-obliteration-BRTO-of-gastric.png

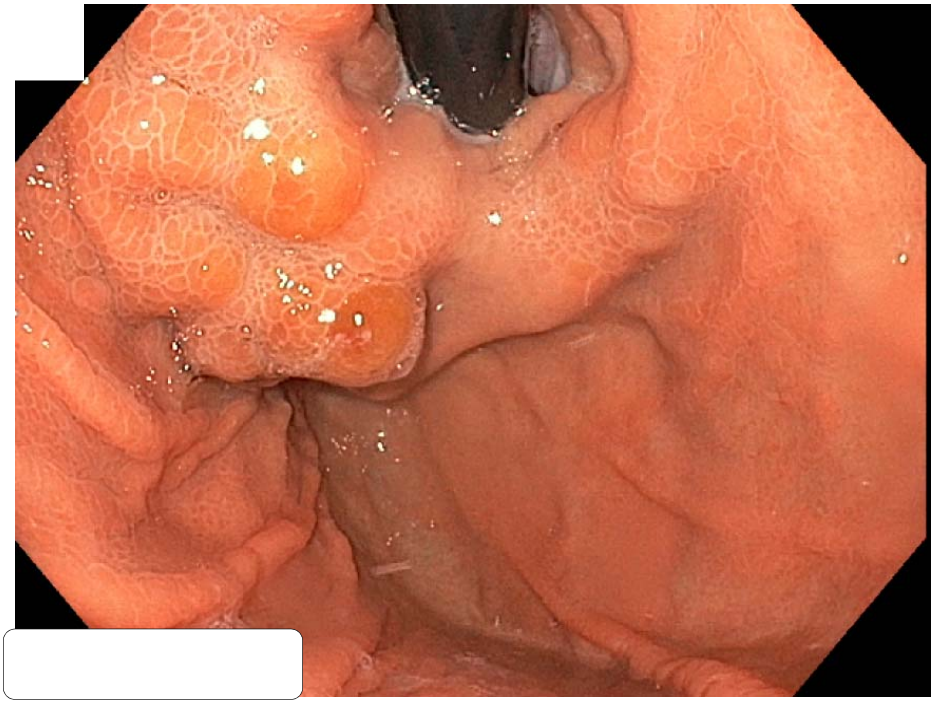


Special thanks to Christopher Ingraham UW IR






Sclerosant
Vascular Plug



BRTO Outcomes

- The technical success rate, and the obliteration rate of gastric varices are estimated to be around 91% and 94%, respectively.
- BRTO is successful in controlling ***active*** gastric variceal bleeding in approximately 95% of cases.
- After BRTO, blood is diverted into the portal circulation.
  - This will cause an increase in portal hypertension, which can ***exacerbate esophageal varices***
  - After successful BRTO, the 1-, 2-, and 3-year esophageal variceal aggravation rates are 27–35%, 45–66%, and 45–91%, respectively.

Special thanks to Christopher Ingraham UW IR

Saad. Semin Intervent Radiol 2012;29:118-128.

BRTO Outcomes

- The gastric variceal rebleed rate after successful BRTO procedures is 3 - 9%
- The global variceal rebleed rate is 19 - 31% (all types of varices)
- Patient 1-, 2-, 3-, and 5-year survival rates are 83–98%, 76–79%, 66–85%, and 39–69%, respectively
  - Patient survival is determined by baseline hepatic reserve and the presence of hepatocellular carcinoma.

Saad. Semin Int Radiol. 2011.

BRTO Follow-up

- No standard follow-up regimen exists
- UW Recommendations after BRTO:
  - Endoscopy (EUS) 24-48 hours after BRTO
  - Endoscopy every three months and then as needed
  - **Some sort of imaging every 3 months (CT or Endo)

BRTO vs Cyanoacrylate Injections (CI)

- Two different philosophies
- CI: Treating the perforating vessels only. Analogy, we do not treat esophageal varices that are outside of the esophagus lumen.
- BRTO: Treating the blood supply, (the source). Can prevent further perforating collaterals from forming.

J Vasc Interv Radiol. 2019 Feb;30(2):187-194

- Newest Study (Feb 2019)
- Retrospective
- 16/71 BRTO's also with TIPS

	BRTO	CI	P
N	71	90	
6 wk Mortality (%)	13.1	14.4	0.85
6 wk Rebleed (%)	3.5	5.1	0.62
1 yr Rebleed (%)	**3.5**	**22.0**	**< 0.01**
Procedure Related Mortality (%)	7.0	1.1	0.09

N-butyl used

BRTO vs. CI: Prospective Study 2009

- Prospective not randomized
- Methods: During 1st endoscopic evaluation
  - If acute hemorrhage, 1st line of treatment was CI
  - If no active bleeding and high risk (below) then BRTO
    - > 5 mm, red spots, CP B or C
- GV hemorrhage or high risk GV
- 2005-2007
- 6 pts treated with rescue BRTO
- N-butyl-Cya used

	BRTO	CI	P
N	13	14	
Technical success (%)	76.9	100	
Significant rebleeding (%)	**15.4**	**71.4**	**< 0.01**
Blood transfused	**4.4**	**1.3**	**< 0.01**
Complications (%)	7.1	15.4	NS
Mortality (%)	50.0	23.1	NS

J Gastroenterol Hepatol. 2009 Mar;24(3):372-8.

BRTO vs. CI vs EVL: Prospective Study 2011

- Prospective Study…maybe, but not randomized
- Only in Korean
- Mean follow up 65.13 months
- "Underpowered study.. Further prospective, large-scale studies are needed."
- N-butyl used

	EVL	CI	BRTO	P
N	36	52	15	
Rebleed	13.9%	21.2%	6.7%	0.515
Times-to-rebleeding (months)	63.59	75.79	51.41	0.515
Mean Survival (months)	70.14	77.42	42.79	0.978

Korean J Gastroenterol. 2011 May 25;57(5):302-8.

Other Approaches

- BRTO assisted cyanoacrylate injection (1)
  - CI while the gastrorenal shunt was temporarily occluded with an occlusion balloon.
- BRTO or BATO and TIPS combination

(1) J Clin Exp Hepatol. 2016 Dec;6(4):326-330.

Summary

- Gastric varices have a different physiology than esophageal varices.
  - Splenorenal shunt and fundal varices
- Old line therapy is still effective and at the very least temporizing.
  - Has higher rebleed rate
- Cyanoacrylate injections various methods are effective.
  - Be careful with handling glue and with glue emboli
- BRTO has shown very good results and has some added benefits but also worsens esophageal varices.
- Endoscopy should be performed in all these cases and endoscopic treatment attempts should be made in actively bleeding varices. If the expertise is present, one can also follow up with BRTO.

Thank You

Special thanks to Christopher Ingraham UW IR

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Anticoagulation in Portal Hypertension: Who, When, How and for How Long?

Cirrhosis is now well-known to be associated with a number of hypercoagulable features including acquired protein C deficiency, elevated endothelial-derived factor VIII, elevated von Willebrand factor, diminished anti-thrombin and circulating activated platelets. These prothrombotic changes counter-balance known decreases in pro-coagulation factors and contribute to thrombotic complications in cirrhosis patients including both peripheral DVT and to portal vein thrombosis (PVT). As a result, it is generally recommended that hospitalized liver disease patients receive routine DVT prophylaxis unless there are concurrent bleeding issues. PVT in liver disease patients is more of a clinical challenge – we will focus on non-cancerous PVT in this discussion. It often presents clinicians with vexing issues of whether to treat with anti-coagulants in patients well-known for their bleeding tendencies or to ignore the finding especially when encountered incidentally and without overt related symptoms. The annual incidence of PVT is estimated at 5-16% with associated symptoms (pain, worse ascites or effusion or variceal bleeding) in about 50%. PVT can be broadly categorized as occlusive or partial - thought of as 50% or less occupation of the lumen determined by contrast enhanced CT or MRI. Asymptomatic partial PVT may resolve spontaneously and so often is best managed with serial imaging. The clearest indications for more aggressive therapies are in patients presenting with associated symptoms, those listed for transplant and those with established clot extension. The benefit of therapeutic intervention in transplant candidates lies in a less complicated portal-portal anastomosis and decreased risk of post-operative complications. The field lacks for prospective RCT's to better define therapy but numerous cohort studies have demonstrated that anti-coagulation therapy for occlusive clot results in a greater chance of repermeation of the PV and better outcomes. However, all therapeutic alternatives have unresolved liver-related issues: with vitamin K antagonists the main issue is reliability of the INR as a therapeutic target, with heparin and similar agents including LMWH diminished levels of the heparin co-factor anti-thrombin (AT III) may result in heparin resistance and interfere with interpretation of the anti-Xa assay, and with DOACs (direct acting oral anti-coagulants) reports are yet early but so far encouraging especially with Child-Pugh A and early B patients. The latter are also now supported by the approval of reversal agents which has been reported in patients called in for liver transplant. Mechanical thrombectomy with TIPs/PV stents may be appropriate with acutely evolving cases especially with associated portal hypertension-related bleeding. Partial occlusion of **spontaneous spleno- or gastro-renal shunts** (SSRS/SGRS: under-recognized risks for PVT) may offer remarkable benefit **if preceded by pharmacological opening of the PV** as seen in the case presentation.

References

1. **Intagliata N, Caldwell S, Tripodi A. Diagnosis, Development, and Treatment of Portal Vein Thrombosis in Patients With and Without Cirrhosis. Gastroenterology. 2019 May;156(6):1582-159.** Provides a recent and comprehensive overview of PVT in both cirrhosis and non-cirrhotic patients
2. **O'Leary JG, Greenberg CS, Patton HM, Caldwell SH. Coagulation in Cirrhosis. Gastroenterology. 2019 Apr 12. pii: S0016-5085(19)35694-X. doi: 10.1053/j.gastro.2019.03.070. [Epub ahead of print]** Provides a succinct and recent overview of coagulation issues in liver disease patients

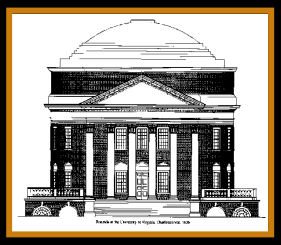
3. **Intagliata NM, Argo CK, Stine JG, Lisman T, Caldwell SH, Violi F; faculty of the 7th International Coagulation in Liver Disease. Concepts and Controversies in Haemostasis and Thrombosis Associated with Liver Disease: Proceedings of the 7th International Coagulation in Liver Disease Conference. Thromb Haemost. 2018 Aug;118(8):1491-1506** www.coagulationinliverdisease.org Provides a recent and comprehensive overview of coagulation issues in liver disease patients

2019 Clinical Hepatology Update

Anticoagulation in Portal Hypertension

Who, When, How and for How Long?

Stephen H Caldwell, MD
Professor, Hepatology
University of Virginia



Disclosures

- Dova – grant support for biennial Coagulation in Liver Disease Symposium
- Shionogi - grant support for biennial Coagulation in Liver Disease Symposium

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Case

- 46 yo M with stable UC on 5ASA and PSC. Athletic
- After 6-7 yr stability, he presented with progressive HE
- Previously known spontaneous spleno-renal shunt
- Small low risk fundal varices at EGD
- Workup revealed HE and occlusive main PVT thrombosis and liver atrophy
- Started Coumadin at baseline INR 1.3 with target of 2.5 -3

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Case:Course

- After 6 months of therapy, re-imaging showed partial recanalization of PV
- Recurrent bouts of HE
- Portal vein velocity was 6.9 cm/second
- Test occlusion of the spontaneous shunt showed increased portal flow velocity to 90 cm/second
- Partial occlusion of the shunt was performed

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Case outcome after anticoagulation followed by partial occlusion of spontaneous splenorenal shunt

	Pre PVT	PVT	Pre-SRS Embolization	Postembolization Until Present
Timeline		0 → 1mth → CT #1	6mths → CT #2	21mths
Total bilirubin (mg/dL)	1.2	1.4	1.6	0.6
Creatinine (mg/dL)	0.7	0.7	0.8	0.8
INR	1.4	1.5	3.0*	2.9*
Albumin (g/dL)	3.3	2.9	3.0	4.0
MELD	11	12	–	–
CTP score	B(7)	B(7)	–	–
Liver volume (mL)	–	–	873	1346
Encephalopathy?	Yes	Yes	Yes	No

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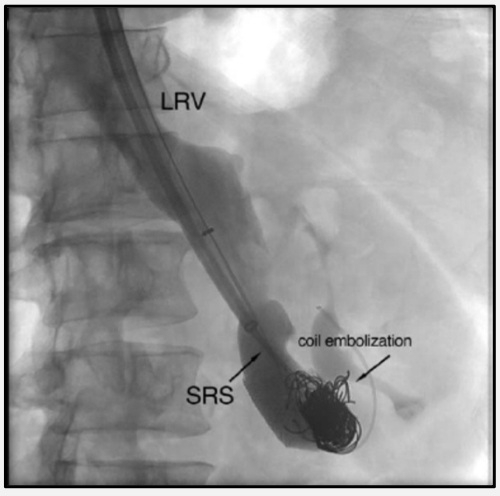
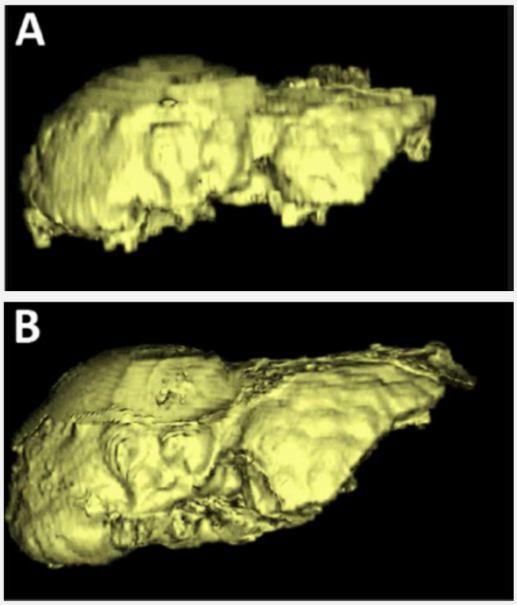
Outcome 15 mos after anticoagulation for PVT and occlusion of SR Shunt





873 cc

1346 cc

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Case take away messages (Intagliata et al Hepatology 2015;61:1088-1099)

- Spontaneous splenorenal shunts (SRS) promote stasis in the portal vein: risk for PVT (Maruyama Am J Gastro 2013;108:568-578)
- Remodeling of vitelline, umbilical and cardinal veins
- SRS's also associated with gastric varices
- Portal blood flow is trophic for liver
- Restoring blood flow can result in a degree of recovery
- May exacerbate portal hypertension
- Predictors of course are uncertain

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UVA NCAA CHAMPIONS 2019

WAHOOWA!

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Anticoagulation in Portal Hypertension

Who should be treated?

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Common indications for anticoagulation in liver disease

- Portal (PVT) & mesenteric vein thrombosis
- Peripheral Deep Vein Thrombosis (DVT)
- Prophylaxis of DVT (in hospitalized patients)
- Prophylaxis of PVT in stable cirrhosis?

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PROCOAGULANT CONDITIONS IN CIRRHOSIS

- Low protein C
- High Factor VIII
- High von Willebrand Factor
- Low anti-thrombin (AT III)
- Circulating activated platelets

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PORTAL VEIN THROMBOSIS IN CIRRHOSIS

RODRIGUEZ-CASTRO TRANSPLANT 2012, GARCIA-PAGAN J HEP 2009, TSOCHATZIS APT 2010, FONTANA GASTRO 2012, SEIJO HEPATOL 2013, YERDEL TRANSPLANT 2000

- Prevalence: 5 - 25%
- Annual Incidence: 5 - 16%
- Symptoms in 50%
  - Abdominal pain
  - Ascites/hydrothorax
  - Variceal bleeding

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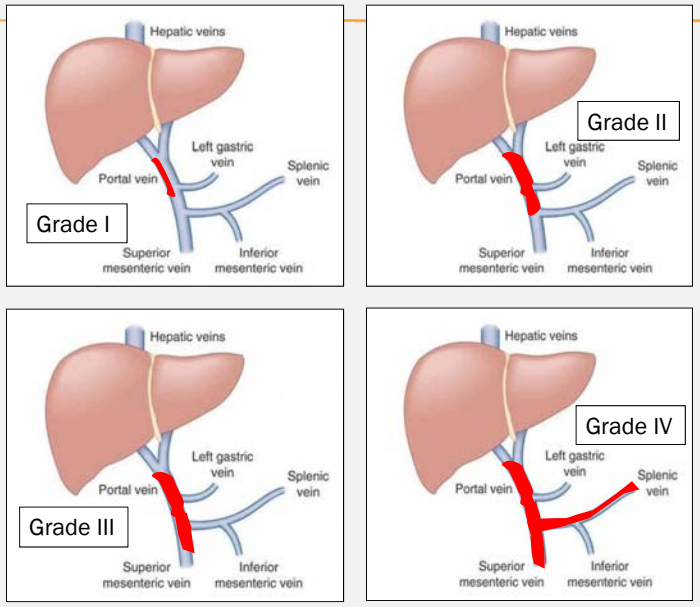
PVT IN CIRRHOSIS: YERDEL CLASSIFICATION

Yerdel et al Transplantation 2000;69:1873



After JC Garcia-Pagan

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Clinical course Intagliata, Caldwell and Tripodi Gastroenterology. 2019 May;156(6):1582-1599

- Highly variable presentation and course
- Ranges from asymptomatic (incidentally discovered)
- To acute symptoms of portal hypertension
- And sometimes (with extension) to mesenteric ischemia
- Clearest impact is on transplant outcomes

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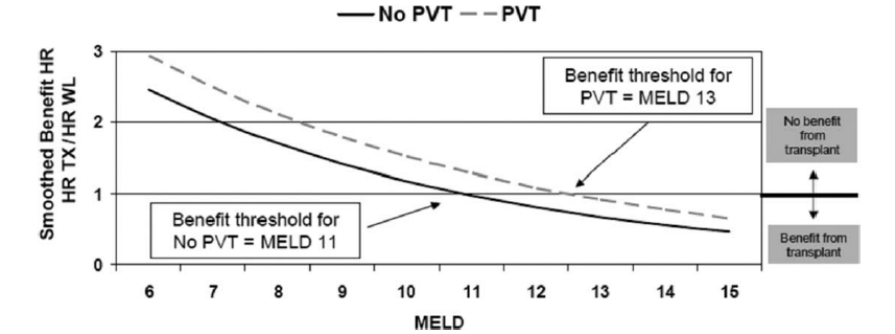
PVT: IMPACT ON TRANSPLANTATION

Englesbe et al Liver Transplantation 2010;16:999-1005

Variable reports on wait-list mortality
Shifts survival benefit of transplant to right
Reflects Post-Op impact on survival



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Anticoagulation in Portal Hypertension

When should you treat?

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CONSIDERING ANTI-COAGULATION

DELGADO CGH 2012, FRANCOZ GUT 2005, AMITRANO JCG 2009, SENZOLO 2012

- Symptoms, acuity, extent of thrombus, thrombophilic risks, transplant status
- Bleeding and Fall risk
- Less effective after 6 months or if cavernous
- Bleeding risk ~ 10% in treated patients
- Offset by potential decreased portal pressure
- Partial PVT: stable or improves in ~ 50%

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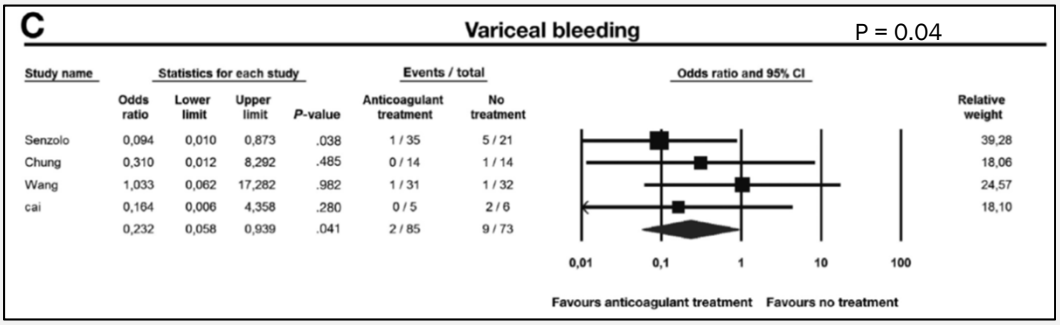
CLINICAL—LIVER Gastroenterology 2017;153:480–487

Effects of Anticoagulants in Patients With Cirrhosis and Portal Vein Thrombosis: A Systematic Review and Meta-analysis

Lorenzo Loffredo,[1] Daniele Pastori,[1,2] Alessio Farcomeni,[3] and Francesco Violi[1]

- N=353, from 8 trials, treated with either LMWH or warfarin or untreated, significantly greater re-permeation 71 vs 42%



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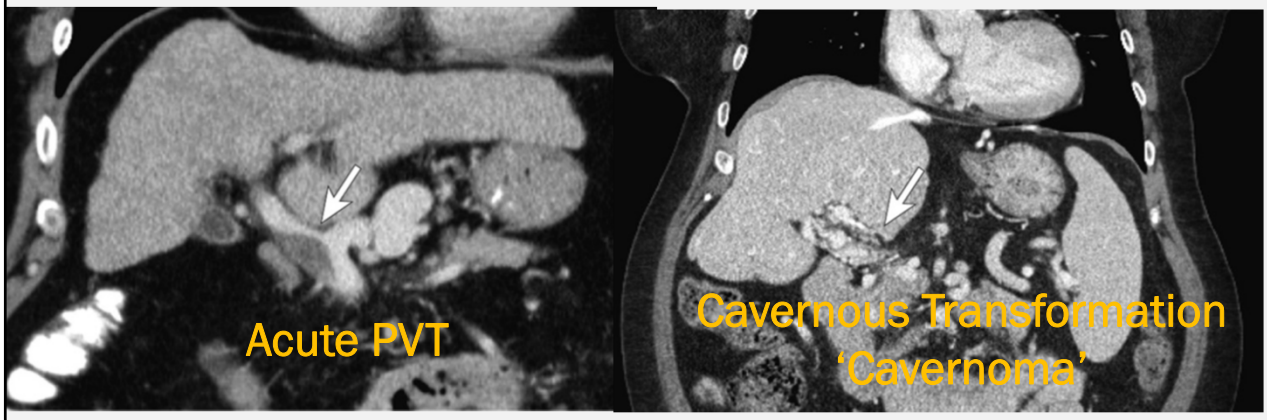
Early Therapy More Effective

Intagliata, Caldwell and Tripodi Gastroenterology. 2019 May;156(6):1582-1599



Cavernous transformation can occur within weeks but usually evolves over months. Adds complexity to surgery

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Anticoagulation in Portal Hypertension

How should you treat?

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MANAGEMENT OPTIONS

- Observe - Serial Imaging
- Anti-coagulation therapy
- Attempt mechanical repermeation
- Combination approach

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Anti-coagulation therapy in cirrhosis

Intagliata, Caldwell and Tripodi Gastroenterology. 2019 May;156(6):1582-1599

- Most studies use LMWH or VKA. DOACs emerging
- No prospective RCTs
- Pre-Rx: EGD and band varices if present
- Repermeation of PV consistently more frequent with Rx
- Spontaneous repermeation in 20-50% esp with partial PVT
- Survival benefit usually in favor of therapy

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VKA therapy in cirrhosis

- VKA: vitamin K antagonists (Warfarin, Coumadin)
- Usual target is INR of 2-3
- Obvious problems with the target in cirrhosis patients
- Inter-lab variation in the INR due to thromboplastin ISI
- Issues remain unresolved

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MONITORING HEPARIN THERAPY IN CIRRHOSIS

- Anti-Xa assay: higher anti-Xa units/ml indicate higher effect
- Heparins depend on AT (AT III) levels to inhibit Xa
- AT levels decline in cirrhosis – heparin resistance
- Unresolved issue in measuring heparin in cirrhosis

CLINICAL STUDIES

Liver International (2010)

Low-molecular-weight heparin in patients with advanced cirrhosis

Lars P. Bechmann[1], Matthias Sichau[1], Marc Wichert[2], Guido Gerken[1], Knut Kröger[3,4] and Philip Hilgard[1,5]

Study Group

'DOAC'S : DIRECT-ACTING ORAL ANTI-COAGULANTS

Intagliata DDS 2016;2:1-7, Intagliata Hepatol 2015;61:738-9, Intagliata Curr Treat Options Gastro 2016;14:247-56

- Apixaban (Eliquis): Xa inhibitor, prolongs PT, renal + liver (70%), caution in CPT B and avoid in CPT C. Reversal Andexanet Alfa
- Rivaroxaban (Xarelto): Xa inhibitor, prolongs PT, renal + liver (35%), avoid in CPT B and C, Reversal Andexanet Alfa
- Edoxaban (Savaysa): Xa inhibitor, prolongs PT, renal + liver (50%), avoid in CPT B and C. Reversal Andexanet Alfa
- Dabigatran (Pradaxa): II inhibitor, prolongs PTT, renal 80%, No recommendations re CPT classes Reversal idarucizumab (Praxbind)
- Reversal pre-transplant: (Intagliata Liver Transplantation 2017;23:396)

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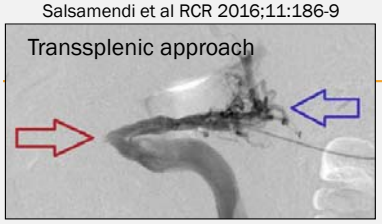
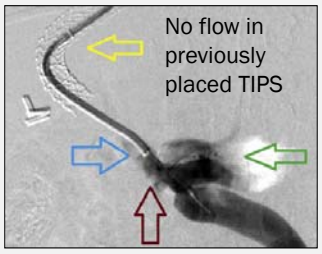
TIPS AND STENTS ?

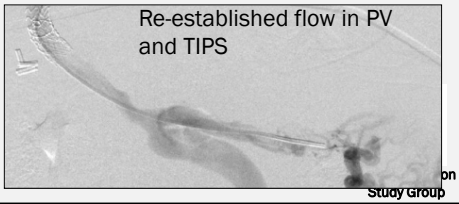
Qi Hepatol Int 2012, Senzolo APT 2006, Salem Transplant 2015

- Success rate of approximately 80%
- Complications up to 17%
- Usually reserved for selected cases
  - Active portal htn related bleeding
  - Uncontrolled ascites / hydrothorax
- May promote simpler end-to-end PV anastomosis at transplant

Salsamendi et al RCR 2016;11:186-9







Study Group

Anticoagulation in Portal Hypertension

How long should you treat?

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MAJOR RISK FACTORS FOR PVT

ZOCCO J HEP 2009, AMITRANO J HEP 2004, FRANCOZ GUT 2005, ROSETTO IEM 2013, PONZIANI WJG 2012 MARUYAMA AM J GASTROENTEROL 2013;108:568–574, INTAGLIATA HEPATOLOGY 2015;61:1088-90

- Acquired Protein C deficiency: Cirrhosis
- Slow portal vein flow (< 15 cm/s by Doppler)
- Spontaneous shunts: spleno- or gastro- renal
- Endothelial injury – related to liver disease
- NASH/Cryptogenic cirrhosis
- Genetic thrombophilia risks in 10-20%
  Prothrombin mutation, Factor V Leiden, MTHFR

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Stopping therapy after repermeation of PV

Pettinari et al Am J Gastroenterol. 2019 Feb;114(2):258-266.

- Treatment periods usually at least 6 months
- Follow-up not consistently reported in past studies
- Recurrence risk appears to be fairly high
- 36% recurrence w/i 3 mos in one recent study of patients treated with either LMWH, fondaparinux or VKA

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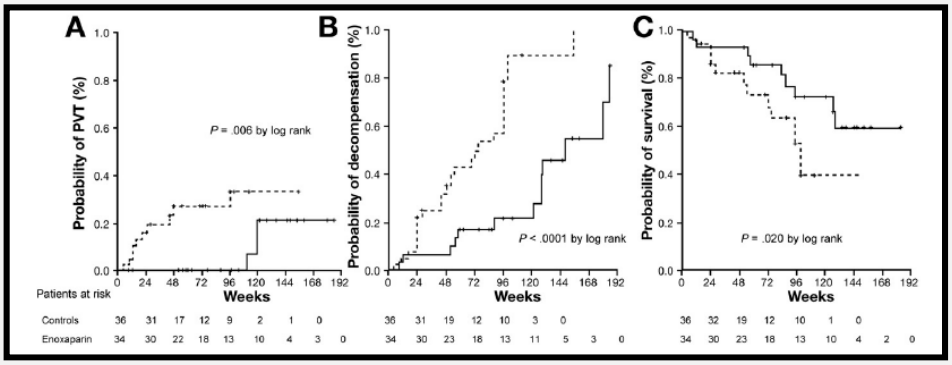
PROPHYLACTIC ANTICOAGULATION IN CIRRHOSIS?

VILLA ET AL GASTRO 2012;143:1253

Prospective, randomized, controlled, unblinded single center study
Advanced cirrhosis without PVT
Prophylactic enoxaparin (n 34), 48 weeks vs controls (n 36)



- Benefit extended beyond treatment period
- Attributed to improved intestinal microcirculation

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Anti-coagulate if platelets are < 50k ?

- Unsettled area
- Recent case where Hematologist stopped Rx with subsequent extension
- Similar recent case where we used Rotem (**intem channel**) to show only mild decrease in MCF in patient responding to LMWH

Whole Blood Clotting Assay

INTEM - Intrinsic Path Coag Process

Order #: 257195134 Accession #: 1

4/19/2019 4:39 PM

Component	Value	Flag	Ref Range	Units
Clotting Time (Cti)	163		122 - 208	SEC
Amplitude After 10 Minutes (A10I)	42		40 - 60	mm
Amplitude After 20 Minutes (A20I)	49	⌄	51 - 72	mm
Maximum Clot Firmness (Mcfi)	50	⌄	51 - 72	mm
Percent Lysis (Pmli)	3		0 - 100	%

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Question 1

What factors would favor treating PVT in cirrhosis?

A. Occlusive thrombus
B. Listed for transplant
C. Associated symptoms such as fluid retention or HE
D. Extension of thrombus into mesenteric or splenic vein
E. All of the above

Answer: E all of these are key considerations

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Question 2

What factors would favor not treating PVT in cirrhosis?

A. Partial occlusion (50% or less)
B. Asymptomatic
C. Not a transplant candidate
D. History of recurring blood loss (such as GAVE)
E. Frail with fall risk
F. All of the above

Answer: F all of these are key considerations

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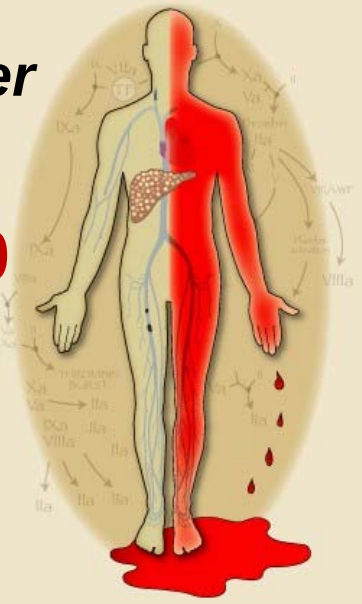
www.coagulationinliverdisease.org

Coagulation in Liver Disease VIII

Sept 27-28 2019
Groningen
Netherlands



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Palliative Interventions: Who, How, What?

Patients with advanced liver disease often suffer a multitude of symptoms which dramatically impact quality of life, these include hepatic encephalopathy and fluid management problems. Many of these problems can be especially difficult to manage or control in the most advanced states of disease. Fluid management issues such as refractory ascites and refractory hepatic hydrothorax result in a need for frequent procedures which can be burdensome for patients and caregivers.

The focus on this session will be to review the most common complications impacting quality of life in advanced liver disease and the current state of evidence for the various treatment options which exist with a specific attention to options for management of refractory ascites and pleural effusions. TIPS may aid in the management of ascites and pleural effusions in selected patients. In other patients TIPS may either be contraindicated or may not adequately control ascites or pleural effusion.

Techniques used for management of pleural effusion include surgical intervention with diaphragmatic repair, chemical pleurodesis, pleurovenous shunts, and placement of indwelling pleural catheters. This presentation will review the outcomes and risks with such procedures.

In addition, I will briefly review other invasive tools which may be used in nutritional support of patients with end-stage liver disease.

References

1. Kniese C, Diab K, Ghabril M, Bosslet G: Indwelling Pleural Catheters in Hepatic Hydrothorax: A Single-Center Series of Outcomes and Complications. *Chest* 2019, 155(2):307-314 Pmc6363815.
2. Lazaridis KN, Frank JW, Krowka MJ, Kamath PS: Hepatic hydrothorax: pathogenesis, diagnosis, and management. *Am J Med* 1999, 107(3):262-267.
3. Lv Y, Han G, Fan D: Hepatic Hydrothorax. *Ann Hepatol* 2018, 17(1):33-46.
4. Porcel JM: Management of refractory hepatic hydrothorax. *Current opinion in pulmonary medicine* 2014, 20(4):352-357.
5. Rössle M, Gerbes AL: TIPS for the treatment of refractory ascites, hepatorenal syndrome and hepatic hydrothorax: a critical update. *Gut* 2010, 59(7):988-1000.
6. Shojaee S, Khalid M, Kallingal G, Kang L, Rahman N: Repeat Thoracentesis in Hepatic Hydrothorax and Non-Hepatic Hydrothorax Effusions: A Case-Control Study. *Respiration; international review of thoracic diseases* 2018, 96(4):330-337.
7. Walker S, Maldonado F: Indwelling Pleural Catheter for Refractory Hepatic Hydrothorax: The Evidence Is Still Fluid. *Chest* 2019, 155(2):251-253.
8. Robson PC, Gonen M, Ni A, Brody L, Brown KT, Getrajdman G, Thom B, Kline N, Covey A: Quality of life improves after palliative placement of percutaneous tunneled drainage catheter for refractory ascites in prospective study of patients with end-stage cancer. *Palliative & supportive care* 2019:1-9.

Palliative Interventions: Who, what, and when?

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2019 AASLD Clinical Hepatology Update
June 14-15, 2019
Bellevue, WA

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Disclosures:

- None

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A case:

76 year old female patient with decompensated liver disease due to PBC presents to clinic for a routine 6-month follow-up appointment. She lives independently with her husband, but neither can drive. She does not have encephalopathy. She has undergone variceal ligation in the past, most recent EGD demonstrated no varices.

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Case continued:

Her case has been complicated in recent months by refractory hepatic hydrothorax currently requiring therapeutic thoracentesis approx. every 7 days. She has been hospitalized 4 times in the last three months, three times for shortness of breath, and once for a pneumothorax (complication of the thoracentesis).

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Case continued:

- Her MELD is 26 (INR 2.1, Cr 1.6, Bilirubin 2.5)
- Hgb 10.2
- Platelets 85 K
- ECHO
  - EF 45%
  - Bi-atrial enlargement
  - Mild depression in RV contractility

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Case continued:

During the clinic visit today, the patient expresses a strong desire to alter her therapy given the hardship she experiences with the frequent thoracentesis and impact on her quality of life.

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What are options for management?

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Hepatic Hydrothorax:

- Transudative pleural effusion associated with portal hypertension
- Incidence varies from 4-15% in cirrhotic patients
- HH accounts for 2-3% of all pleural effusions
- 80% right sided, 17% left sided, and 3% bilateral
- 21-26% are refractory to standard therapies (diuretics and sodium restriction

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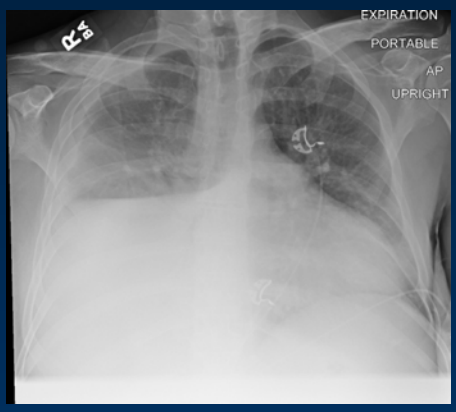
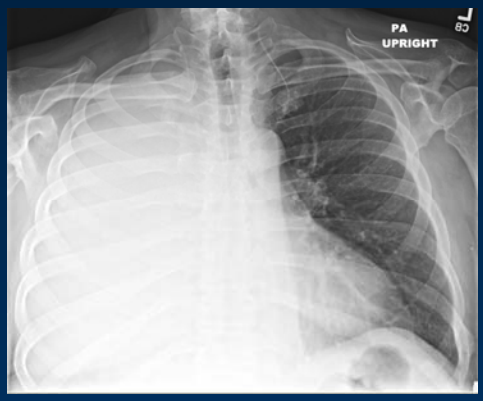
Singh, A., *et al., Respiration* 2013; 86: 155-173

Hepatic hydrothorax:





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Standard options for management of HH

- Liver transplantation
- Sodium restriction + Diuretics
- TIPS
- Repeated thoracentesis
- VATS + Pleurodesis (~50% success rate)
- Indwelling Pleural Catheter

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Standard options for management of HH

- Liver transplantation
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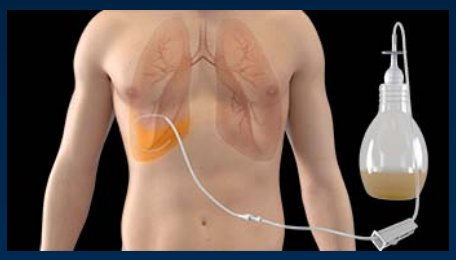
Indwelling pleural catheters:

- Risk of infection?
- Risk of malnutrition?
- Risk of renal injury?
- What is the data?



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Indwelling Pleural Catheters

Outcome	Value
Complications	22 (35.5%)
Type of complication	
Empyema	10 (16.1%)
Skin infection	1 (1.6%)
Catheter clogged	2 (3.2%)
Catheter dislodged	6 (9.7%)
Pneumothorax	2 (3.2%)
Catheter malfunction	5 (8.1%)
Other	3 (4.8%)
Unexpandable lung	3 (4.8%)
Pleurodesis	9 (14.5%)
Time to pleurodesis, d	
Mean ± SD	118 ± 139.6
Range	15-373
Transplant status after IPC[a,b]	
Listed	19 (57.6%)
Not listed	14 (42.4%)
Transplant after IPC[b]	10 (30.3%)
Time to transplant, d	
Mean ± SD	87 ± 49.6
Range	20-175
Death after placement	48 (77.4%)
Time to death, d	
Mean ± SD	180 ± 284.0
Range	0-1,258
Death at 6 months	36 (58%)
Lost to follow-up	5 (8.1%)

Retrospective study of 62 patients with IPC for HH. 53% in patients as a bridge to transplant.

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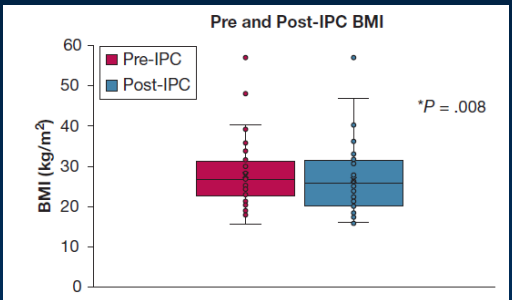
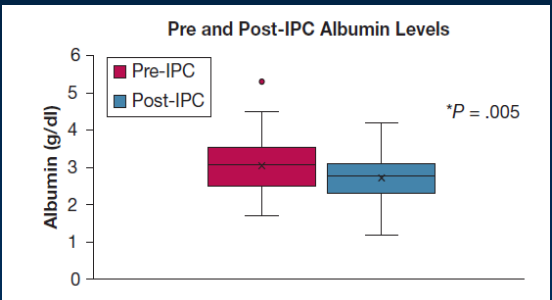
Kniese C., *et al., Chest 2019*; 155: 307-314

Indwelling Pleural Catheters





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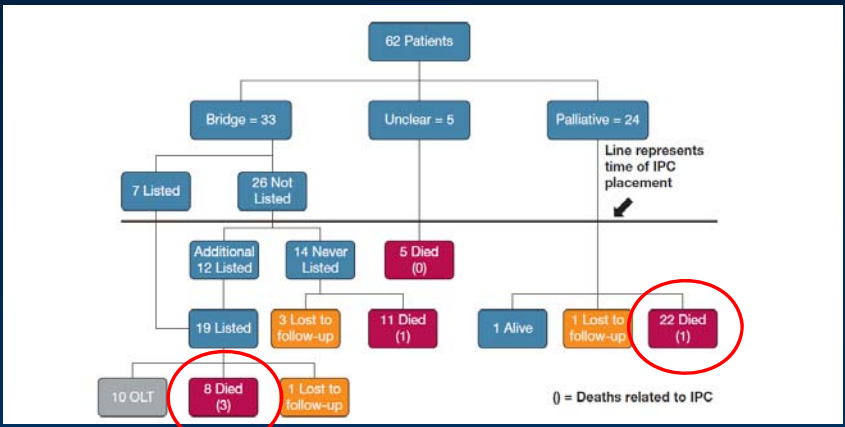
Kniese C., *et al., Chest 2019*; 155: 307-314

Outcomes



37.5%

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Kniese C., *et al., Chest 2019*; 155: 307-314

BRIEF COMMUNICATION

Indwelling Tunneled Pleural Catheters for the Management of Hepatic Hydrothorax

A Pilot Study

Alexander Chen[1], Jennifer Massoni[1], Diana Jung[2], and Jeffrey Crippin[3]

[1]Division of Pulmonary and Critical Care Medicine, and [3]Division of Gastroenterology, Washington University School of Medicine, St. Louis, Missouri; and [2]University of Missouri at Kansas City, Kansas City, Missouri

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Chen, A., *et al., Ann Am Thorac Soc* 2016; 13:862-866

Indwelling Pleural Catheters

- 24 patients eligible for LT
- Spontaneous pleurodesis 8/24 (33%)
- Mean time to pleurodesis 132 days
- Pleural fluid infection occurred in 4/24 (16.7)
- No deaths attributable to infection

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Chen, A., *et al., Ann Am Thorac Soc* 2016; 13:862-866

Take home points:

- IPC are an effective palliative intervention for HH and should be considered in patients without other options
- Risk for infection remains high
- Clinical impact on nutrition and BMI likely not clinically significant
- Further study is required before IPC can be recommended in patients awaiting transplant

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Palliative interventions for refractory ascites

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Refractory Ascites: Definitions

- Refractory ascites occurs in 10-20% of cirrhotic patients
- Diuretic-intractable ascites 80%
  - Unable to achieve therapeutic doses of diuretics due to diuretic-induced complications
- Diuretic-resistant ascites 20%
  - Ascites unresponsive to maximal doses of diuretic therapy (400 mg spironolactone +160 mg furosemide)

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Arroyo, V., *Am J Gastro 1993*; 88: 514

Standard options for management of refractory ascites

- Liver transplantation
- Sodium restriction + Diuretics
- TIPS
- Repeated paracentesis
- Peritoneal venous shunts
- Indwelling peritoneal Catheter

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Indwelling Peritoneal Catheters

Home-based drainage of refractory ascites by a permanent-tunneled peritoneal catheter can safely replace large-volume paracentesis

Philipp Solbach[a,b,c,*], Christoph Höner zu Siederdissen[a,*], Richard Taubert[a], Szilvia Ziegert[a], Kerstin Port[a], Andrea Schneider[a], Katja Hueper[d], Michael P. Manns[a,c], Heiner Wedemeyer[a,c] and Elmar Jaeckel[a]

Study of 24 patients undergoing peritoneal catheter placement for management of refractory ascites

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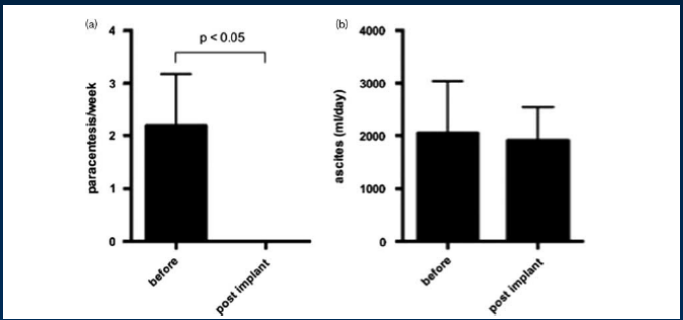
Solbach, P., *et al., Euro J of Gastro & Hep 2017*; 29: 539-546

Effect on ascites management

Average paracentesis per week 2.2 to zero

Daily volume of ascites removed 2047 ml to 1909 ml



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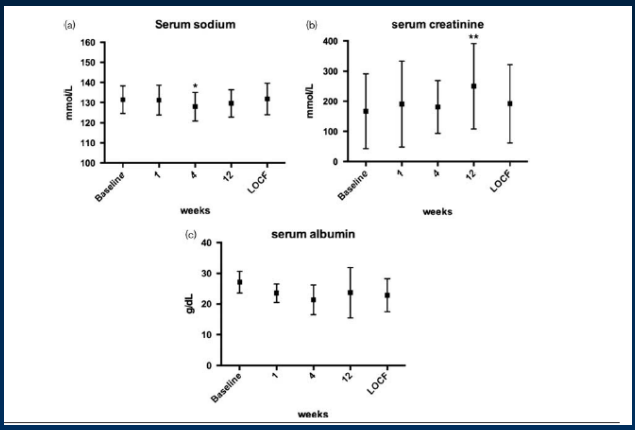
Solbach, P., *et al., Euro J of Gastro & Hep 2017*; 29: 539-546

Additional outcome measures

Statistical decrease in serum sodium at 4 weeks

Statistical increase in creatine at 12 weeks

No change in serum albumin



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Solbach, P., *et al., Euro J of Gastro & Hep 2017*; 29: 539-546

Infection

- 2/24 patients (8.3%) in spite of being on prophylaxis
- Time from insertion to SBP 4 and 10 weeks
- Average in-situ catheter indwelling time ranged from 2-222 days (mean 83.2 days)
- 5 patients underwent transplantation

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Indwelling Peritoneal Catheters

- Retrospective review of 227 drain placements in 149 pts.
- Pts has ascetic fluid cell counts at placement and within 72 hours
- 12% has SBP at time of drain placement excluded from study
- 10% developed peritonitis within 72 hours

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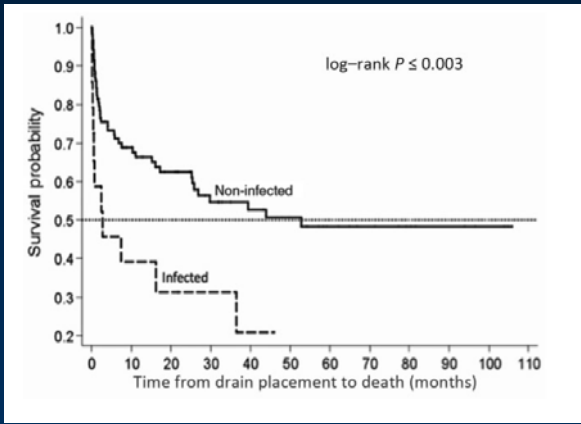
Kathpalia, P., *et al., Internal Med J 2015*; 45: 1026-1031

Outcomes

Infected patients had 50% risk of mortality at 5 months compared to 50 months in those without infection



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Kathpalia, P., *et al., Internal Med J 2015*; 45: 1026-1031

Summary: Who

- True end-stage disease
- Desire palliative interventions
- In whom other options have failed or are contraindicated

Transplant eligible patients

- Controversial
- More data needed
- Discuss with the transplant team

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Summary: What

- Most effective tool
- Least likely to cause harm
- Context of patient condition and desires
  - Indwelling catheters are reasonable options in patients in whom other treatments have failed

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Summary: When

- Quality of life
- Sustained failure of standard therapies
- Standard therapies are contraindicated
- When decompensation is not likely to be reversed

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Thank you!

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Liver Adenomas: Management According to Size, Location, Symptoms and Genetics

Learning Objectives:
Upon completion of this session, the participant should be able to:
1) recognize the spectrum of benign solid and cystic masses of the liver
2) understand the clinical manifestations of hepatic adenomas
3) establish a management strategy for hepatic adenomas

Key take-home points:
1) There is a spectrum of incidentally observed liver mass lesions that are often benign
2) The phenotype of hepatic adenomas has changed recently in that these are often seen in those with obesity and metabolic syndrome
3) Hepatic adenomas are infrequently encountered, can be multiple, and can de-differentiate into malignancy or have rupture potential and such complications are generally restricted to large lesions (≥ 5 cm in size)
4) Multiple therapeutic intervention strategies including surgery and ablative modalities, are infrequently necessary and often pursued in those with large lesions while the rest are followed.

Introduction
The increasing use of imaging studies, either routinely or as part of the work up for a variety of presenting symptoms, has led to a rise in the detection of liver lesions in otherwise healthy individuals. While some of these incidentally discovered masses are malignant, the vast majority of these lesions are benign and must be included in the differential diagnosis if appropriate care is to be provided. The management of benign hepatic tumors ranges from conservative to aggressive depending on the nature of the lesions. New imaging modalities and accumulating experience among radiologists, along with well-defined radiologic characteristics and clinical backgrounds associated with these lesions, are continuously enhancing our ability to make an accurate diagnosis without using invasive diagnostic tools. As a result, management options are constantly being tailored in order to provide the best possible care.

Hepatocellular Adenoma
Hepatocellular adenoma (HCA) is a benign neoplasm that tends to develop in individuals with a hormonal or metabolic abnormality that stimulates hepatocyte proliferation. There is a causal relationship between oral contraceptive steroids (OCPs) and hepatic adenomas. HCAs are found predominantly in women ages 30-50 and are most often solitary and located in the right hepatic lobe. More recently, the phenotype of hepatic adenomas has been such that these are more often seen in those with obesity and metabolic syndrome.

Along with OCP use, and the background of metabolic syndrome, anabolic androgen steroids (AAS) can lead to the development of HCA and another major risk factor is glycogen storage disease (GSD) types Ia and III. Antiepileptic drugs and hepatic hemosiderosis have also been connected to HCA development. Notwithstanding the myriad of risk factors for HCA, otherwise healthy patients – both male and female – with no history of OCP, AAS, antiepileptic drug use, and underlying metabolic conditions have been known to develop these lesions.

Within the past decade, HCAs have been broadly categorized into four subtypes based on genetic and pathological criteria: hepatocyte nuclear factor-1α (HNF1α) inactivating mutations, inflammatory

subtype (IHCA), β-catenin activating mutation, and β-catenin mutation with IHCA features. When characterized pathologically, the various HCA subtypes are associated with specific magnetic resonance imaging (MRI) patterns; these typical MRI findings may make it possible to non-invasively determine the subtype of HCA without resorting to biopsy.

Biopsy can be of risk in HCA because of the vascular nature of these lesions and their propensity to hemorrhage. Nevertheless, new genetic and molecular criteria have been established to ascertain a definitive diagnosis, which can be helpful in the management of these tumors. While there is some benefit in obtaining a biopsy, it should be reserved for select cases where genetic and molecular diagnostic tools are available and are deemed necessary in making treatment decisions.

Liver Adenomatosis

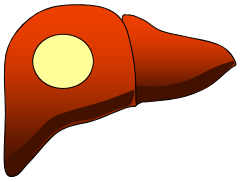
Liver adenomatosis refers to the patient with multiple adenomas, and has been variably defined as anywhere from >3 to ≥10 adenomas in the liver. The optimal mode of management for adenomatosis is not well defined because cases hitherto have been infrequent and the diffuse nature of these lesions makes partial hepatic resection difficult, if not impossible.

Therapy

Multiple therapeutic modalities, including resection and bland embolization have been pursued in those with hepatic adenomas. Therapy has generally been restricted to large lesions (≥ 5 cm in diameter) and in those with complications of bleeding or de-differentiation in HCC.

References

1. Reddy KR, Kligerman S, Levi J, et al. Benign and solid tumors of the liver: relationship to sex, age, size of tumors and outcome. Am Surg 2001; 67(2):173-8.
2. Shaked O, Siegelman ES, Olthoff K, Reddy KR. Benign cystic and solid lesions of the liver: a multidisciplinary approach. Clin Gastroenterol Hepatol 2011;9(7):547-562
3. Marrero J, Ahn J, Reddy KR. ACG Clinical Guideline: The Diagnosis and Management of Focal Liver Lesions. Am J Gastroenterol. 2014 Aug 19. doi: 10.1038/ajg.2014.213. [Epub ahead of print]
4. Bunchorntavakul, C. , Bahirwani, R. , Drazek, D. , Soulen, M. C., Siegelman, E. S., Furth, E. E., Olthoff, K. , Shaked, A. and Reddy, K. R. (2011), Clinical features and natural history of hepatocellular adenomas: the impact of obesity. Alimentary Pharmacology & Therapeutics, 34: 664-674. doi:10.1111/j.1365-2036.2011.04772.x



Liver Adenomas: Management According to Size, Location, Symptoms, and Genetics

K. Rajender Reddy M.D.,
Ruimy Family President Distinguished Professor of Medicine
Director of Hepatology
Medical Director of Liver Transplantation
University of Pennsylvania

Case

- 34-year old otherwise healthy lady
- Left flank pain and microscopic hematuria
- ER Physician orders a CT scan of abdomen
- Mass noted in the liver (4.2 x 3.8 cm). Left renal calculus without hydronephrosis
- No previous H/O abdominal pain, anorexia, jaundice, weight loss, etc.
- Physical examination – normal
- Hepatic biochemical tests – normal
- Patient on oral contraceptive steroid for 14 years

Detection of Lesion(s) in the Liver

- "Incidentaloma"
- History or risk of malignancy
- Symptoms
  - Caution about non-specific nature
- Signs
  - Stigmata of chronic liver disease
  - Jaundice, hepatomegaly
- Hepatic biochemical test abnormalities

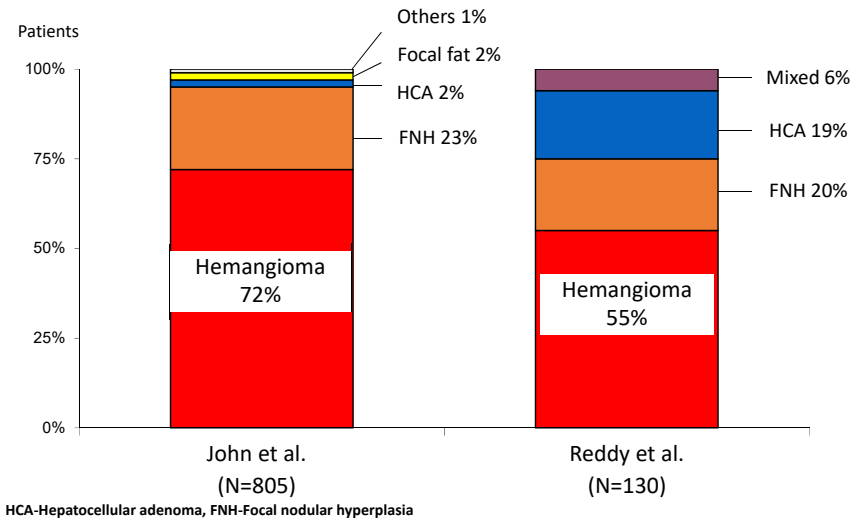
Key Issues – Suspected Benign Lesions

- Biopsy or Not to Biopsy
- Follow up – How often and How
- Oral Contraceptive Steroid Use
- Pregnancy
- Management

Classification of Hepatic Tumors

Origin	Benign	Malignant
Hepatocellular	Adenoma Focal nodular hyperplasia Regenerating nodules	Hepatocellular carcinoma Fibrolamellar carcinoma Hepatoblastoma
Mesenchymal	Hemangioma Lipoma	Angiosarcoma Primary lymphoma
Cholangiocellular	Bile duct adenoma Biliary cystadenoma	Cholangiocarcinoma Cystadenocarcinoma
Heterotopic	Adrenal/pancreatic	Metastases

Distribution of Benign Liver Lesion(s)

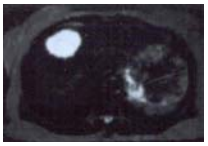


HCA-Hepatocellular adenoma, FNH-Focal nodular hyperplasia

John T, et al. Ann Surg 1994;220:711-19
Reddy KR, et al. Am Surg 2001;67:173-78

Hemangioma

- Most common benign solid lesion (0.4-20%)
- Predominantly in women
- Size – variable (1-20 cm)
- Symptoms – variable (unrelated to size)
- Clinical course – benign

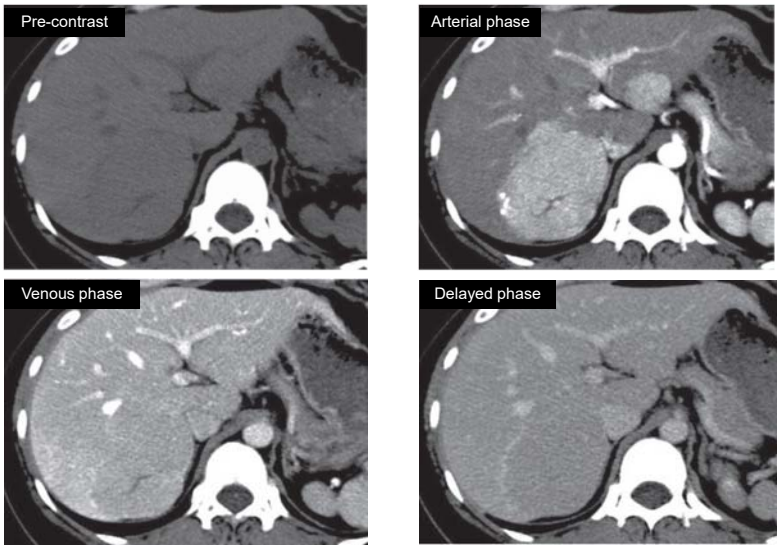


"Almost all patients die with it and not from it"

Focal Nodular Hyperplasia (FNH)

- Second most common
- All ages; women: 50-80%
- Asymptomatic: 50-90%
- OCP – may grow
- Location – often subcapsular
- Size – Majority less than 5 cm
- Number – 7-20% multiple
- Hepatic biochemical tests – generally normal

FNH: CT Scan

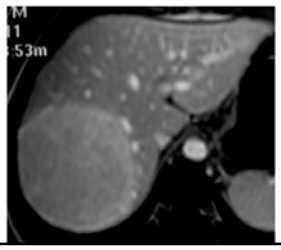


Courtesy of Dr. Claude Sirlin. University of California

Hepatocellula Adenoma (HCA): Epidemiology/Clinical Characteristics

- Epidemiology[1–3]
  - Reported prevalence: 0.001–0.004%
  - ~10x less common than FNH
  - Most common in women (10:1 female to male), especially aged 35–40 years
- Potential role of sex hormones
  - 30–40-fold increase in incidence with long-term OCP use[4]
  - Incidence among males is associated with androgenic steroids[5,6]
- Recent increase in prevalence associated with rising obesity and metabolic syndrome[7–9]
- Significant risk of haemorrhage and malignant transformation
  - Especially with lesions ≥5 cm

HCAs need to be followed more closely than other benign tumours



1. Bonder A, Afdhal N. Clin Liver Dis 2012;16:271–83; 2. Karhunen PJ. J Clin Pathol 1986;39:183–8;
3. Cherqui D, et al. Gastroenterol Clin Biol 1997;21:929–35; 4. Giannitrapani L, et al. Ann NY Acad Sci 2006;1089:228–36;
5. Socas L, et al. Br J Sports Med 2005;39:e27; 6. Nakao A, et al. J Gastroenterol 2000;35:557–62;
7. Bunchorntavakul C, et al. Aliment Pharmacol Ther 2011;34:664–74; 8. Bioulac-Sage P, et al. Liver Int 2012;32:1217–21;
9. Chang CY, et al. Int J Hepatol 2013;2013:604860; EASL CPG benign liver tumours. J Hepatol 2016;65:386–98

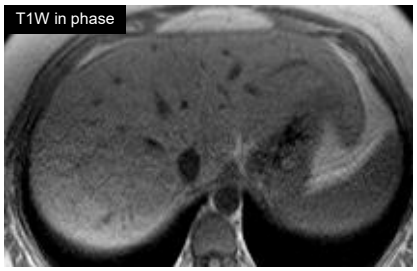
HCA: Course and Progression

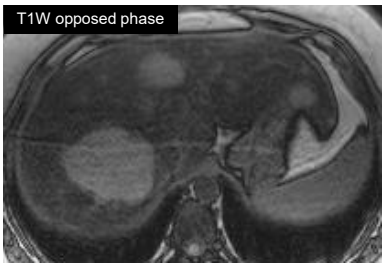
- May decrease in size or disappear after discontinuation of OCP
- Malignant transformation (<6%)
  - Risks – size ≥ 5 cm, β-catenin mutation, GSD
  - Signs – enlargement, symptomatic, capsular irregularity
- Hemorrhage (10-30%)
  - Intratumoral, subcapsular or intraperitoneal
  - Risks – size ≥ 5 cm, prolonged OCP, pregnancy, subcapsular, multiple lesions

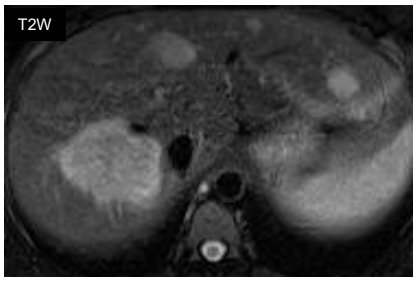
HCA Variants

- Inflammatory/telangiectatic HCA
  - Formally called telangiectatic FNH
  - Inflammatory infiltrates, increased GGT
  - Often multiple
- Liver adenomatosis
  - > 3-≥10 adenomas or more
  - Associated conditions – fatty liver & obesity
  - High risk for complications
  - Management: varied, multi-modality approach

HCA: MRI







34 year-old obese woman who had hepatic lesions detected on routine US examination – fatty liver and HCAs

Hepatocellular Adenomas (HCA) and Obesity

- Retrospective analysis of 60 patients with HCA; median FU; 2.6 years
- 97% were female, median age 36 yr and 55% were obese (BMI ≥30 kg/m^2)

Characteristics	Obese (N=33)	Non-obese (N=27)	p-value
History of contraceptive steroid use	72.7%	77.8%	0.65
Co-morbid conditions			
Fatty liver	**72.7%**	**37%**	**0.006***
Hypertension	**57.6%**	**22.2%**	**0.006***
Diabetes	**46.7%**	**8.7%**	**0.003***
Dyslipidemia	**39.3%**	**12.5%**	**0.03***
Size of lesion, cm	5.0 (1.6-19.7)	4.0 (1.0-14.0)	0.27
Multiple adenomas	**84.8%**	**48.1%**	**0.045***
Bilobar involvement	**66.7%**	**33.3%**	**0.03***
Interventional Rx (Sx and/or TAE)	54.5%	59.3%	0.71
Complete resection rate	8.3%	69.2%	0.004*
Conservative FU result			0.05*
Regression or stable size	66.7%	100%	
Progression	**33.3%**	0	

Bunchorntavakul C, Reddy KR. Aliment Pharmacol Ther. 2011;34(6):664-74

Hepatocellular Adenomas and Size at Diagnosis (2004-2017)

	Largest HCA ≥ 5 cm (n=54)	Largest HCA < 5 cm (n=61)	p-value
Age at diagnosis, yr (mean, SD)	36.6 (8.8)	35.7 (9.8)	0.6
Sex, % female	98.1%	95.1%	0.37
Race, % white	79.2%	81.7%	0.5
weight at dx, kg (mean, SD)	90.4 (27.2)	80.2 (22.9)	0.03
BMI at dx (mean, SD)	33.9 (9)	29.8 (7.8)	0.01
Disease follow up, years (mean, SD)	3.9 (3.9)	5.8 (8.8)	0.15
Single adenoma, %	25.9%	49.2%	0.01
Multiple adenoma, %	35.2%	32.8%	
Adenomatosis, %	38.9%	18.0%	
OCP use within 6 mo dx, %	59.3%	60.7%	0.96
History OCP use >1 year, %	78.8%	72.2%	0.53
DM2, %	27.8%	13.1%	0.09
HTN, %	50.0%	31.1%	0.11
Hyertriglyceridemia, %	5.6%	13.1%	0.3

Indiana University and University of Pennsylvania Experience

Hepatocellular Adenomas and Size at Diagnosis (2004-2017)

	Largest HA ≥ 5cm (n=54)	Largest HA < 5cm (n=61)	p-value
Initial Intervention			
Medication change, %	16.7%	37.7%	0.001
Intravascular treatment, %	40.7%	4.9%	
Surgical resection, %	27.8%	9.8%	
No intervention, %	7.4%	37.7%	
Ever Interventions			
Ever intravascular treatment, %	48.1%	4.9%	0.001
Ever surgical resection, %	37.0%	11.5%	0.001
Ever surgical resection or intravascular treatment, %	77.8%	16.4%	0.001
Never intervention, %	7.4%	37.7%	0.001
Ever Radiology			
Ever steatosis, %	29.6%	29.5%	0.96
Ever hemorrhage, %	14.8%	0.0%	0.002
Ever malignant transformation, %	1.8%	0.0%	0.29

Indiana University and University of Pennsylvania Experience

HCA: Molecular Classification

- Molecular subtype is highly associated with risk of transformation to HCC

Genetic mutation	Pathology	IHC	Clinical features	MRI features†
HNF1-A **(30–40%)**	**Extensive steatosis**	**LFABP –ve**	**Adenomatosis, MODY3**	**Diffuse and homogenous signal dropout on opposed-phase T1**
Inflammatory, *Gp130* (65%), *GNAS* (5%), *STAT3* (5%), *FRK* (10%), *JAK1* (2%)	**Inflammatory infiltration Clusters of vessels Sinusoidal dilatation**	**LFABP +ve SAA (± CRP) +ve**	**Obesity Alcohol consumption**	**Strong hyperintense on T2 and persistent enhancement on delayed phase using extracellular MR contrast agents**
β-catenin* exon 3 (5–10%)	**Cell atypias Pseudoglandular formations Cholestasis**	**LFABP +ve GS +ve (diffuse) β-catenin nuclear +ve**	**Male; androgen use → increased risk of HCC**	**No specific feature; often heterogeneous on T1 and T2 No signal dropout on opposed-phase T1**
β-catenin exons 7–8 (5–10%)	**No typical features or inflammatory phenotype**	**GS +ve (faint and patchy); β-catenin nuclear –ve**		**No specific features**
Unclassified (5–10%)	**None**	**LFABP +ve SAA/CRP –ve β-catenin nuclear –ve**		**No specific features**

*50% also display inflammatory phenotype; †Using hepatospecific MR contrast agents and hepatobiliary sequences, most HCAs appear hypointense but some are iso- or hyperintense on these sequences and seem to mainly correspond to inflammatory HCA. Gd-BOPTA offers the possibility to evaluate both the delayed and the hepatobiliary phases
EASL CPG benign liver tumours. J Hepatol 2016;65:386–98

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Unclassified (5–10%)	None	LFABP +ve SAA/CRP –ve β-catenin nuclear –ve		No specific features

β-HCAs exhibit the highest risk of malignancy; men are at a higher risk of malignancy

*50% also display inflammatory phenotype; †Using hepatospecific MR contrast agents and hepatobiliary sequences, most HCAs appear hypointense but some are iso- or hyperintense on these sequences and seem to mainly correspond to inflammatory HCA. Gd-BOPTA offers the possibility to evaluate both the delayed and the hepatobiliary phases
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Molecular Characterization-Limitations and Use

- Not widely available
- Limited to some tertiary centers; interest of Pathologists varies; " expensive, heterogeneity, etc"
- Seldom is a biopsy recommended

Thus, strategy is to make recommendations based on clinical and radiologic features

Key Issue – Liver Biopsy

- No – if hemangioma, FNH or HCA (generally not) diagnosed clinically and radiologically
- Imaging studies reliable in ~95% of cases
- If uncertain, follow with imaging studies
- Don't let a radiologist talk you into doing something
  - *If clinically indicated..., lesion can be treated with…recommend a biopsy…*
- Biopsy – often a small core or only cytology and not helpful, risk of bleeding ,miss a focus of malignancy

OCP use and Pregnancy Recommendations for Benign Liver Lesion(s)

	OCP use	Pregnancy	Treatment
Hemangioma	Not contraindicated	Not contraindicated	Often conservative FU-NO FU Imaging needed Resect if symptomatic(rare) (alternative: embolization)
FNH	Not contraindicated	Not contraindicated	Often conservative FU-NO FU Imaging needed Resect if symptomatic
HCA	Contraindicated	Treat lesion if ≥ 5 cm and then make informed decision. Less than 5 cm-not contraindicated while monitored	Treat base on size of lesion (≥ 5 cm) and any size in a male
Simple cyst	Not contraindicated	Not contraindicated	Often conservative FU-NO FU Imaging needed Laparoscopic unroofing, if symptomatic (resection rarely needed)

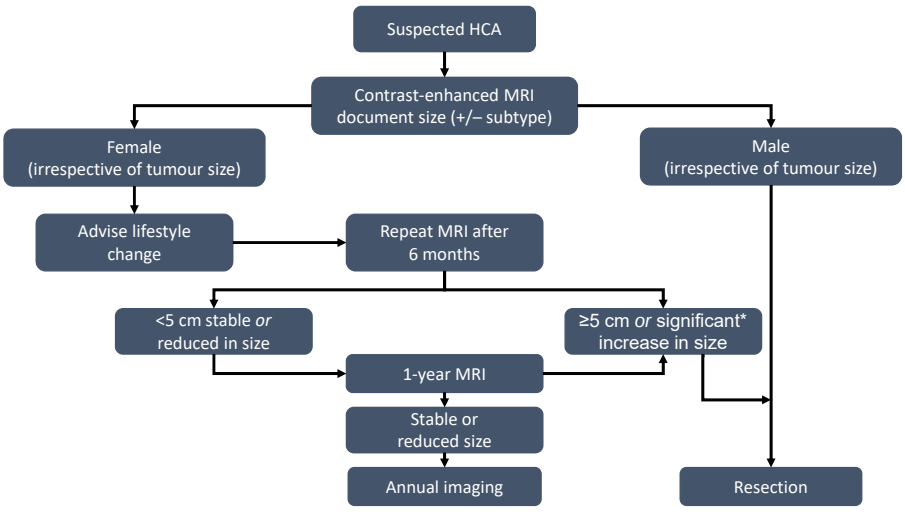
Adapted from Shaked O, Reddy KR. Clin Gastroenterol Hepatol 2011;9(7):547-562
Marrero JA, Ahn, J, Reddy KR. ACG Guideline: The Diagnosis and Management of Focal Liver Lesions: 2014;109:1328-47

Hepatocellular Adenoma (HCA)-Recommendations ACG Guideline

- **Oral contraceptives, hormone-containing IUDs, and anabolic steroids are to be avoided in patients with hepatocellular adenoma** (strong recommendation, moderate quality of evidence).
- **Obtaining a biopsy should be reserved for cases in which imaging is inconclusive and biopsy is deemed necessary to make treatment decisions** (strong recommendation, low quality of evidence).
- **Pregnancy is not generally contraindicated in cases of hepatocellular adenoma < 5 cm and an individualized approach is advocated for these patients** (conditional recommendation, low quality of evidence).
- **In hepatocellular adenoma ≥ 5 cm, intervention through surgical or nonsurgical modalities is recommended, as there is a risk of rupture and malignancy** (conditional recommendation, low quality of evidence).
- **If no therapeutic intervention is pursued, lesions suspected of being hepatocellular adenoma require follow-up CT or MRI at 6- to 12-month intervals. The duration of monitoring is based on the growth patterns and stability of the lesion over time** (conditional recommendation, low quality of evidence).

Marrero JA, Ahn, J, Reddy KR. ACG Guideline: The Diagnosis and Management of Focal Liver Lesions: 2014;109:1328-47

HCA: Management Algorithm-EASL Guideline



*≥20% diameter
EASL CPG benign liver tumours. J Hepatol 2016;65:386–98

Key Take Home Points

- Liver lesions are not uncommon and noted incidentally- mostly benign
- Radiologically they can often be readily characterized
- Biopsy of a lesion is seldom required
- HCAs have a distinct diagnosis, follow up, and management pathway
- OCP use and Pregnancy recommendations are unique for HCA while not applicable to other lesions

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Immunotherapies for Hepatocellular Carcinoma: What the Hepatologist Needs to Know

Oncology has undergone a revolutionary change since the adoption of immunotherapy for multiple cancer types. The immune system has long been known to play a role in protection against the development of cancer. The immune system can recognize a large number of antigens, including those present on normal tissues. As cancer cells develop, our own immune systems can recognize and react to cancer antigens. However, cancer cells are able to evade immune destruction by engaging or enhancing the mechanisms of immune tolerance that protect normal cells from recognition and destruction. As more has been learned about immunological tolerance to self that cancer cells are able to exploit, therapies have now been developed to remove the checkpoints that prevent immune system reaction. These checkpoint inhibitors augment the antitumoral responses of our immune system, thereby allowing immunological destruction of cancer cells.

The immunomodulatory molecules that are currently approved by the FDA for cancer therapies include inhibition of CTLA-4 (ipilimumab, tremelimumab), PD-1 (nivolumab, pembrolizumab), and PD-L1 (atezolizumab, avelumab, durvelumab). These molecules are approved for a multitude of malignancies and are currently being studied also in combination with many known therapies. There are also newer targets that are currently under investigation and will likely become part of the anti-cancer armamentarium in the near future. The checkpoint inhibitors act in part by relieving T cell exhaustion and boosting effector functions in the tumor microenvironment. CTLA-4, PD-1, and PD-L1 are molecules that are present on conventional CD4+ and CD8+ T cells and act as physiologic inhibitors of T cells during acute activation. Inhibiting these molecules allows the T cells to re-activate and participate in cancer cell destruction. The receptors are also present on a multitude of other immune system cells and a better understanding of how each receptor affects all cell types will be critical for understanding both the on-target and off-target effects of these therapies.

In patients with hepatocellular carcinoma, nivolumab and pembrolizumab are currently FDA approved for second line treatment after failure or intolerance of sorafenib. Both drugs received accelerated approval based on promising phase II data of overall response rate and duration of response.

CHECKMATE-040 is a phase I/II open-label, noncomparative dose escalation and expansion trial of nivolumab in patients with advanced hepatocellular carcinoma. A 154-patient subgroup of patients previously treated with or intolerant to sorafenib was evaluated and resulted in approval of nivolumab as second line treatment. Patients were required to have Child-Pugh A or B7 liver disease, total bilirubin <3 mg/dL, AST/ALT $\leq$5x ULN and good performance status. Median duration of exposure was 6 months. Nivolumab showed a manageable safety profile, with 25% of patients having a grade 3/4 toxicity but only 3 patients with a serious adverse event. The overall response rate was 14%, with duration of response 16.6 months and median overall survival 15.1 months. The phase III study of nivolumab (CHECKMATE-459) has completed enrollment and results are awaited.

KEYNOTE-224 is a non-randomized, multicenter, open-label phase II trial of pembrolizumab in patients who had been previously treated with or intolerant to sorafenib. As with CHECKMATE-

040, patients had to have good liver function (CTP A) and performance status. 104 patients were enrolled. Median duration of treatment was 4.2 months. Overall response rate was 17%, with median duration of response not reached but over 9 months in 77% of patients. Median overall survival was 12.9 months. Pembrolizumab also had a manageable safety profile, with 25% of patients having a grade 3/4 toxicity. There was one death related to ulcerative esophagitis. The phase III study of pembrolizumab, KEYNOTE-240, has failed to meet co-primary endpoints of overall survival or progression free survival as reported in a press release, and presentation of the full data set at an upcoming meeting is anxiously awaited. The FDA has not yet commented whether the failed Phase III study will result in removal of FDA approval of pembrolizumab for second line treatment of HCC.

Because of checkpoint inhibitors work in part by re-activating the immune system that has been deactivated to prevent autoimmunity and allergy, the main risk of these therapies is the induction of off-tumor inflammatory responses and development of autoimmune type reactions, termed immune-related adverse events (irAEs). While relatively rare compared to other cancer therapies, irAEs have been reported in nearly every organ system in the body, ranging from skin to brain and everything in between. The irAEs can occur as early as 1 day after the first dose and can even begin after treatment has been stopped. Many of these adverse events are treatable or reversible with immune suppression therapy such as steroids. However, some irAEs can result in irreversible tissue damage, such as occurs with development of endocrine gland inflammation causing insulin dependent diabetes, thyroid dysfunction, adrenal insufficiency, or hypophysitis. While relatively infrequent, there have been reports of multiple deaths related to immune related adverse events in patients receiving checkpoint inhibitors as cancer treatment. While the hepatologist may not be the primary prescriber for these drugs, it is critical that every provider involved in the care of these patients is familiar with the risks, presentations, and treatment of irAEs. Patients must also understand the inherent risks that these therapies present and realize that if they are in the minority of patients that do develop adverse events, that simply discontinuing the treatment may not result in resolution of their symptoms.

Hepatologists will be most often involved with treating immunotherapy-related hepatitis. Ir-hepatitis occurs in 2-10% of patients receiving PD-1/PD-L1 inhibitors, and in 5-12% of patients receiving CTLA-4 inhibitors. The combination of checkpoint inhibitors is associated with a higher rate of all irAEs, and ir-Hepatitis has been reported in 25-30% of patients receiving CTLA-4/PD-1 combinations. Onset can occur at any time, but most commonly occurs 6-12 weeks after initiation of therapy. The mainstay of therapy of immunotherapy-related hepatitis is prednisone. With mild elevations of liver enzymes (up to 250 U/L), patients should have their immunotherapy held and labs monitored every 3-5 days. If liver enzymes worsen, then prednisone should be started at doses of 1-2 mg/kg/d. If liver enzymes do not improve within 3 days, then mycophenolate mofetil should be added. An alternate or additional therapy that may be considered is tacrolimus 0.10-0.15 mg/kg/d. Steroid tapers should be over 4-8 weeks, with close lab monitoring to prevent recurrence of irAEs. Prophylaxis against fungal infections (ie. fluconazole), pneumocystis jirovecii pneumonia (ie. trimethoprim-sulfamethoxazole), and gastritis (PPIs) should be given to patients who require more than 20 mg of prednisone for longer than 4 weeks. The use of corticosteroids for treatment of irAEs has not been shown to reduce anti-tumor efficacy.

Immunotherapy re-challenge can be a difficult decision and must take into account the severity of the AE, the organ involved, and the patient’s tumor status. If immunotherapy is resumed, patients should be monitored closely for recurrence of the irAE. In patients who developed ir-hepatitis, grade 3 or 4 hepatitis warrants permanent discontinuation of immunotherapy.

Immunotherapies have been a major breakthrough in cancer therapy but can result in adverse events that are severe and different than those previously seen with cancer therapies. Early recognition and treatment of these adverse events is critical for to improve the clinical outcome without affecting the benefit of checkpoint inhibitor therapy.

References

1. El-Koueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M et al. Nivolumab in patients with advanced hepatocellular carcinoma (Checkmate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 2017 Jun 24;389(10088):2492-2502.
2. Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (Keynote-224): a non-randomized, open-label phase 2 trial. Lancet Oncol 2018 Jul;19(7):940-952.
3. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018 Jun 10;36(17):1714-1768.
4. National Comprehensive Cancer Network Guidelines Version 2.2019. Management of immunotherapy-related toxicities. www.nccn.org, accessed May 2019.
5. Wang DY, Salem JE, Cohen JV, Chandra S, Menzer C et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. JAMA Oncol 2018;4(12):1721-1728.
6. De Martin E, Michot JM, Papouin B, Champiat S, Mateus C et al. Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors. J Hepatol 2018 Jun;68(6):1181-1190.
7. Greten TF, Sangro B. Targets for immunotherapy of liver cancer. J Hepatol 2018 Jan;68(1):157-166.

Immunotherapies for HCC: What the Hepatologist Needs to Know

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Disclosures

Company	Relationship
Bayer	Speaker's Bureau, Consultant, Research Support
Bristol Meyers Squibb	Speaker's Bureau
Gilead	Speaker's Bureau, Consultant
Salix	Speaker's Bureau
Intercept	Speaker's Bureau, Consultant
Conatus	Consultant, Research Support
Abbvie	Speaker's Bureau
Eisai	Advisory Board
Exelixis	Speaker's Bureau, Consultant
Wako	Consultant
Genfit	Research Support

I will be discussing off-label use of immunosuppressants in the treatment of adverse events of immunotherapy

So what do hepatologists need to know about immunotherapies?

(it's more than just for HCC)

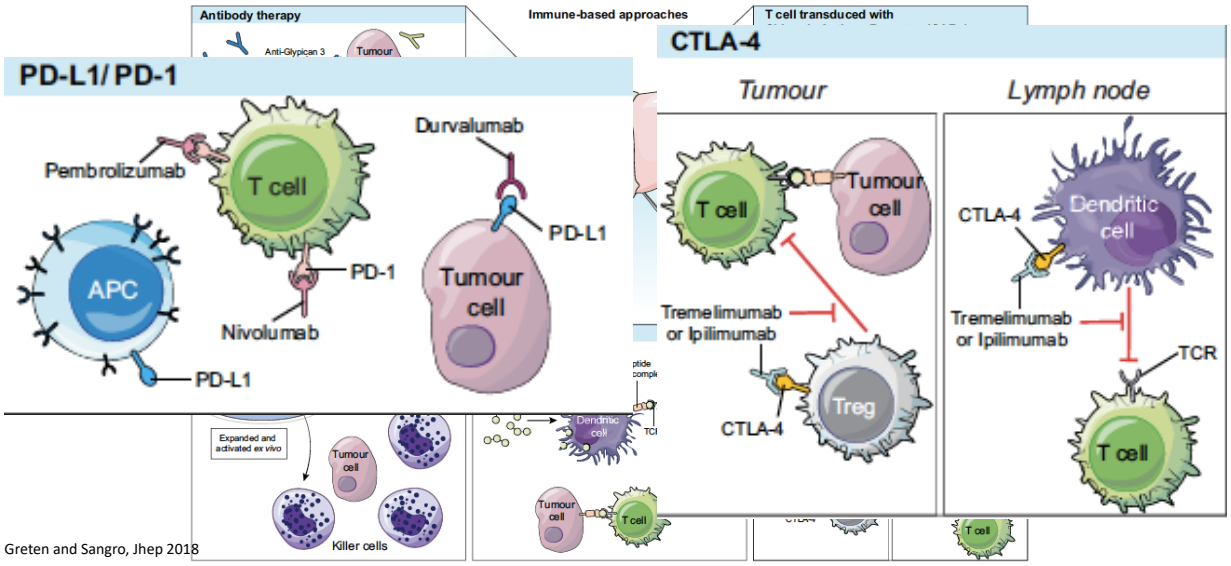
Agenda

- Mechanism of action
- Medications available and data
- Tumor types
- Immune Related Adverse Events (irAEs)
- Treatment of irAEs
- Special situation: the transplant recipient

What is PD-1?

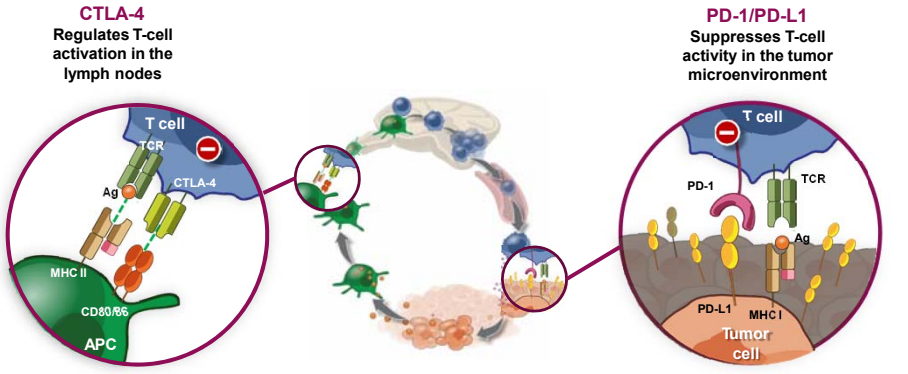
- PD-1: “Programmed Death-1”
- In the family of CD28 family of T cell receptors
- Expressed on activated T cells and other immune cells
- When activated, PD-1 switches off activated T cells and results in T cell “exhaustion”
  - Poor effector function, even in the presence of antigens
- PD-1 helps maintain self-tolerance and limits collateral damage to healthy cells
- Tumor cells can overexpress PD-1 ligands on their surface and can de-activate tumor infiltrating T cells

Immune-Based Approaches in HCC



Greten and Sangro, Jhep 2018

Immune Checkpoint Receptors Modulate T-Cell Immune Responses



CTLA-4 and PD-1/PD-L1 regulate T-cell immune responses at different levels and by different mechanisms[1]

Ag, antigen; CD, cluster of differentiation; TCR, T-cell receptor.
Boutros C, et al. *Nat Rev Clin Oncol*. 2016;13:473-486.

7

Immune Checkpoint Antibodies Approved by FDA

Table 1. Immune Checkpoint–Blocking Antibodies Approved by the Food and Drug Administration.*

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

Postow et al, NEJM 2018

Table 2. Ten Questions Relevant to the Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Blockade.

Questions about Immune-Related Adverse Events	Comments
Why do they occur?	The precise pathophysiology is unknown. Translational studies in patients with immune-related adverse events have shown that T-cell, antibody, and cytokine responses may be involved.
How are they generally treated?	No prospective trials have defined the best treatment approaches, and recommendations are based on consensus opinion. Immunosuppression is used to reduce the excessive state of temporary inflammation. Glucocorticoids are usually the first-line immunosuppressive agent. Additional immunosuppressive agents can be used if glucocorticoids are not initially effective.
When do they occur?	Immune-related adverse events usually start within the first few weeks to months after treatment but can occur anytime, even after treatment discontinuation. Dermatologic adverse events are usually the first to appear.
Why do they occur in some patients and not others?	The reason for the occurrence of immune-related adverse events only in certain patients is unknown. Some studies are investigating whether such factors as germline genetics and the composition of host microbiota are related to risk.
Are they associated with the efficacy of immune checkpoint blockade?	Conflicting data are available regarding whether the occurrence of immune-related adverse events is associated with improved treatment efficacy. The development of immune-related adverse events is not required for treatment benefit. Specific adverse events (e.g., vitiligo) may be more clearly associated with treatment efficacy.
Does immunosuppression to treat such adverse events reduce the antitumor efficacy of treatment?	Clinical outcomes are similar in patients who require immunosuppression to treat immune-related adverse events and in those who do not require such treatment. Beneficial responses can persist despite the use of immunosuppression to treat immune-related adverse events.
Are there unintended effects of immunosuppression to treat adverse events?	Side effects of glucocorticoid use (e.g., hyperglycemia, edema, anxiety, and iatrogenic adrenal insufficiency) can occur. Immunosuppression is a risk factor for subsequent opportunistic infections.
Is it safe to restart treatment after a major adverse event?	Retrospective studies have shown that immune-related adverse events associated with one class of agent (e.g., anti–CTLA-4) may not necessarily recur during subsequent treatment with another agent (e.g., anti–PD-1). The safety of retreatment probably depends on the severity of the initial immune-related adverse event.
Is it necessary to restart treatment after resolution of an adverse event?	Retrospective data suggest that patients who have had a favorable response to immune checkpoint blockade and then discontinue treatment because of immune-related adverse events generally maintain responses. Prospective data are needed to address whether restarting immunotherapy is necessary.
Is it safe to treat patients at potentially increased risk for such adverse events?	Patients at increased risk for immune-related adverse events (e.g., preexisting autoimmune disease) may still benefit from immune checkpoint blockade. Age alone should not be used to exclude patients from treatment, since benefit appears to be similar regardless of age.

Postow et al, NEJM 2018

Immunotherapy as Second Line Therapy

	Nivolumab	Pembrolizumab
Sample size	154 sorafenib-treated patients	104 sorafenib-treated patients
Patient features	2L or 3L Sorafenib-intolerants allowed Effective therapy for HBV+ve patients	2L Sorafenib-intolerants allowed Effective therapy for HBV+ve patients No involvement of portal vein trunk
Response rate	**14%** regardless of etiology or AFP levels	**17%** regardless of etiology or AFP levels
Duration of response	**16.6** months in HCV patients, not reached in other etiologies	≥6 months in 77%
mOS	**15.1** months (95% CI 13.2–18.8)	**12.9** months (95% CI 9.7-15.5)

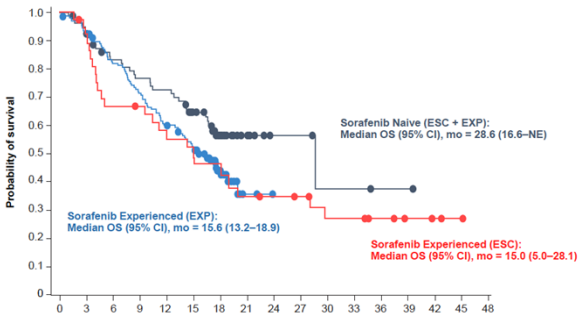
El-Khoueiry et al, Lancet 2017; Zhu et al, Lancet Oncol 2018

Both FDA approved based on Phase 2 non-controlled data

Nivolumab lead to durable responses and likely meaningful survival in Phase II

	SOR naïve	SOR experienced
Objective response Complete Partial	20% 1% 19%	15% 1% 14%
Stable disease	31%	38%
Progression	40%	37%

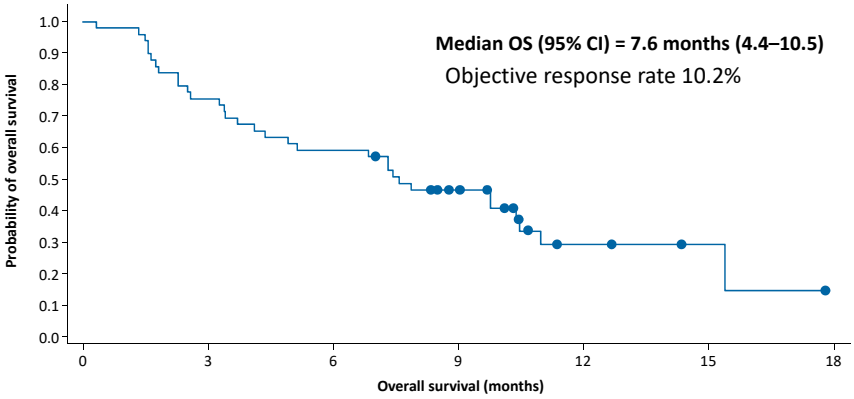
Median duration of response 16.6 months, with 55% having response > 12 months



Lack of predictive biomarker for response: No difference in response by tumor PDL1 expression. MSI high rare (<2%) in HCC

El-Khoueiry et al *Lancet* 2017

Nivolumab In Child's B Cirrhosis



Compared to ~4 months with sorafenib

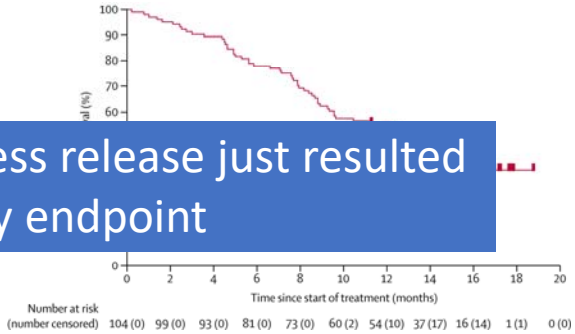
Compared to ~15 months with CTP A patients

Kudo et al. AASLD 2018

Pembrolizumab lead to durable responses and likely meaningful survival in Phase II

Best Response	Patients (n=104)
Objective response	17.3%
Complete	
Partial	
Stable disease	
Progression	32.7%

BUT: Phase 3 data press release just resulted that it missed primary endpoint



- Most common grade 3-4 TRAEs were increased AST (7%), increased ALT (4%), fatigue (4%)
- One death due to ulcerative esophagitis attributed to treatment

Zhu et al *ASCO* 2018

Treatment of irAEs

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

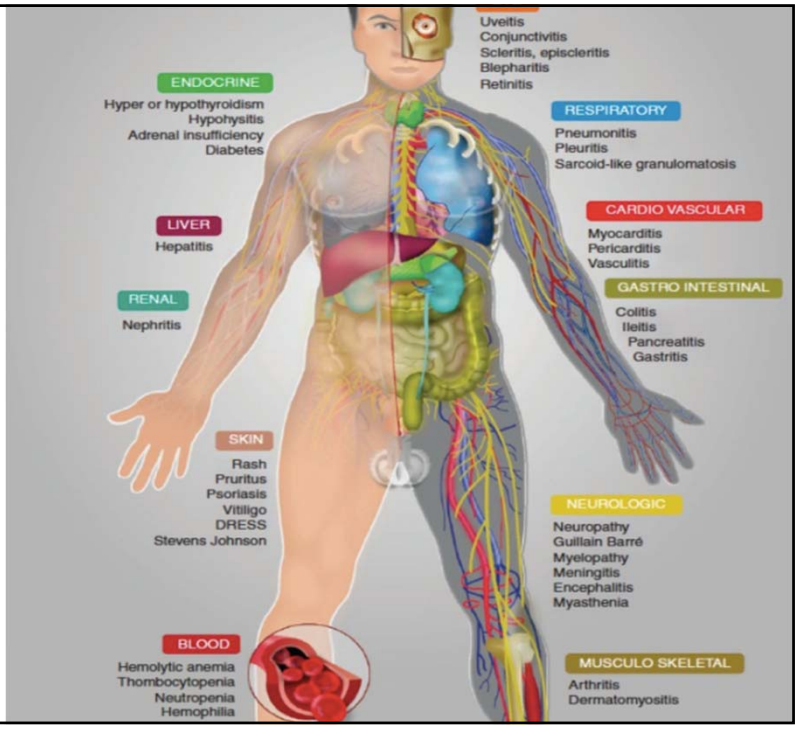
Julie R. Brahmer, Christina Lacchetti, Bryan J. Schneider, Michael B. Atkins, Kelly J. Brassil, Jeffrey M. Caterino, Ian Chau, Marc S. Ernstoff, Jennifer M. Gardner, Pamela Ginex, Sigrun Hallmeyer, Jennifer Holter Chakrabarty, Natasha B. Leighl, Jennifer S. Mammen, David F. McDermott, Aung Naing, Loretta J. Nastoupil, Tanyanika Phillips, Laura D. Porter, Igor Puzanov, Cristina A. Reichner, Bianca D. Santomasso, Carole Seigel, Alexander Spira, Maria E. Suarez-Almazor, Yinghong Wang, Jeffrey S. Weber, Jedd D. Wolchok, and John A. Thompson in collaboration with the National Comprehensive Cancer Network

JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Immunotherapy Side Effects

- Patients should be monitored closely during treatment for immune-mediated endocrinopathies and hepatitis
- Hormone replacement may be necessary
- Corticosteroids are the mainstay of therapy for immune related side effects
- Dose delay may be required in up to 1/3 of patients
- 11% discontinue therapy due to AEs
- Some fatal reactions have been reported

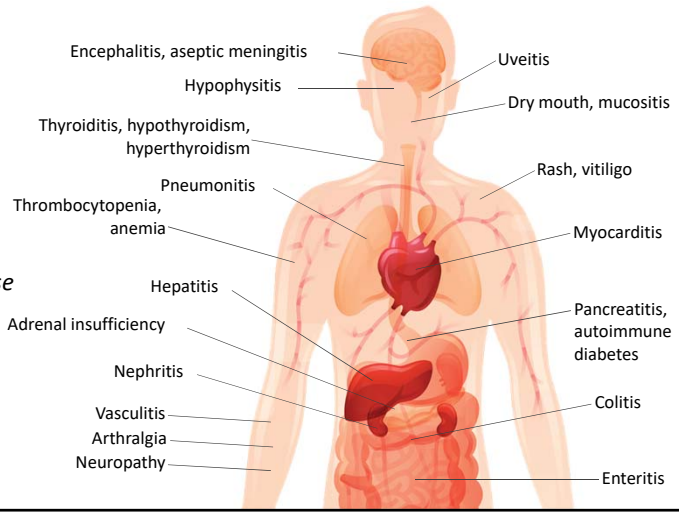
- irAEs can affect any organ system
- Greater rate of discontinuation among patients over age 65
- Discontinuation rates in other tumor types as high as 19%
- Can result in death in up to 5%



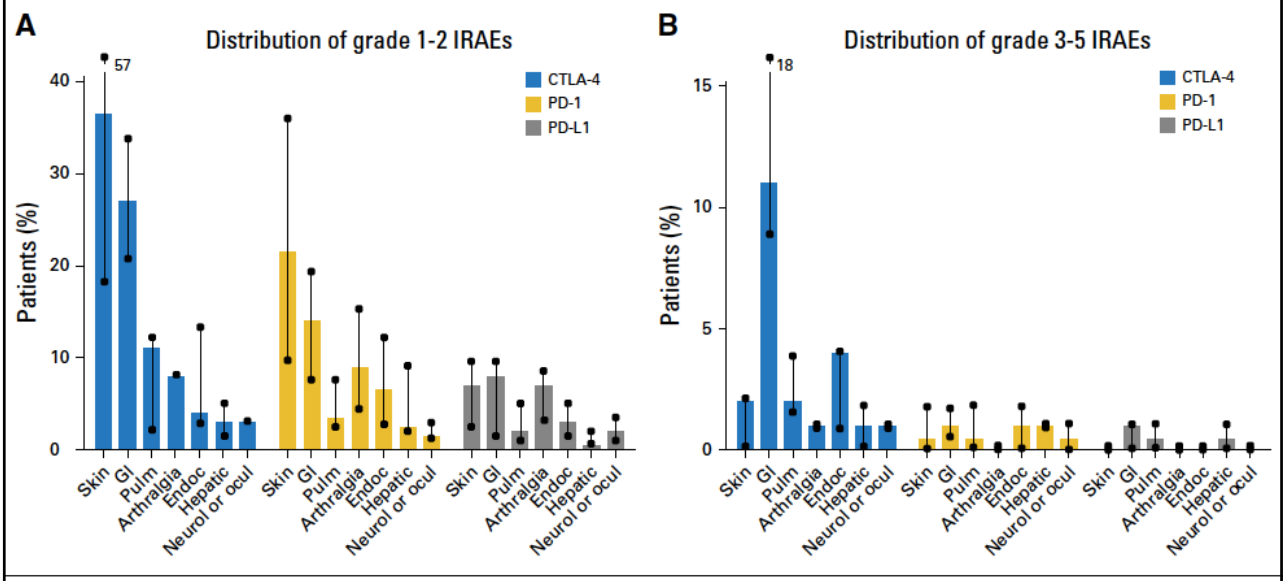
Immunotherapy AEs

"While it is known these agents can induce immune-mediated hepatic injury, their overall safety has not been fully elucidated in the setting ***of chronic liver disease****."*

"Significant ***hepatic injury and death have been reported****, especially in the setting of liver transplants. The results from larger studies assessing efficacy and safety of these medications in the setting of liver disease are eagerly awaited."*



1. Chascsa DM et al. *Curr Hepatol Rep*. 2018;17:153-155.
2. Postow MA et al. *NEJM*. 2018;378(2):158-168.

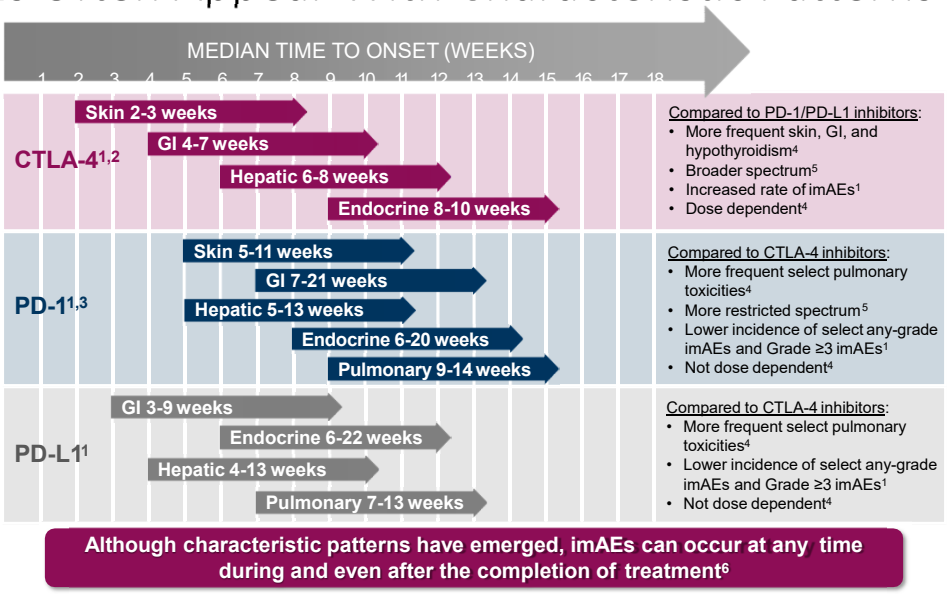


Comparison of irAEs between PD-1/PD-L1 and CTLA-4

Immune-related toxicities	PD-1/PD-L1 inhibitors Relative Risk (95% CI)	CTLA-4 inhibitors Relative Risk (95% CI)	*P*
All- grade			
Colitis	3.36 (1.36–8.33)	11.3 (6.05–21.1)	0.054
AST	1.71 (1.01–2.89)	1.92 (0.94–3.93)	0.745
Rash	1.59 (0.90–2.82)	3.94 (3.02–5.14)	**0.006**
Hypothyroidism	8.05 (4.26–15.2)	4.64 (1.42–15.2)	0.352
Pneumonitis	3.8 5(1.23–12.1)	11.1 (0.62–199.8)	0.562
High-grade			
Colitis	2.47 (0.90–6.72)	22.5 (6.37–79.4)	**0.021**
AST	1.26 (0.38–4.16)	5.06 (1.26–20.3)	0.168
Rash	0.91 (0.40–2.10)	3.55 (1.37–9.19)	0.052
Hypothyroidism	0.85 (0.25–2.84)	2.02 (0.39–10.5)	0.421
Pneumonitis	1.49 (0.80–2.79)	3.02 (0.12–74.0)	0.798

De Velasco et al, Cancer Immunol Res 2017

irAEs Often Appear With Characteristic Patterns



1. Davies M, and Duffield EA. *Immunotargets Ther*. 2017;6:51-71. 2. Weber JS, et al. *J Clin Oncol*. 2012;30:2691-2697. 3. Weber JS, et al. *J Clin Oncol*. 2017;35:785-792. 4. Kumar V, et al. *Front Pharmacol*. 2017;8:49. 5. Boutros C, et al. *Nat Rev Clin Oncol*. 2016;13:473-486. 6. Marrone KA, et al. *Clin Pharmacol Ther*. 2016;100:242-251.

The NCI CTCAE Provides Descriptions Used for Adverse Event Reporting

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]	Life-threatening consequences; urgent intervention indicated	Death related to AE

- CTCAE Version 5.0 can be accessed online ***https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50***

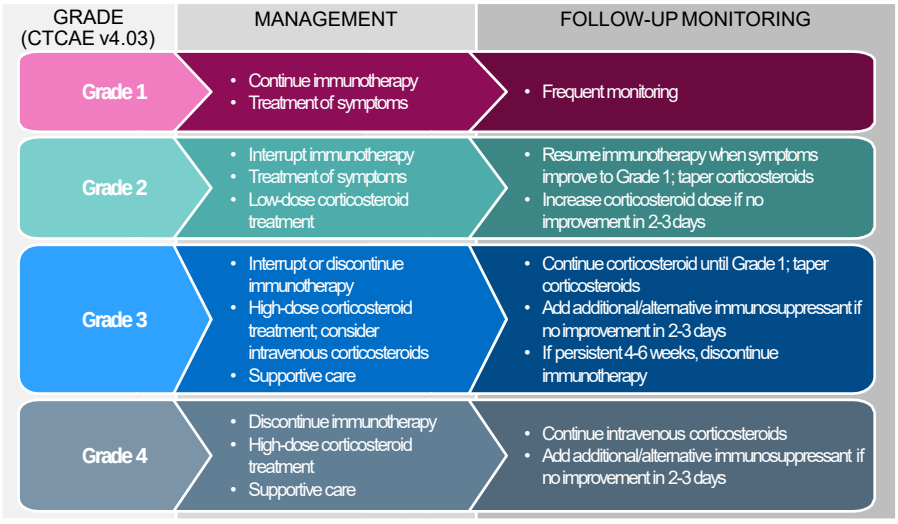
[a]Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. [b]Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

ADL, activities of daily living; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

CTCAE. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Accessed February 27, 2018.

General Principles Guide Management of irAEs

Excluding skin or endocrine toxicities



General principles on the management of irAEs are presented. Consult with the applicable product label for specific recommendations.

1. Haanen JBAG, et al. *Ann Oncol*. 2017;28(suppl_4):iv119-142. 2. Puzanov I, et al. *J Immunother Cancer*. 2017;5(1):95.
3. Brahmer JR, et al. *J Clin Oncol*. 2018; Feb 14:JCO2017776385(epub).

Importance of Steroid Tapering

Once an irAE has resolved to grade 1 per clinical assessment, steroids should be tapered slowly

- **Tapering gives the adrenal glands time to resume their normal function**
- **Abruptly stopping or tapering too quickly may result in a flare of the irAE**

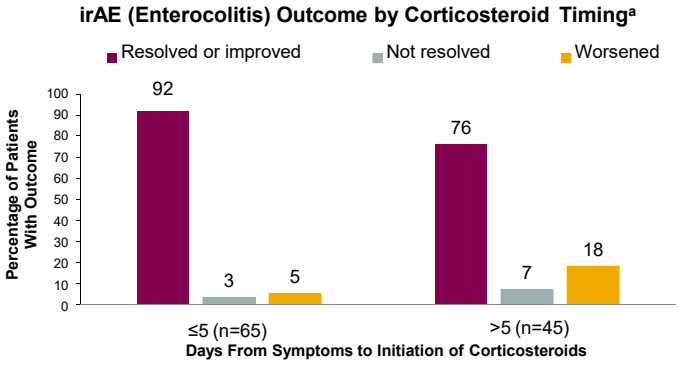
Taper duration depends on the dose and duration of use and other medical considerations

- **In general, steroids should be tapered over at least 4 weeks in grade 3 or 4 toxicities**
  - **In one study, following steroid treatment of immune-mediated hepatitis, once grade 1 hepatotoxicity was reached, steroids were tapered by 10% every 3 to 5 days**

Patients should be monitored weekly during steroid tapering

1. Davies M, et al. *ImmunoTargets Ther*. 2017;6:51-71. 2. Mayo Clinic. Accessed October 31, 2017. 3. Fay AP, et al. *Exp Rev Qual Life Cancer Care*. 2016;1:89-97. 4. Brahmer JR, et al. *J Clin Oncol*. 2018; Feb 14:JCO2017776385 (epub). 5. Huffman BM, et al. *Am J Clin Oncol*. 2017.

Treating irAEs Quickly Is Critical

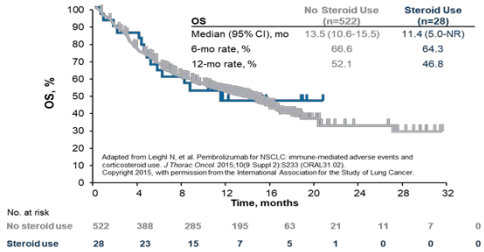


- Prompt corticosteroid treatment is associated with a **lower rate of irAE worsening** vs delayed treatment

[a]Pooled phase II data for diarrhea/colitis during treatment with anti–CTLA-4 (10 mg/kg ipilimumab; N=325; post-hoc analysis). O'Day S, et al. Presented at: ASCO 2011.

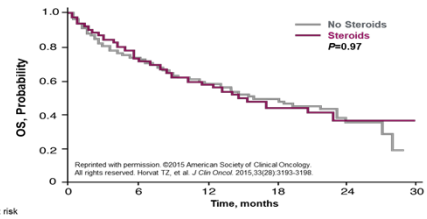
Treatment of irAEs With Systemic Corticosteroids Does Not Appear to Affect Outcomes

Analysis conducted in patients enrolled in KEYNOTE-001 with locally advanced or metastatic NSCLC treated with anti-PD-1 therapy[1,2]



No. at risk									
No steroid use	522	388	285	195	63	21	11	7	0
Steroid use	28	23	15	7	5	1	0	0	0

Retrospective analysis of adult patients with melanoma treated with a checkpoint-blocking antibody (anti-CTLA-4) at a single cancer center[3]



No. at risk						
No steroid use	182	117	71	42	13	1
Steroid use	80	50	31	17	6	1

- These data suggest that the use of systemic corticosteroids does not affect overall survival in patients with NSCLC or melanoma

CI, confidence interval; NR, not reached; OS, overall survival.

1. Garon EB, et al. *N Engl J Med.* 2015;372(21):2018-2028. 2. Leighl N, et al. *J Thorac Oncol.* 2015;10(9 Suppl 2):S233 (ORAL31.02). 3. Horvat TZ, et al. *J Clin Oncol*. 2015;33(28):3193-3198.

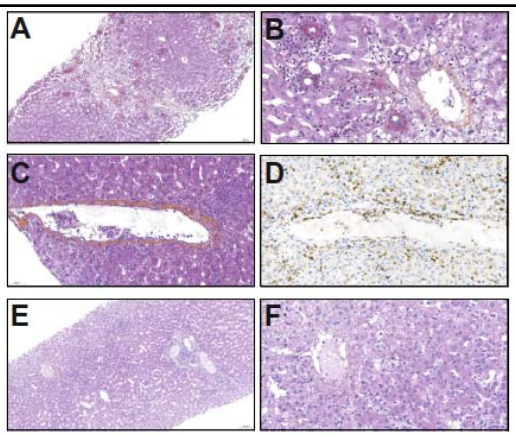


Fig. 2. Histological patterns in patients treated with anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) *vs.* anti-programmed cell death 1 (PD1) monoclonal antibodies (mAbs). (A and B) First liver biopsy of Patient 5 (who received anti-CTLA4 mAbs). (A) Centrilobular confluent necrosis with fibrin ring granulomas [haematoxylin-eosin-saffron (HES) ×100]. (B) Fibrin ring granuloma and sinusoidal inflammatory infiltrates comprising activated lymphocytes and histiocytes, without plasma cell (HES ×300). (C and D) Liver biopsy of Patient 2 (who received anti-CTLA4 mAbs). (C) Endotheliitis of a centrilobular vein with perivenular and subendothelial infiltration by lymphocytes and histiocytes and focal disruption of the endothelium (HES ×40). (D) Perivenular and subendothelial lymphocytes are CD8+ cytotoxic T lymphocytes (immunohistochemistry CD8 ×40). (E and F) Liver biopsy of Patient 8 (who received anti-PD1 mAbs). (E) Active hepatitis with mild periportal and moderate lobular activity (HES ×100). (F) Lobular lymphocytes and histiocytes without plasma cells (HES ×300).

De Martin et al, Jhep 2018

Immunotherapy Related Hepatitis

- Reported in 2-10% of patients receiving monotherapy with nivolumab, pembrolizumab, and ipilimumab
- Combination treatment with ipilimumab and nivolumab worse
  - 25-30% all grade hepatotoxicity
  - 15% incidence grade 3 toxicity
- Generally develops 6-12 weeks after initiation
- Treatment mainstay is prednisone, with mycophenolate mofetil if needed
- Infliximab not recommended (concurrent hepatitis risk)
  - Difficult to treat patients with concurrent hepatitis and colitis

Immunotherapy Related Hepatitis

- Liver tests should be checked prior to each infusion
- For grade 1 abnormality (AST/ALT 1-3xULN and/or Bili 1-1.5x ULN):
  - Do not treat
  - Monitor weekly
- For an liver enzymes higher than grade 1
  1. Rule out all other causes of elevated liver tests (tumor infiltration, viral hepatitis, portal vein or hepatic vein thrombosis, drug, alcohol)
  2. Hold IO until < Grade 1 abnormality or on prednisone <10 mg/d

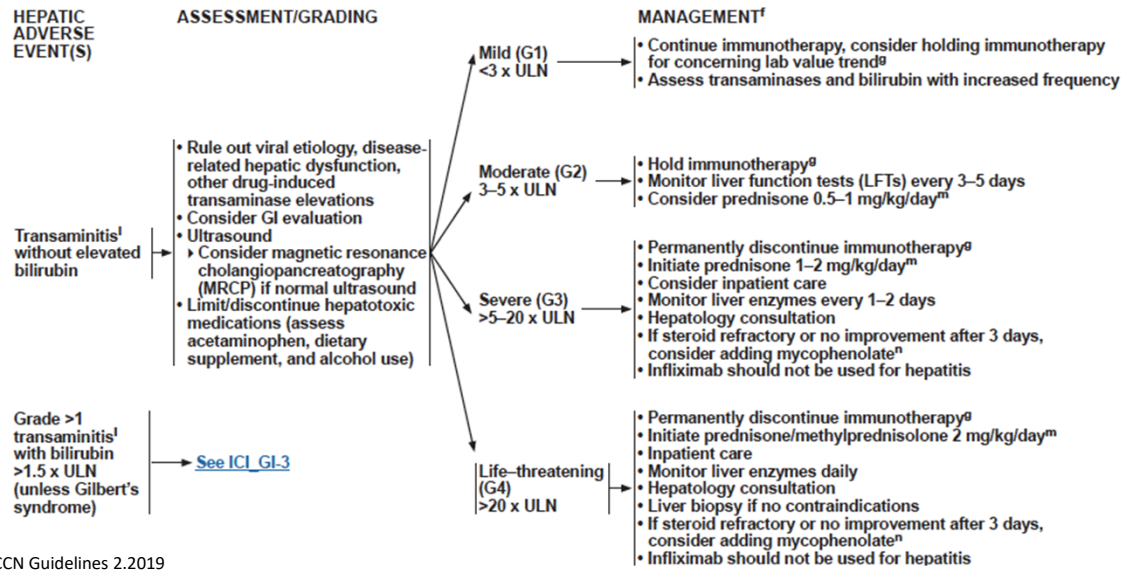
Brahmer et al, J Clin Oncol 2018

Grading Immunotherapy Hepatitis

	AST/ALT	Total Bilirubin	Actual Numbers AST/ALT	Actual Number Total Bilirubin
Grade 1 asymptomatic	> ULN - 3x ULN	> ULN – 1.5x ULN	50-150 U/L	1.3-2 mg/dL
Grade 2 asymptomatic	>3x - ≤5x ULN	>1.5x - ≤3x ULN	150-250 U/L	2-4 mg/dL
Grade 3 symptomatic fibrosis by biopsy cirrhosis reactivation of chronic hepatitis	5-20x ULN	3-10x ULN	250-1000 U/L	4-13 mg/dL
Grade 4 decompensated liver function (ascites, encephalopathy, coagulopathy)	>20x ULN	>10x ULN	>1000 U/L	>13 mg/dL

Brahmer et al, J Clin Oncol 2018

NCCN guidelines 2.2019



NCCN Guidelines 2.2019

Principles of Immunosuppression

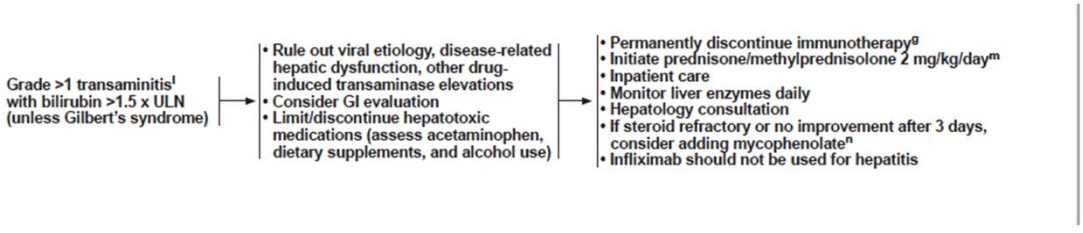
PRINCIPLES OF IMMUNOSUPPRESSION

- These immunosuppression recommendations are for patients receiving immune checkpoint inhibitor immunotherapy.
- Close consultation with disease-specific subspecialties is encouraged.
  - Referral to a tertiary care center may be required for management of complex cases or multi-system irAEs.
- Corticosteroids are the mainstay of treatment of most irAEs related to immunotherapy.
  - Early intervention with corticosteroids is a key goal in general management of immune-related toxicity.
  - Use of corticosteroids to treat irAEs has NOT been shown to reduce anti-tumor efficacy.
    - In the absence of specific indications such as prior infusion reaction or concurrent chemotherapy, routine premedication with corticosteroids is not recommended given the potential mitigation of immunotherapeutic effectiveness in the prophylactic setting.
  - Longer steroid tapers (>4 weeks, sometimes 6–8 weeks or longer) may be required to prevent recurrent irAE events, particularly pneumonitis and hepatitis.
  - See individual toxicity pages for specific recommendations on steroid dose by grade. Where immunotherapy rechallenge is indicated, see the Principles of Immunotherapy Rechallenge (IMMUNO-C) for guidance by organ site.
  - Prophylaxis against pneumocystis jiroveci pneumonia (PJP) can be considered in patients receiving a prednisone equivalent of 20 mg or more daily for 4 or more weeks.
  - Prophylaxis against fungal infections (eg, fluconazole) can be considered in patients receiving a prednisone equivalent of 20 mg or more daily for 6–8 or more weeks.
  - Prophylaxis against herpes zoster reactivation can be considered.
  - Proton pump inhibitor therapy or H2 blockers can be considered for patients at higher risk of gastritis (eg, NSAID use, anticoagulation) for the duration of corticosteroid therapy.
  - Higher potency (eg, Class 2 or 3) topical corticosteroids are preferred for short-term use for immune-related dermatitis, compared to longer term use of lower potency steroids.
  - For neurologic, cardiac, or grade 3 or 4 irAEs, higher dose steroids (eg, methylprednisolone or prednisone 1–2 mg/kg/day) should be given.
  - If patients need to be on long-term steroids, they are at risk for developing osteoporosis. Vitamin D and calcium supplementation should be provided to prevent osteoporosis.
- Selected irAEs including hypothyroidism and other endocrine irAEs may be treated with hormonal supplementation, without the need for corticosteroid therapy. See Endocrine Toxicities section.

Liver	• Transaminitis without elevated bilirubin: following a grade 2 irAE, consider resumption of immunotherapy after ALT/AST return to baseline and steroids, if used, have been tapered to ≤10 mg prednisone equivalent daily. • Permanent discontinuation is warranted in the setting of severe or life-threatening (grade 3–4) hepatitis.

NCCN Guidelines 2.2019

Immunotherapy Related Hepatitis with Jaundice



NCCN Guidelines 2.2019

Encephalitis

7.6 Encephalitis

Definition: As for aseptic meningitis, need to exclude infectious causes, especially viral (ie, HSV).
Confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, speech abnormality

Diagnostic work-up
- Neurologic consultation
- MRI of brain with or without contrast may reveal T2/fluid-attenuated inversion recovery changes typical of what is seen in autoimmune encephalopathies or limbic encephalitis or may be normal
- Lumbar puncture: check cell count and protein glucose and perform Gram stain, culture, PCR for HSV and other viral PCRs depending on suspicion, cytology, oligoclonal bands, autoimmune encephalopathy, and paraneoplastic panels.
- May see elevated WBC count with lymphocytic predominance and/or elevated protein
- EEG to evaluate for subclinical seizures
- Blood: metabolic, CBC, ESR, CRP, ANCA (if suspect vasculitic process), thyroid panel including TPO and thyroglobulin
- Rule out concurrent anemia/thrombocytopenia, which can present with severe headaches and confusion

Grading	Management
G1: Mild, no interference with function and symptoms not concerning to patient. Note: Any cranial nerve problem should be managed as moderate. G2: Moderate, some interference with ADL, symptoms concerning to patient (ie, pain but no weakness or gait limitation) G3-4: Severe, limiting self-care and aids warranted	Hold ICPi and discuss resumption with patient only after taking into account the risks and benefits As above for aseptic meningitis, suggest concurrent IV acyclovir until PCR results obtained and negative Trial of methylprednisolone 1-2 mg/kg If severe or progressing symptoms or oligoclonal bands present, consider pulse corticosteroids methylprednisolone 1 g IV daily for 3-5 days plus IVIG 2 g/kg over 5 days If positive for autoimmune encephalopathy antibody and limited or no improvement, consider rituximab or plasmapheresis in consultation with neurology

7.7 Transverse myelitis

NCCN Guidelines 2.2019

Hepatitis B and IOs

- Several case reports of hepatitis B reactivation in patient receiving PD-1/PD-L1 or CTLA-4 blockade
  - All HBsAg positive DNA negative
  - Nivo, pembro, ipi+nivo
- Unclear if patients should be screened and/or prophylactically placed on antivirals for IO therapy
- Don't forget to check when working a patient up with liver enzyme flares on IOs

Pandey et al, Case Reports in Oncol Med 2018, Lake et al, AIDS 2017, Koksal et al, Ann Oncol 2017

Fatal Toxicities of Immunotherapies

- 613 fatal toxicities reported 2009-2018
- CTLA-4 related:
  - most commonly colitis (70%)
  - Median 14.5 days after initiation
- PD-1/PD-L1 related:
  - pneumonitis (35%), hepatitis (22%), neurotoxic (15%)
  - Median 40 days after initiation
- Combination CTLA-4/PD-1:
  - colitis (37%), myocarditis (25%)
  - Median 40 days after initiation
- Overall 0.6% fatality rate related to IO therapy

Wang et al, JAMA Oncol 2018

Fatal Toxicities of Immunotherapies

613 fatal toxicities reported 2009-2018 in WHO Pharmacovigilance Database

Type of IO	Most Common Fatal AE	Median Time to Onset	Toxicity-Related Fatal Events (overall 0.6%)
CTLA-4	Colitis 135 (70%)	14.5 days	1.08%
PD-1/PD-L1	Pneumonitis 333 (35%) Hepatitis 115 (22%) Neurotoxic 50 (15%)	40 days	0.36% (PD-1) 0.38% (PD-L1)
CTLA-4 + PD-1	Colitis 32 (37%) Myocarditis 22 (25%)	40 days	1.23%

CTLA-4: ipilimumab or tremelimumab
PD-1: nivolumab, pembrolizumab
PD-L1: atezolizumab, avelumab, durvalumab

Wang et al, JAMA Oncol 2018

IO Therapy in Patients with Underlying Autoimmune Disorders

- Limited data available; Retrospective reviews only
- 38% of patients with various autoimmune disorders had flares requiring steroids
  - RA, PMR, Sjogren's, psoriasis, TTP
  - No reports of flares in patients with GI or Neurologic autoimmune disorders

IO Therapy in Patients with Prior Organ Transplant

- Multiple case reports in literature of using immunotherapy after solid organ transplant
- Overall graft rejection rate 25-54%
- Median time to graft rejection 8-19 days after initiation of IO
- Response rates in transplant patients much lower than seen in non-transplant patients
- No clear association between time from transplant and risk of rejection and graft loss

Immunotherapy and Transplant Patients

Table 3 Summary of literature results and study cohort results

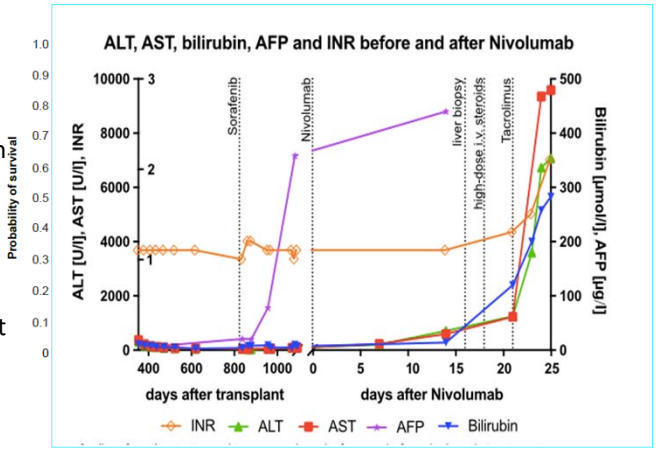
Variables	Liver transplant (literature)	Renal & heart transplant (literature)	PD-1 inhibitors (literature)	CTLA-4 inhibitors (literature)	PD-1 & CTLA-4 inhibitor (literature)	All literature results	Study cohort (liver transplant)	Overall (all results)
Rate of graft rejection	25% (n=12)	43.8% (n=16)	33.3% (n=15)	25% (n=8)	40% (n=5)	32.1% (n=28)	28.6% (n=7)	31.4% (n=35)
Median time to graft rejection (days)	13 (n=2)	8 (n=5)	13.5 (n=6)	–	8 (n=1)	8 (n=7)	24 (n=2)	19 (n=9)
Response rate	33% (n=10)	55.6% (n=9)	66.7% (n=9)	28.6% (n=7)	33.3% (n=3)	47.4% (n=19)	25% (n=4)	43.4% (n=23)
Median PFS (months)	3.8 (n=10)	8 (n=11)	8 (n=11)	5 (n=7)	8 (n=3)	7 (n=21)	1.8 (n=4)	6 (n=25)
Median time to transplant (years)	6 (n=11)	11 (n=15)	9 (n=14)	8 (n=8)	11 (n=4)	8 (n=26)	3 (n=7)	8 (n=33)

PFS, progression free survival; PD-1, programmed death protein-1; CTLA-4, cytotoxic T-lymphocyte-associated protein-4.

DeLeon et al, J Gastrointestin Oncol 2018

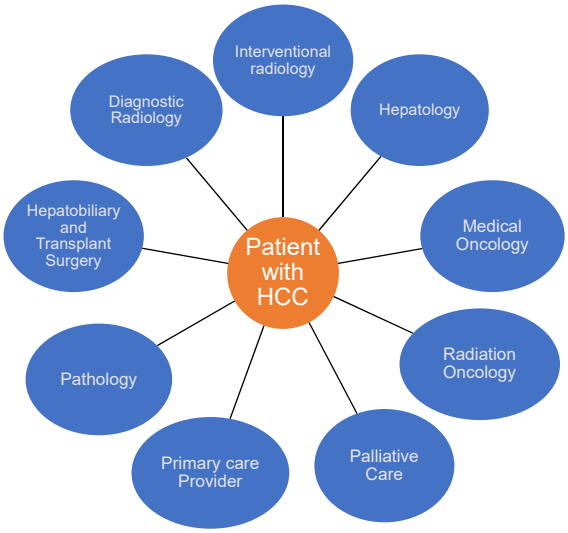
Caution with PD1 inhibitors in pre- and post-OLT patients

- Recurrent HCC 2 yrs. Post OLT
- Disease progression with Sorafenib
- 1 dose Nivolumab
  - 1 wk. later rapid progressive liver dysfunction
  - Liver bx: severe ACR, no response to steroids
  - Pt. died 35 days after Nivolumab
- *Review of literature*
  - 29 cases of solid organ treated w/ checkpoint inhibitor
  - **Graft loss 36% in OLT**



Gassman D et al. Transplantation Direct 2018

Multidisciplinary Management Is Important from Many Specialties



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The Changing Landscape of HCC Management

HCC Surveillance

Surveillance for HCC is recommended in the AASLD guidelines from 2018 in two main groups: 1) patients with chronic HBV with or without cirrhosis 2) cirrhosis of any etiology. For Hepatitis B carriers, HCC surveillance is suggested over age 40 for men and 50 for women. Current recommendations suggest ultrasound every 6 months with or without alpha fetoprotein.

HCC Diagnostic Evaluation

The cornerstone of HCC diagnosis is with cross sectional, multiphase imaging, either with CT or MRI. The choice of between CT or MRI should be based on center expertise. Most patients with HCC should not need to have a liver biopsy as imaging criteria outlined in the LI-RADS: Liver Imaging Reporting and Data System (LI-RADs) establish the imaging diagnosis of HCC. Selected patients with indeterminate lesions may be offered liver biopsy, but this is rare.

One important difference in the LI-RADs system and the Organ Procurement Transplant Network (OPTN) criteria for HCC is that lesions between 10-19mm with arterial enhancement and washout are LR5 lesions but would not qualify as HCC for consideration of liver transplantation. These nuances in the current diagnostic criteria for HCC are best addressed in the auspices of a multidisciplinary liver tumor board.

What is Changing in the HCC MELD Exception Policy for Liver Transplantation HCC?

- Median MELD at transplant (MMaT) will be calculated in a 250nm radius around each transplant center
- After an initial waiting period of being listed at biologic MELD for 6 months, the HCC MELD exception value will go to the MMaT minus 3.
- There is no elevator after the MMaT minus 3.
- For example, median MELD is 31, MMaT minus 3= 28.

References

1. Marrero JA et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases, Hepatology, 2018;68(2):723-750
2. https://optn.transplant.hrsa.gov/media/2799/201901_nlrb_faq_professional.pdf

The Changing Landscape of HCC Management

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Associate Professor
Oregon Health and Science University
VA Portland Health Care System
AASLD Clinical Hepatology Update
June 14, 2019

Clinical case

- 67yo male with recent diagnosis of NASH cirrhosis, comes to see you in clinic to establish care for advanced liver disease.
- Patient has a multiphase CT as part of his initial evaluation, and is found to have a 1.8cm in seg 8 with arterial hyperenhancement and washout.
- Labs: Tbili 1.1, Cr. 1.2, AFP 5, PLT 98
- What are your next steps?

PRACTICE GUIDANCE | HEPATOLOGY, VOL. 68, NO. 2, 2018

Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases

Jorge A. Marrero,[1] Laura M. Kulik,[2] Claude B. Sirlin,[3] Andrew X. Zhu,[4] Richard S. Finn,[5] Michael M. Abecassis,[2] Lewis R. Roberts,[6] and Julie K. Heimbach[6]

TABLE 1. PATIENTS AT THE HIGHEST RISK FOR HCC

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

Abbreviation: LYG, life-years gained.

Marrero JA et al. AALSD Practice Guideline HCC 2018

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Abbreviation: LYG, life-years gained.

Marrero JA et al. AALSD Practice Guideline HCC 2018

AASLD Guidelines for HCC Surveillance

- Ultrasound **<u>with or without AFP</u>**, every 6 months
- Do not perform surveillance in Child's class C cirrhosis unless they are on the transplant waiting list, given the low anticipated survival for patients with Child's C cirrhosis
- Consider comorbidities precluding diagnosis, surveillance, or treatment (renal failure)

Marrero JA et al. AALSD Practice Guideline HCC 2018

AASLD HCC surveillance guidelines regarding HCV after DAA therapy

Guidance Statements

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

Marrero JA et al. AALSD Practice Guideline HCC 2018

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

CT/MRI Diagnostic Table

Arterial phase hyperenhancement (APHE)		No APHE		Nonrim APHE		
Observation size (mm)		< 20	≥ 20	< 10	10-19	≥ 20
Count additional major features: • Enhancing "capsule" • Nonperipheral "washout" • Threshold growth	None	LR-3	LR-3	LR-3	LR-3	LR-4
	One	LR-3	LR-4	LR-4	LR-4 / LR-5	LR-5
	≥ Two	LR-4	LR-4	LR-4	LR-5	LR-5

LR-4 / LR-5

Observations in this cell are categorized based on one additional major feature:
- LR-4 – if enhancing "capsule"
- LR-5 – if nonperipheral "washout" **OR** threshold growth

LIRADS vs. OPTN

TABLE 2. LI-RADS 5 CRITERIA

Size	Criteria	Comments
≥20 mm	APHE (nonrim) **AND** one or more of following: • "Washout" (nonperipheral) • Enhancing "capsule" • Threshold growth	Equivalent to OPTN 5B or 5X
10-19 m	APHE (nonrim) **AND** the following: • "Washout" (nonperipheral) • Enhancing "capsule" • Threshold growth	Equivalent to OPTN 5A
	APHE (nonrim) **AND** "Washout" (nonperipheral)	Equivalent to 2010 AASLD criteria
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Marrero JA et al. AALSD Practice Guideline HCC 2018

LIRADS vs. OPTN

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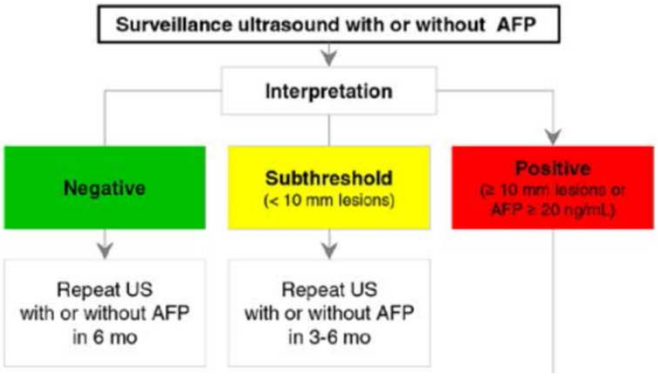
Marrero JA et al. AALSD Practice Guideline HCC 2018

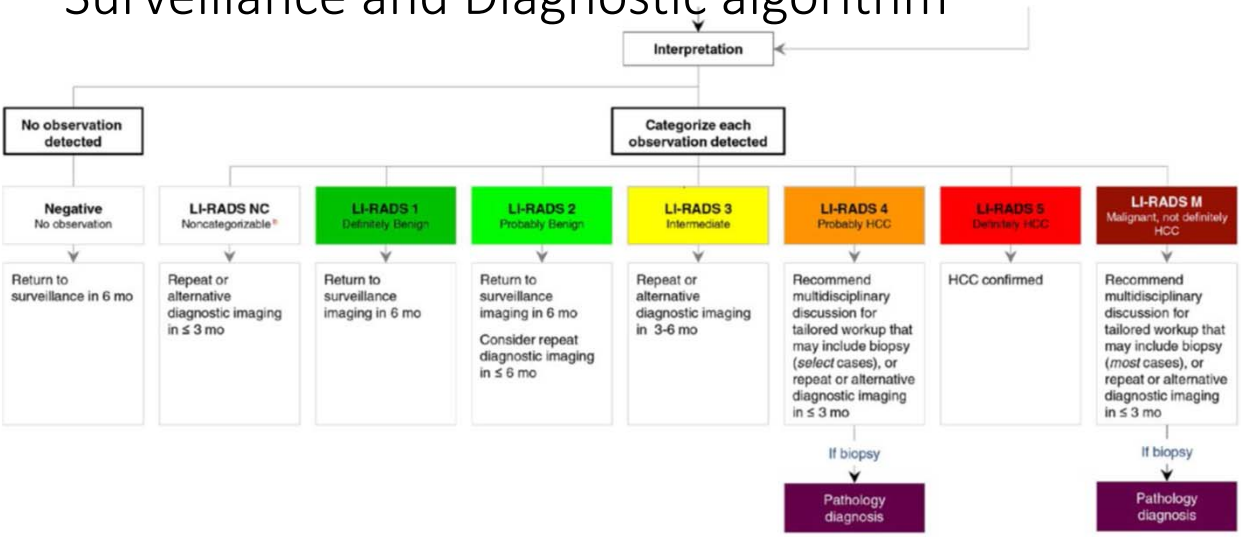
AASLD Guidelines: Surveillance and Diagnostic algorithm



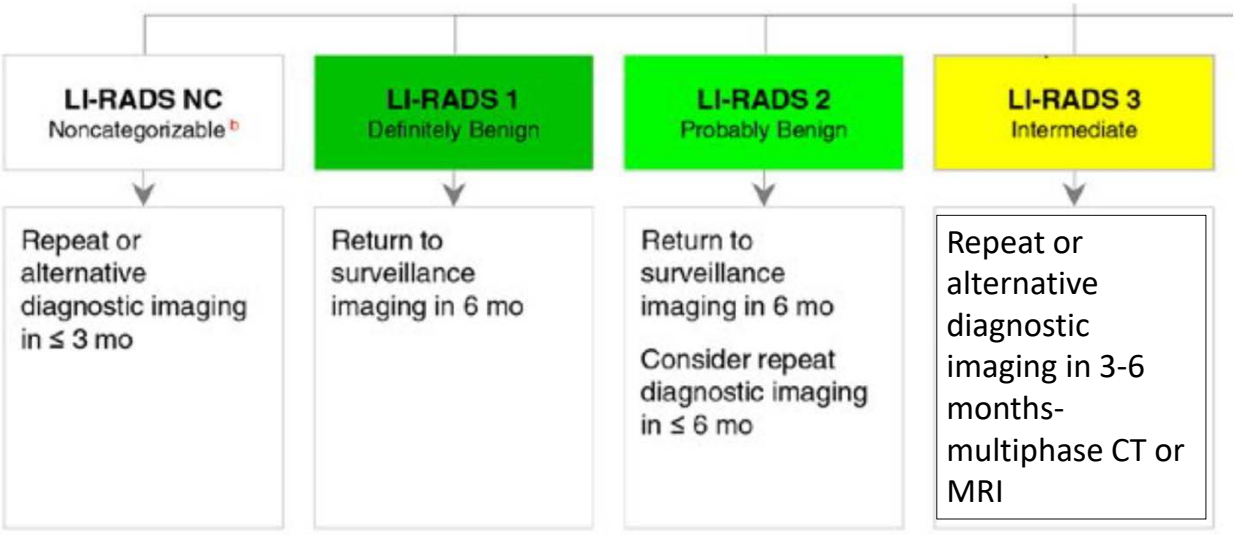
*Some high-risk patients may undergo multiphase CT or MRI for HCC surveillance (depending on patient body habitus, visibility of liver at ultrasound, being on the transplant waiting list or other factors)

Marrero JA et al. AALSD Practice Guideline HCC 2018

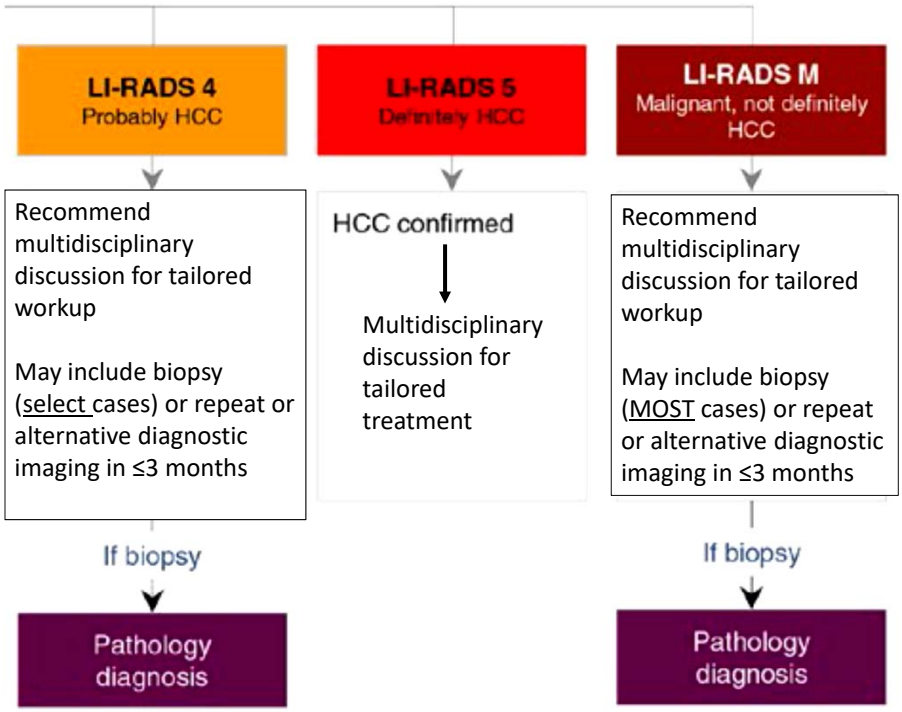
AASLD Guidelines: Surveillance and Diagnostic algorithm



Marrero JA et al. AALSD Practice Guideline HCC 2018

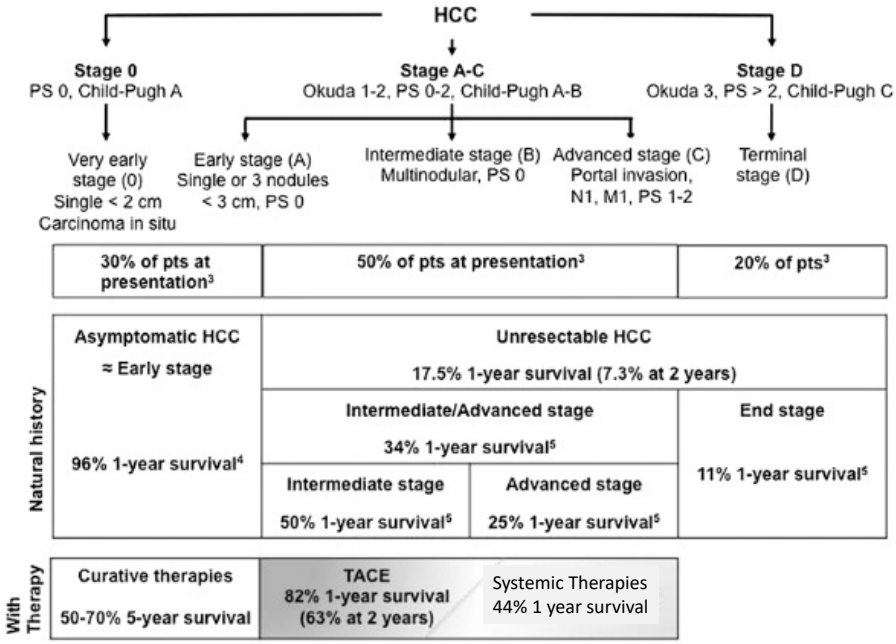


Marrero JA et al. AALSD Practice Guideline HCC 2018



Marrero JA et al. AALSD Practice Guideline HCC 2018

BCLC Staging:



Bolondi L et al. Semin Liver Dis 2012

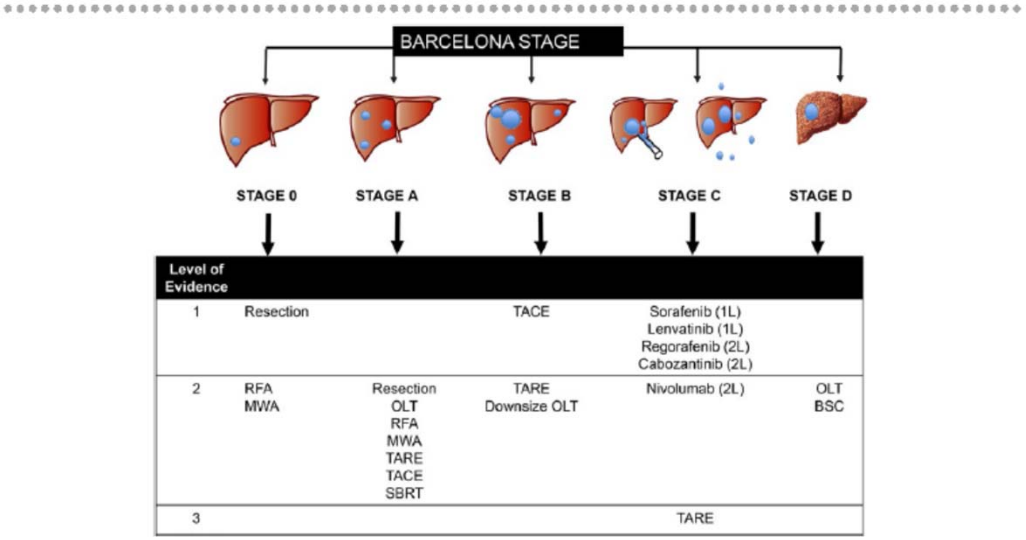


FIG. 3. Treatment recommendations according to BCLC Stage. Abbreviations: MWA, microwave ablation; BSC, best supportive care; 1L, first-line therapy; 2L, second-line therapy.

Marrero JA et al. AALSD Practice Guideline HCC 2018

HCC MELD Exception Points

MELD Exception for HCC 2002

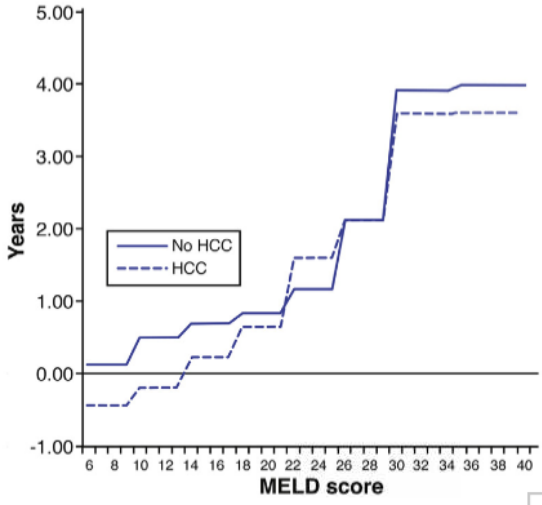
- T1 MELD 24
- T2 MELD 29

Current (Immediately past)

MELD Exception Elevator

- T1- no extra points
- T2
  - Wait 6 months at biologic MELD
  - At 6 months, MELD 28
  - Elevator increases every 3 months with maximum of 34

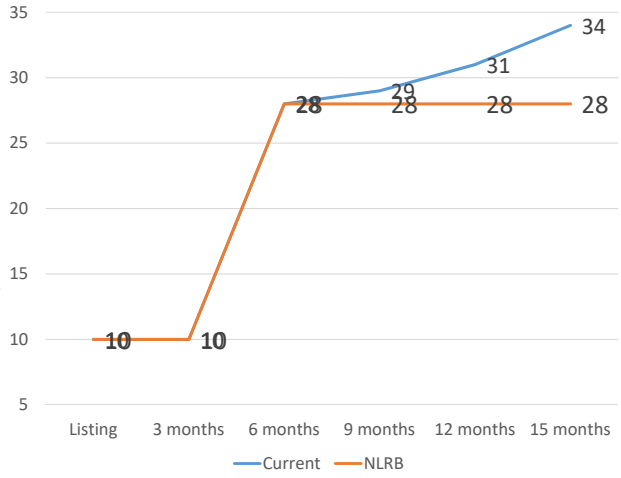
When is the ideal time for LT in HCC?



Berry K, Ioannou GN Gastroenterology 2015;149:669-680

National Liver Review Board: MELD Exception changes

- To be implemented May 14, 2019
- Replaces Regional Review Board
- Median MELD at transplant (MMaT) will be calculated in a 250nm radius around each transplant center
- HCC MELD exception value will be MMaT minus 3
  - Example, Median MELD is 31, MMaT minus 3= 28
- No ELEVATOR



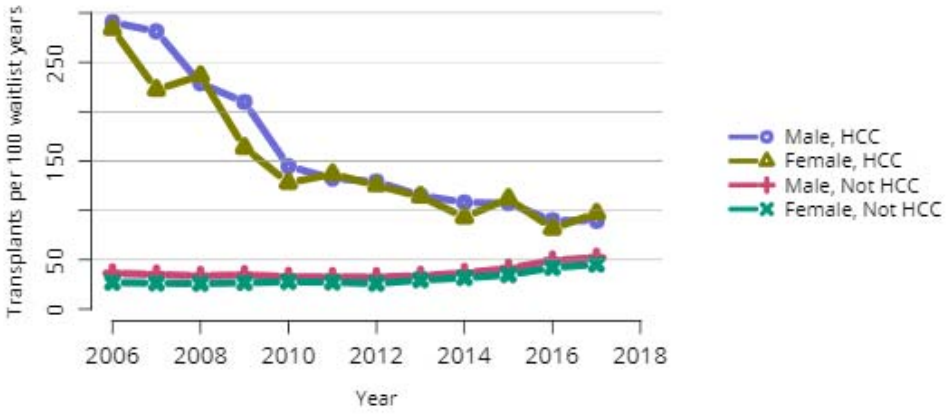
National Liver Review Board: MELD Exception changes

- HCC patients listed for LT will be clumped at the MMaT-3 on each center's wait list
- Time on the list will determine priority amongst the MMaT-3 patients
- Should patients who are close to falling out of Milan Criteria have priority over those who have a solitary lesion that has been stable after curative treatment?
- Stay tuned…

Distribution of adults waiting for liver transplant by diagnosis

American Journal of Transplantation, Volume: 19, Issue: S2, Pages: 184-283, First published: 27 February 2019, DOI: (10.1111/ajt.15276)

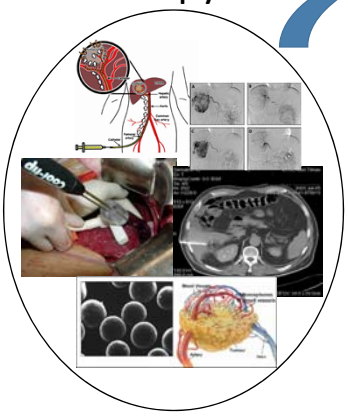
What does this mean for my patients?



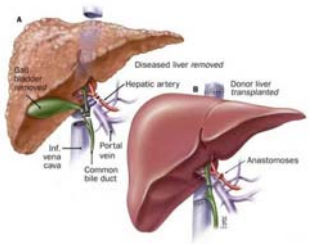
Kim WR et al. Amer J Transpl 2019
https://doi.org/10.1111/ajt.15276

What does this mean for my patients?

Liver directed therapy



Liver Transplantation



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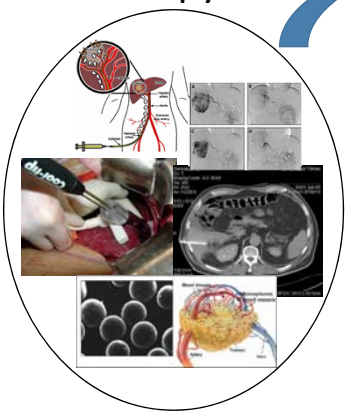

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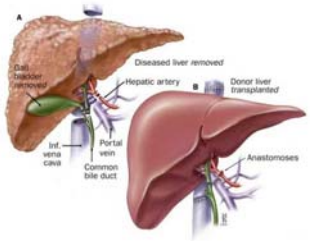
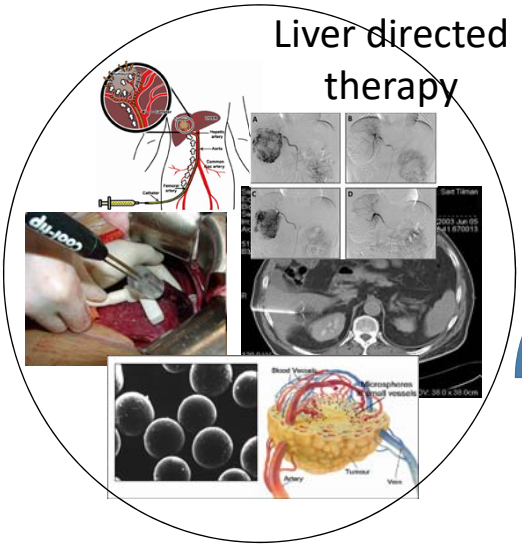


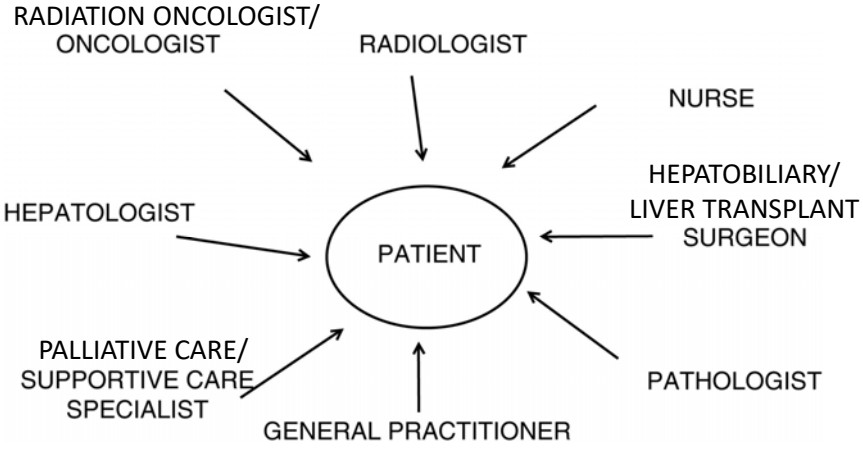
What does this mean for those caring for HCC patients?

Liver directed therapy



Liver Transplantation

Multidisciplinary care of HCC



Barone C et al. Ann Oncol 2013;24:ii15-ii23

Annals of Oncology

Clinical case

- 67yo male with recent diagnosis of NASH cirrhosis, comes to see you in clinic to establish care for advanced liver disease
- Patient undergoes multiphase CT as part of the initial evaluation of cirrhosis
- Found to have a 1.8cm lesion in seg 8 with arterial hyperenhancement and washout
- Labs: Tbili 1.1, Cr. 1.2, AFP 5, PLT 98
- What are your next steps?

Take home points…

- AASLD HCC Guidelines
  - U/S q6 months with or without AFP
  - No surveillance in Child C cirrhosis unless candidate for transplant
  - Once a cirrhotic, ALWAYS a cirrhotic, regardless of treatment history
- Many Non-LT treatment options for HCC
  - Liver directed therapies
  - Systemic therapies
- HCC MELD Exceptions for LT
  - MMaT-3 with no elevator
  - Likely to be doing less LT for HCC
- Utilize Multidisciplinary Liver Tumor Boards to aid in decision making

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Clinical Pearls for Less Common Liver Diseases

Wilson's Disease
Autosomal recessive condition resulting in defect of copper excretion. Presents initially as abnormal LFT's, but many present with acute decompensation; age range usually 10-30, but as high as 55yo. Diagnosis focuses on 3 simultaneous tests: 24 hour urinary copper, slit lamp exam, and serum ceruloplasmin. Liver biopsy is indicated if all 3 tests are not overtly positive – most patients end up with a biopsy. Treatment is based on presentation – symptomatic versus asymptomatic. Chelators include D-penicillamine and trientene. Follow up is based on severity of illness, but requires continued surveillance of bone marrow, kidney, and liver function, in addition to monitoring of copper levels.
Alpha-1 Antitrypsin Deficiency (A1ATD)

Misnomer, in the sense that the liver makes plenty of A1AT. However, due to a genetic substitution, the protein mis-folds and cannot be exported from the hepatocyte. The buildup of A1AT in the liver can lead to apoptosis and cirrhosis, while the absence of A1AT in the blood can lead to early emphysema. Diagnosis is based on 3 findings: low A1AT levels in the serum, presence of the appropriate phenotype, and a liver biopsy demonstrating the appropriate PAS+, diastase negative pink granules of A1AT in the hepatocyte. Rarely associated with carotid artery dissection and neutrophilic panniculitis. High risk of HCC in cirrhosis; condition can be cured with liver transplant.

Iron Overload Syndromes
The overwhelming majority of iron overload syndrome is represented by HFE mutations of C282Y homozygotes or C282Y/H63D compound heterozygotes. Diagnosis is based on high iron saturation (>45%), high ferritin, and a positive HFE gene test. Liver biopsy indicated for ferritin > 1,000 to assess for cirrhosis. Biopsy should show iron INSIDE the hepatocyte; iron in the Kupffer cells (macrophages) suggests hemosiderosis and more workup. Patients with hemochromatosis and cirrhosis have a very high risk for HCC. Phlebotomy can be therapeutic and diagnostic. True hemochromatosis will take years to phlebotomize to a normal ferritin. Many features of hemochromatosis will improve with phlebotomy; importantly, joint damage and gonadal damage to do not improve.
Familial Amyloid Polyposis

Important to recognize as an autosomal dominant condition that leads to transthyretin amyloid buildup. Indication for transplant is NOT cirrhosis; it is the presence of any findings of peripheral neuropathy. FAP livers have no functional disorder or cirrhosis. Contraindications to liver transplant include severe cardiac and renal disease from amyloid. FAP liver can be used in domino transplants where the FAP liver is actually donated to an older patient and the FAP patient gets a new liver. FAP can recur in the recipient, but takes many years – ideal for older donor.

Hereditary Hemorrhagic Telangiectasia (Osler Weber Rendu Disease)
Autosomal dominant genetic disorder leading to the development of large arterio-venous malformations. Diagnosis based on multiple findings. Liver injury based on development of very larter arterio-portal shunts that divert arterial blood directly into the portal vasculature and

create a steal phenomena resulting in localized biliary ischemia and the development of large bilomas. Large shunts can lead to high output cardiac failure and portal hypertension. Important to recognize Nodular Regenerative Hyperplasia (NRH) is associated with HHT and a cause for non-cirrhotic portal hypertension and that most GI bleeding in these patients are AVM related. Liver transplant is indicated NOT because of cirrhosis, but because of high output cardiac failure and portal hypertension and biliary complications.
Urea Cycle Disorder

Rare condition to be diagnosed in adulthood; predominantly a pediatric/metabolic condition. The primary condition associated with late presentation is Arginase Deficiency. First crisis often precipitated by starting valproic acid or a steroid bolus. Liver transplant is curative of this condition. And vast majority are performed in children under the age of 5 years old.

Clinical Pearls for Less Common Liver Diseases

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Oregon Health & Science University

Disclosures

- **No financial disclosures**

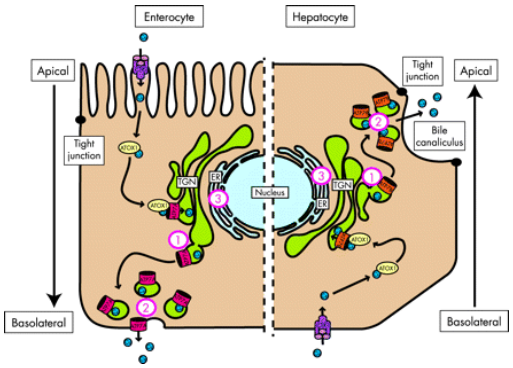
Wilsons Disease

AASLD Guidelines: Diagnosis and Treatment of Wilson Disease: An Update 2008

3

Wilson's Disease

What is it?



- Autosomal recessive disorder leading to build up of copper in the body
- Defect in copper transporter **ATP7B** leads to build up of copper in liver cells. Over 500 distinct mutations can lead to defective gene. (ATP7A = Menke's Disease)
- ATP7B supposed to transport copper into Golgi complex to be bound to ceruloplasmin or loaded into vesicles to be excreted in bile

4

Reproduced from J Med Genetics, P de Bie et al., 44: 679, 2007 with permission from BMJ Publishing Group Ltd

Wilson's Disease

- Presentation
  - Usually in the second and third decades
    - As young as 8 years old
  - Can have variable presentation
    - Neuro-psych (tends to appear in 3rd decade) – 30%
      - Motor disorders – handwriting changes (micrographia), tremors, spasticity, dysphagia
      - Personality changes
      - Depression, anxiety, psychosis
    - Almost always have ophthalmic findings with neuropsych presentation (98%)
- PEARLS
  - Age 3-55, abnormal LFT + neuro/psych, must r/o WD
  - If you are thinking AIH, always include Wilson's in your differential!

5

Wilson's Disease

- Presentation
  - Liver disease
    - Can present with Fulminant Liver Failure
      - Female : male presentation 3:1
      - Helpful key to dx - AlkPhos : Tbili ratio < 2
  - Hemolytic anemia (Coomb's negative)
    - Can occur in setting of liver disease or isolated
    - Schistocytes !
  - Key Lab Features:
    - Low alkaline phosphatase
    - High uric acid
    - Anemia

6

Ferenci P. Alim Pharm Ther 2004; 19:157-165

Wilson's Disease

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o Modified King's Wilson Score

	POINTS			
	1	2	3	4
Tbil	5.8 - 8.8	8.9 - 11.7	11.8-17.5	> 17.6
AST	100-150	151-300	301-400	> 400
INR	1.3 - 1.6	1.7 - 1.9	2.0 - 2.4	> 2.4
WBC	6.8-8.3	8.4-10.3	10.4-15.3	> 15.3
Albumin	3.4-4.4	2.5-3.3	2.1-2.4	< 2.1

Score >10 associated with high risk for transplant/death

Dhawan A, et al. Liver Transpl 2005; 11:441–8

Wilson's Disease

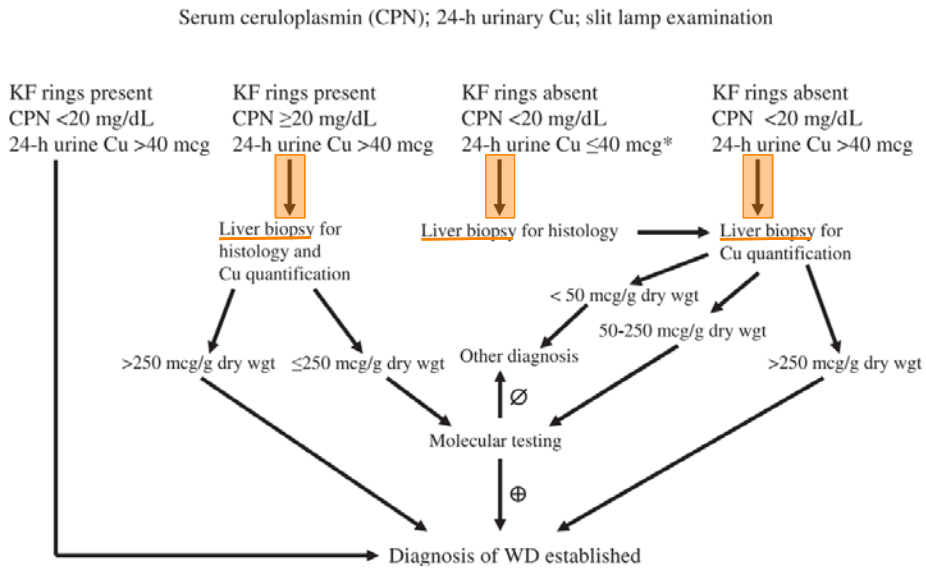
AASLD

o Diagnosis

- If presenting with abnormal liver tests, but not liver failure
  - Check ceruloplasmin level (CPL)
  - 24h urinary copper
  - Slit lamp exam

Get all 3 !

Wilson's Disease



Roberts E, Schilsky ML. Hepatology 2008;47:2089–111

Wilson's Disease

- Diagnosis
  - Can be challenging !
  - In fulminant state, ceruloplasmin levels can be normal or high
    - Acute phase reactant
  - Urinary copper can be elevated with prolonged cholestasis
  - Presence of KF rings plus typical findings very helpful in diagnosis, *only present 50%*
    - KF rings *NOT* pathognomonic for Wilson's

Wilson's Disease

AASLD

- Treatment
  - Penicillamine
    - Multiple side effects
  - Trientene
    - Preferred first line agent due to SE profile
  - Tetrathiomolybdate
    - Not FDA approved in US
  - Zinc
    - Competitive inhibitor of absorption in gut – helpful for maintenance only
  - Diet
    - Avoid copper-rich foods: mushrooms, nuts, liver

11

Scheinberg et al. NEJM 1987; 317: 209-13.

Wilson's Disease

AASLD

Table 3. Pharmacological Therapy for Wilson Disease

Drug	Mode of Action	Neurological Deterioration	Side Effects	Comments
D-Penicillamine	General chelator induces cupruria	10%-20% during initial phase of treatment	• Fever, rash, proteinuria, lupus-like reaction • Aplastic anemia • Leukopenia • Thrombocytopenia • Nephrotic syndrome • Degenerative changes in skin • Elastosis perforans serpingosa • Serous retinitis • Hepatotoxicity	Reduce dose for surgery to promote wound-healing and during pregnancy Maximum dose 20 mg/kg/day; reduce by 25% when clinically stable
Trientine	General chelator induces cupruria	10%-15% during initial phase of treatment	• Gastritis • Aplastic anemia rare • Sideroblastic anemia	Reduce dose for surgery to promote wound-healing and during pregnancy Maximum dose 20 mg/kg/day; reduce by 25% when clinically stable
Zinc	Metallothionein inducer, blocks intestinal absorption of copper	Can occur during initial phase of treatment	• Gastritis; biochemical pancreatitis • Zinc accumulation • Possible changes in immune function	No dosage reduction for surgery or pregnancy Usual dose in adults: 50 mg elemental Zn three times daily; *minimum* dose in adults: 50 mg elemental Zn twice daily
Te[illegible]ate	Chelator, blocks copper absorption	Reports of rare neurologic deterioration during initial treatment	• Anemia; neutropenia • Hepatotoxicity	Experimental in the United States and Canada

Routine CBC's

Routine UA's

50%

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Wilson's Disease

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o Monitoring

1

SYMPTOMATIC
- 6-12 months
- Start D-penicillamine / Trientene
- 10mg/kg split BID ➔ 20mg/kg split QID
- Increase over 2-4 weeks

Weekly

Bi-weekly

Monthly

Q3 months

Q6 months

2

ASYMPTOMATIC
- 12-24 months
- Reduce dose to 15mg/kg
- Monitor for over/under treatment and compliance

TARGET 24-H COPPER URINE LEVELS	
D-penicillamine	250-500
Trientene	150-250
Zinc	30-120

STANDARD LABS
- CBC
- LFT
- Serum Copper
- Ceruloplasmin
- UA
- 24 hour urine copper
- 24 hour urine zinc*

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Schilsky M. Clin Liver Dis 21 (2017) 755–767

Wilson's Disease

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o Prognosis

- Fulminant disease is universally fatal
  - modified King's Wilson score
- Liver, cardiac, and neurologic disease can be improve
  - *Neuropsych symptoms may persist*
- Treatment side effects can be significant and lead to non-compliance with rapid recurrence of disease and/or fulminant failure

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o Clinical Pearls

- Great mimicker of Autoimmune Hepatitis – if AIH is on your differential, always rule out Wilson's
- Decompensated liver disease in the setting of Wilson's has a poor prognosis – consider modified King's Wilson score (>10)
- Treatment is dependent on presentation: symptomatic vs asymptomatic. Follow up and dosing based on presentation.
- Many complications are reversible with treatment – neuropsych symptoms may not be

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A1AT Deficiency

Nelson et al. Clin GastroHep. 2012;10:575–580

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Alpha 1 Antitrypsin

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o What is it?

- **SER**ine **P**rotease **IN**hibitor (SERPIN)
- Inhibits ***neutrophil elastase***, stopping the degradation of connective tissue (elastin)
- Defect in protein folding ➔ defective export ➔ liver buildup
- Result
  - Build up of A1AT in liver ➔ liver damage
  - Deficiency of A1AT in blood ➔ lung damage

Journal of Hepatology 2016 vol. 65 j 413–424

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Alpha 1 Antitrypsin

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o Epidemiology

- Autosomal recessive (>100 mutations)
- 1:2,000 live births (predominantly Caucasian / Northern European)
- ***2-3% carrier rate in U.S. Caucasians***
  - ***~100,000 Americans with A1AT***
- Three phenotypes: M, S, and Z
  - MM phenotype – normal A1AT production
  - SS phenotype – moderate A1AT deficiency
  - ZZ phenotype – severe A1AT deficiency

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Alpha 1 Antitrypsin

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o Diagnosis

- Serum A1AT level below 50-80mg/dl

AND

- Genotype identification of ZZ , or *Z
- Phenotype identification of ZZ, or *Z

AND

- Liver biopsy confirmation of A1AT granules

Alpha 1 Antitrypsin

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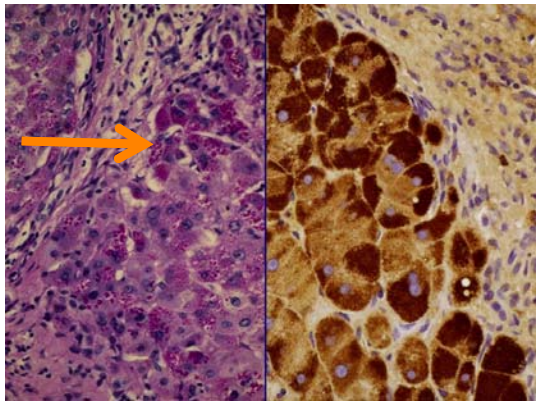
Periodic Acid Schiff positive, diastase resistant globules



Immunohistochemistry

Clin Gastroenterol Hep 2012;10(6):575-580.

Alpha 1 Antitrypsin

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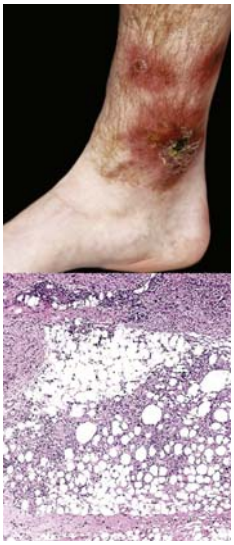
- Clinical Pearls
  - Can be associated with carotid artery dissection and ulcerative, neutrophilic panniculitis
  - High risk of liver cancer in setting of cirrhosis
  - Don't get tripped up with the phenotypes – disease is associated with the 'Z' protein. Null mutations have no liver disease – they do not make A1AT !



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Wick MR. Semin Diagn Pathol. 2017 May;34(3):261-272

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Iron Overload Syndromes

AASLD Practice Guidelines 2011
Pietrangelo. Gastro. 2010;19:393–408

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Hemochromatosis

AASLD

- What is it?
  - Genetic disorder associated with dysregulated iron absorption
    - Most common defect
      - HFE gene mutation (C282Y, H63D)
    - Leads to abnormally low levels of Hepcidin
      - Hepcidin inhibits basilar iron transport
  - HFE Autosomal recessive
    - common in Caucasians
    - 1 in 12 heterozygote
    - 1 in 400 homozygote
  - ***Variable penetrance: 1% of C282Y develops disease***

Beutler E. Lancet 2002; 359:211-8

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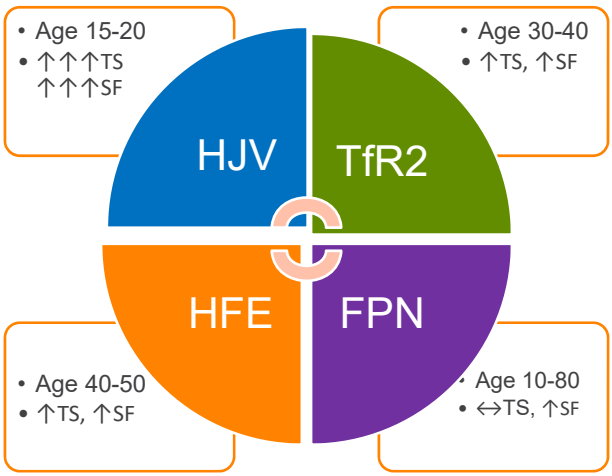
Most Common Genetic Iron Overload Syndromes



Pietrangelo et al. Gastro 2010;139:393–408

Hemochromatosis

AASLD

o Presentation

- Classic triad of cirrhosis, bronze skin, and diabetes *uncommon*
- Most common presentation is during routine laboratory screening and evaluation of abnormal LFT's
- Median age of presentation:
  - Men = 40-50's
  - Women = 60's

25

Hemochromatosis

AASLD

o Diagnosis

- Initial screening test
  - iron saturation (iron / TIBC) > 50%
  - ferritin > 250 women, 300 men
- Who to screen?
  - Liver disease
  - Diabetes
  - Arthritis
  - Unexplained CHF
  - Unexplained sexual dysfunction
- Consider liver biopsy for high iron saturation and ferritin but negative HFE gene

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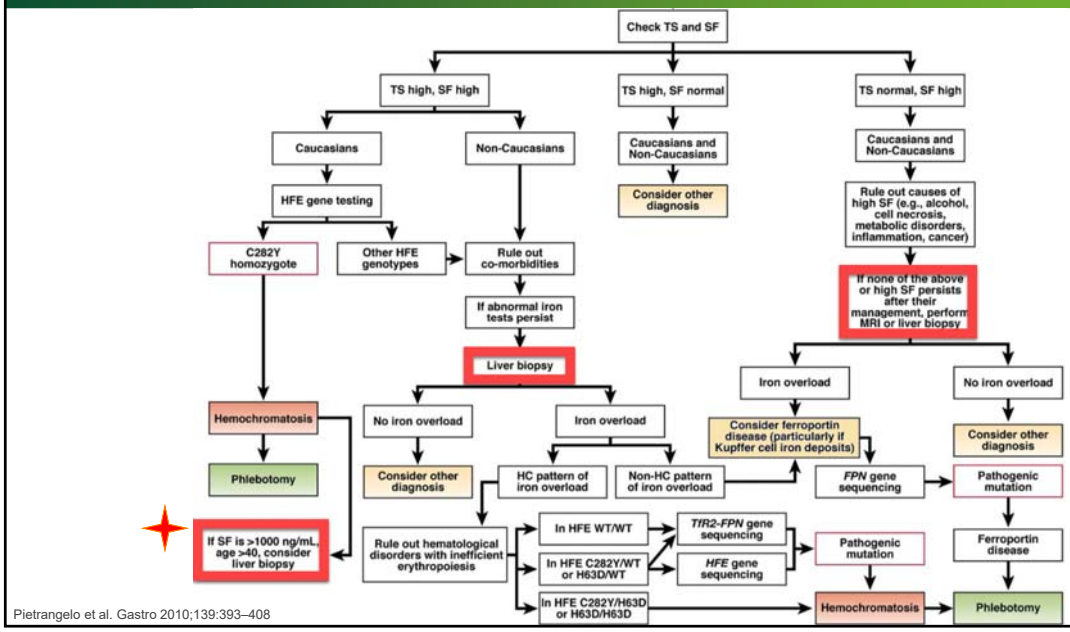

Pietrangelo et al. Gastro 2010;139:393–408

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Hemochromatosis

o Treatment

- Phlebotomy
  - Each 500cc unit contains 200-250 mg iron
  - Iron stores commonly 10 + grams
    - Correlates to 40+ sessions
    - Each unit will reduce ferritin by ~30 ng/dl
  - Goal to reduce ferritin to below 50 ng/dl
  - Once goals reached, phlebotomies 3-4 times / year

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Wheeler et al. Comprhensive Ther. 2006; 32: 10-16

Hemochromatosis

AASLD

o Prognosis

- Excellent prognosis with early detection and phlebotomy
- Similar survival in age matched controls
- Iron depletion is associated with improvements in
  - Varices
  - Cardiac function
  - Fibrosis
  - Fatigue
- No improvement in
  - Arthropathy
  - Hypogonadism

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Hemochromatosis

AASLD

o Clinical Pearls

- High risk of liver cancer in persons with cirrhosis – screen!
- If AST normal and ferritin < 1,000 ng/mL, unlikely to have advanced disease – biopsy not necessary
- Location of iron deposition: hepatocytes for hemochromatosis, macrophages for hemosiderosis

30

Familial Amyloid Polyneuropathy

Adams et al. Curr Opin Neurol. 2017 Oct;30(5):481-489

31

FAP

o What is it?

- Autosomal dominant condition
- Caused by mutation of transthyretin (TTR)
- Predominantly synthesized in the liver
- Results in extracellular deposition of amyloid type protein
- Leads to progressive peripheral and autonomic polyneuropathy
  - Sensory loss, weakness, and autonomic dysfunction
- The liver itself is normal (!)
- Liver transplant cures this condition (ie. A1AT)

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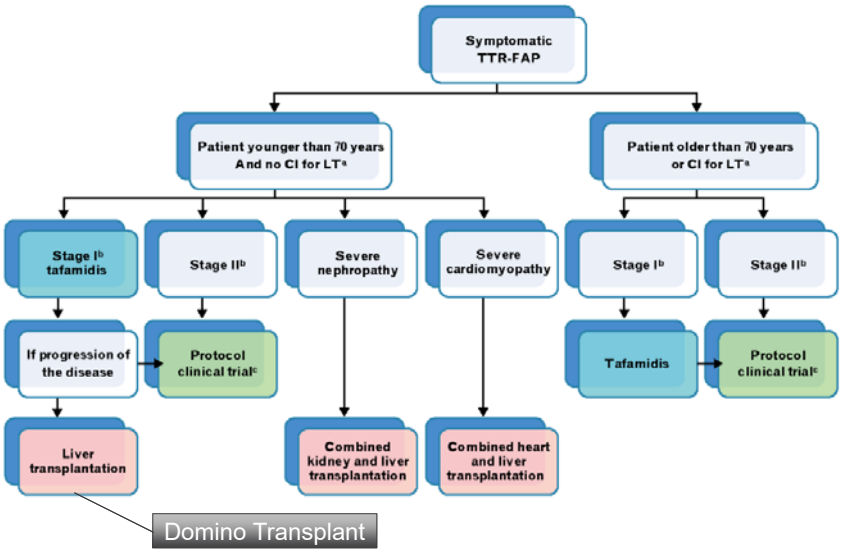
FAP



Adams DH, et al. Curr Opin Neurol. 2012 Oct;25(5):564-72

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AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

Hereditary Hemorrhagic Telangiectasia

Garcia-Tsao et al. NEJM 2000 Sep 28;343(13):931-6.
Garcia-Tsao et al. Liv Trans12:S108-S109, 2006
EASL Guidelines on Vascular Diseases of the Liver 2015

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HHT

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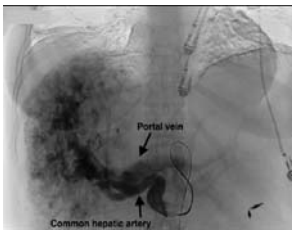
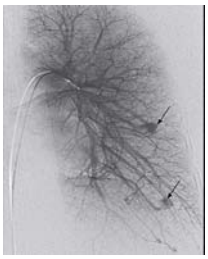
- What is it?
  - Autosomal Dominant
  - Development of large AVM's
  - AVM's usually progress with age
  - Average age of presentation: 10-30yo
- Diagnosis (3 out of 4) – progress with age
  1. Nosebleeds (major cause of death prior to transfusions)
  2. Mucocutaneous telangiectasias (lips, mouth, fingers, nose – prone to rupture with light trauma)
  3. Visceral AVM's (lung, liver, GI, pancreas, spine, brain)
  4. Family history





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HHT

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- Indications for liver transplant
  - **NOT related to cirrhosis**!
  - High output heart failure from liver AVM's
    - New data on bevacizumab (anti-VEGF)
  - Portal hypertension (ascites, GI bleeding)
    - Secondary to arterioportal shunting *or* NRH
    - GI bleeding more common from AVM's than varices
  - Biliary disease
    - Ischemia from steal phenomena
    - Biloma formation and sepsis
  - Exception points awarded by NLRB – not automatic
    - Must assess for pulmonary hypertension in all cases

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HHT

AASLD

- Clinical Pearls
  - Bleeding from cutaneous telangiectasias is marked by brisk bleeding from even minor trauma
  - Prevalence of affected organs
    - Liver 75% → only 8% symptomatic
    - Lung involvement in 50%
    - Brain in 10%
  - Embolization of hepatic artery AVM's – DANGER!
    - leads to biliary ischemia – approach with caution
    - only if not an OLT candidate !
  - NRH is commonly associated with HHT
    - think NRH in HHT with liver mass

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Urea Cycle Defect

Pagon et al. GeneReviews. U Wash, Seattle; 1993-2016. ISSN: 2372-0697. http://www.genereviews.org and copyright 1993-2018 Univ of Washington

Yu et al. Transplant Proc. 2015 Oct;47(8):2413-8.

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UCD

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BACKGROUND

- Urea cycle occurs in the liver
- Defect in metabolism of nitrogen
- Results in accumulation of ammonia
- Autosomal recessive condition (except for OTC which is X-linked)
- Partial deficiencies present from childhood to adulthood
- **Arginase deficiency** uncovered by illness or stress; presents at any time in life cycle

DIAGNOSIS

- Clinical suspicion !
- Ammonia concentration >150 umol/L with a normal anion gap and glucose
- Differentiating between enzyme deficiencies
  - Based on serum amino acids and urinary orotic acid
- Definitive diagnosis based on genetic testing or enzyme activity

UCD

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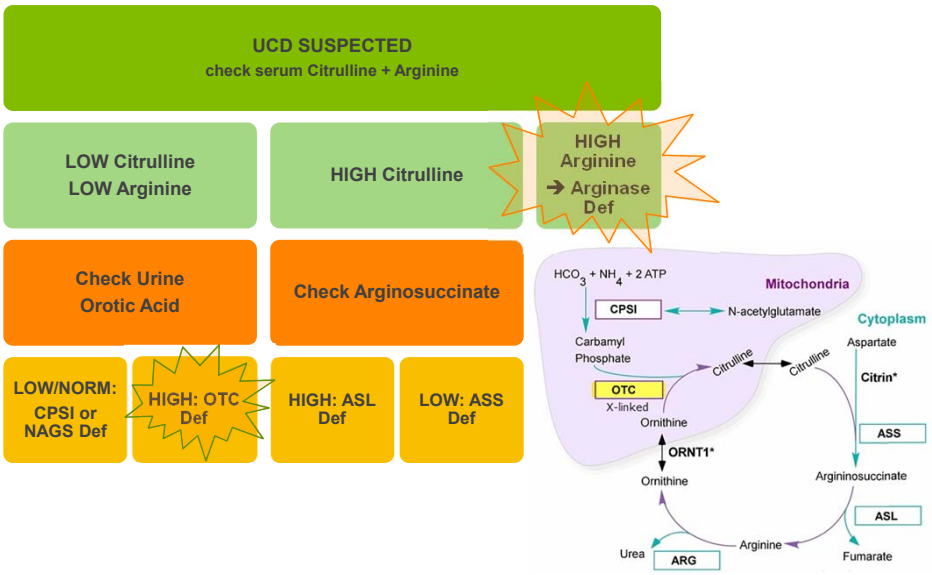
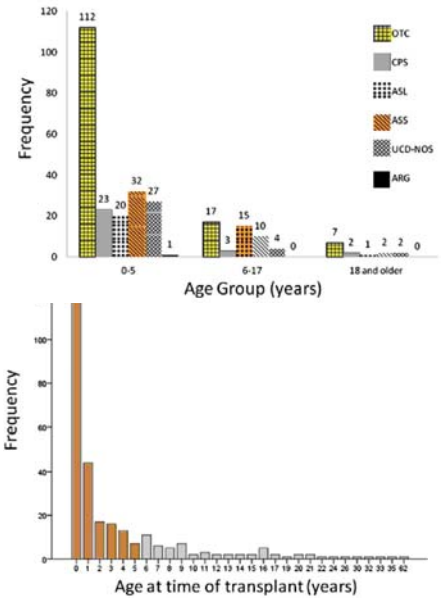
Diagnosis



Liver Transplant

- OLT effective therapy for UCD
- OTC deficiency (x-linked) most commonly transplanted condition
- 70% of transplants occur in children < 5 yo
- Overall survival is excellent



Yu, L., *Transplantation Proceedings*. 47.8 (2015): 2413-418

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UCD

o Clinical Pearls

- Uncommon first presentation can occur in adults – tends to be Arginase Deficiency
- Precipitants: valproate, fasting, intravenous steroids, large protein bolus
- Predominantly a pediatric condition (2/3 OLT in kids < 5yo)
- Liver transplant can cure this condition!

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Robert G. Gish, MD, FAASLD
Hepatitis B Foundation
Doylestown, PA

Email: rgish@robertgish.com

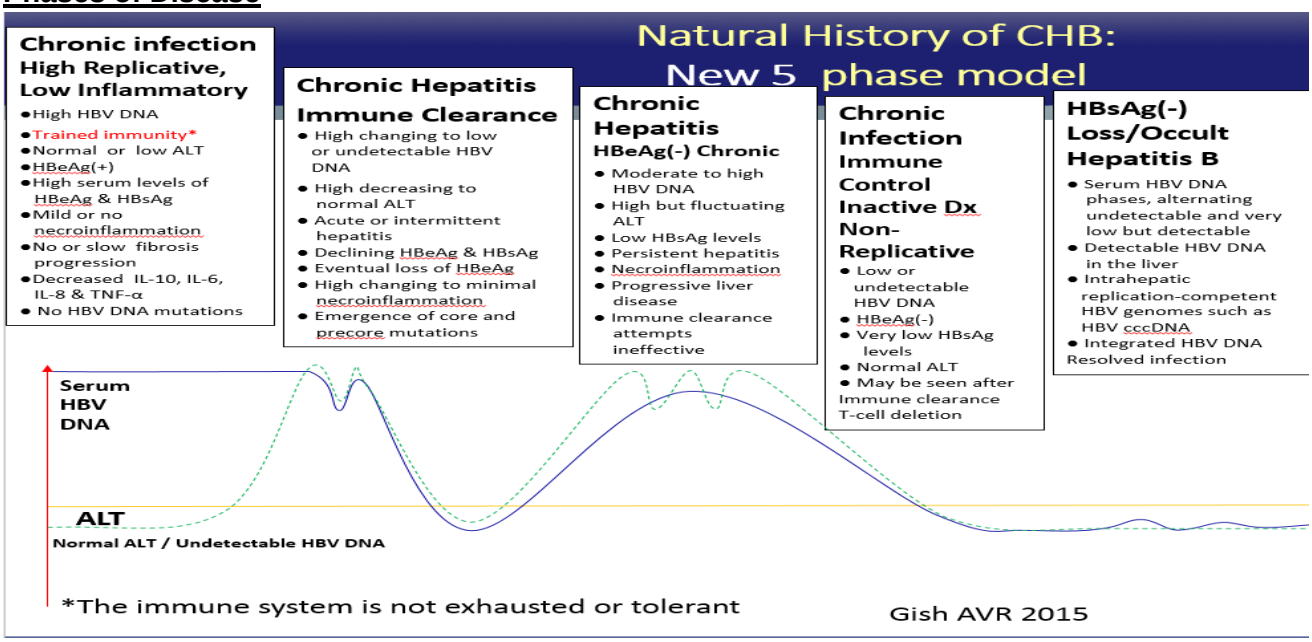
HBV Diagnostics: Anything New

Viral hepatitis is the 7th leading cause of morbidity and mortality worldwide, surpassing HIV, malaria and tuberculosis by annual death rate, and accounting for 1.45 million deaths annually. Worldwide, an estimated 292 million individuals are chronically infected with hepatitis B virus (HBV) and the disease accounts for 1 death every minute in the Asia Pacific region. Chronic HBV (denoted by the seroprevalence of hepatitis B surface antigen [HBsAg] for at least six months) accounts for 50% of viral-hepatitis-related deaths and 21 million disability-adjusted life years owing to progression to cirrhosis and hepatocellular carcinoma. Recognizing the global burden of HBV, the 2016 World Health Assembly championed the elimination of viral hepatitis B along with hepatitis C as a global threat by 2030.

Achievement of this goal requires diagnosis, linkage to care, correct staging of disease, timely and cost-effective treatment options, public health initiatives and, perhaps the most important, accessible, accurate and validated diagnostic means for identifying and monitoring viral activity in infected individuals. These are the keys to achieving the elimination targets. While the means of diagnosing HBV have been available since the 1970's, diagnostic rates remain suboptimal, and we are a long way from the 90% target proposed by the WHO. In 2016, only 10% (29 million) of infected individuals were aware of their HBV serostatus, with estimates as low as 5% in low-income countries` where prevalence of HBV is disproportionately higher.

Diagnosis of HBV infection is intimately linked to determining the natural history of the virus (Figure 1). HBV is an enveloped DNA virus that clinically manifests as self-limited acute hepatitis, chronic hepatitis or fulminant liver failure. A sterilizing cure, defined as the eradication of detectable hepatitis B surface antigen (HBsAg), intra-hepatic covalently closed circular DNA (cccDNA) and integrated HBV DNA, is the ultimate goal for HBV treatment but remains unachievable with the current treatment regimens, nucleos(t)ide analogues (NUCs) and pegylated interferon-alpha (pegIFN-α) and is not seen in acute or chronic disease. A more feasible goal is functional cure, defined by a sustained loss of HBsAg with or without hepatitis B surface antibody seroconversion in patients with undetectable serum HBV DNA. Given the impracticality of using liver biopsies to quantify transcription of intrahepatic cccDNA, surrogate noninvasive biomarkers are necessary to diagnose HBV infection, monitor viral replication, trend disease progression and assess therapeutic response to current and future antivirals.

Phases of Disease



Hepatitis B Surface Antigen (HBsAg)

Hepatitis B surface antigen (HBsAg) plays a vital role in characterizing acute or chronic HBV infection, and guiding treatment in chronic HBV infection (CHB). Quantifying HBsAg can help with prognosis, natural clearance and on treatment clearance prediction, determining level of infectivity, and establishing phases of HBV disease. Levels of HBsAg help differentiate HBeAg-negative chronic hepatitis from HBeAg-negative chronic infection (formerly termed “inactive carrier”) when measured in conjunction with ALT and HBV DNA. HBsAg levels (quantified in IU/mL) correlate with HBV DNA and cccDNA in HBeAg-positive patients; no such correlation exists in HBeAg-negative patients, plausibly because of the expression of HBsAg due to increased HBV integration in the later phase of HBV chronic infections. HBsAg seroclearance is the current goal for functional cure, and loss of HBsAg (testing threshold is 0.05 IU/mL) remains a vital endpoint in studies of novel HBV therapies although more sensitive quantitation assays may confound this standard in the near future. The role of HBsAg quantification in patients on NUC therapy is currently evolving, with the potential to identify patients with low HBsAg levels (<100 IU/mL) who may be candidates for treatment discontinuation owing to low risk of relapse after treatment discontinuation or, if relapse occurs, the chance to clear HBV with an immune flare. HBsAg is detected both by immunoassays and by point of care (POC) tests in resource-limited settings where standard serology testing is more expensive, cumbersome or unavailable.

Quantitative HBV DNA testing

HBV is a DNA-containing enveloped virus. Infectious particles (Dane particles) circulating in the serum contain a single copy of viral DNA that serves as the template for intrahepatic transcription of cccDNA. Peripheral HBV DNA levels thus correlate with intrahepatic transcription. Higher levels of HBV DNA are associated with more advanced liver disease and HCC in a dose-dependent manner. Detection and quantification of serum HBV DNA via PCR amplification or POC nucleic acid tests is essential for diagnosing acute or chronic HBV infection, guiding treatment, and monitoring treatment response and treatment resistance. HBV

DNA plays a vital role in diagnosing the phases or stages of HBV infection as well as helping during the “window period” of acute or recent infection as well as in chronic infections with HBsAg escape mutants that compromise the diagnostic accuracy of serologic assays. Suppression of serum HBV DNA levels is achievable with NA therapy and remains an important endpoint in treatment guidelines.

HBeAg and Anti-HBe

Hepatitis B e antigen (HBeAg) is a non-structural protein derived from precore RNA and secreted from infected hepatocytes. HBeAg plays an essential role in HBV persistence and immune modulation. HBeAg characterizes the phases of CHB and is first detectable 6-12 weeks after HBV exposure. HBeAg and its antibody (anti-HBe) are measured using immunoassays, but no quantitative assays are currently commercially available. Seroconversion from HBeAg positivity to negativity marks an important transition in the natural course of HBV infection from highly infectious chronic disease to HBeAg-negative chronic infection with undetectable or low (<2,000 IU/ml) levels of HBV DNA. Spontaneous HBeAg loss or seroconversion occurs at an annual rate of 5-10% with antiviral therapy. Provided it is accompanied by low HBV DNA levels HBeAg seroconversion denotes better prognosis, making it a viable end-goal for current and future antiviral therapies. Measurements of the basal core promoter and pre-core mutations are available via sequencing assays in commercial laboratories.

Hepatitis B Core Antibody

Hepatitis B core antibody (anti-HBc) is a biomarker of HBV exposure and the presence of cccDNA and is seen in acute (IgM+) and chronic HBV infection (+ total anti-HBc and in some cases + anti-HBc IgM). It is the first antibody to appear after acute HBV infection and persists life-long in most patients. Thus, anti-HBc is a helpful biomarker for diagnosing occult infection, where HBsAg levels are undetectable but hepatitis B surface antibodies have not yet developed. Higher anti-HBc titers predict increased rates of HBeAg seroconversion and reduced risk of relapse after discontinuation of NA treatment as well as reduced risk of HCC. Quantification of anti-HBc is useful for characterizing HBV exposure, differentiating infection from hepatitis, assessing vaccination need, and predicting reactivation, occult HBV infection and treatment response. Anti-HBc has a false positive rate of < 2/1000 (Abbott PI for anti-HBc).

Hepatitis B Surface Antibody

Hepatitis B surface antibody (anti-HBs) is a biomarker representing immune response to HBsAg achieved through vaccination if anti-HBc is negative. There is no such event as “natural” immunity and this term is now removed from our lexicon. Current assays detect anti-HBs not bound to SVPs or virion particles. Further studies are needed to better understand the role of anti-HBs in viral neutralization and immunity control and to test for HBsAg variants.

HBV Genotypes & Subtypes

HBV genotypes can be used clinically for risk of HCC (GTC) and response to interferon GT.

Precore and Basal Core Promoter Mutations

A direct correlation is observed between infection chronicity, older patient age and incidence of basal core promoter mutations. Double BCP mutations, especially in genotype C HBV, correlate with a 3.5-fold increased risk of HCC development due to upregulation of pgRNA. While routine testing for precore and BCP mutations is currently not always utilized it is relevant as our understanding of HBV in risk scores such as that published by Myron Tong.

Treatment

HBV can be effectively controlled (defined by HBV DNA undetectable and HBsAg clearance) using pegIFN-α (17% of patients have HBsAg loss) and/or NUCs (entecavir, TDF or TAF) (10% HBsAg loss) in sequence or in combination or as a single therapy in patients with active inflammation defined by elevated ALT and DNA > 2,000 IU/mL, yet there is no current data that treating in patients with ALT < 25 in woman and < 35 in men changes or increases rates of viral control. Determination of which therapy to use includes careful consideration of duration of treatment, stopping rules, drug efficacy, use of quant(HBsAg), potential side effects, and potential for antiviral resistance with NUCs but rarely reduces cccDNA in all phases of HBV disease. Currently there is no evidence of cccDNA clearance in patients with high replication and healthy ALT levels. Importantly, entecavir and tenofovir are able to maintain extended virologic control over several years where some cccDNA reduction may occur but this data is derived from patients with active inflammation. Using our current medications, it is currently impossible to permanently eliminate HBV infection although treatment in the first phase may decrease HBV integration.

Coinfection: HDV, HCV, HIV

All patients with HBV chronic infection need to be tested for HDV with antibody testing and linked to advanced care if determined to be HDV(+). HIV testing is now recommended for all adults; thus, HIV testing should be in each HBV patient's chart as well as HCV testing due to overlapping risk factors.

Reactivation

HBV reactivation can take place in HCV patients undergoing DAA therapy as well as in patients receiving chemotherapy or immune modulation therapy.

Conclusions

HBV infection is incurable but vaccine preventable (with the new two dose vaccine Heplisav-B, three dose standard vaccine or combination with HAV vaccine) and remains complex with constantly evolving epidemiology, natural history, virology, immunology and treatment. Accurate diagnosis leads to correct determination of the phases of HBV and stage of liver disease and requires a consortium of biomarkers, imaging, and tests that can provide key information on infectivity, treatment response and disease progression. There are effective and safe treatments today to suppress HBV virus and decrease cirrhosis rates, liver failure, liver transplant and death as well as HCC. Newer therapies are emerging and will hopefully lead to higher rates of functional cure and eventually even a sterilizing cure, possibly with extraction of integrated HBV DNA.

2019 Hepatitis B Guidance Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B

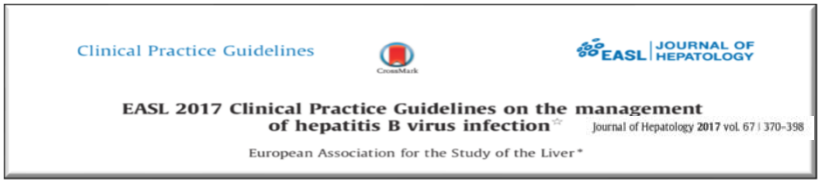
Robert Gish MD

Using AASLD, US, US/Asian, EASL and APASL Guidelines and Guidance documents

Faculty Disclosure

Commercial Interest	Nature of Relevant Financial Relationship (Include all those that apply)	
	What was received	**For what role**
• Antios	• Consulting Fees	• Consulting
• Enyo	• Honorarium/Consulting Fees	• Consulting, Advisory Board
• Gilead	• Honorarium/Consulting Fees	• Consulting, Speakers Bureau
• Ionis	• Honorarium/Consulting Fees	• Consulting, Data Safety Monitoring Board
• Janssen	• Honorarium/Consulting Fees	• Consulting, Advisory Board, Expert Witness
• Spring Bank	• Honorarium/Consulting Fees	• Advisory Board
• See also www.RobertGish.com		

HBV guidelines/guidance documents provide us with a basic outline of care

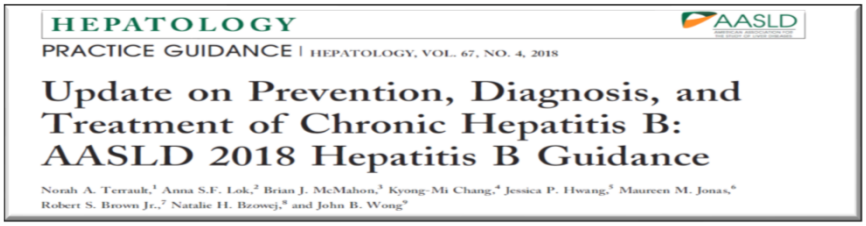

Clinical Practice Guidelines

EASL | JOURNAL OF HEPATOLOGY

EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection

Journal of Hepatology 2017 vol. 67 | 370–398

European Association for the Study of the Liver*


HEPATOLOGY

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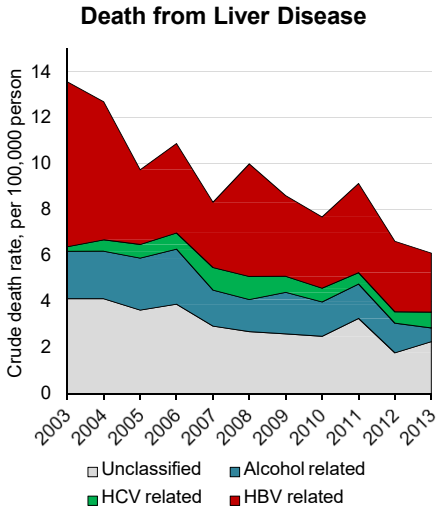
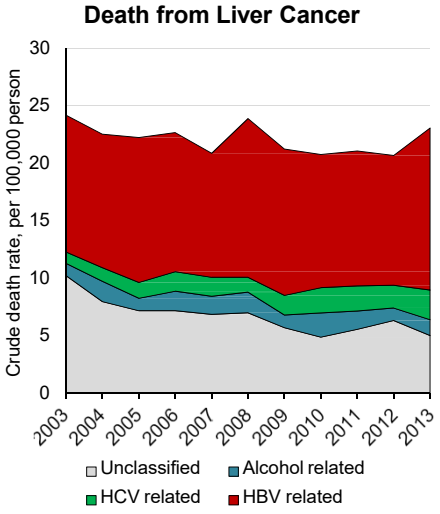
PRACTICE GUIDANCE | HEPATOLOGY, VOL. 67, NO. 4, 2018

Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance

Norah A. Terrault,[1] Anna S.F. Lok,[2] Brian J. McMahon,[3] Kyong-Mi Chang,[4] Jessica P. Hwang,[5] Maureen M. Jonas,[6] Robert S. Brown Jr.,[7] Natalie H. Bzowej,[8] and John B. Wong[9]

Increasing Mortality by HBV-Associated Liver Cancer





Choi J, Lim YS, et al. Hepatology 2017;66:1454-1463.

Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC) database

The basics of test interpretation and linkage to care

Who to screen for HBV:
- infection, exposure, immunity
- all “at risk” patients

HBsAg+ = infection
Anti-HBc + = exposure
Anti-HBs + = immunity of anti-HBc is negative

Non Immune individuals
- HBsAg(-), anti-HBc(-), anti-HBs(-)
- Vaccine

Anti-HBc

Indicates exposure to HBV

HBV is incurable

Anti-HBc = presence of cccDNA in the liver

Post-infection presence and level of anti-HBs indicates a “level” of immune control (in the setting of anti-HBc)

Educate patients about risk of reactivation

Do not vaccinate (vaccine is listed as an option in the AASLD guidance document)

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Candidates for Screening for HBV

- Persons born in high and intermediate endemic areas (≥2% prevalence)
- US born children of immigrants from high-risk areas
- Household and sexual contacts of HBsAg-positive persons
- Persons who have ever injected drugs
- Persons with multiple sexual partner, or history of STDs
- Men who have sex with men
- Inmates of correctional facilities
- Individuals with chronically elevated ALT/AST
- Individuals infected with HIV or HCV
- Patients undergoing dialysis
- All pregnant women

Weinbaum CM, et al. *MMWR Recomm Rep.* 2008;57(RR-8):1-20.
LeFevre ML on behalf of the U.S. Preventive Services Task Force. *Ann Intern Med.* 2014;161:58-66.

7

AASLD

Phases of HBV EASL Terminology

PHASE	1	2	3	4
New terminology	HBeAg positive Chronic *infection*	HBeAg positive Chronic hepatitis	HBeAg negative Chronic *infection*	HBeAg negative Chronic hepatitis
Old terminology	*Immune tolerant*	*HBeAg-positive CHB*	*Inactive carrier*	*HBeAg-negative CHB*
HBsAg	High	High/Intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	>10E7 IU/mL	10E4-10E7 IU/mL	<2,000 IU/mL*	>2,000 IU/mL
ALT	Normal	Elevated	Normal	Elevated**
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe

High Replication
Low Inflammation
Chronic infection

EASL CPG HBV, J Hepatol 2017

AASLD

Diagnostic Criteria and Definitions for CHB

AASLD HBV 2018 Guidance

	ALT	HBV DNA	HBeAg	Liver Histology
"Immune-tolerant" CHB	Normal or minimally elevated ALT and/or AST	Elevated, typically > 1 million IU/mL	Positive	No fibrosis and minimal inflammation
Immune-Active CHB	Intermittently or persistently elevated ALT and/or AST	Elevated ≥ 20,000 IU/mL	Positive	Moderate-to-severe necroinflammation and with or without fibrosis
		Elevated ≥2,000 IU/mL	Negative	
Inactive CHB phase	Persistently normal ALT and/or AST levels	<2,000 IU/mL	Negative	Absence of significant necroinflammation and variable levels of fibrosis

Terrault NB et al. Hepatology 2018; Published online February 5, 2018: doi:10.1002/hep.29800.

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AASLD HBV Guidance: ALT Upper Limits of Normal

2016 ULN for ALT: 30 U/L for males and 19 U/L for females[1]

2018 ULN for ALT: **35 U/L for males and 25 U/L for females**[2]

Therefore, ALT levels warranting HBV therapy consideration (≥ 2x ULN) are 70 U/L for males and 50 U/L for females

Now ULN more consistent with ACG recommendations of 33 U/L for males and 25 U/L for females[3]

1. Terrault NA, et al. Hepatology. 2016;63:261-283. 2. Terrault NA, et al. Hepatology. 2018;67:1560-1599. 3. Kwo PY, et al. Am J Gastroenterol. 2017;112:18-35.

AASLD

Goal of CHB Therapy

AASLD HBV 2016 Guidelines

Aim of treatment of chronic hepatitis B:
Achieve sustained suppression of HBV replication
(associated with normalization of ALT, loss of HBeAg, and improvement in liver histology)

↓

Goals of antiviral treatment:
Decrease CHB-related morbidity and mortality
HCC, Death, Liver Transplant, Transmission

Terrault NA, Bzowej NH, Chang KM, et al. Hepatology. 2016;63(1):261-83.

AASLD

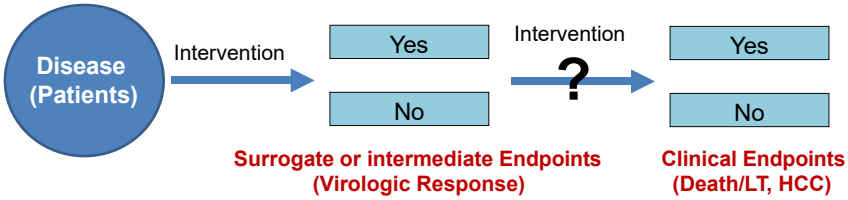
Surrogate Endpoint vs. Clinical Endpoint

Surrogate Endpoint

- Virologic, serologic, biochemical, & histologic responses
- Substitute for clinical endpoints
- High frequency
- Small number of study patients
- Short-term observation

Clinical Endpoint

- Hard outcomes of patients (Death/LT, HCC)
- Low frequency
- Large number of study patients
- Long-term observation



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When to Treat?

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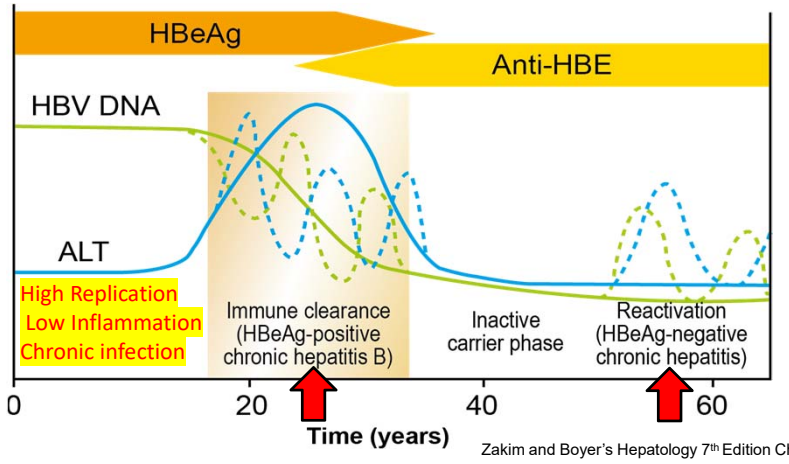
Currently, the decision to start antiviral treatment is depends on ALT levels, HBV DNA and fibrosis levels in non-cirrhotic CHB patients



Zakim and Boyer's Hepatology 7th Edition Chapter 32
AASID Guidance and EASL Guidelines

AASLD

Current Indications for Tx in Non-Cirrhotic CHB HBeAg-Positive

	AASLD 2018	EASL 2017	APASL 2015
ALT ≤ULN	HBV DNA >20,000 IU/ml ➢ No treatment	No treatment	HBV DNA >20,000 IU/ml ➢ Assess fibrosis noninvasively and individualize **biopsy** ➢ Treat if moderate to severe inflammation or significant fibrosis
ALT 1-2 x ULN	HBV DNA >20,000 IU/ml ➢ Monitor and if persist for >6 months, treat ➢ Treat in selected patients (**biopsy**: ≥F2 or A3, age >40)	HBV DNA >2,000 IU/ml, ALT >ULN and/or at least moderate inflammation or fibrosis ➢ Treat (E I, G 1)	HBV DNA >20,000 IU/ml ➢ Assess fibrosis noninvasively and individualize **biopsy** ➢ Treat if moderate to severe inflammation or significant fibrosis
ALT ≥2 x ULN	HBV DNA >20,000 IU/ml ➢ Treat HBV DNA 2000-20,000 IU/ml ➢ Monitor and if persist for >6 months, treat ➢ Treat in selected patients (≥F2 or A3, age >40).	HBV DNA >20,000 IU/ml ➢ Can start treatment even without a liver biopsy (E II-2, G 1).	HBV DNA >20,000 IU/ml ➢ Observation for 3 months and treat.

- **Definitions of normal ALT**
  AASLD: <35 U/L for male, <25 U/L forfemale EASL & APASL: traditional cut-off (40 U/L)

AASLD

Current Indications for Tx in Non-Cirrhotic CHB HBeAg-Negative

	AASLD 2018	EASL 2017	APASL 2015
ALT ≤ULN	HBV DNA <2,000 IU/ml ➢ No treatment HBV DNA ≥2000 IU/ml ➢ Treat in selected patients (**biopsy**: ≥F2 or A3, age >40)	No treatment	HBV DNA >2,000 IU/ml ➢ Assess fibrosis noninvasively and consider **biopsy** ➢ Treat if moderate to severe inflammation or significant fibrosis
ALT 1-2 x ULN	➢ Treat in selected patients (**biopsy**: ≥F2 or A3, age >40)	HBV DNA >2,000 IU/ml, ALT >ULN and/or at least moderate inflammation or fibrosis ➢ Treat (E I, G 1)	HBV DNA >2,000 IU/ml ➢ Assess fibrosis noninvasively and individualize **biopsy** ➢ Treat if moderate to severe inflammation or significant fibrosis
ALT ≥2 x ULN	HBV DNA ≥2,000 IU/ml ➢ Treat HBV DNA<2000 IU/ml ➢ Treat in selected patients (≥F2 or A3, age >40)	HBV DNA >2,000 IU/ml, ALT> ULN and/or at least moderate inflammation or fibrosis ➢ Treat (E I, G 1)	HBV DNA >2,000 IU/ml ➢ Observation for 3 months and treat.

- **Definitions of normal ALT**
  AASLD: <35 U/L for male, <25 U/L forfemale EASL & APASL: traditional cut-off (40 U/L)

AASLD

Treatment of Immune-Active CHB

Definitions	• Defined by
	  • ALT > 2 x ULN* or significant histological disease
	  plus
	  • HBV DNA > 2,000 IU/mL (HBeAg negative) *or*
	  HBV DNA > 20,000 IU/mL (HBeAg positive)

Recommendation	• Antiviral therapy for adults with immune-active CHB • Therapy is also recommended for persons with immune-active CHB and cirrhosis if HBV DNA >2,000 IU/mL, regardless of ALT level
Treatment	• **TAF, TDF, ETV, or Peg-IFN are preferred** • Consider TAF or ETV in patients with or at risk for renal dysfunction or bone disease • TAF is not recommended in patients with CrCl <15 mL/min or those on dialysis • Treat indefinitely or 1 year after HBeAg loss and DNA<LOQ

AASLD HBV 2018 Guidance

CrCl, Creatinine clearance
*ALT ULN: Males 35 U/L, Females 25 U/L
Terrault NB et al. Hepatology 2018; Published online February 5, 2018: doi:10.1002/hep.29800.

AASLD

Treatment of HBeAg-Positive Immune-Active CHB with HBeAg Seroconversion on NA Therapy

Patients Without Cirrhosis

Recommendation	• Discontinuation of NUC after a period of treatment consolidation • Alternative approach is to treat until HBsAg loss
Details	• Period of consolidation therapy generally involves treatment for ≥ 12 months of persistently normal ALT levels and undetectable serum HBV DNA levels • Monitor every 3 months for at least a year after treatment discontinuation for recurrent viremia, ALT flares, seroreversion, and clinical decompensation
Recommendation	• Indefinite antiviral therapy

AASLD HBV 2018 Guidance

Terrault NB et al. Hepatology 2018; Published online February 5, 2018: doi:10.1002/hep.29800.

Duration of Treatment in Persons with HBeAg-Negative Immune-Active CHB

AASLD HBV 2018 Guidance

Recommendation	• Indefinite antiviral therapy • Treatment discontinuation in persons with cirrhosis is not recommended due to the potential for decompensation and death

Terrault NB et al. Hepatology 2018; Published online February 5, 2018: doi:10.1002/hep.29800.

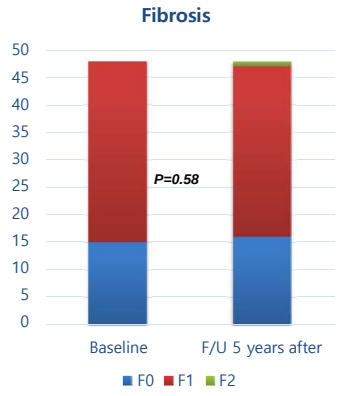
Traditional concept of "immune-tolerant" (IT) phase

Chronic Infection, High replication-low inflammation

- Minimal or no inflammation or fibrosis in the liver
- Negligible risk of progression to cirrhosis
- A very low risk of HCC

Supporting evidence

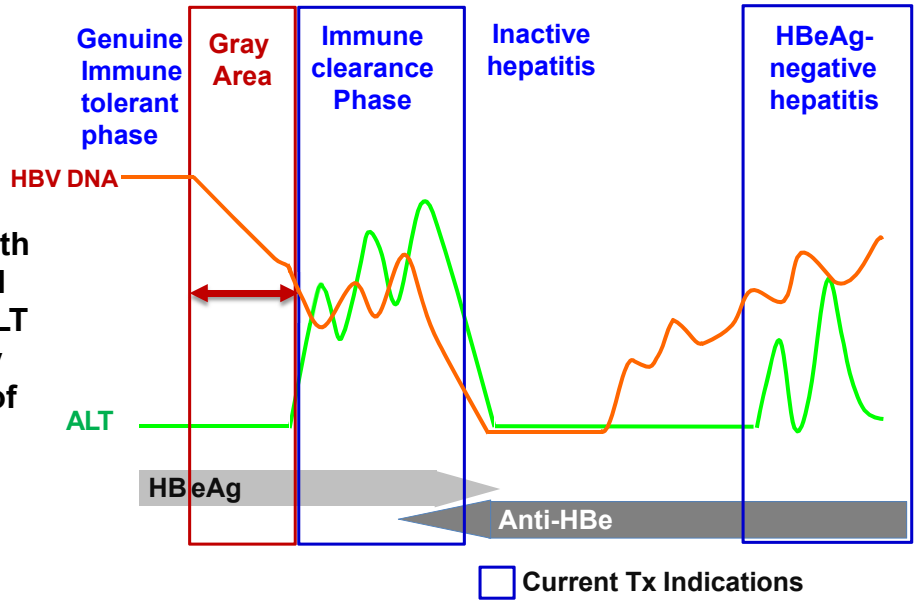
- Hong Kong Liver Fibrosis Study Group
- 48/57 with PNALT remained in IT phase
- Disease progression was minimal
- Median age: 31 years
- ALT 0.5 x ULN
- Median HBV DNA levels: 9.81 log10 IU/mL



Hui CK, et al (Hong Kong Liver Fibrosis Study Group). Hepatology 2007;46(2):395-401

AASLD

HBeAg(+) CHB with Decreasing Viral Load & Normal ALT (Gray Area) May Have High Risk of Clinical Events



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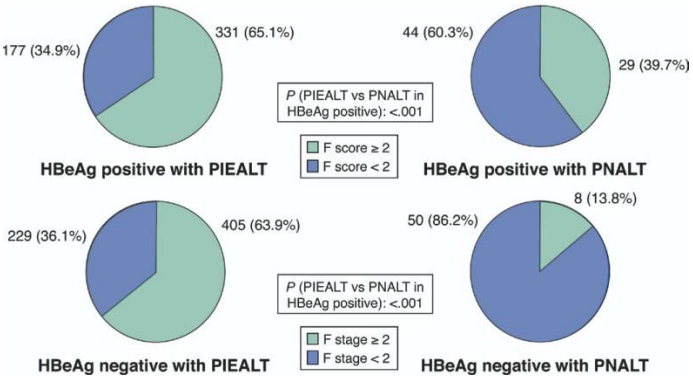
Current Definitions of Chronic Infection Phase of HBV infection Heterogeneous with Gray Zones

Chronic Infection, High replication-low inflammation

	AASLD	EASL	APASL
HBe Ag	(+)	(+)	(+)
Age	≤ 40?	≤ 30? "HBeAg-positive chronic HBV infection"	< 30?
HBV DNA	Elevated, typically 1.0x10^6 IU/mL	High levels of HBV-DNA	High levels of HBV-DNA
ALT	Normal (<35 U/L for male, <25 U/L for female)	Normal (<40 U/L)	Normal (<40 U/L)
Histology	Minimal inflammation and fibrosis	Minimal or no inflammation or fibrosis	Minimal inflammation
Treatment recommendation	Observation (2A), antiviral therapy in the select group of >40 years of age with elevated HBV DNA (>1,000,000 IU/mL) and biopsy showing significant necroinflammation or fibrosis (2C).	Observation, but may be treated if they are older than 30 years (E III, G2)	Observation, Assess fibrosis noninvasively and individualize biopsy Treat if moderate to severe inflammation or significant fibrosis

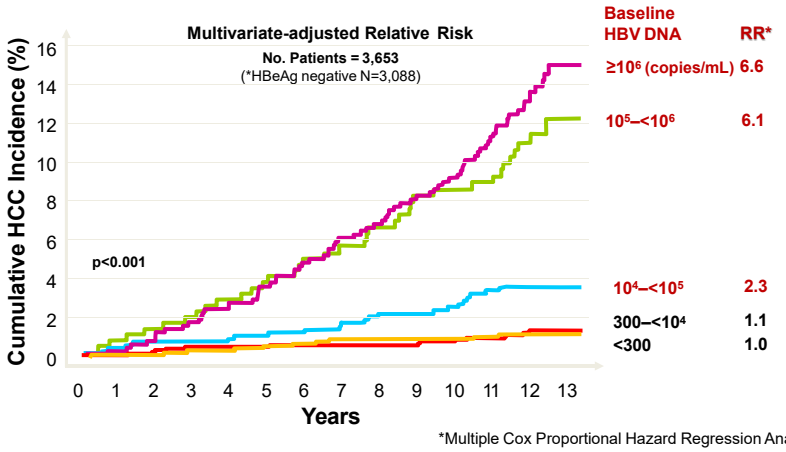
Significant histologic fibrosis with normal ALT in HBeAg positive & negative patients



A fair proportion of patients with CHB infection with PNALT have significant histologic fibrosis.

Kumar M et al. Gastroenterology 2008;134:1376–1384

High serum HBV DNA levels are associated with high risks of HCC and cirrhosis in CHB irrespective of ALT levels

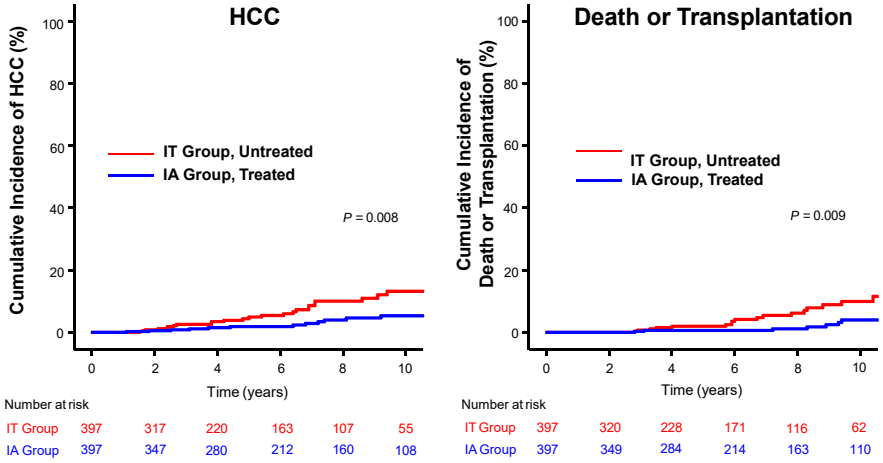


*Multiple Cox Proportional Hazard Regression Analyses

1 Chen CJ. JAMA 2006;295:65-73
2 Iloeje UH. Gastroenterology 2006;130:678-86

Higher Risk of HCC & Death in Untreated Immune Tolerant vs. Treated Immune-Active Phase CHB

- Propensity Score-Matched Cohorts -



Kim GA, Lim YS, et al. Gut 2018;67:945–952.

How to Treat?

AASLD

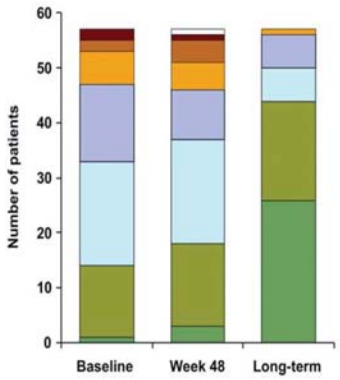
First-Line Antiviral Agents Recommended by Current Guidelines

	AASLD 2018	EASL 2017	APASL 2015
Recommendations	The AASLD recommends peg-IFN, **entecavir, or tenofovir (TDF)** as preferred initial therapy for adults with immune-active CHB	NAs for naïve CHB patients: The preferred regimens are **ETV, TDF and TAF** as monotherapies.	The most potent drugs with the optimal resistance profile, i.e., **tenofovir or entecavir**, should be used as first-line long-term monotherapies (A1).
Evidence levels	Quality and Certainty of Evidence: Low Strength of Recommendation: Strong	Evidence level I, grade of recommendation 1	A1
Comments	TAF is also a preferred initial therapy for adults with immune-active CHB. Consider TAF or entecavir in patients with or at risk for renal dysfunction or bone disease.	LAM, ADV and TBV are not recommended in the treatment of CHB (Evidence level I, grade of recommendation 1).	

AASLD

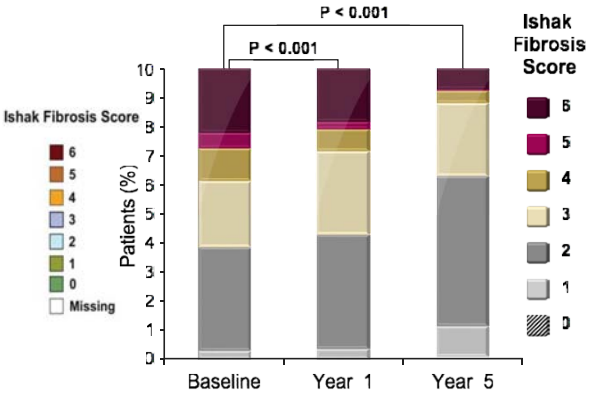
Regression of Fibrosis with Long-Term ETV or TDF Tx

ETV



N = 57 matched biopsies

TDF



N = 344 matched biopsies

- Not head-to-head trials; different patient populations and trial designs

Chang TT, et al. Hepatology. 2010;52:886-893.
Marcellline P, et al. Lancet 2013;381:468-475

AASLD

Summary of TAF Treatment Recommendations

AASLD HBV 2018 Guidance

TAF is recommended as a treatment option for the following patient populations:

- Adults with immune-active CHB as 1st line therapy
- Patients with, or at risk for, renal dysfunction or bone disease, including:
  - Suspected TDF-associated renal dysfunction and/or bone disease
  - Patients with decompensated cirrhosis who have renal dysfunction and/or bone disease
- LAM, ADV, LdT or ETV virologic breakthrough
- Special populations:
  - Acute symptomatic hepatitis B
  - HCV or HDV coinfection
  - HIV coinfection (as part of a full ARV therapy)
  - Immunosuppressive therapy recipients
  - Transplant recipients

Terrault NB et al. Hepatology 2018; Published online February 5, 2018: doi:10.1002/hep.29800.

AASLD

Treatment of CHB in Pregnancy

Recommendation	• Antiviral therapy for HBsAg+ pregnant women with HBV DNA levels >200,000 IU/mL

Treatment	• TDF is preferred
	  • Antivirals started at 28–32 weeks of gestation, and D/C at birth to 3 months post-partum
	  • After D/C, monitor for ALT flares every 3 months for 6 months
	• There are insufficient data to recommend the use of TAF in pregnancy
	• Infants of all HBsAg+ women should receive immunoprophylaxis
	• For pregnant women with immune-active hepatitis B, treatment should be based on recommendations for nonpregnant women
	• Breastfeeding is not contraindicated

AASLD HBV 2018 Guidance

Terrault NB et al. Hepatology 2018; Published online February 5, 2018: doi:10.1002/hep.29800.

AASLD

Treatment of CHB in Children

Recommendation	• Antiviral therapy in HBeAg+ children (ages 2 to < 18 years) with both elevated ALT* and measurable HBV DNA levels • Recommends against antiviral therapy in HBeAg+ children (ages 2 to < 18 years) with persistently normal ALT, regardless of HBV DNA levels
Treatment†	• IFN-α-2b: Approved for children ≥ 1 year old • LAM: Approved for children ≥ 2 years old • ETV: Approved for children ≥ 2 years old • Peg-IFN: not approved for children with CHB • TDF: Approved for children ≥ 12 years old

* ULN: Males 35 U/L, Females 25 U/L is suggested to guide management decisions
††TAF has not been studied in children. There are insufficient data to recommend use of TAF in children 12 years of age and older.

AASLD HBV 2018 Guidance

Terrault NB et al. Hepatology 2018; Published online February 5, 2018: doi:10.1002/hep.29800.

AASLD

Treatment of Patients with Acute Symptomatic Hepatitis B

AASLD HBV 2018 Guidance

Recommendation	Antiviral treatment is indicated for only those patients with acute hepatitis B who have acute liver failure or who have a protracted, severe course*
Treatment	TAF, TDF, or ETV are preferred Peg-IFN is contraindicated
Duration	Treatment should be continued until HBsAg clearance is confirmed or indefinitely in those who undergo liver transplantation

*indicated by total bilirubin >3 mg/dL (or direct bilirubin >1.5 mg/dL), international normalized ratio > 1.5, encephalopathy, or ascites

Terrault NB et al. Hepatology 2018; Published online February 5, 2018: doi:10.1002/hep.29800.

Treatment of Patients with HBV and HCV Coinfection

Testing	• HBsAg+ patients should be tested for HCV infection using the anti-HCV test
Treatment	• HCV treatment is indicated for patients with HCV viremia • HBV treatment is determined by HBV DNA and ALT levels as per the AASLD HBV guidelines for monoinfected patients

Monitoring	• **HBsAg+** patients are at risk of HBV DNA and ALT flares with HCV DAA therapy
	  • Monitoring of HBV DNA levels every 4 to 8 weeks during treatment and for 3 months posttreatment is indicated in those who do not meet treatment criteria for monoinfected patients
	• **HBsAg–, anti-HBc+** patients with HCV are at very low risk of reactivation with HCV DAA therapy.
	  • ALT levels should be monitored at baseline, at the end of treatment, and during follow-up, with HBV DNA and HBsAg testing reserved for those whose ALT levels increase or fail to normalize during treatment or posttreatment

AASLD HBV 2018 Guidance

Terrault NB et al. Hepatology 2018; Published online February 5, 2018: doi:10.1002/hep.29800.

Treatment of Patients with HBV and HIV Coinfection

AASLD HBV 2018 Guidance

Recommendation	• All patients with HBV and HIV confection should initiate ARV therapy, regardless of CD4 count

Treatment	• TAF or TDF plus 3TC or FTC should form the backbone of ARV therapy
	• If already receiving effective ARV therapy without activity against HBV
	  • Change to include TAF or TDF plus 3TC or FTC
	  • ETV is reasonable if patients are receiving fully suppressive ARV therapy

ARV: Anti-retroviral ; 3TC: Lamivudine; FTC: Emtricitabine

Terrault NB et al. Hepatology 2018; Published online February 5, 2018: doi:10.1002/hep.29800.

Treatment of Patients with HBV and HDV Coinfection

AASLD HBV 2018 Guidance

Testing	Anti-HDV screening: • In HIV+ persons, PWIDs, MSM, those at risk for STDs, and immigrants from areas of high HDV endemicity • May screen patients with low HBV DNA and high ALT • Initial test when uncertain regarding the need to test • Periodic retesting in those at risk for HDV acquisition

Treatment	• Peg-IFN for 12 months:
	  • If HDV RNA levels and ALT are elevated
	• TAF, TDF, or ETV:
	  • If HBV DNA levels are elevated

Monitoring	• Periodic assessment of HDV RNA and HBV DNA • HDV relapse if ALT elevation occurs following treatment

PWID: Persons who inject drugs; MSM: Men who have sex with men; STDs: Sexually transmitted diseases

Terrault NB et al. Hepatology 2018; Published online February 5, 2018: doi:10.1002/hep.29800.

Treatment of Patients undergoing Immunosuppressive and Cytotoxic Therapy

Testing	• HBsAg and anti-HBc testing* prior to initiation of any immunosuppressive, cytotoxic, or immunomodulatory therapy
Treatment	• **HBsAg+, Anti-HBc+** patients should initiate anti-HBV prophylaxis before immunosuppressive or cytotoxic therapy • TAF, TDF, or ETV are preferred
Duration	• Anti-HBV prophylaxis should continue during immunosuppressive therapy and for at least 6 months (or for at least 12 months for patients receiving anti-CD20 therapies) after completion of immunosuppressive therapy
Monitoring	• **HBsAg-, Anti-HBc+** patients could be carefully monitored with ALT, HBV DNA, and HBsAg with the intent for on-demand therapy^ • For patients being monitored without prophylaxis, HBV DNA should be obtained every 1-3 months • Patients should be monitored for up to 12 months after cessation of anti-HBV therapy

AASLD HBV 2018 Guidance

* Total or IgG

^ except for patients receiving anti-CD20 antibody or undergoing stem cell transplantation, for whom anti-HBV prophylaxis is recommended

Terrault NB et al. Hepatology 2018; Published online February 5, 2018: doi:10.1002/hep.29800.

AASLD

Guidance Statements for Treatment of Liver Transplant Recipients with Hepatitis B

	HBsAg+ patients	HBsAg- patients
Recommendation	• **All HBsAg+** patients undergoing liver transplantation should receive prophylactic therapy with NAs ±HBIG post transplantation regardless of HBeAg status or HBV DNA level pretransplant	• **HBsAg-** patients receiving **HBsAg-, Anti-HBc+** grafts should receive long-term antiviral therapy to prevent reactivation
Treatment	• HBIG monotherapy should not be used • TAF, TDF, ETV are preferred	• TAF, TDF, ETV are preferred
Duration	Prophylactic therapy should be lifelong	

AASLD HBV 2018 Guidance

Terrault NB et al. Hepatology 2018; Published online February 5, 2018: doi:10.1002/hep.29800.

AASLD

Guidance Statements for Management of Hepatitis B in Nonliver Solid Organ Transplant Recipients

	HBsAg+ patients	HBsAg- patients
Testing	• Transplant recipients should be tested for HBsAg, anti-HBc, and anti-HBs. • Patients without anti-HBs should receive hepatitis B vaccination pretransplant	

Recommendation	• **HBsAg+** organ transplant recipients should receive lifelong antiviral therapy to prevent or treat reactivation of HBV after transplantation
	  • TAF, TDF or ETV are preferred
		• **HBsAg–, anti-HBc+** non-liver organ transplant recipients should be monitored for reactivation without prophylactic therapy
		  • Antiviral therapy for 1st 6-12 months may be considered
		• **HBsAg–** nonliver recipients who received **anti-HBc+ grafts** should be monitored for HBV infection without prophylactic therapy
		• Measure ALT and HBV DNA Q3 months for the first year post transplant and after receipt of T cell-depleting therapies

AASLD HBV 2018 Guidance

Terrault NB et al. Hepatology 2018; Published online February 5, 2018: doi:10.1002/hep.29800.

Thank you!

Key take home points

- HBV is an incurable disease
- anti-HBc = cccDNA
- Stage all patients with imaging and noninvasive testing
- Determine phase of viral/liver disease looking at HBeAg status, ALT and HBV DNA
- Link all patients to care who are HBsAg+
- Determine who should be treated with an integration of ALT, HBV DNA quant and level of fibrosis
- Test all HBsAg patients for anti-HDV, HCV and consider HIV testing
- For patients who are HBsAg+: Test all contacts and family members for HBV using the triple panel of biomarkers
- Know the details of managing special populations
- Be aware of risk for HBV reactivation and guide monitoring according to risk level

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Autoimmune Hepatitis: When to Change and When/If to Stop Therapy

Autoimmune hepatitis (AIH) results from a failure of immune tolerance mechanisms that trigger a continuous immune-mediated liver injury[1]. Genetic and environmental factors may affect the natural history of this condition. If left untreated, AIH results in progressive liver injury that can cause liver cirrhosis, decompensation, hepatocellular carcinoma and death[2]. In less frequent occasions, AIH may cause acute hepatitis and fulminant liver failure.

Corticosteroids were found to lessen or resolve inflammation in autoimmune hepatitis in the early 1950s, and so, AIH became the first medically treatable liver disease. The goal of therapy has been refined over the years, basically showing that the lower the level of transaminitis the better the outlook for the patient, and no evidence of inflammation by liver biopsy is better than mild or moderate inflammatory activity[3].

As with any other chronically drug-treated condition, there are patients who do well, tolerate the medication and have good outcomes, those who have tolerable side effects, those who fail to respond to treatment and those who are intolerant of the prescribed medications. There are situations then that call for alternative therapies and times when the patient and/or the provider want to explore the possibility of treatment discontinuation. Both of these scenarios lack clear guidance.

The most accepted approach to treating AIH consists of corticosteroids at the outset to induce remission and then maintenance of remission with azathioprine[4]. Both these drugs have side effects in the short and long term as well as well-defined contraindications to their use. Switching to alternative therapy is called for when there is intolerance or contraindication to standard of therapy. Mycophenolate mofetil has the most data for this indication and is a valuable second line drug. Other therapies that have been explored and for which data consists of just small series, include Cyclosporine A, Tacrolimus, 6-mercaptopurine, Rituximab, Cyclophosphamide, Methotrexate and Infliximab[5,6,7]. More recently budesonide has been used for its first pass metabolism in the liver to lessen the corticosteroid-related adverse effects[8].

When first line therapy is tolerated and works well, the goal of treatment is normalization of liver biochemistries and resolution of inflammation in the liver. Up to 45% of patients that achieve biochemical remission still show inflammatory activity on a liver biopsy[10]. It has also been described that histology lags biochemical response for up to 2 years[11]. The accepted assessment of histologic remission has been timed at 2 years after achievement of normal liver biochemistries and if those values have remained in the normal range continuously for those 2 years[12].

The question then arises as to when (if ever) is safe to withdraw therapy. The goal is to stop taking medication, avoid cost and side effects, while maintaining remission of disease. While there are several factors known to be poor prognosticators of continued remission[12,13,14], we basically can't accurately assess who will stay in remission and who will relapse. Relapse is associated with new symptoms, progressive liver damage and usually requires, at least for a while, higher doses of medications. Unfortunately in some patients, relapse is associated with loss of response to previously beneficial therapeutic interventions.

Small series have shown that less than 10% of patients with autoimmune hepatitis referred to and mnaged at specialized liver units achieve long term remission[15.16].

References

1. Al-Chalabi T and Heneghan MA. Am J. Gastroenterol 2007;102:1013-1015
2. Manns MP, Czaja AJ, Gorham JD, et al. Diagnosis and management of autoimmune hepatitis. Hepatology 2010; 2193-2213.
3. Muratori L, Muratori P, Lanzoni G, et al. Hepatology 2011;51:1857-1858.
4. Manns M, Czaja AJ, Gorham JD, et al. Heptology 2010;50:2193-2213.
5. Manns MP and Taubert R. Clin. Liv. Dis. 2014;3:15-17.
6. Fernandes NF, Redeker AG, Vierling JM, et al. Am J Gastroenterol 1999;94:241-248.
7. Efe C, Hagstrom H, Ytting H, et al. Clin Gastro and Hepatol 2017;15:1950-1956.
8. Johnson et al. NEJM 1995
9. Gleeson D and Heneghan MA. Gut 2011;60:1611-1629.
10. Dhaliwal HK, Hoeroldt BS, Dube AK, et al. Am J Gastro 2015;110:993-999
11. Vierling JM. Clin Gastro Hep 2015;13:2088-2108.
12. van Gerven NMF, Verwer BJ, Witte BI, et al. J. Hepatol 2013;58:141-147.
13. Montano Loza AJ, Carpenter HA and Czaja AJ. Hepatology 2007;46:1138-1145.
14. Hartl J, Ehlken H, Weiler-Normann C, et al. J. Hepatol 2015;62:642-646
15. Kanzler S, Gerken G, Lohr H et al. J. Hepatol 2016: 355-356.

AUTOIMMUNE HEPATITIS

WHEN TO CHANGE AND WHEN/IF TO STOP THERAPY

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AUTOIMMUNE HEPATITIS

- Incidence: 1-2 cases per 100,000 persons per year
- Women 3.6: 1 Men
- All ages, peak incidence between 16-30 years of age
- Variable presentation and clinical course but most commonly a slowly progressive disease
- Left untreated it decreases lifespan
- First liver disease found to be manageable by drug therapy

Manns et al. Hepatology 2010
Vierling JM. Clin Gastro Hep 2015
Hartl et al. J. Hepatol 2017

PATHOPHYSIOLOGY OF AUTOIMMUNE HEPATITIS

- Environmental triggers +
- A failure of immune tolerance mechanisms +
- A genetic predisposition (HLA- DRB1*0301 and *0401),
- Result in humoral and cellular-mediated immune attack of liver antigens

NATURAL HISTORY

- 70% of asymptomatic patients will become symptomatic
  - Life-long F/U is recommended to monitor for change in activity of the disease
- Liver biopsy at presentation is recommended
  - Establish diagnosis
  - Guide treatment decision

WHO IS SAFE NOT TO TREAT?

- 80% will have histological remission within 3 years
  - Reversal of fibrosis and cirrhosis have been reported
- Untreated asymptomatic patients with mild disease have a lower 10 year survival than treated counterparts
  - 67% vs 98% $p<0.01$
- Patients with inactive disease or burnt out cirrhosis will not benefit from anti-inflammatory therapy
  - Lower risk of reactivation?

Al-Chalabi et al. Am J. Gastroenterol 2007

THE LOWER THE TRANSAMINASES, THE BETTER

	2002 CRITERIA	2010 CRITERIA
Definition of remission	ALT & AST < 2x ULN	ALT & AST in normal range
Entered remission	73%	26%
Long term outcomes	25.8% maintained normal LFTs	
Worsening Histology and Clinical Outcomes	54.5%	4%

Muratori et al. Hepatology 2011

STANDARD TREATMENT REGIMENS

- Corticosteroid monotherapy (prednisone or budesonide)
  - Taper once remission has bee achieved
  - Maintenance until there is resolution of disease, treatment failure or drug intolerance
- Prednisone + azathioprine
  - Preferred treatment for the lower occurrence of corticosteroid-related side effects

CONTRAINDICATIONS TO TREATMENT

STEROIDS	AZATHIOPRINE
Brittle Diabetes	TMPT deficiency (0.3-0.5% of pop)
Untreated or uncontrolled psychosis	Severe cytopenias
Severe osteoporosis	

BUDESONIDE

USE TO DECREASE RISK OF:

- Weight gain
- Type 2 Diabetes
- Osteoporosis
- Hypertension
- Cataract formation
- Psychosis
- Pediatric patients

NO BENEFIT IN:

- Presence of cirrhosis for loss of first pass metabolism benefits

Johnson et al. NEJM 1995
Woynarowski et al. J. Pediatr 2013

TREATMENT ENDPOINTS

- Goal of initial therapy
  - Normalization of transaminitis, gamma glob and IgG
- Once biochemical remission is achieved,
  - Continue treatment for 2 years
- Then perform liver biopsy to assess for histologic remission
  - 25% at 12 months
  - 80% at 36 months*
- ~45% of patients with persistently normal ALT and globulins will have inflammation on liver histology

Gleeson et al. Gut 2011
Dhaliwal et al. Am J Gastro 2015
Vierling JM Clin Gastro Hep 2015

WHEN TO SWITCH TREATMENT

- Inability to normalize ALT within 6 months of starting first line therapy
  - 10-15%
- Evidence of progression of disease (9%) despite adherence
  - Repeat liver biopsy? Elastography?

OTHER THERAPIES	EFFICACY in AZA intolerance	In non-responders
Mycophenolate mofetil	60%	34%
Cyclosporine A	73%	
Tacrolimus	80%	57%
Rituximab		
Others: Cyclophosphamide, Infliximab, Methotrexate, 6-mercaptopurine		

*Manns et al Clin. Liv. Dis. 2014
*Efe et al. Clin Gastro and Hepatol 2017
*Fernandes et al. Am J Gastroenterol 1999

AZATHIOPRINE METABOLITES

- Patients who maintained remission tended to be on lower doses of AZA but had significantly higher concentrations of 6-TGN
  - 237 vs. 177 pmol/8 x 10^8 RBCs
- 6-MMPN concentrations did not affect response but higher levels were associated with cholestasis
- TMPT activity did not predict response
- An avTGN concentration of >220 pmol/8 x 10^8 RBCs best predicted remission (OR 7.7, p=0.003)

Dhaliwal et al. Hepatology 2012

WHEN TO CONSIDER TREATMENT DISCONTINUATION?

- LFTs and IgG have been repeatedly normal for a minimum of 2 years
- Liver biopsy shows no inflammation
  - Histology lags biochemistries by up to 8 months*
- 2015 EASL guidelines recommend liver biopsy prior to considering treatment withdrawal

Center	Hamburg	Mainz
Population	228	103
Withdrew treatment	28	28
Achieved long term remission	15 (6.6%)	7 (6.8%)

Manns et al. Gastroenterology 2010 Hartl et al. J. Hepatol 2015 Kanzler et al. J. Hepatol 2016

RISK FACTORS FOR RELAPSE

- Younger age
- Acute presentation, higher bilirubin levels at presentation
- Higher MELD score at presentation
- Type 2 AIH (LKM-1, LC-1 Ab)
- Slower response to therapy
- Failure to maintain consistently normal transaminases during treatment and at the time of remission
- Liver biopsy is not completely normal
  - Presence of interface hepatitis
  - Plasma cells
- SLA antibodies
- HLA B8, HLA DRB1*03

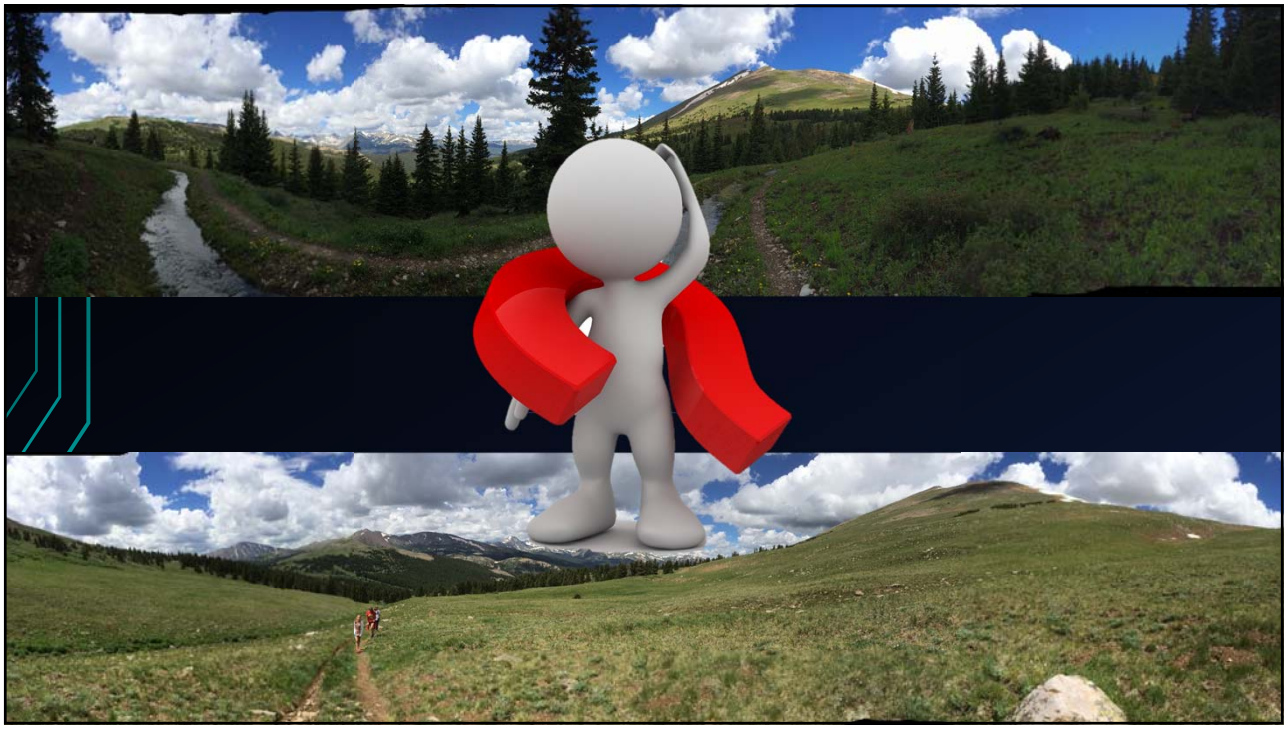
van Gerven et al. J. Hepatol 2013
Montano Loza et al. Hepatology 2007
Dhaliwal et al. Am J Gastroenterol 2004
Vierling JM. Clin Gastro Hep 2015

CONSEQUENCES OF RELAPSE

- Relapse occurs in ~90% of patients who stop medication
- Progression to cirrhosis (38% vs. 4% p=0.004) and death from liver failure or need for liver transplantation (20% vs. 0 p=0.008) are more common in those who relapse vs. those who maintain remission
- Relapse is associated with more treatment related AEs
- Relapse is treated with prednisone + azathioprine induction followed by azathioprine chronic maintenance
  - 87% will stay in treatment-sustained remission
  - Delayed successful drug withdrawal can be achieved in another 13% of patients

CONCLUSIONS

1. Life-long condition
2. Good response to treatment
   - Improved symptoms
   - Improved liver histology
   - Improved outcomes
3. Acceptable alternative treatments
4. We don’t have good tools to assess who and when to stop treatment
5. Less than 10% of patients achieve long term, medication-free remission



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Pearls in the Management of PBC and PSC

Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease characterized by inflammation and destruction of the small interlobular bile ducts. It is immune-mediated and affects predominantly middle-aged females. PBC is diagnosed in the presence of 2 of the following criteria: 1- chronic unexplained cholestasis, 2- positive antimitochondrial antibody (AMA) and 3- histology showing non-suppurative destructive cholangitis and ductopenia. Therefore, a liver biopsy is not always required for the diagnosis and better reserved for patients who are AMA-negative or in whom we are suspecting an alternative diagnosis (such as fatty liver) or the overlap with autoimmune hepatitis.

Treatment with ursodeoxycholic acid (UDCA) 13-15 mg/kg/day has been shown to slow progression of fibrosis and improve survival free of liver transplantation. However, approximately 40% of patients do not respond completely to UDCA and remain at risk for disease progression. It is imperative that we learn to recognize those incomplete responders as early as possible in order to consider second-line therapy. For that reason, it is recommended to monitor liver biochemistries after UDCA initiation, and evaluate for disease response 1 year after UDCA has been started. Non-response can be determined based on serum alkaline phosphatase (ALP) levels, one of many published binary response criteria, or the newer mathematical models such as the GLOBE PBC score or the UK PBC score.

Once we determine that a patient is a non-responder, or an incomplete responder, to UDCA, we can consider starting obeticholic acid (OCA, FXR agonist), which is the only second-line therapy approved by the FDA, and follow the appropriate dose recommendations to avoid hepatic decompensation: for non cirrhotic or child A patients the starting dose is 5 mg/day, whereas for child B or C patients the starting dose is 5 mg twice a week. Itching is the most common side-effect of OCA and physicians should feel comfortable managing this symptom.

For patients who are not candidates for or unwilling to use OCA, off-label options include fibrates (PPAR agonists) and budesonide, for selected cases with increased inflammatory component. Newer agents are under evaluation, with seladelpar (a PPAR delta selective drug) being further along in the drug development process.

Primary sclerosing cholangitis (PSC) is another immune-mediated liver disease that causes inflammation and fibrosis of the intra- and/or extra-hepatic bile ducts, eventually leading to biliary cirrhosis and problems with biliary obstruction and cholangitis. Secondary causes of sclerosing cholangitis must be ruled out prior to establishing the diagnosis of PSC.

There is no FDA-approved medical therapy for PSC, but clinicians have an important role in the surveillance for hepatobiliary malignancies as well as colorectal cancer for patients with associated inflammatory bowel disease (IBD). Furthermore, clinicians need to recognize the presence of cholangitis and understand when to intervene.

In the specific setting of co-existence of PSC-IBD, a colonoscopy is recommended annually for surveillance. Cross sectional imaging should be done annually to survey for cholangiocarcinoma. If suspicious strictures are identified, or in the setting of worsening

symptoms and laboratory tests, efforts should be made to sample the stricture to rule out malignancy.

References

1. Lindor KD et al. Primary biliary cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases. Hepatology 2019;69(1):394-419
2. Levy C. Primary biliary cholangitis guidance update: implications for Liver Transplantation. Liver Transplantation 2018; 24(11):1508-1511
3. Nevens F et al. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. New England Journal of Medicine 2016;375(7):631-43
4. Corpechot C et al. A placebo-controlled trial of bezafibrate in primary biliary cholangitis. New England Journal of Medicine 2018;378(23):2171-2181
5. Lammers WJ et al. Levels of alkaline phosphatase and bilirubin are surrogate endpoints of outcomes of patients with primary biliary cirrhosis: an international follow-up study. Gastroenterology 2014;147(6):1338-49
6. Carrion AF et al. Understanding and treating pruritus in primary biliary cholangitis. Clinics in Liver Disease 2018;22(3):517-32
7. Lindor KD et al. ACG Clinical Guideline: Primary sclerosing cholangitis. American Journal of Gastroenterology 2015;110(5):646-59
8. Ali AH et al. Surveillance for hepatobiliary cancers in patients with primary sclerosing cholangitis. Hepatology 2018;67(6):2338-2351
9. Sedki M et al. Update in the care and management of patients with primary sclerosing cholangitis. Current Gastroenterology Reports 2018;20(7):29
10. Goldstein J and Levy C. Novel and emerging therapies for cholestatic liver diseases. Liver International 2018;38(9):1520-35

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PEARLS IN THE MANAGEMENT OF PBC AND PSC

CLINICAL HEPATOLOGY UPDATE

Cynthia Levy, MD, FAASLD

June 14, 2019

Meet Ms. EG

- 49 yo WF diagnosed with AMA-positive PBC in 2014. Liver biopsy at diagnosis consistent with stage 1 disease.
- On UDCA 1000 mg/day (14 mg/kg/day)
- Mild pruritus
- Liver elastography: LS 11.5 kPa
- Labs:

4.8	11.5 / 33.5	127

8.1	54		0.8
4.0	49	357	

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PBC PEARL #1:
AMA Positivity ≠ PBC

- FACTS about PBC and antimitochondrial antibody (AMA)
  - 90-95% of patients with PBC are AMA (+)
  - The prevalence of (+) AMA in the general population is 1:1000
  - The prevalence of PBC is 0.4:1000

Only 1 in 6 individuals with (+) AMA and normal ALP will develop PBC in 5 years

You need more than a (+) AMA to diagnose PBC

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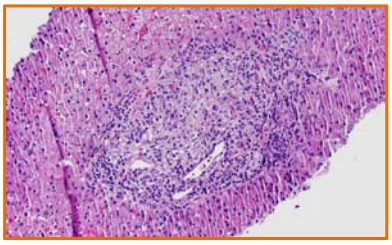
PBC Diagnosis

- Unexplained Elevation of ALP ≥ 1.5x ULN
- Positive anti-mitochondrial antibody or PBC-specific ANA
- Non-suppurative destructive cholangitis on histology



Two out of these 3 criteria are required for the diagnosis of PBC

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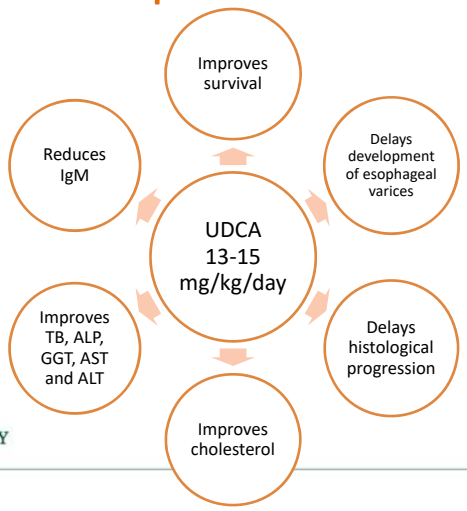
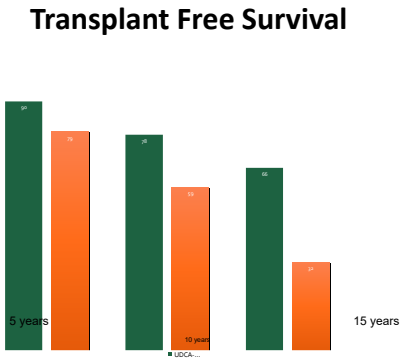
PBC PEARL #2:

Response to UDCA is NOT Universal





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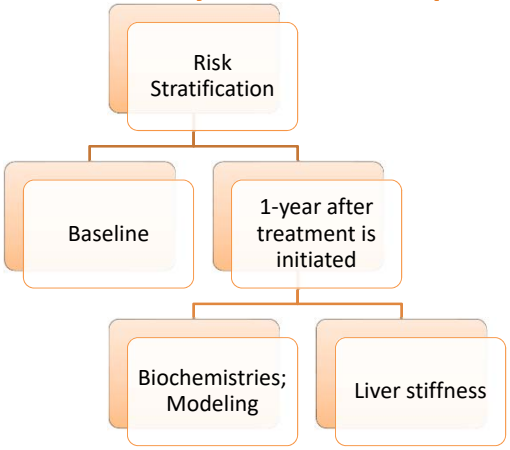
PBC PEARL #3:

Risk Stratify and Identify Non-Responders



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HIGH RISK FOR PROGRESSION

Baseline factors

Younger than 45	Male gender, Hispanic ethnicity	Elevation total bilirubin, lower albumin	Presence of gp-210, anti-centromere	APRI > 0.54	Liver stiffness > 9.6 kPa

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Carbone M et al Gastro 2013; Levy C et al CGH 2011; Corpechot C et al Hepatology 2006; Kuiper E et al Gastro 2009; Trivedi P et al J Hepatol 2014; Nakamura et al. Hepato Res 2007

Up to 40% of Patients are Non-Responders or Incomplete Responders

Binary definitions	Time (months)	Treatment failure
Rochester[1]	6	ALP ≥2 ULN
Barcelona[2]	12	Decrease in ALP ≤40% and ALP ≥1x ULN
Paris-I[3]	12	ALP ≥3x ULN or AST ≥2x ULN or bilirubin >1 mg/dl
Rotterdam[4]	12	Bilirubin ≥1x ULN and/or albumin <1x ULN
Toronto[5]	24	ALP >1.67x ULN
Paris-II[6]	12	ALP ≥1.5x ULN or AST ≥1.5x ULN or bilirubin >1 mg/dl
Ehime[7]	6	Decrease in GGT ≤70% and GGT ≥1 ULN
Continuous scoring	Time (months)	Scoring parameters
UK-PBC[8]	12	12 months: bilirubin, ALP and AST (or ALT); Baseline: albumin and platelets
GLOBE[9]	12	12 months: bilirubin, ALP, albumin, and platelet count; Baseline: age

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EASL Clinical Practice Guidelines. J Hepatol 2017

At a Minimum…

- Look at serum ALP, TB, albumin after 1 year of therapy with UDCA
- If ALP > 2x ULN or abnormal bilirubin ➔ Consider incomplete response to UDCA

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PBC PEARL #4:

There are Options for Non-Responders!!!

- **Obeticholic Acid is FDA-Approved**
  - In combination with UDCA for patients with PBC who have been treated with UDCA for > 1 year and have incomplete response
  - As monotherapy for patients with PBC who are intolerant to UDCA

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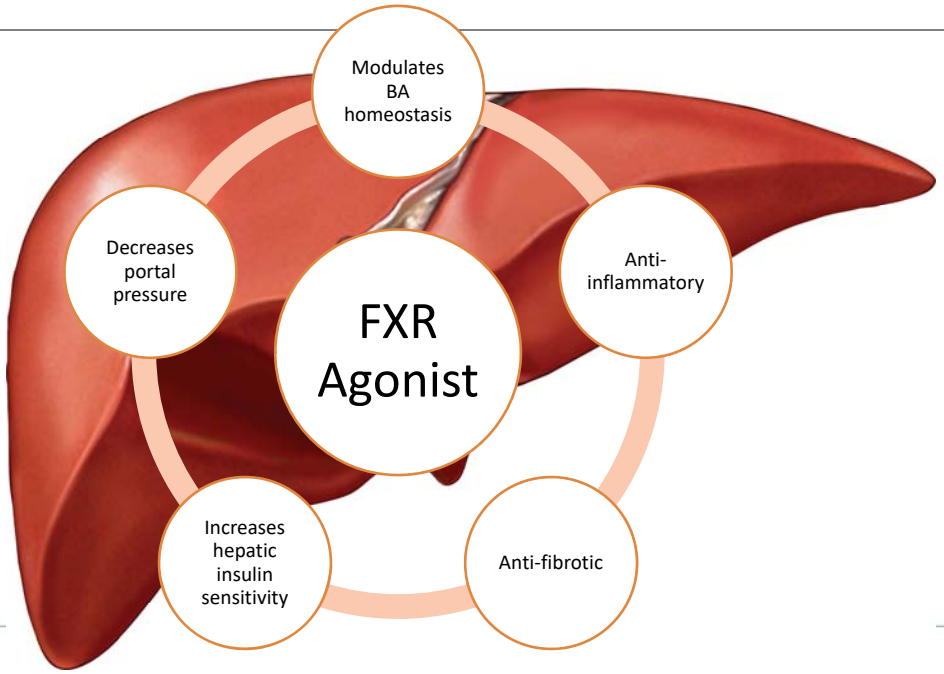

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Obeticholic Acid for PBC: POISE trial

- 46% of patients on OCA met the primary endpoint compared to 10% of pts on placebo
- Significant drop in ALP, AST, ALT, GGT, TB
- Significant reduction in inflammatory markers
- Reduction in HDL-cholesterol
- No change in liver stiffness scores

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Nevens F, et al. *N Engl J Med.* 2016;375:631-643.

OCA Dosing Recommendations

OCA Dose	Disease Stage	
	Non-cirrhotic or compensated cirrhosis (Child-Pugh A)	Decompensated cirrhosis, Child B or C (including prior decompensation)
Starting dose – 1st 3 months	5 mg/day	5 mg/week
Dose titration at 3 months	10 mg/day	5 mg twice a week, at least 3 days apart May increase to 10 mg twice a week, at least 3 days apart
Maximum dose	10 mg/day	10 mg twice a week

DOSE TITRATION IS RECOMMENDED TO MINIMIZE ITCHING

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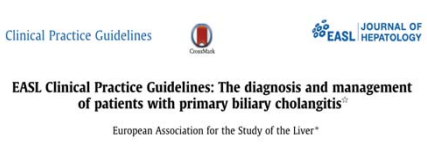
Use of Fibrates in PBC


Clinical Practice Guidelines

EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis

European Association for the Study of the Liver*


HEPATOLOGY

Practice Guidance | Free Access

Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases

Keith D. Lindor, Christopher L. Bowlus, James Boyer, Cynthia Levy, Marlyn Mayo

First published: 02 August 2018 | https://doi.org/10.1002/hep.30145

- Available: Bezafibrate & Fenofibrate
- PPAR agonists
- Several ongoing clinical trials
- Currently off-label use only

- ↑ BA detoxification
- ↑ BA secretion
- ↓ BA synthesis
- ↑ Fatty acid oxidation
- Down-regulates NF-KB pathway

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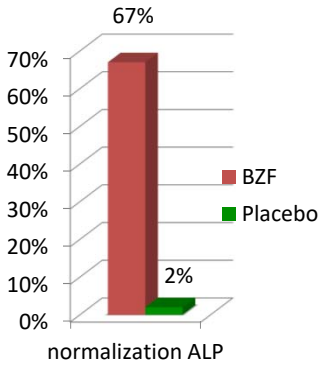
BEZURSO: Bezafibrate + UDCA vs. Placebo + UDCA

- ✓ 100 patients with incomplete response to UDCA
- ✓ Randomized to BZF 400 mg/day or placebo, for 2 years
- ✓ Primary endpoint* at 2 years:

  30% BZF vs. 0% Placebo
- ✓ Itch score, LSM and ELF improved in BZF group



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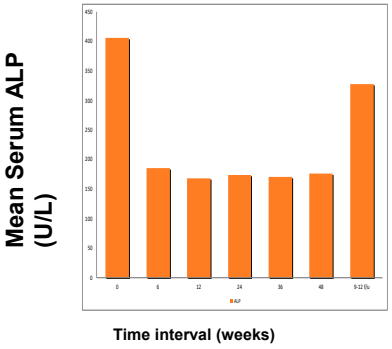
Corpechot C et al. *N Engl J Med* 2018;378:2171-2181

Fenofibrate + UDCA—Phase II Findings in PBC Patients with Incomplete Response to UDCA

- o Open-label (n = 20)
- o ALP levels decreased significantly
- o Rebound in ALP levels occurred following fenofibrate discontinuation



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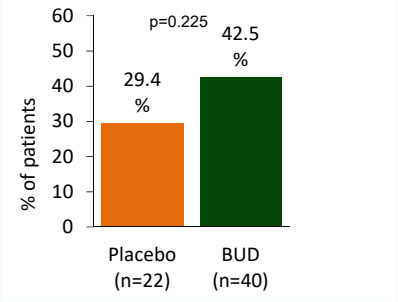
Levy C et al *Aliment Pharmacol Ther.* 2011;33:235-242. 2.

Budesonide add-on therapy in PBC patients: Phase 3 trial

- Randomized, double-blind, placebo-controlled trial (NCT00746486)
- 62 patients randomized and treated (ITT population) with 36 months of treatment with UDCA (12–16 mg/kg BW/day) with or without BUD (3 mg tid*)

Improved liver histology†



Improved liver function

ALP < 1.67x ULN and >15% drop in ALP:

43% BUD vs. 23% PBO (p=0.038)

- Pruritus: 15% (6/40) in BUD group and 31.8% in placebo group (7/22)
- SAEs: 10 in BUD group and 7 in placebo group

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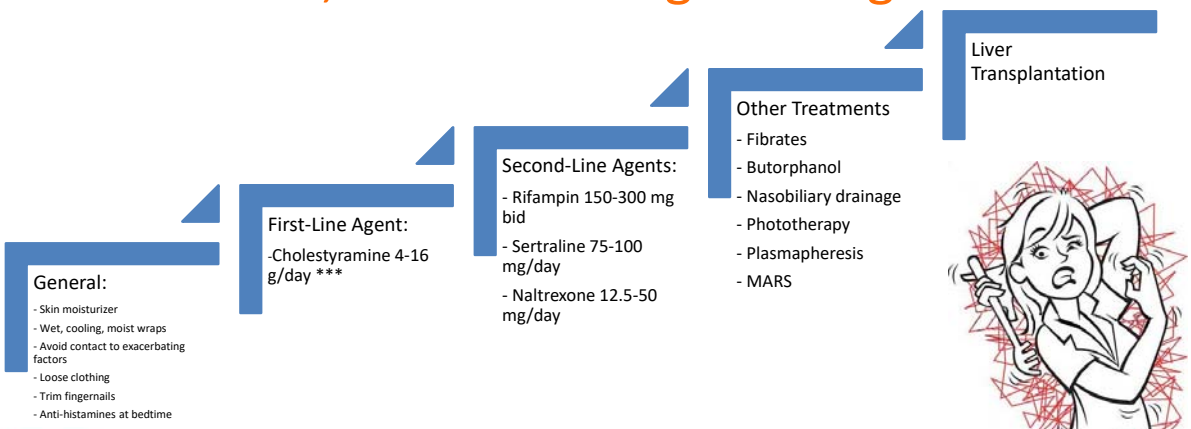
Hirschfield G, et al. ILC 2018, #2095 (GS-011)

PBC PEARL #5:

Yes, we can manage itching!



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Carrion AF et al. Clin Liver Dis 2018; Lindor KD et al. Hepatology 2019

Management of Moderate to Severe Itching During OCA Treatment

- If on 10 mg/day, reduce dose to 5 mg/day
- If on 5 mg/day and no contra-indication consider adding rifampin or cholestyramine*
- If no improvement, consider alternating days: OCA 5 mg qod, or even a short drug holiday of a few days or a week, then resuming OCA

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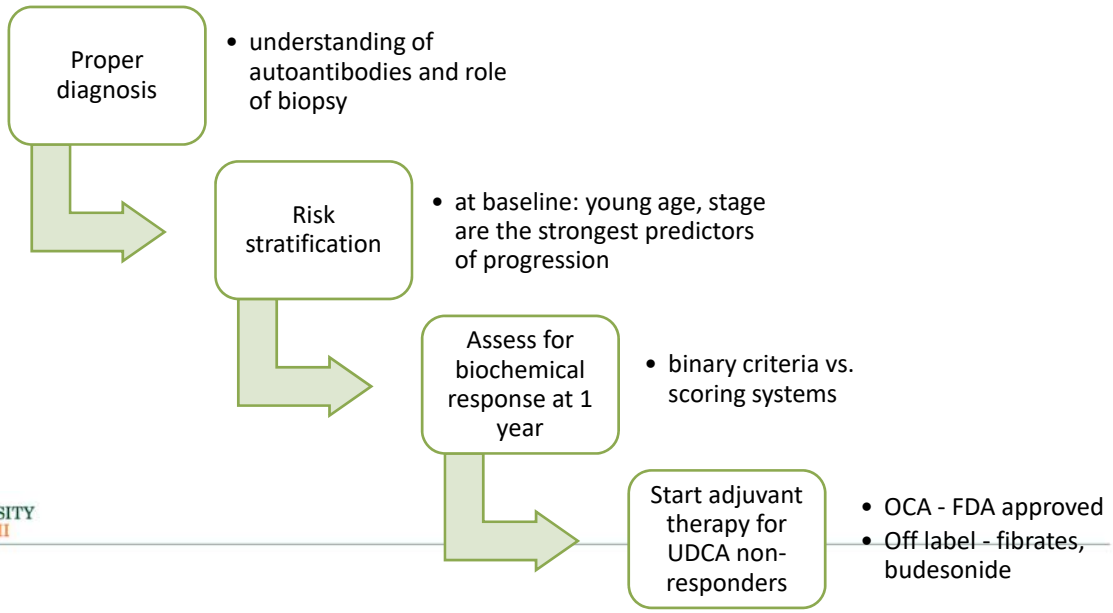
* As is the case with UDCA, cholestyramine must be administered 1 hour before or > 3 hours after OCA

Take Home Message: The New PBC Paradigms



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Key points about our patient:

- Recognize that she is an incomplete responder to UDCA
- Recognize that she has evidence of disease progression - thrombocytopenia, transient elastography LS 11.5 kPa
- Offer adjuvant therapy. Options are OCA, fibrates and less likely budesonide (would avoid in cirrhotics). Mild itching is NOT a contra-indication for OCA.
- Remember to screen for varices and survey for HCC

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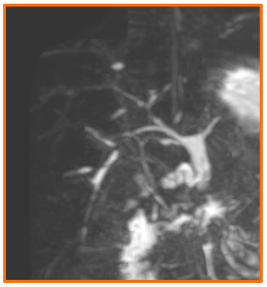
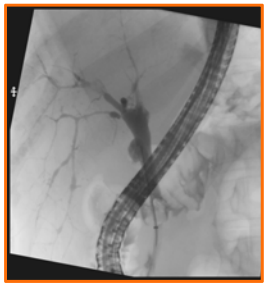
Meet Ms. CS

- 50 yo WHF with large duct PSC diagnosed in 2010
- h/o CUC with high grade dysplasia, s/p TPC +IPAA 2010
- h/o cholecystectomy 2009 for symptomatic cholelithiasis – had GB CA *in situ*
- Referred for jaundice x 1 week
  - On UDCA 17 mg/kg/day
  - ERCP: severe intrahepatic disease, dilated CBD, CBD stricture, stone + sludge in CBD
  - Labs:

    TB 8.8 → 4.3 → 2.6

    ALP 680 → 431 → 241





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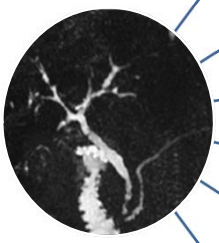
PSC PEARL #1:

We must rule out secondary causes of sclerosing cholangitis prior to diagnosing PSC



- **Infection**
  - Bacterial
  - Recurrent pyogenic cholangitis
  - HIV
  - Combined immunodeficiency
- **Mechanical/ Toxic**
  - Cholelithiasis/ choledocholithiasis
  - Surgical bile duct trauma
  - Intra-arterial chemo
  - Drug-induced sclerosing cholangitis
- **Ischemic**
  - vascular trauma
  - hepatic allograft arterial insufficiency
  - PNH
- **Systemic**
  - IgG4-RD
  - Sarcoidosis
  - GVHD
  - Hypereosinophilic syndrome
- **Cholangiography mimics**
  - Caroli
  - cholangiocarcinoma
  - Hodgkin's
  - Amyloidosis
- **Pancreaticobiliary disease**
  - Cystic fibrosis
  - Sclerosing cholangitis of the critically ill
  - ABCB4-associated cholangiopathy
  - Chronic pancreatitis

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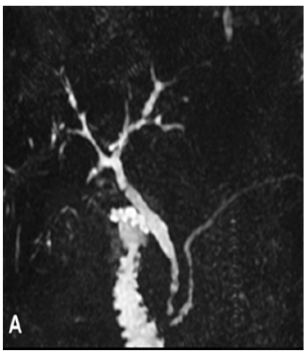
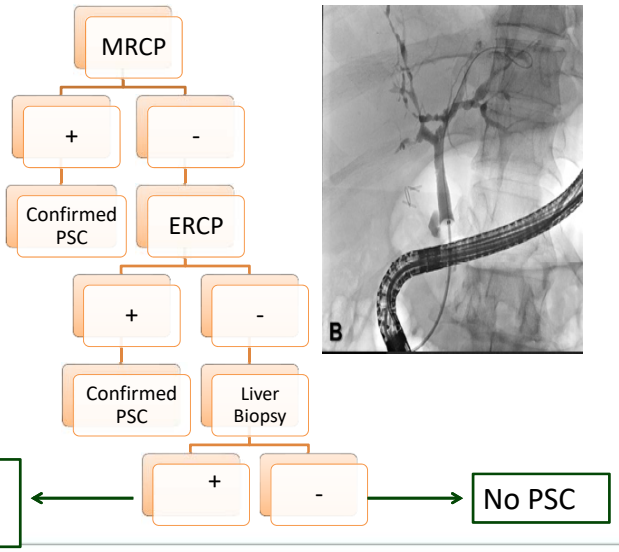
DIAGNOSTIC PROCESS





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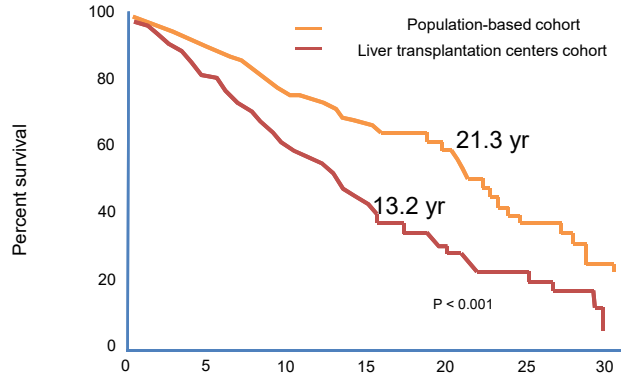
Aabakken L et al. Endoscopy 2017; EASL Practice guidelines 2009; Chapman et al Hepatology 2010; Lindor et al Am J Gastro 2015

Natural History:
Survival Without Liver Transplantation



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Boonstra et al. Hepatology 2013

PSC PEARL #2:
There is no FDA-Approved Therapy

- ACG 2015 Recommendations

"UDCA in doses >28 mg/kg/day should not be used for management of PSC"

" (…) patients who normalize liver biochemistries (…) have a better prognosis. This has led some to revisit the issue of UDCA treatment for PSC; many practitioners are using a dose of ≈ 20 mg/kg/day although data from well controlled clinical trials are lacking."

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Lindor et al. Am J gastro 2015

Role of UDCA in PSC

- Used by 50% US pts and 57.8% International pts – Kuo et al CGH 2018
- Improves liver biochemistries
- No demonstrable improvement in survival except for *trend* in Scandinavian study
- High dose UDCA >28 mg/kg/day is detrimental – Lindor et al Hepatology 2009

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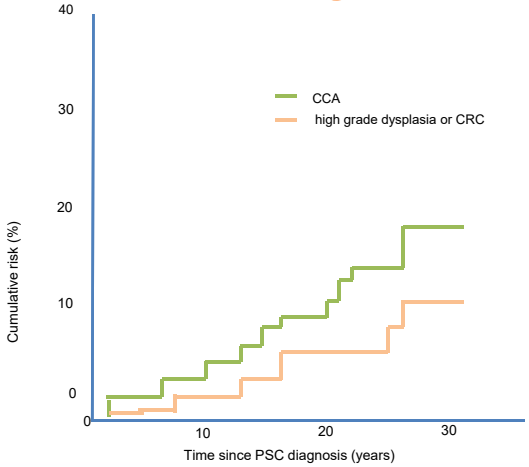
PSC PEARL #3:

PSC is a Pre-Malignant Condition



Lifetime risk of cholangiocarcinoma: 15-20%

Annual rate: 0.5-1.5%

Risk of GB Ca 10X increased

Cumulative risk of CCA and high-grade colon dysplasia or CRC in PSC patients.

Boonstra et al. Hepatology 2013

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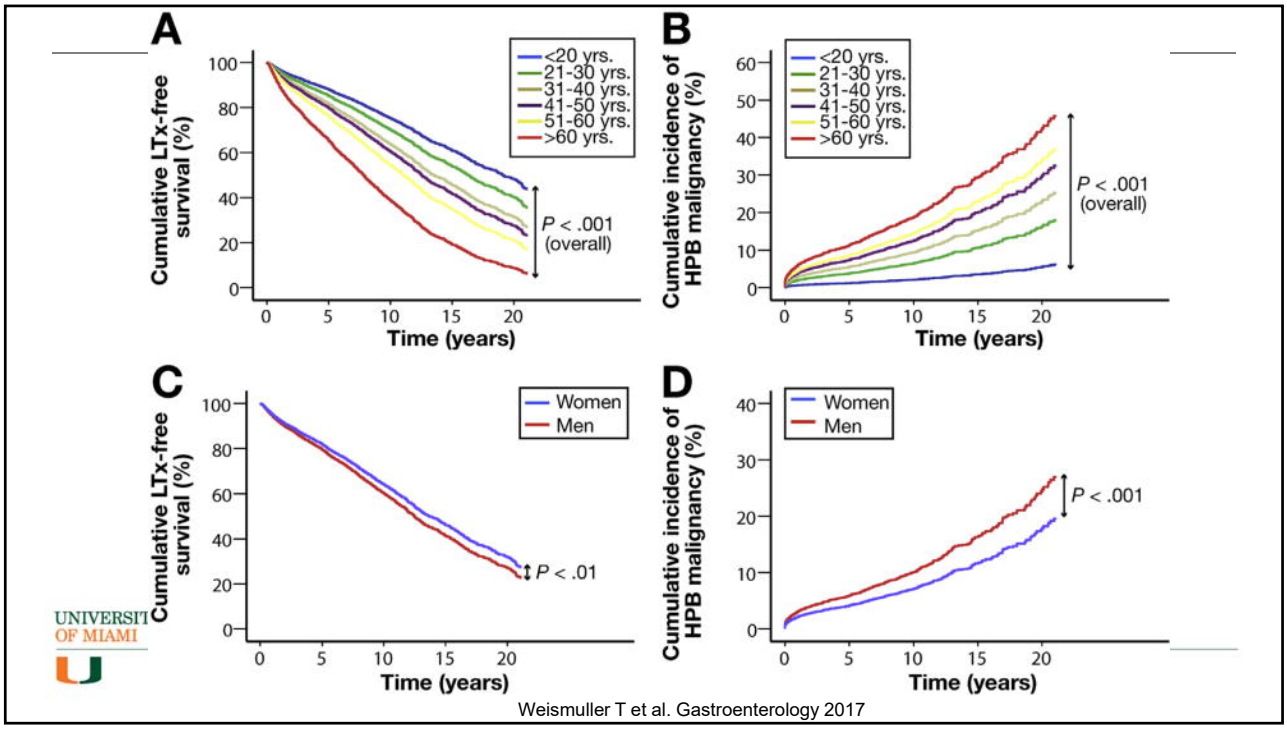
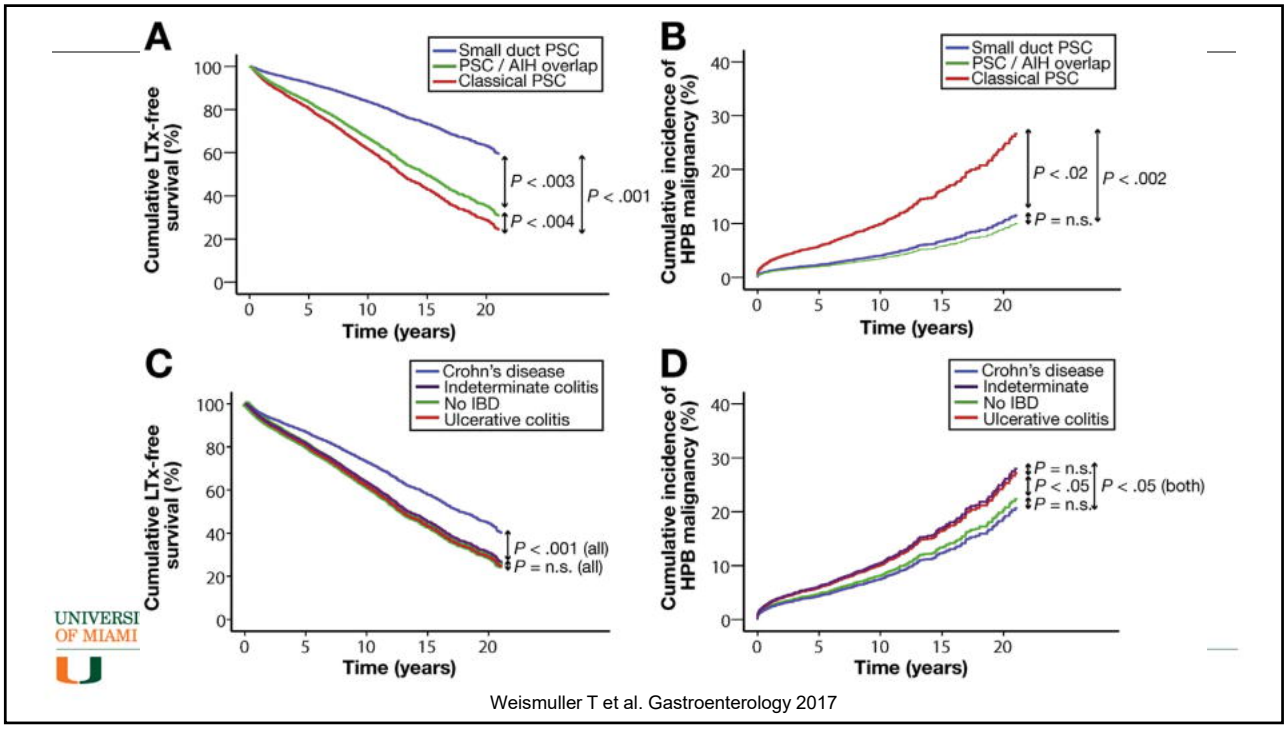
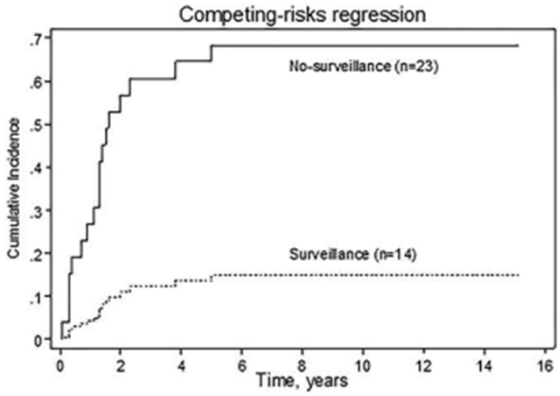


Weismuller T et al. Gastroenterology 2017



Weismuller T et al. Gastroenterology 2017

Surveillance for Malignancy is Associated with improved Outcomes in PSC



Patients who undergo surveillance have fewer cancer-related events (recurrence or cancer-related death). All-cause mortality 5.5x higher in patients NOT undergoing surveillance.

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Ali, Tabibian, et al. Hepatology 67(6);2018

Surveillance for CCA

- Cost effective program has not been demonstrated
- Use of CA 19-9 is problematic
  - 5-10% of population do not express it
  - It can be elevated in multiple other conditions
  - >30% of patients with high CA 19-9 DO NOT have CCA
  - Lower cut off (20U/mL) has very low PPV 20%

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Levy et al. Dig Dis Sci 2005; Razumilava et al. Hepatology 2011; Sinakos et al. Clin Gastroenterol Hepatol 2011

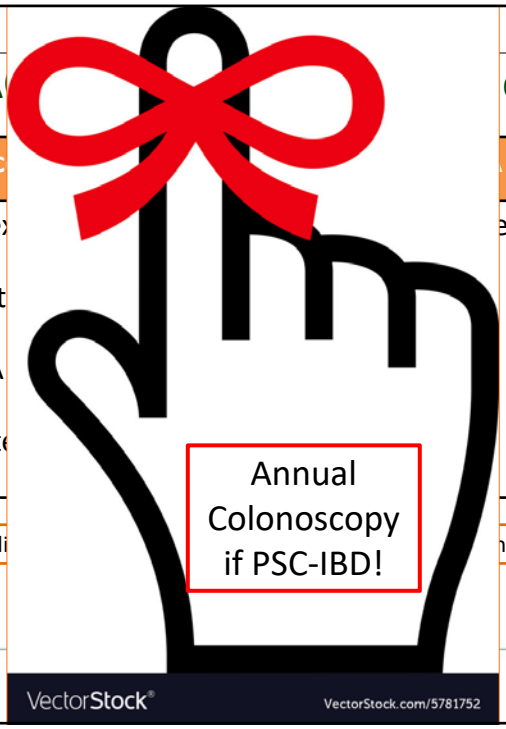
A ce

Surveillanc

Based on ex ence

- Cross sect
- Serum CA
- Cholecyste

Current guideli noma in children



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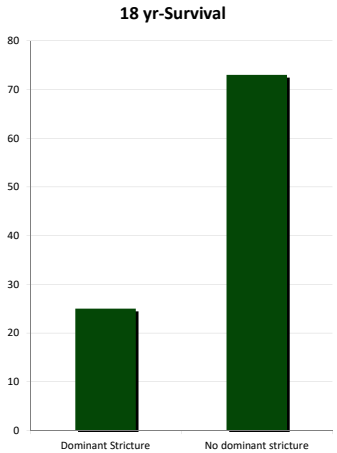
PSC PEARL #4:

Dominant Strictures Influence Survival

- Stenosis < 1.5 mm in the CBD or < 1mm in the hepatic ducts within 2 cm from bifurcation*
- Occur in ≈ 50%
- May cause sudden worsening with jaundice and cholangitis
- More frequently benign, but 22-26% are malignant



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Culver EL and Chapman R. AP&T 2011; Chapman MH et al. Eur J Gastro & Hepatol 2012; Rudolph et al. J Hepatology 2009; Tischendorf et al. Endoscopy 2006; Lindor KD AJG 2015

ACG Guideline PSC: Endoscopic Management

- ERCP with balloon dilatation is recommended for PSC patients with dominant stricture and pruritus, and/or cholangitis, to relieve symptoms.
- PSC with a dominant stricture seen on imaging should have an ERCP with cytology, biopsies, and fluorescence *in-situ* hybridization (FISH), to exclude diagnosis of cholangiocarcinoma.
- PSC patients undergoing ERCP should have antibiotic prophylaxis to prevent post-ERCP cholangitis.
- Routine stenting after dilation of a dominant stricture is not required, whereas short-term stenting may be required in patients with severe stricture.

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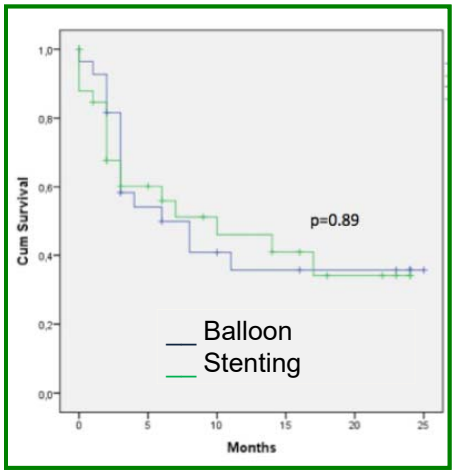
Lindor KD et al. Am J Gastro 2015

DILSTENT Study:

RCT Balloon Dilatation vs. Stenting



Recurrence occurred in:

- 48% of balloon dilatation
- 42% of stented patients

No difference in recurrence-free survival

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Ponsioen et al. Gastroenterology 2018

Procedure-Related SAEs

	Balloon Dil (N=30)	Stenting (N=33)	OR (95% CI)	P value
All SAEs	2 (6.7%)	15 (45%)	11.7 (2.4-57.2)	0.001
Cholangitis/ cholecystitis	1 (3.3%)	4 (12%)	4.0 (0.42-38)	0.36
Post-ERCP pancreatitis	1 (3.3%)	8 (24%)	9.3 (1.1-79.4)	0.03
Post-procedural pain	0	2 (4.5%)	NA	
ascites	0	1 (3%)	NA	

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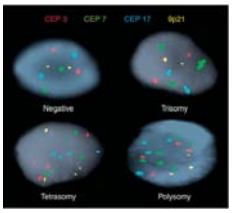
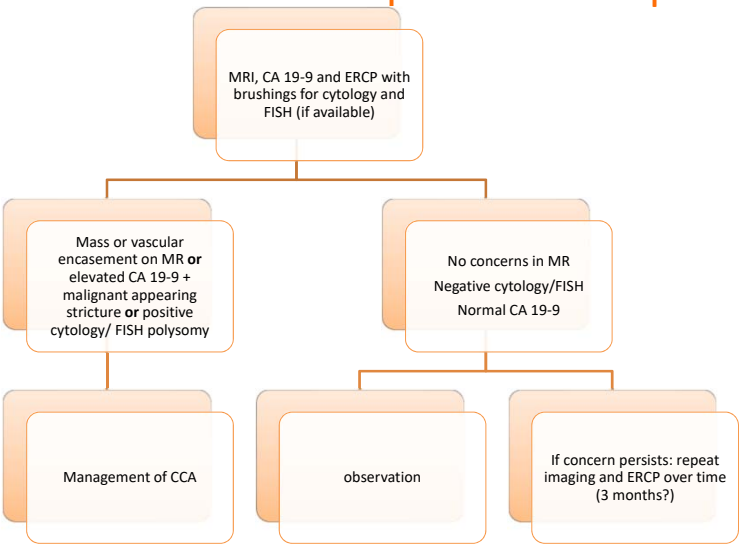
RR stent vs. Balloon – 6.8

PSC PEARL #5:

Suspicious strictures need special work-up!





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Chapman et al. Hepatology 2010; Razumilava et al Hepatology 2011; Navaneethan U et al Gastrointest endosc 2014

PSC - Take Home Message

- MRCP is the preferred method for diagnosis, but ERCP should be obtained if there is still doubt or if intervention is anticipated
- No FDA-approved medical therapy available; refer for clinical trials if possible
- **Survey! Survey! Survey!** – high risk for CCA, GB ca and CRC (if patient has IBD-PSC)
- Work-up suspicious strictures with ERCP with brush cytology, biopsy and FISH if available
- Liver transplant remains only curative option: 5-yr survival 80-85%

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Key points about our patient

- Interestingly she has already had 2 malignancies: CRC and GB CA. Would have high index of suspicion for CCA.
- Now with worsening liver biochemistries, jaundice and itching. Had repeat ERCP. Note presence of intrahepatic stones ➔ frequent in PSC. Role of cholangioscopy?
- No dominant stricture found. Cytology and FISH negative for malignancy
- Repeat ERCP based on labs and symptoms only
- MRI abd q 6-12 months for CCA surveillance

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Jasmohan S. Bajaj, MD, FAASLD
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Email: jasmohan.bajaj@vcuhealth.org

It’s All About the Microbiome: A State-of-the-Art Lecture

In patients with cirrhosis, the gut microbiome are affected by multiple gut and systemic alterations. These changes lead to dysbiosis in the microbiota of different parts of the body, resulting in inflammation. The constant immune stimulation resulting in part from dysbiosis is associated with morbidity in patients with cirrhosis. Dysbiosis as a dynamic event worsens with decompensation such as with hepatic encephalopathy, infections or acute-on-chronic liver failure (ACLF). These microbial patterns could be applied as diagnostic and prognostic measures in cirrhosis in the outpatient and inpatient setting. Current therapies for cirrhosis have differing impacts on gut microbial composition and functionality. Dietary modifications and the oral cavity have emerged as newer targetable factors to modulate the microbiome, which could affect inflammation and, potentially improve outcomes. Additionally, fecal microbial transplant is being increasingly studied to provide compositional and functional modulation of the microbiome. Ultimately, a combination of targeted therapies may be needed to provide an optimal gut milieu to improve outcomes in cirrhosis.

References

1. Acharya C et al 2019 Clin Gastro Hep
2. Allaband et al 2019 Clin Gastro Hep

It's All About the Microbiome: A State-of-the-Art Lecture

Jasmohan S Bajaj, MD, MS, AGAF, FACG, FAASLD, FRCP (London)

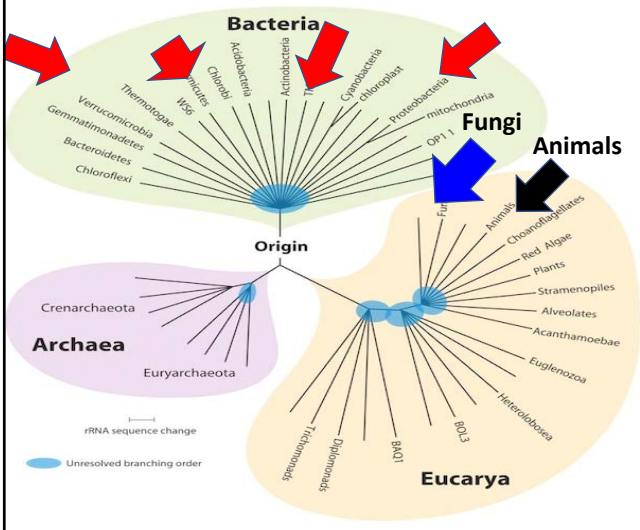
Tenured Professor of Medicine
Division of Gastroenterology, Hepatology and Nutrition,
Virginia Commonwealth University and McGuire VA Medical Center, Richmond, Virginia, USA

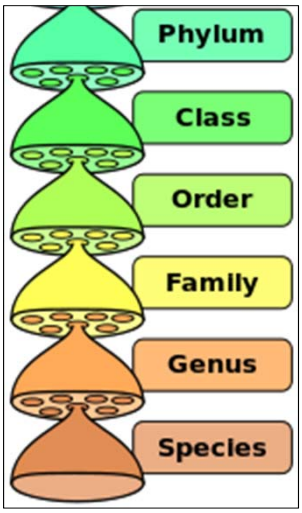
Outline and Questions to be asked

- Why is it relevant to study microbial change in liver disease?
- What is lacking in the current microbial therapies for liver disease?
- What are the levels of therapy in reducing the severity of liver disease?
- Is microbial therapy going to be enough?

Microbial Analysis and Outputs

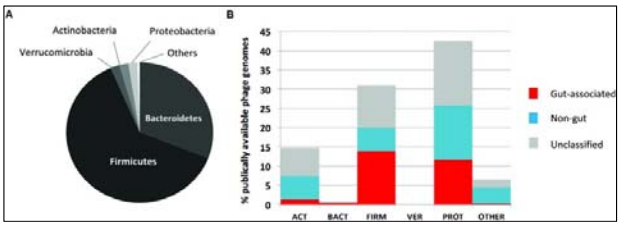
Phylogenetic Tree of Life: Microbes, Fungi and Humans



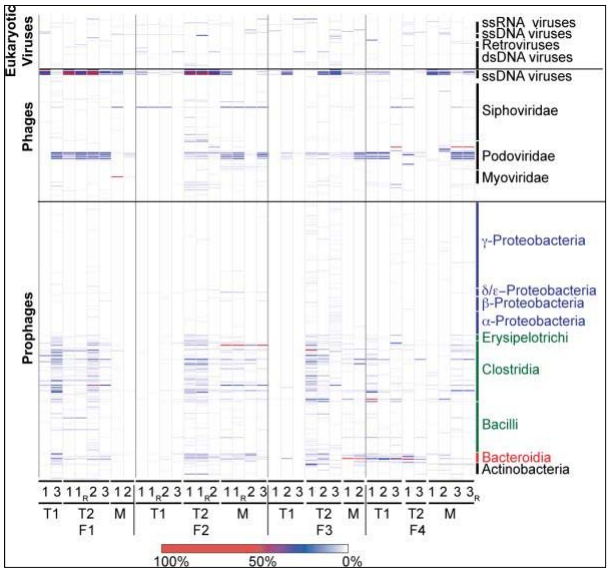


- *Proteobacteria*
- *Gammaproteobacteria*
- Enterobacteriales
- *Enterobacteriaceae*
- *Escherichia*
- *Escherichia coli*

Phages and virome in Human Gut



Ogilvie et al 2012
Reyes et al 2015



Products of bacterial metabolism

- Carbohydrates : Short chain fatty acids
- Phytochemicals: Phenolic acids
- Protein: Phenolic acids, Ammonia, Polyamides
- Fat: Bile acids with taurine and secondary bile acids
- Xenobiotics: Carcinogens
- Alcohol: Acetaldehyde

Microbial Outputs

- Type of bacteria
- Presence/absence
- Richness: count of individual bacterial types
- Diversity: count of individual types and their abundance
- Relative abundance: percent present compared to the total abundance

Levels of study in microbiome research

- Which microbes are present in the GI tract? (culture-dependent or independent techniques)
  - Stool
  - GI tract mucosa
  - In peripheral systems
- What are GI tract microbes doing? (metatranscriptomics, metaproteomics, metabonomics/metabolomics).
- What microbial genes are present in the GI tract? (metagenomics)

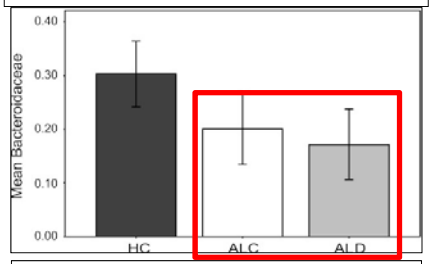
Ultimately, the relationship with host state and outcomes is essential

Relevance of microbial change in liver disease

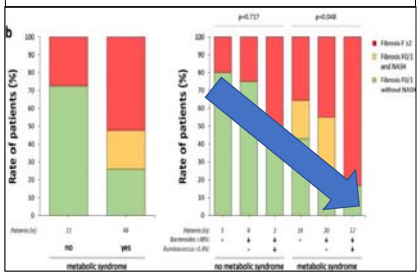
- Liver diseases, especially alcohol and NAFLD, initiate microbial change independent of liver injury
- This microbial change could worsen the liver injury phenotype
- Cirrhosis of the liver, the end-stage of fibrosis, can affect the microbiota
- Microbial change, including bacterial translocation, is associated with systemic and intestinal inflammation

Mutlu et al AJP 2012, Hartmann et al Hepatol 2015, Boursier et al Hepatol 2017, Bajaj et Nature 2015 Chen et al Hepatol 2011, Bajaj et al J Hepatol 2014

Alcohol with/without Cirrhosis



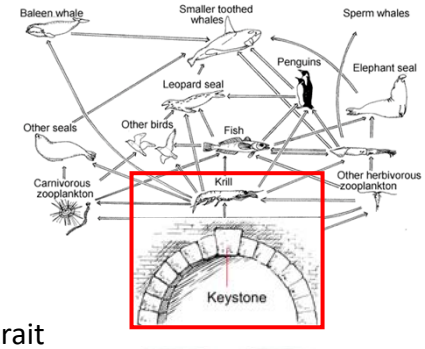
NAFLD with/without Cirrhosis



Biosensors: Keystone and Indicator organisms

Keystone organisms: that has a disproportionately large effect on its environment relative to its abundance

Adequate presence=Good health of the overall ecosystem

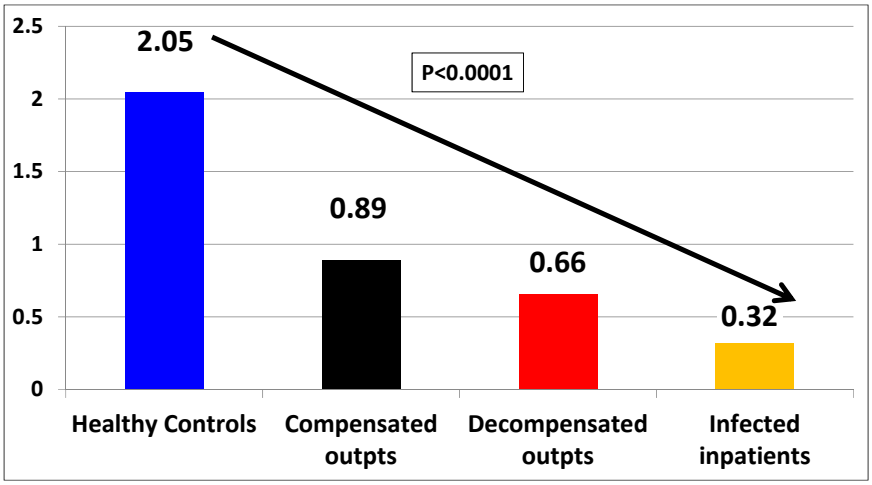


Indicator organisms : that defines a trait of the environment which are also known as sentinel organisms, i.e. organisms which are ideal for biomonitoring

E.g. Coliforms to monitor water quality

Ideal Biosensor: Combination of Keystone and Indicator Organisms

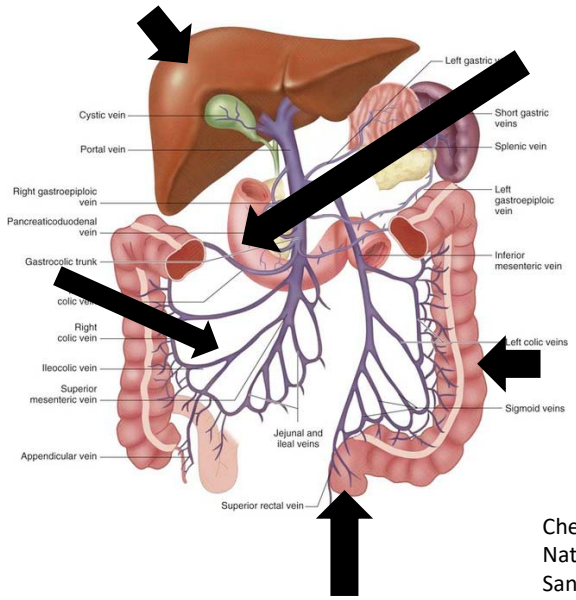
The Cirrhosis Dysbiosis Ratio Parallels Cirrhosis Severity

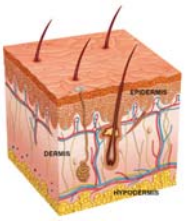


Cirrhosis Dysbiosis ratio was also stable over time, worsened with the development of the first episode of hepatic encephalopathy and was worse in those who were subsequently hospitalized

Bajaj JS et al J Hepatol 2014, Bajaj JS Sci Rep 2015

Microbial Changes are widespread in Cirrhosis not just the Gut-Liver Axis but Saliva, Blood and Skin



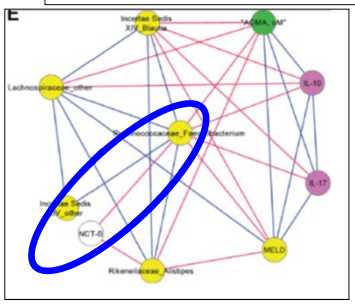


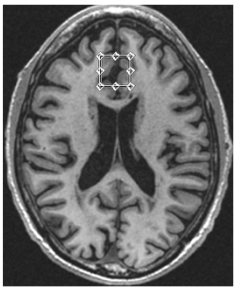
Chen et al Hepatol 2011, Bajaj et al AJP 2011, 2012, Qin et al Nature 2014, Bajaj et al Nature 2015, Bajaj et al Hepatol 2015, Santiago et al Sci Rep 2016, Chen et al Sci Rep 2016, Bajaj et al Clin Gastro Hep 2019

Microbial change is linked to outcomes in cirrhotic outpatients

- Microbial change can predict inpatient and outpatient outcomes in cirrhotic patients
- Microbiota are associated with an altered gut-liver-brain axis resulting in ***Hepatic encephalopathy (HE)***

Cognitive function and brain inflammation and edema are related to microbes in cirrhosis= HE



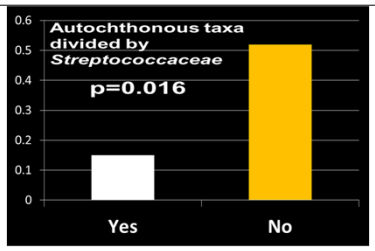


Bajaj et AJP 2011/2013, Chen et al J Gastro Hepatol 2015, Bajaj et al J Hepatol 2014, Bajaj et al Hepatol 2015, Ahluwalia et al Sci Rep 2016, Bajaj et al Am J Gastro 2019

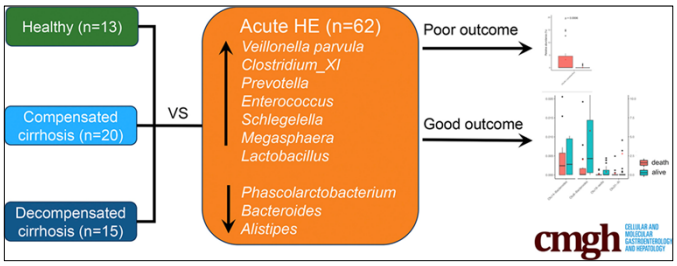
Microbiota can be used to exclude significant cognitive dysfunction in cirrhosis

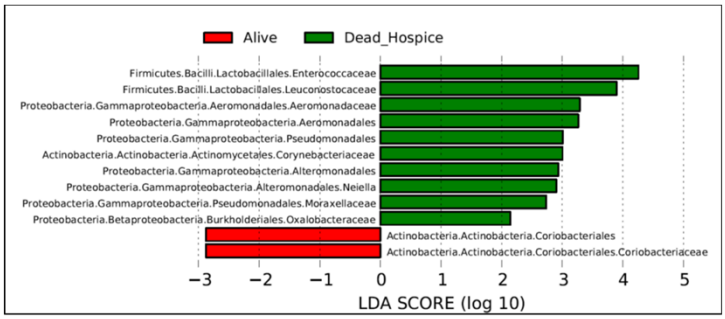
Ruminococcus and Clostridium XIVb in stool and saliva were associated with healthy cognition regardless of testing modality

Hospitalizations in Outpatients

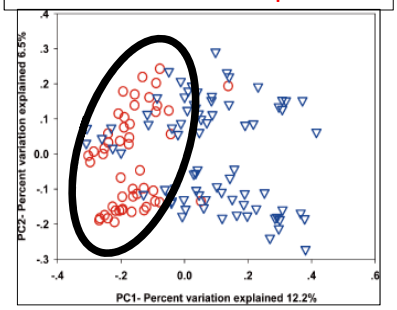


Microbiota and prediction of Outcomes in Cirrhotic Inpatients





Death in Cirrhotic Inpatients

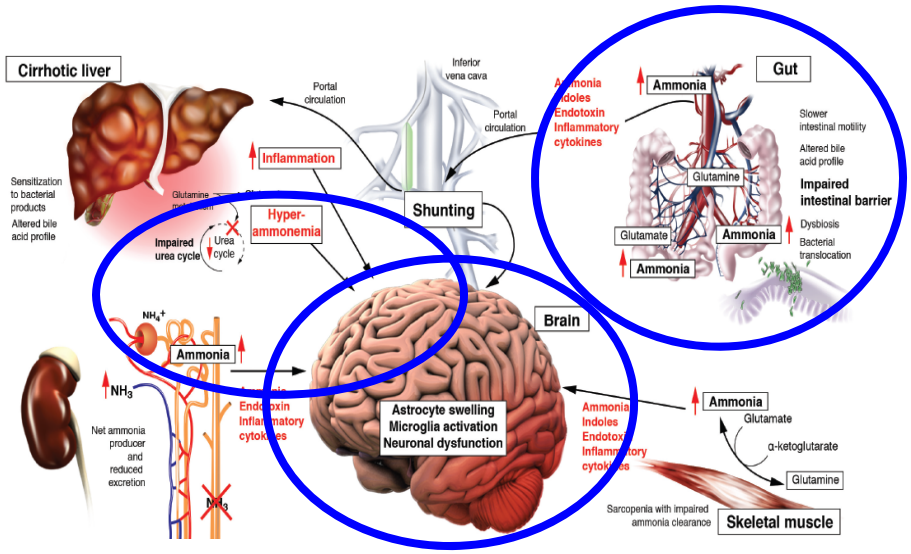


Microbial composition can predict

A. Death
B. ACLF
C. ICU transfer
D. Recovery and recurrence of HE

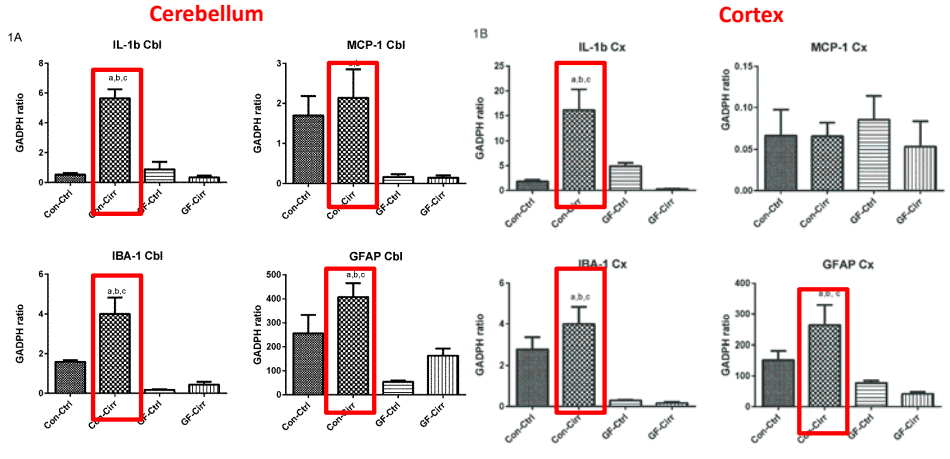
Lin et al CMGH 2019, Chen et al J Gastro Hep 2015, Bajaj et al J Hepatol 2014, Bajaj et al Clin Gastro Hep 2018

Pathophysiology of HE



Bajaj JS Hepatology 2015, Dasarathy et al J Hepatol 2016

Gut microbiota are necessary for brain inflammation (microglial and glial) in cirrhotic mice



4 mouse groups: GF, GF made cirrhotic using CCL4 gavage, Conventional control and Conventional mice made cirrhotic using CCL4 gavage

Kang, Bajaj et al Hepatology 2016

Current microbial therapies need more precision

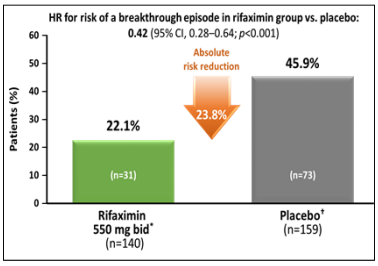
Pre-cirrhosis

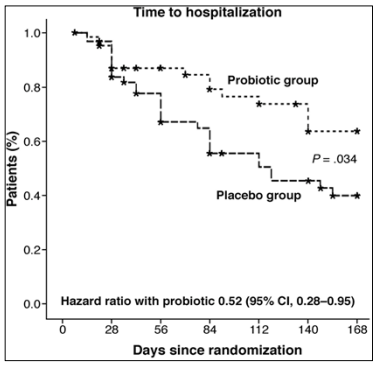
- Probiotics: very poor evidence in NAFLD and alcoholic liver disease with multiple formulations used and for very small durations

Cirrhosis : Hepatic Encephalopathy

- Probiotics: Good data with VSL#3 for readmission prevention but not recurrence of hepatic encephalopathy
- Prebiotics/Laxatives: Poor evidence for lactulose and mechanistically likely to be a laxative
- Antibiotics: Rifaximin has the best evidence profile but it is expensive and also does not prevent all HE episodes

Bass et al NEJM 2010, Dhiman et al Gastro 2014, Sharma et al Gastro 2009, Bajaj et al Metab Brain Dis 2011, Bajaj et al Hepatol 2017



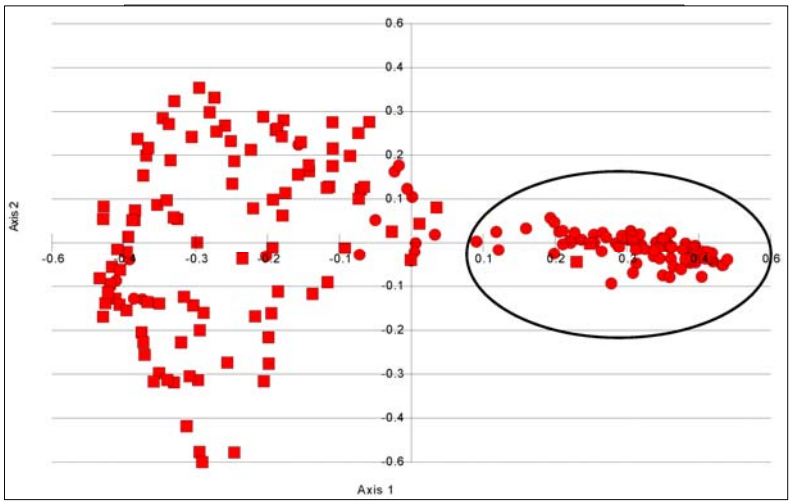


Levels of therapy in reducing the severity of liver disease

- Control etiology: Not likely microbial
- Affect inflammatory milieu locally and systemically: Oral cavity
- Change gut microbial composition and hopefully function: FMT, Proton pump inhibitors, Engineered bacteria and Dietary modification
- Change gut microbial interaction with other microbiota: Interaction with fungi

Systemic and Local Inflammatory Control

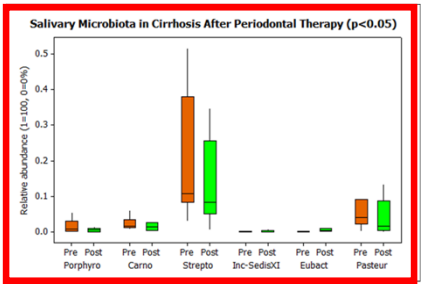
Oral Microbiota is different from stool microbiota compositionally in healthy controls and in cirrhotic patients

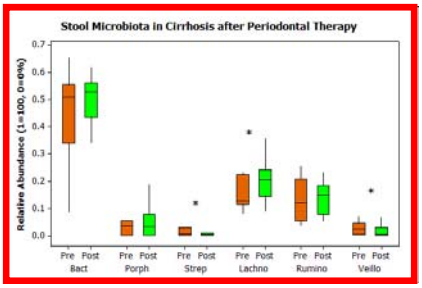


Human Microbiome Project Nature, Bajaj et al Hepatol 2015

Periodontal therapy improves gut microbiota and endotoxemia

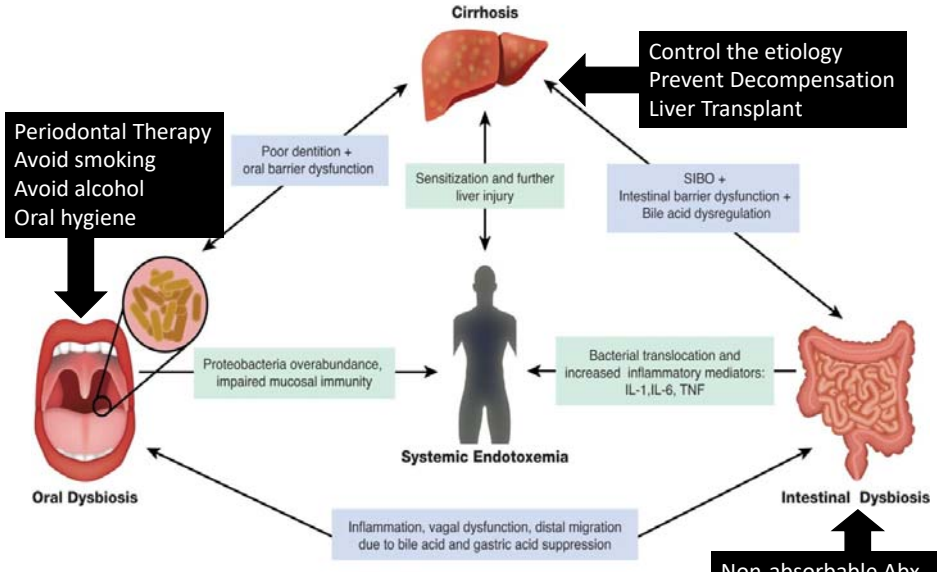
#p<0.05 pre vs post *p<0.05 cirrhosis vs controls	Cirrhosis		Controls	
	Pre-therapy	Post-therapy	Pre-therapy	Post-therapy
MELD score	9.5±3.3	8.6±2.7*	_	_
WBC count	6.11±1.90	5.67±1.85*	7.12±1.7	7.01±1.5
Endotoxin(EU/ml, median, IQR)	0.18(0.05)*	0.12(0.07)#	0.11(0.09)	0.14(0.10)
TNF (pg/ml, median, IQR)	17.3(9.1)*	15.1 (8.3)*#	12.1(6.3)	9.5(10.1)*





Bajaj et al
Am J Physiol 2018

Oral-Gut-Hepatic Axis

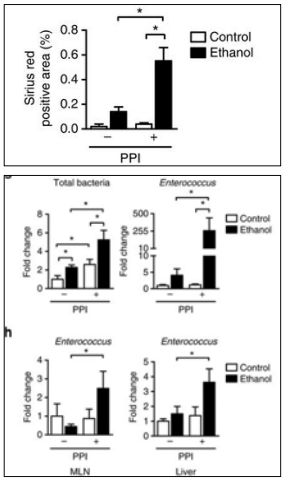


Acharya, Sahingur and Bajaj
JCI Insight 2018

Microbial Composition and Functional Change

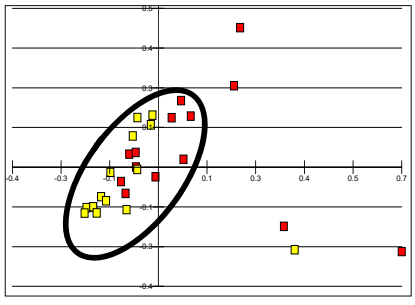
Proton Pump Inhibitors Initiation and Withdrawal can Change Microbiota in Liver Disease

PPIs Exacerbate Murine Alcoholic Liver Injury Through *Enterococcus*



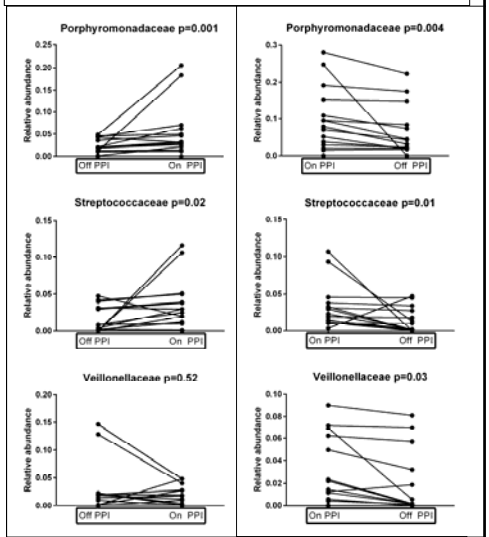
Adding PPIs Oralizes Stool Microbiota in Compensated Cirrhosis and Healthy Controls

Microbiota changes
Yellow: PRE Red=POST



Llorente et al Nat Comm 2017, Bajaj et al AJP 2014, Bajaj et al Am J Gastro 2018

Similar changes are found in Advanced Cirrhosis with Reversal after PPI Withdrawal



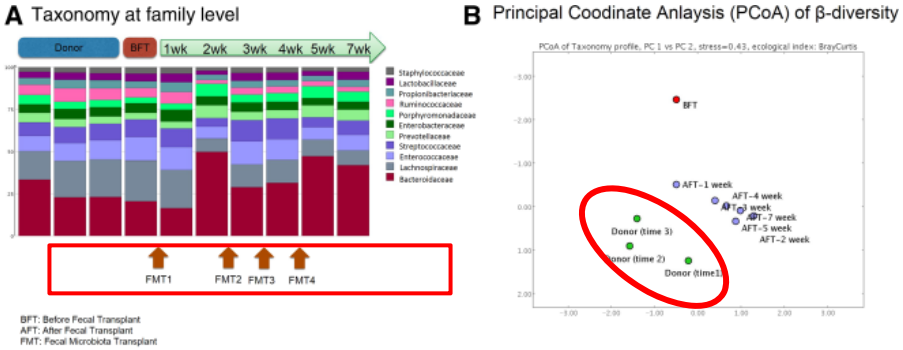
Adding PPIs | Withdrawing PPIs

Manipulation of microbiota: Fecal Microbiota Transplant

Particular challenges of FMT in HE

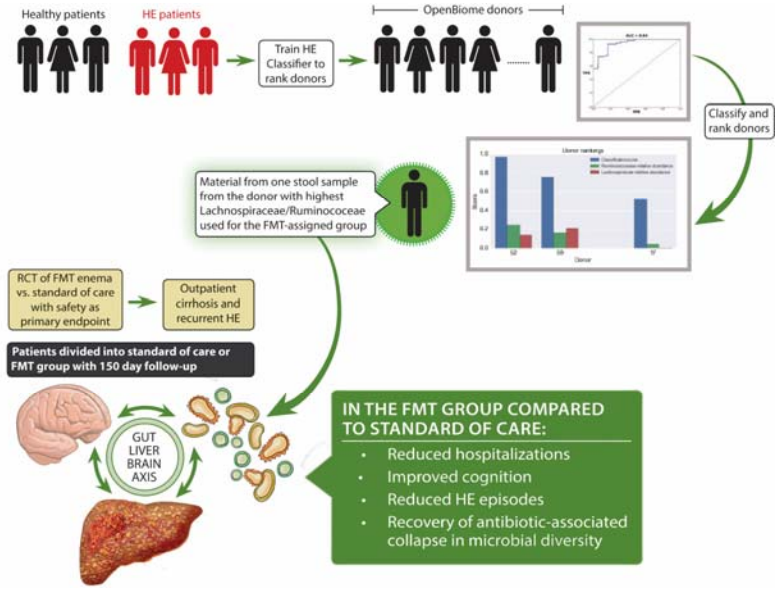
- Generally a much more advanced population
- Prone to potentially life-threatening infections, including those that are initiated from the gut
- Avoiding antibiotics post-FMT may not be feasible
- Many are already on rifaximin and SBP prophylaxis
- Directed donor vs. universal donor?

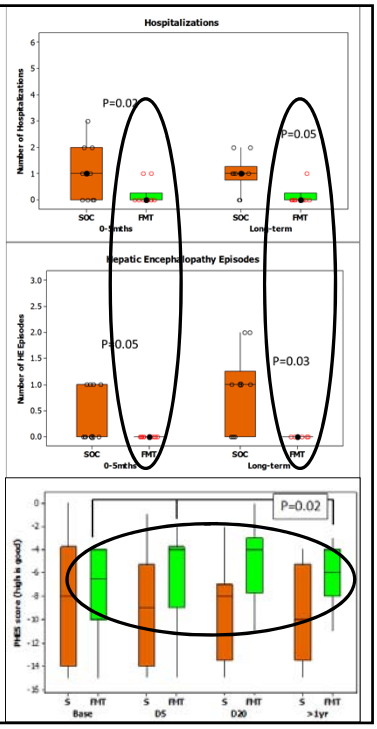
Case Report of FMT in the management of hepatic encephalopathy



Kao et al Hepatology 2015

Enema FMT is safe short-term and long-term

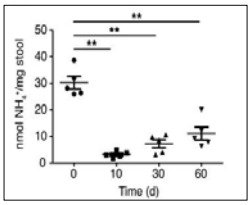


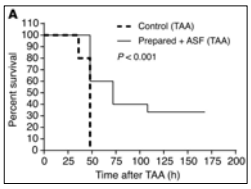


Bajaj et al Hepatology 2017, Bajaj et al Gastro 2019

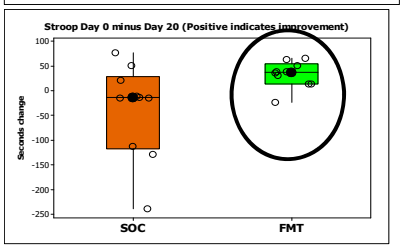
Fecal Microbiota Transplant Changes Microbial Function

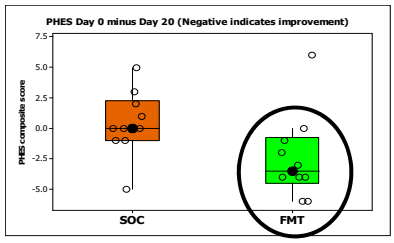
Specific Microbes
Reduce Ammonia
And improve survival
In Murine models

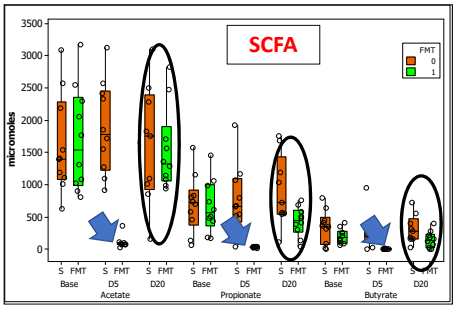


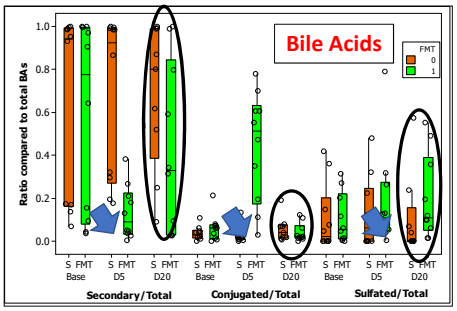


In Humans FMT improves cognition, restores SCFA and Bile Acid profile



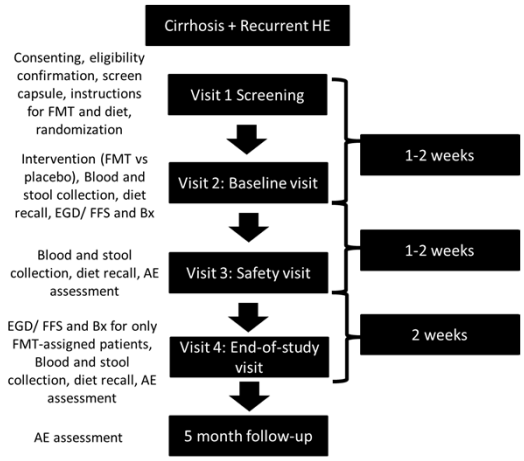


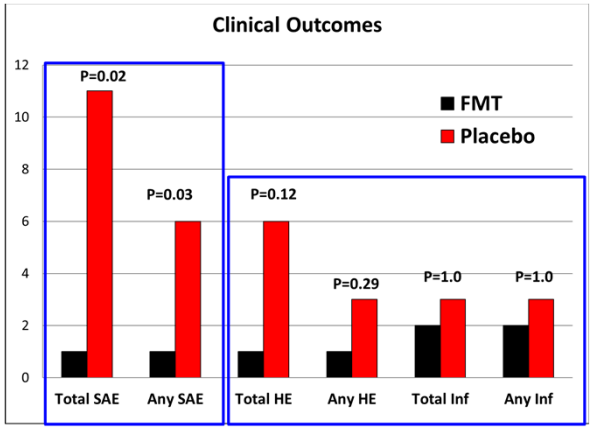




Shen et al JCI 2015, Kao et al Hepatol 2015
Bajaj et al Hepatol 2017, Bajaj et al Hepatol 2018

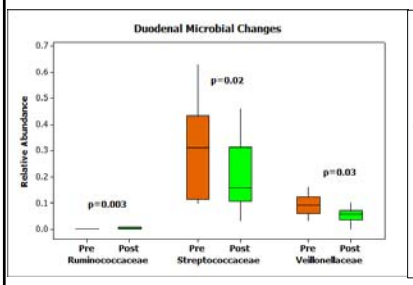
Oral capsular FMT is safe and shows benefit in HE

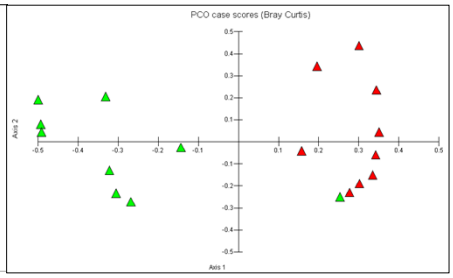


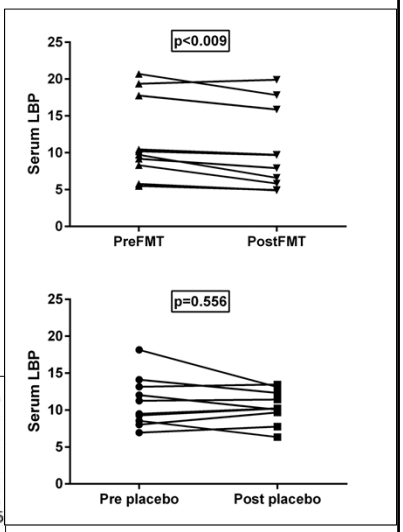


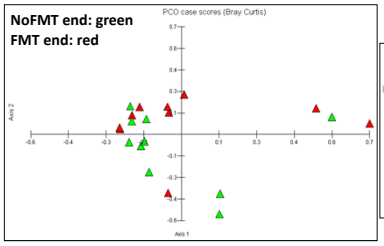
Bajaj JS et al Hepatology 2019

Beneficial changes in LBP, stool and duodenal microbial composition after FMT

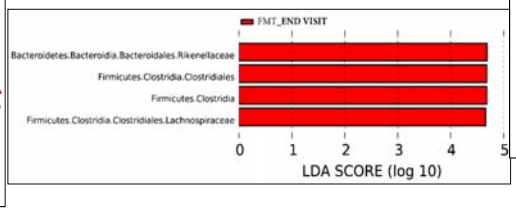








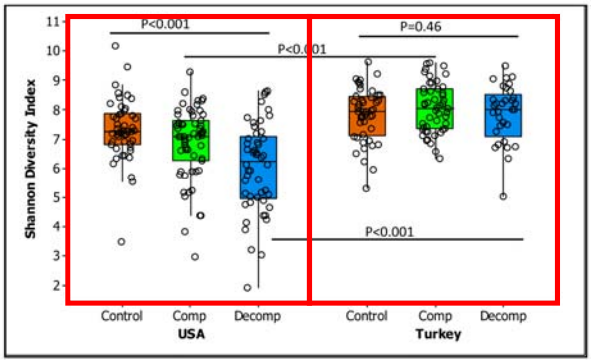
Stool changes with higher Lachnospiraceae



Bajaj JS et al Hepatology 2019

Mediterranean diet in cirrhosis=better diversity and lower hospitalizations compared to Western Diet

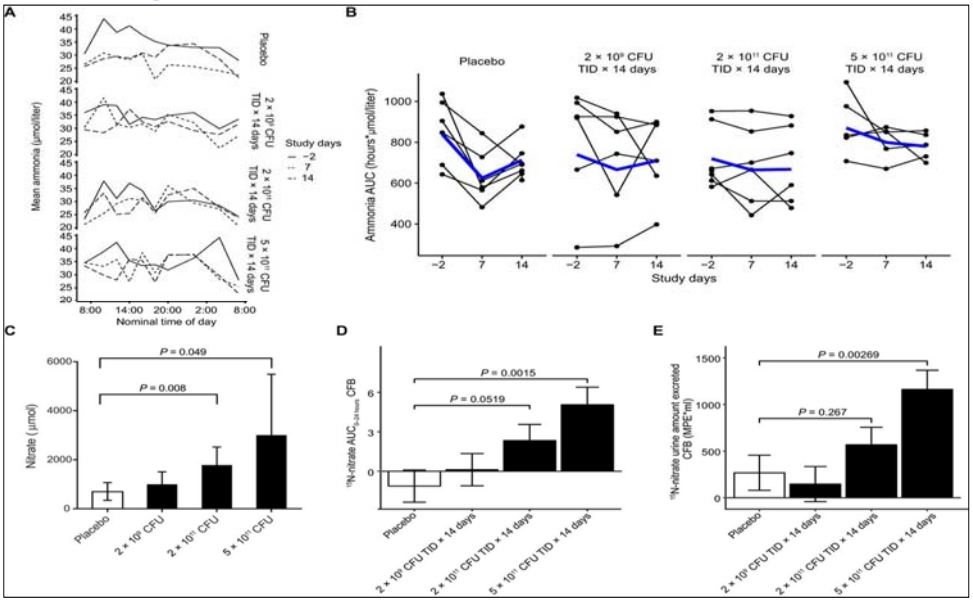
- Cohort of 296 Turkish and US-based controls, compensated and decompensated cirrhotic patients was included and followed for 90 days
- Turkish subjects had similar diversity due to greater consumption of fermented milk products.



- **There was a significantly lower risk of 90 day hospitalization in Turkish compared to American cirrhotic patients**
- **On Cox and binary logistic regression, microbial diversity was protective against 90-day hospitalizations, along with coffee/tea, vegetable and cereal intake.**

Bajaj JS, Idilman R et al, Hepatol 2018

Engineering Probiotic Bacteria to Consume Ammonia

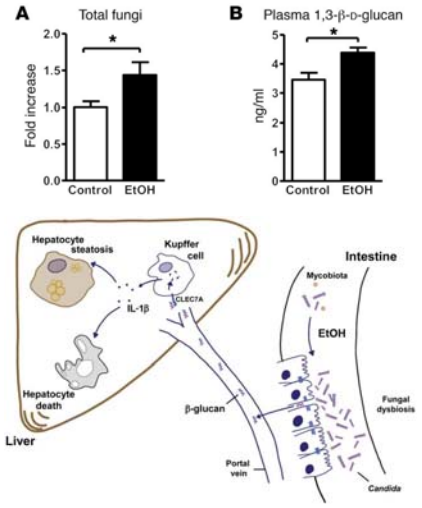


Curtz CB et al Sci Transl Med 2019, Slide courtesy of Synlogic Pharmaceuticals

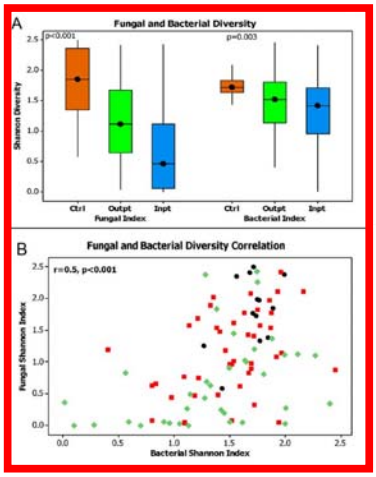
Microbial Interactions

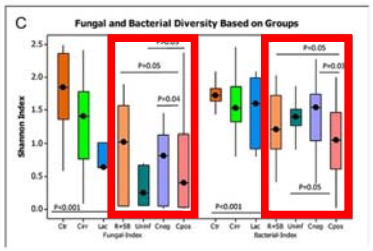
Bacterial and fungal interactions are relevant in liver disease

Fungi Worsen Alcoholic Liver Injury
In Murine models



Gut Fungi are Related to Gut Bacterial Diversity and Worsen with Antibiotic use, being replaced by *Candida*





Yang et al JCI 2017, Bajaj et al Gut 2017

However, are cirrhosis and chronic liver disease microbial diseases?

In other words without controlling the liver disease etiology, can we expect an improvement by just affecting the microbiota?

Liver cirrhosis requires liver injury: microbes potentiate but do not cause it independently

Stool Donor	Systemic Inflamm-ation	Liver Inflamm-ation	Liver injury/ cirrhosis	Bacterial translocation
Healthy human	+	-	-	-
Non-drinking Cirrhotic human	+	+	-	-
Non-drinking Cirrhotic with HE	+	+	-	-
Actively drinking non-cirrhotic human	+	+	Only if fed alcohol	Only if fed alcohol
Actively drinking cirrhotic human	+	+	-	+

Kang et al Hepatology 2016, Kang et al Clin Transl Gastro 2016, Llopis et al Gut 2015, Kang et al Hepatol Comm 2017

Conclusions

- Microbial changes are an integral part of the altered gut-liver axis in cirrhosis and pre-cirrhotic liver disease
- They are complicit but not necessarily causative of liver injury without the direct liver injury also
- Microbial treatment in liver disease has to be accompanied by treatment of the liver disease etiology
- Current therapies can be improved by precision changes in microbiota
- Specific means by which we can potentially improve outcomes
  - Regular dental cleaning and avoid periodontitis
  - Withdraw unnecessary PPI use
  - Carefully re-evaluate the need for antibiotics, which could encourage fungal infections
  - Focus on therapies related to bacterial function
  - Emphasis on fermented, probiotic foods
  - Make every effort to combine microbial therapy with etiological therapy as well

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Quality of Care in Cirrhosis

Patients with cirrhosis experience care of variable quality and quality of care is directly associated with important patient outcomes such as survival and readmission. The modern practice of quality improvement for cirrhosis began with a consensus document led by Dr. Fasiha Kanwal in 2010. Thereafter, our field had consistent guidance on process measures that defined best practice and created targets for quality improvement. These included screening for hepatocellular carcinoma, timely paracentesis to exclude infection among hospitalized patients with ascites, and vaccination against viral hepatitis. In 2016 the AASLD founded a Practice Metrics committee. This committee has worked to extend the prior effort to define process measures of care to now include clinical and patient reported outcomes (PROs). In parallel, a group called the Cirrhosis Quality Collaborative (CQC) is developing a platform in which each center can routinely survey the health and wellbeing of their patients.

Cirrhosis impacts many PROs, from overall quality of life (QOL) to specific domains such as sleep, concentration, sexual dysfunction, and physical symptoms (i.e. abdominal pain from ascites, pruritus, muscle cramps). Although each symptom is important to the afflicted patients, they are frequently not queried in clinical practice. This talk will review the importance of PROs, simple means to survey patients about their symptoms as well as the available effective management strategies. A summary of 4 high yield domains is provided below

Sample Question(s)	Therapeutic Options
• How often during the last 2 weeks have you had muscle cramps?	• Normalize electrolytes and fluid balance • Taurine (3 g daily) • Vitamin E (300 mg three times a day) • Baclofen (5–10 mg three times a day as needed)
• How much of the time have you been troubled by itching during the last 2 weeks?	• Moisturizing cream for dry skin • Cholestyramine (4 g daily) • Naltrexone (50 mg daily) • Sertraline (75–100 mg daily) • Ursodeoxycholic acid (13–15 mg/kg/day in 2 doses)
• Have you had difficulty sleeping at night? • Have you felt sleepy during the day?	• Optimize treatment for HE • Optimize sleep hygiene • Referral to sleep specialist to assess for sleep apnea • Mindfulness training • Melatonin (3–5 mg daily)
• Have you had any sexual activity in the past few weeks? • How satisfied were you with your sexual function during the past few weeks?	• Phosphodiesterase inhibitors (e.g., sildenafil 25–100 mg as needed) • Sex therapy referral • Referral to Urology

Am J Gastroenterol 2018;113: 927–931

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Quality of Care in Cirrhosis

(Re)Focusing on Patients

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This presenter has the following declarations of relationship with industry:

- NIH/MICHR KL2 research grant
- Gilead – research grants to Michigan Medicine
- Valeant – research grants to Michigan Medicine
- Novartis - consultant in research projects
- Norgine – participation fee at satellite symposium

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Structure

Philosophy

Targets

Actions

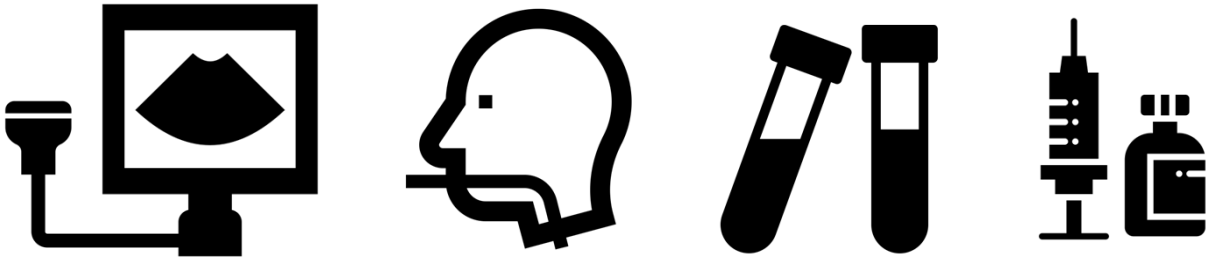
Cirrhosis quality 2010

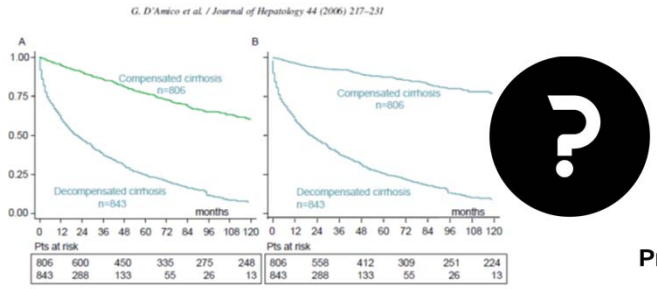
An Explicit Quality Indicator Set for Measurement of Quality of Care in Patients With Cirrhosis

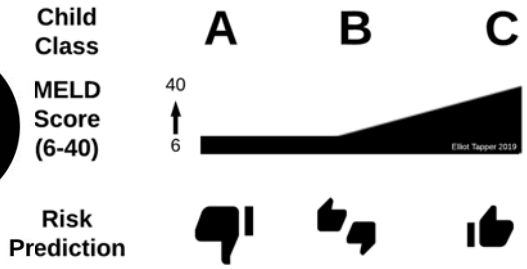
FASIHA KANWAL,[*,‡] JENNIFER KRAMER,[§,‖] STEVEN M. ASCH,[¶,#] HASHEM EL-SERAG,[§,‖] BRENNAN M. R. SPIEGEL,[¶,#] STEVEN EDMUNDOWICZ,[**] ARUN J. SANYAL,[‡‡] JASON A. DOMINITZ,[§§] KENNETH R. MCQUAID,[‖‖] PAUL MARTIN,[¶¶] EMMET B. KEEFFE,[##] LAWRENCE S. FRIEDMAN,[***] SAMUEL B. HO,[‡‡‡] FRANCISCO DURAZO,[#,§§§] and BRUCE R. BACON[‡]

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2010;8:709–717

The lived experience of ‘quality’







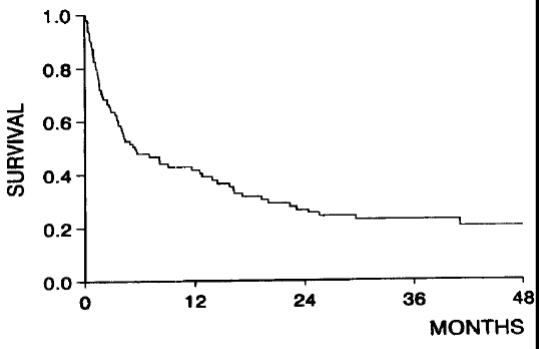


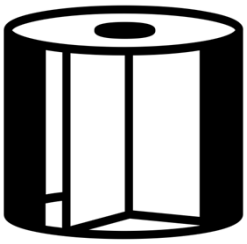
Fig. 1. Survival probability of 111 cirrhotic patients pre-senting their first episode of acute hepatic encephalopathy

Journal of Hepatology 1999; **30**: 890–895

The hidden burden of survival

Structure

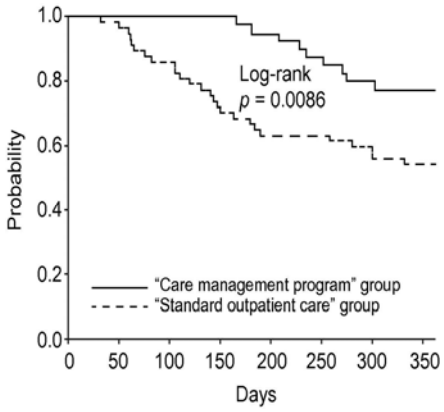
Targets



Care management check-up

Morando F, J Hepatol 2013;

Care Management Program Improves 1-year Survival after Admission for Cirrhosis and Ascites



Care Management Program: Improved outcomes, reduced costs

	Care Management	Standard Care	P value
30-day readmissions	15.4%	42.4%	<.01
1-year all-cause mortality	23.1%	45.7%	<0.025
1-year liver-related mortality	15.4%	35.6%	<0.05
Global costs	1479 ± 2184	2816 ± 3893	<0.05

Morando F, J Hepatol 2013; 59: 257

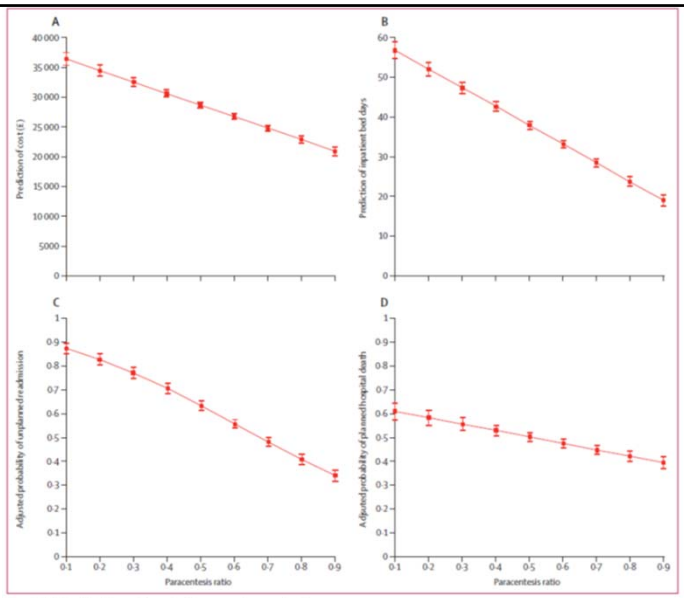
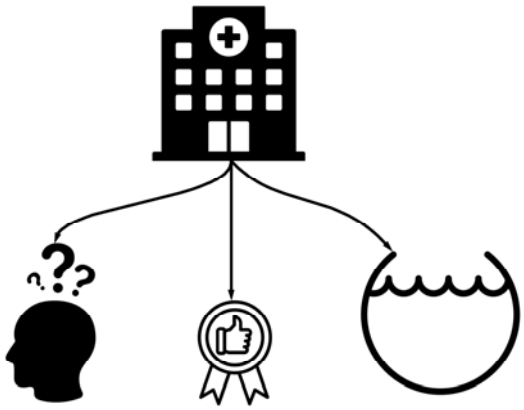


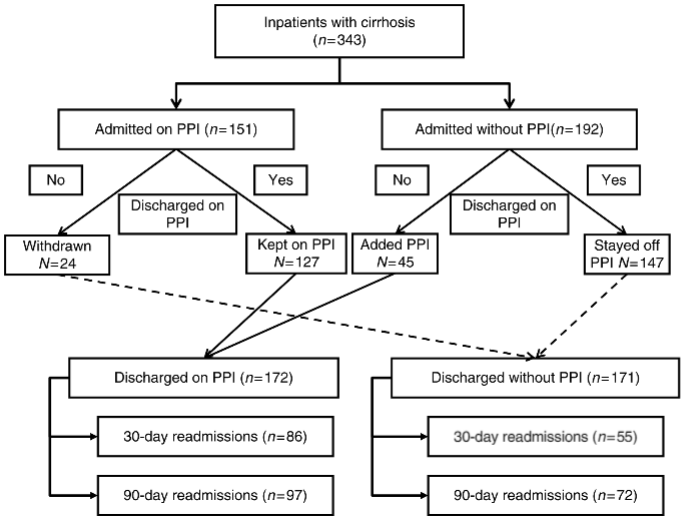
Figure 2: Relationship between increasing day-case service use and outcomes
Association between the paracentesis ratio (proportion of total large-volume paracentesis procedures in the last year of life done in a day-case setting) and outcomes in the last year of life. Results adjusted for all independent variables in generalised linear (A, B) and logistic (C, D) regression models. (A) Cost. (B) Inpatient bed days. (C) Probability of any early unplanned readmission. (D) Probability of unplanned hospital death.

Lancet Gastro Hep 2018;3(2):95-103

A Quality Improvement Initiative Reduces 30-day Readmissions

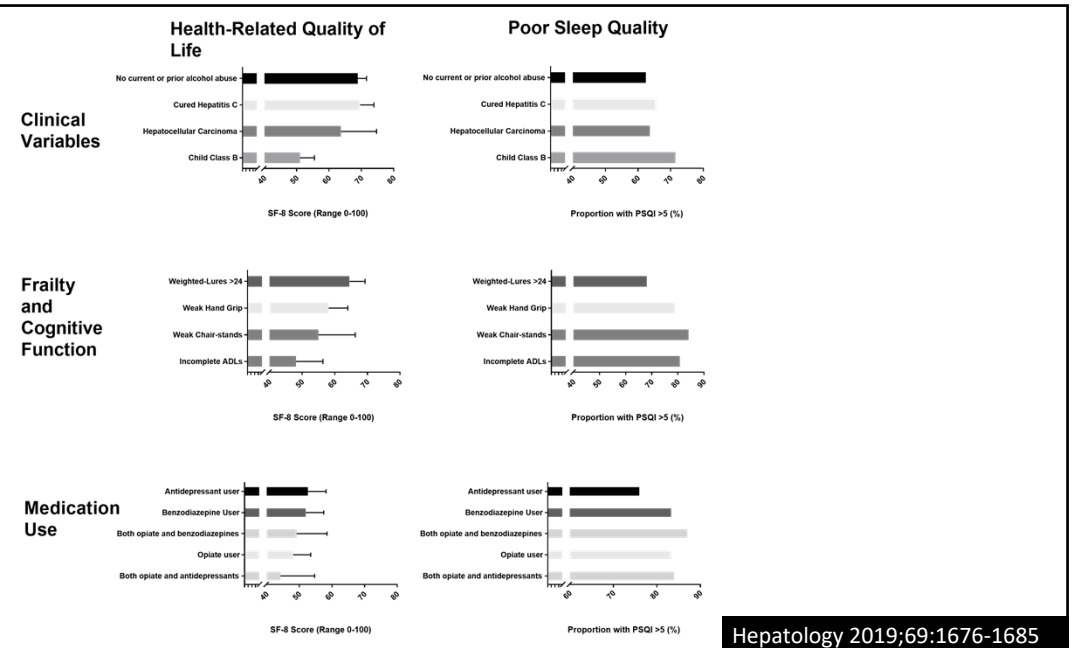


Tapper E, Clin Gastroenterol Hepatol 2016; 14: 753

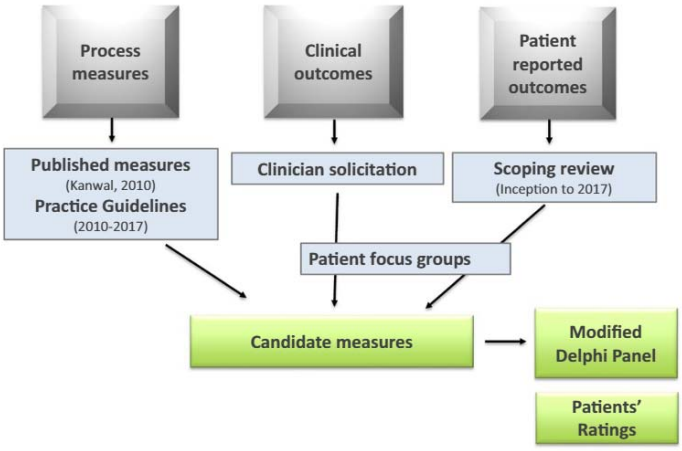


Am J Gastroenterol. 2018;113(8):1177-1186

Cirrhosis quality 2020



Hepatology 2019;69:1676-1685

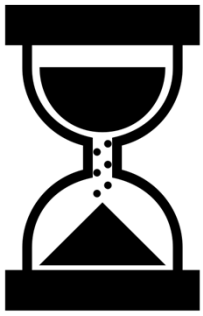


Hepatology. 2019;69(4):1787-1797

TABLE 3. Patient Ratings of Patient-Reported Outcomes

Patient-Reported Item	Not Important (%)	Somewhat Important (%)	Very/Extremely Important (%)
Fluid in the legs (edema)	8.9	14.1	76.9
Fluid in the belly (ascites)	3.8	5.1	91.1
Confusion (encephalopathy)	1.3	10.1	88.6
Concentration/memory	6.4	16.7	76.9
Itching (pruritus)	5.2	12.9	81.8
Muscle cramps	12.9	36.4	50.7
Falls	12.8	17.9	69.2
Medication side effects	8.9	17.9	73.1
Depression	7.6	21.7	70.5
Stigma of having liver disease	5.1	14.1	80.8
Ability to drive	10.1	22.8	67.1
Burden on family	35.1	5.2	59.8
Ability to avoid alcohol	17.1	18.4	64.4

Hepatology. 2019;69(4):1787-1797



PLoS One 2010;5:e15591

BMJ open. 2017 Jun 1;7(6):e015516

Sample Question(s)	Therapeutic Options
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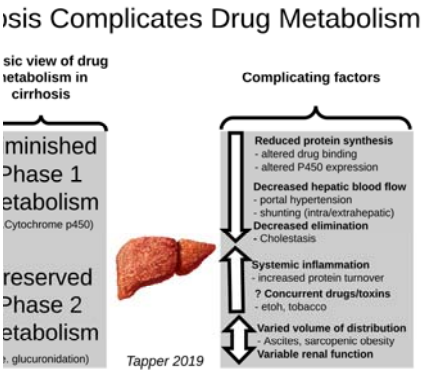
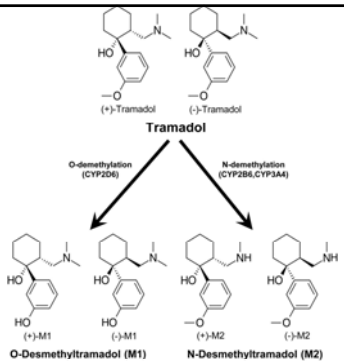
• How much of the time have you been troubled by itching during the last 2 weeks?	• Moisturizing cream for dry skin • Cholestyramine (4 g daily) • Naltrexone (50 mg daily) • Sertraline (75–100 mg daily) • Ursodeoxycholic acid (13–15 mg/kg/day in 2 doses)
• Have you had difficulty sleeping at night? • Have you felt sleepy during the day?	• Optimize treatment for HE • Optimize sleep hygiene • Referral to sleep specialist to assess for sleep apnea • Mindfulness training • Melatonin (3–5 mg daily)
• Have you had any sexual activity in the past few weeks? • How satisfied were you with your sexual function during the past few weeks?	• Phosphodiesterase inhibitors (e.g., sildenafil 25–100 mg as needed) • Sex therapy referral • Referral to Urology

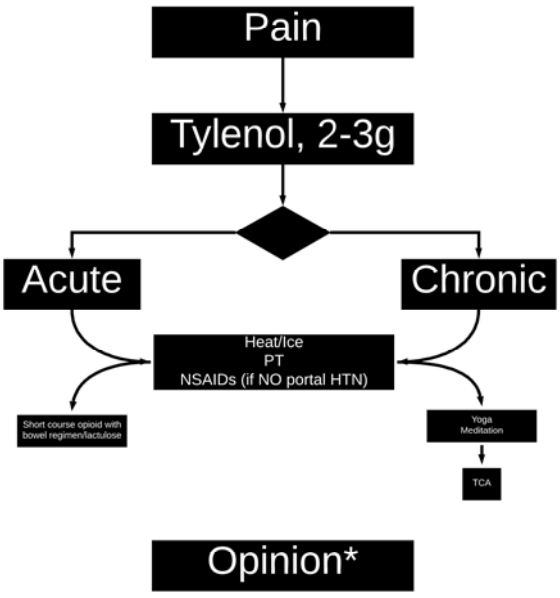
Am J Gastroenterol 2018;113: 927–931

Pain control for patients with cirrhosis





Journal of Opioid Management 4:2 ■ March/April 2008



Quality 2019

Systems to the hospital

Discover symptoms

Treat symptoms

The End

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MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

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Frailty: Impact of Sarcopenia and Overcoming Management Challenges

Originally described in the field of geriatrics, frailty has commonly been defined as "a distinct biological syndrome of decreased physiologic reserve and increased vulnerability to health stressors". [1] When applied to patients with cirrhosis, frailty is reported in approximately 1 out of every 5 patients and is strongly associated with outcomes including hospitalization and mortality. [2,3]. Conceptually speaking, frailty is a multi-dimensional construct that captures the effects of hepatic synthetic dysfunction, relative immobility, decreased energy expenditure, and under-nutrition. Sarcopenia, on the other hand, is the metric of clinically-relevant skeletal muscle depletion that can be objectively measured in clinical practice and is least likely to be affected by acute illness or alterations in cognitive function. Sarcopenia is only one – but likely the dominant – component of the larger construct of frailty. While frailty is the manifesting symptom of impaired global physical functioning, loss of muscle mass is an obvious sign that frailty may be present.

Strategies to manage – or more ideally, to prevent – the development of frailty consists of a 3-pronged approach.

1) Measure. Multiple tools to measure frailty have been studied in patients with cirrhosis. An expert opinion statement from the American Society of Transplantation recommends the use of one or several tools from the frailty toolkit (Table), depending upon the clinical scenario and resources available.[4] It has been recommended that frailty be measured objectively in every patient with cirrhosis at every clinic visit, much like a vital sign. Systematic measurement is critical to early identification of those most in need of aggressive management to prevent further progression and ideally, reverse existing frailty.
2) Strengthen. Patients with cirrhosis should be provided specific recommendations to exercise that consists of a range of activities and exercises that involve one of 3 areas: aerobic fitness, resistance training, and flexibility/balance. For those who have preserved physical function, in office counseling by their clinical provider on specific exercises is a critical first step. Provision of on-line tools such as www.wellnesstoolbox.ca may be useful. Referral to a physical therapist is recommended for those who are experiencing a decline in their physical function or currently meet criteria for frailty. For men with cirrhosis and low testosterone, a randomized clinical trial has demonstrated that 1 year of testosterone replacement improves lean muscle mass and decreases fat mass. [5]
3) Nourish. Several strategies are recommended to improve nutritional status in patients with cirrhosis. [6] These include ingestion of a late evening snack,[7] nocturnal feeds (with 2 nutritional supplements at night), [8] and adequate protein intake consisting of 1.2-1.5 grams per kilogram body weight per day. [9]. While enteral feeds through a feeding tube may be necessary to improve nutritional status, a trial of oral intake should be tried first, given the lack of evidence demonstrating superiority of enteral feeds over oral feeds.[10]

Table. Frailty toolkit as recommend by experts at the American Society of Transplantation Consensus Conference on Frailty in Liver Transplantation

Tool	Rationale for inclusion in the frailty tool kit	Estimated time to assess	Populations studied
Karnofsky performance status	Intuitive and instant No cost Low floor effects Can be assessed by the patient or the provider	<10 s	Inpatient and outpatient
Activities of daily living/instrumental activities of daily living	No cost Patient reported Well-accepted patient-oriented outcome	2-4 min	Inpatient and outpatient
Liver frailty index	Objective, performance-based Continuous scale without ceiling or floor effects Quickly administered Can be repeatedly performed in the outpatient setting	1-3 min	Outpatient
6-minute walk test	Objective, performance-based Continuous scale without ceiling or floor effects No need for specialized equipment	6 min	Outpatient

References

1. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):146-156.
2. Sinclair M, Poltavskiy E, Dodge JL, Lai JC. Frailty is independently associated with increased hospitalisation days in patients on the liver transplant waitlist. *World J Gastroenterol*. 2017;23(5):899–8. doi:10.3748/wjg.v23.i5.899.
3. Lai JC, Rahimi RS, Verna EC, et al. Frailty Associated With Waitlist Mortality Independent of Ascites and Hepatic Encephalopathy in a Multicenter Study. *Gastroenterology*. January 2019. doi:10.1053/j.gastro.2019.01.028.
4. Frailty in Liver Transplantation : An Expert Opinion Statement from the American Society of Transplantation Liver and Intestinal Community of Practice. *American journal of transplantation*. April 2019:ajt.15392–29. doi:10.1111/ajt.15392.
5. Sinclair M, Grossmann M, Hoermann R, Angus PW, Gow PJ. Testosterone therapy increases muscle mass in men with cirrhosis and low testosterone: A randomised controlled trial. *J Hepatol*. 2016;65(5):906-913. doi:10.1016/j.jhep.2016.06.007.
6. Lai JC, Tandon P. How I Approach It: Improving Nutritional Status in Patients With Cirrhosis. *Am J Gastroenterol*. 2018;38:1-3. doi:10.1038/s41395-018-0080-1.
7. Tsien CD, McCullough AJ, Dasarathy S. Late evening snack: Exploiting a period of anabolic opportunity in cirrhosis. *Journal of Gastroenterology and Hepatology*. 2012;27(3):430-441. doi:10.1111/j.1440-1746.2011.06951.x.

8. Plank LD, Gane EJ, Peng S, et al. Nocturnal nutritional supplementation improves total body protein status of patients with liver cirrhosis: A randomized 12-month trial. *Hepatology*. 2008;48(2):557-566. doi:10.1002/hep.22367.
9. Plauth M, Cabré E, Riggio O, et al. ESPEN Guidelines on Enteral Nutrition: Liver disease. *Clinical Nutrition*. 2006;25(2):285-294. doi:10.1016/j.clnu.2006.01.018.
10. Moreno C, Deltenre P, Senterre C, et al. Intensive Enteral Nutrition Is Ineffective for Patients With Severe Alcoholic Hepatitis Treated With Corticosteroids. *Gastroenterology*. 2016;150(4):903-910.e908. doi:10.1053/j.gastro.2015.12.038.

Frailty: Impact of Sarcopenia and Overcoming Management Challenges

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Case: 57 year old man

A 57 year old man with NASH cirrhosis complicated by ascites and hepatic encephalopathy comes to clinic for a follow up visit after a **recent 3-day hospitalization for hepatic encephalopathy**. He tells you that his son has now moved in with him to provide additional care as he has increasing difficulty running errands.

He has temporal and upper arm muscle wasting. His MELDNa score is 14.

Cirrhosis is a State of Accelerated Physiologic Aging

Average 57 years old

- ~20% are physically frail
- ~40% are functionally impaired
- ~30% have difficulty with at least 1 basic ADL

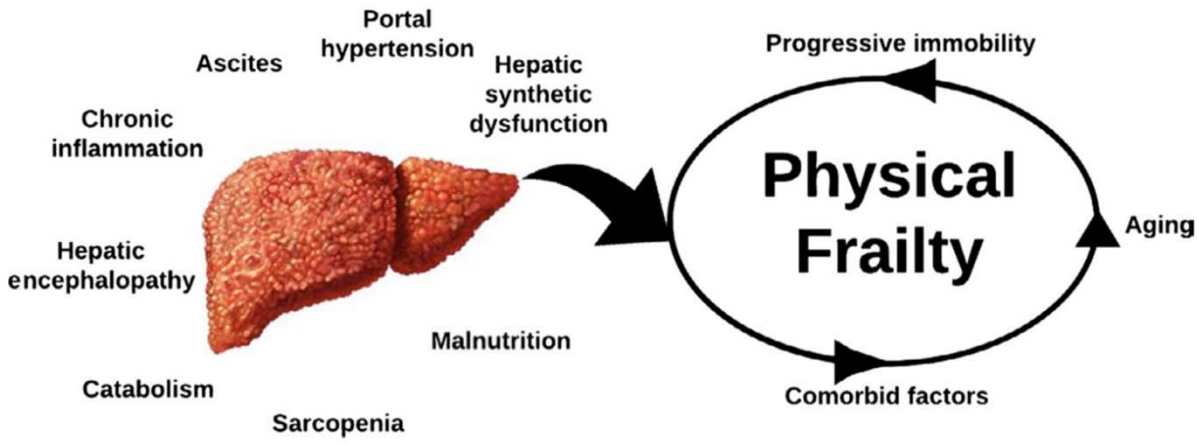
=

85 year old community-dwelling adult

Lai JC, et al. AJT 2014.

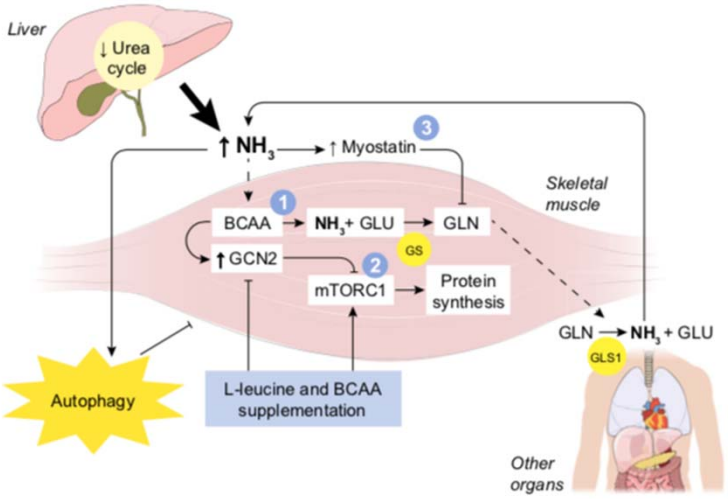
Fried L, et al. J Gerotol Biol Sci 2001.

THE CYCLE OF FRAILTY



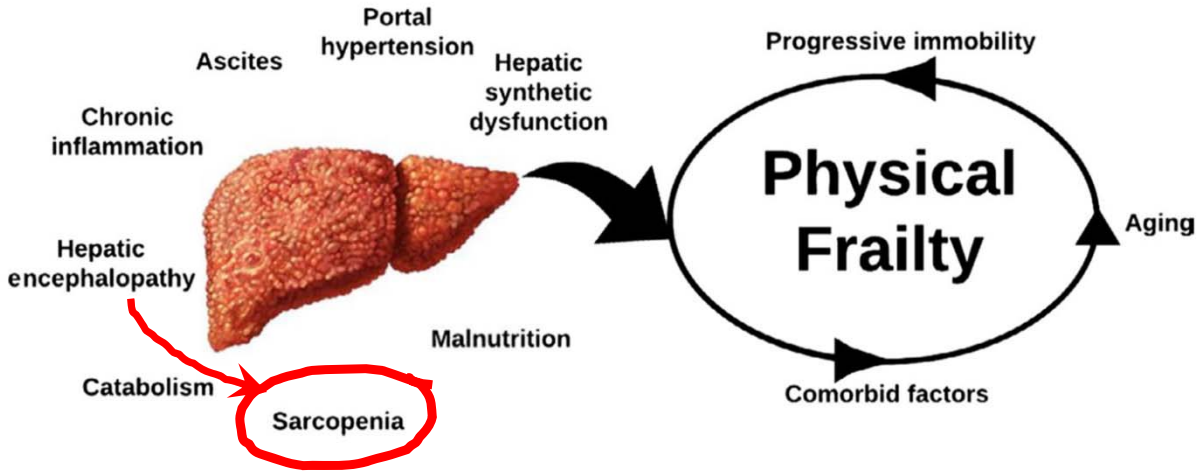
Lai JC, *et al*. Am J Transpl 2019. Figure developed by Dr. E Tapper.

Hepatic Encephalopathy → Sarcopenia



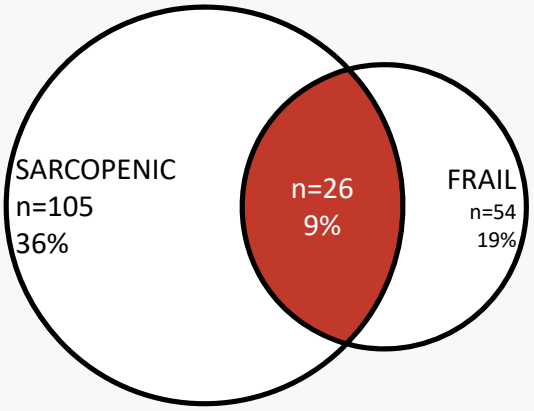
Tandon P, *et al*. J Hepatol 2018.

THE CYCLE OF FRAILTY



Lai JC, *et al*. Am J Transpl 2019. Figure developed by Dr. E Tapper.

Overlap between frailty and sarcopenia



n=291 patients with cirrhosis

- Among sarcopenic patients, 25% are frail.
- Among frail patients, 48% are sarcopenic.

Fozouni L / Lai JC. Under review 2019.

…3 day hospitalization for HE…

Starvation

Wrist restraints

NPO after midni procedure?

Sequential devices

Din reakfast @ 8am

72-hour calorie count

Falls precautions

Immobilization

Impact of “NPO after midnight”

Metabolic profile of a *cirrhotic* after an **overnight fast**

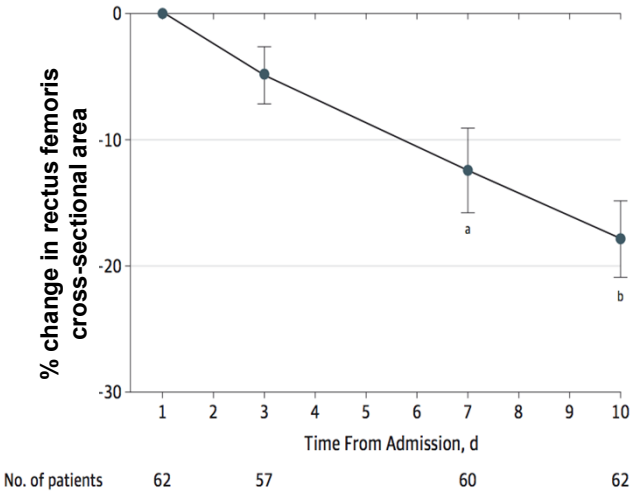
=

Metabolic profile of a *healthy control* after an **3 days starvation**

Owen OE; J Clin Invest 1971.

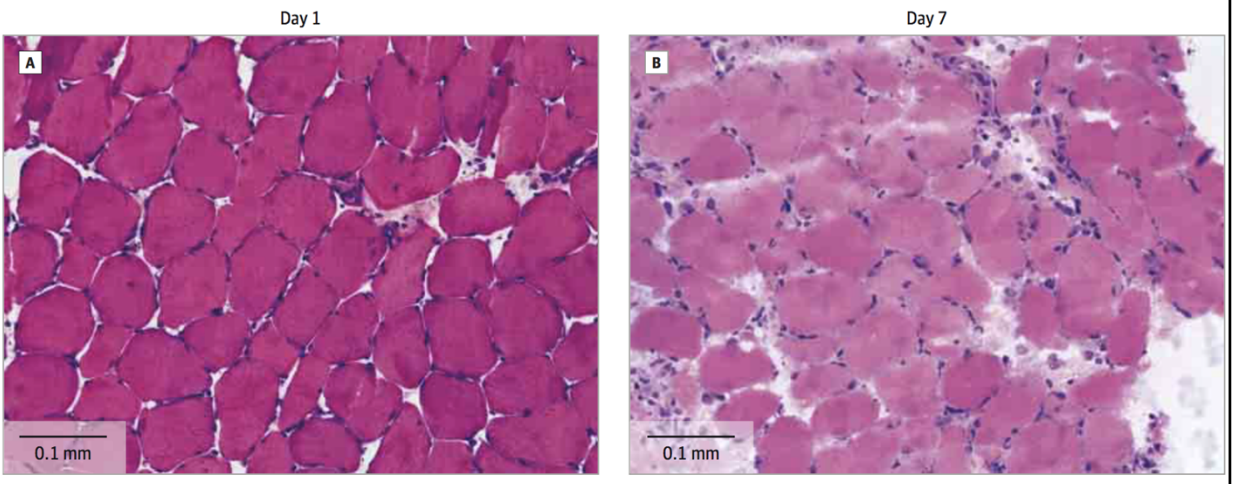
Impact of critical illness on muscle

- 63 critically ill patients
- Recruited within 24 hours of ICU admit
- Serial rectus femoris muscle U/S



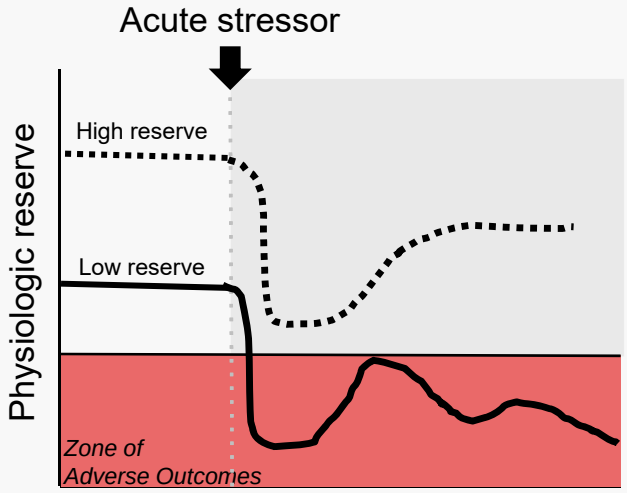
Puthucheary ZA, et al. JAMA 2013.

~40% developed muscle necrosis

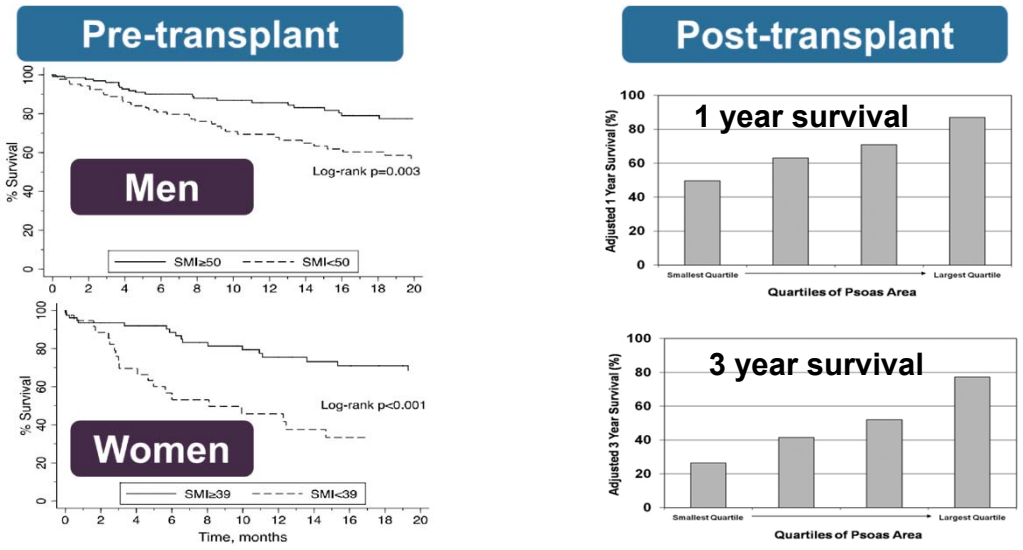


Puthucheary ZA, et al. JAMA 2013.

Overarching principles of management



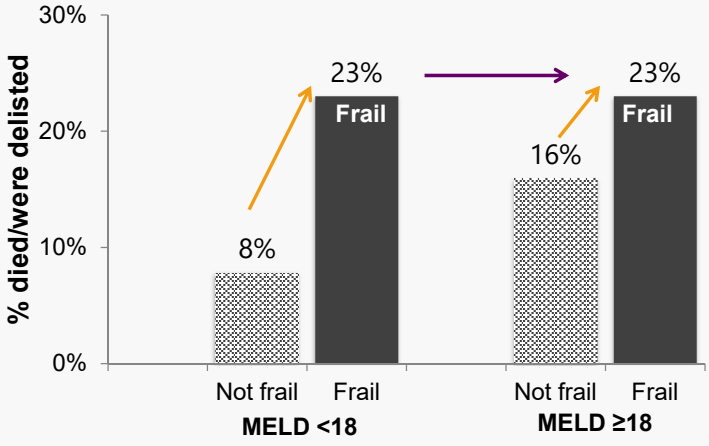
Sarcopenia is associated with death



Carey/Lai; Liver Transpl 2017.

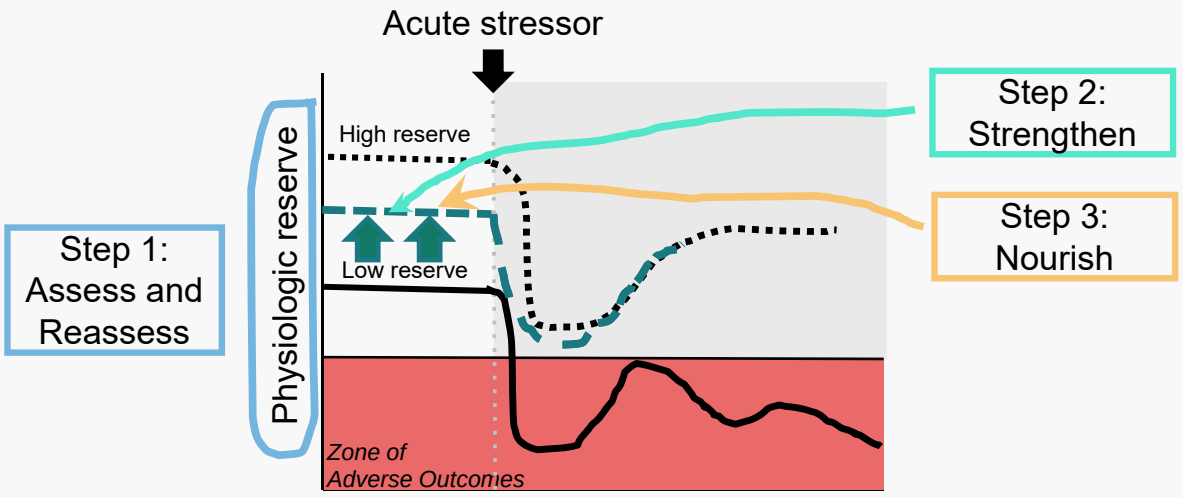
Englesbe MJ, J Am Coll Surg 2010.

Frailty is associated with death



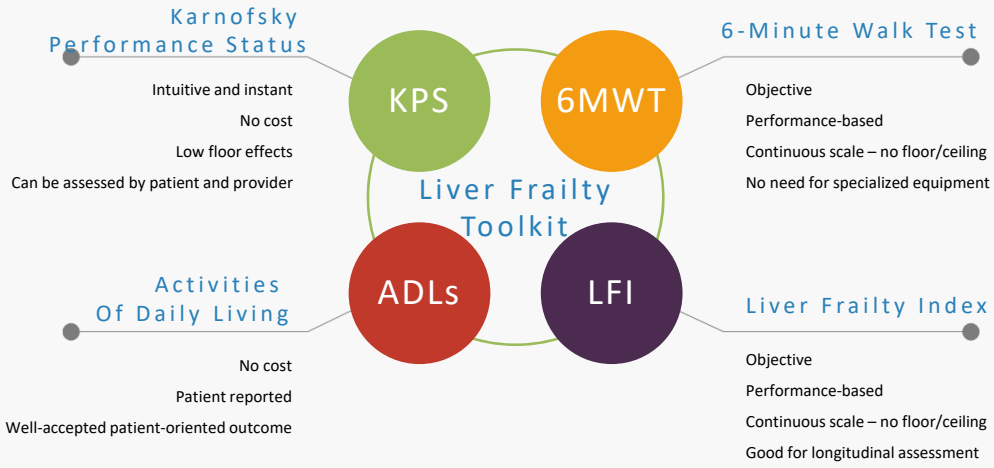
Lai JC, *et al.* Am J Transplant 2014.

Overarching principles of management



THE LIVER FRAILTY TOOLKIT

A consensus from experts in hepatology and liver transplantation.



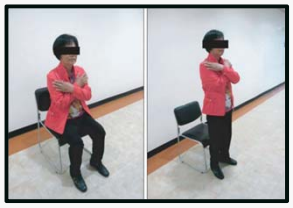
www.liverfrailtyindex.ucsf.edu

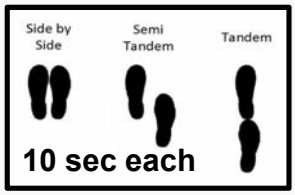
LIVER FRAILTY INDEX

- Simple (~90s)
- Objective
- Continuous

Prognostic for mortality in patients with cirrhosis

Grip + **Chair stands** + **Balance**



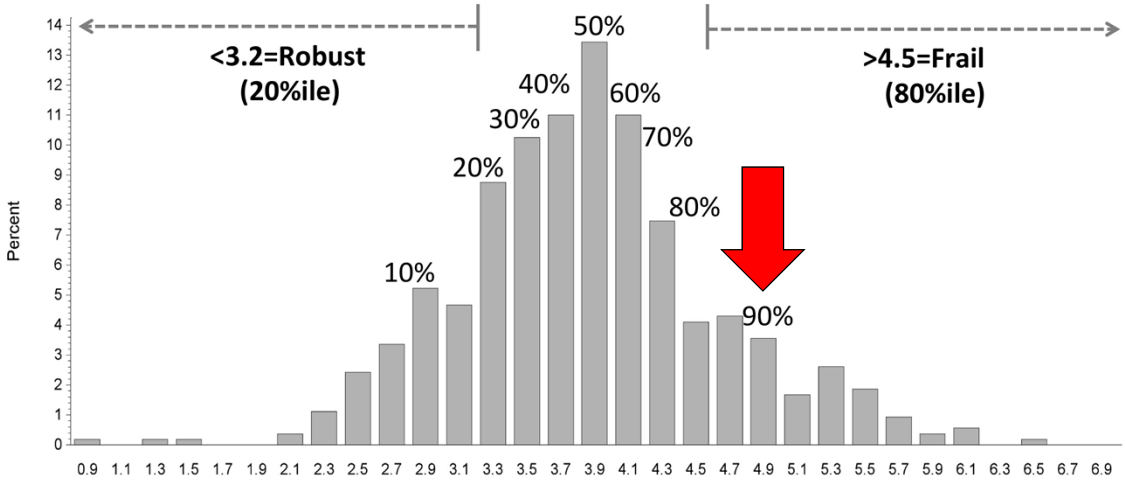


Reliable and reproducible. Norms available.
Wang C, *et al*. Liver Transpl 2019.

Lai JC, *et al*. Hepatology 2017.

Using the Liver Frailty Index in clinical practice

SHOW PATIENTS HOW THEY COMPARE

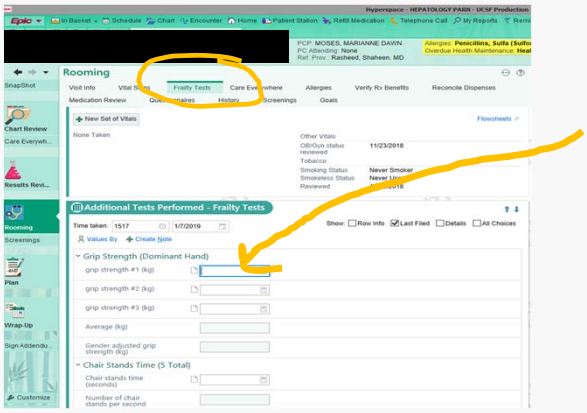


Lai JC, et al. Hepatology 2017. Liverfrailtyindex.ucsf.edu.

Using the Liver Frailty Index in clinical practice

AVAILABLE IN EPIC

Through the Epic Community Users Library



Use smart phrase to pull in values into your note

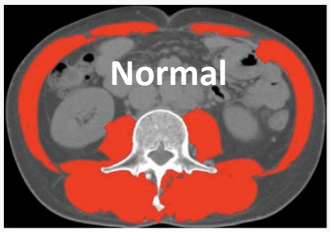
.liverfrailtyindex

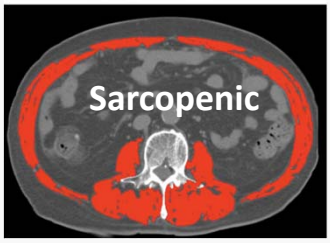
.lfi

LFI	12/14/17	3/22/18	6/28/18
3-component Liver Frailty Index	4.28	4.36	3.95

QUANTIFYING MUSCLE MASS

May be most suitable in the inpatient setting

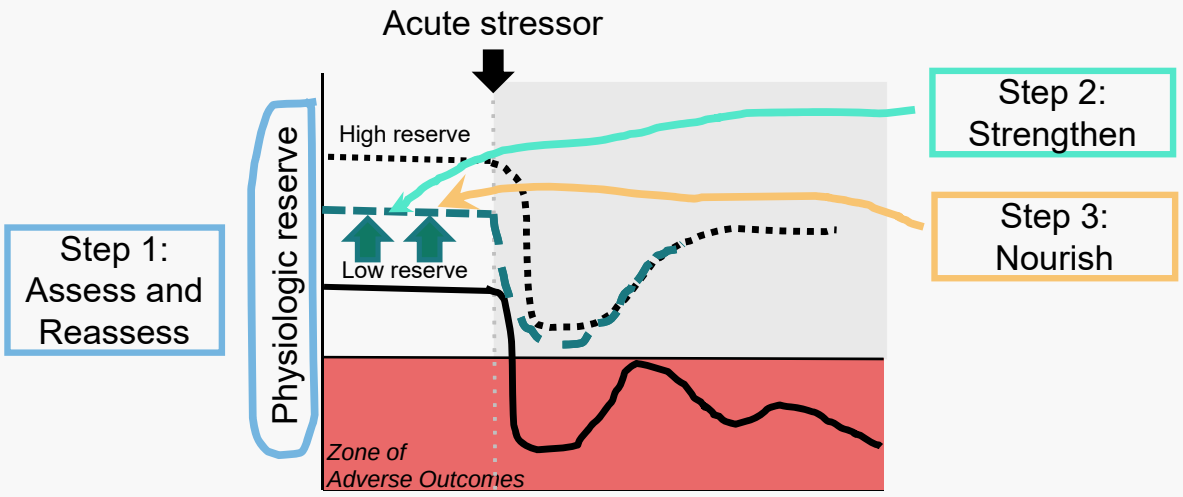




- Quantify muscle area at L3 or L4 vertebral levels on cross-sectional imaging
  - Psoas muscle area or index
  - Skeletal muscle index (SMI) = psoas + abdominal wall + lumbar
- Can be done by your radiologist
- Requires specialized software (that your radiologist may already have)
- SMI cut-points have been proposed to predict pre- and post-transplant mortality in patients with cirrhosis*

*Carey E, Lai JC, *et al*. Liver Transpl 2017. Kuo S, Wang S, *et al*. Transplant 2019.

Overarching principles of management



EXERCISE

The bedrock for preserving and improving muscle function

"Activity requiring physical effort, carried out especially to sustain or improve health and fitness."

Walking is not enough

Aerobic | **Resistance** | **Flexibility & Balance**

Dictionary.com

EXERCISE IN PATIENTS WITH CIRRHOSIS

Summary of multiple clinical trials

- Sample sizes small : n= 17 to 50 (for a total of ~100 patients who underwent exercise programs)
- Most with Child Pugh A cirrhosis
- Duration : 8-16 weeks
- Exercise : supervised center-based exercise

Zenith L CGH 2014, Roman E Dig Dis Sci 2014, Macias-Rodriguez CTG 2016, Berzigotti Hepatology 2017, Kruger Scient Rep 2018.

"FITT" RECOMMENDATIONS FOR EXERCISE

BE SPECIFIC!

FREQUENCY | INTENSITY | TIME | TYPE

AEROBIC ACTIVITY
3-5 days/week
150 minutes total per week
5-6/10 intensity

RESISTANCE TRAINING
≥2 days/wk
upper and lower body days
2-3 sets of 10-15 repetitions

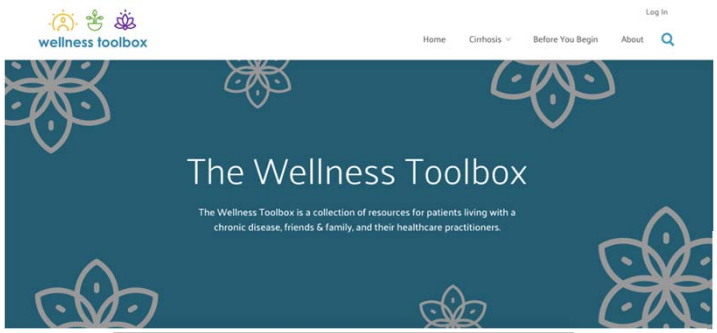
The "talk test" to guide intensity:
be short of breath but still be able to talk

Adapted from American College of Sports Medicine. Tandon P, J Hep 2018.

Slide courtesy of Nancy Howes, Physical Therapist, London Canada

EXERCISE RESOURCES

CONSIDER EMBEDDING THESE INTO A SMART PHRASE

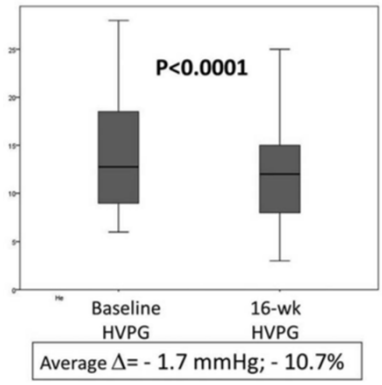


www.wellnesstoolbox.ca

Tandon P et al, J Hepatol 2018 ; Duarte-Rojo A – El Fit, AASLD innovation fund

EXERCISE REDUCES HVPG

Physiologic benefits of exercise



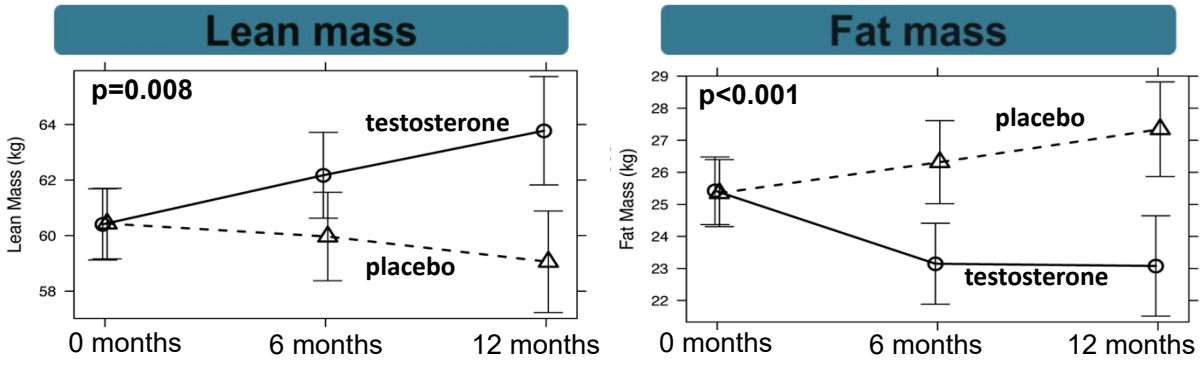
Among 50 patients with compensated cirrhosis who underwent 16 weeks of supervised exercise, HVPG *decreased* by ~11%

Berzigotti A, Hepatology 2017.

PHARMACOTHERAPY

INTRAMUSCULAR TESTOSTERONE FOR MEN

Doubled-blinded/placebo-controlled RCT in men with cirrhosis and low testosterone



O = testosterone n=50

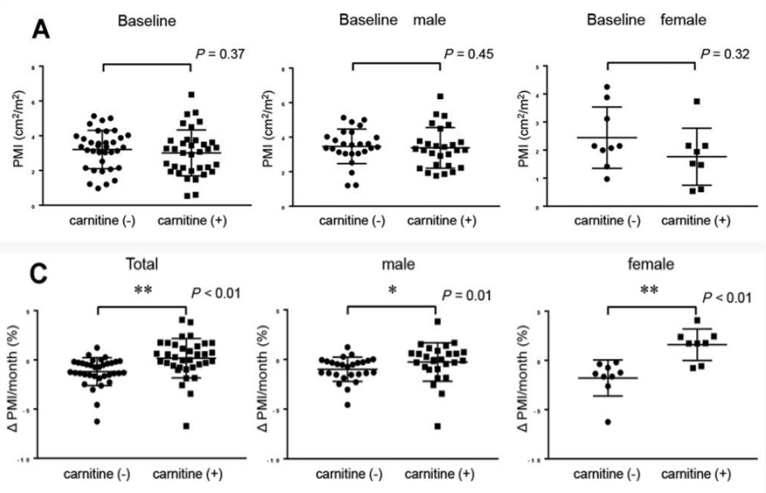
Δ = placebo n=50

Sinclair M, J Hep 2016.

PHARMACOTHERAPY

L-CARNITINE improves muscle mass

Small pilot study of patients with cirrhosis (35 in L carnitine arm)

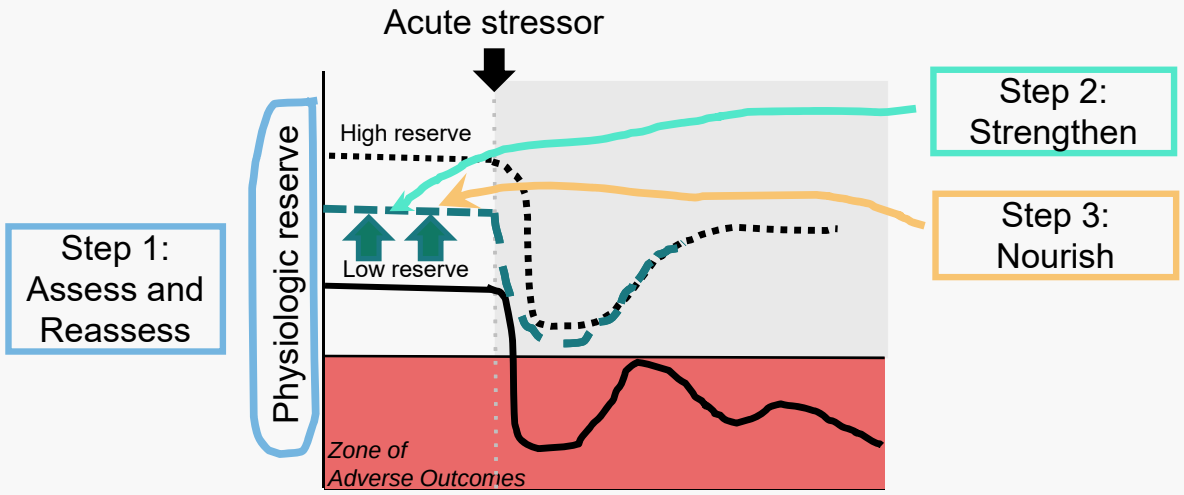


No difference in baseline mass

L carnitine arm has more improvement in muscle mass

Ohara M, *et al*. Hepatol Commun 2018.

Overarching principles of management



Puneeta Tandon, MD, FRCPC
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Canada
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Practical Tips for Closing the "Know-Do Gap" to Enhance Nutrition in the Lives of Patients with Cirrhosis

Malnutrition is one of the most common complications associated with cirrhosis It's etiology is multifactorial resulting from combined disturbances of oral intake, absorption, and metabolism of nutrients [1]. As with other conditions such as sarcopenia, frailty and deconditioning that are also characterized by "impaired muscle health", malnutrition is associated with an increased risk of mortality, higher prevalence of portal hypertension-related complications, and infections, as well as longer stays in hospital[2].

As a potentially modifiable condition, it is of particular relevance to identify malnourished patients so that nutritional therapy can be instituted. The Royal Free Hospital-Nutritional Prioritizing Tool (RFH-NPT) was developed as a nutritional screen by validation against the RFH-SGA [3]. It takes ~3 minutes to complete, discriminates patients into low, medium, or high risk categories, and includes the variables of alcoholic hepatitis, fluid overload and impact on dietary intake, BMI, unplanned weight loss, and reduced dietary intake In a series of 148 patients, the RFH-NPT was identified as an independent predictor of clinical deterioration and transplant-free survival [4]. The components of a detailed nutritional assessment incorporate the severity of underlying liver disease, dietary intake, barriers to intake, body composition and functional assessment[2]. It is preferable but not mandatory to have this performed by a Registered Dietitian (RD) or a dedicated person with specialized knowledge**.**

The Information-Motivation-Behavioral Skills (IMB) model for health behavioral change (Figure) can be used to more effectively engage patients and caregivers in adapting new behaviours.[4] The IMB framework postulates that individuals who are knowledgeable about the harms of malnutrition, motivated to focus on their nutritional status, and empowered with specific behavioral skills will take action to enhance their nutritional intake thereby improving their nutritional status. Encouraging patients to effectively change their behavior surrounding nutritional intake requires exploration of the personal and social factors that motivate the patient as an individual. Questions framed in a collaborative approach (e.g., "What were the barriers to eating a reduced salt intake today?") rather than confrontational or condescending (e.g., "You shouldn't have eaten that much salt for lunch"). Patients should be provided with educational materials – the Nutrition guide for cirrhosis (developed by patients and health care professionals) is a beautifully illustrated comprehensive guide that can be ordered through the Canadian liver foundation at: https://www.liver.ca/nutrition-cirrhosis-guide/ (free apart from shipping). Materials can be found online at www.wellnesstoolbox.ca.

There are several key evidence-based behavioral skills that can be implemented immediately into a patient's daily routine.

- **Target caloric intake**. Based on existing guidelines, specific caloric targets, stratified by the patient's body mass index (dry weight) can be provided. [9] The nutrition prescription calculator at https://wellnesstoolbox.ca/cirrhosis/nutrition/nutrition-prescription-calculator/ can bypass the challenges of calculating a dry weight or ideal body weight and is a practical tool for estimation of calorie (and protein needs) in a busy practice, when a dietitian is not

available to see the patient on the same day. Practical tips that may help to improve overall intake:

a) Avoid drinks around meal time (reduce appetite and provide little nutrition);
b) If necessary, supplement or substitute some meals with liquid foods such as cream soups, protein smoothies, or high protein meal replacement drinks as patients may find them easier to digest than solid foods;
c) Set an alarm to eat every 3-4 hours during the day (to avoid fasting).

- **Adequate protein intake**. Importantly, dietary protein restriction is not necessary in patients with hepatic encephalopathy concurrent with cirrhosis. A landmark study by Cordoba et al. [5] randomized patients hospitalized with hepatic encephalopathy to a low protein diet (gradual increase from 0 g/kg/d of protein for the first 3 days to 1.2 g/kg/d for the last 2 days) or a normal protein diet (1.2 g/kg/d) for 14 days. Although all patients showed similar recovery from their hepatic encephalopathy, those patients randomized to the low-protein diet group showed higher protein breakdown using glycine-N15 infusion method. [5]. The recommended daily protein intake target is 1.2-1.5 grams/kg protein,[10] which we translate into a "rounded number" of total grams of protein for the patient and their caregiver. For example, if the patient is 80 kg, we set the daily target at ~100 grams of protein. Patients can be advised to obtain protein from multiple sources to reduce "food boredom". These sources may include: meal supplements, protein powder, meat, dairy, and vegetable proteins (e.g., beans, tofu). The following food items contain ~20-25 grams of protein: 3 ounces of chicken or fish (size of the hand's palm), 1 cup of Greek yogurt, and 1 scoop of whey protein powder.

- **Avoid the nighttime "fast"**. A late evening snack – taken shortly before bedtime – or eating during nighttime hours can significantly increase muscle mass.[11,12] It has also been associated with reduced lipid oxidation, improved nitrogen balance as well as improved quality of life and reduced hepatic encephalopathy (93,94). The ideal snack consists of at least 50 grams of complex carbohydrates such as 2 slices of toast with peanut butter and 1 glass of milk. Patients put a snack at the bedside to eat if/when they wake up at night, such as a handful of unsalted walnuts or a protein snack bar.

  BCAAs have been used in patients with liver disease to preserve or restore muscle mass and to improve hepatic encephalopathy [6]. Though there are studies reporting no significant improvement in nitrogen balance with BCAAs supplementation [7-10], some studies report significant clinical improvement in hepatic encephalopathy [6, 11] and one study showed an increase in the mid-arm muscle circumference [12]. Japanese guidelines for comprehensive treatment of cirrhosis recommend the use of BCAA granules (L-valine, L-leucine, and L-isoleucine at a ratio of 1.2:2:1) to preserve liver function [13] and inhibit hepatic carcinogenesis [14]. ESPEN most recently recommended 0.25 g/kg/d in patients with advanced cirrhosis "in order to improve event-free survival or quality of life" [15]. The practical limitations are cost, availability and palatability.

  Lastly, clinicians get little training in behaviour change methodologies although this is at the crux of what we do daily. Motivational interviewing is "a way of being with a client" that can help to reduce ambivalence and increase the likelihood of behaviour change [16 17]. Although many medical practitioners may find that time pressures and lack of training make it challenging to implement the full motivational interviewing style into every patient encounter, following some of its principles may facilitate successful outcomes. Formal training in motivational interviewing is available world-wide with varying course durations, enhancing the practitioner's ability to build on techniques such as patient engagement, focus on the patient's goals for change, evoke their reasons for change and plan steps towards change.

References

1. Cheung K, Lee SS, Raman M. Prevalence and mechanisms of malnutrition in patients with advanced liver disease, and nutrition management strategies. Clin Gastroenterol Hepatol 2012;10(2):117-25.
2. Tandon P, Raman M, Mourtzakis M, Merli M. A practical approach to nutritional screening and assessment in cirrhosis. Hepatology 2017;65(3):1044-1057.
3. Amodio P, Bemeur C, Butterworth R, et al. The nutritional management of hepatic encephalopathy in patients with cirrhosis: International Society for Hepatic Encephalopathy and Nitrogen Metabolism Consensus. Hepatology 2013;58(1):325-36.
4. Borhofen SM, Gerner C, Lehmann J, et al. The Royal Free Hospital-Nutritional Prioritizing Tool Is an Independent Predictor of Deterioration of Liver Function and Survival in Cirrhosis. Dig Dis Sci 2016;61(6):1735-43.
5. Cordoba J, Lopez-Hellin J, Planas M, et al. Normal protein diet for episodic hepatic encephalopathy: results of a randomized study. J Hepatol 2004;41(1):38-43.
6. Marchesini G, Dioguardi FS, Bianchi GP, et al. Long-Term Oral Branched-Chain Amino-Acid Treatment in Chronic Hepatic-Encephalopathy - a Randomized Double-Blind Casein-Controlled Trial. Journal of Hepatology 1990;11(1):92-101.
7. Mcghee A, Henderson JM, Millikan WJ, et al. Comparison of the Effects of Hepatic-Aid and a Casein Modular Diet on Encephalopathy, Plasma Amino-Acids, and Nitrogen-Balance in Cirrhotic-Patients. Annals of Surgery 1983;197(3):288-293.
8. Horst D, Grace ND, Conn HO, et al. Comparison of Dietary-Protein with an Oral, Branched-Chain Enriched Amino-Acid Supplement in Chronic Portal-Systemic Encephalopathy - a Randomized Controlled Trial. Hepatology 1984;4(2):279-287.
9. Christie ML, Sack DM, Pomposelli J, Horst D. Enriched Branched-Chain Amino-Acid Formula Versus a Casein-Based Supplement in the Treatment of Cirrhosis. Journal of Parenteral and Enteral Nutrition 1985;9(6):671-678.
10. Swart GR, Vandenberg JWO, Vanvuure JK, Rietveld T, Wattimena DL, Frenkel M. Minimum Protein-Requirements in Liver-Cirrhosis Determined by Nitrogen-Balance Measurements at 3 Levels of Protein-Intake. Clinical Nutrition 1989;8(6):329-336.
11. Egberts EH, Schomerus H, Hamster W, Jurgens P. Branched-Chain Amino-Acids in the Treatment of Latent Portosystemic Encephalopathy - a Double-Blind Placebo-Controlled Crossover Study. Gastroenterology 1985;88(4):887-895.
12. Les I, Doval E, Garcia-Martinez R, et al. Effects of branched-chain amino acids supplementation in patients with cirrhosis and a previous episode of hepatic encephalopathy: a randomized study. Am J Gastroenterol 2011;106(6):1081-8.
13. Muto Y, Sato S, Watanabe A, et al. Effects of oral branched-chain amino acid granules on event-free survival in patients with liver cirrhosis. Clin Gastroenterol Hepatol 2005;3(7):705-13.
14. Muto Y, Sato S, Watanabe A, et al. Overweight and obesity increase the risk for liver cancer in patients with liver cirrhosis and long-term oral supplementation with branched-chain amino acid granules inhibits liver carcinogenesis in heavier patients with liver cirrhosis. Hepatology Research 2006;35(3):204-214.
15. Plauth M, Bernal W, Dasarathy S, et al. ESPEN guideline on clinical nutrition in liver disease. Clin Nutr 2019.
16. Miller WR, Rollnick, S. Motivational Interviewing: Preparing People for Change.: Bew York: Guildford Press.; 2013.
17. Mellinger JL, Winder GS. Alcohol Use Disorders in Alcoholic Liver Disease. Clin Liver Dis 2019;23(1):55-69.

Practical tips for closing the "Know-Do Gap" to enhance nutrition in the lives of patients with cirrhosis

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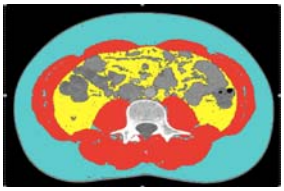
Clinical Hepatology Update 2019

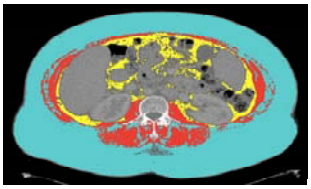
Disclosures and Aims

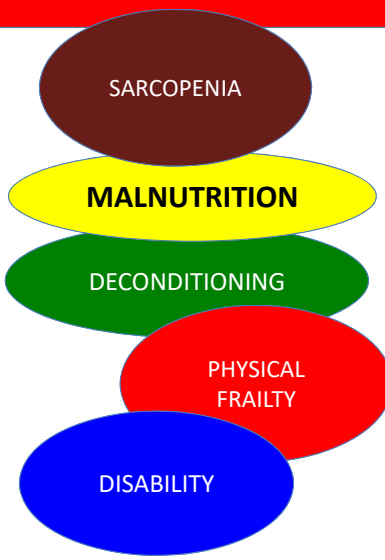
- **None relevant to this presentation**
- **My Aims**
  - **Promote practical nutrition tips you can use in your clinic next week!**
  - **Reinforcing the importance of behaviour change principles**

"The Know-Do gap , the often neglected work of getting effective therapies (the know) to the people who need them (the do)"
-Paul Farmer, MD

Impaired "Muscle Health"







4 Vulnerable – While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up", and/or being tired during the day.

5 Mildly Frail – These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 Moderately Frail – People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.

Lai J Am J T 2014; Montano-Loza CGH 2014 ; Dunn AJG 2016; Tandon CGH 2014 ; Tandon Hepatology

Malnutrition definitions all include muscle mass/function

2012 ASPEN/Academy of Nutrition & Dietetics consensus statement

Two or more of the following:

- Insufficient energy intake
- Weight loss
- Loss of muscle mass
- Loss of subcutaneous fat
- Localized or generalized fluid accumulation
- Decreased functional status

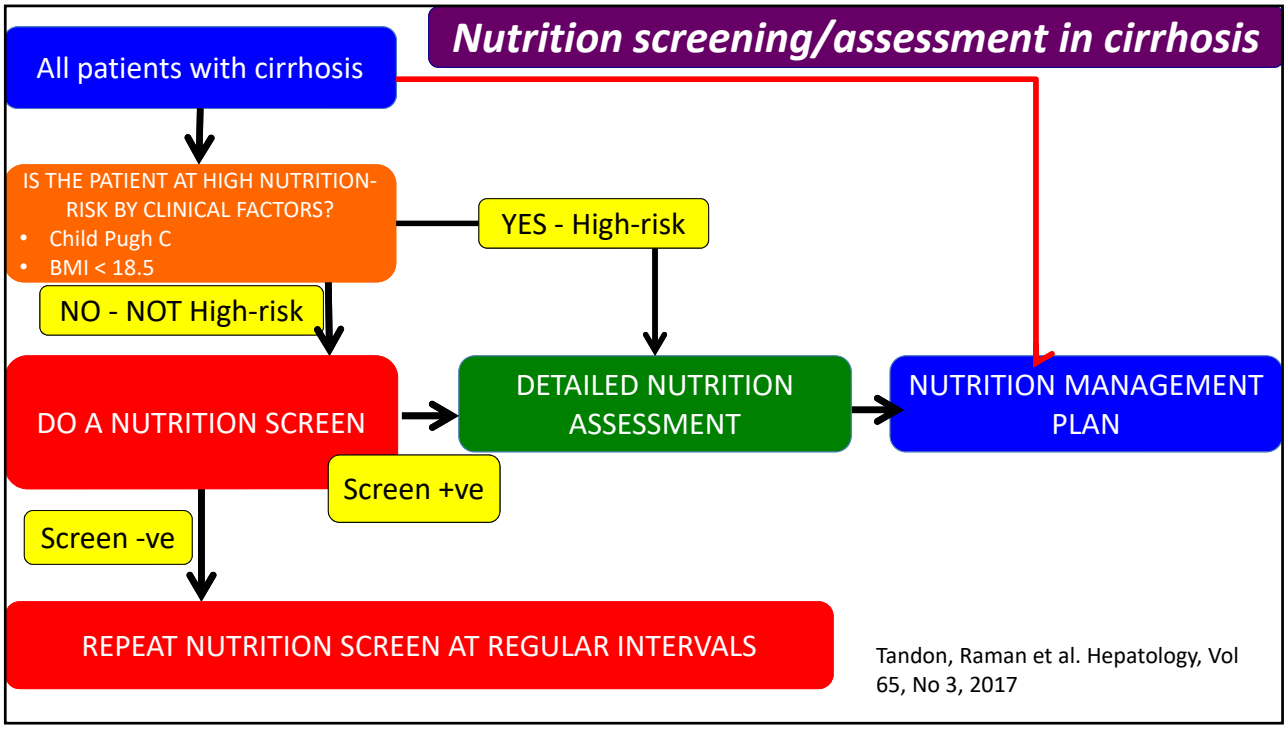
2018 Global Leadership Initiative on Malnutrition (GLIM)

One of the following:

- Non-volitional weight loss
- Low body mass index (BMI)
- Reduced muscle mass

And one of the following:

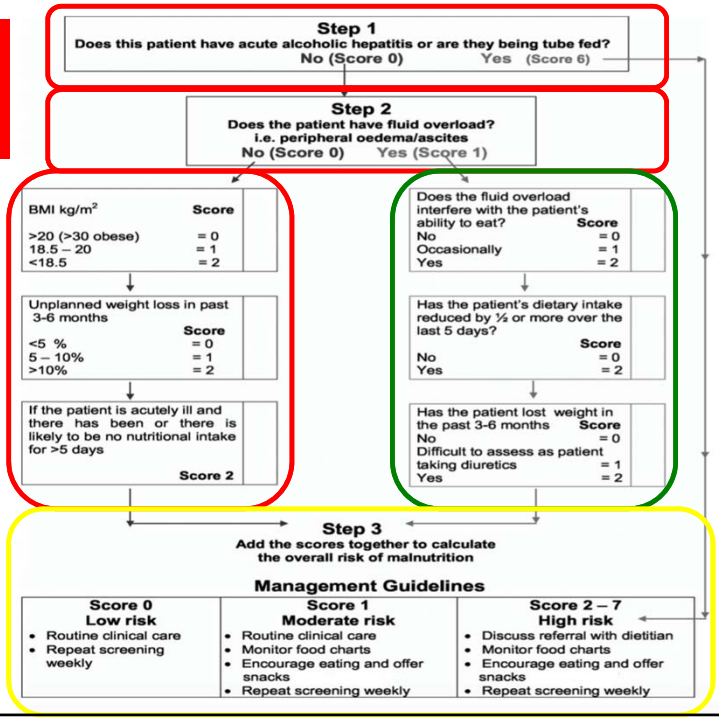
- Reduced food intake or assimilation
- Disease burden/inflammation



Tandon, Raman et al. Hepatology, Vol 65, No 3, 2017

Royal Free Hospital – Nutrition Prioritizing tool

- ~3 minutes to complete
- Includes relevant variables such as:
  - Alcoholic hepatitis
  - Fluid overload and impact on dietary intake
  - BMI
  - Unplanned weight loss
  - Reduced dietary intake
- ANYONE can complete!



Minimum Components of a Detailed Nutritional Assessment for patients with cirrhosis

1. Inflammation & cirrhosis severity

- Non-elective hospitalization or Child-Pugh C?
- Severe cirrhosis and/or complications?

2. Dietary intake & possible barriers

- Estimate dietary intake versus recommended
- Identify barriers to intake (taste, food access, symptoms)?

3. Weight loss & BMI

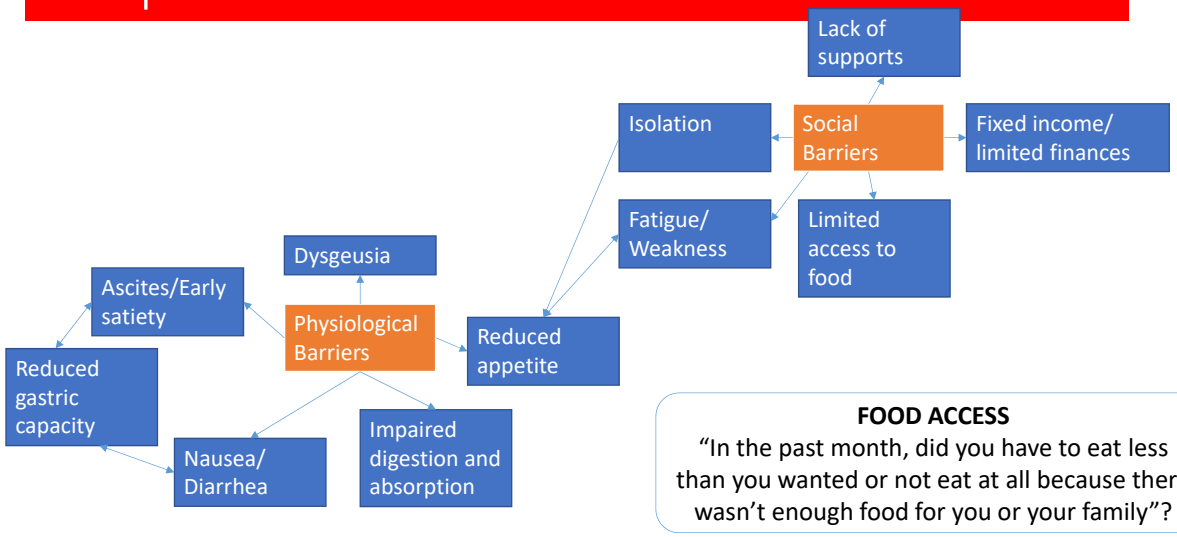
- Interpretation limited with fluid retention or ascites.
- Estimate percent weight loss in past 1-3 months
- Estimate BMI using dry weight
- If obese (BMI ≥30), consider specific nutritional advice

4. Muscle assessment

- Mass change: at a minimum use mid-arm muscle circumference (MAC)
- Function change: at a minimum use hand grip strength
- ***Lower sensitivity for females

Tandon, Raman et al. Hepatology, Vol 65, No 3, 2017

Nutrition Assessment – Potential barriers to adequate intake



FOOD ACCESS

"In the past month, did you have to eat less than you wanted or not eat at all because there wasn't enough food for you or your family"?

EASL Clinical Practice Guidelines on nutrition in chronic liver disease☆

European Association for the Study of the Liver*

ESPEN guideline on clinical nutrition in liver disease

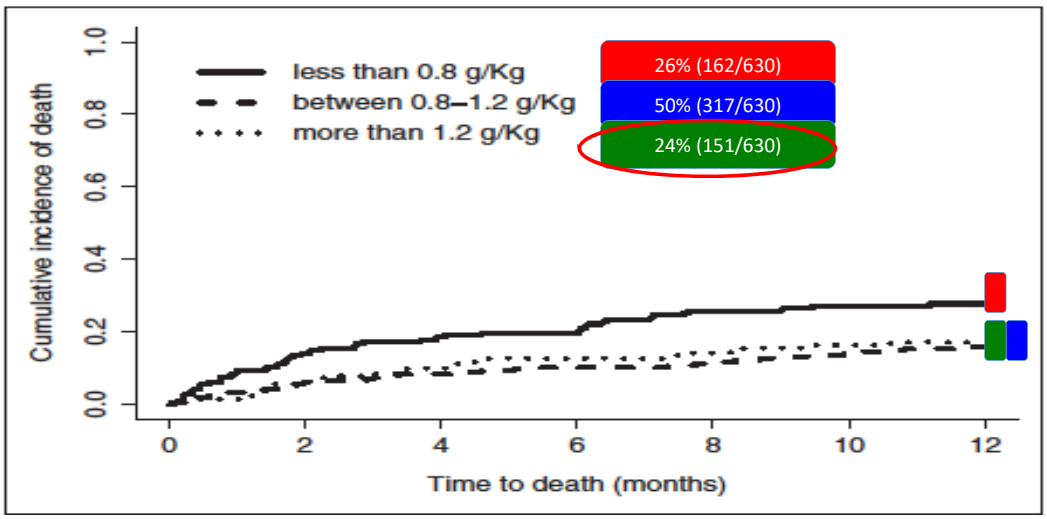
Mathias Plauth [a,*], William Bernal [b], Srinivasan Dasarathy [c], Manuela Merli [d], Lindsay D. Plank [e], Tatjana Schütz [f], Stephan C. Bischoff [g]

The Nutritional Management of Hepatic Encephalopathy in Patients With Cirrhosis: International Society for Hepatic Encephalopathy and Nitrogen Metabolism Consensus

Piero Amodio,[1] Chantal Bemeur,[2] Roger Butterworth,[3] Juan Cordoba,[4] Akinobu Kato,[5] Sara Montagnese,[1] Misael Uribe,[6] Hendrik Vilstrup,[7] and Marsha Y. Morgan[8]

"The Know-Do gap , the often neglected work of getting effective therapies (the know) to the people who need them (the do)"
-Paul Farmer, MD

Only 24% of patients awaiting liver tx meet protein targets



Ney M, Abraldes JG, Tandon P et al. Nutrition in Clinical Practice 2015

Even fewer patients meet targets while hospitalized

- 137 patients, 3 hospitals
- Age 55.5, 59% male, mean MELD 18.2, Etoh 41%, HCV 33%

- **By day 3 of hospital admission, guideline intake was met in:**
  - CALORIES – 7%
  - PROTEIN – 20%

- **In patients still admitted on ~ day 8**
  - CALORIES – 11%
  - PROTEIN – 14%

Shaikh T, Pai R, Ameen R, Qumosani K, Aljudaibi B et al. CDDW 2015

Nutrition therapy

- Assessment of barriers to intake, Nutrition Prescription, Nutrition Education and (ideally) book an assessment with a dietitian

1. ENERGY TARGET – 1750-2100 kcal/day

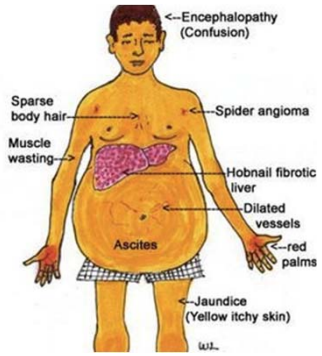
2. PROTEIN TARGET - 84-105 g/day

3. LATE EVENING SNACK –
- 50 grams complex carbs and 20 grams protein – can give culturally specific alternatives

4. VITAMIN D and CALCIUM supplementation

Coming back to the case – Mr. QT

- A 57 year old man, NASH cirrhosis, ascites, hepatic encephalopathy
- Temporal and upper arm muscle wasting.
- MELDNa score is 14.
- Poor appetite, fatigue, dysguesia
- Moderate ascites, pedal edema to knees
- Weight 155 kg, height 170 cm



Provide your patient with a target for calorie and protein intake

EASL Clinical Practice Guidelines on nutrition in chronic liver disease☆

- Optimal daily energy intake should not be lower than the recommended 35 kcal/kg. actual BW/d (in non-obese individuals). (**Grade II-2, B1**)
- Optimal daily protein intake should not be lower than the recommended 1.2–1.5 g/kg. actual BW/d. (**Grade II-2, B1**)
- A tailored, moderately hypocaloric (-500–800 kcal/d) diet, including adequate protein intake (>1.5 g proteins/kg ideal BW/d) can be adopted to achieve weight loss without compromising protein stores in obese cirrhotic patients. (**Grade II-1, C2**)

- **BMI stratified targets for caloric intake**
- **Actual body weight** = estimated dry weight
- **Ideal body weight =** BMI of 25

"The Know-Do gap , the often neglected work of getting effective therapies (the know) to the people who need them (the do)"
-Paul Farmer, MD

Plauth M et al. Clinical Nutrition 2006 ; Nutrition Support Manual (Adult) and *Daily Amodio P et al. Hepatology 2013*

Calculating the estimated dry weight

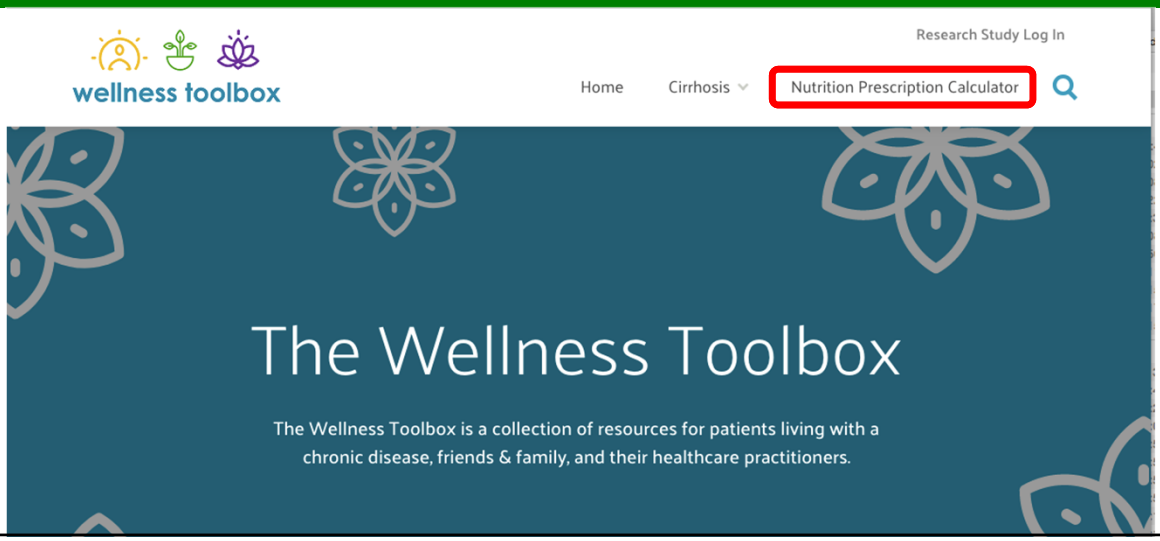
- **Can use the Estimated dry weight (EDW)**

Based on Imaging or physical exam:
- Small ascites: 5% of measured weight
- Moderate ascites: 10% of measured weight
- Large/tense ascites: remove 15% of measured weight

Edema – Pitting edema beyond ankles remove additional 5%

Combination of data from weight history, post tap weights, and imaging data can also be used to estimate dry weight

A basic Nutrition prescription for Mr QT?
www.wellnesstoolbox.ca
Nutrition prescription calculator



Nutrition prescription

This was generated using the patient's ideal body weight 72.3 kg

The patient's daily calorie intake range is: 1445 to 1806.3 kcal/day

The patient's daily protein intake range is: 86.7 to 108.4 g/day

Snacks and Late Night Snacks:

Set a timer to eat every 4 hours during the daytime.
Remember to eat a snack containing 10 to 20 g of protein and 50 g of carbohydrates shortly before bed-time or during the night.

Examples are:

- 1 bottle (235 ml) high calorie meal supplement (carbohydrates 44 g, protein 20 g)
- 2 slices of whole wheat toast with 2 tbsp peanut butter and 1 cup milk (optional: 1 tbsp whey protein powder)
- 3/4 cup Greek style yoghurt, 1 cup strawberries, 2 tbsp hemp seeds, 1 tsp honey on top
- smoothie made with 1 banana, 1 cup milk, 1/2 cup plain Greek yoghurt or 1 tbsp whey protein powder (chocolate or vanilla), 1 tbsp cocoa, and 1 tbsp peanut butter

AVAILABLE AT THE wellnesstoolbox.ca & can order hard copies from the *CANADIAN LIVER FOUNDATION WEBSITE*

Chapter 2

What should I eat and what to avoid?

Protein

2.5 oz of meat is:
the size of a deck of cards

Food Item	Measure	Equivalents	Weight (g)	Protein (g)	Sodium (mg)
Meat and Meat Alternatives					
Beef, Pork, cooked	2.5 oz	deck of cards	75	25	45
Chicken, Turkey, cooked	2.5 oz	"	75	20	50
Fish, baked/fried/steamed	2.5 oz	"	75	18	40
Canned fish in water, low sodium	75 g (⅓ cup)		75	18	50-70
Egg	1 large		50	6	65
Shrimp, boiled/steamed	6 small		30	6	67
Chick Peas, Beans, Lentils, canned (rinse first) /boiled	¾ cup	tennis ball	175 ml	11	30
Peanut Butter (commercial)	2 tbsp		30 ml	8	149
Peanut Butter (natural)	2 tbsp	golf ball	30 ml	7	2
Peanuts, Almonds (unsalted)	½ cup	2 golf balls	37	8	2
Tofu (regular, firm, extra firm)	150 g	hockey puck	150	21	26
Dairy Products and Supplements					
Milk, skim, 1%, 2%, whole	1 cup		258	9	105
Milk, 1% chocolate	1 cup		258	9	152
Soy beverage, unsweetened	1 cup		257	7	95
Skim milk powder	~ ⅓ cup		25	9	120
Yogurt, Greek, plain, flavoured	¾ cup	tennis ball	180	16	65

What is **my BMI**?

Nutrition Facts
Serving Size ¾ cup (55g)
Servings Per Container 5

Amount Per Serving
Calories 250 Calories from Fat 50

	% Daily Value*
Total Fat 6g	9%
Saturated Fat 0.5g	3%
Cholesterol <5mg	<2%
Sodium 200mg	8%
Total Carbohydrate 40g	13%
Dietary Fiber 4g	16%
Sugars 18g	
Protein 9g	18%

Vitamin A 25% • Vitamin C 50% • Calcium 30% • Iron 25%
*Percent Daily Values based on a 2,000 Calorie diet.

No need for protein restriction with hepatic encephalopathy

Normal protein diet for episodic hepatic encephalopathy: results of a randomized study

Juan Córdoba[1,*], Juan López-Hellín[2], Mercé Planas[3], Pilar Sabín[4], Francesc Sanpedro[1], Francisco Castro[1], Rafael Esteban[1], Jaume Guardia[1]

- In-patient cirrhotics with HE randomized to protein 0.5 g/kg/d and slow increase **versus** 1.2 g/kg/d x 14 days
- No differences in the course of HE
- Increased protein breakdown (glucine-N^{15} infusion method) in the low protein group

Cordoba J et al. J Hepatol 2004

Weak evidence that vegetable protein may have advantages

- **Type of protein**
  - Vegetable protein diet
    - Dried beans, peas, lentils, nuts, tofu
    - May be superior to meat and fish protein
    - Have increased dietary fiber – prebiotic properties that reduce transit time, intraluminal pH and increase fecal ammonia excretion
    - Promote beneficial alterations in the microbiota
    - Their breakdown results in less HE producing compounds

- Encourage the consumption of vegetables and dairy protein. (**Grade II-3, B1**)

Amodio et al. Hepatology 2013 ; EASL guideline 2018

Branched chain amino acids?

- In addition to providing protein, there is some evidence that BCAA's reduce HE and may impact rates of clinical decompensation.
- Poor palatability, cost have led to variable utilization.

Food	Serving	Protein	BCAA
Chicken	6 oz	36 g	6.6 g
Salmon	6 oz	34 g	5.9 g
Egg	1	6.3 g	1.3 g
Peanuts	6 oz	12 g	6.8 g

- BCAA supplements and leucine enriched amino acid supplements should be considered in decompensated cirrhotic patients when adequate nitrogen intake is not achieved by oral diet. (**Grade II-1, C1**)

- BCAA supplementation should be considered to improve neuropsychiatric performance and to reach the recommended nitrogen intake. (**Grade I-1, A1**)

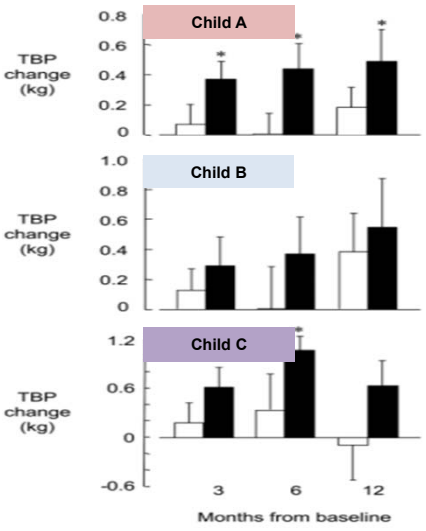
In cirrhotic patients who are protein "intolerant", vegetable proteins or BCAA (0.25 g × kg^{-1} × d^{-1}) should be used by oral route to facilitate adequate protein intake. (BM).
Grade of recommendation B – Consensus (89% agreement)

Long-term oral BCAA supplements (0.25 g × kg^{-1} × d^{-1}) should be prescribed in patients with advanced cirrhosis in order to improve event-free survival or quality of life (BM)
Grade of recommendation B – Consensus (89% agreement)

Marchesini G et al Gastro 2003, Muto Y et al. Clin Gastroenterol Hepatol 2005 ; EASL guideline 2018 ; ESPEN guideline 2019

Shortening the fasting window: Late night snack ↑muscle mass

- 103 patients. 710 kcal daytime vs evening (21:00 7:00) supplementation
- Improved muscle mass by 2 kg over 1 y
- Other studies: ↑ HRQOL and may reduce the frequency and severity of HE



Plank LD et al. Hepatology 2008 ; Tsien C et al. J Gastroenterol Hepatol 2011

Late night snack – practical recommendations

- Avoid fasting for longer than 3-4 h during the day
- Take a snack containing 50 grams of complex carbohydrates at night with a small source of protein.
- Eat breakfast

<u>Some night snack options</u>

- Meal replacement drink
- 2 slices of toast with peanut butter and a glass of milk
- 1 cup cereal with 1 cup milk and 1 piece of fruit

Plank LD et al. Hepatology 2008 ; Tsien C et al. J Gastroenterol Hepatol 2011

Chapter 3

Tips for when you do not feel like eating

1 "When I eat, I get full very quickly."

The sensation of early fullness is also called "early satiety". This decreases the amount of food you can eat, and can lead to weight loss and malnutrition.

Suggestions:

- Eat smaller, more frequent meals and snacks every 2-4 hours.
- Limit fluid intake when eating to reserve room for food.
- Avoid drinks like coffee, tea, and water since they can reduce your appetite overall and provide you with little nutrition.

Make your calories count!

ement drinks or cream soups.

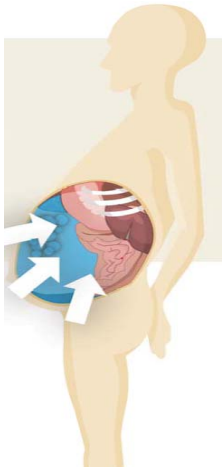
Tip:

Keep a granola bar and meal supplement in the nightstand or bathroom for easy access during the night.

4 "I don't have enough money to buy food."

Tips for overcoming barriers to nutrition intake

- **Dietitian consultation**
- **Early satiety** – "Grazing", separate fluid intake from solid foods, nutrient dense foods, liquid nutrition
- **Anorexia –** See food as a drug, cold foods may cause less aversion, external cues to stimulate intake
- **Medical appointments –** Pack snacks, address NPO policies
- **Food security –** Social work involvement – assess ability to access food, grocery budget, Income supports



Chapter 4

Recipe List

For the Nutrition in Cirrhosis Guide

Hummus

1x15-ounce can chickpeas, rinsed
1 clove garlic
1/4cup olive oil
2tbsp fresh lemon juice
2tbsp tahini
1tsp ground cumin
1/4tsp paprika

Add all ingredients to food processor. Blend until smooth consistency, if too thick, add water until you reach desired consistency.

Gourmet Homemade Hamburgers

½ cup minced onions
¼ tsp garlic powder
¼ tsp dried basil
1 tbsp olive or canola oil
1 tbsp lemon juice
2 tsp dried parsley
1 tsp water
1 lb lean ground beef

Mix all ingredients together in large bowl. Form patties ~4 inch diameter, and ½ inch thickness. Makes 4 patties. Fry on medium heat or cook on BBQ, until burger is no longer pink throughout.

Chapter 5

Using Meal Supplements

Nutrition in Cirrhosis Guide

Using nutritional meal supplements can improve your diet. If you don't eat enough nutrients, meal supplements can help you get enough nutrients.

When choosing a meal supplement, it is important to find a meal supplement that best suits your needs. Use this chapter to guide your choice if you are using a meal supplement

Nutritional meal supplement	Serving size	Calorie (kcal)	Protein (g)	Sodium (mg)	Calcium (mg)	Highlights
Ensure® Regular	1 bottle (237 ml)	235	9.4	250 (10% DV)	300 (27% DV)	Maintain a healthy weight, Increase energy, Prepare easy meals, balanced nutrition for supplemental use between or with meals.
Ensure® Plus Calories	1 bottle (237 ml)	355	14	250 (10% DV)	300 (27% DV)	50% more protein and 120 more calories per bottle than regular Ensure®, Helps maintain or gain weight.
Ensure® High Protein	1 bottle (237 ml)	225	12	290 (12% DV)	275 (25% DV)	Help maintain a healthy weight and ensure® adequate protein intake, 28% more protein than regular Ensure®
Ensure® Enlive®	1 bottle (235 ml)	350	20	240 (10% DV)	550 (50% DV)	Has the unique ingredient HMB (certain medical foods to help provide nutritional support for people with muscle wasting , plus 20 grams of protein, to h elp rebuild muscle for strength and energy .

Sarcopenic obesity management

- Very little cirrhosis specific research in this area
- RD involvement essential

ENERGY INTAKE

- Use BMI stratified caloric intake targets
- Target 5-10% weight loss in patients with dry weight BMI >30 kg/m2
- Tailored, moderately hypocaloric diet (-500-800 kcal/day)
- Combine energy restriction with exercise to reduce muscle mass loss

PROTEIN INTAKE

- 1.2-1.5 g/kg protein per day

AVOID FASTING

- Avoid fasting for longer than 4 hours

EXERCISE

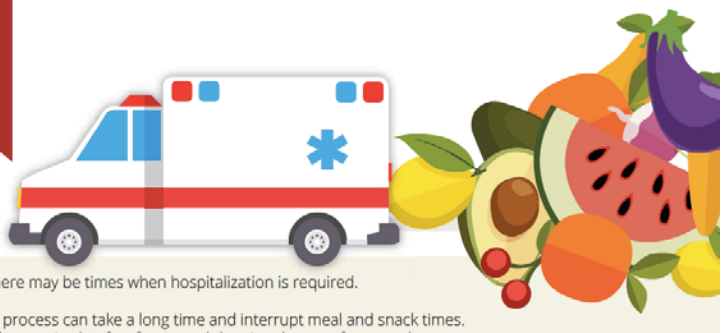
- Moderate intensity exercise of at least 150 minutes per week
- Resistance exercise is key

***The majority of weight that is lost when calories are restricted is from the loss of fat (75%). The rest is from the loss of muscle (25%).

Eslamparast T, Liver International 2018 ;
EASL guideline 2018

Chapter 7

What to expect in the hospital?



In cirrhosis, there may be times when hospitalization is required.

The admitting process can take a long time and interrupt meal and snack times. You may also be required to fast for several days in advance of a procedure.

Not eating for more than 8 hours increases the risk for unwanted weight and muscle mass loss. Here are several helpful strategies:

1) What can I do?

- Bring snacks to eat during your hospital stay
- Ask the nursing staff when and what you are allowed to eat
  - ask often since this is important!

Nutrition recommendations for inpatients

ACG Clinical Guideline: Nutrition Therapy in the Adult Hospitalized Patient

Stephen A. McClave, MD[1], John K. DiBaise, MD, FACG[2], Gerard E. Mullin, MD, FACG[3] and Robert G. Martindale, MD, PhD[4]

Specialized nutrition therapy in the form of EN should be initiated promptly in the hospitalized patient who is at high nutritional risk and is unable to maintain volitional oral intake.

In cirrhotic patients, who cannot be fed orally or who do not reach the nutritional target through the oral diet, EN should be performed. (BM)
Grade of recommendation B – Strong consensus (100% agreement)

Esophageal varices are no absolute contraindication for positioning a nasogastric tube (BM)
Grade of recommendation 0 – Strong consensus (100% agreement)

ASPEN Guidelines for Enteral Nutrition 2016, McClave SA et al. AJG 2016 ; ESPEN guideline 2019

A Comprehensive Nutrition-Focused Quality Improvement Program Reduces 30-Day Readmissions and Length of Stay in Hospitalized Patients

Krishnan Sriram, MD, FCCM, FRCS(C), FACS[1]; Suela Sulo, PhD[1,2];
Gretchen VanDerBosch, RD, LDN[1]; Jamie Partridge, PhD, MBA[2];
Josh Feldstein, BA[3]; Refaat A. Hegazi, MD, PhD[2]; and Wm. Thomas Summerfelt, PhD[1]

- Malnutrition risk screen, oral nutrition supplements, dietitian consultation as needed, patient and care-giver nutrition education
- **25% reduction in length of stay and 30-day readmission rates**

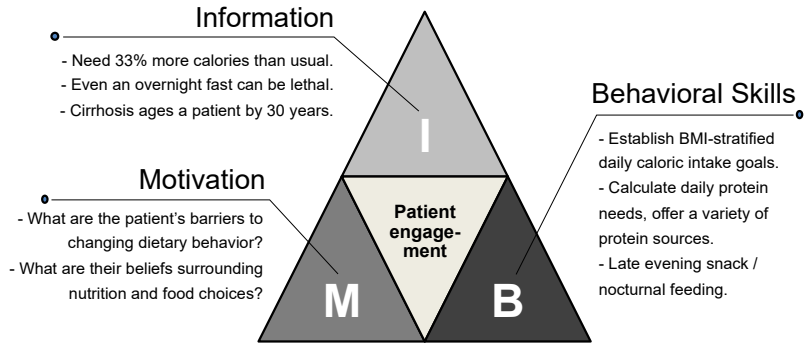
Journal of Parenteral and Enteral Nutrition Vol 41, 2017

What micronutrients should I test for and recommend?

- **Vitamin A, D, E, folic acid and Vit B12** if anemia, **zinc, selenium** if malnourished.
- We routinely recommend a **daily multivitamin** without iron
- Vitamin D start with 1000 IU daily and then adjust based on levels
- Zinc 25 mg daily x 3 weeks if deficient – can improve dysgeusia, weak evidence for HE
- Selenium 200 ug daily x 3 weeks if deficient
- Need 4 servings of milk products daily to get enough **calcium** in the diet (target 1200-1500 mg/day):
  - 1 serving = 1 cup milk/soy, ¾ cup yogurt, 1-2 oz cheese, 2 cups cottage cheese. Make up the rest with a supplement
- Hospitalized patients – risk of re-feeding, thiamine deficiency

Plauth M et al. Clinical Nutrition 2019

Behaviour change requires patient buy-in and ability



Lai J, Tandon P. American Journal of Gastroenterology 2018
Tandon P et al. Hepatology 2016

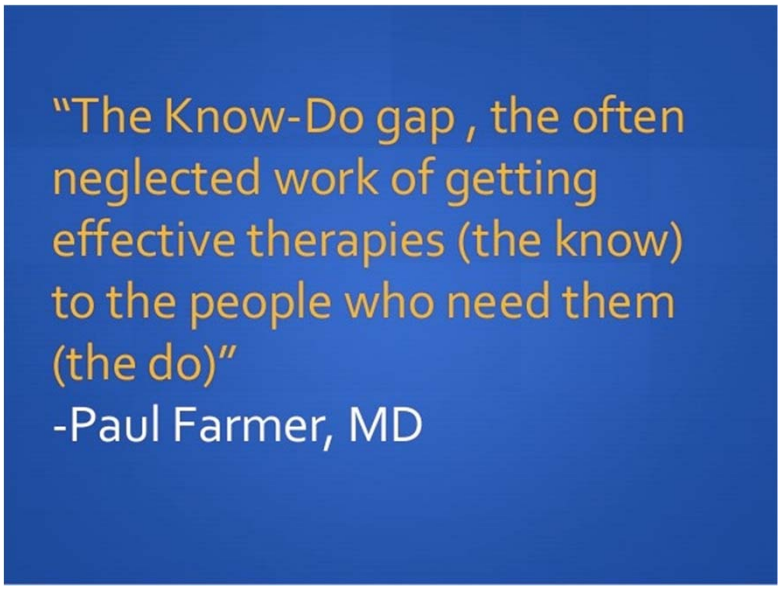
Motivational Interviewing

"an empathetic, person-centered counseling approach that prepares people for change by helping them to resolve ambivalence, enhance intrinsic motivation and build confidence to change"

MINT
excellence in motivational interviewing

MAYO CLINIC

Mayo Clinic Wellness Coach Training Program



Take home: Pick one or two things to incorporate into your clinic next week

- **Provide your patient with education around nutrition –**
  - https://www.liver.ca/nutrition-cirrhosis-guide/ -- 8 dollars for shipping 100 books!
  - Link them to the www.wellnesstoolbox.ca for an online version
- **Perform the RFH nutrition screen. At a minimum, start consulting a dietitian in all of your decompensated patients and obese patients**
- **Ask about dietary intake and barriers, including food security**
- **Provide all patients with a basic nutrition prescription**
  - www.wellnesstoolbox.ca nutrition prescription calculator
    - Target BMI stratified energy intake (for stable outpatients)
    - Target protein intake 1.2-1.5 g/kg/day.
    - Avoid fasting. Late night snack with 50 g of complex CHO + protein
- **Consider signing up for a 1-2 day course on motivational interviewing**

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ALBERTA HEALTH SERVICES | UNIVERSITY OF ALBERTA

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Palliative Care: When to Refer

Palliative Care: The Basics

Palliative care is best defined as an approach to medical care that improves the quality of life of patients and their families facing a chronic, life-limiting illness[1]. Dimensions of palliative care include 1) physical symptom management; 2) mental health management; 3) advance care planning; 4) addressing social and cultural issues; 5) addressing spiritual, religious, and existential issues; and 6) end of life care[2]. It is important to recognize that palliative care is not synonymous with end of life care and that it can thus be provided to patients and families throughout the trajectory of chronic illness**.** In fact, early palliative care interventions have been associated with improvements in patient and caregiver satisfaction as well as lower healthcare utilization, particularly in populations with advanced cancer[3]. Specialist palliative care is provided ideally through an interdisciplinary team, which can include clinicians trained in palliative care, nurses, social workers, chaplains, and pharmacists. Generalist palliative care, on the other hand, is delivered by a healthcare provider who is knowledgeable on basic principles of palliative care but has not completed specialized training[4]. To meet the demand of suffering in patients with chronic illness, investing in generalist palliative care has been widely advocated.

Unmet Palliative Needs in Patients with Advanced Liver Disease

Patients with advanced liver diseases such as decompensated cirrhosis and hepatocellular carcinoma (HCC) often experience a great deal of suffering through the course of their illness and at the end of life[5]. While certain physical symptoms such as ascites, pruritus, and encephalopathy are well-managed by gastroenterologists and hepatologists, pain and mental health issues are often under-recognized and less optimally handled[6]. Caregiver burden often increases steadily throughout a patient's illness trajectory but is often unaddressed[7]. Patients are unprepared for making decisions as their illnesses progress and nearing the end of life[8]. Advance directives, which include appointing a surrogate decision maker, are infrequently completed and goals of care conversations are only common near the time of death[9].

Overcoming Barriers to Delivering Palliative Care

Despite these unmet needs, specialty palliative care is rarely involved in a patient's management, even at the end of life[10,11]. Reported barriers include fear of misperception by patients, fear of reducing hope, and concern that patients do not require consultation since they are too healthy. Some physicians also report that the goals of liver transplantation and palliative care for seriously ill patients seem inconsistent[12,13]. Despite these concerns, there have been successful collaborations between liver transplantation teams and palliative care teams in intensive care, outpatient, and hospice settings[14-16].

Suggestions for Integrating Palliative Care and Referral into Practice

1. Ensure that physical symptoms, including pain, and mental health issues are being recognized and addressed for your patients.
2. Develop skill in performing advance care planning for your patients. This includes encouraging your patients to complete advance directives, ideally before they develop hepatic encephalopathy.

3. Recognize caregiver burden and spiritual distress.
4. Invest in building relationships with outpatient and inpatient palliative care teams. Consider referral when the above issues (1-3) are challenging to manage.

References

1. Sepulveda C, Marlin A, Yoshida T, Ullrich A. Palliative Care: the World Health Organization's global perspective. J Pain Symptom Manage. 2002;24(2):91-96.
2. Ahluwalia SC, Chen C, Raaen L, et al. A Systematic Review in Support of the National Consensus Project Clinical Practice Guidelines for Quality Palliative Care, Fourth Edition. J Pain Symptom Manage. 2018;56(6):831-870.
3. Kavalieratos D, Corbelli J, Zhang D, et al. Association Between Palliative Care and Patient and Caregiver Outcomes: A Systematic Review and Meta-analysis. JAMA. 2016;316(20):2104-2114.
4. Quill TE, Abernethy AP. Generalist plus specialist palliative care--creating a more sustainable model. N Engl J Med. 2013;368(13):1173-1175.
5. Roth K, Lynn J, Zhong Z, Borum M, Dawson NV. Dying with end stage liver disease with cirrhosis: insights from SUPPORT. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment. J Am Geriatr Soc. 2000;48(5 Suppl):S122-130.
6. Hansen L, Leo MC, Chang MF, Zucker BL, Sasaki A. Pain and self-care behaviours in adult patients with end-stage liver disease: a longitudinal description. J Palliat Care. 2014;30(1):32-40.
7. Bajaj JS, Wade JB, Gibson DP, et al. The multi-dimensional burden of cirrhosis and hepatic encephalopathy on patients and caregivers. Am J Gastroenterol. 2011;106(9):1646-1653.
8. Low JTS, Rohde G, Pittordou K, et al. Supportive and palliative care in people with cirrhosis: international systematic review of the perspective of patients, family members and health professionals. J Hepatol. 2018.
9. Patel AA, Gery Ryan, Anne Walling, Emmeline Chuang, Cindy Cain, Dan Tran, Nikhil Gupta et al. "Advance Care Planning for Patients with Decompensated Cirrhosis: Preliminary Results of a Multi-Center Qualitative Study." In HEPATOLOGY, vol. 68, pp. 453A-454A. 111 RIVER ST, HOBOKEN 07030-5774, NJ USA: WILEY, 2018.
10. Patel AA, Walling AM, Ricks-Oddie J, May FP, Saab S, Wenger N. Palliative Care and Health Care Utilization for Patients With End-Stage Liver Disease at the End of Life. Clin Gastroenterol Hepatol. 2017;15(10):1612-1619 e1614.
11. Rush B, Walley KR, Celi LA, Rajoriya N, Brahmania M. Palliative care access for hospitalized patients with end-stage liver disease across the United States. Hepatology. 2017;66(5):1585-1591.
12. Ufere NN, Donlan J, Waldman L, et al. Physicians' Perspectives on Palliative Care for Patients With End-Stage Liver Disease: A National Survey Study. Liver Transpl. 2019;25(6):859-869.
13. Esteban JPG, Rein L, Szabo A, Saeian K, Rhodes M, Marks S. Attitudes of Liver and Palliative Care Clinicians toward Specialist Palliative Care Consultation for Patients with End-Stage Liver Disease. J Palliat Med. 2019.
14. Lamba S, Murphy P, McVicker S, Harris Smith J, Mosenthal AC. Changing end-of-life care practice for liver transplant service patients: structured palliative care intervention in the surgical intensive care unit. J Pain Symptom Manage. 2012;44(4):508-519.
15. Baumann AJ, Wheeler DS, James M, Turner R, Siegel A, Navarro VJ. Benefit of Early Palliative Care Intervention in End-Stage Liver Disease Patients Awaiting Liver Transplantation. J Pain Symptom Manage. 2015;50(6):882-886 e882.
16. Medici V, Rossaro L, Wegelin JA, et al. The utility of the model for end-stage liver disease score: a reliable guide for liver transplant candidacy and, for select patients, simultaneous hospice referral. Liver Transpl. 2008;14(8):1100-1106.

Palliative Care: When to Refer?

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Case # 1

A 67 y.o. man with decompensated cirrhosis from NASH, DM, ESRD on HD, comes to see you for a routine visit.

- PMH: well-controlled HE, requires LVP's every 2 weeks; history of EV bleed but controlled with banding, no SBP.
- Tbili 1.8, Cr 2.8, INR 1.6, Na 135, Meld-Na: 29
- Not LT candidate since has no support (lives with wife who is disabled and unable to care for him).

During your appointment, he states that one of his doctors brought up getting **palliative care** involved.

Which of the following best describes the overall goal of palliative care?

A. To provide hospice care to patients with chronic, life-limiting illnesses.

B. To ensure that critically ill patients receive comfort measures only.

C. To improve the quality of life of patients with chronic, life-limiting illnesses.

D. To withdraw life-prolonging treatments for patients receiving futile care.

Perceptions of Palliative Care for ESLD Among Hepatologists

- 73% believe it is reasonable to defer specialty palliative care consultation when a patient is not imminently dying[1].
- >80% believe that advance care planning and physical symptom management are best performed by hepatologists.
- Only 27% believe that palliative care is best provided by hepatologists[2].

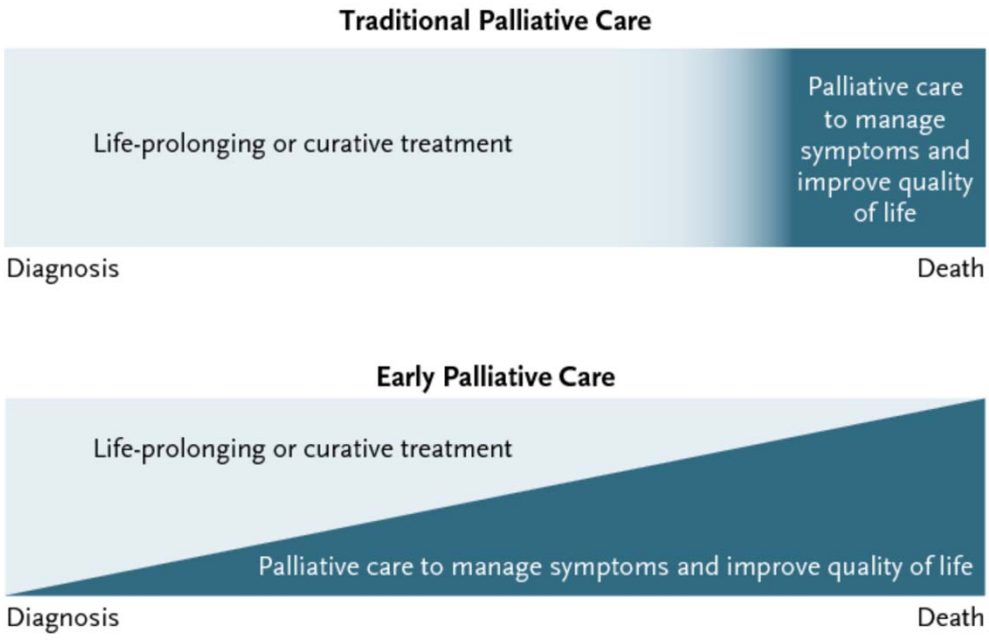
[1]Esteban et al. Journal of Palliative Medicine. 2019

[2]Ufere et al. Liver Transplantation. 2019

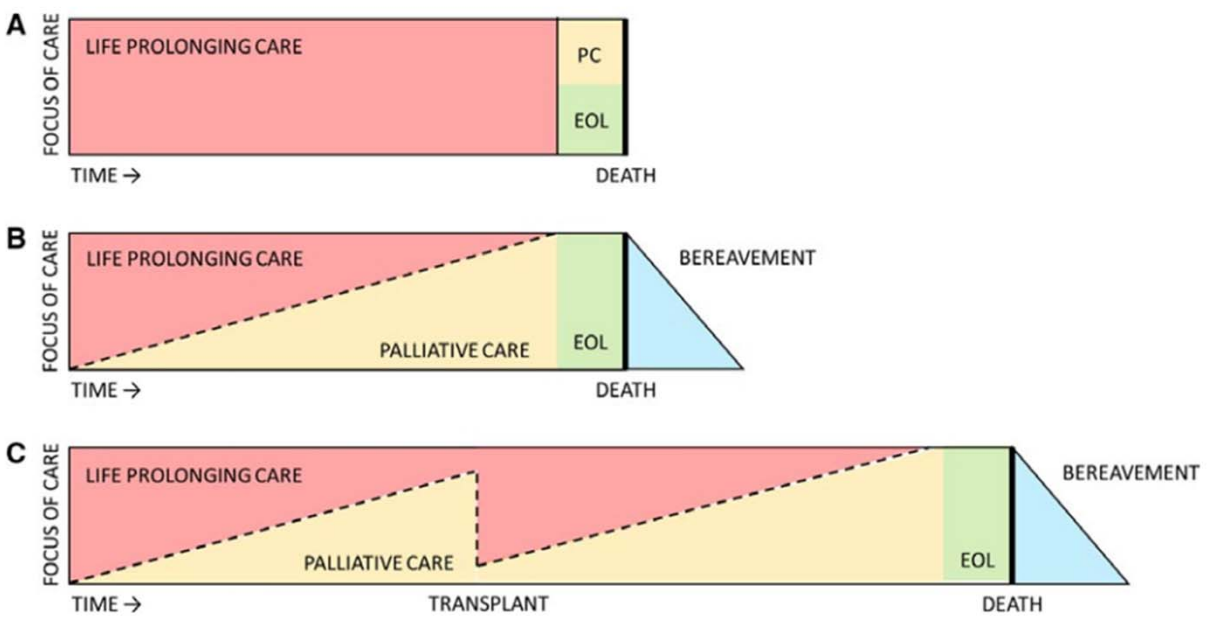
World Health Organization

Definition of Palliative Care

"..an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness."



Parikh et al. NEJM 2013.



Wentlandt et al. Am J Transplant 2017.

Who Provides Palliative Care?

"Specialist" Model

- Interdisciplinary team (IDT)
  - Clinician (specialized training in PC)
  - Nurse
  - Social worker
  - Chaplain
  - Pharmacist
- Care in any setting
- Continuity
- Comprehensive assessments

"Generalist" Model

- Clinicians trained in basic principles of PC.
- Can work alone or in conjunction with an IDT.
- Critically needed alongside the specialist model.

Quill et al. NEJM. 2013.

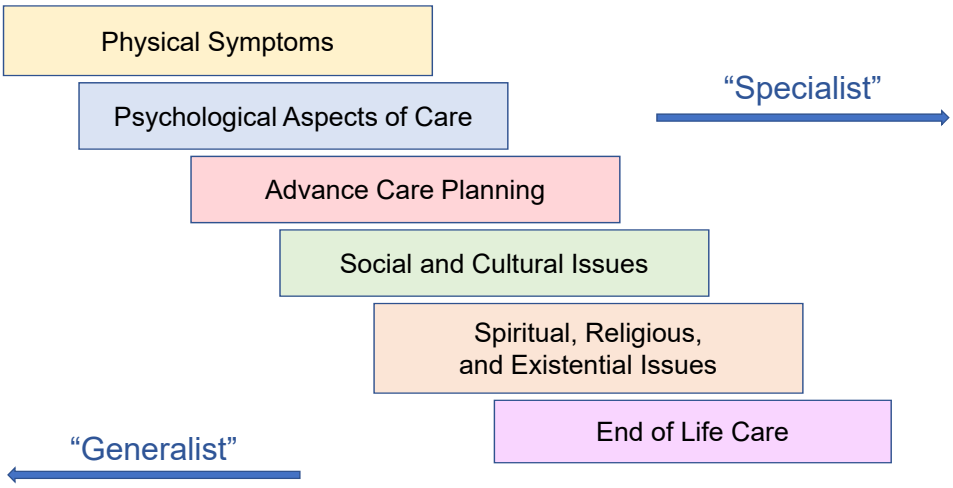
Lupu et al. JPSM. 2010.

Domains of Palliative Care

- Physical Symptoms
- Psychological Aspects of Care
- Advance Care Planning
- Social and Cultural Issues
- Spiritual, Religious, and Existential Issues
- End of Life Care

Adapted from National Consensus Project, 4th ed.

Domains of Palliative Care



Adapted from National Consensus Project, 4th ed.

Case # 2

A 59 y.o. woman with compensated cirrhosis from HCV complicated by an 8 cm HCC presents to your clinic with dull RUQ pain radiating to her shoulder, mild SOB, and fatigue. She states the pain keeps both her and her husband up in the middle of the night.

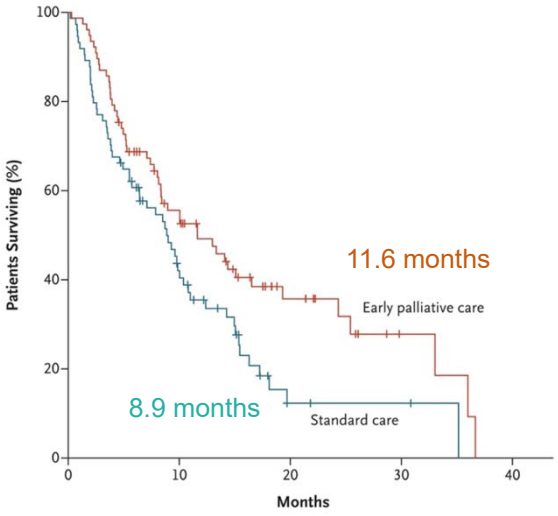
She has been prescribed Tylenol for pain but this provides little symptomatic relief. She is hoping for better pain control and better sleep.

Data from RCTs has shown which of the following effects of specialty palliative care?

A. Improved physical symptom burden.
B. Improved spiritual well-being.
C. Reduced caregiver burden.
D. Reduced survival.
E. A, B, and C only.
F. A, B, C, and D.

Survival not reduced in patients receiving early palliative care for metastatic NSCLC

- N=151 patients, randomized to standard care vs. standard care and early palliative care (PC).
- Early PC group had reduced depressive symptoms and improved QOL.



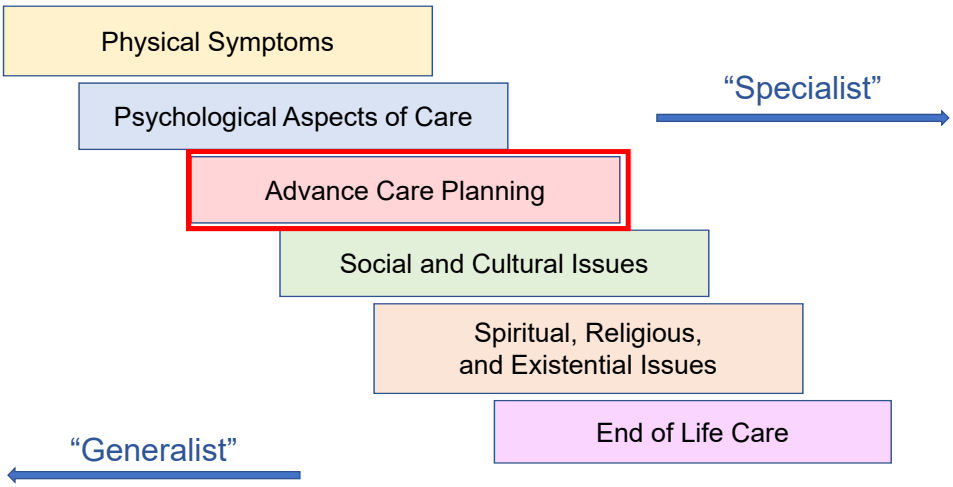
Temel et al. NEJM. 2010

Support for Early Palliative Care

- Advanced cancer
- Congestive Heart Failure (CHF)
- Chronic Obstructive Pulmonary Disease (COPD)
- End-Stage Renal Disease (ESRD)
- Alzheimer's Disease/Dementia
- Stroke
- Idiopathic Pulmonary Fibrosis and Cystic Fibrosis

No subspecialty societies have offered guidelines for integrating early palliative care in management of patients with liver disease.

Domains of Palliative Care



Adapted from National Consensus Project, 4th ed.

Advance Care Planning (ACP)

A **process** that supports adults in understanding and sharing their personal values, life goals, and preferences regarding future medical care

Brinkman-Stoppelenberg et al. Palliative Med. 2014

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Liver Disease in the Pregnant Patient

Normal Pregnancy

- Physical exam changes: spider angiomas/palmar erythema
- Expected laboratory changes: increased AFP, alkaline phosphatase, clotting factors; Decreased albumin/hemoglobin
- AST, ALT, bilirubin, total bile acid, prothrombin time remain normal

3 categories of pregnancy related liver disease

- Unique to pregnancy- gestational age aids in differential diagnosis
- Coincidental to pregnancy
- Exacerbated by pregnancy

Liver disease unique to pregnancy

- Occurs only during pregnancy and resolves post partum
- Hyperemesis gravidarum- no difference in fetal outcome; liver chemistry abnormalities resolve with rehydration/gut rest
- Intrahepatic cholestasis- bile acid level < 40 µmol/L better prognosis; may recur with pregnancy/OCP use; genetic predisposition; Ursodiol treatment of choice
- Pre-eclampsia syndromes: Acute fatty liver and HELLP- overlap between diseases which occur late in pregnancy; requires early recognition and delivery

Liver disease coincidental to pregnancy

- Autoimmune hepatitis
- Drug induced liver injury
- Viral infections
    - Hepatitis A-E
    - Herpes simplex – start acyclovir early

Liver disease exacerbated by pregnancy

- Biliary disease- laparoscopic cholecystectomy best performed 2nd trimester
- Vascular- Budd-Chiari syndrome
- Pre-existing liver disease: cirrhosis/portal hypertension, liver transplantation, autoimmune hepatitis, hepatitis B
    - Risk of flare with autoimmune hepatitis in pregnancy and post- partum

Mother-to-child transmission of hepatitis B

- Transmission generally during delivery
- Consider antiviral therapy at week 32 if HBV DNA > 2 X 10^5 IU/ml
- Infants of HBsAg positive mothers should receive HBIG (0.5 ml) within 12 hours of birth and 1st dose of hepatitis B vaccine

Portal hypertension during pregnancy

- Risk of variceal hemorrhage greatest in 2nd trimester and during labor

- Portal pressure increases due to increased plasma volume/increased cardiac output/external compression of IVC
- Banding is treatment of choice (prophylactic and with hemorrhage)
- Minimize 2nd part of labor
- Octreotide and propranolol appear safe; AVOID vasopressin/nadolol
- Screen for splenic artery aneurysm

Hepatic adenomas

- Accelerated growth during pregnancy
- If > 5cm, symptomatic or bleeding – consider surgical treatment before conception

Pregnancy after liver transplantation

- Delay pregnancy 1-2 years
- Increased risk of hypertension/pre-eclampsia; intrauterine growth retardation
- Discontinue mycophenolic acid; less data for sirolimus/everolimus

References

1. Westbrook RH, Dusheiko G, Williamson CJJoh. Pregnancy and liver disease. Journal of hepatology. 2016;64(4):933-45.
2. Tran TT, Ahn J, Reau NS. ACG clinical guideline: liver disease and pregnancy. The American Journal of Gastroenterology. 2016;111(2):176.
3. Ludvigsson JF, Marschall HU, Hagström H, Höijer J, Stephansson OJH. Pregnancy outcome in women undergoing liver biopsy during pregnancy: A nationwide population-based cohort study. Hepatology. 2018;68(2):625-33.
4. Bacq Y, Sentilhes L. Intrahepatic cholestasis of pregnancy: Diagnosis and management. Clinical Liver Disease. 2014;4(3):58-61.
5. Fitzpatrick KE, Hinshaw K, Kurinczuk JJ, et al. Risk factors, management, and outcomes of hemolysis, elevated liver enzymes, and low platelets syndrome and elevated liver enzymes, low platelets syndrome. Obstetrics & Gynecology. 2014;123(3):618-27.
6. Liu J, Ghaziani TT, Wolf JL. Acute fatty liver disease of pregnancy: updates in pathogenesis, diagnosis, and management. The American journal of gastroenterology. 2017;112(6):838.
7. Aggarwal N, Negi N, Aggarwal A, et al. Pregnancy with portal hypertension. Journal of clinical and experimental hepatology. 2014;4(2):163-71.
8. Terrault NA, Lok AS, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67(4):1560-99.
9. Jourdain G, Ngo-Giang-Huong N, Harrison L, et al. Tenofovir versus placebo to prevent perinatal transmission of hepatitis B. New England Journal of Medicine. 2018;378(10):911-23.
10. Deshpande NA, James NT, Kucirka LM, et al. Pregnancy outcomes of liver transplant recipients: a systematic review and meta-analysis. Liver transplantation. 2012;18(6):621-9.

Pregnancy and Liver Disease

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Disclosures

- I have no disclosures.

"Help- my OB patient has liver disease"

- What are normal findings in pregnancy?
- What liver diseases are unique to pregnancy?
- When is liver biopsy indicated?
- When is immediate delivery indicated?

A 28 week pregnant woman presents with pruritus and abnormal liver chemistries. Her pregnancy has been otherwise uncomplicated. Her lab testing reveals AST of 95 U/L, alkaline phosphatase of 180 U/L, total bilirubin of 1.8 mg/dl, INR of 1.6 and total bile acid level of 40 μmol/L. Her ultrasound is normal.

Which is the best management plan:

a. ERCP for likely choledocholithiasis
b. Immediate delivery given concern for acute fatty liver disease of pregnancy
c. Reassurance only
d. Begin therapy with ursodeoxycholic acid and vitamin K. Early delivery if fetal distress

Normal pregnancy

Liver enzyme	1st trimester	2nd trimester	3rd trimester
ALT	⇔	⇔	⇔
AST	⇔	⇔	⇔
Bilirubin	⇔	⇔	⇔
GGT	⇔	⇔	⇔
ALP	⇔	⇧	⇧⇧
Bile acids	⇔	⇔	⇔
Albumin	⇔⇩	⇔⇩	⇔⇩
AFP	⇔⇧	⇧	⇧

PE: spider angiomas/palmar erythema/hyperdynamic circulation/small varices

Liver biopsy RARELY indicated

Key Concepts

- Elevations in aminotransferases, bile acids and bilirubin are **ABNORMAL**.
- Cholestasis can occur with normal alkaline phosphatase, GGTP and bilirubin levels

Key Concepts – 3 categories

- Diseases UNIQUE to pregnancy
- Diseases COINCIDENTAL to pregnancy
- Diseases EXACERBATED by pregnancy

Unique to pregnancy

- Occurs ONLY during pregnancy and RESOLVES post partum
  - Hyperemesis gravidarum (HG)
  - Intrahepatic cholestasis (IC)
  - Acute Fatty Liver of pregnancy (AFLP)
  - Pre eclampsia/ syndrome of hemolysis, elevated liver chemistries, low platelets (HELLP)
  - Hepatic rupture

Unique to pregnancy

Gestational age aids in differential diagnosis

Hyperemesis gravidarum (HG)

- Severe nausea/vomiting with dehydration/ ketosis/weight loss > 5%
- Week 4-20
- 1-1.5% of pregnancies –no differences in fetal outcome
- Increased transaminases- 50% of cases: ALT > AST
  - Low 100's but up to 20 X normal
  - Severity correlates with vomiting
  - Resolves with rehydration/gut rest
- Rare increased bilirubin
- Treat with thiamine, fluids and anti-emetics
- Liver biopsy – little or no abnormalities

Intrahepatic cholestasis (ICP)

- Cholestasis: a reduction of canalicular bile flow with an associated rise in serum bile acid level
- IC of pregnancy: pruritus and elevated serum bile acids occurring in 2nd half of pregnancy that resolves after birth (6 weeks)

ICP

- Elevated fasting serum total bile acids (10-100x)
  - Some define as bile acid level > 10 μmol/L; 2nd-3rd trimesters
- Pruritus – severe at night; palms and soles (no rash)
- 15% develop jaundice (< 6 mg/dl); alk phos (1-4x), aminotransferases(2-10x); GGT-nl or mild increase
- Vit K deficiency due to malabsorption

- Liver biopsy – cholestasis without inflammation
- **MAY RECUR** – pregnancy, OCP use
- ↑ risk of hepatobiliary disease later in life (? cancer, autoimmune disease, cardiovascular disease)

ICP – RISK FACTORS

- HCV
- Seasonal onset (winter)
- Low selenium levels
- Low Vitamin D
- Multiple gestations
- Advanced age

Floreani, A and Gervasi, M. New Insights on Intrahepatic Cholestasis of Pregnancy, Clin Liver Dis 20 (2016), 177-189.

ICP – Etiologic factors

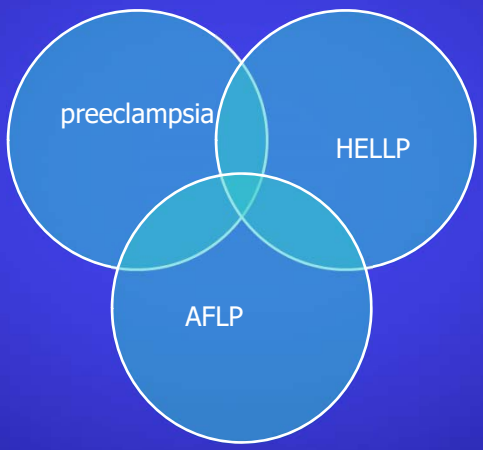
- Genetic predisposition
  - Strong regional clustering (Sweden, Chile)
  - Higher prevalence in family members
  - Variable genotypes, penetrance, environmental
  - Defects in at least 6 canalicular transporters

Floreani, A and Gervasi, M. New Insights on Intrahepatic Cholestasis of Pregnancy, Clin Liver Dis 20 (2016), 177-189.

ICP – treatment/outcome

- Maternal outcome – good, may recur 66%
- Fetal outcome – can be poor (worse if earlier onset)
  - Meconium ileus, prematurity, stillbirth
  - Best outcomes: bile acid < 40μmol/L
- Treatment
  - Ursodeoxycholic acid (10-15 mg/kg), replete Vit K
  - Delivery – soon after fetal maturity (32 weeks if fetal distress or 38 weeks if no distress)
  - Cholestyramine - ↓ absorption Vit K, urso

Overlap syndromes



Preeclampsia/eclampsia

- Systolic BP >140 or diastolic > 90; Proteinuria (> 300 mg/24h); >20 weeks gestation in prev. normotensive pt
- Eclampsia if seizures or altered mental status
- 5-10% of pregnancies but liver involvement not common
- RUQ pain, aminotransferases (10-20 X nl), bilirubin < 5
- Liver biopsy - not needed for diagnosis but shows fibrin deposition, ischemic lesions, microvesicular fat, periportal hemorrhage

HELLP syndrome: hemolysis, elevated liver chemistries and low platelets

- Endotheial/microvascular injury from activation of complement, increased vascular tone, plt aggregation
  - Low haptoglobin, + schistocytes
  - Normal PT/PTT, LDH > 600 IU/L
  - Aminotransferases – mean 150 U/L (2-20X);
  - Total bilirubin > 1.2 mg/dl
  - Platelets < 50,000-100,000/mm3
- Complication of severe pre-eclampsia
  - 0.1-0.6% all pregnancies; ~12% in severe eclampsia
  - 2/3 occur in 3rd trimester, 1/3 **after** delivery

HELLP SYNDROME

- Symptoms/signs
  - Epigastric/abdominal pain
  - Liver normal or increased in size
- Maternal lab abnormalities peak in first 2 days post partum
- Maternal mortality: 1-2%; 1% - hematoma
  - Mortality – 30% with rupture
- Fetal mortality: 10-35%(depends upon gest.age)
- Mississippi and Tennessee classification systems

Martin, JN, Rose CH, Briery CM. Understanding and managing HELLP syndrome: the integral role of aggressive glucocorticoids for mother and child. Am J Obstet Gynecol 2006;195 (4): 914-34.

Acute fatty liver of pregnancy

- Hepatic microvesicular steatosis and mitochondrial dysfunction
- 1:10,000 pregnancies
- Inherited mutations with deficiency of long-chain 3-hydroxyacyl coenzyme A dehydrogenase (LCHAD) – a fatty acid beta-oxidation enzyme
- Mother is heterozygote; fetus is homozygote

Acute fatty liver of pregnancy (AFLP)

- Overlap with HELLP
- Nulliparous, ↑ maternal age, multiparity
- Nausea/vomiting, epigastric pain, jaundice
- Symptoms/signs of liver failure
- Liver frequently small
- Elevated PT, creatinine, NH3
- Transaminases – variable elevation

Swansea criteria – 6 or more with absence of another cause

- Vomiting
- Abdominal pain
- Polydipsia/polyuria
- Encephalopathy
- Elevated bilirubin
- Hypoglycemia
- Elevated urea
- Leukocytosis
- Ascites or bright liver on ultrasound
- Elevated transaminases
- Elevated ammonia
- Renal impairment
- Coagulopathy
- Microvesicular steatosis on liver biopsy

Ch'ng CL, Morgan M, Hainsworth I et al. Prospective study of liver dysfunction in pregnancy in Southwest Wales. Gut 2002;51: 876-80.

LCHAD abnormalities

- LCHAD deficiency caused by genetic defect of mitochondrial trifunctional protein (MTP)
- Mothers – obligate heterozygotes with reduced capacity to oxidize LC fatty acids
- Fetus – homozygote; unable to oxidize LC fatty acids
- Fatty acids spill into maternal circulation via placenta
- Accumulation of hepatoxic long chain fatty acid metabolites in mothers - ? 3-hydroxy-fatty acids

LCHAD deficiency in infants

- AFLP and possibly severe HELLP may indicate fatty oxidation disorder in fetus
- Fetus – if homozygous LCHAD deficiency– at risk for hypoketotic hypoglycemia
- Acylcarnitine profile and molecular screening should be done
- Early detection and treatment of LCHAD deficiency improves prognosis of newborn

Treatment of AFLP

- Early recognition and delivery!
- Disease systemic – acute pancreatitis, renal failure/oliguria, GI bleeding, DIC
- Case reports of successful liver transplantation and plasma exchange but decreasing mortality with supportive care

A 28 week pregnant woman presents with pruritus and abnormal liver chemistries. Her pregnancy has been otherwise uncomplicated. Her lab testing reveals AST of 95 U/L, alkaline phosphatase of 180 U/L, total bilirubin of 1.8 mg/dl, INR of 1.6 and total bile acid level of 40 μmol/L. Her ultrasound is normal.

Which is the best management plan:

a. ERCP for likely choledocholithiasis
b. Immediate delivery given concern for acute fatty liver disease of pregnancy
c. Reassurance only
d. Begin therapy with ursodeoxycholic acid and vitamin K. Early delivery if fetal distress

Correct answer: D

This patient presents with cholestasis (highly elevated total bile acid level, elevated INR consistent with vitamin K deficiency) in the 2nd trimester. Her presentation is consistent with intrahepatic cholestasis of pregnancy. Although maternal outcome is generally good, the fetal outcome can be poor, particularly with early onset cholestasis or with bile acid level > 40 μmol/L. Answer "a" is not correct as there is no evidence of biliary obstruction on imaging or abdominal pain. Answer "b" is not correct as she has more cholestasis than would be expected for acute fatty liver of pregnancy. Answer "c" is not correct as the fetal outcomes can be poor.

Answer "d" is the correct course of treatment as ursodiol therapy has been shown to contribute to improvement in maternal and fetal consequences of intrahepatic cholestasis of pregnancy.

COINCIDENTAL to pregnancy

- Autoimmune
- Drug induced liver injury
- Viral infections – hepatitis A-E, Herpes Simplex
  - Not unique but more severe in pregnancy

Herpes Simplex Hepatitis

- 3rd trimester - History! - √ HSV PCR
- Prodrome of fever, malaise, URI for 4-14 days
- PE: RUQ pain, <50% cutaneous lesions
- Labs: ↑ bilirubin but very high aminotransferases, often > 1000 U/L
- CT scan – multiple low density, nonenhancing areas: hemorrhagic necrosis/microabscess
- Maternal mortality – 43%. **Start acyclovir early!**
- Transmission to infants – 33-50%

Viral Hepatitis

- Most common cause of jaundice in pregnancy in US
- Increased risk of transmission of hepatitis A and B during delivery if mother viremic. HAV immunoglobulin can be given
- Less risk for transmission of hepatitis C unless coinfected with HIV. No effective passive immunoprophylaxis
- Hepatitis E - Enteric transmission to mother
  - travel to Asia, Africa, Middle East and Mexico. Vertical transmission reported. History!
    - Check HEV-IgM; treatment supportive

EXACERBATED by pregnancy

- Biliary disease - cholelithiasis
- Vascular – Budd-Chiari syndrome
- Pre-existing liver disease
  - Hepatitis B
  - Cirrhosis and portal hypertension
  - Post- liver transplantation
  - Autoimmune hepatitis

Cholelithiasis and cholecystitis

- Pregnancy promotes bile lithogenicity and sludge
  - Estogen increases cholesterol synthesis
  - Progesterone impairs gallbladder motility
- ~ 10% of pregnant women have cholelithiasis
- Pregnancy does not increase frequency or severity of complications; ERCP - consider tertiary center
- Cholecystectomy-best performed in 2nd trimester
  - 1st trimester – increased fetal death
  - 3rd trimester – premature labor
- Laparoscopic cholecystectomy

"Help- my liver patient is pregnant"

- When is antiviral therapy indicated?
- When is C-section indicated?
- Is breast feeding safe?
- Autoimmune hepatitis treatment
- Pre-exising portal hypertension
- Hepatic adenomas
- Pregnancy post liver transplantation

Mother-to-child transmission- Hep B

- Placenta excellent barrier - transmission generally during delivery (no role for c-section)
- Lamivudine/telbivudine/tenofovir – CONSIDER therapy at 32 weeks if HBV DNA > 2 X 10^5 IU/ml

  0glvfrqwlqxh#70;#zhhnv#srvw#sduwp

- **Infants of HBsAg-positive mothers should receive HBIG (0.5 ml) within 12 hours and 1st dose of hep B vaccine (prevents transmission in ~90-95%)**

Hepatitis B - infant

- Check for antiHBs between 9-18 months/maternal anti-HBc detected up to 24 months
- American Academy of Pediatrics – breastfeeding not contraindicated for infants born to mothers who are HbSAg+ (after vaccination/HBIG)
- Controversy regarding breast feeding and anti-viral therapy
- Lactation – longer duration (> 6 months) associated with lower risk of NAFLD in mid life

Ajmera et al. Longer lactation duration is associated with decreased prevalence of non-alcoholic fatty liver disease in women. Journal of Hepatology 2019 vol. 70 : 126–132

Vertical transmission of Hepatitis C

- Risk of vertical transmission from ~ 5%
  - Test infants with HCV RNA 2 occasions between 2 and 6 months
- Risk factors:
  - High levels of hepatitis C RNA/ HIV coinfection
  - Long duration between membrane rupture and delivery
  - No recommendation for C-section
  - Avoid fetal scalp monitoring
  - Breast feeding acceptable unless nipple trauma

Autoimmune hepatitis

- Up to 20% flare during pregnancy
- Best outcome if stable for > 1 year before pregnancy
- Treatment options:
  - Azathioprine: no increased risk of adverse fetal outcomes in small studies but possible higher pre-term delivery rates; Breast feeding – generally considered safe
  - Prednisone: Meta analysis with increased risk of cleft palate if mother exposed in first trimester but no risk in prospective studies; Breast feeding safe
  - Mycophenolate therapy contraindicated
  - No data on budesonide
- Flares twice as common in postpartum period
  - up to 20-50%; check liver chemistries at delivery and then every 4-6 weeks for first 3 months post partum.

Peters, Marion; Management of autoimmune hepatitis in pregnant women. Gastroenterology & Hepatology Volume 13, Issue 8 August 2017

Portal Hypertension during Pregnancy

- Portal pressure ↑ - increased plasma volume / cardiac output / external compression of IVC
  - Higher risk: preeclampsia, preterm delivery, low birth weight, fetal death
- Risk of variceal hemorrhage - ↑ 2nd trimester and during labor (75% if pre-existing varices with 20-50% maternal mortality); EGD in 2nd trimester. Banding preferred treatment.
- Avoid vasopressin but propranolol/octreotide appear safe (cat. B)
- Minimize second part of labor, avoid excessive fluids
  - ? cesarean section

Splenic artery aneurysm

- Splenic artery rupture occurs in ~ 2.5 % of cirrhotic women during pregnancy/screen with Doppler ultrasound
- Consider surgical or IR therapy if > 2 cm
- Clinical findings: abdominal pain, pulsatile left upper quadrant mass, abdominal bruit

Hepatic adenomas

- Accelerated growth from high estrogen levels
- Complications:
  - Hemorrhage and intraperitoneal rupture
- Adenomas > 5 cm or symptomatic or intralesional bleeding should be considered for surgical resection before contraception

Contraception and pregnancy post liver transplantation

- Delay pregnancy 1-2 years
- Increased risk of HTN and pre-eclampsia in mother and IUGR in fetus
- Most immunosuppressive regimens with acceptable risk profiles except mycophenolic acid. Less data for sirolimus/everolimus
- Graft rejection 4-17%; fetal malformation 3%
  - Check labs monthly initially then weekly
- Breast feeding – no recommendations for tacrolimus

Medications commonly used in pregnancy

Indication	Drug	FDA	Safety of fetus
HG	Antihistamines Dopamine antagonists Phenothiazines Anticholinergics Serotonin antagonists	A B B B B	Ondansetron – little controlled data in humans
IC	Ursodeoxycholic acid Rifampicin Cholestyramine	B C C	Urso - no adverse fetal effects Rifampicin – risk of teratogenicity in 1st trimester; likely safe in 3rd
Immunosuppression	Tacrolimus Sirolimus Mycophenolate Azathioprine Cyclosporine	C C D D C	Azathioprine – additional data with good safety profiile Mycophenolate – teratogenic Sirolimus – not recommended
Hypertension	Labetolol Hydralazine Nifedipine	C C C	All generally safe
Portal hypertension	Propanolol Terlipressin Octreotide	C D B	Terlipressin – uterine ischemia Octreotide – no human data Propranolol – not teragenic but fetal bradycardia, hypoglycemia and growth issues
Viral infections	Lamivudine Tenofovir Telbivudine Ribavirin Acyclovir	C B B X B	Ribavirin – Teratogenic Acyclovir – appears safe Telbivudine – data only for 3rd trimester

R. Westbrook, G Dusheiko, C. Williamson. Pregnancy and Liver Disease, Journal of Hepatology 2016 Vol. 64. 933-945.

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Hepatology in and Around the OR:
Pre-op Risk Assessment and Perioperative Management

For the practicing liver specialist, a common clinic encounter is the patient who presents for "clearance" for surgery or invasive procedure (including dental procedures). Routine questions include safety and relative risk surgical procedures in patients with liver disease, the role of pre-operative treatment of viral hepatitis, and management of abnormal tests of coagulation.

The goal of this presentation is to review evidence based surgical risk stratification for patients with cirrhosis undergoing major surgery. To outline evidence based guidelines for addressing concerns regarding perceived bleeding diatheses in patients with liver diseases undergoing procedural based therapies. In addition, I will review common questions which arise in the care of liver disease by non-liver disease specialists to include cardiac catheterization, transesophageal echocardiography and dental procedures.

References

1. Burger-Klepp U, Karatosic R, Thum M, Schwarzer R, Fuhrmann V, Hetz H, Bacher A, Berlakovich G, Krenn CG, Faybik P: Transesophageal echocardiography during orthotopic liver transplantation in patients with esophagoastric varices. *Transplantation* 2012, 94(2):192-196.
2. Liu E, Guha A, Dunleavy M, Obarski T: Safety of Transesophageal Echocardiography in Patients with Esophageal Varices. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2019.
3. Nigatu A, Yap JE, Lee Chuy K, Go B, Doukky R: Bleeding Risk of Transesophageal Echocardiography in Patients With Esophageal Varices. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography* 2019.
4. Townsend JC, Heard R, Powers ER, Reuben A: Usefulness of international normalized ratio to predict bleeding complications in patients with end-stage liver disease who undergo cardiac catheterization. *Am J Cardiol* 2012, 110(7):1062-1065 4506690.
5. Lisman T, Porte RJ: Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. *Blood* 2010, 116(6):878-885.
6. Westerkamp AC, Lisman T, Porte RJ: How to minimize blood loss during liver surgery in patients with cirrhosis. *HPB (Oxford)* 2009, 11(6):453-458 2756630.
7. Tripodi A, Salerno F, Chantarangkul V, Clerici M, Cazzaniga M, Primignani M, Mannuccio Mannucci P: Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. *Hepatology* 2005, 41(3):553-558.
8. Shore-Lesserson L, Manspeizer HE, DePerio M, Francis S, Vela-Cantos F, Ergin MA: Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. *Anesth Analg* 1999, 88(2):312-319.
9. Teh SH, Nagorney DM, Stevens SR, Offord KP, Therneau TM, Plevak DJ, Talwalkar JA, Kim WR, Kamath PS: Risk factors for mortality after surgery in patients with cirrhosis. *Gastroenterology* 2007, 132(4):1261-1269.

Pre-op Risk Assessment and Perioperative Management

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2019 AASLD Clinical Hepatology Update
June 14-15, 2019
Bellevue, WA

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Disclosures:

- None

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A case:

A 47 year old male patient with alcohol related cirrhosis is referred to your office for pre-operative “clearance” prior to undergoing coronary artery bypass surgery for advanced symptomatic coronary artery disease.

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The case continued:

- He has no history of hepatic encephalopathy
- EGD demonstrates small varices without high risk stigmata
- He previously had ascites, but has resolved with alcohol cessation

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Laboratory studies:

- Sodium 137 mmol/L
- Creatinine 1.9 mg/dL
- T. bilirubin 1.6 mg/dL
- Hgb 12.5 g/dL
- Platelets 87K/mm^3
- Fibrinogen 201 mg/dL
- TEG Normal

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What is your advice to the surgical team?

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Pre-operative risk assessment

- Cannot give “clearance”
- Provide a risk assessment
- Will often be asked about coagulopathy

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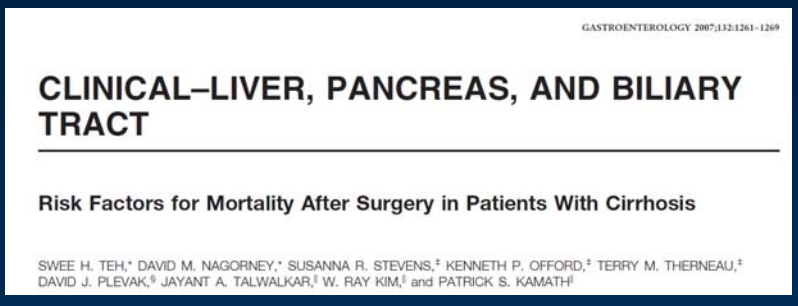
Pre-operative risk assessment



GASTROENTEROLOGY 2007;132:1261–1269

CLINICAL–LIVER, PANCREAS, AND BILIARY TRACT

Risk Factors for Mortality After Surgery in Patients With Cirrhosis

SWEE H. TEH,* DAVID M. NAGORNEY,* SUSANNA R. STEVENS,‡ KENNETH P. OFFORD,‡ TERRY M. THERNEAU,‡ DAVID J. PLEVAK,§ JAYANT A. TALWALKAR,‖ W. RAY KIM,‖ and PATRICK S. KAMATH‖

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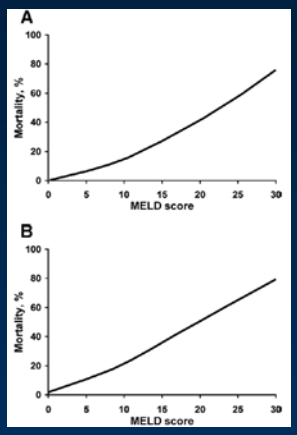
Teh, S.H., Nagorney, DM., *et al., Gastroenterology* 2007; 132: 1261-1269

Mayo Pre-operative risk assessment

Table 3. Relationship Between MELD Score and Postoperative Mortality

	Mortality, % (No. of patients at risk)					
MELD score	7 Days	30 Days	90 Days	1 Year	5 Years	10 Years
0–7 (n = 351)	1.9 (314)	5.7 (301)	9.7 (287)	19.2 (253)	50.7 (123)	72.6 (57)
8–11 (n = 257)	3.3 (236)	10.3 (219)	17.7 (200)	28.9 (170)	58.5 (83)	78.1 (35)
12–15 (n = 106)	7.7 (94)	25.4 (78)	32.3 (69)	45.0 (56)	69.5 (24)	87.3 (10)
16–20 (n = 35)	14.6 (29)	44.0 (19)	55.8 (15)	70.5 (10)	94.1 (2)	94.1 (2)
21–25 (n = 13)	23.0 (7)	53.8 (4)	66.7 (3)	84.6 (2)	92.3 (1)	100 (0)
≥26 (n = 10)	30.0 (6)	90.0 (1)	90.0 (1)	100 (0)	100 (0)	100 (0)



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Key findings:

- Surgery itself may result in liver related mortality best assessed by MELD score
- Age and ASA status (other than V) must be considered modifiers of the MELD score
- Mortality is sufficiently low in patients with MELD <11
- Risk of mortality is high in MELD > 20 thus surgery should be reserved for select conditions

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Teh, S.H., Nagorney, DM., *et al., Gastroenterology* 2007; 132: 1261-1269

Our patient

- Estimated Post-operative mortality
  - 7 day 1.5%
  - 30 day 6.1%
  - 90 day 9.6%

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Cholecystecomy

- Proceed with caution
  - Does the patient truly require cholecystectomy?
  - Avoid in patients with Childs Class C disease or refractory ascites
  - When indicated cholecystectomy should be performed in a center with expertise in cirrhotic patients

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Bariatric Surgery

- Obesity and NASH are leading causes of cirrhosis
- In centers with expertise bariatric surgery can be performed but still carries increased risk
- Avoid in cases with significant decompensation or portal hypertension
- Sleeve gastrectomy may be performed
- Consider dual procedures (OLT + sleeve gastrectomy)

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Do patients with cirrhosis or varices need an EGD prior to undergoing TEE?

Nigatu *et al., J Am Soc of Echo* 2019; 32:674-676

Risk of bleeding approached 0% in patients undergoing routine EGD

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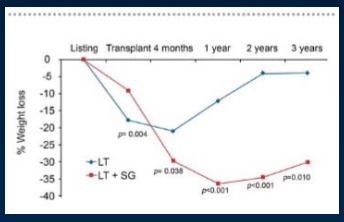
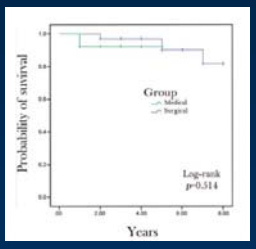
OLT + Sleeve Gastrectomy

HEPATOLOGY
AASLD
HEPATOLOGY, VOL. 68, NO. 2, 2018 STEATOHEPATITIS/METABOLIC LIVER DISEASE

Long-Term Outcomes of Patients Undergoing Simultaneous Liver Transplantation and Sleeve Gastrectomy

Daniel Zamora-Valdes,[1] Kymberly D. Watt,[2] Todd A. Kellogg,[3] John J. Poterucha,[2] Sara R. Di Cecco,[2] Nicki M. Francisco-Ziller,[2] Timucin Taner,[4] Charles B. Rosen,[1] and Julie K. Heimbach[1]





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Peri-operative Management

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Peri-operative management of ascites

- Ascites can complicate post-surgical management
- Aggressive control of ascites is warranted
- Use of paracentesis as needed
- Thoracentesis for moderate or large pleural effusion
- Consider temporary drains while inpatient
- No role for pre-emptive TIPS*
  - No difference in bleeding during liver tx

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*Schlenker, C., *et al., Surg Endosc* 2009; 23:1594-1598

*Guerrini, GP *et al., Am J Transplant* 2009; 9:192-200

Management of coagulation test abnormalities

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Standard tests in liver disease

- PT (INR), aPTT, and platelet count are typically abnormal in liver disease
  - These abnormalities are not necessarily associated with increased risk of bleeding
  - In fact patients may be HYPERcoaguable

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Myth of INR as a predictor of bleeding risk in cirrhosis:

- Leads to artificial requirements for “safe” INR
- Significant overuse of FFP in cirrhosis without an evidence basis for support
- Failure to treat patients at risk for DVT when hospitalized

In cirrhosis, INR is a valuable test of liver function *not bleeding risk*

(Exception: Pts. on warfarin)

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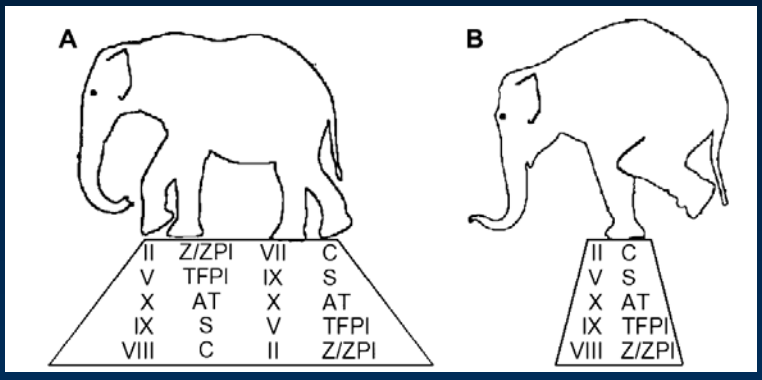

Monroe and Hoffman (2009), *Clin Liv Dis* ; 13: 1-9

Does "correcting" the INR prevent bleeding or improve outcomes?

Table 2. Outcome of patients who did and did not receive fresh frozen plasma (FFP) transfusion

Outcome	FFP (n = 44)	No FFP (n = 71)	*p* Value
New bleeding episodes, n (%)	3 (6.8)	2 (2.8)	.369
New onset acute lung injury, n (%)	8 (18.2)	3 (4.2)	.021
Hospital mortality, n (%)	11 (25.6)	20 (28.2)	.763
Median (IQR) ICU length of stay, days[a]	2.4 (1.7–6.8)	2 (0.9–3)	.184

IQR, interquartile range; ICU, intensive care unit.
[a]In survivors.

Median dose of FFP in patients who achieved an INR <1.5 17 ml/kg

INR corrected to <1.5 in 16/44 patients

Dara SI, *et al., Critical Care Med* (2005); 33: 2667-2671

Does "correcting" the INR prevent bleeding or improve outcomes?

bjh research paper

Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials

Is fresh-frozen plasma clinically effective? An update of a systematic review of randomized controlled trials

Lucy Yang, Simon Stanworth, Sally Hopewell, Carolyn Doree, and Mike Murphy

CONCLUSION: Combined with the 2004 review, 80 RCTs have investigated FP with *no consistent evidence* of significant benefit for prophylactic and therapeutic use across a range of indications evaluated.

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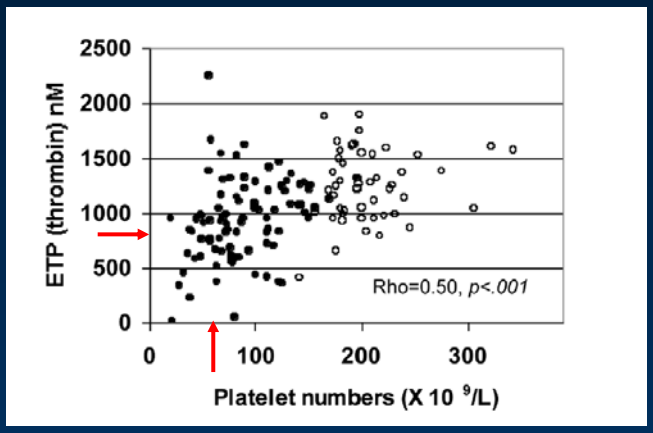
Stanworth *et al. Br J Haem* 2004; 126: 139-152

Yang *et al. Transfusion* 2012; 52: 1673-1686

Role of platelets

Platelets in cirrhosis are qualitatively sufficient to support thrombin generation, thrombocytopenia impairs normal thrombin generation.

Thus a platelet count of 50,000 may be an appropriate target for patients undergoing surgery.



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Tripodi, A., *et al., Hepatology* 2006; 44:440-445

Fibrinogen

- Levels below 100 mg/dL are associated with increased risk of bleeding in cirrhotics
- Optimal level unknown
- Surgical guidelines suggest a level >150 mg/dL

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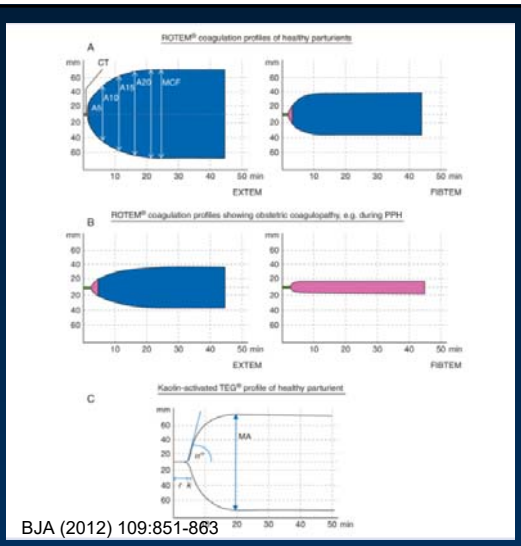
Viscoelastic testing



BJA (2012) 109:851-863

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Pain and Medication Management

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Medication management:

- Acetaminophen safe!
- Avoid NSAIDS in cirrhosis
- Benzodiazepines should generally be avoided
- Opioids at lower doses and with decreased frequency
  - Avoid constipation
  - Consider PEG vs. lactulose in abdominal surgery

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Take home points

- Careful assessment of risk vs. benefit is imperative for all patients with cirrhosis undergoing surgery
  - CTP, Mayo Surgical Risk Calculator
- Avoid unnecessary cholecystecyomy
- Multi-disciplinary teams should be utilized for this complex patient population
- For patients with MELD >15, consideration of pre-surgical transplant evaluation/listing is appropriate
- Avoid “correction” of INR as a matter of routine
- Use viscoelastic testing when available

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Thank you!

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Behavioral Therapy in Liver Disease

Patients with liver disease often present to hepatology practice providers with challenging and complex psychosocial problems. Because a significant proportion of patients acquire their liver disease from excessive alcohol consumption and illicit drug use, they are at greater risk for co-morbid psychiatric and substance abuse disorders.

The purpose of this summary is to familiarize hepatology practice providers with the role of the transplant psychiatrist and to describe examples of psychosocial interventions that can maximize their patients' liver outcomes and quality of life. Because patients may interpret being referred to a mental health specialist as unnecessary or even insulting, understanding the patient's underlying emotions and how to address these interactions will be described. In addition, screening tools for substance use and psychiatric disorders will be reviewed and various treatment interventions for psychosocial problems that are commonly seen in their liver patients will be explained.

Formal screening tools for psychiatric and substance use disorders have been shown to markedly reduce the likelihood that such problems will be missed in primary care settings (1). The simplest screening tool for alcohol and drug use is the "Single Question Screen for Alcohol and Drug Use Disorders" (2). For Alcohol Use Disorders in men, the question asks "how many times in the past year did you consume 5 or more drinks in one day", or for women, "4 or more drinks in one day". If your patient is very ill, they may only be able to tolerate fewer drinks than the screen calls for, but still meet criteria for an Alcohol Use Disorder. Screening for drug use is probed by asking "how many times in the past year have you used an illegal drug or prescription medication for nonmedical reasons?"

Once a provider has determined that their patient needs to be referred for a mental health or addictions assessment, recognizing how the patient-provider interaction can be affected by a patient's unconscious response to the interaction is important. For example, the patient's response to being referred to see a psychiatrist may be tempered with undue suspicion, anxiety or defensiveness (transference). These responses can, in turn, result in the provider's unwitting reaction to the patient's behavior that has been colored by their own life experience (counter-transference). When the responses of a patient make a provider feel attacked or disrespected, and those responses seem out of proportion to the situation, it is incumbent on the provider to recognize that these actions are not personal, and respond accordingly. Providers must be careful not to "return fire". For example, if a patient is asked to go to an alcoholism treatment program and becomes angry, it may be because the patient feels he isn't trusted by the provider, and deserves credit for gotten sober. The provider should be supportive and praise the patient for becoming sober and acknowledge that you believe they are sincere about wanting to stay sober, but mistakes (relapses) happen, so going to treatment is warranted. The provider can further reassure the patient that both of you are working toward the same goal of getting them a new liver. However, obtaining substance abuse treatment is more effective than just avoiding drinking because it is an active coping mechanism, which gives patients greater likelihood of remaining sober than passive coping mechanisms.

An effective evidence-based treatment that motivates patients with addictions toward lasting change called “Motivational Interviewing or MI” (3). MI is especially useful in liver patients because oftentimes, many stop drinking or using drugs without formal treatment and feel they have conquered their problem. MI can help patients see the benefits of going to substance abuse treatment and feel proud that they did. There are four processes in MI; Engaging, Focusing, Evoking and Planning. Definitions and examples can be found in the slide talk. Some commonly used responses by providers that increase patients’ resistance are also described in greater detail in the slide talk. These include The Expert Trap, The Q and A Trap and the Repair the Knowledge Gap Trap. These responses make both parties feel frustrated, contribute to poor engagement and give little room for patients to develop autonomy to foster change. Brief video examples found online are “Effective use of MI https://youtu.be/uL8QyJF2wVw vs. What Not to Do” https://youtu.be/ZGETDcFcAb.

Effective interventions for Alcohol and Substance Use Disorders in liver patients have not been well studied. The available research suggests that patients have lower rates of return to drinking if they receive counseling both before and after transplant compared to seeking treatment only before or only after transplant (4). Embedding a substance use disorder treatment program in the liver clinic combined with Baclofen to reduce craving has also shown positive results (5). Naltrexone is an FDA approved anti-craving agent that can blunt alcohol-induced euphoria. It has not been studied in the liver population, but can be very helpful for some patients. Methods of detecting of drug and alcohol use in liver patients such as phosphatidylethanol (PEth) and Ethyl Glucuronide (EtG) are found on an extra slide included at the end of the slide talk.

Smoking, drug and alcohol use are tightly linked behaviors. In fact, if patients recovering from substance use disorders don’t quit smoking before transplant, they are very unlikely to quit afterwards (6). Thus, the importance of addressing smoking cessation in the pre-transplant phase cannot be overstated. Behavioral interventions combined with medications such as Varenicline and Bupropion have been found to be safe and effective against smoking in patients without liver diseases, and it is not unreasonable to assume they would be effective for some liver patients despite the lack of data. More information about smoking cessation and on-line resources are provided in the slide talk.

Co-morbid Depressive and Anxiety Disorders are commonly seen by Hepatology Practice Providers. A rapid screening tool for depression is the Physician’s Health Questionnaire (PHQ)–2, and one can screen for Generalized Anxiety Disorder and Panic Disorder using the GAD-2 and the PHQ-PD, respectively (7, 8). If a patient screens positive in either the pre-or post-transplant phase, many antidepressants can be used safely and effectively (9), however, some mood stabilizers and stimulants like Modafinil or Armodafinil can induce the metabolism of immunosuppressants, but alternative medications are available.

To summarize, the path to an effective outcome for liver patients with psychiatric and substance use disorders begins with the use of standardized screening tools. Hepatology providers who are mindful of their responses to challenging patients can more readily form an alliance with their patient that supports their motivation to change. Finally, maintaining ongoing communication between the hepatology provider and the consulting psychiatrist is an essential tool for maximizing patient outcomes.

References

1. Saitz R, Mulvey KP, Plough A, Samet JH. Physician unawareness of serious substance abuse. Am J Drug Alcohol Abuse. 1997;23:343–354.
2. Saitz R, Cheng DM, Allensworth-Davies D, Winter MR, Smith PC. The Ability of Single Screening Questions for Unhealthy Alcohol and Other Drug Use to Identify Substance Dependence in Primary Care. J Stud Alcohol Drugs. 2014 Jan; 75(1): 153–157.
3. DiClemente CC, Corno CM, Grayson MM, Wiprovnick AE, Knoblach DJ. Motivational interviewing, enhancement, and brief interventions over the last decade: A review of reviews of efficacy and effectiveness. Psychology of Addictive Behaviors, 31(8), 862-887 2017.
4. Rodrigue JR, Hanto DW, Curry MP. Substance abuse treatment and its association with relapse to alcohol use after liver transplantation. Liver Transpl 2013; 19: 1387-1395 [PMID: 24123780 DOI: 10.1002/lt.23747]
5. Addolorato G, Leggio L, Ferrulli A, Cardone S, Vonghia L, Mirijello A, et al. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. Lancet 2007;370:1915–1922
6. Weinrieb RM, Van Horn DH, Lynch KG, Lucey MR. A randomized, controlled study of treatment for alcohol dependence in patients awaiting liver transplantation. Liver Transpl. 2011 May;17(5):539-47. doi: 10.1002/lt.22259.
7. Kroenke K, Spitzer RL, Williams JB, Monahan PO, Löwe B. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. Ann Intern Med. 2007;146:317-25.
8. Spitzer RL, Kroenke K, Williams JB, Patient Health Questionnaire Primary Care Study Group. Validation and utility of a self-report version of PRIME-MD: The PHQ primary care study. JAMA. 1999;282(18):1737–1744. pmid:10568646
9. Mullish BH, Kabir MS, Thursz MR, Dhar A. Review article: depression and the use of antidepressants in patients with chronic liver disease or liver transplantation. Aliment Pharmacol Ther. 40(8):880-92. 2014 Oct; doi: 10.1111/apt.12925. Epub 2014 Sep 1.

Behavioral Interventions in Liver Disease for Hepatology Practice Providers

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June 15, 2019

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AASLD Disclosure: Robert Weinrieb, MD

With respect to the following presentation, there has been no relevant (direct or indirect) financial relationship between the party listed above (and/or spouse/partner) and any for-profit company in the past 24 months which could be considered a conflict of interest.

Introduction

- Liver patients with addictions and psychiatric illness present unique and challenging problems
- Improving a clinical hepatology provider's knowledge about the transplant psychiatrist's role can maximize patients' liver outcomes

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3

Broad Goals: A Roadmap of the Transplant Psychiatry Referral Process

- To learn methods to screen for signs/symptoms of psychiatric and substance use problems that merit referral for a psychiatric evaluation
- To understand patients' preconceptions and reactions to referral for a transplant psychiatric evaluation, and ways to address them
- To be knowledgeable of mental health treatment options for liver patients

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4

Topic: Patient-Provider Interactions

- How can patients' behaviors (transference reactions and defenses) affect the patient-provider relationship?

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Patient-Provider Interactions

- Transference is a patient's unconscious response to a situation. It's usually out of proportion to the situation, with suspicion, defensiveness or anxiety, often based on childhood reactions to stress/trauma

- Counter-transference is a provider's unwitting reaction to a patient, colored by their own life experience, sometimes interfering with objectivity toward the patient

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Example of Transference-Countertransference

Provider: "I think you need to get treatment for your alcoholism to get this transplant"

Patient: "I'm strong-willed, not like your other patients, I don't need to go". I've been to AA, AA is for losers"

Provider: "I'm in charge here, you can do what I ask or go somewhere else"

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Example of Transference-Countertransference

Patient feels insulted, not trusted, angry, also shame and guilt

- accepting help means acknowledging failure
- wish to distance themselves, protect their self-esteem

Defense Mechanism: Denial/Rationalization

Provider feels angry, attacked, disrespected

Perhaps there was addiction in the family; the patient triggers feelings of helplessness and anger in the provider

Defense mechanism: Projection (shifting feelings that cause anxiety to a less risky target)

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8

Appropriate Transference-Countertransference Response

Constructive response by provider: "I hear that you are angry. I think you deserve to be proud about quitting drinking, and I trust you are sincere about staying sober, but mistakes happen".

"We're on the same team. Going to treatment is an act of strength, and active coping is more effective than passive coping. Treatment can help with the guilt and shame that many people feel who are going through this".

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Topic: Screening Tools for Psychiatric, Alcohol and Drug Problems

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Screening: Alcohol Use Disorders

CAGE (>/= 2 positive responses)
Predictive Positive Value = up to 75% (higher in men)
Predictive Negative Value = up to 97%

Cut down on your drinking? ("I can stop anytime")
Annoyed (or argue) when others criticize your drinking?
Guilty about your drinking? (do you hide it?)
Eye opener in the AM? (drink earlier in the day?)

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11

Single Q. Screen for Alcohol/Drug Use Disorders*

Alcohol: (88% sensitive, 84% specific, for 8 or > times)

(Men) "How many times in the past year have you consumed 5 or more drinks in a day?"

(Women) "How many times in the past year have you consumed 4 or more drinks in a day?"

Drugs: (97% sensitive, 79% specific, for 3 or > times)

"How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?"

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* Saitz, et al. *Journal of Studies on Alcohol and Drugs 75(1), 2014*

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Screening : Mood and Anxiety Disorders

- **Why screen?**

- **Only 50% of depressed patients are identified without screening**
- **Untreated depression and anxiety are associated with poorer quality of life, worse health outcomes and suicide**

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DSM-5 Screen for Major Depression

DSM-V diagnosis: 5 or more symptoms for at least 2 weeks.(Depressed mood, anhedonia, Sleep and appetite disturbances, etc.)

Screening tool: PHQ – 2 (Physician's Health Questionnaire). Scores of 3-6 are 75%-93% sensitive and should be followed up with a clinical interview

Over the past two weeks, how often have you been bothered by any of the following problems?"

1. **Little interest or pleasure in doing things?**
2. **Feeling down, depressed or hopeless?**

Score is 0 (not at all), 1 (several days), 2 (more than half the days), 3 (nearly every day).

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Screen: Generalized Anxiety Disorder (GAD)

- **Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities**
- **Screening Tool: GAD-2: Cutoff Score 3. Sensitivity: .76 Specificity: .81**

Over the last 2 weeks, how often have you been bothered by the following problems?

1. **Feeling nervous, anxious or on edge**
2. **Not being able to stop or control worrying**

Score is 0 (not at all) 1 (several days) 2 (more than half the days) 3 (nearly every day)

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Screen: Panic Disorder: Expected vs. Not-Expected

Four or more of the following symptoms: Palpitations, pounding heart, accelerated heart rate, Sweating, Trembling, shortness of breath, Fear of losing control or going crazy, Fear of dying, etc.

Screening Tool: PHQ-PD (Yes/No) Cutoff is 3. Sensitivity: .81 Specificity: .99

Nightmares
Avoidance
Hypervigilant
Numb, detached
Blaming self or others

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Motivating Patients with Alcoholic Liver Disease to Achieve Abstinence

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Why Motivate?

1. At the initial interview, very few of the pre-transplant patients have ever had alcohol treatment, and most feel they don't need it
2. Patients who engage in both pre- and post-transplant alcoholism counseling have lower relapse rates and lower mortality than those who get just pre- or post-

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Topics of Discussion

- 5 Myths that patients carry to the initial interview
- Role of the Psychiatrist vis-a-vis transplant team members in motivating patients toward seeking alcoholism treatment
- What is Motivational Interviewing (MI)?
- How does MI engage and guide patients toward lasting abstinence?

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Myth (#1): Psychiatrist's Role

"You're the last one I have to see to "pass the test" so I can get my liver"

- **View of psychiatry as a unilateral decision maker (Roman Emperor)**
- **Introduce myself, my role, my expectations, limits of confidentiality**
- **To learn about strengths, challenges, to create a path to listing, if possible**

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* Motivational Interviewing: *Helping People Change*

What is MI?

"A collaborative conversation style for strengthening a person's own motivation and commitment to change"

What is the spirit of MI?

- **Partnership** (dancing, not wrestling)
- **Compassion** (to promote pts welfare, to give priority to their needs)
- **Evocation** ("you have what you need, together we can draw it out")

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*Miller & Rollnick,2013

Four Processes in Motivational Interviewing*

1. **Engaging**: "This team understands me"
2. **Focusing**: Chronic disease management, which includes alcoholism treatment
3. **Evoking**: Patient identifies goals, and uses their own ideas and feelings about why and how to achieve them. i.e. "I want to drink socially"
4. **Planning**: Patient feels they have "flipped the light switch", takes ownership for plan

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*Miller & Rollnick,2013

* Some Common Traps

1. **(Expert Trap):** *"I am the expert on why and how my patients should change"* **Creates atmosphere of resistance, then**

   patient is seen as "in denial, unmotivated"

2. **(Q and A Trap)** *"I gather information about problems, ie. "how many beers do you drink, etc."*

   Accumulate evidence, then deliver a verdict

3. ***(Repair knowledge Gaps Trap)*** **To lift off the top of their head, pour in the knowledge, hope it sinks in!**

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*Miller & Rollnick,2013 23

A Few More Common Traps

4. **(Frightening information is helpful)**

   Clearly, the horrors of death and disease have not been enough to scare them sober

5. **(I need to just tell them clearly what to do)** *"I think you need to quit drinking altogether"*

   Both parties feel frustrated, engagement is poor, there is little room for autonomy vs. skillful advising to foster change

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*Miller & Rollnick,2013 24

* Doctor A; What Not to Do

https://youtu.be/ZGETDcFcAbI

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* Doctor B; Effective Use of MI

https://youtu.be/uL8QyJF2wVw

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Alcohol/Drug Use, Smoking, Mood and Anxiety in Liver Patients

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Scope of the Problem; Post-Transplant "Relapse" Rates 2000-2014

- 9 observational studies
  - Any drinking 10%-48%.
  - Heavy drinking: 3%-26%
  - Impact of drinking on survival: 4 of 5 studies

Meta-analysis 50 studies 1983-2005*

- Any drinking: 5.6 patients/100 patients/year
- Excessive drinking: 2.5 patients/100 patients/year

*Dew, et al. Liver Transplant, et al. 2008

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Is What We Tell Patients to Do Effective?

- **Effectiveness of Alcoholics Anonymous (AA)**
  - Not studied in this population
  - high drop out rate
  - patients don't feel like they belong, AA stimulates cravings, passive coping
- **Effectiveness of Intensive Outpatient Program (IOP)**
  - Not well studied in our population, but some patients thrive
  - More patients attended individual MET/Case Management sessions than IOP/AA

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Summary of Findings: Treatment Outcome Research for Alcohol Use Disorders in Liver Transplantation

- **Patients do best if they get psychosocial interventions both pre- and post-transplant**
- **Intervention requires sufficient number of sessions (>3)**
- **Embedded alcohol treatment unit in the liver clinic**
- **Baclofen, 10mg tid with psychosocial support and AA**
- **May be a role for naltrexone, 25mg-100mg or Vivitrol (IM, monthly)**

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Interventions for Nicotine Dependence*

1. **All smokers should be advised to quit smoking**
2. **Combination of behavioral interventions plus pharmacotherapy is best**
3. **For meds, either Varenicline (Chantix) or two nicotine replacement therapy (NRT) products; patch plus gum or lozenge**
4. **Bupropion (Wellbutrin) can be 2nd line**
5. **Varenicline not associated with increase neuropsychiatric effects, suicide or adverse cardiovascular events**

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* Up To Date, last updated 8/9/18

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Interventions for Nicotine Dependence

4. **Behavioral therapy options:**
   a. Brief counseling for withdrawal, cues, coping and stress management
   b. Telephone (proactive management best)
   c. Texting
   d. Web:
      - **Great American Smokeout**
      - **Stop Smoking** (American Lung Assoc)
      - **Smokefree** (National Cancer Institute)
   5. Pts who don't quit pre-transplant, don't quit post-transplant
   6. Quitting benefits post-op recovery, lower rates of post-transplant head/neck cancers

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Drug-Drug Interactions with Psychoactive Drugs and Direct Acting Antivirals (DAAs)

Drug	Studies Performed (Yes/No)	Interaction
Escitalopram (Lexapro)	Yes	No
(Citalopram) Celexa	Yes	No
Sofosbuvir	No	No
Ledipasvir	No	No
Boceprevir	No	Inhibits P450 CYP 3A4 Calcineurin Inhibitors Midazolam Seroquel
Simeprevir	No	
Paritaprevir/ritonavir plus Ombitasvir with Dasabuvir	No	

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Medications for Mood and Anxiety Disorders in Liver Disease

Pre-Transplant (cirrhosis):

1. Most antidepressants are safe
2. Avoid benzodiazepines (except alcohol withdrawal), GABA agonists, diphenhydramine, opioids
3. For anxiety, consider Buspirone, 5-10mg po bid-tid

Post-Transplant (immunosuppressants)

1. CYP3A 4 inducers (Tegretol, Trileptal, Dilantin, modafinil, armodafinil, St. John's Wort
2. CYP3A4 inhibitors (Fluvoxamine)
3. QT prolongation with immunos and antipsychotics

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Take Aways

1. Patient outcomes improve when hepatology providers work with mental health providers
2. Identifying and referring patients to a transplant psychiatrist should include being mindful of *your* response to difficult patient interactions
3. Recognition and amelioration of barriers to motivation for treatment of Alcohol Use Disorders is critical for adherence
4. Once your patient is referred to a transplant psychiatrist, try to maintain communication with them and ask your patients how they're doing with the referral

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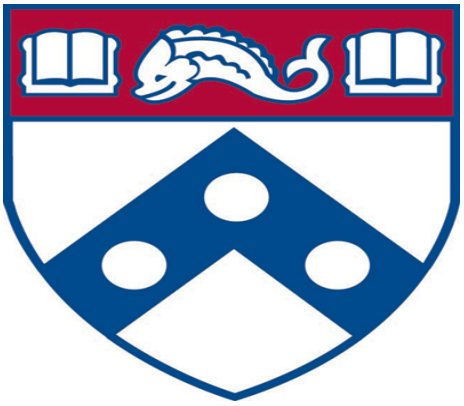

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Methods of detection of alcohol in blood, urine, and hair (extra slide)

- **Breathalyzer: 12-24 hours in cirrhosis**
- **Serum Alcohol: 12-24 hours in cirrhosis**
- **Ethylglucuronide/Ethylsulfide (EtG/EtS) (urine)**
  - 4-5 days
  - false positive; food, hand sanitizer, mouthwash, renal failure
- **EtG (hair): 4 drinks/day X 2 weeks**
  - 1.5 inch = 3.5 months
- **Phosphatidylethanol (P-Eth) 4 drink/day X 2-3 weeks.**
  No false pos, not affected by sex, liver disease, age

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Transplant Medicine Back Home: Pearls for the Non-Transplant Provider

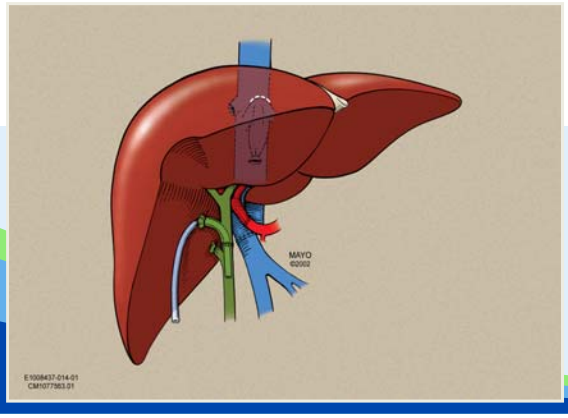
Liver Transplant (LT) outcomes continue to improve with approximately 92-94% one year survival. Alcoholic liver disease and NAFLD have become leading indications for LT and hepatitis C has become less common due to the advent of effective cures. There is an ongoing donor organ shortage as reflected by year-end data from 2017 showing that 13,239 individuals remain on the wait-list while, 8082 underwent liver transplantation (4.5% living donor). The MELDNa system is used to prioritize candidates for liver transplantation. A MELNa score ≥ 15 (confers survival benefit) or evidence of decompensated cirrhosis (ascites, jaundice, variceal hemorrhage, hepatic encephalopathy, hepatorenal syndrome) are indications for evaluation for liver transplantation. Multiple diseases/conditions are also eligible for exception MELD points which give patients a higher priority for transplantation based on their risk of death. Exception MELD points can be granted for hepatocellular carcinoma, hepatopulmonary syndrome, portopulmonary hypertension, hilar cholangiocarcinoma, familial amyloidotic polyneuropathy, primary hyperoxaluria, and cystic fibrosis related hepatic disease. Patients with acute liver failure, defined by lack of prior liver disease, coagulopathy, and hepatic encephalopathy, are listed at the highest priority, referred to as status 1. Living donor liver transplant (LDLT) accounts for only 4.5% of all LT and have increased risk of biliary complications (35%). Infections are among the most common cause of mortality in the early post-transplant period. Prophylaxis with valganciclovir for 6 months is recommended for the combination of CMV + donor/CMV negative recipient. Sulfamethoxazole-trimethoprim is utilized to prevent pneumocystis jirovecii. Induction immunosuppressive regimens most commonly employ a calcineurin inhibitor (tacrolimus > cyclosporine) plus mycophenolate mofetil and prednisone, though some centers use the IL2 receptor blocker basiliximab in this phase. The maintenance phase of immunosuppression (after 2-4 months) generally involves a calcineurin inhibitor alone, but sometimes in conjunction with mycophenolate mofetil when patients have endured multiple episodes of rejection or have chronic kidney disease. The goal of immunosuppression is to prevent T-cell mediated rejection (highest risk in the first 30 days) which is effectively treated with IV corticosteroid boluses in 85-90% of cases. Antibody mediated rejection is rare in LT recipients. Overall, the candidates for transplant have become older (2 fold increase in age >65) and obesity has become increasingly prevalent. Calcineurin inhibitors promote the development of diabetes, hypertension, hyperlipidemia, and chronic kidney disease. Thus, management of weight, diabetes, and the metabolic syndrome have become very important post transplantation, especially considering that cardiovascular disease and malignancy are leading causes of death post LT. Drug-drug interactions are common and new medications should be reviewed with the transplant center or an experienced pharmacist.

References

1. Liver Transpl. 2013 Jan;19(1):3-26. doi: 10.1002/lt.23566.Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Lucey MR1, Terrault N, Ojo L, Hay JE, Neuberger J, Blumberg E, Teperman LW.
2. Am J Transplant. 2010 Jun;10(6):1420-7. doi: 10.1111/j.1600-6143.2010.03126.x. Epub 2010 May 10.Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. Watt KD1, Pedersen RA, Kremers WK, Heimbach JK, Charlton MR.

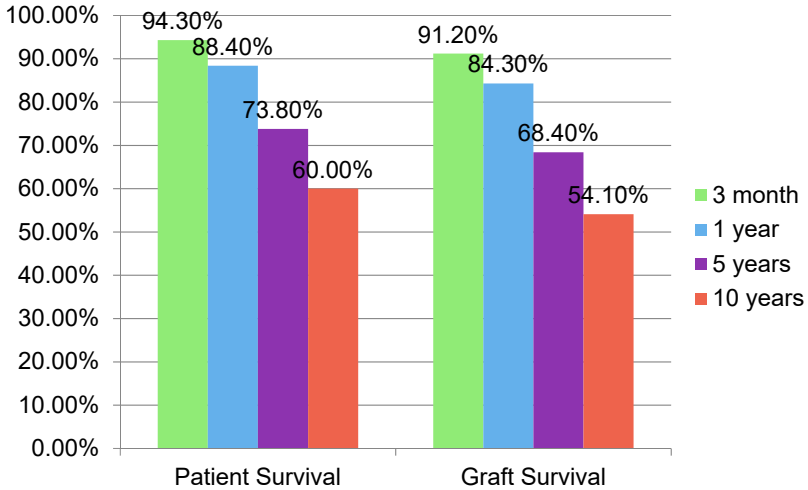
3. Clin Transplant. 2019 Feb 28:e13512. doi: 10.1111/ctr.13512. [Epub ahead of print] Cytomegalovirus in solid organ transplant recipients-Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. Razonable RR1, Humar A2,3.
4. Am J Transplant. 2011 May;11(5):965-76. doi: 10.1111/j.1600-6143.2011.03486.x. Epub 2011 Apr 5. Reduced-dose tacrolimus with mycophenolate mofetil vs. standard-dose tacrolimus in liver transplantation: a randomized study. Boudjema K1, Camus C, Saliba F, Calmus Y, Salamé E, Pageaux G, Ducerf C, Duvoux C, Mouchel C, Renault A, Compagnon P, Lorho R, Bellissant E.
5. Am J Transplant. 2018 Jan;18 Suppl 1:172-253. doi: 10.1111/ajt.14559. OPTN/SRTR 2016 Annual Data Report: Liver. Kim WR1,2, Lake JR1,3, Smith JM1,4, Schladt DP1, Skeans MA1, Harper AM5,6, Wainright JL5,6, Snyder JJ1,7, Israni AK1,7,8, Kasiske BL1,8.

Liver Transplantation: Overview and Pearls



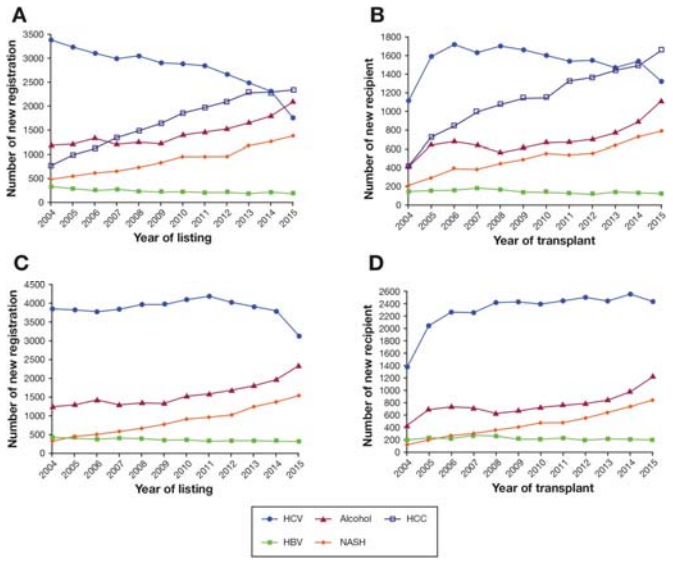
Michael D. Leise, M.D.

Liver Transplant Survival in the U.S. '99-'08



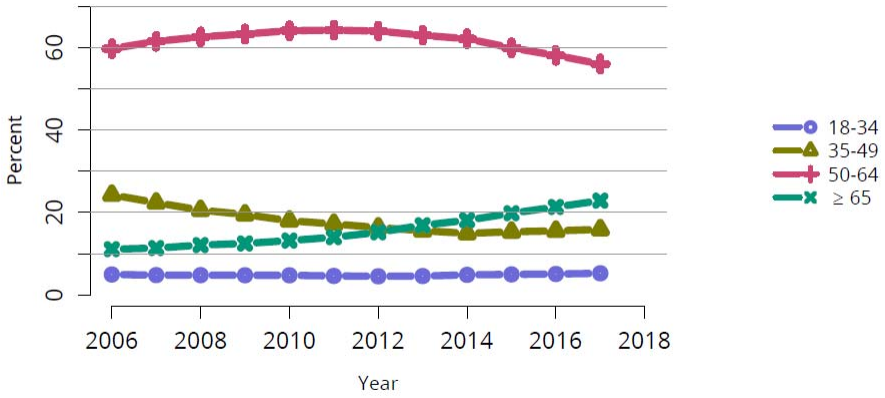
Thuluvath et al. *Am J of Transpl* 2010

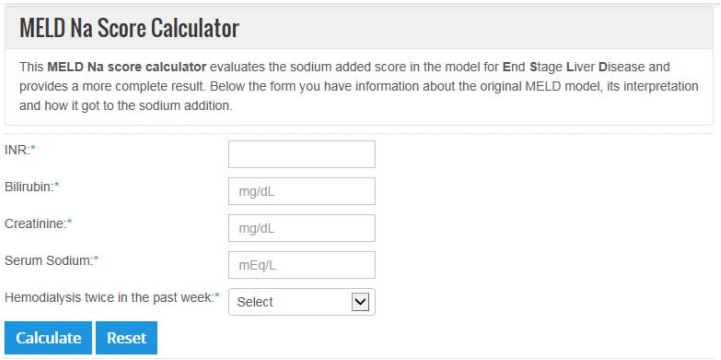
Trends in Listing and LT by Indication



Yang, Leise et al *CGH* 2017

Age >65 at listing has increased 2x over 10yrs





- **Range 6-40**
- **Predicts 3 mo mortality**
- **INR - highest weight**
- **Creatinine – cap at 4.0**
- **Adding Na to MELD improves prediction**

MELDNa ≥ 15 = Transplant Survival Benefit
MELDNa 28 = Median MELD at LTx

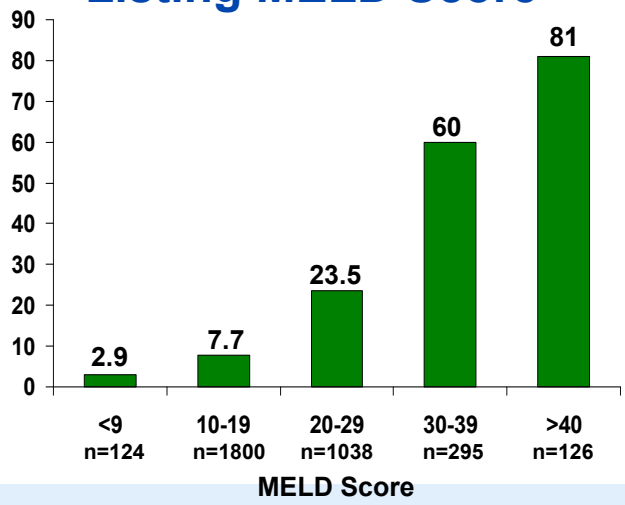
https://www.thecalculator.co/health/MELD-Na-Score-Calculator-846.html

When to Refer for Liver Transplantation

- Cirrhosis with decompensation:
  - Variceal hemorrhage
  - Ascites
  - Hepatic Encephalopathy
  - Hepatorenal Syndrome
  - Hepatocellular Carcinoma
  - OR hepatic dysfunction
    - MELDNa ≥ 15
- Let the transplant center determine adequate length of sobriety

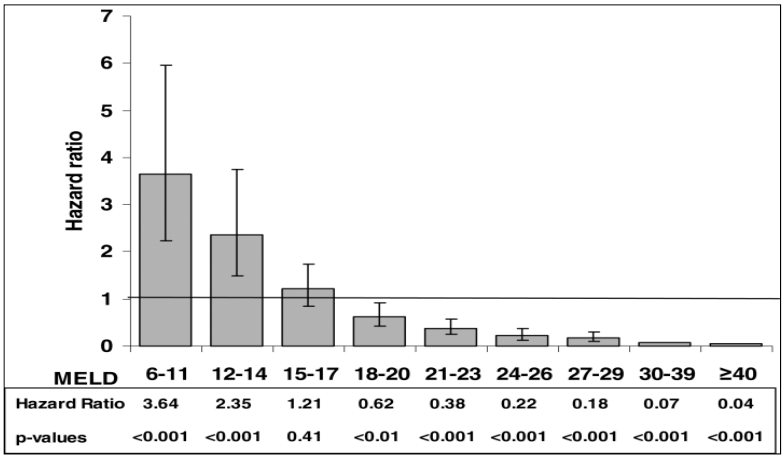
Martin P. et al. AASLD Guidelines *Hepatology* 2014

3-Month Mortality Based on Listing MELD Score



Wiesner et al. Gastro 2003

Risk of Transplant Mortality Vs. Waitlist Mortality By MELD Score



MELD	6-11	12-14	15-17	18-20	21-23	24-26	27-29	30-39	≥40
Hazard Ratio	3.64	2.35	1.21	0.62	0.38	0.22	0.18	0.07	0.04
p-values	<0.001	<0.001	0.41	<0.01	<0.001	<0.001	<0.001	<0.001	<0.001

Median MELD at Transplant in the U.S. =27 (SRTR 7/15/13)

Merion R. Am J of Transpl 2005

Accepted Indications for Liver Transplantation

- Acute liver failure
- Decompensated cirrhosis with MELD ≥ 15
- Hepatocellular Carcinoma within Milan Criteria
- Hilar Cholangiocarcinoma, highly selected pts
- Hepatopulmonary Syndrome
- Portopulmonary Hypertension
- Familial Amyloidotic Polyneuropathy
- Primary Hyperoxaluria
- Cystic Fibrosis with liver involvement

Other Indications for Liver Transplant

- PSC with recurrent cholangitis
- Polycystic liver disease
- Neuroendocrine tumors (**NET**)
- HCC outside of Milan Criteria
- +/- Hereditary Hemorrhagic Telangiectasia (**HHT**)

Absolute Contraindications to LTX

- Nervous System
  - Brainstem herniation (ALF)
  - Severe intracranial hypertension (ICH >50mmHg) (ALF)
- Cardiovascular/Pulmonary
  - Advanced cardiopulmonary disease
  - Hemodynamic instability requiring high dose or multiple pressors
  - Severe portopulmonary hypertension despite treatment
- Uncontrolled Infection
- Multi-organ Failure
- Neoplastic
  - Current/recent extrahepatic malignancy unless tumor free ≥ 2 years and ↓ low risk of recurrence
- Psychosocial
  - Untreated alcoholism/drug use
  - Severe, uncontrolled mood disorder that may affect compliance

Relative Contraindications

- Lack of social support
- Advanced age
- Previous extensive abdominal surgery
- Extensive porto-mesenteric venous thromboses
- Severe muscle wasting/severe deconditioning

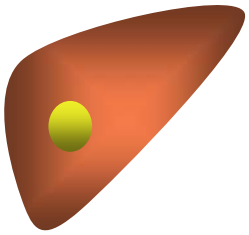
Patients can be listed in the MELD system in several different ways

1. Status I – highest priority
   - Acute Liver Failure, Acute Wilson's, Hepatic Artery Thrombosis, Primary Non-Function
2. Calculated MELD Score
3. Exception MELD Points
   - HCC, Hilar cholangiocarcinoma*, Familial Amyloidotic Polyneuropathy, Portopulmonary Hypertension, Hepatopulmonary Syndrome, Primary Hyperoxaluria, Cystic Fibrosis
4. Appeal to Regional Review Board (ie. HHT)

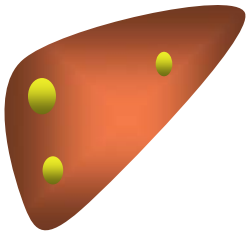
LIVER TRANSPLANTATION FOR HCC

MILAN CRITERIA

1 lesion ≤ 5 cm



2 to 3 lesions, ≤3 cm



+

Absence of Macroscopic Vascular Invasion

Absence of Extra-hepatic Spread

- Lesion must be ≥ 2cm (T2) to receive exception points
- Lesions < 2cm (T1) do not get exception points except in rare instances

Mazzaferro, et.al. *N Engl J Med* 1996

Pulmonary Vascular Diseases – MELD Exception

- Hepatopulmonary Syndrome
  - Evidence of portal hypertension ± cirrhosis
  - Evidence of shunt
    - Agitated saline echo or macroaggregated albumin
  - PaO2 < 60mmHg on room air
- Portopulmonary Hypertension
  - Portal HTN ± Cirrhosis
  - Mean Pulmonary Arterial Pressure ≥ 25
  - Pulmonary Capillary Wedge Pressure < 15
  - Pulmonary Vasc. Resistance > 240 dynes.s.cm^{-5}
  - Post-Tx MPAP < 35 mmHg and PVR < 400

Which of the following is true of living donor liver transplant (LDLT):

A. Higher risk of biliary complications for the recipient

B. Survival of the graft is better than deceased donor transplant

C. Rejection is less with LDLT due to matching with close family member

D. Indicated only in patients with very high MELD scores

E. Donor mortality is > 1 in 10

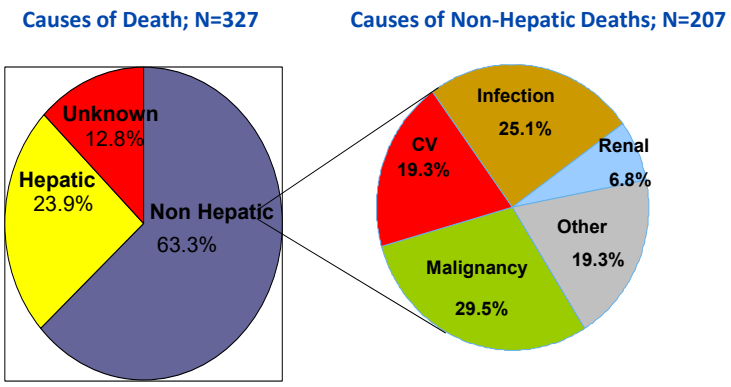
Living Donor Liver Transplantation (LDLT)

- U.S. Waitlist – 13,239 (end of 2017)
- U.S. LTx 2017: DDLT – 7715; LDLT – 367 (4.5%)
- Advantages over deceased liver (DDLT) are
  - availability of the organ (earlier LTx)
  - presumed good quality graft
  - ↓ cold ischemia time
  - expansion of donor pool
- Disadvantages: LDLT has biliary and vascular complications –bile leak 30%, HAT 6%, PVT 3%
- Overall graft and patient survival same
- Donor morbidity (8-26%) and mortality (0.5%)

Olthoff K et al *Ann Surg* 2005

Kim, WR et al. AJT 2019

CAUSES OF DEATH AFTER LIVER TRANSPLANTATION



Watt KD, et al. *Am J Transpl* 2010

EARLY LIVER TRANSPLANTATION COMPLICATIONS: OVERVIEW

- Early
  - Graft – Primary Non-Function (0.5-4%), Small for Size Syndrome (LDLT or Split)
  - Surgical – bleeding (10-15% return to OR), bile leak (30% - highest for LDLT), biliary stricture (5-10% DDLT, LDLT 25-30%)
  - Vascular - hepatic artery thrombosis (≈2.9% DDLT, 6% LDLT), hepatic vein outflow obstruction, portal vein thrombosis
  - Immunologic – acute cellular rejection (25-30%)
  - Infectious – <1mo –nosocomial bacteria, HSV (w/o prophylaxis), donor derived; 1-6 months – opportunistic - fungal, atypical bacterial; CMV)

LIVER TRANSPLANTATION COMPLICATIONS: GRAFT DYSFUNCTION

- Early: preservation injury, rejection, infection, bile leak, vascular
- Late: biliary stricture (may be due to hepatic artery thrombosis), recurrence of disease, rejection if inadequate immune suppression

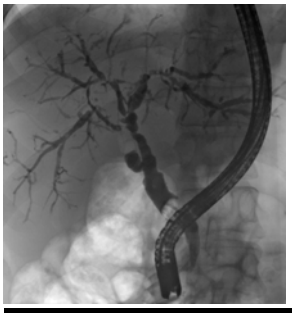
LIVER TRANSPLANT COMPLICATIONS: INFECTIONS

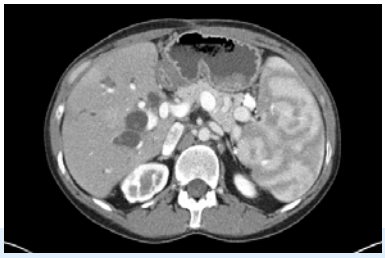
- #1 cause of death in 1st 3 years post LTx*
- Early
  - <1month –nosocomial bacteria, surgical (abscess), donor derived, HSV (w/o prophylaxis)
  - 1-6 months – CMV (w/o prophylaxis), Opportunistic ie. Pneumocystis, fungal, atypical bacterial – MTB, nocardia
- Late – > 6 months – community acquired infections, EBV-PTLD, recurrent HCV, late onset CMV (with prophylaxis)

*Watt K et al *Amer J of Trans* 2010

LIVER TRANSPLANT COMPLICATIONS: HEPATIC ARTERY THROMBOSIS

- Incidence: 2.5-10% in adults
- 10% in children
- Early vs. late
- Risk factors: small arteries, complex arterial anastomoses, vascular grafts, prolonged clamping, living donor, hypercoagulability, poor functioning graft, smoking, Roux-Y bilioenteric anastomosis





LIVER TRANSPLANT COMPLICATIONS: BILIARY STRICTURES

- Anastomotic
  - Most common site, peak onset1-4 months, but can present at any time
    - cholestasis, fever, pruritus
  - LLDT>>DDLT
  - Most can be managed endoscopically or PTC; minority require surgical revision
- Non-Anastomotic
  - Less common, median=3 months
  - Seen w/ HAT, DCD donors
    long ischemia times
  - 50% require retransplantation or die

52 y.o. man is 3 months following LDLT for PSC. Donor was his 24 year-old son. Post-LT course was notable for steroid-resistant acute cellular rejection requiring thymoglobulin Rx 1 week post-LT. He now presents with nausea, vomiting, profuse diarrhea, and fever.

Exam: toxic appearing, dry mucous membranes, no rash. Generalized abdominal tenderness w/o rebound/guarding.

Labs: WBC 1.9, Hgb 11.4, AP 168, AST 119, ALT 132, TBili 0.9, Cr 2.9

Current Rx: tacrolimus, prednisone 10 mg QD, MMF 1g BID.

Which is the most likely diagnosis?

- 1. Bile leak
- 2. CMV gastroenteritis
- 3. Recurrent acute cellular rejection
- 4. Graft-vs-Host disease
- 5. Ascending cholangitis

Risk of CMV Disease

Table 2 Estimated incidence of CMV disease during the first 12 mo after liver transplantation

	Use of anti-CMV prophylaxis	
	Yes[1]	No
CMV D+/R-	12%-30%	44%-65%
CMV D+/R+	2.7%	18.2%
CMV D-/R+	3.9%	7.9%
CMV D-/R-	0	0
All patients	4.8%	18%-29%

Prophylaxis = 3 months of antiviral medication for this table
Recommended Prophylaxis: D+/R- and R+ (Oral Valganciclovir – not FDA approved)

- CMV Syndrome (fever with myelosuppression)
- Tissue Invasive Disease (most common is GI tract)
- Dx: CMV PCR
- Tx: IV Ganciclovir

Razonable, R World J Gastro 2008

Early Acute Cellular Rejection (ACR)

- Incidence: ≈30% of pts in the first 6 weeks
- Immunology: T cell driven
- Features: mild to moderate elevation AST/ALT ± alkaline phosphatase, bilirubin; rarely fever
- Diagnosis: liver bx w /characteristic triad of portal infiltrate, lymphocytic cholangitis, endothelitis
- Treatment: IV corticosteroid boluses (ex. 1000mg); 85-90% respond
- Outcome: no negative affect on graft outcome except HCV (graft survival worse)

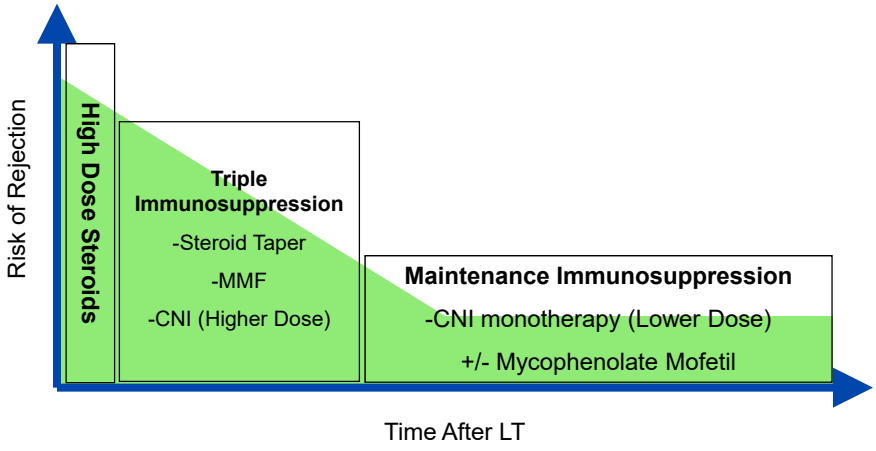
Categories of Immunosuppression (IS)

- Small Molecules
  - Calcineurin Inhibitors – Tacrolimus, Cyclosporine
  - mTOR inhibitors - Sirolimus/Everolimus
  - Purine Antagonist - Azathioprine, Mycophenolate
- Biologics
  - Lymphocyte Depleting: OKT3, Thymoglobulin
    - Known for cytokine release/systemic reaction
  - Non-Lymphocyte Depleting
    - Monoclonal Ab or Fusion Proteins
      - No cytokine release
    - Examples: IL-2 Ab (Basiliximab, ~~Daclizumab~~)

Immunosuppression Overview

- Phases
  - Induction – peak alloreactivity during 1st 30 days requires highest amounts of IS
    - Common regimen is corticosteroids, Tacrolimus or Cyclosporine, & Mycophenolate
  - Maintenance - >30 days
    - Attempt to ↓ number and dosages of IS due to decreasing alloreactivity
    - Common regimen :monotherapy with a Calcineurin Inhibitor (Tacrolimus or Cyclosporine)

Immunosuppressive Rx After LT



Side effects of immunosuppressive drugs

	TAC/CyA*	MMF	Sirolimus
Renal dysfunction	++		+(proteinuria)
Hypertension	+		
Diabetes	+(Tac)		
Neurotoxicity	+		
Cytopenias		+	+
Hyperlipidemia	+		++
GI side effects		+	
Pulmonary Fibrosis			+
Others	hypertrichosis*		HAT
			wound healing

45 y.o. man presents with abnormal liver tests. He underwent OLT 4 yrs ago for PSC. His chronic meds have been tacrolimus and metoprolol. 1 mo ago, he developed fever and seizures. He had a prolonged hospitalization and was dismissed 14 d ago on multiple new medications. Seven days ago, liver tests were elevated and the tacrolimus level was < 2.0 despite the fact that he has been on the same tacrolimus dose for 2 yrs and previous levels had been 5-8. Which of the following medications is most likely to cause this clinical picture?

1. Phenytoin
2. Itraconazole
3. Diltiazem
4. Fluconazole
5. Levetiracetam (Keppra)

Important Drug-Drug Interactions

Drug Interactions with Calcineurin Inhibitors (CNIs)		
Drugs that Increase levels of CNIs		
Antimicrobials	**Calcium Channel Blockers**	**Others**
-Caspofungin	-Diltiazem	-Danazol
-Azoles	-Verapamil	-Grapefruit Juice
-Macrolides	-Amlodipine (less)	-Diazepam, alprazolam
-Chloroquine	-Felodipine (less)	-Allopurinol
-Protease Inhibitors	-Nicardipine	-Sertraline
-Ofloxacin		
Drugs that Decrease levels of CNIs		
Antimicrobials	**Anticonvulsants**	**Others**
-Rifampin	-Carbamazepine	Orlistat
-Rifabutin	-Phenobarbital	St. John's Wort
	-Phenytoin	

Hilar Cholangiocarcinoma (CCA) – MELD Exception

- Diagnostic criteria:
  - malignant stricture on cholangiography + 1 of following:
    - CA-19-9 ≥ 100
    - Biopsy or cytology positive for malignancy
    - Aneuploidy on FISH studies
- Transplant candidate if:
  - Radial tumor dimension ≤ 3cm
  - Unresectable
  - No transperitoneal aspiration/biopsy
  - Exclude extrahepatic spread – EUS, CT chest/abd/pelvis
  - Pre-transplant chemoradiation tx effective – no spread
  - Operative staging negative
  - MELD starts at 22 with ↑10% every 3 months

Liver Transplant Complications: LATE

- Surgical – ventral hernias
- Vascular - late hepatic artery thrombosis
- Immunologic – late acute cellular rejection, chronic rejection
- Infectious – > 6 months – community acquired infections, EBV-PTLD, recurrent HCV, late onset CMV (with prophylaxis)
- Metabolic - Diabetes, HTN, hyperlipidemia, osteoporosis
- Neoplastic - Higher risk for malignancies such as PTLD, non-melanoma skin CA, Colon (PSC), lung and oropharyngeal (smokers) CA

Recurrent Disease Rates: 5 years

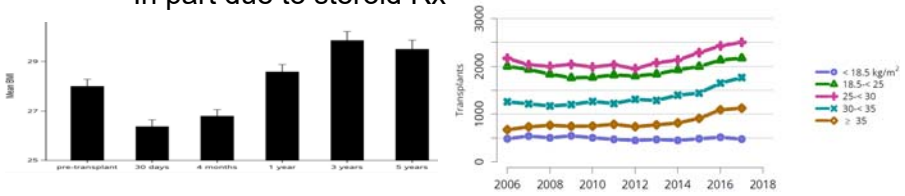
LIVER TRANSPLANT COMPLICATIONS: RENAL IMPAIRMENT

- Renal impairment (creat >1.5mg/dL) common in pre-LT patients
  - Up to 30% prevalence pre-LT (age, hepatorenal syndrome)
  - Due to allocation system, increasing numbers of patients on RRT prior to LT
- Renal toxicity is the major long-term adverse effect of CNI immunosuppressive Rx
  - Up to 20% cumulative rate of GFR < 30 mL/min/1.73m^2 by 5 years post-LT
- Risk of renal impairment reduced by close management of immunosuppressive levels by transplant center
- Other renal risk factors (DM, HTN) need to be aggressively controlled

Pfitzmann, Transpl Int 2007
Watt KDS, AJT 2010

Obesity

- Weight gain is very common following LT
  - Median gain of 6-9 kg
- Most weight gain during the first 6-16 months post-LT with relative stability thereafter
  - In part due to steroid Rx during early post-LT time frame



- Patients who are overweight/obese at LT gain more weight after transplant
- Associated with adverse metabolic complications and fatty infiltration of allograft

Everhart. *Liver Transpl Surg* 1998
Richards. *Transpl Int* 2005
Fussner et al. *Liver Transpl* 2015

Metabolic Syndrome

- High incidence of metabolic syndrome in post-LT recipients
  - Increasing incidence in the general population
  - Post-LT weight gain
  - Steroid induced hyperglycemia
  - Immunosuppressive induced HTN, dyslipidemia, diabetes
- Diabetes mellitus
  - Hyperglycemia common in early post-LT setting
    - 50% immediate post-LT, 24% long term post LT
  - Pre-LT diabetes is increasingly common (especially in patients with NAFLD)
    - Likely worsen post-LT during steroid Rx

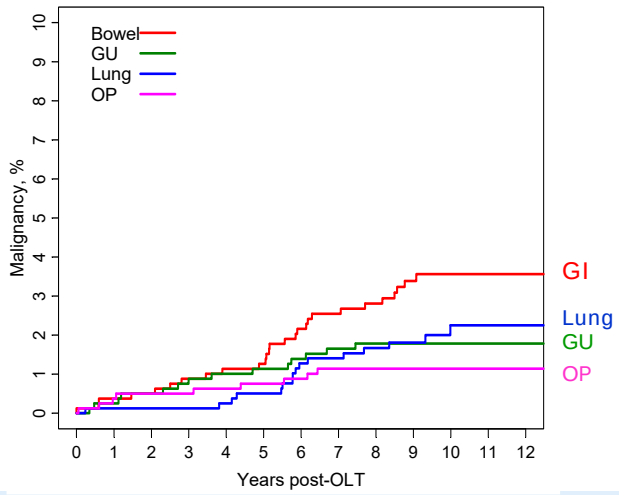
Metabolic Syndrome

- Hyperlipidemia and hypertension are rare pre-LT, but are common adverse effects of immunosuppressive Rx
- Hypertension is a very common complication of immunosupressive Rx
  - 71% of patients will develop BP ≥ 140/90
  - Vasoconstrictive (systemic and renal) effect of CNIs
  - HTN should be aggressively managed
  - Non-CYP450 metabolized CCBs may be first line Rx
- Dyslipidemia
  - Occurs in up to 74% of pts maintained on cyclosporine and up to 52% of pts maintained on tacrolimus

Cardiovascular Morbidity

- Metabolic syndrome is associated with CV events in ~ 25% LT recipients
- Cardiovascular disease remains a leading cause of late post-LT death
- Aggressive control of weight, HTN, dyslipidemia and diabetes is often best managed by primary provider in cooperation with the transplant center

Probability of Developing Solid Organ Cancer



	10yr
ALL	13.6%
CDC	6.5%
GI	3.6%
CDC	.62
GU	1.8%
CDC	.13-.54
Lung	2.2%
CDC	.7
Oropha	1.1%
CDC	.07-.21

LIVER TRANSPLANTATION Summary

- LT is standard of care for decompensated liver disease and some other accepted indications
- LT recipients are increasingly >65 and obese
- Long-term effects of immunosuppression result in major long-term complications that are managed by the non-LT clinician
  - Obesity, DM, Hyperlipidemia, CV disease, malignancy
- Infections and drug-drug interactions are common issues for the the non-LT clinician
- Recurrent disease is common but generally only leads to graft loss in malignancy and PSC

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Controversies to Consider When Treating HCV Before or After Liver and/or Kidney Transplant

The development of multiple safe and highly effective direct-acting antivirals (DAA) to treat Hepatitis C (HCV) has led to the elimination of mortality from cholestatic HCV post-transplant, reduced viremia in HCV antibody (HCV Ab+) positive wait listed patients, and to near universal post-transplant sustained viral response (SVR) rates in those undergoing HCV treatment after transplant. At the same time, an inconvenient truth of the U.S opioid epidemic was a dramatic rise from 8,269 in 2013 to 10,722 in 2018 in deceased donors. Many of these additional deaths identified as donors were associated with PHS increased risk behaviors, for instance active injection drug use at the time of death or high-risk sexual behaviors. As a result of this an increased prevalence of HCV antibody positivity (HCV Ab+) is found within these donors. The current HCV Ab+ donors had a median age of 32 years in 2016 as compared to 48 years for HCV Ab+ donors in 2006. These donors also have a higher prevalence HCV RNA positivity greater prevalence of genotype 3 as compared to this genotype's prevalence in the general HCV infected population. These donors also have a low incidence of donor liver fibrosis. The converging events of a greater number hepatitis C NAT positive (HCV D+) donors, a diminishing number of HCV NAT+ wait listed patients, highly effective treatments for HCV and, a low likelihood of fibrosis in those infected with HCV culminated in, on September 11, 2016, the first intentional transplantation of a HCV D+ liver donor into a HCV Ab and NAT negative recipient (HCV R-). Since then the United Kingdom implemented policies to make HCV D+ into any recipient a standard of care for all willing recipients and, in the U.S., the number of transplants of HCV D+ into HCV R- went to 22/month and 12/month over 2 years for kidney and liver transplants recipients respectively.

The presentation will provide an overview of where benefit exist in treating particular wait list patients before transplant. This presentation will also detail the current knowledge and processes associated with donor and recipient selection and the subsequent management for HCV D+ offers with management algorithms provided. An outline of current patient and allograft outcomes following transplant of HCV D+ organs and HCV Ab+ NAT- will then be contrasted against HCV D-R- organs. Finally the presentation will describe where potential pitfalls associated offer and acceptance of HCV Ab+ and/or NAT+ organs exist and how to identify and avoid these.

Over the last 3 years controversies were generated within the membership of the transplant community surrounding concerns for potentially significant negative consequences related to the practice of accepting these organs for uninfected recipients. Over the last 12 months many of these controversies have dissipated as a greater understanding of the potential benefits associated with these offers came to be realized and how, with time, the concerns for negative consequences failed to be realized.

References

1. Agarwal K, Castells L, Müllhaupt B. et al. Sofosbuvir/velpatasvir for 12 weeks in genotype 1-4 HCV-infected liver transplant recipients. J Hepatol. 2018 Sep;69(3):603-607
2. Reau N, Kwo PY, Rhee S, et al. Glecaprevir/Pibrentasvir Treatment in Liver or Kidney Transplant Patients With Hepatitis C Virus Infection. Hepatology. 2018 Oct;68(4):1298-1307

3. Cotter TG, Paul S, Sandıkçı B, et al. Improved Graft Survival After Liver Transplantation for Recipients With Hepatitis C Virus in the Direct-Acting Antiviral Era. Liver Transpl. 2019 Apr;25(4):598-609
4. Bowring MG, Shaffer AA, Massie AB, et al Center-level trends in utilization of HCV-exposed donors for HCV-uninfected kidney and liver transplant recipients in the United States. Am J Transplant. 2019 Mar 12. [Epub ahead of print]
5. Levitsky J, Formica RN, Bloom RD, et al. The American Society of Transplantation Consensus Conference on the use of hepatitis C viremic donors in solid organ transplantation; Am J Transplant. 2017;(11):2790-2802
6. https://optn.transplant.hrsa.gov/data/view-data-reports/national-data
7. Reese PP, Abt PL, Blumberg EA, et al. Twelve-month outcomes after transplant of hepatitis C-infected kidneys into uninfected recipients: a single-group trial. Ann Intern Med. 2018;169:273-281.
8. Kwong AJ, Wall A, Melcher M, et al. Liver transplantation for hepatitis C virus (HCV) non-viremic recpients with HCV viremic donors. Am J Transplant. 2018; [Epub ahead of print]
9. McLean RC, Reese PP, Acker M, et al. Transplanting hepatitis C virus-infected hearts into uninfected recipients: A single-arm trial. Am J Transplant.. 2019; [Epub ahead of print]
10. Abdelbasit A, Hirji A, Halloran K, et al. Lung transplantation from hepatitis C viremic donors to uninfected recipients. Am J Respir Crit Care Med. 2018;197(11):1492-1496.
11. Wong RJ, Jain MK, Therapondos G, et al. Race/ethnicity and insurance status disparities in access to direct acting antivirals for hepatitis C virus treatment. Am J Gastroenterol. 2018;113(9):1329-1338
12. Gowda C, Lott S, Grigorian M. Absolute Insurer Denial of Direct-Acting Antiviral Therapy for Hepatitis C: A National Specialty Pharmacy Cohort Study. Open Forum Infect Dis. 2018 Jun 7;5(6)

Controversies in Treating HCV Before or After Liver and/or Kidney Transplant

Dr Richard Gilroy

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Intermountain Health Care

Utah

Learning Objectives:

- Who might one consider for pre-transplant therapy
- Why providers seek to facilitate organ utility
- Detail where concerns with these organ offers exists for Patients, Providers and Institutions, including OPTN
- Create the ability to recognize where opportunities and pitfalls exist when considering HCV antibody positive donors and recipients
- Summarize what I believe to be best practices in this area

Not covered

- Actual treatment regimens
- Economic costs associated with the decision to accept or decline a HCV offer
- Resources, in particular what additional resources and infrastructure may be needed
- Histopathology
- The other Myths and facts associated with donors

QUESTION: You are a 54 yo female on a Liver Transplant Waiting List with Hepatitis C and MELD score 19. You "stopped drinking" and this time you are not going to restart. Your AST is 160, ALT 82, BR 8.0, INR 1.5, Cr 0.8. USS Imaging shows a liver with span 13 cm and irregular edge with no masses, spleen 14 cm, some ascites. EGD shows grade 1 varices and portal gastropathy, Your AFP is 19, you have a couple of cases and 1+ protein on your UA and the median MELD at transplant for the Mississippi program, pre-allocation change, is 18. You live in West Virginia and you have health insurance that covers HCV therapy….. and you also know a few sex workers from a previous job.

Should you:

- A. take HCV therapy
- B. decline HCV therapy because you have an increased risk for HCC based upon the AFP value and are likely to be allocated to as you are HCV positive
- C. decline the offer as you may end up in MELD purgatory as your MELD is greater than 16
- D. check with your insurance company to see if retreatment is possible if you fail therapy
- E. Decline as you will likely get better as you really only recently stopped drinking

Pretransplant Therapy

Data We Have on HCV Treatment in Decompensated Cirrhosis

Table 1 Some Important Studies on Treatment of HCV Infection in Decompensated Cirrhosis and in Recurrent HCV Infection After LT.

Study name	Patient population	Genotype (GT)	Numbers	Drugs used	SVR rates pre-transplant	SVR rates post-transplant
Curry et al. (2015)[31]	Awaiting LT	72% GT-1	61	SOF + RBV	93% RNA negative by time of transplantation	70% of these had SVR after transplantation
SOLAR-1 (US)[36]	Decompensated cirrhosis	1 and 4	108	SOF + LDV + RBV	CTP stage B: 86% (12 week)/89% (24 week); CTP stage C: 86% (12 week), 90% (24 week)	96–98% (without cirrhosis or with compensated cirrhosis), 85–88% (moderate hepatic impairment), 60–75% (severe hepatic impairment), and all 6 patients with FCH
SOLAR-2 (Europe)[41]	Decompensated cirrhosis	1 and 4	108	SOF + LDV + RBV	CTP stage B: 87% (12 week)/96% (24 week); CTP stage C: 85% (12 week), 78% (24 week)	CTP stage B: 95% (12 week)/ 100% (24 week); CTP stage C: 50% (12 week), 80% (24 week)
ALLY-1[42]	Compensated/ decompensated cirrhosis	GT-1 to 4	60/53	DCV + SOF + RBV	CTP stage A/B: 93%; CTP stage C: 56%	GT-1: 95%; GT-3: 91%
ASTRAL-4[43]	Decompensated cirrhosis	All GTs	267	SOF + VLP with/ without RBV	83% (12 weeks without RBV), 94% (12 weeks with RBV) and 86% (24 weeks without RBV)	–
SATURN[44]	Post-transplant recurrent HCV	All except 3	21 (METAVIR: F1-F2) and 14 (METAVIR: F3-F4)	SMV + DCV + RBV	–	90–93%
CORAL-1[45]	Post-transplant recurrent HCV	GT-1 to 4	34	3D (PTV/rt + OMB + DSB) + RBV	–	97%
HCV-TARGET[46]	Decompensated cirrhosis	GT-1 to 4	170	SOF + LDV ± RBV	87.9	–
French ATU study[47]	Before and after transplantation	All except 3	147	DCV + SOF ± RBV	95–100%	–
UK EAP Study[48]	Decompensated cirrhosis	GT-1 and 3	467	By clinician's choice: SOF + LDV/DCV + RBV	GT-1: 60–86%; GT-3: 43–71%	–
EU CUP Trial[49]	Advanced liver disease/ decompensated cirrhosis	GT-1 and 3	485/196	DCV + SOF ± RBV	CTP stage B/C: 85–88%	–
French CUP[50]	Compensated and decompensated cirrhosis	GT-3	196	DCV + SOF ± RBV for 12/24 weeks	CTP stage B/C: 33–71%	–
Spanish study[51]	Decompensated cirrhosis	GT-1	739	SOF + SMV (45%), SOF + DCV (22%), and LDV/SOF (16%)	94%	–
Saxena et al. (2015)[39]	Compensated and decompensated cirrhosis	GT-1	160	SOF + SMV ± RBV	CTP stage B/C: 73%	–
Aqel et al. (2015)[52]	Compensated and decompensated cirrhosis	GT-1	119	SOF + SMV ± RBV	CTP stage B/C: 68%	–
Anand et al. (2017)[53]	Post-transplant recurrent HCV	GT-3 and 1	63	SOF + RBV for 24 weeks	–	93.7% (GT-1: 92.3%; GT-3: 95.9%)

Note: CTP: Child–Turcotte–Pugh; CUP: compassionate use program; DCV: daclatasvir; DSB: dasabuvir; EAP: early access program; FCH: fibrosing cholestatic hepatitis; GT: genotype; LDV: ledipasvir; LT: liver transplantation; PTV/rt + OMB: paritaprevir/ritonavir + ombitasvir; RBV: ribavirin; SMV: simeprevir; SOF: sofosbuvir; SVR: sustained virological response; VLP: Velpatasvir.

Pre-transplant therapy
(diminishing demand)

- The current second generation DAAs are well tolerated irrespective of disease stage
- SVR rates are lowest in decompensated cirrhosis with Genotype 3
- INF and RBV Ladder regimen (CPT $\leq$ 7) 25% SVR
- DAA SVR rates 56 – 93 % CPT $\geq$ 7 (SOF/LDV or SOF/VEL +/-RBV, SOF/DCV
- HVP and markers of these improve in ~25% in those with portal HT
- Predictors of progression: Obesity, alcohol,
- Transplant avoided in: 103 listed patients, 1/3rd inactivated, 19.2% delisted at 60 weeks, CPT <2pt, MELD < 3.4 pt in the 34 patients inactivated (MELD $\leq$ 20)

Impact of HCV treatment

- MELD and prediction for progression after clearance
  - 11 European centers between February 2014 and February 2015.
  - The cumulative incidence of inactivated and delisted patients was respectively
    - 15.5% and 0% at 24weeks
    - 27.6% and 10.3% at 48 weeks
    - 33.3% and 19.2% at 60 weeks
  - Thirty-four patients who were inactivated showed:
    - a median improvement of 3.4 points for MELD (delta MELD, P < 0.0001)
    - 2 points for CTP score (delta-CP, P < 0.0001)
  - A multivariate competing risk model as predictors of inactivation showed three significant variables:
    - baseline MELD classes (MELD 16–20: HR = 0.120; P = 0.0005, MELD >20: HR = 0.042; P < 0.0001)
    - delta MELD (HR = 1.349; P < 0.0001) after DAA therapy
    - delta albumin (HR = 0.307; P = 0.0069) after DAA therapy

Algorithm Guiding Therapy

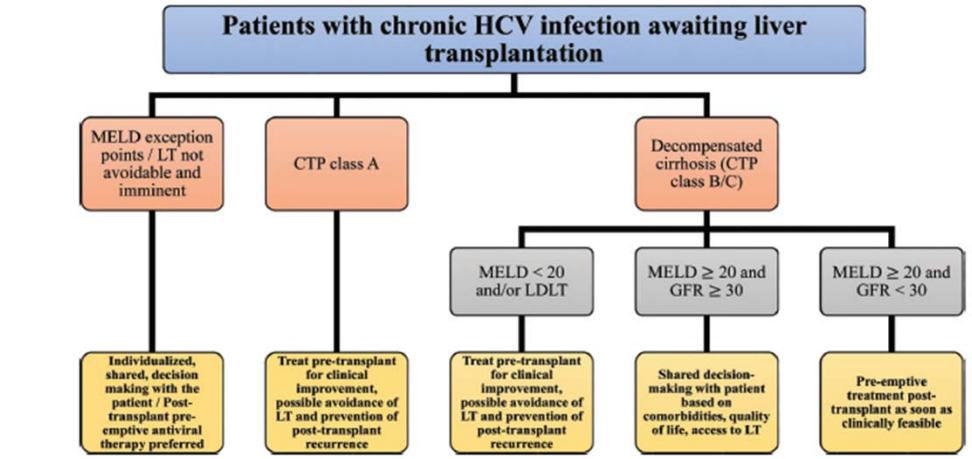


Fig. 1. Algorithm for treatment of HCV-infected liver transplant candidates.

Abbreviations: MELD, model for end-stage liver disease; LT, liver transplantation; CTP, Child-Turcotte-Pugh; LDLT, living donor liver transplantation; GFR, glomerular filtration rate.

Journal of Clinical and Translational Hepatology **2017** vol. 5 | 363–367 365

QUESTION: You are a 54 yo female on a Liver Transplant Waiting List. You have PSC with a dominant stricture that is FISH positive with concerning cytology for cholangiocarcinoma. Your MELD after biliary intervention is 12 (Delta 16). You just received an expedited local offer of a 33 yo sex worker who died with a needle in her arm. The offer is HCV NAT pos, HBV cAb pos and HIV NAT neg. AST and ALT peaked at 1000 and are falling (162 and 100 at procurement) BR 1.4. INR 1.3. imaging is normal. The OPO in Philadelphia refused to provide a pre-procurement liver biopsy and the late reallocation is because the local read shows S1/4 G 3/4 and 30% fat. You live in Chicago, you have BCBS insurance and you know a few sex workers from a previous job.

Should you:

- A. accept the organ outright
- B. declined the organ because you will receive better and more offers opportunities after you get your exception points of median MELD -3.
- C. Ask your hepatology friend to review the biopsy (quickly) and If he agrees on the read decline
- D. Ask your hepatology friend to review the biopsy (quickly) and If he agrees on the read accept
- E. Decline as you MELD is below 15 and transplant benefit, in particular in accepting high risk offers, is not present

Why do we consider HCV positive Donors for HCV negative patients?

Justification

Intermountain Healthcare

Circulation. 2016 Feb 9; 133(6): 601–609.
Published online 2016 Feb 8. doi: 10.1161/CIRCULATIONAHA.115.017719
PMCID: PMC4741409
PMID: 26858290

Introduction to the Analysis of Survival Data in the Presence of Competing Risks

Peter C. Austin, PhD,[✉] Douglas S. Lee, MD, PhD, and Jason P. Fine, PhD

- A competing events risk occur when the occurrence of one precludes the occurrence of the primary event of interest.
- - e.g., in a study in which the primary outcome was time to death attributable to a cardiovascular cause, death attributable to a non-cardiovascular is a competing event.
- In Liver Transplantation:
- We often encounter competing risk with the most notable:
  - Waiting list mortality/removal as compared to post-transplant survival

Intermountain Healthcare

What are we trying to address?

Balance Sheet

For Year Ending December 31, 2013

(all numbers in $000)

	2018	2017	2016	2015	2014	2013	2012	2011
ASSETS	17,566	16,467	15,946	15,069	14,416	14,258	14,010	14,149
Current Assets	10,722	10,286	9,971	9,079	8,596	8,269	8,143	8,126
Cash	6,844	6,181	5,975	5,990	5,820	5,989	5,867	6,023

Accounts receivable				$650
(less doubtful accounts)		-188		230
Inventory		150	Current portion of long-term notes	180
Temporary investment		10	Interest payable	45
Prepaid expenses		5	Taxes payable	30
Total Current Assets		$627	Accrued payroll	45
Fixed Assets			**Total Current Liabilities**	$1,180
Long-term investments		$400	**Long-term Liabilities**	
Land		889	Mortgage	$960
Buildings		506	Other long-term liabilities	450
(less accumulated depreciation)		-120	**Total Long-term Liabilities**	$1,410
Plant & equipment		447		
(less accumulated depreciation)		-200	**Shareholders' Equity**	
Furniture & fixtures		98	Capital stock	$400
(less accumulated depreciation)		-78	Retained earnings	-421
Total Net Fixed Assets		$1,942	**Total Shareholders' Equity**	($21)
TOTAL ASSETS		$2,569	**TOTAL LIABILITIES & EQUITY**	$2,569

HCV Donor Characteristics Over Time

- People Who Inject Drugs (PWID), more often acquire and also generally overdose leading to death in their first 5 years of use
- The current HCV + donor has a median age of ~ 32 years (c/w 46 years 10 years ago)
- Fibrosis is uncommon in donors, fat increased in obese and genotype 3
- Concurrent HBV cAb, sAb and sAg is seen more often in this group
- Excess alcohol consumption is not uncommon in donors

PHS Increased Risk

"increased risk" refers to the donor characteristics that could place the potential recipient at increased risk of disease transmission

PHS identified risk, deceased donors recovered during 2005-2015

Table 2: Estimated risk of window period infection (per 10,000 donors)

Risk per 10,000 donors	HIV ELISA	HIV NAT	HCV ELISA	HCV NAT
IV drug users	12.1 (0.12%)	4.9 (<0.1%)	300.6 (3%)	32.4 (0.32%)
Commercial sex worker	6.6 (<0.1%)	2.7 (<0.1%)	114.9 (1.2%)	12.3 (0.12%)
Blood product exposure	1.5 (<0.1%)	0.6 (<0.1%)	4 (<0.1%)	0.4 (<0.1%)

2005 2006 2007 2008 2009 2010

Year of Recovery

Intermou Healthcar

Affected Policies: None
Sponsoring Committee: OPTN/UNOS Ad-hoc Disease Transmission Advisory Committee
Public Comment Period: March 27, 2017 to April 25, 2017

What has been the change to utilization of these donors

- DNAT Donor NAT) -/R+ transplants decreased from 2010 in 2008 to 1334 in 2017, particularly noticeable since 2015.
- DNAT +/R- KTs increased from 1/month in 2015 to 22/month in 2018 (LTs: 0/month to 12/month).
- DNAT -/R+ patients in the DAA era (n = 7107) were older, had higher rates of hepatocellular carcinoma, and lower Model for End-Stage Liver Disease scores
- There were 11,270 $DNAT^-$ /R^- ; 4,748 $DNAT^-$ /R^+ ; 87 $DNAT^+$ /R^- ; and 753 $DNAT^+$ /R^+ patients, with 2-year graft survival similar across all groups: $DNAT^-$ /R^- 88%; $DNAT^-$ /R^+88%; $DNAT^+$ /R^- 86%; and $DNAT^+$ /R^+ 90%.
- It is important to note that D Ab +, DNAT – in one small series had recipient transmission occur in 16%

Use of Organs From Hepatitis C Virus-Positive Donors for Uninfected Recipients: A Potential Cost-Effective Approach to Save Lives?

Patrick B. Trotter, MBChB,[1,2] Dominic M. Summers, PhD,[1,2] Ines Ushiro-Lumb, MSc,[2] Matthew Robb, PhD,[2] J. Andrew Bradley, PhD,[1] James Powell, MD,[3] Christopher J.E. Watson, MD,[1] and James Neuberger, DM[4]

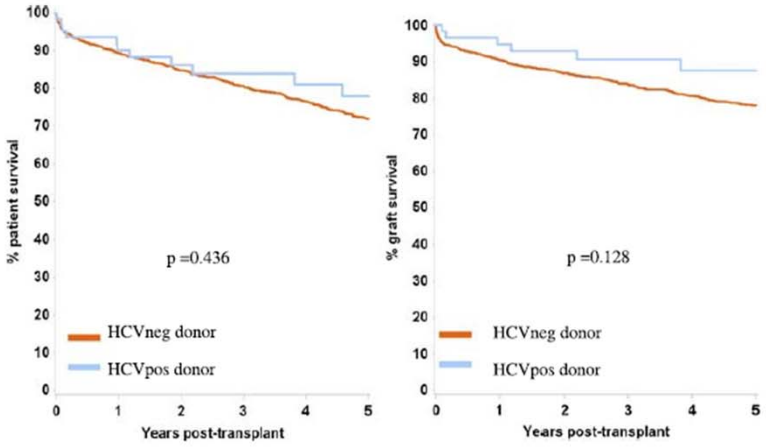
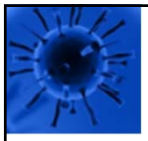
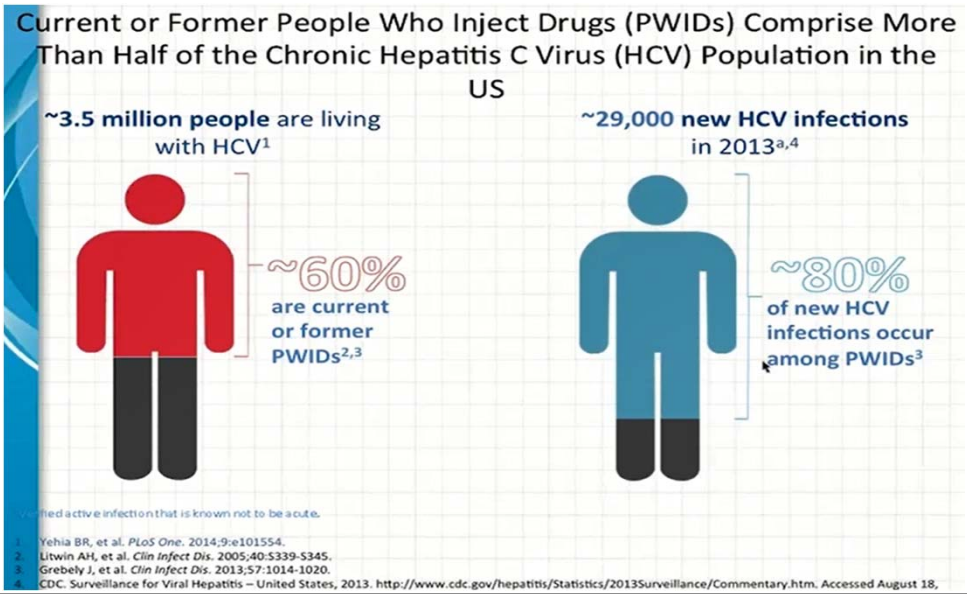


FIGURE 2. Patient survival and death censored graft survival of recipients who received livers from HCVneg donors compared with those who received livers from HCVpos donors.

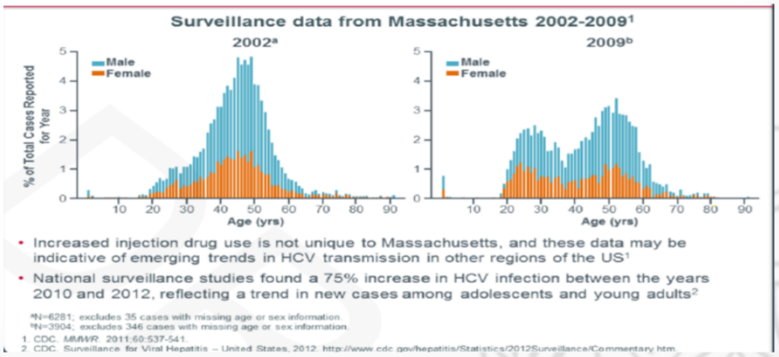
HCV Donor characteristics over time and why greater donor potential exists



Hepatitis C



Increased Injection Drug Use In Adolescents and Young Adults is Shifting the US HCV Demographic



- Increased injection drug use is not unique to Massachusetts, and these data may be indicative of emerging trends in HCV transmission in other regions of the US[1]
- National surveillance studies found a 75% increase in HCV infection between the years 2010 and 2012, reflecting a trend in new cases among adolescents and young adults[2]

[a]N=6281; excludes 35 cases with missing age or sex information.
[b]N=3904; excludes 346 cases with missing age or sex information.
1. CDC. *MMWR*. 2011;60:537-541.
2. CDC. Surveillance for Viral Hepatitis – United States, 2012. http://www.cdc.gov/hepatitis/Statistics/2012Surveillance/Commentary.htm

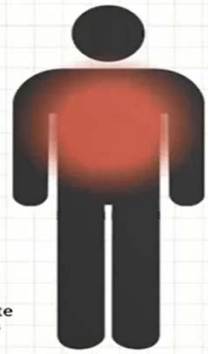
HCV Transmission Among PWIDs

HCV transmission is highly efficient among PWIDs, with young injectors frequently acquiring HCV soon after transitioning to injection.[1]

Host Factors
Propensity of young/new PWIDs to share needles and syringes[1]

Viral Factors
- HCV can survive outside the body on inanimate surfaces, cookers, and filters for days, and longer in the barrel of a syringe[2-4]
- In controlled healthcare environments, HCV is transmitted at up to a 10-fold rate relative to HIV following needle sticks[5,6]

PWIDs in the US



1. Greater percentage genotype 3
2. ^80% 17-35 years of age
3. Greater percentage than before are women !!
4. Distribution of disease to the Coasts and Midwest with an epicenter West Virginia

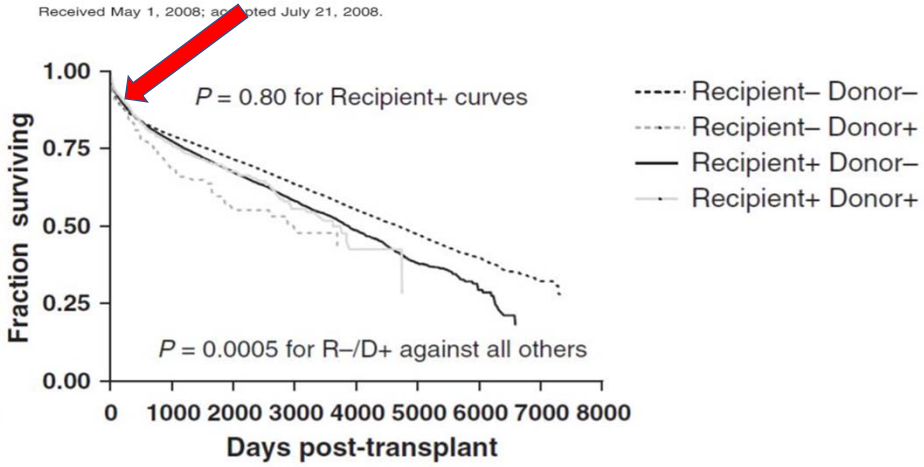
HIV = human immunodeficiency virus.
DHHS Young PWID Consultation Report. Feb 26-27, 2013.
Paintsil E, et al. *J Infect Dis*. 2010;202:984-990.
Doerrbecker J, et al. *J Infect Dis*. 2011;204:1830-1838.
4. Doerrbecker J, et al. *J Infect Dis*. 2013;207:281-287.
5. Beltrami EM, et al. *Clin Microbiol Rev*. 2000;13:385-407.
6. Chen JY, et al. *Nat Rev Gastroenterol Hepatol*. 2014;11:362-371.
7. DHHS Action Plan 2014-16. February 2014.

Outcomes of an Uncontrolled/Exploratory Action

Risk of Extended Criteria Donors in Hepatitis C Virus–Positive Recipients

Marina Berenguer
Hepatology, Hospital Universitario La Fe, Valencia, Spain; and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Spain

Received May 1, 2008; accepted July 21, 2008.



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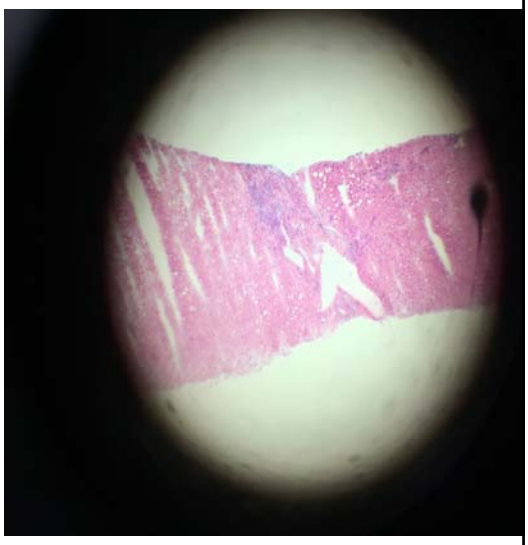
Where we see common Barrier between HCV and Transplantation Rx

Table 1 Most common barriers to engagement of persons who inject drugs into care for hepatitis C virus infection

Domain	Specific barrier
Patient-level	Low perceived treatment need
	Fear of side effects
	Lack of knowledge of serostatus
	Fear of liver biopsy
	Needles may promote relapse
	Coexisting mental health diagnosis
	Lack of insurance, poverty, low socioeconomic status
Physician-level	Concerns about reinfection
	Biases against PWID
	Adherence concerns
	Dual diagnoses
Health system-level	Navigation can be complex
	Mistrust between PWID and medical community
	High cost of HCV treatment
	Stigmatization in health care venues

Donor Histology

- Inflammation is expected and largely ignored
- Fat is not uncommon, in particular in genotype 3 (accept up to 50%)
- Fibrosis is what matters and trichrome is generally not available
- 2 cm core, 15 guage and at least 14 portal tracts
- Don't expect to get histology from some OPOs
  - Dry runs
- Be able to read pathology as local reads often overcall



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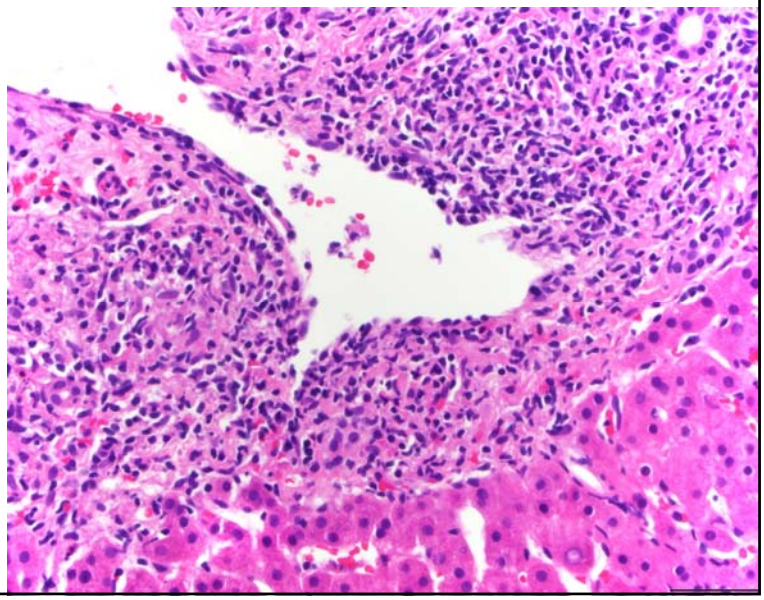
Day 55 Post-Transplant 38 year old Male

- Immunosuppression at target
- ALT rising to ~600 and AST ~300 with Alk Phos then rising
- Normal BR
- Biopsy



Current Protocols

Post-transplant HCV treatment	
Genotypes 1,4,5,6	
Once daily ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks
Once daily sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)a	12 weeks
Genotypes 2 and 3	
Once daily sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)a	12 weeks
(Note: In instances where a history of DAA failures exist, please refer to the most recent guidelines at www.hcvguidelines.org for guidance on treatment selection)	

- Adapted from HCVguidelines.com

Intermountain Healthcare

Post-OLT Graft Function

- 5/17 patients diagnosed with mild ACR
  - Treated with increase in CNI if below target
  - Rx delayed likely a reason for these rises
  - two patients post-treatment re-developed abnormal Liver Enzymes
    - Steroid responsive c/w alloimmune hepatitis
- Currently all patients with excellent graft function to date
  - Average tbili 0.5/AST 24/ALT 23 (for pts that have completed Rx)
  - No occurrences of cholestatic HCV

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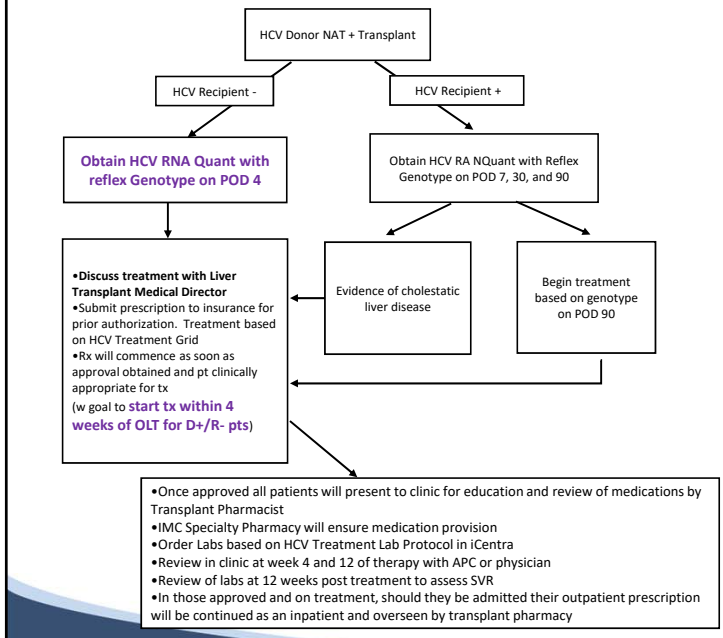
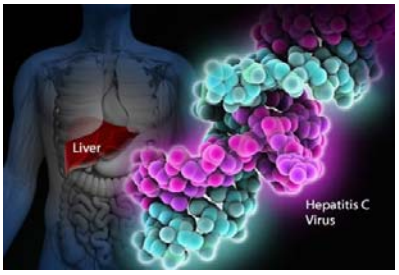
Intermountain Medical Center HCV Treatment Protocol Algorithm





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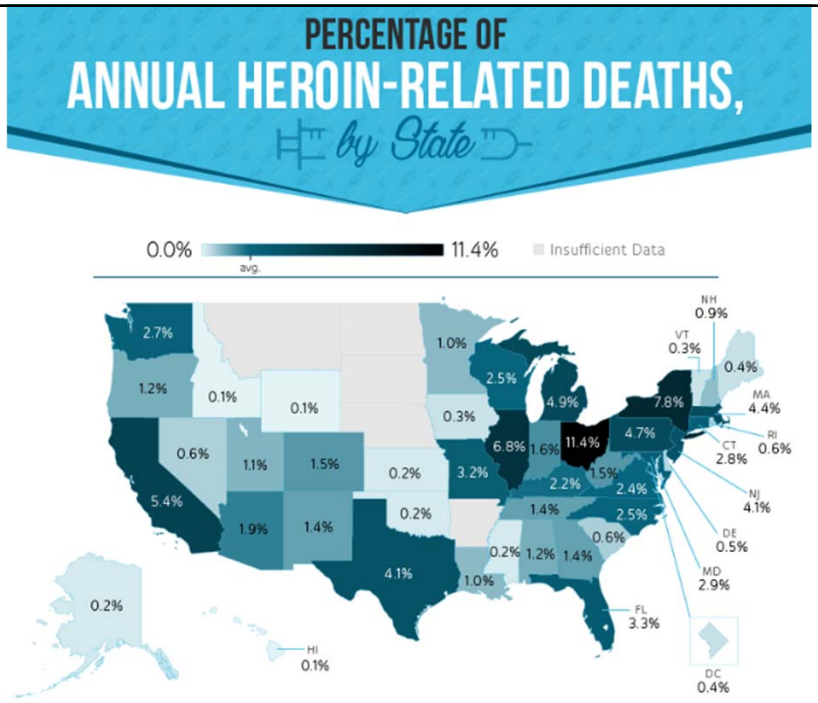
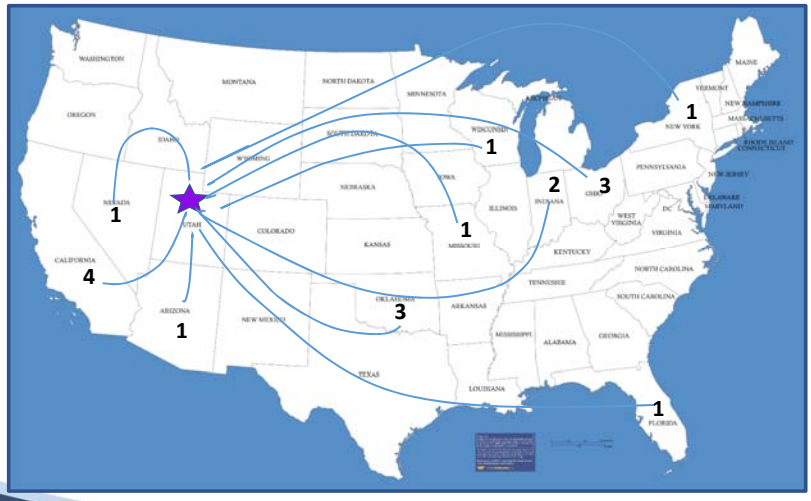


Originating Donor OPO



<u>16 Organs</u>

10 National Offers

6 Regional Offers

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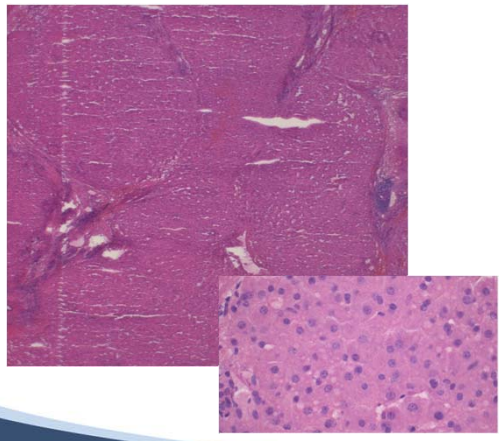
Impact On Staff/Process

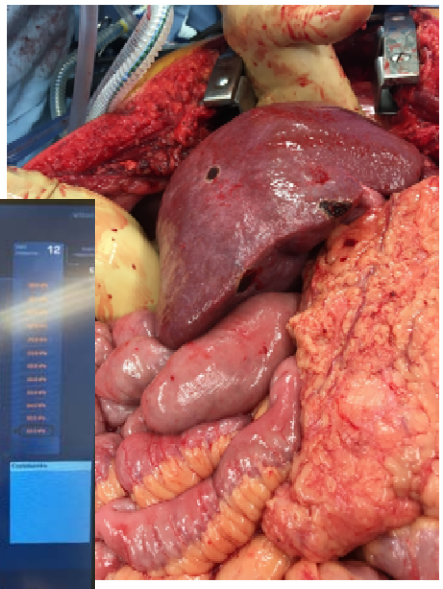
- Significant increase in call burden
  - 2 physician discussion with biopsy slide and CT reviews and 2 person accept or decline
    Increase in travel frequency
  - DSA – 51% w avg flight time of 1.2-2 hrs
    - Cost ~ $15,000
  - HCV D+/R- donor group - 100% w flight times 3-4.5 hours one way, excluding ground travel and fuel stop (East coast)
    - Cost ~$32,000 (charter $60,000-120,000)

Intermountain Healthcare

Impact On Staff/Process

- Increased dry run fly outs (n=3)
  - Avg annual fly out dry run 2-3/yr





Intermountain Healthcare

What Ended Up As Likely A World First Approach

Intermountain among first in U.S. to use diseased livers for transplant

By Daphne Chen @DaphneChen_
Published: Dec. 13, 2016 2:45 p.m.

2 Comments

1 of 8

Liver and Kidney Recipient Selection of HCV-Infected Donors – Meeting Consensus Report from 2019 Controversies in Transplantation

James R. Burton, Jr., David Goldberg, Roy Bloom, Norah Terrault, Richard Gilroy, Julie Heimbach, Robert Brown, Gregory Everson, Erin Rubin, Russ Wiesner and Elizabeth Pomfret

Bottom Line

- The incidence of CLD is increasing and not decreasing
- Indications for Liver Transplant continue to expand
  - Older recipients
  - Recipients with greater comorbidities
  - Metabolic hepatitis
- New Allocation systems which create new disparities
  - Cholangiocarcinoma underserved
  - Regional disparity in access to MELD exceptions remains

EVERY CLOUD HAS A SILVER LINING

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The Genomics Revolution

SEPTEMBER 20–21, 2019
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Program Chairs:

Richard J. Thompson, MD, PhD
Kathleen M. Loomes, MD, FAASLD

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Philippe Mathurin, MD, PhD
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Mark Thursz, MD

Scientific Program Advisor

Vijay Shah, MD, FAASLD

This meeting will bridge critical gaps in ALD diagnosis, management and clinical trial design. Speakers will present evidence-based knowledge on ALD's potential triggers, the role of alcohol dependence, various stages of disease, gender differences, and potential biomarkers for diagnosis, disease severity and prognosis. The program will provide guidance on ways to create effective multidisciplinary teams to manage ALD patients.

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