AT THE FOREFRONT
UChicago Medicine

THE UNIVERSITY OF CHICAGO
Section of Gastroenterology, Hepatology & Nutrition and the Transplant Institute

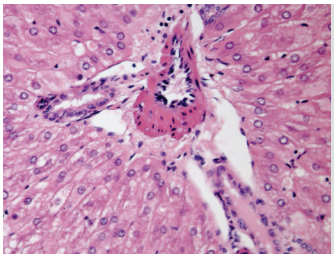
AT THE FOREFRONT OF HEPATOLOGY

CONFERENCE CO-DIRECTORS
Andrew Aronsohn, MD
Anjana A. Pillai, MD
Michael Charlton, MD
John J. Fung, MD, PhD

GLEACHER CENTER
450 North Cityfront Plaza Dr.
Room 100
Chicago, IL 60611

cme.uchicago.edu/hepatology2019

MAY 4 2019



AT THE FOREFRONT OF HEPATOLOGY

University of Chicago Gleacher Center

May 4, 2019

DESCRIPTION

The goal of this educational intervention is to provide up-to-date evidence-based education in the diagnosis and management of liver diseases that will help healthcare professionals improve patient care.

TARGET AUDIENCE

This activity is designed for physicians and other healthcare professionals dedicated to the diagnosis and management of liver diseases.

LEARNING OBJECTIVES

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

- *Discuss how to implement up-to-date evidence-based medicine in the diagnosis and treatment of liver diseases;*
- *Describe the role of emerging technologies for medical and surgical management of liver diseases;*
- *Analyze treatment strategies for hepatocellular carcinoma;*
- *Summarize the diagnosis and treatment options for different types of hepatitiss;*
- *Assess new and emerging therapies for liver diseases;*
- *Identify how to apply new knowledge to challenging cases in hepatology.*

ACCREDITATION AND CREDIT DESIGNATION

Physician Credit

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

The University of Chicago Pritzker School of Medicine designates this live activity for a maximum of 4 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nursing Credit

The University of Chicago Medicine is an approved provider of continuing nursing education by the Ohio Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation. (OBN-001-91).

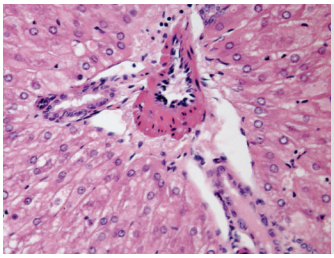
This live activity has been approved for a maximum of 4 nursing credit hours.

American Board of Internal Medicine MOC Part II Credit

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 4 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Other Healthcare Professions Credit

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



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EDUCATIONAL GRANTS/COMMERCIAL SUPPORT

Educational grant funding has been generously provided by:

BTG International Inc.

Genzyme Corporation

Gilead Sciences Inc.

We would also like to thank our exhibitors:

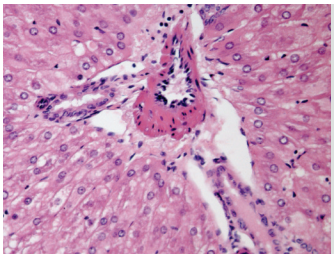
Abbvie

American Liver Foundation, Great Lakes Division

Bayer Oncology

Gilead Sciences Inc.

Novartis



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DISCLOSURE DECLARATIONS

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

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

COURSE FACULTY AND PLANNERS

The following individuals have disclosed no relevant financial relationships:

Andrew Aronsohn, MD
Talia Baker, MD
Diego DiSabato, MD
John Fung, MD, PhD
Michael R. Lucey, MD
Amy Majkowski
Sonali Paul, MD, MS
Kimberly Vlodek, MSN
Steven Zangan, MD

Kimberly A. Brown, MD has received research funding from Gilead, Novartis, Conatus, Allergan, and Novonordisk. Dr. Brown has served on the advisory board for Gilead and Pfizer and on the speakers bureau for Gilead.

Michael R. Charlton, MBBS has served as a consultant for Gilead, Bristol Myers, Novartis, NGM Bio, Lipocene, Metacrine, and Intercept and has received research support from Gilead, Bristol Myers, Novartis, NGM Bio, Lipocene, Metacrine, Northsea, and Intercept.

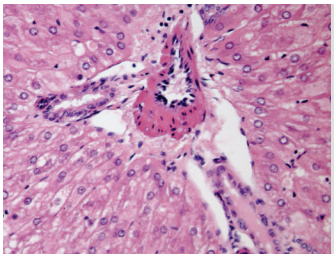
Anjana A. Pillai, MD has served as a speaker for BTG, Inc. and Eisai, Inc. and on the advisory board for Wako Diagnostics.

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

DISCLAIMER

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

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



AT THE FOREFRONT OF HEPATOLOGY

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May 4, 2019

CONFERENCE FACULTY

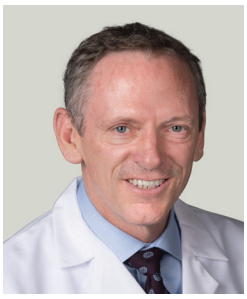
Course Directors

Andrew Aronsohn, MD

Associate Professor of Medicine

Director, GI Telehealth

Chair, Digestive Diseases Alumni Committee

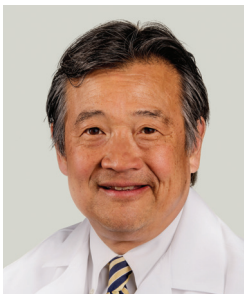


Michael Charlton, MD, FRCP

Professor of Medicine

Medical Director, Transplantation Institute

Director, Center for Liver Diseases



John J. Fung, MD, PhD

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Co-Director, Transplantation Institute

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Associate Professor of Medicine

Medical Director,
Liver Tumor Program

Associate Director, Gastroenterology, Hepatology & Nutrition Fellowship Program

University of Chicago Speakers and Planning Committee

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Director, Living Donor Liver Transplant Program

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Surgical Director, Living Donor Liver Transplant Program

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Director, Metabolic and Fatty Liver Clinic

Kimberly Vlodek, MSN, RN

Nurse Associate

Steven Zangan, MD

Associate Professor of Radiology

Associate Program Director, Interventional Radiology Residency

Invited Speakers

George Behrens, MD

Interventional Radiologist

Portal Hypertension Clinic and Liver Diseases

Vascular and Interventional Professionals

Hinsdale, IL

Kimberly A. Brown, MD

Chief, Division of Gastroenterology and Hepatology

Henry Ford Health System

Claus J. Fimmel, MD

Clinical Professor

Northshore Medical Group

Michael R. Lucey, MD

Professor of Medicine

Chief, Division of Gastroenterology and Hepatology

Medical Director, UW Liver Transplant Program

Co-Medical Director, Digestive Health Center

University of Wisconsin School of Medicine and Public Health

Dhiren A. Shah, MD

Clinical Assistant Professor of Medicine

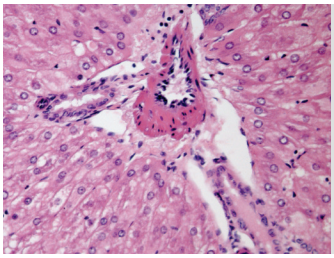
Northshore Medical Group

CONFERENCE AGENDA

SATURDAY, MAY 4, 2019

7:30am	**Breakfast/Registration**
8:00	**Welcome** Andrew Aronsohn and Anjana Pillai
	Session I **Moderator:** Michael Charlton
8:10	**Downstaging for Hepatocellular Carcinoma** Anjana Pillai
8:30	**Treatment of Decompensated HCV Cirrhosis** Andrew Aronsohn
8:50	**Hepatitis B Reactivation and Special Populations** Sonali Paul
9:10	**Panel Discussion** Pillai, Aronsohn and Paul
9:35	**Break**
	Session II **Moderator:** Andrew Aronsohn
9:50	**All Roads Lead to Fatty Liver Disease** Michael Charlton
10:10	**Living Donor Liver Transplantation** Diego DiSabato
10:30	**Interventional Radiology for Portal Hypertension** Steven Zangan
10:50	**Panel Discussion** Charlton, DiSabato and Zangan
11:15	**Break**
	Session III **Moderator:** Anjana Pillai
11:30	**Alcoholic Hepatitis and Liver Transplantation** Michael Lucey
11:50	**Transplant Out of the Box** John Fung
12:10 pm	**Too Sick for Liver Transplantation?** Kimberly Brown
12:30	**Panel Discussion** Lucey, Baker, Brown and Fung
12:55	**Closing Remarks**
1:00	**Lunch Breakout Sessions** Claus Fimmel, George Behrens and Dhiren Shah (Lunch on 6th floor, Room 621)

Agenda and speaker selection subject to change.



Downstaging for Hepatocellular Carcinoma

Anjana Pillai

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Digestive Diseases Center

Downstaging for HCC

Anjana A. Pillai, MD
Associate Professor of Medicine
Medical Director, Liver Tumor Program
University of Chicago Medicine

Disclosures

- Speaker's Bureau for: Simply Speaking Hepatitis, BTG, Inc. and Eisai, Inc.
- Medical advisory board: Wako Diagnostics

- I will not discuss off label use or investigational use in my presentation.

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Hepatocellular carcinoma is 4th leading cause of cancer-related death worldwide

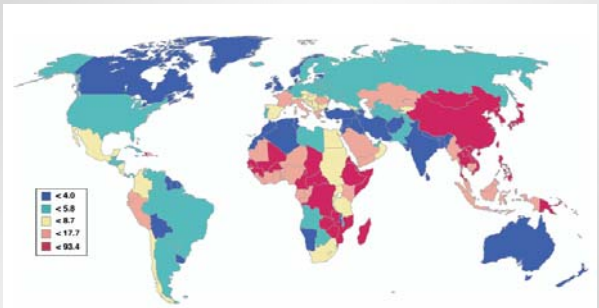

Figure 1. Regional variations in the mortality rates of HCC categorized by age-adjusted mortality rates. The rates are reported per 100,000 persons.

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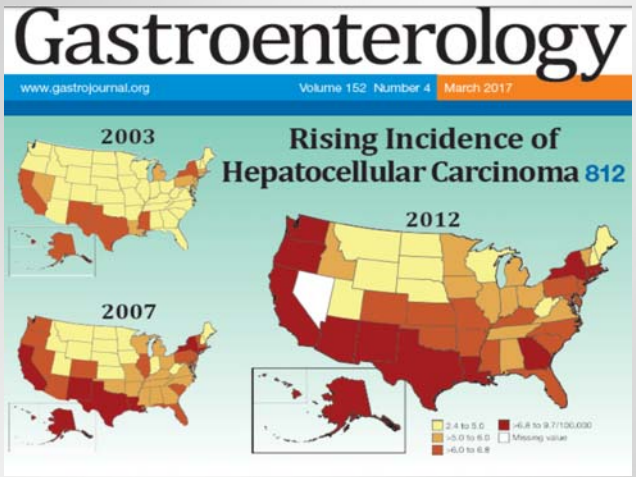
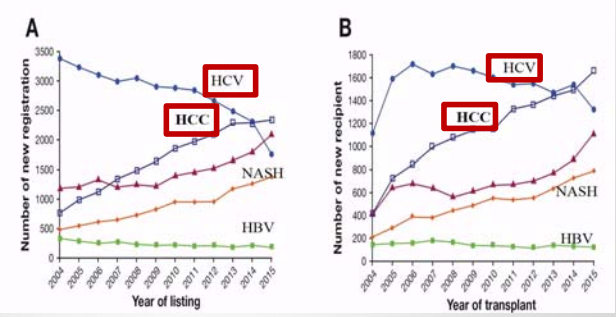
El-Serag H, Rudolph KL. Gastro 2007; 132:2557-2576



LT wait list registrants and recipients in US 2004-2015



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Yang JD, et al. Clin Gastro and Hep 2017

Unique Benefits of LT for HCC

- Chance of cure for the cancer
- Chance of cure for the underlying field defect

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Patient Case

- 61 yo Japanese man with HCV cirrhosis presents to local ER with abdominal pain. He underwent cross sectional imaging which showed a 6.5 cm lesion in segment 6 of the liver consistent with HCC with no other evidence of vascular invasion or other lesions. His AFP is 200.
- What is acceptable downstaging criteria for liver transplant?

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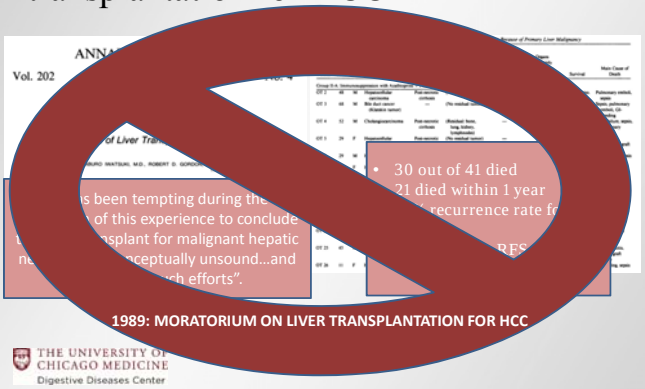
The swinging pendulum of liver transplantation for HCC



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Milan Criteria

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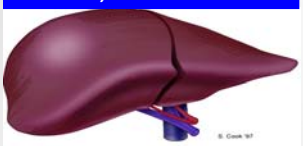
Milan Criteria

1 lesion ≤ 5 cm

3 lesions, none > 3 cm



48 patients
No evidence of extrahepatic spread

Adopted by UNOS for expedited work-up for HCC pts in 2002

with > 1000 patients
5 yr survival >70%
Recurrence < 15%

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Mazzoferro et al N Engl J Med 1996;334(11):693-9.

UCSF Criteria

Liver Transplantation for Hepatocellular Carcinoma: Expansion of the Tumor Size Limits Does Not Adversely Impact Survival

Francis Y. Yao,[1,5] Linda Ferrell,[2,5] Nathan M. Bass,[1,5] Jessica J. Watson,[3] Peter Bacchetti,[3,5] Alan Venook,[1,5] Nancy L. Ascher,[4,5] and John P. Roberts[4,5]

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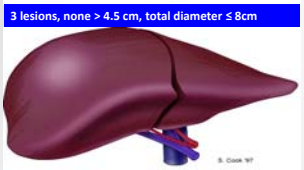
Yao et al. *Hepatology* 2001;33(6):1394-403.

UCSF Criteria

1 lesion ≤ 6.5 cm

3 lesions, none > 4.5 cm, total diameter ≤ 8cm



- *No evidence of vascular invasion*
- *No evidence of extrahepatic spread*
- *Based on <u>explant</u> pathology*
- *1 and 5 year survival – 90% and 75%*
- *1 year survival 50% in patients outside UCSF criteria*

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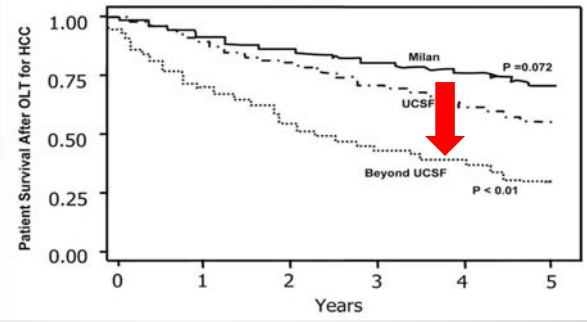
Yao et al. *Hepatology* 2001;33(6):1394-403.

Survival Following OLT for HCC: Milan and UCSF criteria



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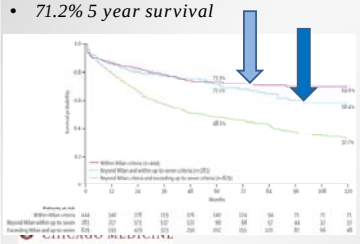
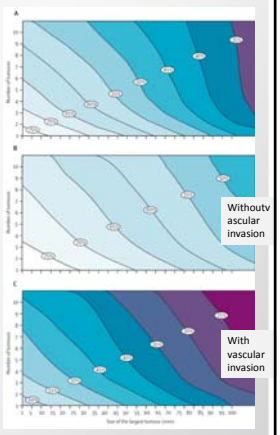
Yao, Liver Transplantation 8:769, 2002
Duffy JP, Ann Surg 2007; 246:502

"Up to 7" Criteria

- *Criteria: 7 as sum of largest tumor (cm) diameter and number of tumors*
- *Retrospective survey of 1112 LT for HCC exceeding Milan, compared to 444 within Milan*
- *71.2% 5 year survival*





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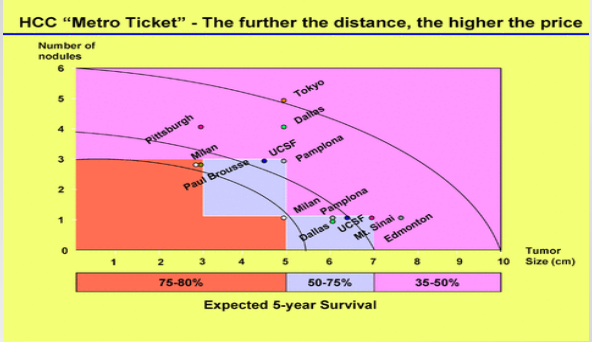
Mazzaferro V, Lancet Oncol 2009; 10:35

The Original METRO ticket



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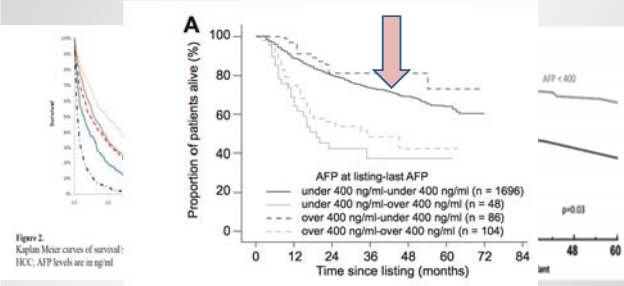
AFP and its role: *Has been shown to be an important prognostic marker for recurrence risk in the setting of liver transplant*



Tyson et. al. Clin Gastro and Hep 2011

Dubay et al. Ann Surgery 2011
Merani et al. JI of Hepatology 2011

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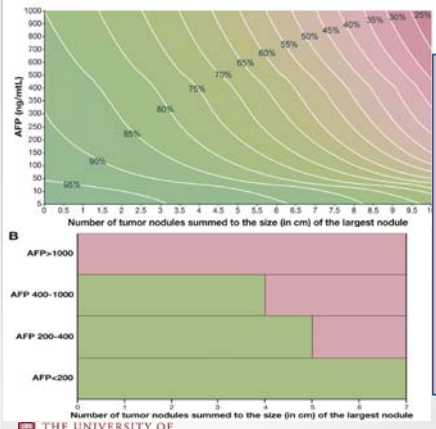

- *Metroticket 2.0*
- *1018 patients who underwent liver transplantation for HCC from January 2000 through December 2013 at 3 tertiary centers in Italy*
- *validated from 341 patients from a single center in Shanghai, China*

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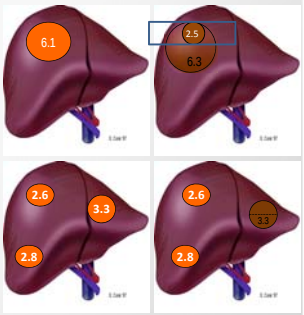
Mazzaferro V, et al. Gastro 2018

"Downstaging"

- *Inclusion criteria:*
  - *tumor size/number, AFP, tumor grade*
- *Type of therapy to downstage*
- *Criteria for response:*
  - *within Milan, degree of necrosis, decline in AFP/DCP*
- *Mandated period of observation to determine success of downstaging procedure*
  - *3 vs. 6 months*



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HEPATOLOGY

AASLD

PRACTICE GUIDELINE | HEPATOLOGY, VOL. 67, NO. 1, 2018

AASLD Guidelines for the Treatment of Hepatocellular Carcinoma

Julie K. Heimbach,[1] Laura M. Kulik,[2] Richard S. Finn,[3] Claude B. Sirlin,[4] Michael M. Abecassis,[5] Lewis R. Roberts,[6] Andrew X. Zhu,[7] M. Hassan Murad,[8] and Jorge A. Marrero[9]

Role of downstaging			
17. Transplantation may be considered after successful downstaging		5 (P)	Weak
18. Liver transplantation after successful downstaging should achieve a 5-year survival comparable to that of HCC patients who meet the criteria for liver transplantation without requiring downstaging		5 (P)	Strong
19. Criteria for successful downstaging should include tumour size and number of viable tumours		4 (P)	Strong
20. α-fetoprotein concentrations before and after downstaging may add additional information		4 (P)	Weak
21. Based on existing evidence, no recommendation can be made for preferring a specific locoregional therapy for downstaging over others		NA	None

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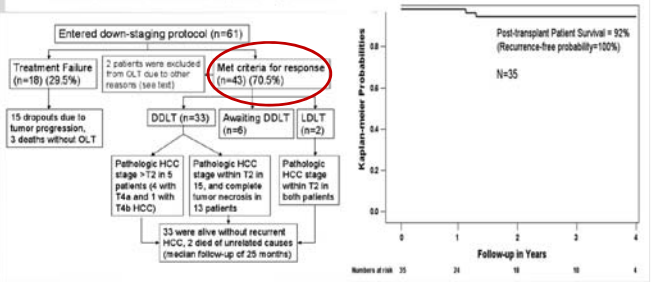
Excellent Outcome Following Down-Staging of Hepatocellular Carcinoma Prior to Liver Transplantation: An Intention-to-Treat Analysis

Francis Y. Yao,[1,2] Robert K. Kerlan, Jr.,[1] Ryutaro Hirose,[2] Timothy J. Davern III,[1] Nathan M. Bass,[1] Sandy Feng,[2] Marion Peters,[1] Norah Terrault,[1] Chris E. Freise,[2] Nancy L. Ascher,[2] and John P. Roberts[2]



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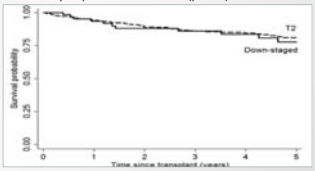
Yao et al Hepatology 2008

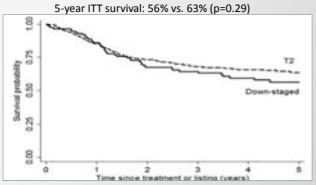
Downstaging can result in good outcomes

- Prospective cohort study comparing 118 patients in downstaging protocol to 488 patients meeting Milan
  - One lesion 5-8 cm; 2-3 lesions 3-5 cm, or 4-5 lesions each < 3cm, with total tumor volume <8cm
- 1-year waitlist drop-out: 24% vs. 20%
  - Predictors of drop-out included AFP > 1000 ng/mL and Child B cirrhosis (vs. Child A)

5-year post OLT: 78% vs.81% (p=0.69)



5-year ITT survival: 56% vs. 63% (p=0.29)

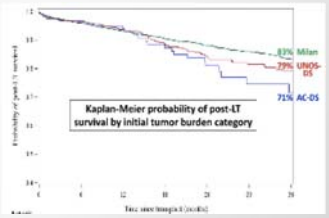


Yao et al Hepatology 2015

Downstaging can result in good outcomes

- Analysis of UNOS database comparing Milan (n=3276) vs. UNOS-downstage criteria (n=422) vs. tumors beyond UNOS-downstage criteria (n=121)
  - UNOS-DS same as prior study
  - Latter groups required downstaging to T2
- 3-year post-OLT survival in UNOS-DS patients differed by region
  - 92% for long wait-time regions vs. 73-79% for medium and short wait time regions

UNOS-DS vs. Milan: p=0.17
Beyond UNOS-DS vs. Milan: p=0.04



Mehta et al. AASLD 2008

Downstaging for transplant criteria

- Eligibility for downstaging protocol:
  - One lesion >5 cm and ≤8 cm
  - Two or three lesions each <5 cm and total diameter of all lesions ≤8 cm
  - Four or five lesions *each <3 cm and total diameter of all lesions ≤8 cm*
- *Candidates who are eligible and then complete locoregional therapy must be successfully downstaged into T2 (Milan) criteria to receive a MELD exception* ***without need for special case.***

Mehta et al. AASLD 2008

Conclusions

- Increasing incidence of hepatocellular carcinoma (HCC)
- Unique benefits of liver transplantation (LT) for HCC
- There *IS* a role for AFP as a prognostic marker for recurrence risk in setting of liver transplant
- Patients outside Milan criteria can be downstaged successfully with excellent outcomes with LT so referral to a transplant center is KEY!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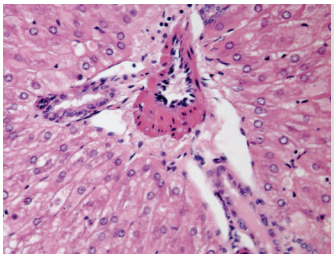
apillai1@medicine.bsd.uchicago.edu
Give thanks. Give life



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Treatment of Decompensated HCV Cirrhosis

Andrew Aronsohn MD
Associate Professor of Medicine
University of Chicago

Disclosures

- I have no relevant financial relationships to disclose
- I will not discuss of label use or investigational use in my presentation

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Case

- DW is 55 year old with Genotype 1b HCV who is naïve to treatment. Staging via fibroscan reveals cirrhosis. She has no evidence of decompensation. EGD is normal. CTP score is A. MELD score is 8.

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Case

- Which of the following is true?
- 1. This patient should be referred to a transplant center prior to treatment
- 2. If she is cured, she can discontinue HCC screening
- 3. Ribavirin will be necessary for most regimens in cirrhosis
- 4. Glecaprevir / pibrentasvir x 12 weeks would be a safe and effective regimen to treat her

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Objectives

- Defining decompensated cirrhosis
- Treatment options
- Outcomes of treatment
- To transplant or not to transplant (that is the question)

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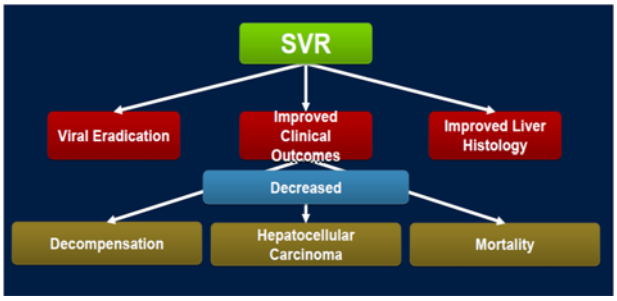
Treatment Outcomes after Sustained Virologic Response (Cure)



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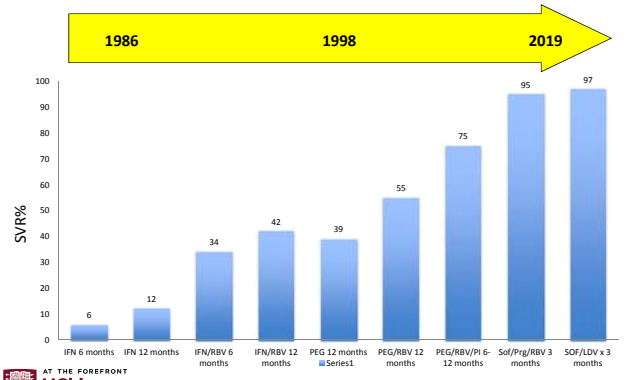
Timeline of HCV Therapeutics



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Currently Available DAAs

DAA Class	Sofosbuvir/ Velpatasvir/ Voxilaprevir	Sofosbuvir/ Velpatasvir	Sofosbuvir/ Ledipasvir	Glecaprevir/ Pibrentasvir	Elbasvir/ Grazoprevir
Protease Inhibitor	X			X	X
NS5A inhibitor	X	X	X	X	X
Nucleoside Polymerase Inhibitor	X	X	X		

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Big Questions in HCV and Cirrhosis

- What are the treatment options for patients with cirrhosis?
- Who should be treated by non hepatologists?
- When is a patient too sick to be treated?

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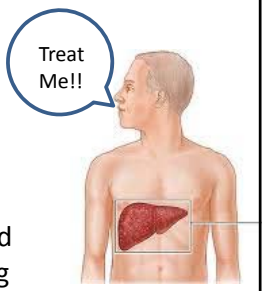
Compensated Cirrhosis

- Treatment options are essentially the same
- May be some differences in duration of therapy
- Protease inhibitors OK
  - But only for use in Childs A
- In most cases can be treated outside of transplant setting



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One Stop Shopping…

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Treatment in Noncirrhotic vs Cirrhotic

No Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:
Treatment-Naive Genotype 1a Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs* for elbasvir	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)†	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are non-black, HIV-uninfected, and whose HCV RNA level is <6 million IU/mL	8 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A

Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:
Treatment-Naive Genotype 1a Patients With Compensated Cirrhosis*

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs* for elbasvir	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)†	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A

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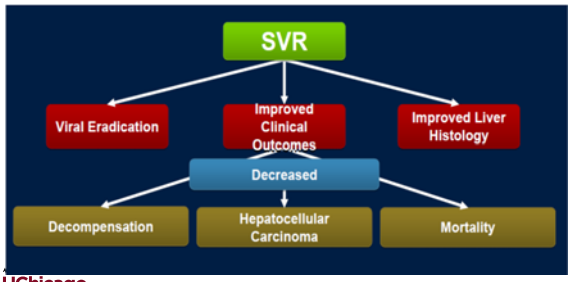
Treatment Effect in Cirrhosis



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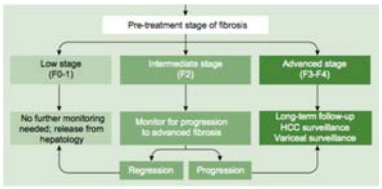
Post Treatment Management



Terrault J Hep 2016

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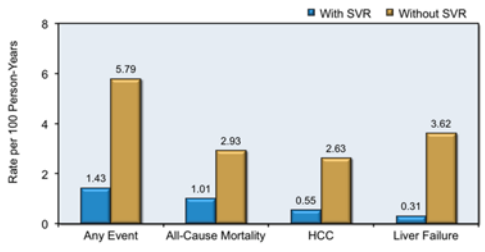
Benefits of Treatment



Van der Meer et al JAMA 2012

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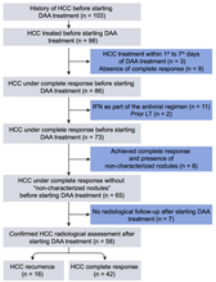
Controversy: HCV Treatment and HCC



- Hypothesis: immune dysregulation
- Highly effective DAA therapy eradicates HCV but may dismantle the immune "brake" on HCC

Reig et al 2016 J Hep

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Survival Free of HCC Recurrence

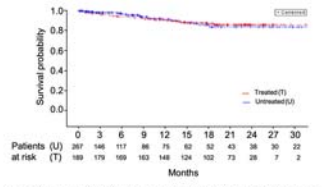

Fig. 2. Recurrence of HCC according to DAA treatment in the ANRS CO22 HEPATHER cohort. Pseudo-survival curves were plotted for time-dependent DAA treatment.

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Case #2

- WR is a 62 year old with HCV genotype 2 who is a nonresponder to interferon based therapy. She has no encephalopathy and mild ascites which is controlled with low dose lasix and aldactone. Bilirubin= 2.7, Albumin 2.2, INR = 2. Creatinine 1.1 Sodium 129

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Case 2

- What is this patients Childs Classification?
- 1. A
- 2. B
- 3. C
- 4. D

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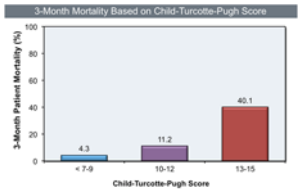
Childs-Turcotte-Pugh Review

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
	Points*		
	1	2	3
Encephalopathy	None	Grade 1-2 (or precipitant induced)	Grade 3-4 (or chronic)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
INR	<1.7	1.7-2.3	>2.3
*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)			
Class A = 5 to 6 points (least severe liver disease)			
Class B = 7 to 9 points (moderately severe liver disease)			
Class C = 10 to 15 points (most severe liver disease)			



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https://www.hepatitisc.uw.edu/page/clinical-calculators/ctp

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Case 3 Continued

- Would you…
- 1. Treat this patient
- 2. Refer the patient to a transplant center
- 3. Arrange for palliative care / hospice services

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Childs B and C

Recommended for All Patients With HCV Infection Who Have Decompensated Cirrhosis	
RECOMMENDED	RATING
Patients with HCV infection who have decompensated cirrhosis—moderate or severe hepatic impairment, ie, Child-Turcotte-Pugh (CTP) class B or class C—should be referred to a medical practitioner with expertise in that condition, ideally in a liver transplant center.	I, C

www.hcvguidelines.org

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Avoiding Protease Inhibitors in Decompensated Cirrhosis

Regimens not recommended for: Patients With Decompensated Cirrhosis (Moderate or Severe Hepatic Impairment; Child-Turcotte-Pugh Class B or C)	
NOT RECOMMENDED	RATING
Paritaprevir-based regimens	III, B
Simeprevir-based regimens	III, B
Elbasvir/grazoprevir-based regimens	III, C
Glecaprevir/pibrentasvir	III, C
Sofosbuvir/velpatasvir/voxilaprevir	III, C

www.hcvguidelines.org

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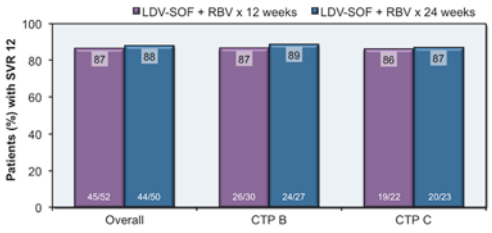
Treatment In Decompensated Cirrhosis: SOLAR 1



Chalrton et al Gastroenterology 2015

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Patients, n (%)	CTP B + C (n=215)
Any AE	208 (97)
Grade 3–4 AE	51 (24)
Serious AE	61 (28)
Serious treatment-related AE	5 (2)
AE leading to D/C of LDV/SOF	9 (4)
Death	10 (5)
Liver transplantation	11

- Treatment-related SAEs were mostly related to RBV treatment
- Deaths and AEs that led to D/C of LDV/SOF were not attributed to study treatment

Samuel D, et al. EASL 2015, P0774

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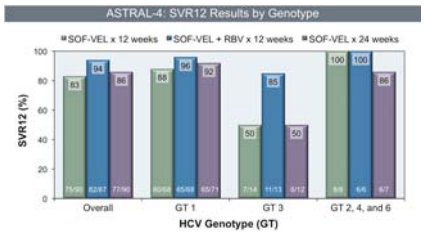

- Open-label, randomized (1:1:1) US study (NCT02201901)
- HCV GT 1–6 treatment-naïve or -experienced patients with Child-Pugh-Turcotte (CPT) B cirrhosis
- Key eligibility criteria: creatinine clearance (CL_{cr}) >50 mL/min, platelets >30,000/mm^3; no hepatocellular carcinoma or liver transplant

Curry et al NEJM 2015

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Treatment in Decompensated Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:
Patients With Decompensated Cirrhosis[a] Who Have Genotype 1, 4, 5, or 6 Infection and Are Ribavirin Ineligible

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	24 weeks	I, A[b]
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	24 weeks	I, A[c]
Genotype 1 or 4 infection only: Daily daclatasvir (60 mg)[d] plus sofosbuvir (400 mg)	24 weeks	II, C

Recommended regimens listed by evidence level and alphabetically for:
Patients With Decompensated Cirrhosis[a] Who Have Genotype 1, 4, 5, or 6 Infection and Are Ribavirin Eligible

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	I, A[b]
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin[e]	12 weeks	I, A[c]
Genotype 1 or 4 infection only: Daily daclatasvir (60 mg)[d] plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	I, B

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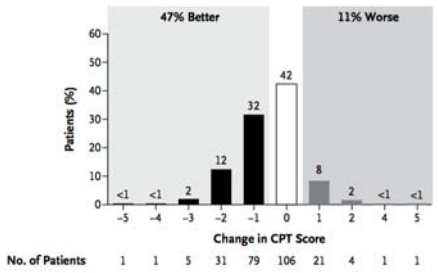
CTP Score In Decompensated Patients After SVR



Curry et al NEJM 2015

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ASTRAL 4: Change in MELD in Patients with Baseline MELD <15

Curry et al NEJM 2015

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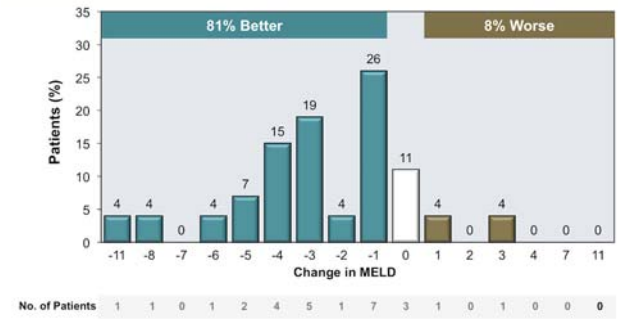
ASTRAL 4: Change in MELD in Patients with Baseline MELD ≥15



Curry et al NEJM 2015

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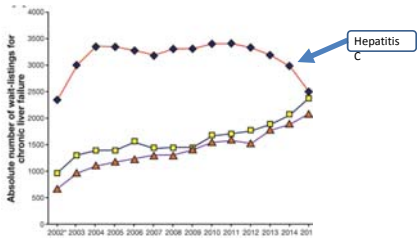
Decrease in Wait list additions for HCV



Goldberg et al Gastro 2017

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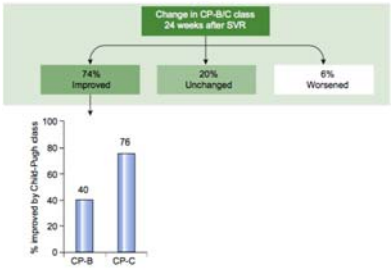
What to Tell Patients



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Take Home: HCV and Cirrhosis

- In most cases Low MELD (<15) and Childs A are OK to treat in non transplant setting
- In cirrhosis (compensated and decompensated) outcomes improve, on all metrics, after SVR
- All patients with cirrhosis require HCC monitoring, variceal screening– even after SVR

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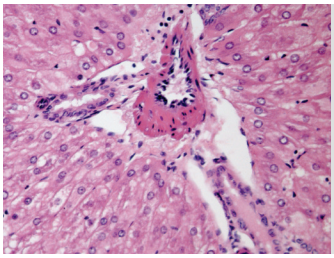

Hepatitis B Reactivation and Special Populations

Sonali Paul

AT THE FOREFRONT UChicago Medicine

Hepatitis B Reactivation & Special Populations

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

Disclosures

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- I will not discuss off label use or investigational use in my presentation

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High Worldwide HBV Prevalence

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

WHO. HBV Fact Sheet. CDC. 2012.

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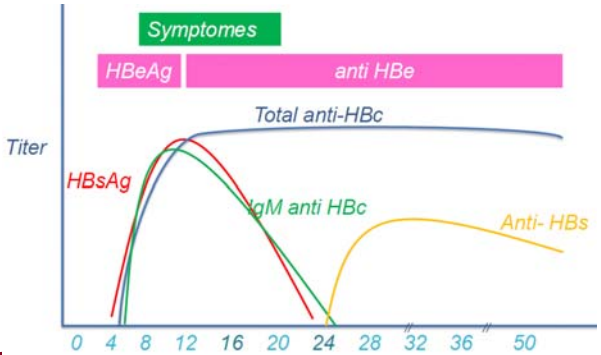
Acute HBV Serology



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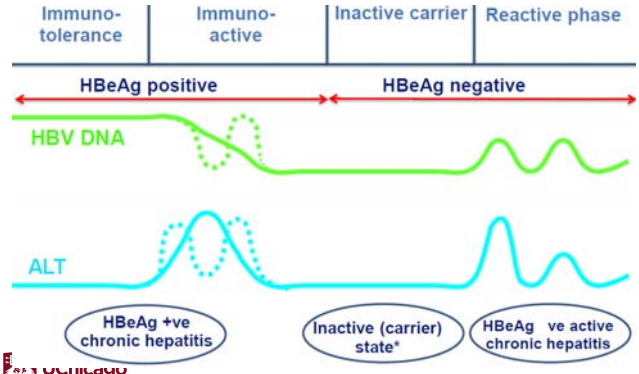
Natural History of Chronic HBV Infection



Yim HJ et al. Hepatology. 2006.

Is HBV Ever Curable?

- Immune control, not clearance
- "Resolved HBV" misnomer

Werle-Lapostolle et al. Gastroenterology. 2004.

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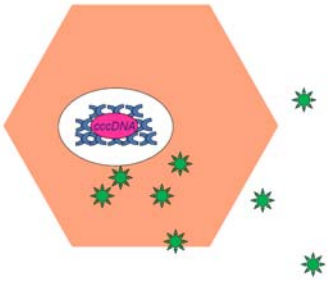

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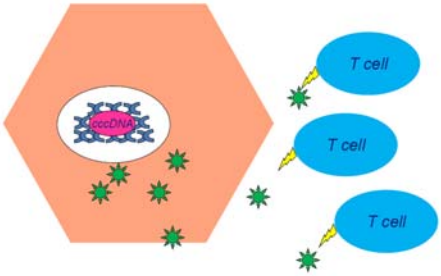


Werle-Lapostolle et al. Gastroenterology. 2004.

Is HBV Ever Curable?

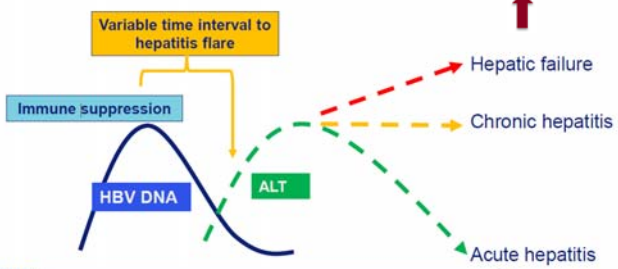
- Immune control can be lost
- Immune mediated liver damage with immune reconstitution

Immunosuppression
HIV
Steroids

Werle-Lapostolle et al. Gastroenterology. 2004.

HBV Reactivation

- **Interruption of Therapy**
- **Hepatitis**
- **Acute Liver failure**
- **Death**



Hoofnagle JH. Hepatology. 2009.

HBV Reactivation

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

Hoofnagle JH. Hepatology. 2009.

Risk of Reactivation (15 – 80%)

Patient

- Male
- Young age

Virus

- HBsAg +
- HBeAg +
- Viral load > 2000 IU/mL & HBeAg+
- Viral load > 20,000 IU/mL & HBeAg-
- Precore-core mutation

Therapy

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

Hwang JP et al. Suppor Care Cancer. 2012.

Risk of Reactivation

Gastroenterology 2015;148:215–219

AGA SECTION

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

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

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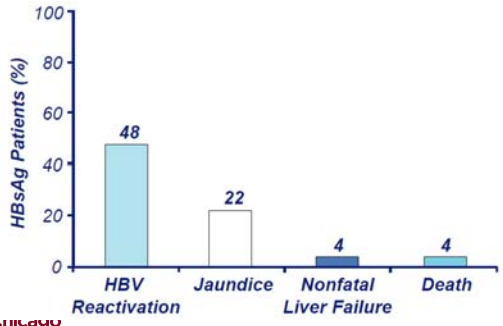
Hematological Malignancy

- 27 HBsAg+ patients with NHL undergoing CHOP therapy



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Lok AS et al. Gastroenterology. 1991.

High Risk Agents

Risk of Reactivation > 10%

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

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

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

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Reddy et al. Gastroenterology. 2015.

Rituximab

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

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

AT THE FOREFRONT UChicago Medicine

Hui et al. Gastroenterology. 2016.

Rituximab

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

Cox proportional hazard analysis

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

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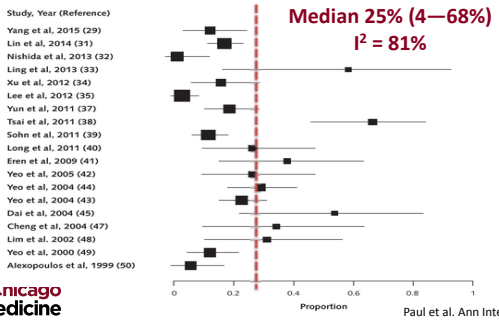
Hui et al. Gastroenterology. 2016.

Solid Tumor Chemotherapy, HBsAg+

- ↑ Breast cancer
- ↑ Anthracycline regimens



Median 25% (4—68%)
I^2 = 81%

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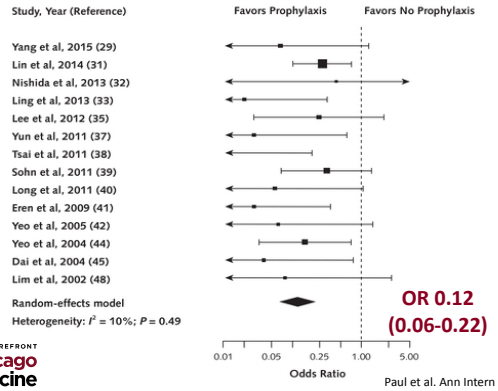
Paul et al. Ann Intern Med. 2015.

Solid Tumor Chemotherapy, HBsAG+



OR 0.12 (0.06-0.22)

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Paul et al. Ann Intern Med. 2015.

Intermediate Risk Agents

Risk of Reactivation 1 - 10%

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

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

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

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

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Antiviral prophylaxis (or can monitor)

Reddy et al. Gastroenterology. 2015.

TNF-Alpha Inhibitors (Infliximab)

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

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Perez-Alvarez R et al. Medicine. 2011.

Intermediate Risk Agents

Risk of Reactivation <1%

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

No antiviral prophylaxis

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Reddy et al. Gastroenterology. 2015.

Corticosteroids

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

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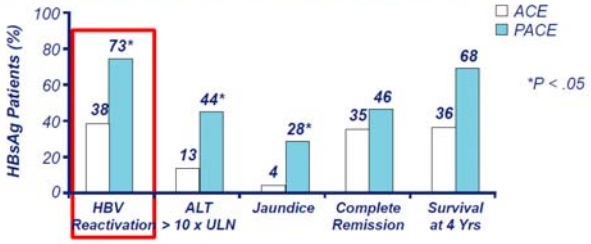
Lam et al. NEJM. 1981.

Corticosteroids

50 patients with NHL who were HBsAg positive randomized to epirubicin, cyclophosphamide and etoposide (ACE) ± prednisolone (PACE)



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Cheng AL et al. Hepatology. 2003.

Corticosteroids & HBVr

High Risk

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

Intermediate Risk

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

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

Low Risk

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

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

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

Reddy et al. Gastroenterology. 2015.

HBV, HCV, & DAA Therapy

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

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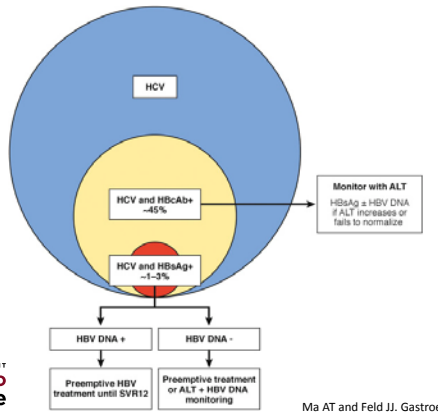
Algorithm for HBV-HCV Infection + DAAs



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Ma AT and Feld JJ. Gastroenterology. 2018.

Who Should Be Screened?

- **AASLD** recommends high-risk individuals
- Immigrants
  - Asia, Africa, Pacific Islands, Middle East, Eastern European, Central America, Caribbean
- Children of immigrants
- Men who have sex with men
- HIV / HCV positive
- History of IVDU, incarceration
- Hemodialysis patients

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Lok et al. Hepatology. 2009.

Who Should Be Screened?

- **ASCO**
  - All patients before starting anti-CD20 therapy
  - High risk individuals
  - *two panel members recommended universal screening
- **AGA**
  - Patients at moderate or high risk for HBV reactivation (>1%)
- **CDC and EASL**
  - Universal screening prior to chemotherapy
- **Prior to HCV Therapy (universal)**

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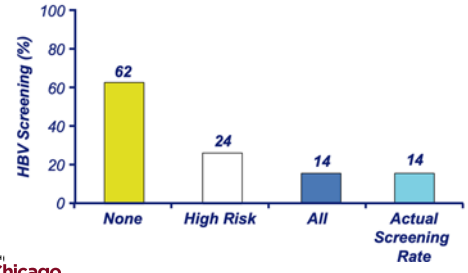
Hwang JP et al. J Clin Onc. 2015.
Reddy et al. Gastroenterology. 2015.
Weinbaum CM et al. MMWR Recomm Rep. 2008.

High Risk Screening is Difficult

- Few oncologists routinely screen all or high risk patients



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Khokhar et al. Chemotherapy. 2009.

Optimal Screening Strategy

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

Unless anti-CD20 treatment, then anti HBc

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Treatment or Prophylaxis for HBVr

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

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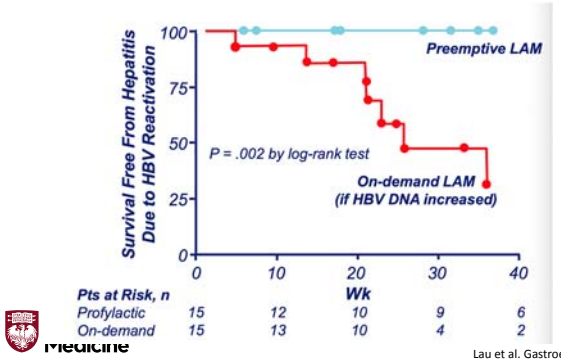
Reddy et al. Gastroenterology. 2015.

Treatment or Prophylaxis for HBVr

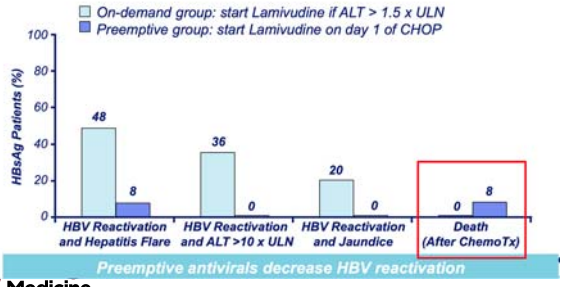
HBsAg+ patients with lymphoma treated high-dose chemotherapy



Lau et al. Gastroenterology. 2003.

Treatment or Prophylaxis for HBVr

- HBsAg patients with NHL treated with CHOP



Hsu et al. Hepatology. 2008.

Which Antiviral Treatment is Best

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

EASL. J Hepatol. 2009.

Antiviral Therapy Timing

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

EASL. J Hepatol. 2009.

Thanks for your attention!

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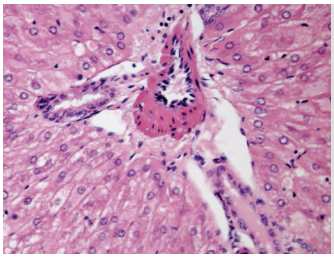


All Roads Lead to Fatty Liver Disease

Michael Charlton

AT THE FOREFRONT
UChicago Medicine

Advances in Diagnosis and Management of NASH in 2019

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

1

Disclosures

- Research Support: Gilead, Bristol Myers, Novartis, NGM Bio, Lipocene, Metacrine, Northsea, Intercept
- Consulting: Gilead, Bristol Myers, Novartis, NGM Bio, Lipocene, Metacrine, Intercept

Agenda

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

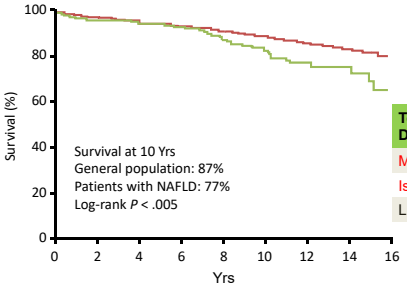
The scale of the problem

NAFLD	Estimated number of NAFLD patients in the USA 80 million[1, 2]
NASH	Estimated number of NASH patients in the USA 16.5 million[1,2]
F3/F4 fibrosis due to NASH	Estimated number of F3/F4 fibrosis patients due to NASH in the USA : 3.3 million[1,2]

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

Causes of Mortality in NAFLD

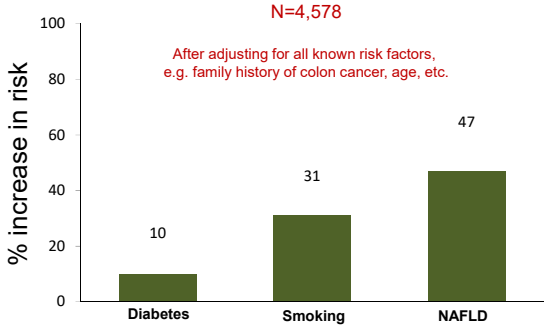
- Patients with NAFLD (N = 420) matched by age and sex to general population in Minnesota, followed for 7.6 ± 4.0 yrs



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

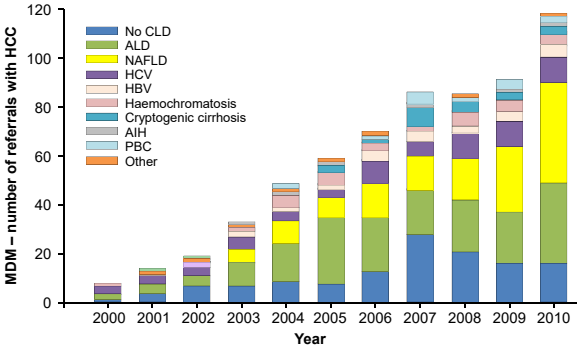
Adams LA, et al. Gastroenterology. 2005;129:113-121.

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



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

NAFLD is becoming the leading cause of HCC

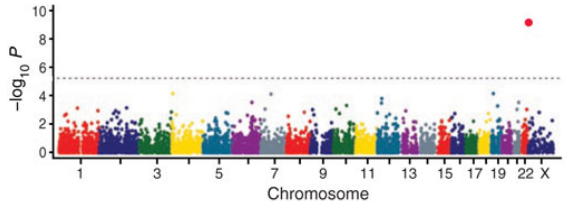


Dyson J, et al. J Hepatol 2014;60:110–7

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

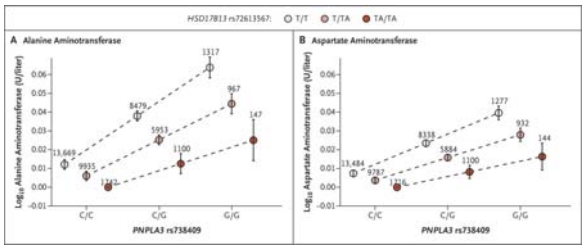
Genetic Susceptibility to NASH

PNPLA3



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

Association of *HSD17B13* rs72613567 with Aminotransferase Levels in Persons with Each *PNPLA3* p.I148M Genotype.



NS Abul-Husn et al. N Engl J Med 2018;378:1096-1106.

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

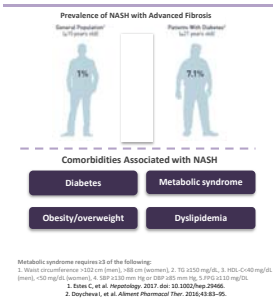
Michael Charlton,[1] Anuradha Krishnan,[1] Kimberly Viker,[1] Schuyler Sanderson,[2] Sophie Cazanave,[1] Andrea McConico,[1] Howard Masuoko,[1] and Gregory Gores[1]

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

1 3 August 2011

Prevalence of NASH with advanced fibrosis Varies with Comorbidities

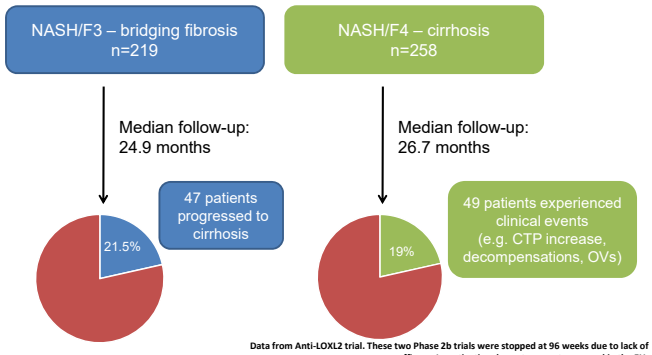
Patients at high risk for NASH with advanced fibrosis



Metabolic syndrome requires ≥3 of the following:
1. Waist circumference >102 cm (men), >88 cm (women), 2. TG ≥150 mg/dL, 3. HDL-C<40 mg/dL (men), <50 mg/dL (women), 4. SBP ≥130 mm Hg or DBP ≥85 mm Hg, 5.FPG ≥110 mg/DL

1. Estes C, et al. *Hepatology*. 2017. doi: 10.1002/hep.29466.
2. Doycheva I, et al. *Aliment Pharmacol Ther*. 2016;43:83–95.

Risk of liver disease progression in NASH patients with advanced fibrosis

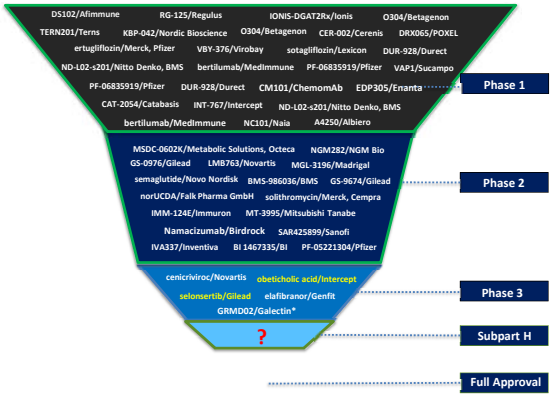


Data from Anti-LOXL2 trial. These two Phase 2b trials were stopped at 96 weeks due to lack of efficacy. Investigational agents are not approved in the EU.

CTP: Child–Turcotte–Pugh; EMA: European Medicines Agency; LOXL2: lysyl oxidase homolog 2; OV: oesophageal varices

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

Global Pipeline for NASH



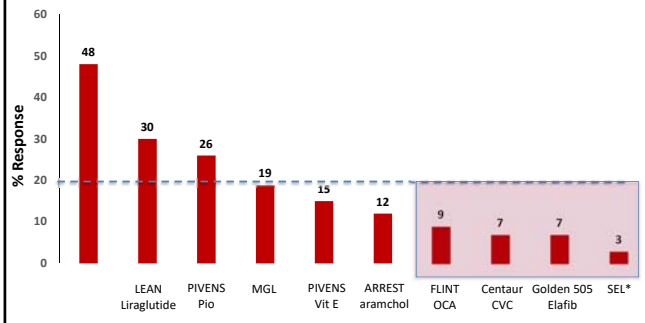
NASH Phase 2b/3 Pipeline

Status	Therapy	Target	Current Trial	Earliest Expected Approval	Route	Dose Freq
Phase 3	Elafibranor	PPAR-α/δ	RESOLVE-IT	2020	Oral	QD
	Obeticholic Acid	**FXR**	**REGENERATE**	**2020**	**Oral**	**QD**
	Obeticholic Acid	FXR	REVERSE	2020	Oral	QD
	Selonsertib	**ASK1**	**STELLAR 3**	**2019**	**Oral**	**QD**
	Selonsertib	**ASK1**	**STELLAR 4**	**2019**	**Oral**	**QD**
	Cenicriviroc	CCR2/5	AURORA	2019	Oral	QD
Phase 2 (completed)	GR-MD-02	Galectin-3	NASH-CX	Approved Phase 3	IV	Q2W
	MGL-3196	THRβ	NCT02912260	Completed	Oral	QD
	IMM-124E	LPS	NCT02316717	Completed	Oral	TID
	Aramchol	SCD1	ARREST	Completed	Oral	QD

LPS: lipopolysaccharide; IV: intravenous; QD: daily; Q2W: every 2 weeks; TID: 3 times a day; R: **receptor FDA. www.accessdata.fda.gov. Accessed 6/12/18**

Frontrunner Efficacy

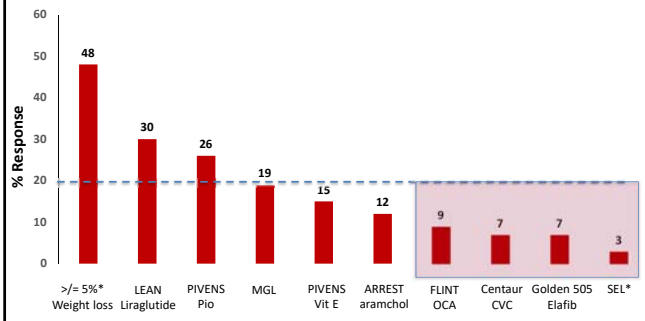
NASH Resolution – Margin over Placebo



* ≥2 point NAS reduction

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

NASH Resolution – Margin over Placebo

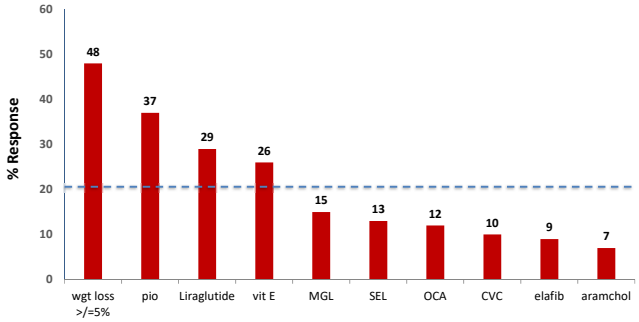


* ≥2 point NAS reduction

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

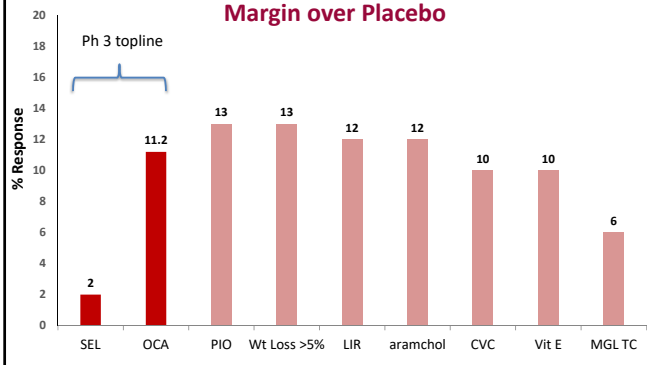
NASH Resolution – vs. 10% Standard Placebo

(equivalent to 0-5% weight loss*)



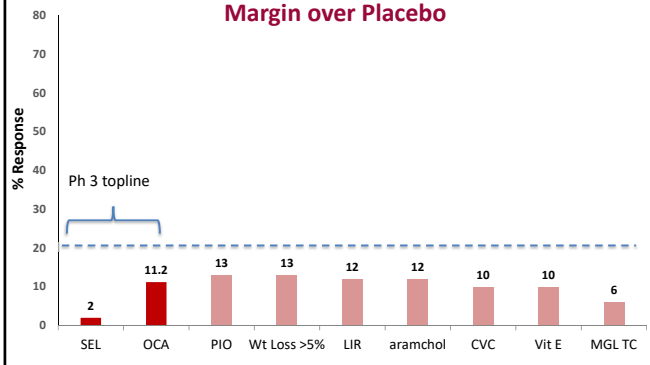
Gastro 2015;149:367–78; AASLD #104; AASLD #LB4; Lawitz et al. EASL 2018 ; AASLD #14; Sanyal et al. *Lancet*, accepted; Petit et al. *Clin Endocrinol Metab*, February 2017; AASLD #736; AASLD #LB23; AAASLD #LB5; Loomba et al. *Hepatology* 2018

Fibrosis Improvement ≥1 Stage – Margin over Placebo



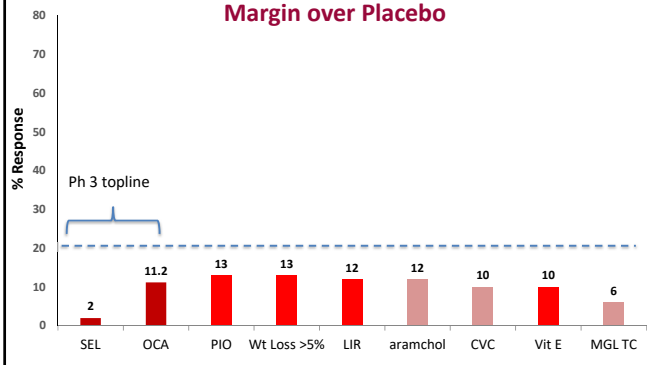
Gastro 2015;149:367–78; AASLD #104; AASLD #LB4; Lawitz et al. EASL 2018 ; AASLD #14; Sanyal et al. *Lancet*, accepted; Petit et al. *Clin Endocrinol Metab*, February 2017; AASLD #736; AASLD #LB23; AAASLD #LB5; Loomba et al. *Hepatology* 2018
SHG = second harmonic generation digital image analysis

Fibrosis Improvement ≥1 Stage – Margin over Placebo



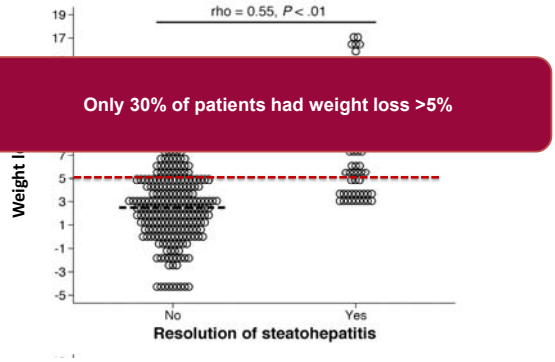
Gastro 2015;149:367–78; AASLD #104; AASLD #LB4; Lawitz et al. EASL 2018 ; AASLD #14; Sanyal et al. *Lancet*, accepted; Petit et al. *Clin Endocrinol Metab*, February 2017; AASLD #736; AASLD #LB23; AAASLD #LB5; Loomba et al. *Hepatology* 2018
SHG = second harmonic generation digital image analysis

Fibrosis Improvement ≥1 Stage – Margin over Placebo



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

NAS Resolution by % Weight Loss

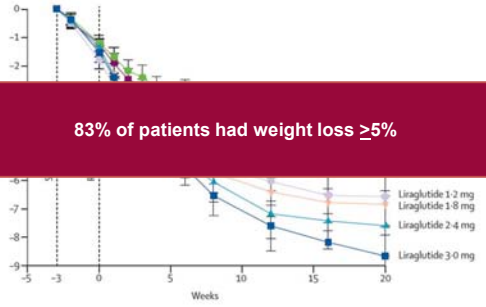


Only 30% of patients had weight loss >5%

Vilar-Gomez E, et al. Gastroenterology 2015;149:367–78

The New York Times

Longitudinal Pattern of Weight Loss with GLP1 Agonists



83% of patients had weight loss ≥5%

Astrup A, Rössner S, Van Gaal L, Rissanen A, Niskanen L, Al Hakim M, Madsen J, Rasmussen MF, Lean ME; NN8022-1807 Study Group : Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet*. 2009 Nov 7;374(9701):1606-16. doi: 10.1016/S0140-6736(09)61375-1.

To biopsy, or not to biopsy?

Current invasive tools available for staging fibrosis

Current standard: Liver Biopsy

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

Liver biopsy evaluates histology

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

- The procedure can cost from $1k to $3k[2]
- Mis-staging fibrosis in up to 41% of cases[3]
- 0.35% risk of serious bleeding and 0.14% risk of death[4]

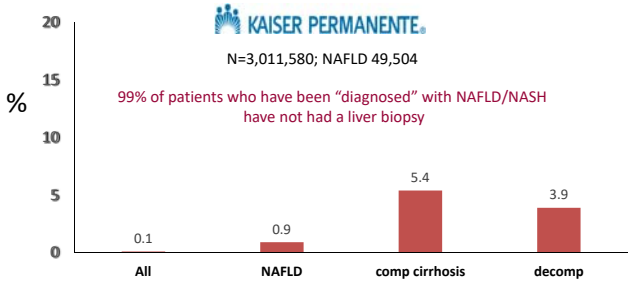
Sources: 1. Chalasani N, et al. *Hepatology*. 2017. doi:10.1002/hep.29367. 2. Franciscus A. Hepatitis C Support Project 2014. 3. Ratziu V, et al. *Gastroenterology*. 2005;128:1898-1906. 4. Myers RP, et al. *Liver Int*. 2008;28:705-712.

Frequency of Liver Biopsies in Large Community-Based Healthcare System

KAISER PERMANENTE®

N=3,011,580; NAFLD 49,504

99% of patients who have been "diagnosed" with NAFLD/NASH have not had a liver biopsy

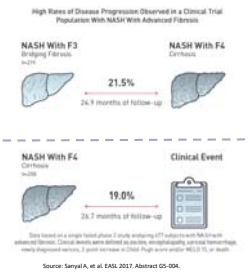


- Included patients ≥18 yrs with ICD-10 code for NAFLD, NASH, or cryptogenic cirrhosis between 1/2015 – 12/2016, absent other liver disease/alcohol abuse

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

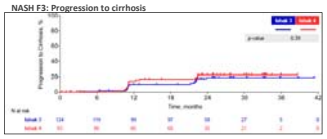
Can I predict bridging fibrosis and cirrhosis without a biopsy?

Fibrosis is a weak determinant of Progression and Clinical Events in Patients with Advanced Disease

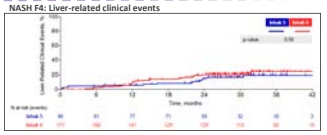


Source: Sanyal A, et al. EASL 2017. Abstract 05-004.

NASH F3: Progression to cirrhosis

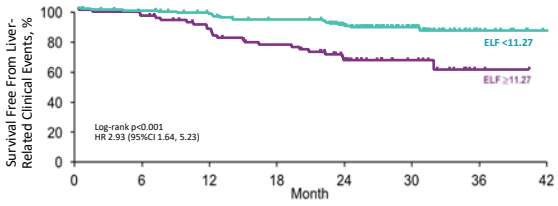


NASH F4: Liver-related clinical events



ELF Score Predicts Progression More Accurately than Biopsy

Liver-Related Clinical Events According to Baseline ELF

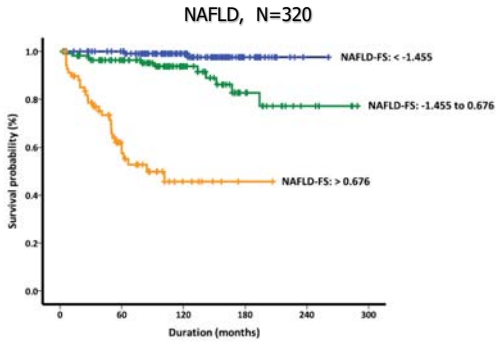


Optimal threshold of baseline ELF: 9.76 (sensitivity 77%, specificity 66%)

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

Harrison, AASLD 2017, Poster 2122

NFS Predicts Mortality



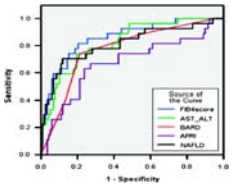
Angulo, *Gastroenterology* 2015.

Clinical Prediction of Advanced Fibrosis

NAFLD Fibrosis Score

Parameter
Age, yrs
AST
ALT
Platelet count, cells x 10^9
BMI
Albumin, g/L
Impaired fasting glucose/diabetes

FIB-4 score



Limitations:
Most useful in excluding advanced disease
Performance characteristics vary with age
Less accurate in diabetic patients
May underestimate disease in leaner patients

Negative Predictive Value:
NAFLD Fib Score: 92%
FIB-4: 95%

Angulo P, et al. Hepatology. 2007;45:846-854; Sterling RK, et al. Hepatology. 2006;43:1317-1325; Angulo et al. Gastroenterology 2013

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

Comparison of the Diagnostic Performance of Simple Tests for Advanced Fibrosis

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

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

Slide courtesy of Michael Charlton, MBBS
BARD: scoring system that incorporates BMI, AST/ALT ratio, presence of T2DM; APRI: AST to platelet ratio; PPV: positive predictive value; NPV: negative predictive value.
McPherson S, et al. *Gut* 2010;59:1265-1269; McPherson S, et al. *Am J Gastroenterol* 2017;112:740-751.

Imaging to Assess NASH Fibrosis: Elastography

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

MRE

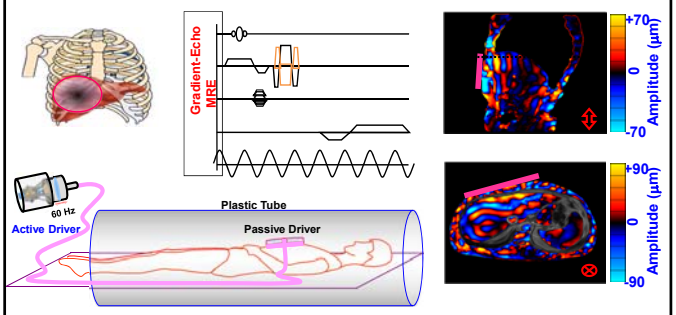
- Most accurate of the imaging modalities
- Costly, no point of care access

Elastography Point Quantification

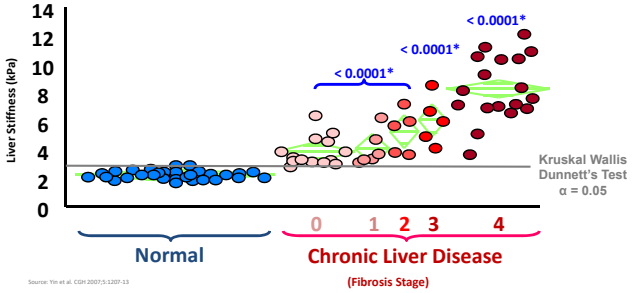
- Emerging ultrasound-based system
- Measures real-time liver stiffness during an ultrasound scan
- Non-inferior level of accuracy compared to TE

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

MR elastography of the liver

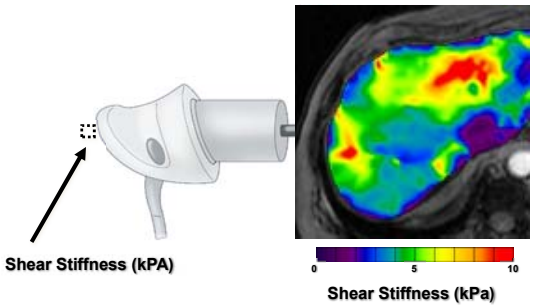


Liver stiffness correlates with fibrosis stage



Source: Yin et al. CGH 2007;5:1207-13

Fibroscan MRE

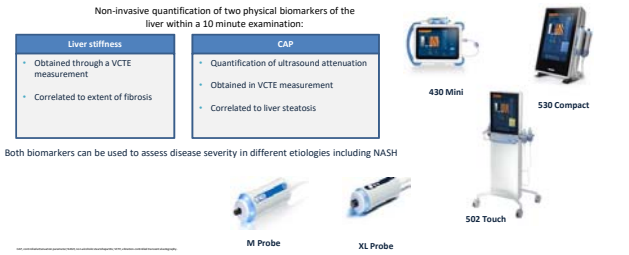


VCTE (FibroScan) technology overview

Non-invasive quantification of two physical biomarkers of the liver within a 10 minute examination:

Liver stiffness	CAP
• Obtained through a VCTE measurement • Correlated to extent of fibrosis	• Quantification of ultrasound attenuation • Obtained in VCTE measurement • Correlated to liver steatosis

Both biomarkers can be used to assess disease severity in different etiologies including NASH

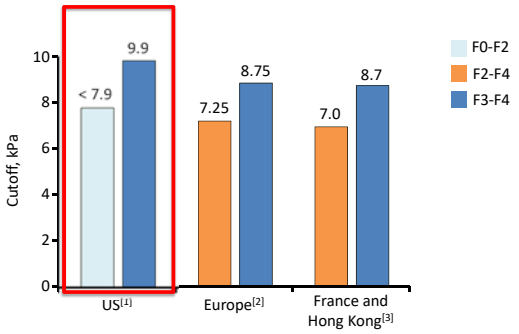


The FibroScan Report PDF

Measurement thumbnails

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

Vibration-Controlled Transient Elastography: Cutoffs for Fibrosis



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

Clinical Decision Making in Chronic Liver Disease

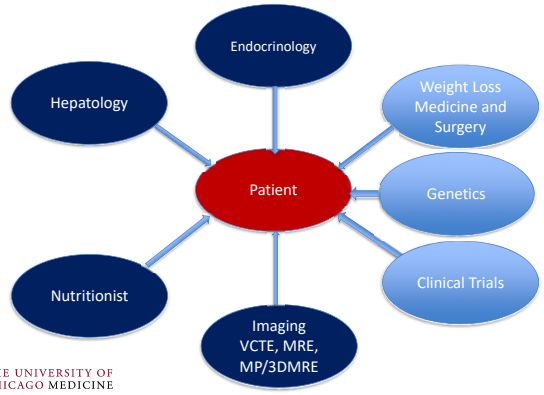
	VCTE <7.9 kPa Or FIB-4 ≤1.3 Or ELF ≤10.5 ETOH/viral hep, 9.3 NAFLD	VCTE ≥7.9 kPa Or FIB-4 >1.3 Or ELF >10.5 ETOH/viral hep, 9.3 NAFLD
High Clinical Suspicion of advanced disease	Further testing (e.g. MRE or Bx)	Treat as high risk
Low Clinical Suspicion of advanced disease	Treat as low risk Re-eval in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

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

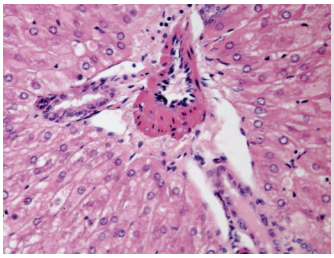
Evolving Medical Therapy for Fibrosing NASH

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

UChicago Metabolic Liver Clinic



THE UNIVERSITY OF CHICAGO MEDICINE



Living Donor Liver Transplantation Line

Diego DiSabato

AT THE FOREFRONT UChicago Medicine

Living Donor Liver Transplantation

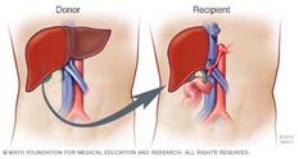
Diego di Sabato,MD

Intra-Abdominal Transplant Surgeon

UChicago Medicine Transplant Institute

Living Organ Donation

- **Living Organ Donation takes place when one healthy living person donates an organ or part of an organ to another living person in need.**
- **Living organ donation usually involves**
  - A single kidney
  - A segment of the liver
  - A lobe of one lung
  - A portion of the pancreas
  - A portion of the intestine



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History of LDLT

- ✓ 1st LDLT were performed in Brazil by Raia (1988)
- ✓ 1st successful LDLT (left hepatic lobe) is credited to Strong in Australia (1990s)
- ✓ The first report of successful LDLT was by Dr. Christoph Broelsch at the University of Chicago Medical Center in November 1989, when two-year-old Alyssa Smith received a portion of her mother's liver
- ✓ 1st AALDT of RL was reported by Yamaoka, Japan (1993)
- ✓ 1st successful LDLT (RL) in US was performed by Wachs in 1997


The New York Times

MONDAY, NOVEMBER 27, 1989

First U.S. Liver Transplant From Live Donor Is Set

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- Key points in AALDLT
  - More complex surgery
  - Donor risk (mobility/mortality)
  - Similar results than DDLT
- Why Adult to adult LDLT?
  - Scarcity of deceased donor
  - High waiting list mortality (10% to 25%) based on areas.
  - We ***would not do LDLT if enough DD*** organs were available
  - Areas where there is ***not alternative to LDLT***, recipient benefit from LDLT is maximal and donor risk is acceptable.

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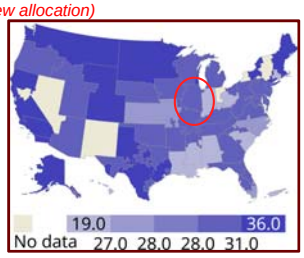
- The risk of death for a recipient of LDLT is less than half of the risk of a pt who does not have a LD.
- Depend on MELD score in DSA that results in Tx
- No benefit for HCC with MELD 15 *(not true with new allocation)*
- Benefit in HCC pts diminished secondary to allocation preference for HCC pts *(not true with new allocation)*
- Benefit depend on DD availability.

Median MELD scores for adult deceased donor liver transplant recipients by DSA, 2017



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Liver Transplant USA – " Mind the Gap"

- Liver Transplant Waitlist: May, 2018
  - 14,225
- Liver Transplants 2017
  - 8082 (LD: 367 /DD : 7715)
- Wait list Deaths 2017
  - 1209

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Source: SRTR

Living Donor Liver Transplant : Advantages

- Living donor liver transplantation is an attractive practice
  - ***not only because it can be a significant source for expanding the pool of liver donors,***
- But also because it
  - assures the recipient a healthy portion of liver with minimal preservation damage,
  - allows for the surgery to be done when the recipient has a better functional status,
  - and frees the recipient from the uncertainty and vagaries of the waiting list and its inherent hazards of complication and potential waitlist mortality.

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- Perhaps more important, when viewed in an intention-to-treat analysis, A-A LDLT is associated with *lower mortality than the alternative of waiting for a deceased-donor liver transplantation (DDLT), even when the LDLT is being performed for patients with a MELD score of <15.*
- Further reductions in mortality occur after transplant centers gain experience with LDLT and exceed a learning-curve threshold of 20 procedures.

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Living Donor Liver Transplant: Disadvantages

- Most important are the risks of mortality and morbidity for donors. These short-term and long- term risks span the period of time from surgery through postoperative recovery and beyond,
- The most severe and threatening complication is donor death.

  estimated as 2/1000–5/1000 for left and right lobe, respectively
- Other disadvantages of LDLT include the technical complexity of the surgery, the labor-intensiveness of maintaining an LDLT program, and the risks to reputations of transplant surgeons and teams, institutions, and the entire field if donors are seriously injured or die.

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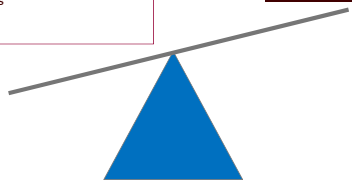
Advantages vs Disadvantages

- Decrease waitlist MORTALITY
- Decreased waiting time
- Transplant prior to recipient becoming critically ill
- Planned operation
- Minimal CIT
- Immunologic advances
- Adds to cadaver pool
- Financial benefits

- Short-term risks to DONOR
- Long-term risks to DONOR
- Surgical problems
- Not enough liver
- Ethical conflicts??



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Ethical Principles in living donation: Four foundational principles

- respect for persons including their **autonomy** (in support of informed and voluntary consent),
- the duty of healthcare professionals to benefit patients (**beneficence**)
- and to avoid needlessly harming and putting them at risk (**nonmaleficence**),
- and the fair distribution of the scarce resource of solid organs (**distributive justice**).

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Ethical conflicts in LDLT

- These ethical principles work together to protect patients by positively assuring their freedom to make their own decisions and by restricting the actions of healthcare providers.

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Ethical conflicts in LDLT

Living organ donation puts two basic principles of medical ethics in conflict: autonomy and non-maleficence.

Autonomy refers to the rights of the patient to make decisions about their healthcare without the doctor or other provider trying to influence their decision.

Non-maleficence is the Hippocratic maxim that obligates healthcare providers to avoid intentionally harming a patient.

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Ethical conflicts in LDLT

- In the case of living organ donation, these principles come into conflict especially with respect to the donor,
  - who makes the decision freely to donate,
  - but does not physically benefit from the surgery.
- This pretext therefore puts transplant physicians in the position of possibly willfully opposing the principle of non-maleficence.

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Ethical Principles in living donation: Four foundational principles

- To adequately justify living organ donation, the 4 central ethical principles need to be further operationalized through.
- assessing and optimizing donor safety,
- evaluating expected recipient outcomes,
- and considering individual and societal needs.

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A2ALL Adult to Adult Living Donor Liver Transplantation Cohort Study

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Donor Outcomes

- Intra-operative and post-operative complications: 9% to 67%
  Morbidity 50 % (A2ALL study group)
- Donor complications rate is higher for right hepatectomy than left.
- Mortality *0.1% to 0.5 %* (there are 34/14000 donations known donor mortality)
  30 Right L/ 4 Left L (Vancouver forum transp (2006)
- Threshold of donor acceptance *must not be low*!! (donor evaluation protocols/ multidisciplinary team)
- Psychological disorders
  1suicide (donor)

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Recipients Outcomes

- A2ALL consortium (9 US centers)
  - Patient survival:
    - 94% (90 days)
    - 89% (1 year)
  - Graft survival:
    - 87% (90 days)
    - 81% (1 year)
  - Graft failed (first 90 days):
    - 13.2%
  - Common cause:
    - Vascular thrombosis
    - PNF
  - Complications:
    - Biliary complication were common (30%)

- Older recipients
- CIT

- greater than 20 cases

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HYPOTHESIS

- Early access to transplantation with living donor (LD) and higher donor risk (HDRI) deceased donors matched with moderate MELD risk recipients will decrease wait list mortality and improve long term patient survival.

Summary and Future Directions

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METHODS

- UNOS data set of 43,497 patients from Mar 2002-Aug 2006
- 22,863 patients underwent liver only transplantation
- Patient survival was analyzed by Kaplan-Meier analysis with log-rank test and Cox proportional hazards regression for time-to-event analysis.
- We calculated the relative waitlist mortality risk by MELD, as well as the MELD-dependent post-transplant survival in recipients who received living donor(LD), low DRI (LDRI) deceased donor(<1.5), and high DRI (HDRI) deceased donor(>2.0).
- Overall 5 year recipient mortality was calculated from the time of listing by MELD to include the expected waitlist mortality in addition to the post-transplant mortality by donor type. We modeled the optimal early timing of high DRI transplantation by calculating the "break even" mortality at 5 years for both low DRI and high DRI recipients.

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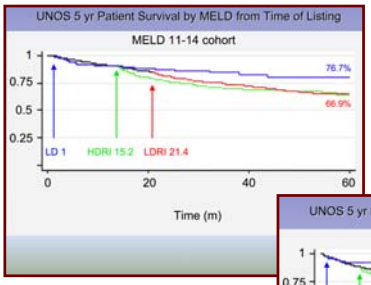

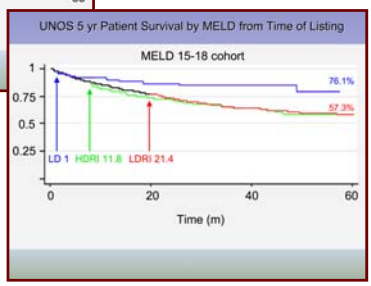

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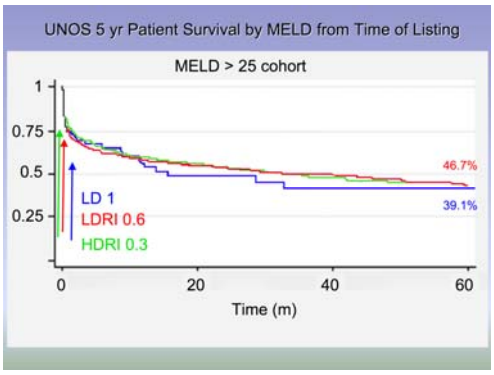

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Conclusions

- Patients with MELD<10 live longer on the waiting list than after transplantation
- Early access to transplant with LD allografts in MELD 11-14 offers significant reduction in predicted mortality compared to deceased donor allografts
- Patients with MELD 15-18 have significant benefit from early transplant with either LD or HDRI allografts if transplanted within 12 months of listing

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Summary and Future Directions

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

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Conclusion

- ALDLT outcomes have shown *acceptable levels of graft and patient survival in experienced* centers, despite a high rate of complications.
  - Outcomes improve with experience
  - Donor complications persist (30 %)
- LDLT can *reduce mortality* on the waiting list; specially in areas of transplantation with *higher MELD scores.*
- The decision to proceed must be balanced against the possibility of deterioration or dying on the waiting list and based on ability to provide a survival advantages.
- Left Lobe is a potential way to increasing the number of donor organs with lower donor risk.
  - ***transferring risk donor -> recipient***
- ***LDLT is NOT the LAST*** resort but rather the first and best resort.

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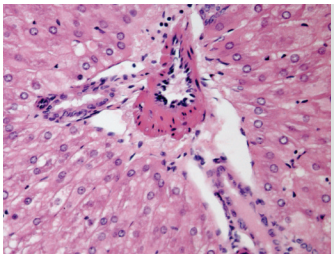
Thanks a lot !!!



Interventional Radiology for Portal Hypertension

Steven Zangan

INTERVENTIONAL RADIOLOGY FOR PORTAL HYPERTENSION

Steven M Zangan MD
Associate Professor of Radiology
Vice Chair for Business Development
Associate Program Director, IR Residency
Ombudsman, Uchicago Medicine

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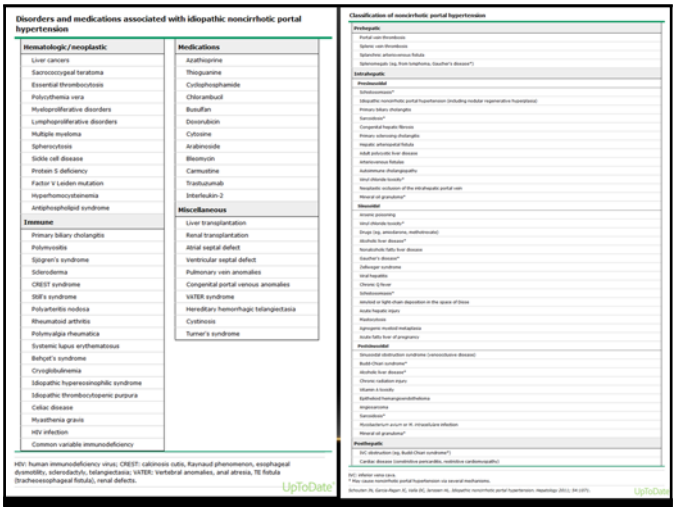
UChicago Medicine

AT THE FOREFRONT OF HEPATOLOGY STEVEN M ZANGAN MD

- I have no financial relationships to disclose
- I will not discuss off label use or investigational use in my presentation

IR & PORTAL HYPERTENSION

- Diagnosis
- Control of recurrent variceal bleeding
- Control of refractory ascites
- Anatomic optimization for liver transplant



Disorders and medications associated with idiopathic noncirrhotic portal hypertension

Hematologic / neoplastic	Medications
Liver cancers	Azathioprine
Sacrococcygeal teratoma	Thioguanine
Essential thrombocytosis	Cyclophosphamide
Polycythemia vera	Chlorambucil
Myeloproliferative disorders	Busulfan
Lymphoproliferative disorders	Doxorubicin
Multiple myeloma	Cytosine
Spherocytosis	Arabinoside
Sickle cell disease	Bleomycin
Protein S deficiency	Carmustine
Factor V Leiden mutation	Trastuzumab
Hyperhomocysteinemia	Interleukin-2
Antiphospholipid syndrome	**Miscellaneous**
Immune	Liver transplantation
Primary biliary cholangitis	Renal transplantation
Polymyositis	Atrial septal defect
Sjögren's syndrome	Ventricular septal defect
Scleroderma	Pulmonary vein anomalies
CREST syndrome	Congenital portal venous anomalies
Still's syndrome	VATER syndrome
Polyarteritis nodosa	Hereditary hemorrhagic telangiectasia
Rheumatoid arthritis	Cystinosis
Polymyalgia rheumatica	Turner's syndrome
Systemic lupus erythematosus	
Behçet's syndrome	
Cryoglobulinemia	
Idiopathic hypereosinophilic syndrome	
Idiopathic thrombocytopenic purpura	
Celiac disease	
Myasthenia gravis	
HIV infection	
Common variable immunodeficiency	

HIV: human immunodeficiency virus; CREST: calcinosis cutis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia; VATER: Vertebral anomalies, anal atresia, TE fistula (tracheoesophageal fistula), renal defects.

UpToDate

Classification of noncirrhotic portal hypertension

Prehepatic
Portal vein thrombosis
Splenic vein thrombosis
Splenic arteriovenous fistula
Splenomegaly (eg, from lymphoma, Gaucher's disease*)
Intrahepatic
Presinusoidal
Schistosomiasis*
Idiopathic noncirrhotic portal hypertension (including nodular regenerative hyperplasia)
Primary biliary cholangitis
Sarcoidosis*
Congenital hepatic fibrosis
Primary sclerosing cholangitis
Hepatic arteriportal fistula
Adult polycystic liver disease
Arteriovenous fistulas
Autoimmune cholangiopathy
Vinyl chloride toxicity*
Neoplastic occlusion of the intrahepatic portal vein
Mineral oil granuloma*
Sinusoidal
Arsenic poisoning
Vinyl chloride toxicity*
Drugs (eg, amiodarone, methotrexate)
Alcoholic liver disease*
Nonalcoholic fatty liver disease
Gaucher's disease*
Zellweger syndrome
Viral hepatitis
Chronic Q fever
Schistosomiasis*
Amyloid or light-chain deposition in the space of Disse
Acute hepatic injury
Mastocytosis
Agnogenic myeloid metaplasia
Acute fatty liver of pregnancy
Postsinusoidal
Sinusoidal obstruction syndrome (veno-occlusive disease)
Budd-Chiari syndrome*
Alcoholic liver disease*
Chronic radiation injury
Vitamin A toxicity
Epithelioid hemangioendothelioma
Angiosarcoma
Sarcoidosis*
Mycobacterium avium or M. intracellulare infection
Mineral oil granuloma*
Posthepatic
IVC obstruction (eg, Budd-Chiari syndrome*)
Cardiac disease (constrictive pericarditis, restrictive cardiomyopathy)

IVC: inferior vena cava.
* May cause noncirrhotic portal hypertension via several mechanisms.

Schouten JN, Garcia-Pagan JC, Valla DC, Janssen HL. Idiopathic noncirrhotic portal hypertension. Hepatology 2011; 54:1071.

UpToDate

DIAGNOSING PORTAL HYPERTENSION

- Known risk factor for portal hypertension + clinical manifestation of portal hypertension
- When in doubt, hepatic venous pressure gradient (HVPG)
  - Quantify portal HTN due to sinusoidal resistance to blood flow
  - PHTN when HVPG ≥ 6 mmHg
  - Clinically signficant when HVPG ≥ 10 mmHg
  - Bleeding and ascites when HVPG ≥ 12 mmHg

HVPG - TECHNIQUE

- HVPG = Wedge – Free
- Free hepatic venous pressure (FHVP)
  - Reflects intra-abdominal perssure
- Wedged hepatic venous pressures (WHVP)
  - Reflects portal perssure
  - Typically obtained via transjugular hepatic vein catheterization
    - Wedge end hole catheter in end tributaries
    - Balloon occlusion technique
- Can perform transjugular liver biopsy at the same time (18 or 19g)
- US and MR Elastography have secondary roles

STANDARDS OF PRACTICE

Quality Improvement Guidelines for Transjugular Intrahepatic Portosystemic Shunts

Sean R. Dariushnia, MD, Ziv J Haskal, MD, Mehran Midia, MD, FRCPC, Louis G. Martin, MD, T. Gregory Walker, MD, Sanjeeva P. Kalva, MD, Timothy W.I. Clark, MD, Suvranu Ganguli, MD, Venkataramu Krishnamurthy, MD, Cindy K. Saiter, NP, and Boris Nikolic, MD, MBA
(for the Society of Interventional Radiology Standards of Practice Committee)

J Vasc Interv Radiol 2016; 27:1–7

AASLD PRACTICE GUIDELINE UPDATE

The Role of Transjugular Intrahepatic Portosystemic Shunt (TIPS) in the Management of Portal Hypertension: Update 2009

Thomas D. Boyer[1] and Ziv J. Haskal[2]

DOI 10.1002/hep.23585

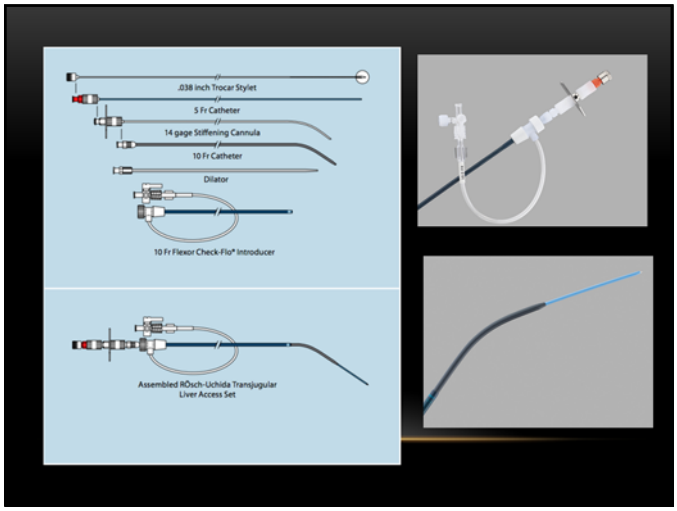
Table 4. Indications for TIPS

Efficacy determined by controlled trials
Secondary prevention variceal bleeding
Refractory cirrhotic ascites
Efficacy assessed in uncontrolled series
Refractory acutely bleeding varices
Portal hypertensive gastropathy
Bleeding gastric varices
Gastric antral vascular ectasia
Refractory hepatic hydrothorax
Hepatorenal syndrome Type 1 Type 2
Budd-Chiari syndrome
Veno-occlusive disease
Hepatopulmonary syndrome

INDICATIONS

TIPS creation is indicated for the following (22–48):

1. Uncontrollable (ie, "rescue") variceal hemorrhage;
2. Recurrent variceal hemorrhage despite endoscopic therapy;
3. Portal hypertensive gastropathy;
4. Refractory ascites;
5. Hepatic hydrothorax; and
6. Budd–Chiari syndrome.



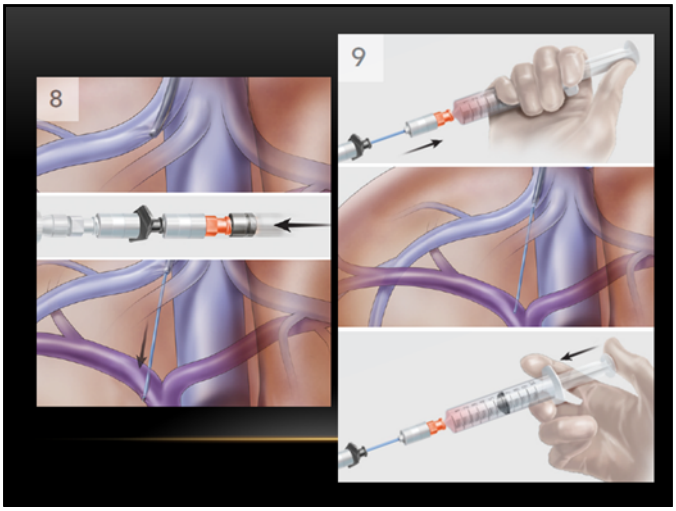


Table 1. Success Rates for TIPS Creation (22,23,25–27,31–33,37,38,80–83)

Type of Success	Rate (%)
Technical	
Creation of patent TIPS between hepatic vein and branch of portal vein*	95
Hemodynamic	
Reduction of portosystemic gradient to level targeted by operator†	95
Clinical	
Resolution of clinical indication for which procedure was performed	
Variceal bleeding (22,23,25–27)	> 90
Ascites (31–33,37,38,82,83)‡	55

TIPS = transjugular intrahepatic portosystemic shunt.
*The technical complexity of TIPS creation may be challenging, especially in centers with lower-volume TIPS referrals, and, as a result, lower success rates may be encountered. Therefore, a single threshold is difficult to set, and departments may need to alter their thresholds as needed to higher or lower levels to meet their own quality-improvement program needs.
†In general, the target portosystemic gradient is ≤ 12 mm Hg for esophageal variceal bleeding (80,81). The authors recognize that the final portosystemic gradient for gastric variceal bleeding may require a different gradient threshold. Additionally, the final portosystemic gradient in patients with ascites may need to be lower than the threshold for bleeding varices.
‡The clinical success rates in the literature for ascites nonrecurrence is broad, ranging from 55% to 80%, with the majority of studies reporting approximately 55%.

COVERED VERSUS BARE METAL STENTS

	GORE® VIATORR® Device (n = 39)	Bare Metal Stents (n = 41)	p Value
Two Year Primary Patency	76%	36%	0.001
Revisions	9	31	< 0.05
Clinical Relapse	10%	29%	< 0.05
Encephalopathy	33%	49%	< 0.05
Two Year Survival	58%	45%	NS

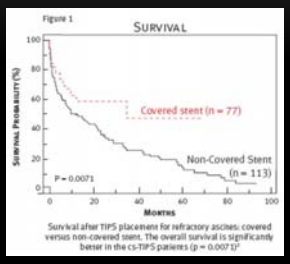
Bureau C, Pagan JCG, Layrargues GP, *et al.* Patency of stents covered with polytetrafluoroethylene in patients treated by transjugular intrahepatic portosystemic shunts: long term results of a randomized multicentre study. *Liver International* 2007;27(6):742-747.

	GORE® VIATORR® Device (n = 89)	Bare Metal Stents* (n = 89)	p Value
Three Month Survival	93%	76%	0.001
One Year Survival	88%	64%	0.001
Two Year Survival	76%	53%	0.001

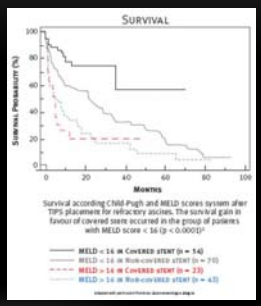
* 1:1 matched (Age, Child-Pugh, TIPS Indication)

1. Angermayr B, Cejna M, Koenig F, *et al.* Vienna TIPS Study Group. Survival in patients undergoing transjugular intrahepatic portosystemic shunt: PTFE-covered stentgrafts versus bare stents. *Hepatology* 2003;38(4):1043-1050.

COVERED VS BARE METAL



Survival after TIPS placement for refractory ascites: covered versus non-covered stent. The overall survival is significantly better in the cs-TIPS patients (p = 0.0071)[2]

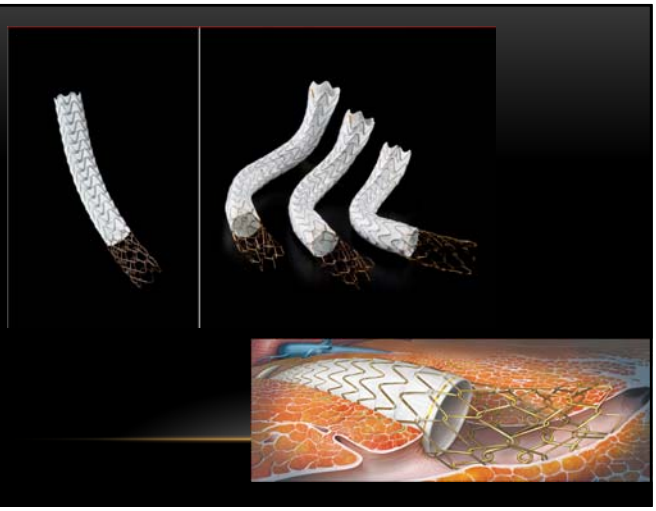


Survival according Child-Pugh and MELD scores system after TIPS placement for refractory ascites. The survival gain in favour of covered stent occurred in the group of patients with MELD score < 16 (p < 0.0001)[2]

Maleux G, Perez-Gutierrez NA, Evrard S, *et al.* Covered stent versus bare stent for transjugular intrahepatic portosystemic shunts in cirrhotic patients with refractory ascites: a retrospective cohort study Acta Gastro-Enterologica Belgica 2010;73(3):336-341.

PRIMARY PATENCY OF COVERED TIPS

			Primary Patency %		
Year	Author	N	0.5 Year	1 Year	2 Year
2007	Bureau[1]	39			76
2006	Amarapurkar[2]	11	90.9		
2006	Rossle[3]	100		90	84
2006	Tripathi[4]	157	93	92	89
2005	Barrio[5]	20	100	100	
2005	Echenagusia[6]	12		100	88.8
2005	Vignali[7]	113	91.9	79.9	75.9
2004	Angeloni[8]	32		76.3	
2004	Charon[9]	100		84	
2004	Hausegger[10]	71	87.4	80.8	
2004	Maleaux[11]	56		89.3	
2004	Rossi[12]	53		83.8	
2002	Otal[13]	20		80	
2001	Cejna[14]	16	82		
Weighted Average			91.5	86.2	83.1



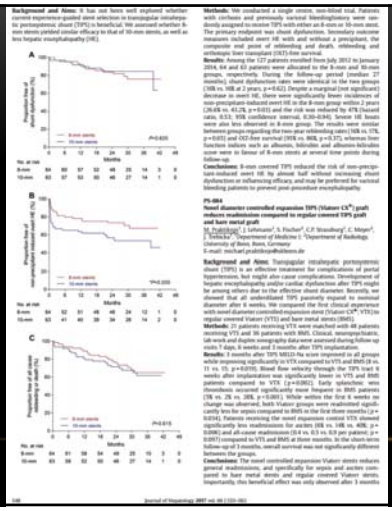


Table 4. Indications for TIPS

Efficacy determined by controlled trials
Secondary prevention variceal bleeding
Refractory cirrhotic ascites
Efficacy assessed in uncontrolled series
Refractory acutely bleeding varices
Portal hypertensive gastropathy
Bleeding gastric varices
Gastric antral vascular ectasia
Refractory hepatic hydrothorax
Hepatorenal syndrome Type 1 Type 2
Budd-Chiari syndrome
Veno-occlusive disease
Hepatopulmonary syndrome

INDICATIONS

TIPS creation is indicated for the following (22–48):

1. Uncontrollable (ie, "rescue") variceal hemorrhage;
2. Recurrent variceal hemorrhage despite endoscopic therapy;
3. Portal hypertensive gastropathy;
4. Refractory ascites;
5. Hepatic hydrothorax; and
6. Budd–Chiari syndrome.

EARLY TIPS COMPARED TO DRUG THERAPY PLUS EBL FOR VARICEAL BLEEDERS

Multi-center randomized controlled trial

	Early TIPS Procedure with GORE® VIATORR® Device (n = 32)	Pharmacotherapy Plus Endoscopic Band Ligation (n = 31)	p Value
One Year Control of Bleeding	97%	50%	0.001
One Year Survival	86%	61%	0.001
One Year Hepatic Encephalopathy	28%	40%	0.13

García-Pagán JC Early TIPS (Transjugular Intrahepatic Portosystemic) Shunt Cooperative Study Group. Early use of TIPS in patients with cirrhosis and variceal bleeding. *New England Journal of Medicine* 2010; 362(25):2370-2379.

Table 5. Surgical Shunts and TIPS Versus Endoscopic Therapy in the Prevention of Rebleeding

Number of Patients	Rebleeding Rate		Encephalopathy		Mortality	
	Endo	PCS	Endo	PCS	Endo	PCS
376	49.8%	12.4%*	8.6%	17.2%**	28.8%	28.8%
	Endo	TIPS	Endo	TIPS	Endo	TIPS
811	46.6%	18.9%*	18.7%	34.0%**	26.5%	27.3%

Endo, endoscopic therapy; PCS, portacaval shunt. *By meta-analysis, rebleeding significantly less with PCS or TIPS compared to Endo. **By meta-analysis, incidence of encephalopathy greater with PCS or TIPS compared to Endo. Data taken from D'Amico et al.[73] and Papatheodoridis et al.[81]

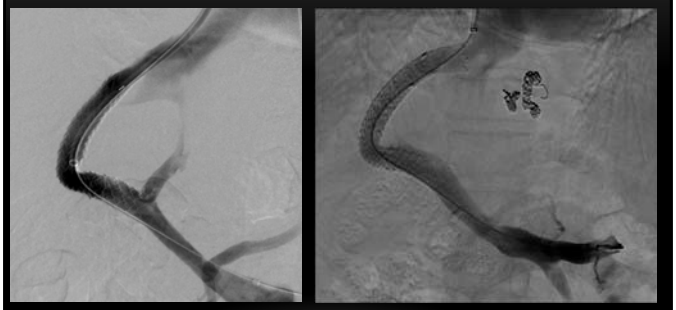
EMBOLIZATION OF VARICES?

PROS

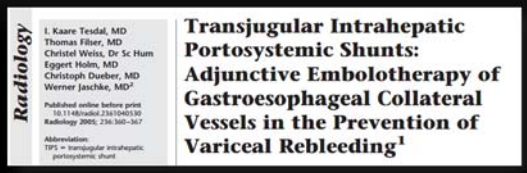
- Improve TIPS patency by reducing competing shunts
- Reduce risk of bleeding in setting of subsequent TIPS dysfunction

CONS

- With advent of covered stent (Viatorr), less concern about TIPS patency and TIPS dysfunction
- Closure of varices/competing shunts increases portosystemic gradient



EMBOLIZATION OF VARICES?


Radiology

I. Kaare Tesdal, MD
Thomas Filser, MD
Christel Weiss, Dr Sc Hum
Eggert Holm, MD
Christoph Dueber, MD
Werner Jaschke, MD[2]

Published online before print
10.1148/radiol.2361040530
Radiology 2005; 236:360–367

Abbreviation:
TIPS = transjugular intrahepatic portosystemic shunt

Transjugular Intrahepatic Portosystemic Shunts: Adjunctive Embolotherapy of Gastroesophageal Collateral Vessels in the Prevention of Variceal Rebleeding[1]

% Free of Bleeding	2 yrs	4 yrs
TIPS	61%	53%
TIPS + embolization of varices	84%	81%

Lower incidence of rebleeding, but no survival benefit

EMBOLIZATION OF VARICES?

- Metaanalysis (6 studies)
- TIPS + variceal embolization had significantly lower incidence of variceal rebleeding (p = 0.002) compared with TIPS alone
- But no additional advantages with regards to TIPS patency, encephalopathy, survival


META-ANALYSIS AND SYSTEMATIC REVIEW

Transjugular intrahepatic portosystemic shunt in combination with or without variceal embolization for the prevention of variceal rebleeding: A meta-analysis

Qi et al. *J Gastroenterol Hepatol* 2014

EMBOLIZATION OF VARICES?

Embolize if:

- In setting of acute ongoing variceal bleeding
- Varices still seen on post-TIPS venogram?
- Portosystemic gradient decreases too much?

Table 4. Indications for TIPS

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Refractory cirrhotic ascites
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TIPS creation is indicated for the following (22–48):

1. Uncontrollable (ie, "rescue") variceal hemorrhage;
2. Recurrent variceal hemorrhage despite endoscopic therapy;
3. Portal hypertensive gastropathy;
4. Refractory ascites;
5. Hepatic hydrothorax; and
6. Budd–Chiari syndrome.

AASLD PRACTICE GUIDELINE

Management of Adult Patients with Ascites Due to Cirrhosis: Update 2012

TABLE 4. TREATMENT OPTIONS FOR PATIENTS WITH CIRRHOSIS AND ASCITES

First-Line
- Cessation of alcohol use, when present
- Sodium restricted diet and diet education
- Dual diuretics, usually spironolactone and furosemide, orally with single daily dosing
- Discontinue non-steroidal anti-inflammatory drugs
- Evaluation for liver transplantation

Second-Line
- Discontinue beta blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers
- Consider adding midodrine especially in the profoundly hypotensive patient
- Serial therapeutic paracenteses
- Evaluation for liver transplantation
- Transjugular intrahepatic portasystemic stent-shunt (TIPS)

Third-Line
- Peritoneovenous shunt

Radiology

Hector Ferral, MD
Pablo Gamboa, MD
Darren W. Postoak, MD
Vanessa S. Albernaz, MD
Carmen R. Young, RN
Kermitt V. Speeg, MD
C. Alex McMahan, PhD

Index terms:
Hypertension, portal, 957.723
Liver, interventional procedures, 957.1268
Shunts, portosystemic, 957.1268

Published online before print
10.1148/radiol.2311030967
Radiology 2004; 231:235–236

Survival after Elective Transjugular Intrahepatic Portosystemic Shunt Creation: Prediction with Model for End-Stage Liver Disease Score[1]

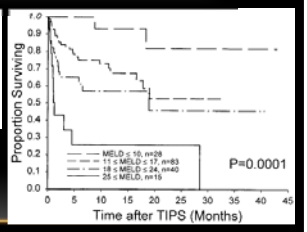
PURPOSE: To evaluate the ability of a model of end-stage liver disease (MELD) score to predict survival in a diverse group of patients who underwent elective transjugular intrahepatic portosystemic shunt (TIPS) creation in two tertiary care institutions.

MATERIALS AND METHODS: Patients who underwent elective TIPS creation in

TABLE 2
Mortality Based on MELD Score

MELD Score	No. of Patients	Mortality Rate (%)		
		30 days	3 months	6 months
≤10	28	0 (0, 0)	0 (0, 0)	0 (0, 0)
11–17	83	7.3 (3.7, 12.9)	16.0 (8.0, 24.0)	24.9 (15.1, 34.7)
18–24	40	17.9 (5.9, 29.9)	34.8 (19.4, 50.2)	38.6 (22.4, 54.9)
≥25	15	42.6 (16.7, 68.4)	65.5 (39.9, 91.2)	74.2 (50.0, 98.3)

Note.—Numbers in parentheses are 95% CIs.



MELD
- Originally designed to predict mortality in patients undergoing elective TIPS
- Tbili, Cr, INR
- MELD 18+, significantly decreased 3mo survival

TABLE 3
Mortality Based on MELD Score and Cause of Cirrhosis

MELD Score	Group*	No. of Patients	Mortality Rate (%) 30 Days	3 Months	6 Months
≤17	A	39	5.1 (0, 12.1)	7.7 (0, 16.1)	13.9 (2.5, 25.2)
	B	72	5.6 (0.3, 11.0)	14.4 (6.1, 22.7)	21.4 (11.3, 31.4)
≥18	A	14	42.9 (16.9, 68.8)	57.1 (31.2, 83.1)	57.1 (31.2, 83.1)
	B	41	17.9 (5.9, 29.9)	37.9 (22.0, 53.7)	45.9 (28.1, 63.2)

Note.—Numbers in parentheses are 95% CI.
* Cause in Group A, ethanol-induced liver disease; cause in group B, non–alcohol-induced cirrhosis.

TABLE 4
Mortality Based on MELD Score and Ascites

MELD Score	Ascites	No. of Patients	Mortality (%) 30 Days	3 Months	6 Months
≤17	No	48	4.2 (0, 9.8)	4.2 (0, 9.8)	4.2 (0, 9.8)
	Yes	63	6.4 (0.3, 12.5)	18.4 (8.6, 28.3)	31.3 (18.6, 43.9)
≥18	No	18	22.2 (3.0, 41.4)	39.8 (16.8, 62.8)	46.5 (22.6, 70.4)
	Yes	37	25.4 (11.0, 39.8)	44.4 (27.4, 61.4)	48.7 (31.1, 66.3)

Note.—Numbers in parentheses are 95% CIs.

TIPS COMPARED TO LARGE VOLUME PARACENTESIS (LVP)

- *Transjugular Intrahepatic Portosystemic Shunt for Refractory Ascites: A Meta-Analysis of Individual Patient Data*[1]

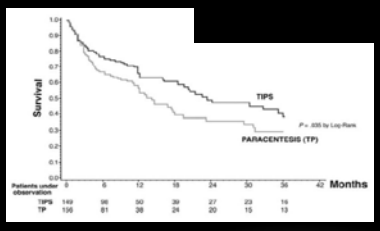


Figure 1. Cumulative probability of transplant-free survival according to treatment with TIPS or total paracentesis.

1. Salerno F. *et al.* Transjugular intrahepatic portosystemic shunt for refractory ascites: A meta-analysis of individual patient data. *Gastroenterology* 2007: 133 (3): 825-834

TIPS FOR ASCITES

Transjugular Intrahepatic Portosystemic Shunts With Covered Stents Increase Transplant-free Survival of Patients With Cirrhosis and Recurrent Ascites

Christophe Bureau[1, 2], Dominique Thabut[3], Frédéric Oberti[4], Sébastien Dharancy[5], Nicolas Carbonell[6], Antoine Bouvier[4], Philippe Mathurin[5], Philippe Otal[2, 7], Pauline Cabarrou[1], Jean Marie Péron[1, 2], Jean Pierre Vinel[1, 2]

Gastroenterology 2016

- 62 patients randomized to TIPS (n=29) or LVP (n=32)
- **Primary endpoint: 1 year transplant free survival**
  - **TIPS 93% vs LVP 52% (p=0.003)**
- Total # of paracenteses: 32 in TIPS group vs 320 in LVP group
- Portal HTN related bleeding: TIPS 0% vs LVP 18% (p=0.01)
- Days hospitalized in 1 year: TIPS 17 vs LVP 35 (p=0.04)
- 1 year probability of remaining free of encephalopathy
  - 65% in both groups

TABLE 5. LARGE-SCALE RANDOMIZED CONTROLLED TRIALS OF TIPS VERSUS SERIAL LARGE-VOLUME PARACENTESES

REF NO	INCLUSION CRITERIA	METHOD OF RANDOMIZATION AND ANALYSIS	N	CONTROL OF ASCITES	SURVIVAL	ENCEPHALOPATHY
99	Tense ascites & failure of 4 weeks of therapy	No details	60	61% vs. 18% (*P* =.006)	69% vs. 52% (*P*=.11)	58% vs. 48%*
100	Ascites refractory to medical therapy	Sealed opaque envelope Intention to treat	70	51% vs. 17% (*P* =.003)	41% vs. 35%* (*P* =.29)	All 77% vs. 66% Severe 60% vs. 34% (*P* =.03)
102	Refractory ascites	No details Intention to treat	109	58% vs. 16% (*P* <.001)	40% vs. 37%*	Moderate-Severe 38% vs. 12% (*P* =.058)
103	Refractory or recidivant	No details	66	79% vs. 42% (*P* =.0012)	77% vs. 52% (*P* =.021)	Severe (*P* =.039)

**P value not significant.*

Table 6. TIPS Versus Large Volume Paracentesis in Treatment-Refractory Cirrhotic Ascites

Reference Number	Number of Patients		Ascites Improved		Survival#		New or Severe Encephalopathy	
	TIPS	LVP	TIPS	LVP	TIPS	LVP	TIPS	LVP
98	13	12	38%	0%	29%	60%	15%	6%
99	29	31	84%*	43%	58%	32%	23%	13%
100	35	35	51%*	17%	26%	30%	60%*	34%
23	52	57	58%*	16%	35%	33%	38%	21%
101	33	33	79%*#	42%	59%*	29%	61%	39%

*Significant difference between two groups. #End-point was failure which was defined as need for at least 4 LVPs for recurrent ascites. #Transplant-free survival after 2 years for first three studies.
LVP, large volume paracentesis; TIPS, transjugular intrahepatic portosystemic shunt.

Table 1. Success Rates for TIPS Creation (22,23,25–27,31–33,37,38,80–83)

Type of Success	Rate (%)
Technical	
Creation of patent TIPS between hepatic vein and branch of portal vein*	95
Hemodynamic	
Reduction of portosystemic gradient to level targeted by operator†	95
Clinical	
Resolution of clinical indication for which procedure was performed	
Variceal bleeding (22,23,25–27)	> 90
Ascites (31–33,37,38,82,83)‡	55

TIPS = transjugular intrahepatic portosystemic shunt.
*The technical complexity of TIPS creation may be challenging, especially in centers with lower-volume TIPS referrals, and, as a result, lower success rates may be encountered. Therefore, a single threshold is difficult to set, and departments may need to alter their thresholds as needed to higher or lower levels to meet their own quality-improvement program needs.
†In general, the target portosystemic gradient is ≤ 12 mm Hg for esophageal variceal bleeding (80,81). The authors recognize that the final portosystemic gradient for gastric variceal bleeding may require a different gradient threshold. Additionally, the final portosystemic gradient in patients with ascites may need to be lower than the threshold for bleeding varices.
‡The clinical success rates in the literature for ascites nonrecurrence is broad, ranging from 55% to 80%, with the majority of studies reporting approximately 55%.

Table 2. Contraindications to Placement of a TIPS

Absolute
- Primary prevention of variceal bleeding
- Congestive heart failure
- Multiple hepatic cysts
- Uncontrolled systemic infection or sepsis
- Unrelieved biliary obstruction
- Severe pulmonary hypertension

Relative
- Hepatoma especially if central
- Obstruction of all hepatic veins
- Portal vein thrombosis
- Severe coagulopathy (INR > 5)
- Thrombocytopenia of < 20,000/cm^3
- Moderate pulmonary hypertension

CONTRAINDICATIONS

Although there are no absolute contraindications to TIPS creation, several relative contraindications exist. Creating a TIPS in patients with the following conditions is likely to increase the rates of procedural or TIPS-related complications:

1. Elevated right or left heart pressures;
2. Heart failure or severe cardiac valvular insufficiency;
3. Rapidly progressive liver failure;
4. Severe or uncontrolled HE;
5. Uncontrolled systemic infection or sepsis;
6. Unrelieved biliary obstruction;
7. Polycystic liver disease;
8. Extensive primary or metastatic hepatic malignancy; and
9. Severe, uncorrectable coagulopathy.

Table 2. Complication Rates and Thresholds (106–113)

Complication	Reported Rate (%)	Suggested Complication-Specific Threshold (%)
Major	3	5
Hemoperitoneum*	0.5	1
Biliary peritonitis	1	2
Stent malposition†	1	1
Hemobilia	2	2
Radiation skin burn	0.1	0.1
Hepatic infarction	0.5	0.5
Renal failure requiring chronic dialysis	0.25	0.5
Hepatic artery injury	1	2
Accelerated liver failure‡	3	–
Severe or controlled encephalopathy§	–	–
Death‖	1	2
Minor	4	8
Transient contrast medium–induced renal failure	2	5
Encephalopathy controlled by medical therapy	15–25	15–25
Fever	2	5
Transient pulmonary edema	1	1
Entry site hematoma	2	5

Table 3. Complications of TIPS

Complications	Frequency (%)
TIPS dysfunction	
Thrombosis	10–15
Occlusion/stenosis	18–78
Transcapsular puncture	33
Intraperitoneal bleed	1–2
Hepatic infarction	~1
Fistulae	Rare
Hemobilia	<5
Sepsis	2–10
Infection of TIPS	Rare
Hemolysis	10–15
Encephalopathy	
New/worse	10–44
Chronic	5–20
Stent migration or placement into IVC or too far into portal vein	10–20

Data from Boyer and Vargus[126] and Rössle et al.[127]

*Hemoperitoneum warranting blood transfusion or other directed interventions.

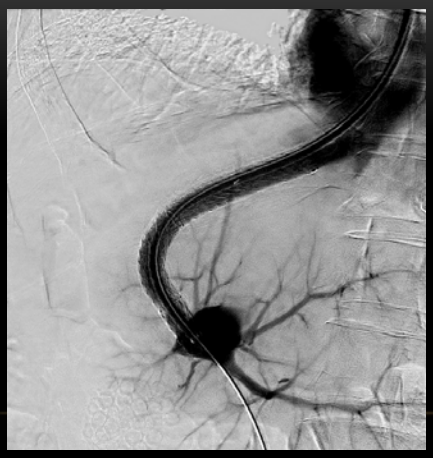
†A major stent malposition includes conditions such as free stent migration within the portal or systemic venous circulations or malposition resulting in vascular perforation.

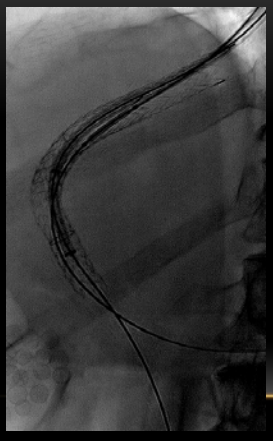
‡The rate of accelerated liver failure after TIPS creation is highly dependent on patient selection, final shunt diameter, and comorbid factors such as preexisting multiple organ system failure, increased MELD scores, and high Child–Pugh scores. Part of this risk is not specific to the creation of a TIPS, but is shared by surgical forms of portosystemic diversion as well. As such, as specific threshold for this complication cannot be assigned.

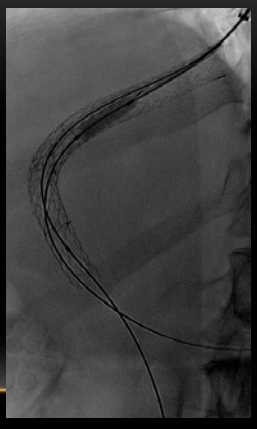
§Encephalopathy rates are directly dependent upon patient selection, as with any form of portosystemic diversion. For example, patients with severe or refractory ascites may manifest severe encephalopathy (requiring hospitalization) in 30%–40% of cases (106) (107). In contrast, elective patients with Child–Pugh class A/B hepatocellular disease may manifest severe, uncontrolled encephalopathy in 3%–10% of cases (108–113).

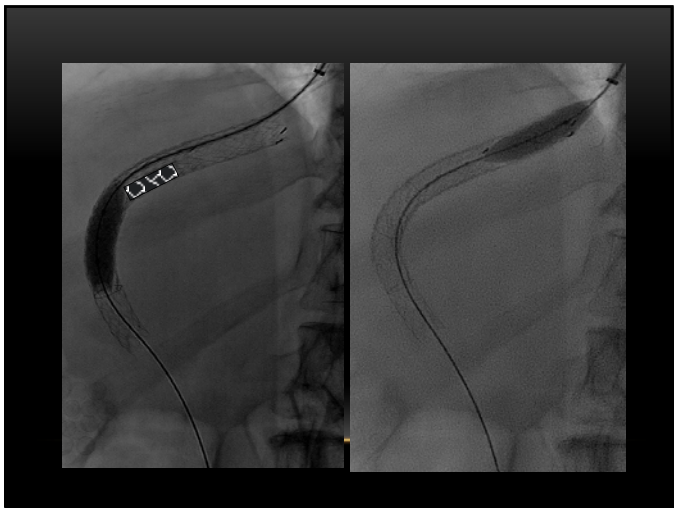
‖Death refers to 30-day mortality directly related to a complication of TIPS creation. As with accelerated liver failure after TIPS‡, the majority of deaths after TIPS are dependent upon preexisting comorbid factors such as elevated MELD scores, Child-Pugh scores, and multi-organ failure. The existence of these pre-TIPS conditions can greatly increase the rate of 30-day mortality after TIPS or surgical forms of portosystemic diversion. Proper patient selection and minimization of procedural complications can greatly reduce death rates.

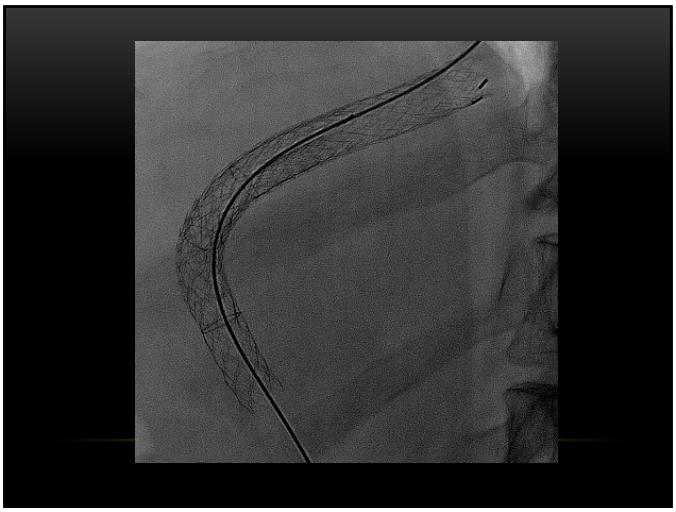
TIPS REDUCTION

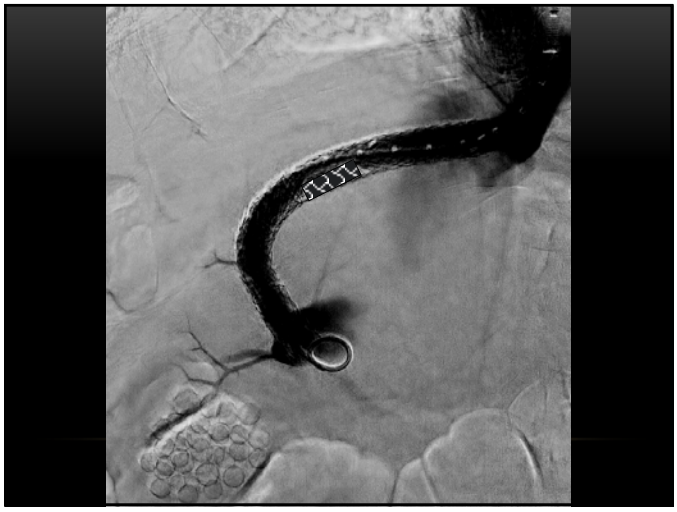












AASLD PRACTICE GUIDELINE

Management of Adult Patients with Ascites Due to Cirrhosis: Update 2012

TABLE 4. TREATMENT OPTIONS FOR PATIENTS WITH CIRRHOSIS AND ASCITES

First-Line
- Cessation of alcohol use, when present
- Sodium restricted diet and diet education
- Dual diuretics, usually spironolactone and furosemide, orally with single daily dosing
- Discontinue non-steroidal anti-inflammatory drugs
- Evaluation for liver transplantation

Second-Line
- Discontinue beta blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers
- Consider adding midodrine especially in the profoundly hypotensive patient
- Serial therapeutic paracenteses
- Evaluation for liver transplantation
- Transjugular intrahepatic portasystemic stent-shunt (TIPS)

Third-Line
- Peritoneovenous shunt

Table 2. Contraindications to Placement of a TIPS

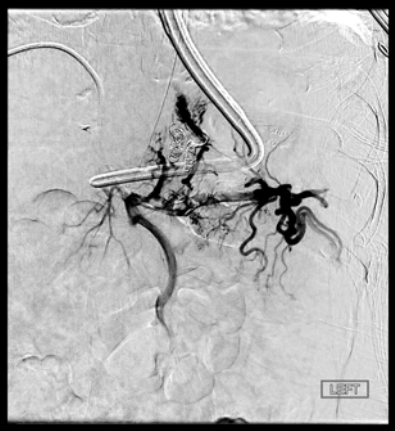
Absolute
- Primary prevention of variceal bleeding
- Congestive heart failure
- Multiple hepatic cysts
- Uncontrolled systemic infection or sepsis
- Unrelieved biliary obstruction
- Severe pulmonary hypertension

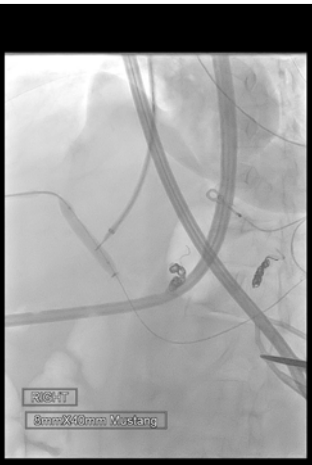
Relative
- Hepatoma especially if central
- Obstruction of all hepatic veins
- Portal vein thrombosis
- Severe coagulopathy (INR > 5)
- Thrombocytopenia of < 20,000/cm³
- Moderate pulmonary hypertension

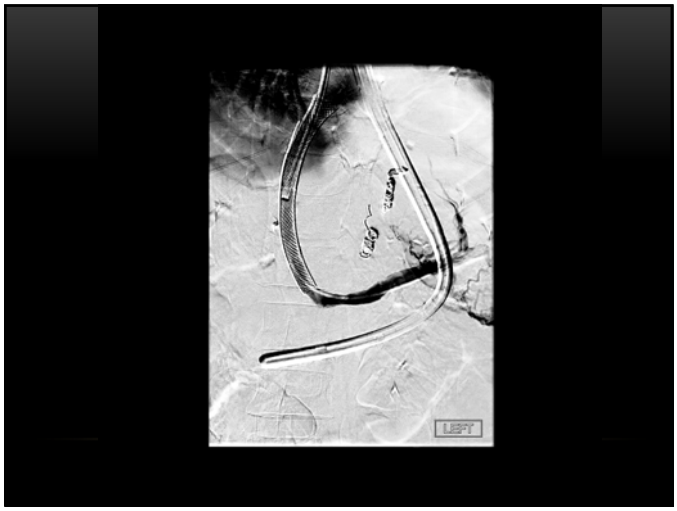
CONTRAINDICATIONS

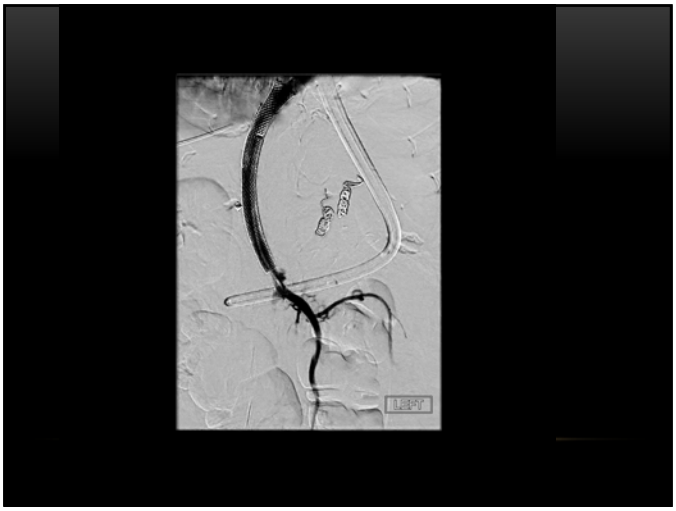
Although there are no absolute contraindications to TIPS creation, several relative contraindications exist. Creating a TIPS in patients with the following conditions is likely to increase the rates of procedural or TIPS-related complications:

1. Elevated right or left heart pressures;
2. Heart failure or severe cardiac valvular insufficiency;
3. Rapidly progressive liver failure;
4. Severe or uncontrolled HE;
5. Uncontrolled systemic infection or sepsis;
6. Unrelieved biliary obstruction;
7. Polycystic liver disease;
8. Extensive primary or metastatic hepatic malignancy; and
9. Severe, uncorrectable coagulopathy.









Pretransplantation Portal Vein Recanalization and Transjugular Intrahepatic Portosystemic Shunt Creation for Chronic Portal Vein Thrombosis: Final Analysis of a 61-Patient Cohort

Bartley Thornburg, MD, Kush Desai, MD, Ryan Hickey, MD, Elias Hohlastos, MD, Laura Kulik, MD, Daniel Ganger, MD, Talia Baker, MD, Michael Abecassis, MD, MBA, Juan C. Caicedo, MD, Daniela Ladner, MD, Jonathan Fryer, MD, Ahsun Riaz, MD, Robert J. Lewandowski, MD, and Riad Salem, MD, MBA

ABSTRACT

Purpose: To report the final analysis of the safety and efficacy of portal vein (PV) recanalization (PVR) and transjugular intrahepatic portosystemic shunt (TIPS) creation (PVR-TIPS) in patients with PV thrombosis (PVT) in need of liver transplantation.

Materials and Methods: Sixty-one patients with cirrhosis and PVT underwent PVR-TIPS to improve transplantation candidacy. Median patient age was 58 years (range, 22–75 y), and median pre-TIPS Model for End-Stage Liver Disease score was 14 (range, 7–42). The most common etiologies of cirrhosis were nonalcoholic fatty liver disease in 18 patients (30%) and hepatitis C in 13 patients (21%). Twenty-seven patients (44%) had partial PVT, and 34 patients (56%) had complete thrombosis. Forty-nine patients (80%) had Yerdel grade 2 PVT, and 12 (20%) had Yerdel grade 3 PVT. Twenty-nine patients (48%) had cavernous transformation of the PV.

Results: PVR-TIPS was technically successful in 60 of 61 patients (98%). PV/TIPS patency was maintained in 55 patients (92%) at a median follow-up of 19.2 months (range, 0–105.9 mo). Recurrent PV/TIPS thrombosis occurred in 5 patients (8%), all of whom initially presented with complete PVT. The most common adverse events were TIPS stenosis in 13 patients (22%) and transient encephalopathy in 11 patients (18%). Twenty-four patients (39%) underwent transplantation, 23 of whom (96%) received an end-to-end anastomosis. There were no cases of recurrent PVT following transplantation, with a median imaging follow-up of 32.5 months (range, 0.4–75.4 mo). Five-year overall survival rate was 82%.

Conclusions: PVR-TIPS is a safe, effective, and durable treatment option for patients with chronic PVT who need liver transplantation.

Journal of Vascular and Interventional Radiology
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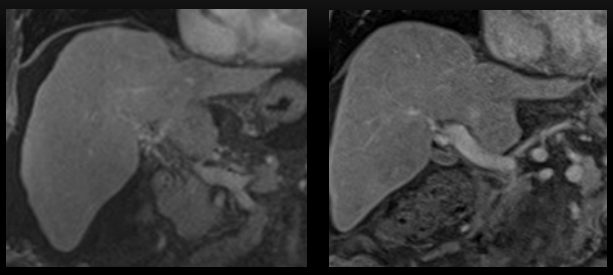

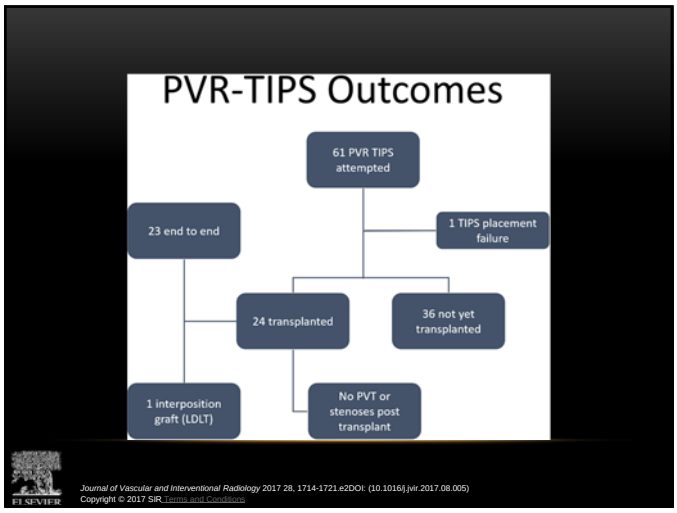

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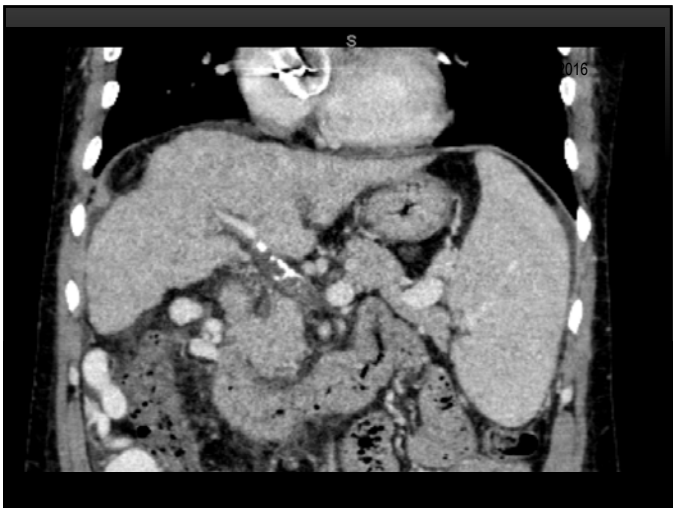

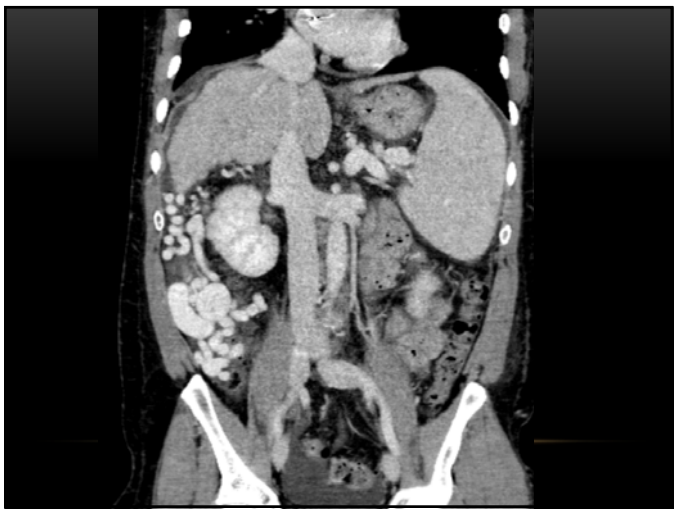

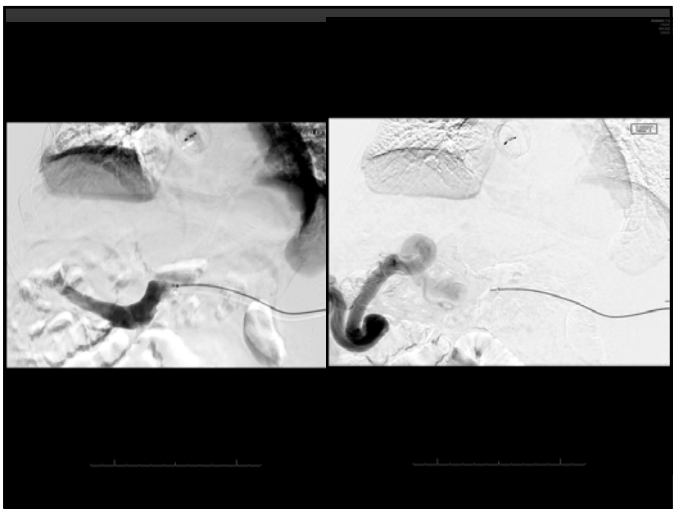

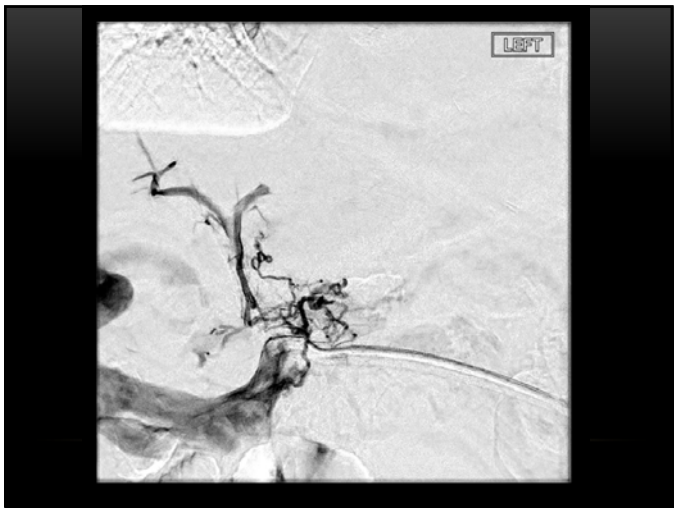
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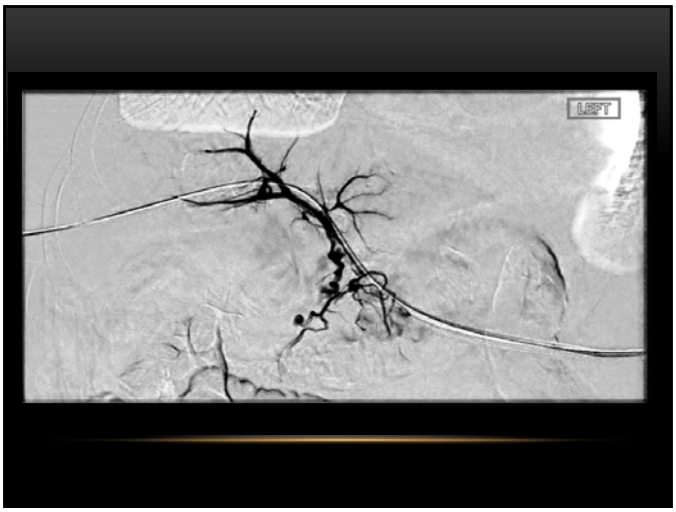
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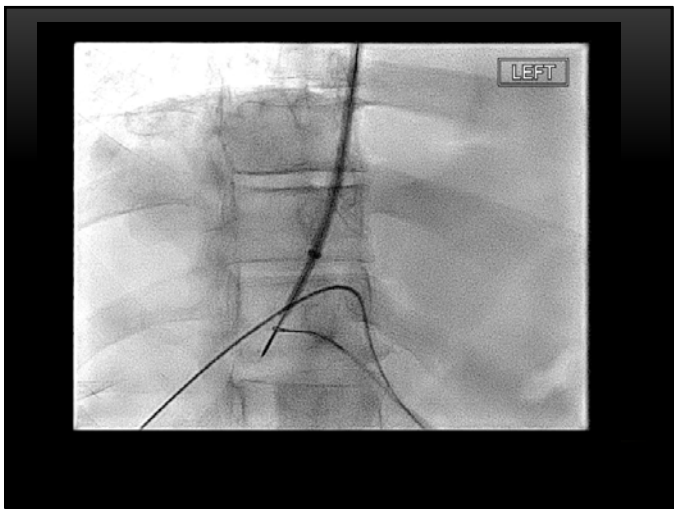
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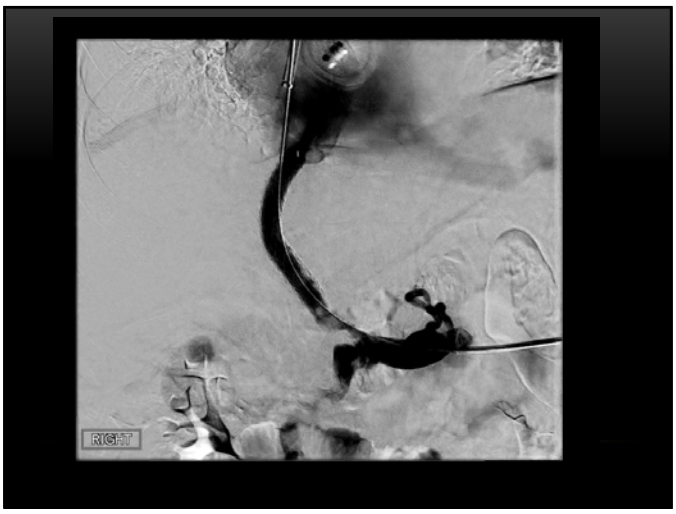
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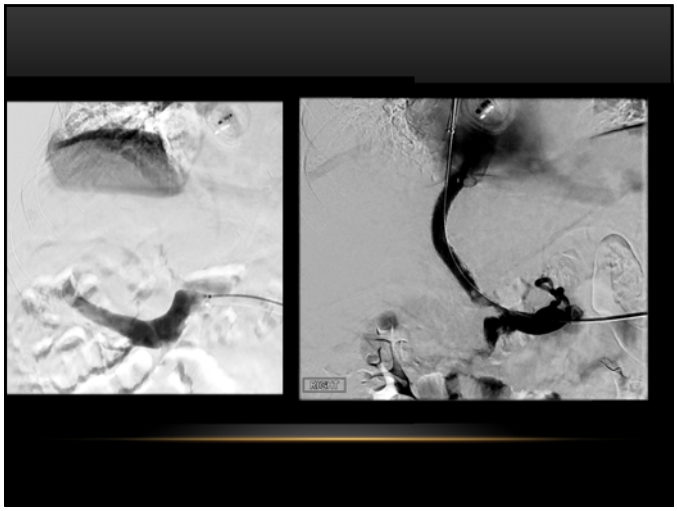


Table 2. Complication Rates and Thresholds (106–113)

Complication	Reported Rate (%)	Suggested Complication-Specific Threshold (%)
Major	3	5
Hemoperitoneum*	0.5	1
Biliary peritonitis	1	2
Stent malposition†	1	1
Hemobilia	2	2
Radiation skin burn	0.1	0.1
Hepatic infarction	0.5	0.5
Renal failure requiring chronic dialysis	0.25	0.5
Hepatic artery injury	1	2
Accelerated liver failure‡	3	–
Severe or controlled encephalopathy§	–	–
Death‖	1	2
Minor	4	8
Transient contrast medium–induced renal failure	2	5
Encephalopathy controlled by medical therapy	15–25	15–25
Fever	2	5
Transient pulmonary edema	1	1
Entry site hematoma	2	5

Table 3. Complications of TIPS

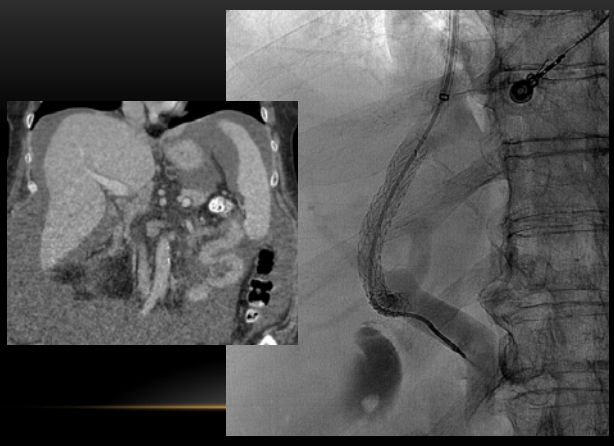
Complications	Frequency (%)
TIPS dysfunction	
Thrombosis	10–15
Occlusion/stenosis	18–78
Transcapsular puncture	33
Intraperitoneal bleed	1–2
Hepatic infarction	~1
Fistulae	Rare
Hemobilia	<5
Sepsis	2–10
Infection of TIPS	Rare
Hemolysis	10–15
Encephalopathy	
New/worse	10–44
Chronic	5–20
Stent migration or placement into IVC or too far into portal vein	10–20

Data from Boyer and Vargus[126] and Rössle et al.[127]

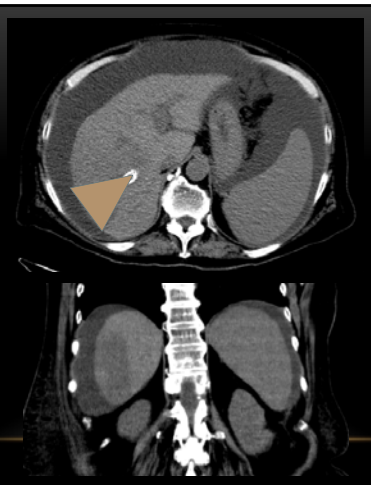
CASE

- 60F with NASH cirrhosis, 5-year history of methotrexate (stopped after cirrhosis confirmed)
- TIPS for recurrent ascites (weekly paracentesis)

MELD	
Bili	0.5
Cr	0.7
INR	1.1
Na	132
TOTAL	7



PRE	
AST	19
ALT	10
Alk Phos	103
Bili	0.5



POD #2 (36 hrs)	
AST	547
ALT	298
Alk Phos	96
Bili	1.1

POD #3	
AST	286
ALT	254
Alk Phos	100
Bili	1.0

LIVER ISCHEMIA

- Presentation
  - RUQ pain
  - Marked transient increases in LFTs (5x normal)
  - Triangular perfusion defect
  - Rarely, acute liver failure with high mortality rates
  - Clinical evolution depends on:
    - Preexisting liver reserve
    - Size of ischemia/infarct
- Potential mechanisms
  - Hepatic arterial problems (thrombosis, pseudoaneurysms, AVF) caused by needle puncture injury or compression of hepatic artery by stent
  - Hepatic vein thrombosis

CLINICAL STUDY

Segmental Liver Ischemia/Infarction after Elective Transjugular Intrahepatic Portosystemic Shunt Creation: Clinical Outcomes in 10 Patients

Jorge E. Lopera, MD, Venkata Katabathina, MD, Brian Bosworth, MD, Deepak Garg, MD, Ghazwan Kroma, MD, Andres Garza-Berlanga, MD, Rajeev Suri, MD, and Michael Wholey, MD

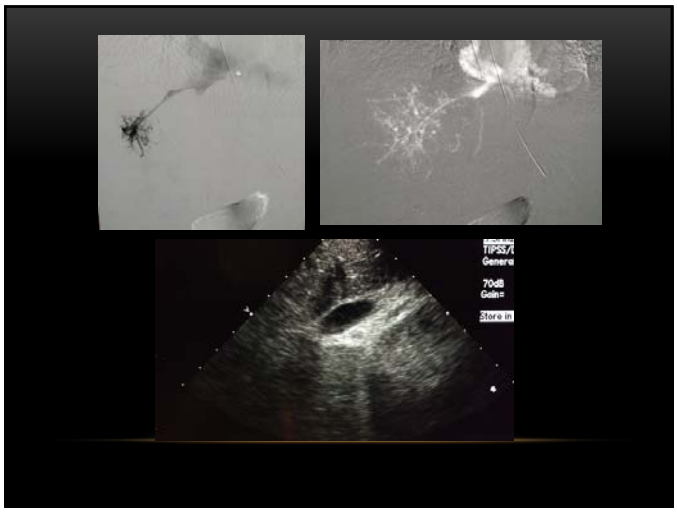
- Retrospective study of 77 contrast-enhanced scans after TIPS
  - Imaging not routinely obtained after TIPS
- Incidence of perfusion defects: 13%

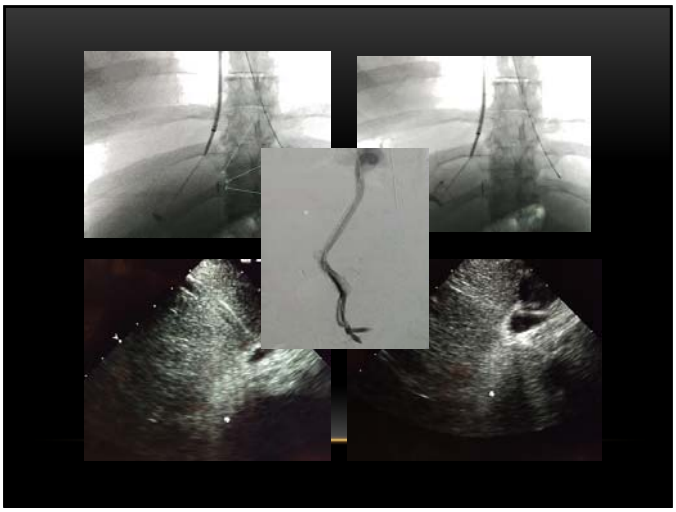
Clinical Management

- Conservative (majority)
- Liver transplantation
  - May be only livesaving procedure if severe liver failure after TIPS
- TIPS reduction
  - Unknown role in management of ischemia

DIPS DIRECT INTRAHEPATIC PORTOSYSTMIC SHUNT

- "Dotter" DIPS = transcaudate
  - Need IVUS/ICE
- Most other DIPS are just TIPS variants (like "Ace TIPS")
- DIPS Indications
  - Budd Chiari
  - To avoid vascular masses

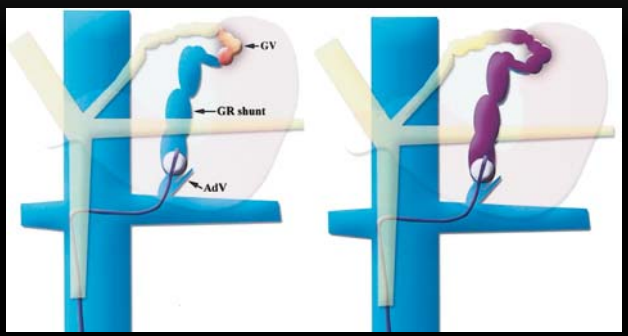




BALLON-OCCLUDED TRANVENOUS RETROGRADE OBLITERATION

- ACR Appropriateness Committee on IR has recognized BRTO as a viable alternative to TIPS for the management of gastric varices
- But it did not define the anatomic or clinical scenarios
  - Reserved for patients who are not TIPS candidates (MELD >18/25 ?)
  - Favorable anatomy
  - Operator preference
- Key merits of BRTO over TIPS
  - Preserve hepatic function
  - Reduce risk of hepatic encephalopathy
- BARTO, CARTO, PARTO

BRTO – BALLON-OCCLUDED TRANVENOUS RETROGRADE OBLITERATION



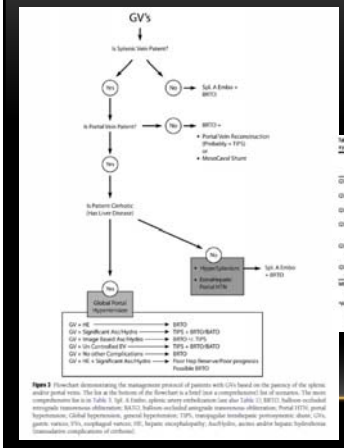
Indications for BRTO	Poor candidates for TIPS
Actively bleeding GV with GRS	MELD > 19
H/O bleeding GV with GRS	Encephalopathy
GV with GRS with signs of impending bleeding	H/O lobar TACE
Refractory encephalopathy with GRS	HCC and a candidate for TACE
	Portal vein thrombosis

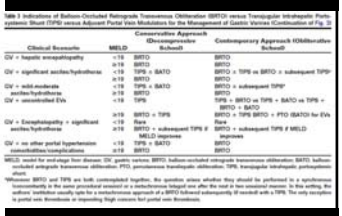
Immediate	Long-term
Hemoglobinuria (15-100%)	Encephalopathy (18%)
PE (2-4%)	Portal hypertensive gastropathy (5-13%)
Arrhythmia (2%)	Post-BRTO gastropathy (57%)
Anaphylaxis (2-5%)	Worsening esophageal varices (14-68%)
Hepatic failure (5-7%)	Bleeding esophageal varices (17-24%)
Renal failure (5%)	

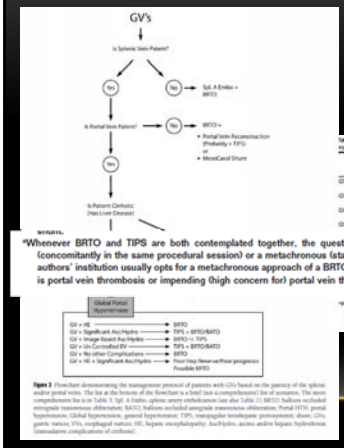
Table 1 Indications of BRTO of Gastric Varices in Native Livers (Nontransplanted Patients) With and Without Adjunctive Portal Modulators

Indications Based on Presentation	Supporting Indications Based on Hepatic Comorbidities[a]
• Gastric varices with active bleeding (emergent) • Gastric varices with previous bleeding (secondary prophylaxis: urgent/elective) • High-risk gastric varices with no previous bleeding (primary prophylaxis: elective) • Refractory hepatic encephalopathy (elective: not comatosed) • Refractory hepatic encephalopathy (urgent: coma)	• H/O HCC with transcatheter regional therapy • HCC with intention to treat by transcatheter regional therapy • H/O significant or current hepatic encephalopathy • Patient refusing TIPS • MELD >18
Indications for Adjuvant Portal Flow Modulators (TIPS or splenic artery embolization)	
±TIPS (MELD <19)	**±Splenic Artery Embolization (MELD independent)**
• Significant ascites/hydrothorax[b] • Uncontrolled esophageal varices • Portal vein thrombosis after recannulation[c]	• Splenic vein thrombosis ±PVT • Thrombocytopenia (hypersplenism) • Idiopathic portal hypertension without liver disease (splenomegally) • Esophageal varices or concern for worsening/bleeding esophageal varices

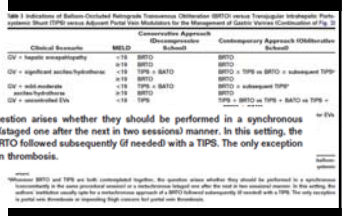
H/O, history of; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; PVT, portal vein thrombosis; TIPS, transjugular intrahepatic portosystemic shunt.







*Whenever BRTO and TIPS are both contemplated together, the question arises whether they should be performed in a synchronous (concomitantly in the same procedural session) or a metachronous (staged one after the next in two sessions) manner. In this setting, the authors' institution usually opts for a metachronous approach of a BRTO followed subsequently (if needed) with a TIPS. The only exception is portal vein thrombosis or impending (high concern for) portal vein thrombosis.



EDUCATION EXHIBIT

Radiographics

Transcatheter Obliteration of Gastric Varices

Part 1. Anatomic Classification[1]

Hiro Kiyosue, MD • Hiroaki Mori, MD • Hisato Matsumoto, MD
Tomomi Yamada, MD • Yuzo Abe, MD • Yuichi Ohkura, MD

Since its introduction in the mid-1990s, balloon-occluded retrograde transvenous obliteration (BRTO) has become widely accepted in Japan as a minimally invasive, highly effective treatment for gastric varices. Sufficient filling and stagnation of the sclerosing agent in the entire varix are important for successful treatment with BRTO. In this context, however, the success of BRTO in this context also requires familiarity with the hemodynamic features of the varices, including the patterns of their afferent and draining veins, which affect the degree of difficulty in performing BRTO. Thus, accurate assessment of the hemodynamic pattern before and during each procedure is essential for successful treatment. Sixty cases of gastric varices that were successfully treated with transcatheter techniques over the past 5 years were reviewed and analyzed. From this study, a classification system for gastric varices was developed that is based on the hemodynamic pattern of the varices.

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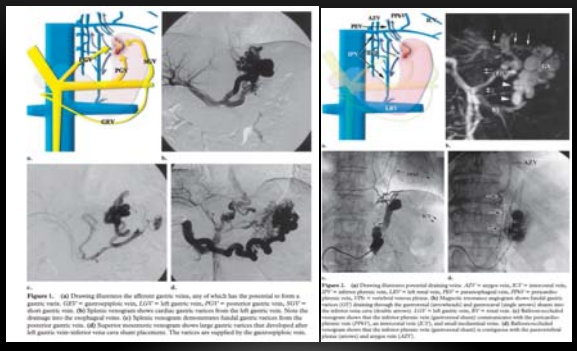


Figure 1. (a) Drawing illustrates the efferent gastric veins, any of which has the potential to form a gastric varix. *GEV* = gastroepiploic vein, *LGV* = left gastric vein, *PGV* = posterior gastric vein, *SGV* = short gastric vein. (**b**) Splenic venogram shows cardiac gastric varices from the left gastric vein. Note the drainage into the esophageal veins. (c) Splenic venogram demonstrates funnel gastric varices from the posterior gastric vein. (**d**) Superior mesenteric venogram shows large gastric varices that developed after left gastric vein–inferior vena cava shunt placement. The varices are supplied by the gastroepiploic vein.

Figure 2. (a) Drawing illustrates potential draining veins. *AZV* = azygos vein, *ICV* = intercostal vein, *IPV* = inferior phrenic vein, *LRV* = left renal vein, *PEV* = paraesophageal vein, *PPeV* = pericardiophrenic vein, *VBs* = vertebral venous plexus. (**b**) Magnetic resonance angiogram shows funnel gastric varices (*GV*) draining through the gastrorenal (arrowheads) and gastrocaval (single arrow) shunts into the inferior vena cava (double arrows). *LGV* = left gastric vein, *RV* = renal vein. (**c**) Balloon-occluded venogram shows that the inferior phrenic vein (gastrocaval shunt) communicates with the pericardiophrenic vein (*PPeV*), an intercostal vein (*ICV*), and small mediastinal veins. (**d**) Balloon-occluded venogram shows that the inferior phrenic vein (gastrocaval shunt) is contiguous with the paravertebral plexus (arrows) and azygos vein (*AZV*).

Figure 3. Drawings illustrate the standard BRTO method for gastric varices that drain through the gastrorenal shunt. Right femoral access is used to insert a balloon catheter into the outlet of the gastrorenal (GR) or gastrocaval shunt. Balloon-occluded venography is performed, and 5% EOI is injected via the balloon catheter until the gastric varices (GV) are completely filled with EOI. The EOI is then allowed to stagnate for 30–45 minutes. *AzV* = adrenal vein.

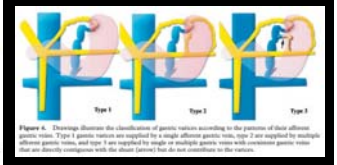


Figure 4. Drawings illustrate the classification of gastric varices according to the patterns of their afferent gastric veins. Type 1 gastric varices are supplied by a single afferent gastric vein, type 2 are supplied by multiple afferent gastric veins, and type 3 are supplied by single or multiple gastric veins with coexistent gastric veins that are directly contiguous with the shunt (arrow) but do not contribute to the varices.

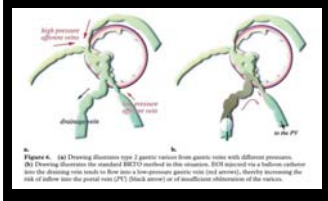


Figure 6. (**a**) Drawing illustrates type 2 gastric varices from gastric veins with different pressures. (**b**) Drawing illustrates the standard BRTO method in this situation. EOI injected via a balloon catheter into the draining vein tends to flow into a low-pressure gastric vein (red arrow), thereby increasing the risk of inflow into the portal vein (*PV*) (black arrow) or of insufficient obliteration of the varices.

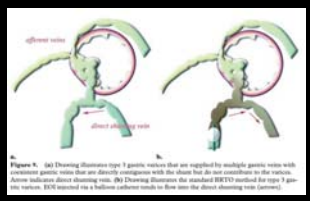


Figure 7. (**a**) Drawing illustrates type 3 gastric varices that are supplied by multiple gastric veins with coexistent gastric veins that are directly contiguous with the shunt but do not contribute to the varices. Arrow indicates direct shunting vein. (**b**) Drawing illustrates the standard BRTO method for type 3 gastric varices. EOI injected via a balloon catheter tends to flow into the direct shunting vein (arrows).

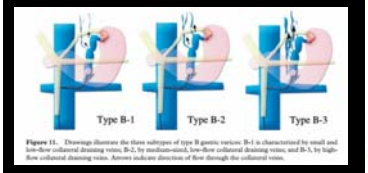


Figure 11. Drawings illustrate the three subtypes of type B gastric varices. B-1 is characterized by small and low-flow collateral draining veins; B-2, by medium-sized, low-flow collateral draining veins; and B-3, by high-flow collateral draining veins. Arrows indicate direction of flow through the collateral veins.

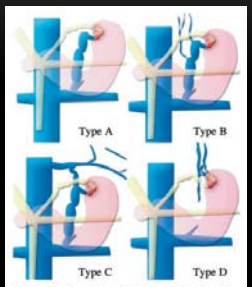


Figure 10. Drawings illustrate the classification of gastric varices according to the pattern of their draining veins. Type A gastric varices are contiguous with a single shunt alone, type B are contiguous with a single shunt and collateral veins, type C are contiguous with both the gastrorenal and gastrocaval shunts, and type D are not contiguous with a catheterizable shunt.

RESULTS

- Technical success: 79-100%
  - Balloon rupture: 15%
    - 50% of balloon ruptures are early and cause technical failure
  - 6.5% of technically successful BRTO are hemodynamic failures (fail to completely obliterate flood flow within gastric varices)
- Clinical success
  - Reduction of encephalopathy (100%)
  - Control of actively bleeding varices (91-100%)
    - GI rebleed rate <10%

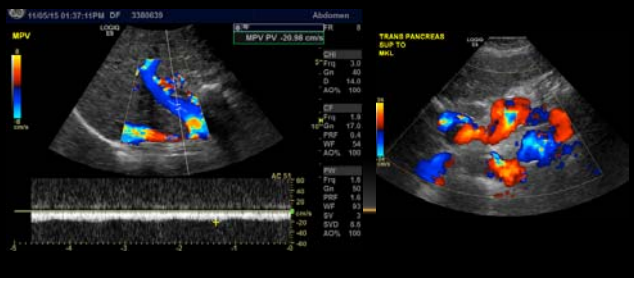
DRAWBACKS

- Occlusion of spontaneous gastrorenal shunt aggravates portal hypertension
  - Contrary to decompressive ideology of managing portal hypertension

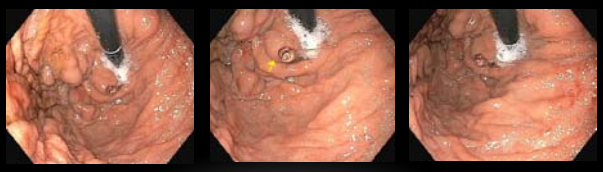
REFRACTORY UPPER GI/VARICEAL BLEED

Ultrasound (3 months prior)

- Cirrhotic morphology of liver
- Portal vein: main portal vein patent but demonstrates reversed flow (20 cm/s)



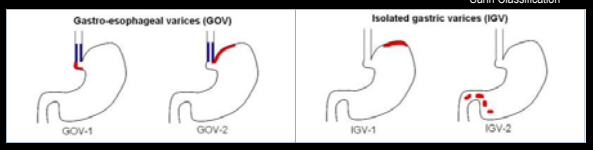
EGD: Large blood clot overlying site of previous gastric varices in fundus of stomach



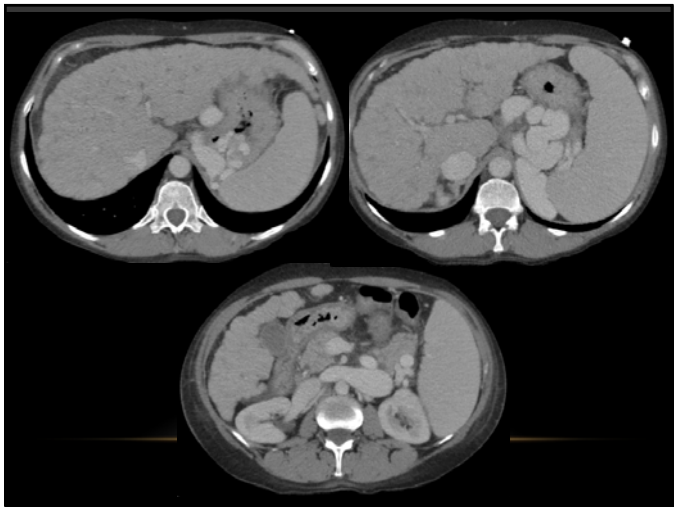
ENDOSCOPY

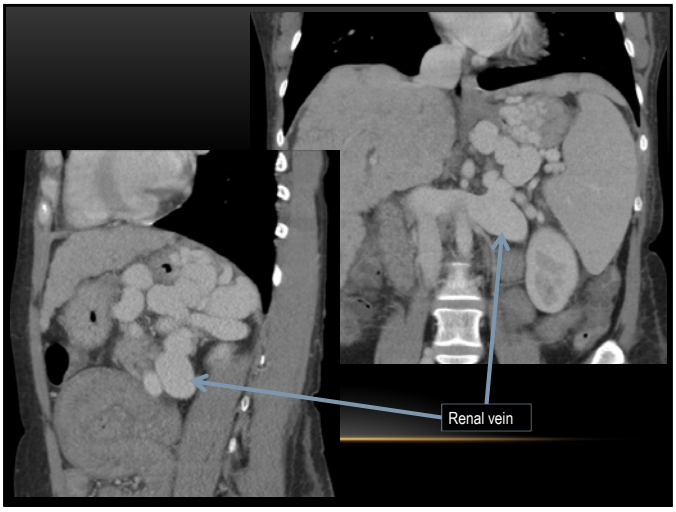
- Endoscopy is 1st line for diagnosis

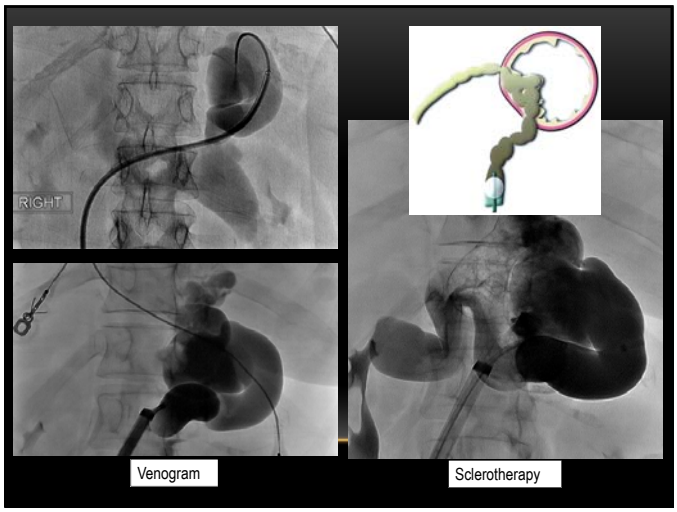
Sarin Classification

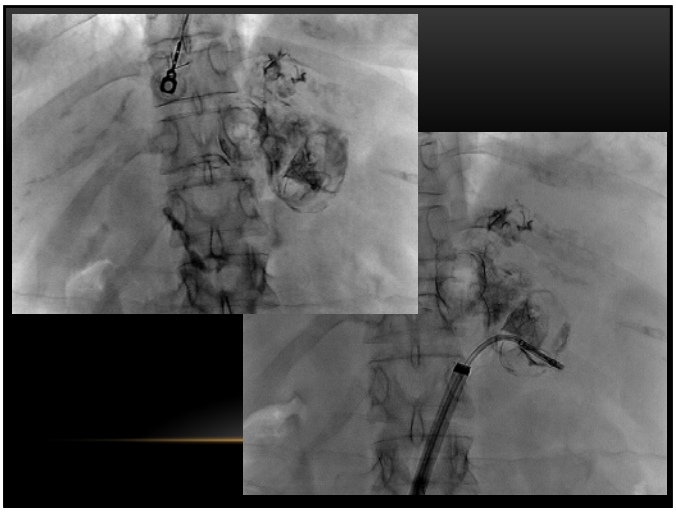


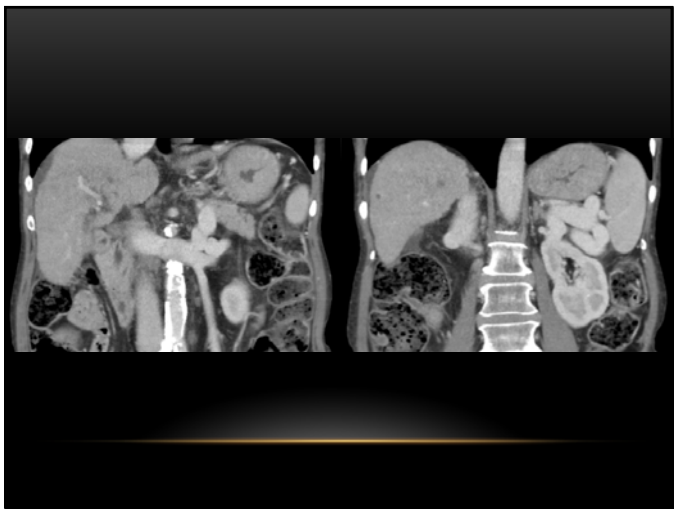
  - GOV-1 can be treated just like esophageal varices
  - GOV-2 and IGV respond better to TIPS and/or BRTO
- Sclerotherapy +/- banding
  - Poor results in controlling active GV bleeding
- Endoscopic-guided cyanoacrylate injection*

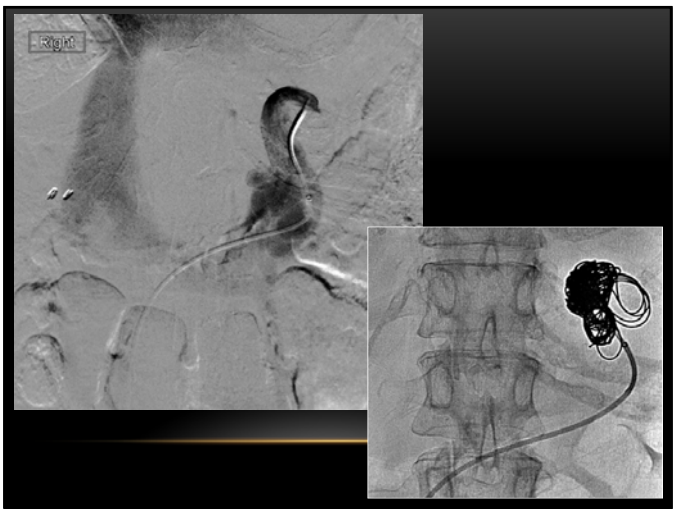





RIGHT
Venogram
Sclerotherapy






Right

TIPS OR BRTO?

- Similar effectiveness for active gastric variceal bleeding
- Lower rebleed rate with BRTO*

	TIPS	BRTO
Control of active GV bleeding	90-96%	90%
Rebleed rate (@ 6-12 mo)	26-31% *bare stents	<5-10%
Survival	No statistically significant difference Ninoi et al. *AJR* 2004	

Review: Saad et al. *CVIR* 2014

COMBINED TIPS + BRTO?

- From a hemodynamic standpoint these are opposing procedures
  - BRTO: occlusion of spontaneous portosystemic shunts which increases portal pressure
  - TIPS: creation of a portosystemic shunt which decreases portal pressure
- Combined TIPS + BRTO
  - Spontaneous shunt is replaced by a controlled, well-defined, man-made shunt
  - The increased portal pressure caused by the BRTO is tempered

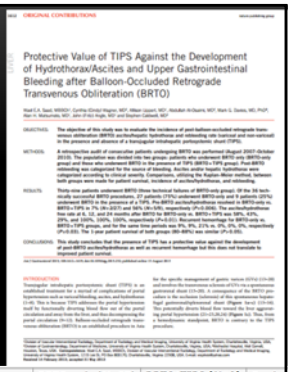
COMBINED TIPS + BRTO?

- Single-institution, retrospective study
- N=36; 27 BRTO only, 9 BRTO+TIPS

Combined TIPS + BRTO

- Decreased ascites/hydrothorax rates
- Reduced esophageal variceal bleeding
- Reduced overall gastric variceal bleeding rates

Saad et al. *Am J Gastroenterol* 2013

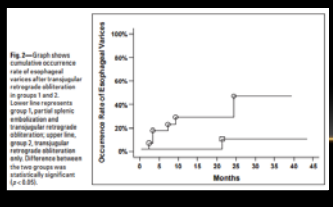


Protective Value of TIPS Against the Development of Hydrothorax/Ascites and Upper Gastrointestinal Bleeding after Balloon-Occluded Retrograde Transvenous Obliteration (BRTO)

Criteria	BRTO-only (*N*=27)	BRTO+TIPS (*N*=9)	*P* value
Ascites improved	*N*=2/27 (7.4%)	4/9 (44%)	0.025
Hydrothorax improved	*N*=0/27 (0.0%)	1/9 (11%)	0.250
Ascites and/or hydrothorax improved	*N*=2/27 (7.4%)	5/9 (56%)	0.006
New ascites	6/27	0/9	0.303
Worse ascites	3/27	0/9	0.558
New or worse ascites	9/27	0/9	0.076
Worse ascites and/or hydrothorax	9/27	0/9	0.076

SPLENIC ARTERY EMBOLIZATION

- Adjunctive splenic embo may reduce the effects of increased portal HTN following BRTO
  - By decreasing splenic vein contribution to portal circulation



Gastric Varices with Gastrorenal Shunt: Combined Therapy Using Transjugular Retrograde Obliteration and Partial Splenic Embolization

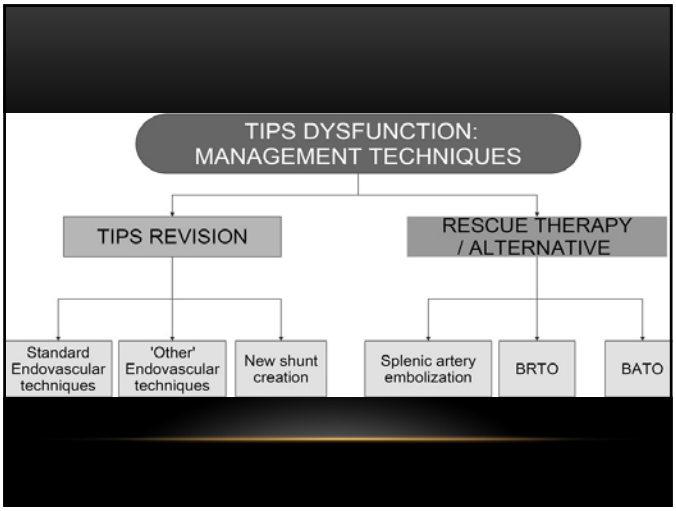
Chikamori et al. *AJR* 2008

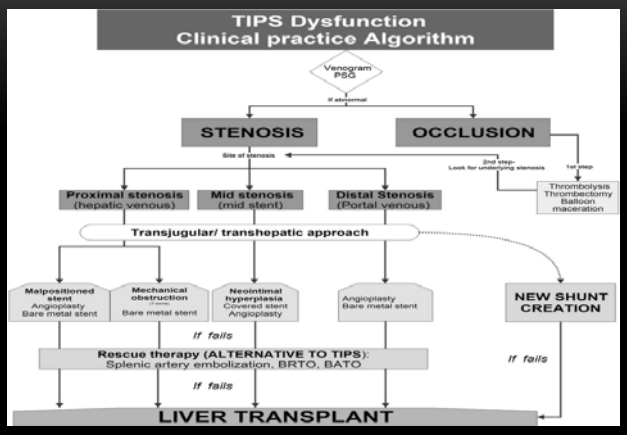
SPLENIC ARTERY EMBOLIZATION

- Decreases splenic blood pressure → portal venous pressure
- Diverts blood flow to hepatic artery → improves liver function
  - Decreases incidence of hepatic encephalopathy?
- Contraindications
  - Hepatofugal portal flow – increases risk of portal vein thrombosis

Smith M, Ray CE. Splenic Artery Embolization as an Adjunctive Procedure for Portal Hypertension. Semin Intervent Radiol. 2012;29(2):135-9

Yoshida H et al. Long-term results of partial splenic artery embolization as supplemental treatment for portal-systemic encephalopathy. Am J Gastroenterol. 2005;100(1):43-7





IR & PORTAL HYPERTENSION

- Diagnosis
- Control of recurrent variceal bleeding

Table 5. Surgical Shunts and TIPS Versus Endoscopic Therapy in the Prevention of Rebleeding

Rebleeding Rate		Encephalopathy		Mortality	
Endo	PCS	Endo	PCS	Endo	PCS
49.8%	12.4%*	8.6%	17.2%**	28.8%	28.8%
Endo	TIPS	Endo	TIPS	Endo	TIPS
46.6%	18.9%*	18.7%	34.0%**	26.5%	27.3%

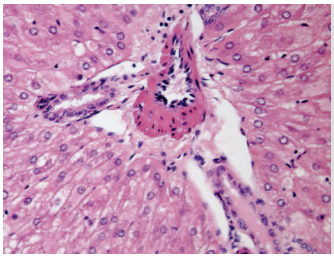
x therapy; PCS, portacaval shunt. *By meta-analysis, rebleeding significantly less with PCS or TIPS compared to Endo. **By meta-analysis, incidence greater with PCS or TIPS compared to Endo. Data taken from D'Amico et al.[79] and Papatheodoridis et al.[81]

- Control of refractory ascites

Table 6. TIPS Versus Large Volume Paracentesis in Treatment-Refractory Cirrhotic Ascites

Number of Patients		Ascites Improved		Survival‡		New or Severe Encephalopathy	
TIPS	LVP	TIPS	LVP	TIPS	LVP	TIPS	LVP
13	12	38%	0%	29%	60%	15%	6%
29	31	84%*	43%	58%	32%	23%	13%
35	35	51%*	17%	26%	30%	60%*	34%
52	57	58%*	16%	35%	33%	38%	21%
33	33	79%*#	42%	59%*	29%	61%	39%

- Anatomic optimization for liver transplant



Alcoholic Hepatitis and Liver Transplantation

Michael Lucey

Alcohol Hepatitis and Liver Transplantation

At the Forefront of Hepatology,
University of Chicago
May 4, 2019

Michael R. Lucey MD
Professor and Chief, Division of Gastroenterology and Hepatology
University of Wisconsin School of Medicine and Public Health

Why is rescue LT not standard of care for life-threatening AH?

Why is rescue LT not standard of care for life-threatening AH?

Outcome
- **Confusion about the endpoint**
- **Lack of definitive (American) data**

Process
- **Inconsistency in process of patient selection**
- **Uncertainty about treatment of AUD**

Social viability
- **Dynamics of transplantation/impact on stakeholders ~ stigma**

LT for AH: Pro and Con

Lets consider the arguments?

LT for AH: Pro and Con

Arguments against LT for AH

- **AH is a self-inflicted condition so these patients are less deserving of this limited resource, than patients with other forms of liver disease.**

Arguments in favor of LT for AH

LT for AH: Pro and Con

Arguments against LT for AH

- **AH is a self-inflicted condition so these patients are less deserving of this limited resource, than patients with other forms of liver disease.**

Arguments in favor of LT for AH

- **AUD is a disease with a complex genetic, psychological and social foundation. Personal behavior also influences many other indications for LT such as ALF (suicide attempt), NAFLD (excessive caloric intake), HBV/HCV (high risk behaviors), HCC related to NAFLD, HBV, HCV.**

LT for AH: Pro and Con

Arguments against LT for AH

- **A required interval of abstinence (6-month rule) allows for liver recovery to obviate the need for LT.**

Arguments in favor of LT for AH

-

LT for AH: Pro and Con

Arguments against LT for AH

- **A required interval of abstinence (6-month rule) allows for liver recovery to obviate the need for LT.**

Arguments in favor of LT for AH

- **Many patients with severe AH without response to medical care will die during a required interval of abstinence, so LT saves lives. Validated and widely used models (Lille+/-MELD) can accurately predict survival, especially in life-threatening AH.**

LT for AH: Pro and Con

Arguments against LT for AH

- **A required interval of abstinence (6-month rule) allows a patient demonstrate a commitment to abstinence and gives the opportunity to implement preventive strategies against future relapse.**

Arguments in favor of LT for AH

LT for AH: Pro and Con

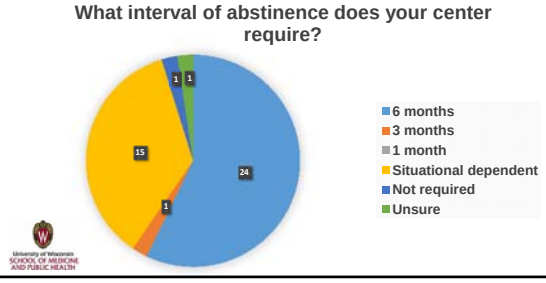
Arguments against LT for AH

- **A required interval of abstinence (6-month rule) allows a patient demonstrate a commitment to abstinence and gives the opportunity to implement preventive strategies against future relapse.**

Arguments in favor of LT for AH

- **While duration of pre-LT sobriety predicts the likelihood of post-LT relapse, it is imprecise at 6-months as a single predictor. Reliance on the 6-month rule discriminates against patients with favorable psychosocial profiles, who have a low risk of relapse despite recent drinking.**

In a 2015 pilot survey, we received responses from 42 of 134 US LT Centers (comprising 50% of all transplants in 2014)



LT for AH: Pro and Con

Arguments against LT for AH

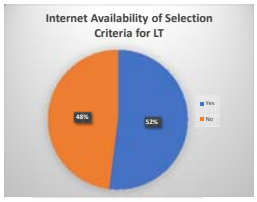
- **Public perception of LT for AH is negative and it will lead to reduced organ donation.**

Arguments in favor of LT for AH

- **Evidence for this is lacking and recent public surveys demonstrate that a majority has a neutral opinion of LT for AH.**

The Lack of Transparency Surrounding Eligibility of AUD Patients for LT

US Liver Transplant Centers:	141
Website:	141
Any eligibility criteria:	73 (52%)
Any discussion of ETOH:	24 (17%)
Stated 6-month abstinence requirement	3(2%)



LT for AH: Pro and Con

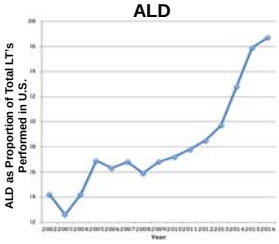
Arguments against LT for AH

- **Transplantation of AH patients in greater numbers will lead to more recipients with post LT alcohol relapse and greater rates of allograft loss.**

Arguments in favor of LT for AH

National Trends in LT for AALD in U.S.

ALD

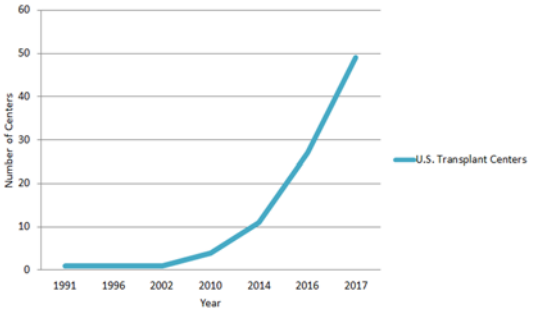


AH

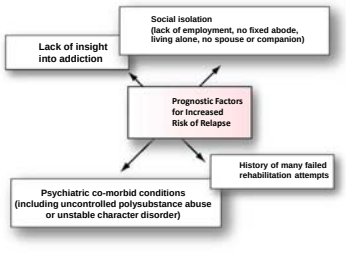
UNOS listing diagnoses 2012-2016

Lee BP et al, JAMA 2019

Centers performing liver transplantation for alcoholic hepatitis in the US



Alcoholic Relapse



Codifying Relapse Risk in LT Candidates

- U of M Alcoholism Prognosis Score: poor insight, isolation/ no spouse, # prior treatments of AUD, substance abuse/psych
- Alcohol Relapse Risk Assessment: (Retrospective, single center, post LT): poor insight, isolation, no spouse
- High-risk Alcoholism Relapse (HAR): (prospective FU of male veterans with AUD): duration of heavy drinking; usual # daily drinks, # prior treatments of AUD
- Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT): poor insight, isolation, substance abuse
- SALT score: (ACCELERATE): >10 drinks per day at initial hospitalization (+4 points), # prior treatments of AUD (+4 points), prior alcohol-related legal issues (+2 points), substance abuse (+1 point).
-

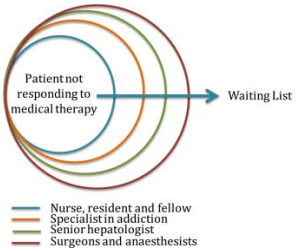
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early Liver Transplantation for Severe Alcoholic Hepatitis

Philippe Mathurin, M.D., Ph.D., Christophe Moreno, M.D., Ph.D., Didier Samuel, M.D., Ph.D., Jérôme Dumortier, M.D., Ph.D., Julia Salleron, M.S., François Durand, M.D., Ph.D., Hélène Castel, M.D., Alain Duhamel, M.D., Ph.D., Georges-Philippe Pageaux, M.D., Ph.D., Vincent Leroy, M.D., Ph.D., Sébastien Dharancy, M.D., Ph.D., Alexandre Louvet, M.D., Ph.D., Emmanuel Boleslawski, M.D., Ph.D., Valerio Lucidi, M.D., Thierry Gustot, M.D., Ph.D., Claire Francoz, M.D., Christian Letoublon, M.D., Denis Castaing, M.D., Jacques Belghiti, M.D., Vincent Donckier, M.D., Ph.D., François-René Pruvot, M.D., and Jean-Charles Duclos-Vallée, M.D., Ph.D.

Selection of AH patients for LT: le modèle français



Clinical Liver Disease
Volume 6, Issue 6, pages 149-152, 21 JAN 2016 DOI: 10.1002/cld.521
http://onlinelibrary.wiley.com/doi/10.1002/cld.521/full#cld521-fig-0002

AASLD

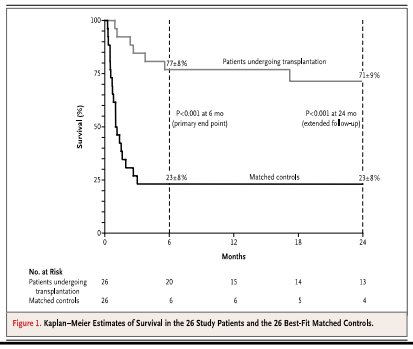


Figure 1. Kaplan–Meier Estimates of Survival in the 26 Study Patients and the 26 Best-Fit Matched Controls.

21

American Consortium of Early LivER Transplantation for Alcoholic Hepatitis (ACCELERATE-AH)

12 Centers from 8 UNOS regions

ACCELERATE –AH Study Design

- **Retrospective study of consecutive patients transplanted at each center for AH**
- **Standardized data collection forms:**
  - **Patient characteristics**
  - **Alcohol/drug use histories**
  - **Medical management**
  - **Explant histology**
  - **Survival outcomes**
  - **Frequency / patterns of alcohol alcohol use post-LT**

Clinical Characteristics

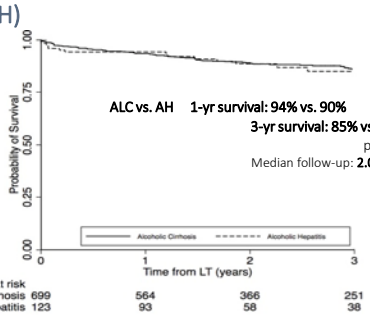
Maddrey's Score (severe if ≥32)*	78 (58-102)
Steroid Use	54%
Day 7 Lille Score (non-responder if >0.45)	0.82 (0.56-0.97)
Na-MELD Score at Listing*	38 (34-40)
Days Listed Before LT*	7 (3-12)
Days from Last Drink to LT*	55 (36-91)

*Median (IQR)

Patient Survival in Alcoholic Cirrhosis (ALC) vs. Alcoholic Hepatitis (AH)

Limited to 12 ACCELERATE-AH sites

N=147 AH
N=699 ALC



ALC vs. AH **1-yr survival: 94% vs. 90%**
3-yr survival: 85% vs. 83%
p=0.85
Median follow-up: **2.0** years

Causes of Death

N=147

18 deaths

9* within 90 days of LT
- **5** sepsis
  - **1** fungal
  - **1** bacteremia
  - **1** pneumonia
  - **1** abdominal
  - **1** unclear source

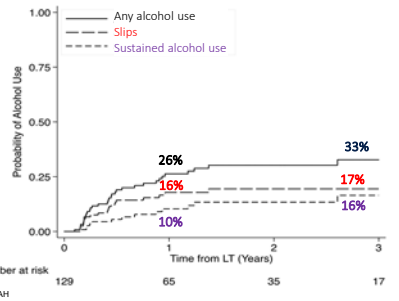
9 >1-year post-LT
- **7** alcohol-related
  - **1** overdose
  - **6** graft failure

*8 of 9 received steroids pre-LT for AH (p=0.04)

ACCELERATE-AH

Lee BP et al, Gastroenterology, 2018;155:422-430

Alcohol Use Post-LT: Slips vs. Sustained



ACCELERATE-AH

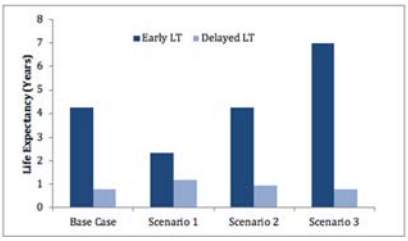
Early-versus-Delayed Liver Transplantation for Alcoholic Hepatitis: Modeling of Harms and Benefits

- A mathematical model that simulated a virtual trial comparing early versus delayed LT in several AH patients
- Considered different post-LT alcohol use categories: none, slip (alcohol use followed by sobriety), sustained.
- Pre-LT mortality was determined by joint-effect model (MELD and Lille score).

Jag Chhatwal, PhD
Senior Scientist
Harvard Institute for Technology Assessment

ACCELERATE-AH

Survival Benefit with Early Transplant Regardless of Alcohol Relapse Rate



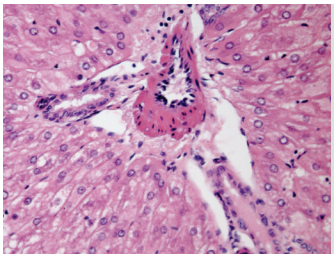
Base case: equal incidence of sustained alcohol use and slips post-LT in early vs delayed LT

Scenario 1: all patients after early LT have sustained alcohol use and no patient after delayed LT has any alcohol use.

Scenario 2: assumes no patient offered delayed has any alcohol use in the 6-month pre-LT period.

Scenario 3: assumes no patient offered early LT has any alcohol use after LT.

Should We Transplant Patients with Alcoholic Hepatitis?



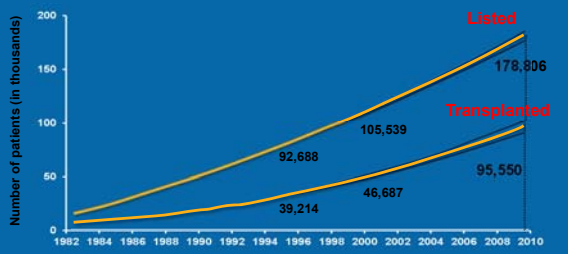
A New Paradigm in Organ Preservation: Ex-Vivo Normothermic Perfusion

John J. Fung, MD

Disclosure Information
At the Forefront of Hepatology
John Fung, MD, PhD

- I have the following financial relationships to disclose:
  Consultant for: OrganOx (DSMB)
  Investigator with the Cleveland Clinic NMP program
- I will discuss the investigational use of NMP in my presentation

The Transplant Waiting List Is Growing



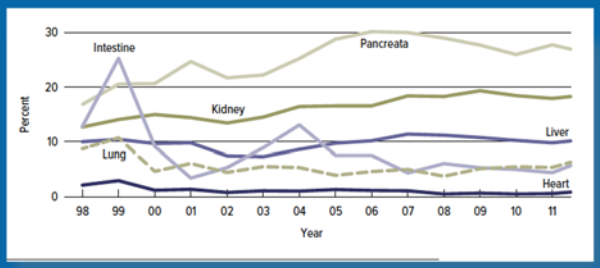
US Organ Procurement and Transplantation Network and Scientific Registry of Transplant Recipients Annual Report 2008; Available at: http://optn.transplant.hrsa.gov/ar2008/Preface_Contributors.htm?cp=1, accessed 28 August 2012

1967

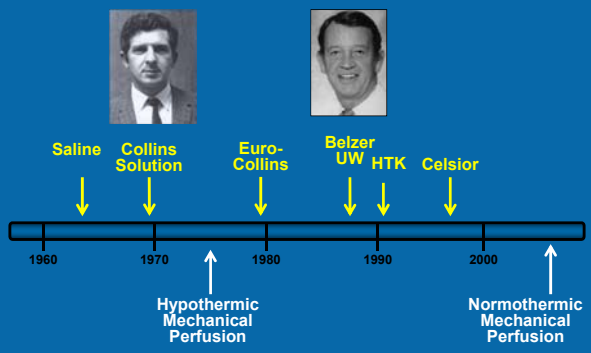
"Experiences in Hepatic Transplantation"
Dr. Thomas Starzl (University of Colorado)

"The provision of a viable and minimally damaged homograft is undoubtedly the most important single factor in the determinant of success."

Organ Discard Rate is Increasing



Source: SRTR



Ischemia-Reperfusion Injury

- Ischemia starts by interrupting blood supply to organs or tissues
- Metabolism is not arrested in cold conditions, but slowed by a factor of 1.5–2 for each 10° C fall in temperature
- Anaerobic metabolism results in accumulation of end products of metabolism: e.g. protons, lactate, hypoxanthine
- Upon reperfusion, these by-products contribute to the generation of oxygen free radicals, which damage tissues termed ischemia-reperfusion injury (IRI)

Serracino-Inglott F, et al. 2001. The American Journal of Surgery. 181: 160-166

Limitations Of Static Cold Storage

- Cooling
  - Loss of cell membrane functions
- No oxygen delivery
  - Anaerobic metabolism
- Accumulation of metabolites
  - Ischemia-reperfusion
- Limited viability assessment
  - Injury occurs at time of reperfusion

Acceptable for high quality, but not marginal organs

Expanded Criteria Donor Organs Are More Sensitive to IRI

- Steatotic grafts
- Older livers – fibrosis, arteriosclerosis,
- Donors after Cardiac Death (DCD)
- Prolonged preservation

Clinical Impact of IRI

- Problems associated with IRI of allografts:
  - –Contributes to morbidity
  - –Leads to primary non-function or primary dysfunction
  - –Associated with an increase in graft rejection
  - –Increases discard of allografts due to outcome concerns

Clavien P, et al. 1992. Transplantation. 53: 957-978

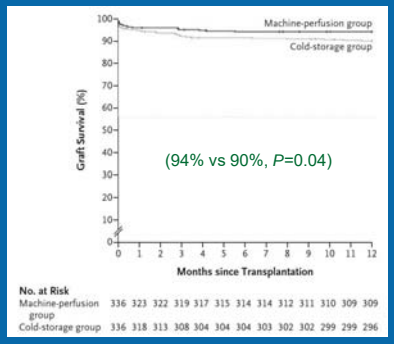
Hypothermic Machine Preservation


The NEW ENGLAND JOURNAL of MEDICINE

JANUARY 1, 2009

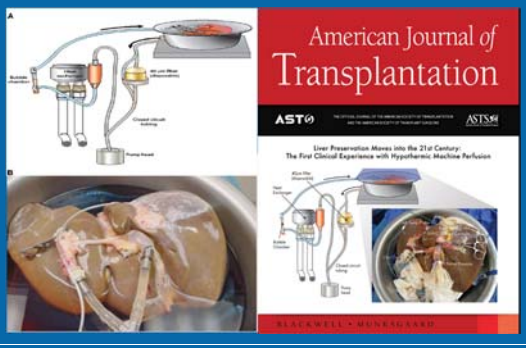
Machine Perfusion or Cold Storage in Deceased-Donor Kidney Transplantation

Kidney Allograft Survival Was Superior in the Machine-Perfusion Group

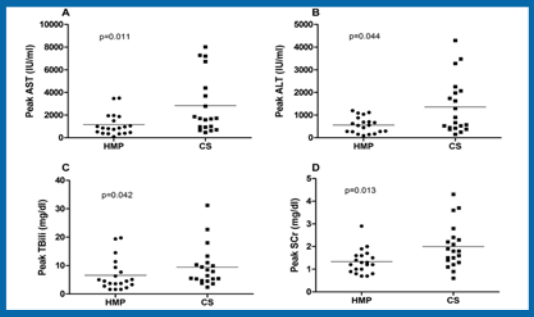


Moers C et al. *N Engl J Med.* 2009;360:7.

Columbia Ex-Vivo Liver Hypothermic Machine Perfusion



Hypothermic Machine Perfusion Reduced Peak AST, ALT, TBIL and Creatinine



Guarrera et al., AJT, 2009

Normothermic Perfusion

Hypothermic preservation: suppresses metabolism up to 96%

"non-damaged" organ > cold ischemia inhibition of metabolism > reimplant > graft IRI

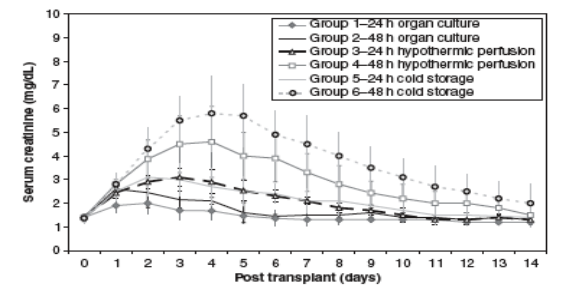
"damaged" organ > cold ischemic inhibition of metabolism > reimplant > PGD/PNF

Normothermic perservation: resuscitates oxidative metabolism of sufficient magnitude to support new protein synthesis that initiates cellular reparative processes

What Can Normothermic Perfusion Do?

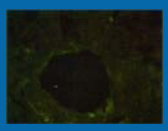
- Improved preservation
  - –Physiological environment
  - –Supports normal cellular function
- Viability assessment
  - –Testing of functioning organ
  - –Metabolic, synthetic, immunological biomarkers; tissue analysis
- Cellular repair
  - –Deliver nutrients
  - –Intrinsic cellular recovery
  - –Organ-specific therapies

Recovery of ATN in DCD Kidneys Using Normothermic Perfusion



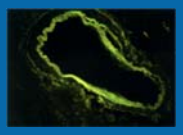
Brasile et al: AJT, 2005, 5:300

Initiation of Reparative Process During Normothermic Preservation



De novo protein synthesis of GFP transfection

< CS EMS>



0 WI 2 h WI 2 h WI + 6h EMS 2 h WI + 18h EMS 2 h WI + 24h EMS

Cytoskeletal Injury Marker - ZO-1 (key protein involved in the regulation of barrier function)

2+/-0.5 80+/-5 76+/-5 32+/-8 8+/-3

Repair Marker of Active DNA Synthesis - PCNA

2+/-0.3 4+/-2 23+/-3 57+/-8 88+/-7

Brasile et al: AJT, 2005, 5:300

American Journal of Transplantation
Wiley Periodicals Inc.

doi: 10.1111/ajt.12179

Renal Transplantation After *Ex Vivo* Normothermic Perfusion: The First Clinical Study

M. L. Nicholson* and S. A. Hosgood

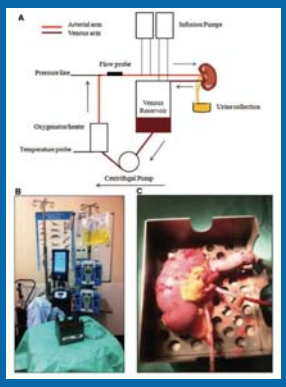
Aim: to assess the effects of NMP in kidneys from marginal donors (ECD)

18 kidneys underwent a period of NMP immediately before transplantation. (63 ± 16 min)

Kidneys were perfused with a plasma free red cell based solution at a mean temperature of 34.6◦C.

The outcome of these kidneys was compared to a control group of 47 ECD kidneys that underwent static cold storage (CS).

Results



The delayed graft function rate (DGF), defined as the need for dialysis within the first 7 days after surgery was 5.6% in the NMP group vs. 36.2% in the CS group (p = 0.014)

Normothermic Machine Perfusion of the Kidney is safe feasible

Liver Perfusion Challenges

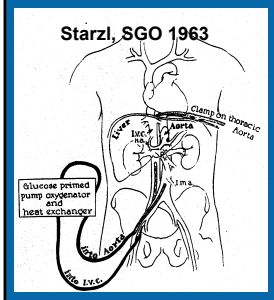
The liver has dual inflow, in which the arterial and portal venous system are subjected to completely different flows and pressures

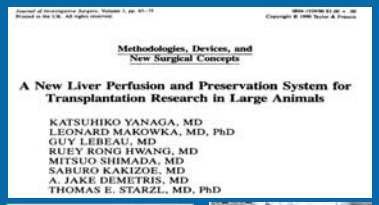
- Portal Vein = Low resistance with high flows
- Hepatic artery = High resistance with low flows

The hepatic arterial buffer response, is a compensatory mechanism that buffers the effect of changes in PV blood flow on total liver blood flow, mediated by adenosine

In addition, the liver is an extremely metabolic organ, requiring oxygen and nutrients for function.

Mechanical Perfusion of Abdominal Organs

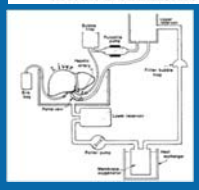




Methodologies, Devices, and New Surgical Concepts

A New Liver Perfusion and Preservation System for Transplantation Research in Large Animals

KATSUHIKO YANAGA, MD
LEONARD MAKOWKA, MD, PhD
GUY LEBEAU, MD
RUEY RONG HWANG, MD
MITSUO SHIMADA, MD
SABURO KAKIZOE, MD
A. JAKE DEMETRIS, MD
THOMAS E. STARZL, MD, PhD

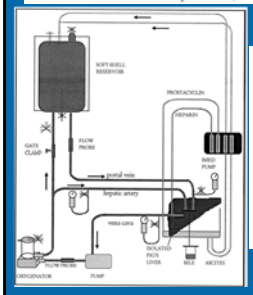


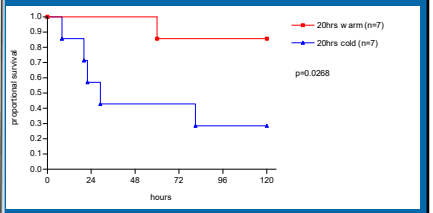
Annals of Surgery • Volume 250, Number 1, July 2009

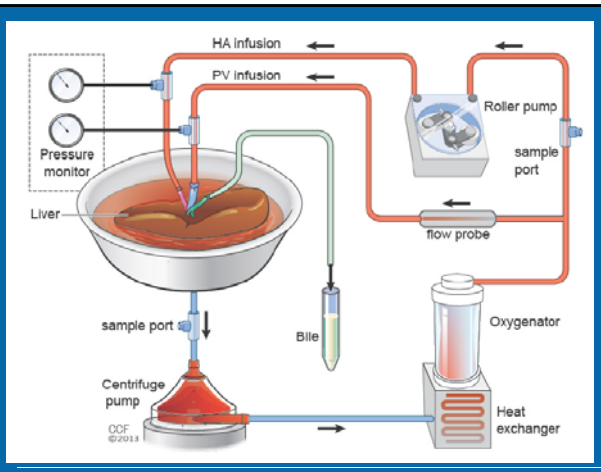
Normothermic Perfusion

A New Paradigm for Organ Preservation

Jens Brockmann, MD,¶ Srikanth Reddy, FRCS,* Constantin Coussios, PhD,‡ David Pigott, FRCA,§ Dino Guirriero, MPhil,* David Hughes, PhD,¶ Alireza Morovat, PhD,‖ Debabrata Roy, FRCS,*¶ Lucy Winter, MBBS,** and Peter J. Friend, MD, FRCS*¶*









Product Specification: What Matters?

- Physical parameters: weight, size, materials
- Usability: transportability, automation, ease of setup
- Functionality (what features are essential?):
  - –Blood or oxygen carrier?
  - –In-line or off-line blood gas analysis?
  - –Gas bottles or on-board gas production?
  - –Mains power/DC power/battery power?
  - –Parameters measured and displayed to the user?
- Regulatory compliance
- Cost

Cleveland Clinic Circuit

Time from cannula connection → physiologic state = 2-5 minutes

- •Flows and pressures modified by changing RPMs independently in the HA and PV pumps
- •Stable set up from the time of connection
- •Minute changes possible

⇩

- •Extremely easy and reproducible

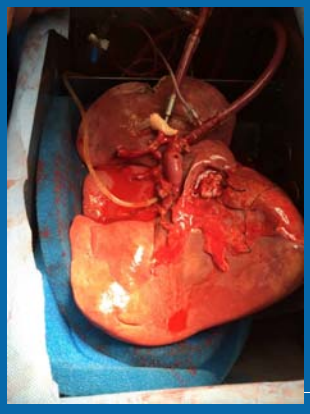

Monitoring:

Continuous blood pressure monitor

Continuous Arterial Blood gas monitor

Frequent sampling with instant results

Bile production measurement



Brief Communication

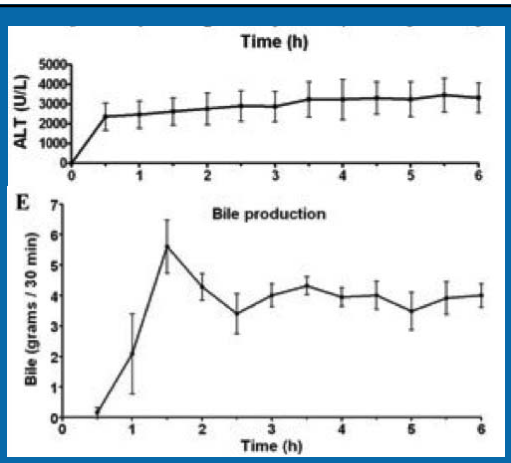
Ex vivo Normothermic Machine Perfusion and Viability Testing of Discarded Human Donor Livers

S. op den Dries[a,b], N. Karimian[a,b], M. E. Sutton[a,b], A. C. Westerkamp[a,b], M. W. N. Nijsten[c], A. S. H. Gouw[d], J. Wiersema-Buist[b], T. Lisman[a,b], H. G. D. Leuvenink[b] and R. J. Porte[a,*]

GT, gamma-glutamyl transferase; LDH, lactate dehydrogenase.

Received 31 October 2012, revised 07 January 2013 and accepted for publication 10 January 2013

4 Livers
6 hrs
NMP



Peter J. Friend, Oxford

Liver kept 'alive' outside body in medical first

March 15, 2013

By Kate Kelland, Reuters

LONDON - A donated human liver has been kept alive, warm and functioning outside a human being on a newly-developed machine and then successfully transplanted into patients in a medical world

University Of Oxford / Reuters

The King's College Hospital, Oxford University and OrganOx team pose for a photograph following the successful connection of the first human liver for transplant onto the OrganOx Metra device, in this undated picture provided by the University of Oxford in southern England.

American Journal of Transplantation 2016; 16: 1779–1787
Wiley Periodicals Inc.

doi: 10.1111/ajt.13708

Liver Transplantation After _Ex Vivo_ Normothermic Machine Preservation: A Phase 1 (First-in-Man) Clinical Trial

R. Ravikumar[1,2,†], W. Jassem[3,†], H. Mergental[4], N. Heaton[3], D. Mirza[4], M. T. P. R. Perera[4], A. Quaglia[3], D. Holroyd[2], T. Vogel[1], C. C. Coussios[2] and P. J. Friend[1]

- Increasing donor risk (Age; steatosis; transaminases)
- All 20 livers functioned, patients discharged
- No difference in 30 day survival
- More than 50% reduction in postoperative enzyme release
- Device functioned in clinical environment
- Transport logistics feasible
- Positive feedback from clinical teams (surgical & anesthetic)
- Clinicians started to change practice

A randomized trial of normothermic preservation in liver transplantation

David Nasralla[1]*, Constantin C. Coussios[2]*, Hynek Mergental[3], M. Zeeshan Akhtar[1,4], Andrew J. Butler[5,20], Carlo D. L. Ceresa[1], Virginia Chiocchia[6,7], Susan J. Dutton[8], Juan Carlos García-Valdecasas[9], Nigel Heaton[10], Charles Imber[11], Wayel Jassem[10], Ina Jochmans[12,13], John Karani[10,14], Simon R. Knight[1,15], Peri Kocabayoglu[16], Massimo Malagò[11], Darius Mirza[3], Peter J. Morris[1,15], Arvind Pallan[17], Andreas Paul[16], Mihai Pavel[9], M. Thamara P. R. Perera[3], Jacques Pirenne[12,13], Reena Ravikumar[1], Leslie Russell[18], Sara Upponi[19], Chris J. E. Watson[5,20], Annemarie Weissenbacher[1], Rutger J. Ploeg[1], Peter J. Friend[1]* for the Consortium for Organ Preservation in Europe

European multi-center NMP liver trial

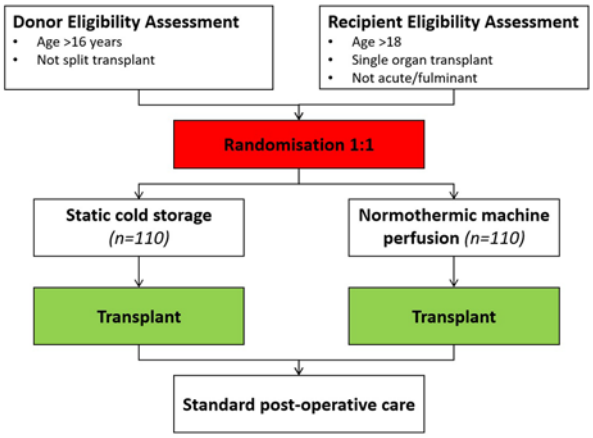
UK (Oxford)
- Birmingham
- Cambridge
- London, KCH
- London, Royal Free

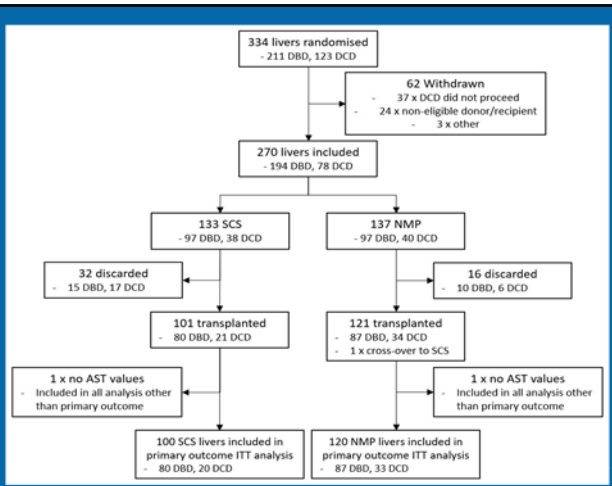
Belgium
- Leuven

Germany
- Essen

Spain
- Barcelona

220 livers transplanted

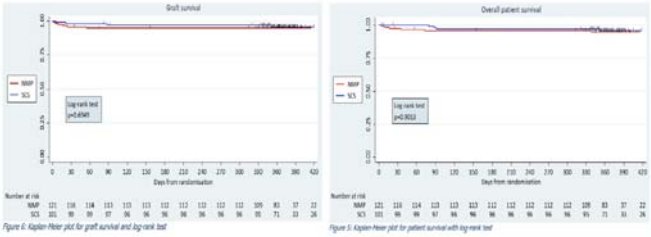




	NMP (n=121)	SCS (n=101)	p-value
Total preservation time	11hr 20min	7hr 9min	p < 0.0001
Machine perfusion time	10hr 8min		

	NMP	SCS	Total
Transplanted	121	101	222
Discarded	16 (11.7%)	32 (24.1%)	48 (17.8%)
Pearson chi^2 – 7.0774			p-value = 0.008

Graft & Patient Survival



Post-reperfusion Syndrome

	NMP	SCS	Total
No	106 (87.6%)	68 (67.0%)	171 (78.44%)
Yes	15 (12.4%)	29 (33.0%)	47 (21.6%)
Total	121	97	218
Difference = -21% (95% C.I. -32%, -10%)			p = 0.0002

Post-reperfusion bolus	41 (33.9%)	60 (59.4%)	p<0.001
(missing)	4 (3.3%)	9 (8.9%)	
Post-reperfusion vasopressor infusion	65 (53.7%)	80 (79.2%)	p<0.001
(missing)	1 (0.8%)	9 (8.9%)	

Allograft Dysfunction – Peak AST and EAD

	NMP	SCS	Difference (% reduction)	p-value
Obs	120	100		
Mean (95% C.I.)	484.5 (406.4, 577.6)	973.3 (795.2, 1192.3)	489.2 (50.2%)	p < 0.0001

	NMP	SCS	Total
No	107 (89.9%)	68 (70.1%)	175 (81.0%)
Yes	12 (10.1%)	29 (29.9%)	41 (19.0%)
Total	119	97	216
Difference = -0.198 (95% C.I -0.30, -0.09)			p = 0.0002

Ischemic Cholangiopathy

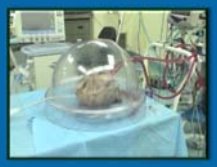
Radiological (MRCP) diagnosis

	Non-anastomotic strictures		
	NMP n=81	SCS N=74	P value
DBD	4/54 (7%)	3/55 (5%)	0.678
DCD	3/27 (11%)	5/19 (26%)	0.180

1 liver in each arm required retransplant for cholangiopathy

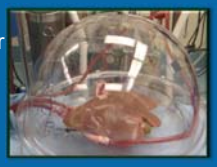
The "Organ Repair Center"

Lung



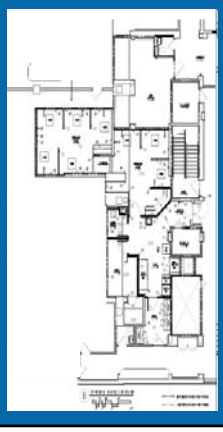
Heart

Liver



Kidney

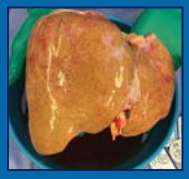
The Cleveland Clinic Organ Repair Center

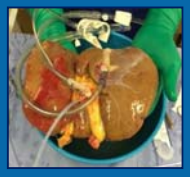


Future Applications

- Assessing organ viability (marginal donor)
- Organ repair (physiologic event in-vivo)
- Reconditioning of DCD livers (rTPA, medications)
- Defatting steatotic grafts (CCF steatotic liver model)
- Immunological intervention during ex-vivo phase

Active Removal Of Fat During Perfusion

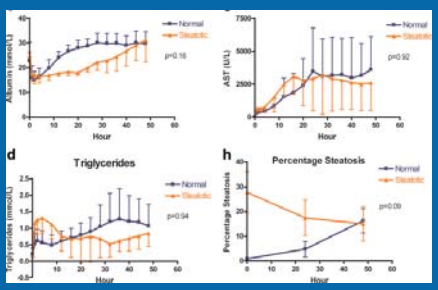


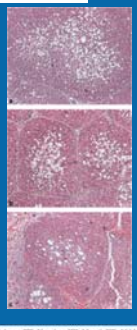


Accurate control of 'physiological' milieu
Normothermic perfusion for 48 hours
Active lipid mobilization & removal

Hepatic Steatosis and Normothermic Perfusion—Preliminary Experiments in a Porcine Model

Russell W. Jamieson,[1] Miguel Zilvetti,[1] Debabrata Roy,[1] David Hughes,[1] Alireza Morovat,[2] Constantin C. Coussios,[3] and Peter J. Friend[1,4]

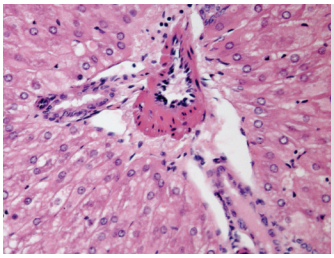




Transplantation • Volume XX, Number XX, Month XX, 2011

Summary

- Allograft shortage remains the biggest barrier to the increased application of solid organ transplantation
- All options for increasing donation and utilization should be explored
- The availability of novel technology and a paradigm shift from cold storage to normothermic perfusion may enhance the safety of expanding the donor pool



Too Sick for Liver Transplantation?

Kimberly Brown

When is a Patient Too Sick for Liver Transplantation?

Kimberly Brown, MD, FAASLD, FAST, AGAF
Professor of Medicine, Wayne State University
Chief, Division of Gastroenterology and Hepatology
Associate Medical Director Henry Ford Hospital Transplant Institute
Henry Ford Hospital, Detroit

Disclosure

Research: Gilead, Novartis, Allergan, Conatus

Advisory Boards: Gilead, Pfizer, Merck

Speaking: HCV Viewpoint, Simply Speaking

Board Participation: CLDF

Learning Objectives

To review the general indications and contraindications for liver transplantation

To outline the challenges with determining when a patient is "too sick" for transplant

To discuss possible strategies to determine a consistent approach in patient selection in the extremes

When is a Patient Too Sick for Liver Transplant?

- We all agree these patients exist
- We can't agree on a definition
- When limited answers exist (and you've been given 15 minutes) …..
- Frame the issue

"One man's meat
Is another man's
Poison"

Minimal Listing Criteria

Minimal Criteria for Placement of Adults on the Liver Transplant Waiting List: A Report of a National Conference Organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases

Michael R. Lucey, Kimberly A. Brown, Gregory T. Everson, John J. Fung, Robert Gish, Emmet B. Keeffe, Norman M. Kneteman, John R. Lake, Paul Martin, Sue V. McDiarmid, Jorge Rakela, Mitchell L. Shiffman, Samuel K. So, and Russell H. Wiesner

" Sick enough for transplant" — Listed Patients — " Too sick for transplant"

CTP score ≥ 7 or predicted 1-year survival ≤ 90%

???

Liver Transplantation and Surgery, Vol 3,No 6(November),1997:pp628-63

???Maximal Listing Criteria

Summary report of a national conference: Evolving concepts in liver allocation in the MELD and PELD era

Oltoff KM, Brown RS, Delmonico RL, Freeman RB, McDiarmid SV, Merion RM, Millis JM, Roberts JP, Shaked A, Wiesner RH, Lucey ML

"It is likely that an expected survival rate below which transplant is not warranted would range from 40 to 60%"

Liver Transplantation 2004: 10 (S10); A6-A22

Contraindications to Liver Transplant

Absolute

- Advanced cardiopulmonary disease
- Sepsis
- Malignancy outside the liver
- PVT
- Liver cancer
- Active substance use
- HIV
- Advanced age
- Organ failure outside the liver

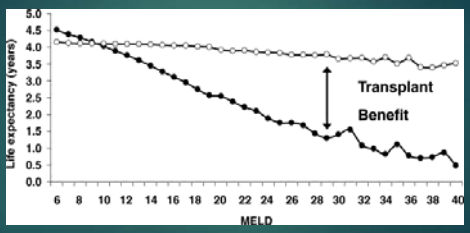
Relative

- Poor compliance
- Poor functional status
- Limited social support

Definition of "Too Sick"

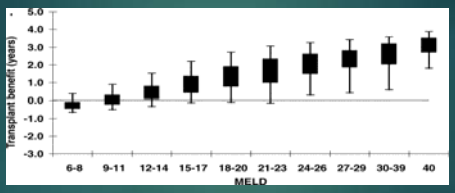
- Medically? Surgically? Functionally? Socially? Economically?
- Patients who are not deemed candidates may end up in this category
- Little consensus both on when not to list as well as when to remove from the list
- Varies by patient, provider and program

Mean 5 Year Future Lifetime by MELD



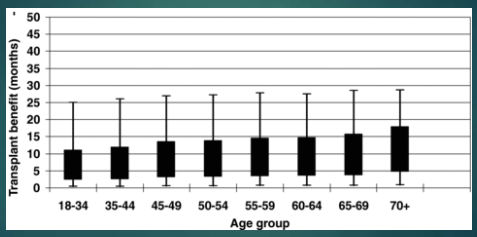
Schaubel DE. American J Transplant 2009; 9(4 Pt 2): 970-81

Benefit Score Distribution by MELD



Schaubel DE. American J Transplant 2009; 9(4 Pt 2): 970-81

Benefit Scores by Age Patients with Benefit > 0



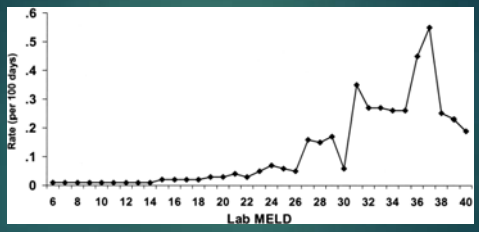
Schaubel DE. American J Transplant 2009; 9(4 Pt 2): 970-81

What Can Change Over Time?

- Advancing Age
  - 25% of patients wait over 4 years on the list
  - Increased odds wait list mortality, decreased odds of transplant, increased odds of graft loss patients age 65 or over
- Sarcopenia
  - Increased wait list mortality and hazard of death post transplant
- ACLF
- Worsening medical conditions
  - BMI > 35, CAD, DM, COPD, Chronic renal insufficiency
- Frailty

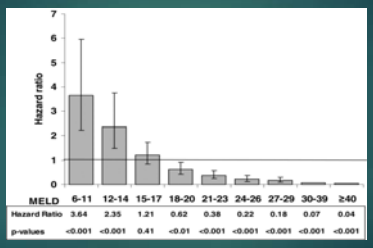
Malinis MF, Ann Transplant 2014;19:478-87, Tandon P, Liver Transpl 2012;18:1209-16, Englesbe MJ, J Am Coll Surg 2010:211:271-278, Moreau R, Gastroenterology 2013;144:1426-37, Gustot T, Hepatology 2015;62:243-252, Rana A, Am J Transplant 2008;8:2537-46, Tovikkai C, BMJ Open 2015;5:e006971-e16971, Volk ML, Liver Transpl 2007;13:1515-20

Inactive Status by MELD Score



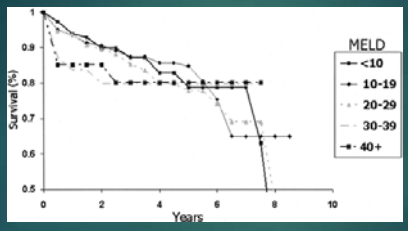
Merion RM, Liver Transplantation 2004. Volume: 10 (S10); S69-73

Mortality Risk by MELD Score



Merion RM, American Journal of Transplantation 2004;5(2):307-13

Post Transplant Mortality Predictions



Oltoff KM, Liver Transplantation: 10 (S10); A6-A22

Post Transplant Survival

Recipient Factors in Posttransplant Model

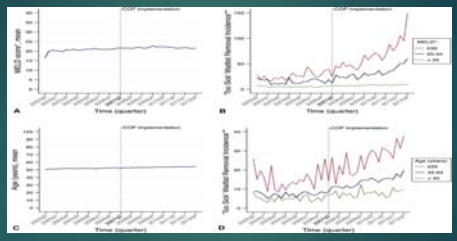
Factor	HR	Factor	HR
Age (yrs)			
<18	1.09	AHN	1.21
18–25	.98	Previous PNF	1.83
25–35 (ref)	1	Previous Liver Tx	1.55
35–45	1.22	Non-chol cirrhosis (ref)	1
45–55	1.26	Chol cirrhosis	.93
55-65	1.34	Biliary atresia	.89
65 Plus	1.76	Metabolic disease	.80
Race			
Hispanic	.90	Malignant neoplasm	1.41
Black	1.25	Other diagnosis	.27
White (ref)	1	Previous transfusion	1.11
Other race	.88	Previous abdominal surg	1.14

Oltoff KM, Liver Transplantation: 10 (S10); A6-A22

Risk of Non-Standard Criteria

- Selection (and hence opportunity) becomes variable
- Unintended bias is likely present
- Outside influence (CMS and contract expectations)

Influence of CMS



Dolgin NH, J Am College Surgeons 2016;222(6): 1054-65

Does 1 + 1 = 2 (or 3, or 4…)

NASH DM	NASH DM BMI 39	NASH DM BMI 39 GFR 47	NASH DM BMI 39 GFR 47 Cardiac Sten	NASH DM BMI 39 GFR 47 Cardiac Sten Age 65	NASH DM BMI 39 GFR 47 Cardiac Sten Age 65 Wheelchair

What are we left with?

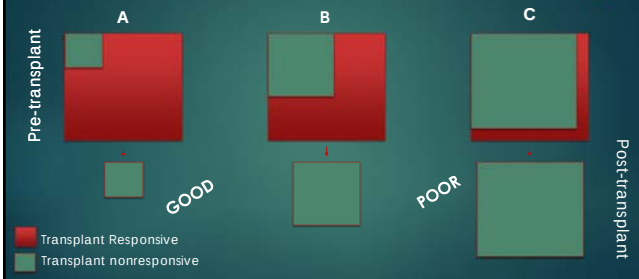
- 1.

The Eyeball test

I have searched the Literature and find no supporting evidence For either

- 2. Pure as Caesar's Wife

Framework for Evaluating Patients Deemed "Too Sick" (What Can We Fix With Transplant?)



Lai, JC, Current Opinion in Transplantation 2016;21(2):127-132

Should There be Criteria for Delisting or Deactivation of Patients?

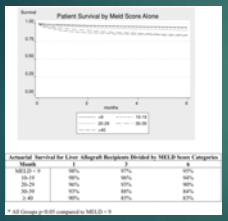
- Because patients likely deemed "too ill" for transplant are the most critically ill, the outcome without transplant in this group is likely exceedingly poor
- This any criteria for delisting need to be strongly evidence based, validated in the MELD allocation era, and biased in favor of transplantation

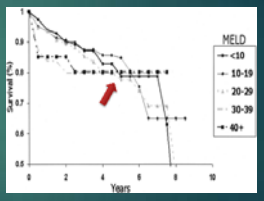
Survival With Transplant

Survival Without Transplant

Individual Transplant Benefit

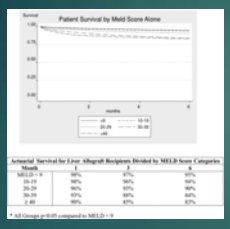
Post Transplant Survival Based on MELD

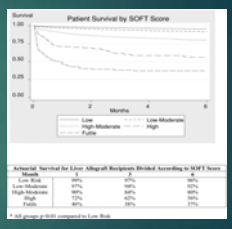




Desai NM, Transplantation 2004; 77: 99–106. Oltoff KM, Liver Transplantation: 10 (S10); A6-A22

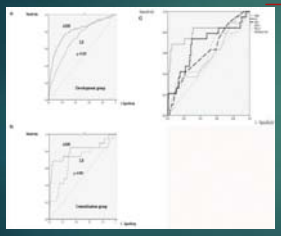
Recipient Survival by SOFT Score





Rana A, Am J Transplant 2008;8(12):2537-46

Artificial Neural Networks



Estaban MB, Clinics in Surgery 2018. 3:2122, Dutkowski P, Ann Surg 2011;254(5):745-53

Conclusions

- We currently have no standard criteria for “too sick to transplant”
- Imperfect understanding leads to selection via the “eyeball” technique
- Outside influences (CMS) run contrary to the notion of transplant benefit and undermine our ability to help many patients who would benefit from transplant
- Critically important to standardize our approach to selection (and de-selection) to create fairness and opportunity
- The criteria to delist or deactivate a patient awaiting liver transplantation requires modeling to better understand the overall interaction of multiple variables leading to transplant survival and guide discussion around if and where a cut-off for “too sick” may be