OCTOBER 16, 2019

2019: CHRONIC LIVER DISEASE MANAGEMENT FOR THE GASTROENTEROLOGIST

2019 NASPGHAN SINGLE TOPIC SYMPOSIUM

TO BE HELD IN CONJUNCTION WITH 2019 ANNUAL MEETING

SHERATON GRAND CHICAGO * CHICAGO, IL

WEDNESDAY, OCTOBER 16 – SINGLE TOPIC SYMPOSIUM
2019: Chronic Liver Disease Management for the Gastroenterologist

Sheraton Chicago Ballroom – Level 4

Directors:

Saeed Mohammad, MD

Mercedes Martinez, MD

Advised by the Hepatology Committee

Objective: The objective of this program is to provide guidance on practical aspects of the management of children with chronic liver disease and liver transplantation, including updates on new therapies for chronic liver diseases.

WEDNESDAY, OCTOBER 16 – SINGLE TOPIC SYMPOSIUM
2019: Chronic Liver Disease Management for the Gastroenterologist

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Wednesday, October 16, 2019

PROGRAM

Session 1 – Diagnostic Challenges in Pediatric Liver Disease

Moderators: Saeed Mohammad MD and Vania Kasper MD

8:10-8:30 How do I best evaluate a cholestatic infant?
Sanjiv Harpavat MD Texas Children's Hospital
Objectives:

- Identify limitations of commonly-ordered diagnostic tests
- Review new diagnostic tests that may soon be a part of routine clinical care
- Generate an algorithm to efficiently evaluate cholestatic infants, including those less than 30 days old

8:30-8:50 How do I interpret genetic results?
Saul J. Karpen MD, PhD, Emory University School of Medicine/Children's Healthcare of Atlanta
Objectives:

- Understand the fundamental features of genetic test technologies available to clinicians
- Understand the language common to genetic testing reports—benign, pathogenic, VOUS, etc.
- Determine when your approach to diagnosis and care may benefit from early incorporation of genetic testing— i.e., genotype before phenotype
- Avoiding over-and under-interpretation of genetic variant reports

8:50-9:10 What do abnormal liver enzyme levels mean in a tween?
William F. Balistreri MD, Cincinnati Children's Hospital Medical Center
Objectives:

- Discuss the differential of abnormal liver enzyme levels in a toddler and adolescent
- Understand the initial approach to evaluate a patient presenting with this profile
- Review the next level diagnostic strategy - non-invasive approaches and the indications for liver biopsy

9:10-9:30 What do I do with this abnormal radiology finding?
Jean Molleston MD, Riley Children's Hospital
Objectives:

- Outline the differential diagnosis and evaluation of focal liver lesions
- Recognize congenital and acquired vascular abnormalities of the liver
- Identify appropriate imaging approaches to suspected biliary tract disease
- Differentiate various parenchymal liver abnormalities

9:30-9:50 Discussion/Question

9:50- 10:00 Break

Session 2 – Frontiers in Liver Therapeutics

Moderators: Mercedes Martinez MD and Parvathi Mohan MD

10:00- 10:20 Keynote Speaker: Outcomes for the future: How do we improve on the status quo?
Ronald J. Sokol, MD, FAASLD, Children's Hospital Colorado
Objectives:

- Understand current gaps in therapies for pediatric liver diseases
- Understand new technologies for development of novel therapeutics
- Understand the pipeline of new therapeutics, based on biology of cholestatic liver diseases

10:20-10:40 Recognition and stabilization of the pediatric patient with acute liver failure
Robert Squires MD Children's Hospital of Pittsburgh at UPMC
Objectives:

- Recognize variable presentations of acute liver failure
- Implement a prioritized immediate management plan for acute liver failure
- Identify clinical features of acute liver failure that prompt early contact with and transfer to a pediatric liver transplant center

10:40-11:00 Should I offer treatment for my patients with Hepatitis B or Hepatitis C?
Regino P. Gonzalez-Peralta MD, AdventHealth for Children
Objectives:

- Review the life-cycle of HBV and HCV
- Understand currently available treatment options for HBV and HCV in children
- Identify patients who would most benefit from treatment (and those who would not)

11:00-11:20 Are there any medical therapies for NASH?
Marialena Mouzaki, MD, Cincinnati Children's Hospital Medical Center
Objectives:

- Present the gaps in the therapeutic armamentarium for pediatric NASH
- Evaluate the preliminary data on the efficacy of novel medications currently being investigated for the treatment NASH

11:20-11:40 Discussion/Question

11:45-12:45: Lunch Session - Group discussion on difficult cases
Moderator: Cara Mack MD
Panel: *Simon Ling MD, Hospital for Sick Kids*
Ronald J. Sokol MD, Children's Hospital Colorado
Estella Alonso MD, Ann and Robert H. Lurie Children's Hospital

Session 3 – Update on Portal HTN: Assessment and Management

Moderators: Samar Ibrahim MD and Alexander Weymann MD

12:45-1:15 When there is good function, but the flow is all wrong: Approach to non-cirrhotic portal hypertension

Evelyn Hsu, MD, Seattle Children's Hospital

Objectives:

- Understand the key aspects of the diagnostic evaluation of children with portal hypertension
- Evaluate and understand the pathogenesis of nodular regenerative hyperplasia and non-cirrhotic portal fibrosis

1:15-1:35 What do I do now? The management of portal hypertensive complications: Varices, ascites, and encephalopathy

Rene Romero, MD, Children's Hospital of Atlanta

Objectives

- Understand appropriate medical management (including pharmacologic and endoscopic) of acute variceal hemorrhage
- Understand dosing and monitoring of diuretics in the management of ascites, and the appropriate use of paracentesis
- Approaches to the recognition and management of chronic encephalopathy in pediatric liver disease

1:35-1:55 The role of the interventional radiologist in the treatment of portal HTN: How can I help you?

Jared R. Green, MD, Ann and Robert H. Lurie Children's Hospital

Objectives:

- Understand role of interventional radiology in management of pediatric portal hypertension
- Evaluate interventional radiology techniques available to address complications of portal hypertension
- Evaluate interventional radiology options to restore or improve antegrade portal flow

1:55-2:15 When to consider surgery in the treatment of portal HTN?

Riccardo Superina, MD, FRCS(C), FACS, Northwestern University

Objectives:

- Learn about the different types of procedures available for the treatment of portal hypertension in children
- Learn about the differences in physiological consequences between the procedures that restore blood flow to the liver and those that divert blood flow from the liver
- Learn about how to determine who needs a shunt and who needs a transplant
- Learn about indications for meso Rex bypass and when the best time to do it is

2:15-2:30 Discussion/Questions

2:30-2:45 Break

Session 4 – Liver Transplant: Pre- and Post-Transplant Considerations

Moderators: James Squires MD and Jennifer Vittorio MD

2:45-3:05 Referring your patient for liver transplantation
Shikha S. Sundaram, MD MSCI, FAASLD, Children's Hospital Colorado
Objectives
- Understand when to refer a patient for a transplant evaluation
- Understand what happens during a transplant evaluation
- Understand indications/contraindications for liver transplantation
- Understand how to help your patient choose a transplant program

3:05-3:25 Where will we get our organs from in 2020?
Jean Emond MD, Columbia University Medical College
Objectives:
- Understand the role of living donation and split livers in a pediatric program
- Understand current data on PHS increased risk donations
- Be familiar with updates in xeno and bioengineered organs

3:25-3:45 What should I do if my liver transplant patient has elevated liver tests?
Udeme Ekong MD, Georgetown University Hospital
Objectives:
- Recognize the differential diagnoses of elevated liver tests in a pediatric liver transplant recipient
- Become familiar with testing to consider in the setting of liver allograft dysfunction
- Become familiar with proposed diagnostic criteria for acute and chronic antibody mediated rejection

3:45-4:05 What is a "normal" childhood after liver transplantation?
Estella Alonso MD, Ann and Robert H Lurie Children's Hospital
Objectives:
- Be able to identify the common physical and psychosocial challenges children experience following liver transplantation
- Be able to identify risk factors for lower than expected physical function and school performance following liver transplantation
- Be able to design screening programs to implement in a post-transplant ambulatory care setting that will identify children with high risk for lower psychosocial outcomes

4:05-4:25 Discussion/Questions

4:25-4:30 Closure
Mercedes Martinez MD, Columbia University School of Medicine

4:30-6 pm Reception

How do I best evaluate a cholestatic infant?

Sanjiv Harpavat, MD PhD
harpavat@bcm.edu

Texas Children's Hospital

Baylor College of Medicine

Disclosures

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Case

A 3 week former full-term infant is referred for persistent jaundice and an elevated serum direct bilirubin level.

- Born full-term without complications
- PCP noticed jaundice at two weeks
- PCP measured fractioned serum bilirubin levels*
- Labs: AST 43, ALT 32, GGT 453, Direct bili 2.3
- Exam: 50th percentile for weight, yellow stools

What next?

- Labs: AST 43, ALT 32, GGT 453, Direct bili 2.3
- Exam: 50th percentile for weight, yellow stools

A) Follow-up with PCP until labs completely normalize

B) Re-draw liver panel and return to clinic in 1-2 weeks

C) Initiate full cholestatic evaluation, including laboratory tests, imaging, and/or liver biopsy

Objectives

1) Identify limitations of commonly-ordered diagnostic tests

2) Review new diagnostic tests that may soon be a part of routine clinical care

3) Generate an algorithm to efficiently evaluate cholestatic infants, including those less than 30 days old

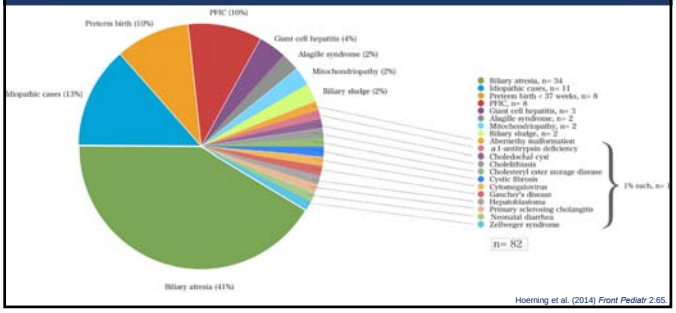
Cholestasis

"…reduced bile formation or flow resulting in the retention of biliary substances within the liver normally excreted into bile and destined for elimination into the intestinal lumen…"*

- **elevation of serum conjugated (or direct) bilirubin**
- **elevation of serum bile acids**

*Joint NASPGHAN/ESPGHAN guidelines: Fawaz et al. (2017) *JPGN* 64: 154-168.

What's the rush?



Hoerning et al. (2014) *Front Pediatr* 2:65.

Biliary Atresia

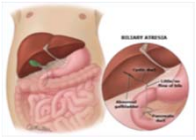


Table 1. Primary diagnosis at transplant of patients weighing 5 kg or below, N = 530

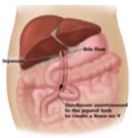
Diagnosis	Number of patients (%)
Biliary atresia	235 (41.2)
Acute liver failure	83 (11.1)
Metabolic disease	62 (10.9)
Neonatal hepatitis	43 (7.5)
TPN	37 (6.5)
Hemochromatosis	30 (5.3)
Alagille syndrome	15 (2.6)
Cirrhosis	12 (2.1)
Other	34 (6.0)
Unknown	39 (6.8)

Liver Transplant	
Age ≤1 year	
1. **BA**	**59.0%**
2. Hepatoblastoma	2.7%
3. Idiopathic Acute Liver Failure	2.3%
4. TPN-Associated Liver Disease	2.2%
5. Alpha-1-Antitrypsin Disease	1.2%
Age 0-17 years	
1. **BA**	**30.7%**
2. Hepatoblastoma	6.4%
3. Idiopathic Acute Liver Failure	4.0%
4. TPN-Associated Liver Disease	3.1%
5. Alagille Syndrome	2.9%
All Solid Organ Transplant (Heart, Lung, Liver, Kidney, Small Bowel, Pancreas, Intestine)	
Age ≤1 year	
1. **BA**	**31.0%**
2. Congenital Heart Defect†	24.8%
3. Dilated Cardiomyopathy	13.7%
4. Hepatoblastoma	1.4%
5. Idiopathic Acute Liver Failure	1.2%
Age 0-17 years	
1. Congenital Heart Defect†	9.7%
2. **BA**	**9.2%**
3. Dilated Cardiomyopathy	8.4%
4. Renal Dysgenesis/Agenesis	5.3%
5. Focal Glomerular Sclerosis	4.5%

*Data collected from United Network for Organ Sharing online publicly-available database.[3]
†Includes all congenital heart defects with or without prior surgery.

Erlichman J and Loomes KM, In: UpToDate, Post TW (Ed) 2018; Arnon et al. (2011) *Pediatric Transplantation* 15:650-8; Mysore et al. (2019) *JPGN* [Epub ahead of print].

Earlier treatment = Better outcomes



Study	Outcome	*N*	Time of KP: 30 days	60 days	90 days	120 days
United States 1976-1989	5-year overall survival	816	63%	44%	40%	29% / 29%
Canada 1985-2002	4-year transplant-free	312	49%	36%		28%
France 1986-2002	5-year transplant-free	695	58%	41% / 42%	36%	26% / 27%
United States 1997-2000	2-year transplant-free	100	70%	54%	50%	50%

Erlichman J and Loomes KM, In: UpToDate; Mysore et al. (2019) *JPGN* [Epub ahead of print].

Exclude Biliary Atresia

(Intraoperative cholangiogram, examination of the biliary remnant)

Approach 1:
Identify another disease

- Newborn screening *Metabolic disease*
- Chest radiography *Alagille Syndrome*
- PI Typing *A1AT deficiency*
- Abdominal ultrasound *Choledochal cyst*

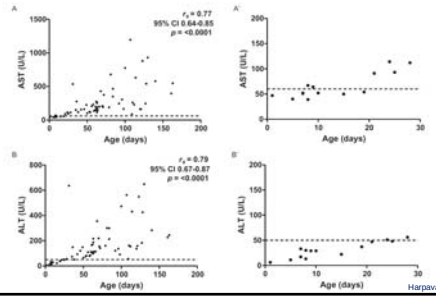
- **Genetic testing**

Approach 2:
Detect liver injury

- Laboratory tests
  - GGT
  - AST, ALT
  - **MMP-7**
- Abdominal ultrasound
  - Triangular cord sign
  - **Liver stiffness**
- Liver biopsy

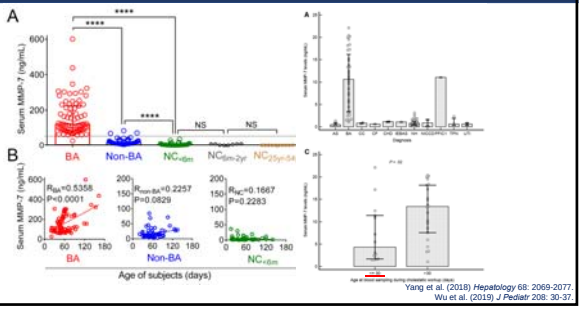
Good, but…

AST and ALT are normal initially



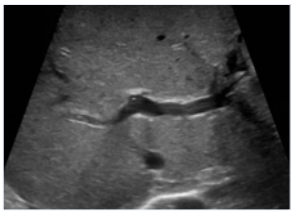
Harpavat et al. (2018) *JPGN* 66: 850-6.

MMP-7 as new marker (except early)?



Yang et al. (2018) *Hepatology* 68: 2069-2077.
Wu et al. (2019) *J Pediatr* 208: 30-37.

Triangular cord sign appears over time



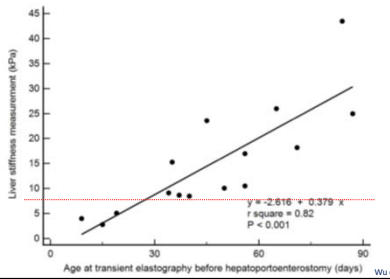
Variables	Younger BA group (n = 12)	Older BA group (n = 62)	*P*-value
Triangular cord thickness, mm*	2.5 ± 0.9	4.0 ± 1.2	<0.001
Positive triangular cord sign	2/12 (17%)	35/62 (56%)	0.024

No.	Age (days)*			Change of US findings (Initial US → follow-up US)			
	Initial US	Follow-up US	Kasai procedure	TC sign	GB abnormalities	HA enlargement	Signs of portal HTN
1	2	10	49	(-) → (-)	(+) → (+)	(+) → (+)	(-) → (+)
2	11	13	24	(-) → (-)	(+) → (+)	(-) → (-)	(-) → (-)
3	21	35	42	(+) → (+)	(+) → (+)	(+) → (+)	(-) → (+)
4	1	26	50	(-) → (+)	(+) → (+)	(-) → (+)	(-) → (-)
5	29	40	46	(-) → (-)	(+) → (+)	(-) → (-)	(-) → (-)
6	9	16	19	(-) → (-)	(+) → (+)	(-) → (-)	(-) → (-)
7	7	10	21	(-) → (-)	(+) → (+)	(-) → (-)	(+) → (+)
8	1	28	35	(-) → (+)	(+) → (+)	(+) → (+)	(-) → (+)

US ultrasound; *TC* triangular cord; *GB* gallbladder; *HA* hepatic artery; *HTN* hypertension
*Age (days) at the time of US examinations or Kasai procedure

Hwang et al. (2018) *Eur J Radiology* 28:1771-7.

Liver stiffness increases with time



Wu et al. (2018) *Hepatology* 68: 616-24.

Liver biopsy is standard of care (?)

(Duct proliferation and plugging, portal fibrosis and inflammation)

Liver Biopsy

Study	TP	FP	FN	TN	Sensitivity (95% CI)
Cox 1987	9	2	0	13	1.00 [0.66, 1.00]
Dehghani 2006	19	2	0	44	1.00 [0.82, 1.00]
Esmaili 2007	37	2	3	16	0.93 [0.80, 0.98]
Ferry 1985	64	3	5	71	0.93 [0.84, 0.98]
Guelrud 1991	11	0	11	10	0.50 [0.28, 0.72]
Hays 1967	9	3	3	6	0.75 [0.43, 0.95]
Lai 1994	39	2	3	82	0.93 [0.81, 0.99]
Manolaki 1983	38	7	4	33	0.90 [0.77, 0.97]
Park 1997	18	1	2	23	0.90 [0.68, 0.99]
Rastogi 2009	26	2	4	17	0.87 [0.69, 0.96]
Tolia 1986	22	1	1	9	0.96 [0.78, 1.00]
Wongsawasdi 2008	15	0	1	9	0.94 [0.70, 1.00]
Yang 2009	34	2	0	33	1.00 [0.90, 1.00]

"It is however important to recognize that the earliest histologic changes of BA may be relatively non-specific, and biopsies performed too early in the course of the disease may result in a falsely negative diagnosis."

	Patient 1
Gender	Female
Ethnicity	White
Bilirubin (wk; mg/dL, T/C)	2.7/.7/4.2 5.7/.4/5.2 9.8/.7/5.7 19/10.5/6.9
GGT (wk: U/L)*	NA
Excretory studies	No bile excretion to bowel
Sonogram	Gallbladder not visualized

Fawaz et al. (2017) *JPGN* 64: 154-168; Azar G et al. (2002) *JPGN* 134: 212-15; Lee et al. (2016) *J Ped Surg* 51:753-761.

What next?

- Labs: AST 43, ALT 32, GGT 453, Direct bili 2.3
- Exam: 50th percentile for weight, yellow stools

A) Follow-up with PCP until labs completely normalize

B) Re-draw liver panel and return to clinic in 1-2 weeks

C) Initiate full cholestatic evaluation, including laboratory tests, imaging, and/or liver biopsy

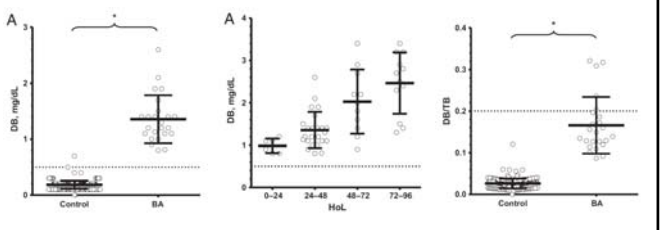
Approach 3: Detect biliary injury

Time	Biliary findings
Birth	Elevated direct/conjugated bilirubin levels
Gest. Age 15-22 weeks	Abnormal gall bladder
Gest. Age 18-19 weeks	Abnormal amniotic fluid GGT levels

Implication: Given an in utero time of onset, earlier treatment with the Kasai operation before 30 days of life is possible and attainable.

Harpavat et al. (2011) *Pediatrics* 128: e1428-33; Shen et al. (2017) *Early Human Development* 111: 16-9; Moon et al. (2010) *Ultrasound in Ob Gyn* 35: 556-559.

Directed/conjugated bilirubin is elevated



Harpavat et al. (2011) *Pediatrics* 128: e1428-33.

Gall bladder abnormalities are present

Variables	Younger BA group (n = 12)	Older BA group (n = 62)	*P*-value
Triangular cord thickness, mm*	2.5 ± 0.9	4.0 ± 1.2	<0.001
Positive triangular cord sign	2/12 (17%)	35/62 (56%)	0.024
Gallbladder abnormalities	11/12 (92%)	55/62 (89%)	1.000
Not visualised	1/12 (8%)	5/62 (8%)	1.000
Small gallbladder	8/11 (73%)	36/57(63%)	0.734
Size, cm*	1.5 ± 0.7	1.7 ± 0.7	0.514
Wall irregularity	10/11 (91%)	43/57 (75%)	0.433

	Age (days)*			Change of US findings (Initial US → follow-up US)			
No.	Initial US	Follow-up US	Kasai procedure	TC sign	GB abnormalities	HA enlargement	Signs of portal HTN
1	2	10	49	(-) → (-)	(+) → (+)	(+) → (+)	(-) → (+)
2	11	13	24	(-) → (-)	(+) → (+)	(-) → (-)	(-) → (-)
3	21	35	42	(+) → (+)	(+) → (+)	(+) → (+)	(-) → (+)
4	1	26	50	(-) → (+)	(+) → (+)	(-) → (+)	(-) → (-)
5	29	40	46	(-) → (-)	(+) → (+)	(-) → (-)	(-) → (-)
6	9	16	19	(-) → (-)	(+) → (+)	(-) → (-)	(-) → (-)
7	7	10	21	(-) → (-)	(+) → (+)	(-) → (-)	(+) → (+)
8	1	28	35	(-) → (+)	(+) → (+)	(+) → (+)	(-) → (+)

US ultrasound; *TC* triangular cord; *GB* gallbladder; *HA* hepatic artery; *HTN* hypertension
*Age (days) at the time of US examinations or Kasai procedure

Hwang et al. (2018) *Eur J Radiology* 28:1771-7.

Measures of patency

- Acholic stools in BA: in 77% at 30 days, 83% at 45 days, and 97% at 60 days

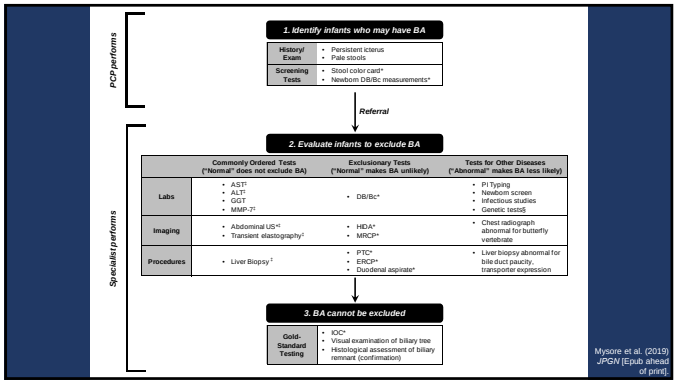
- HIDA Scan, MRCP, ERCP Percutaneous cholangiogram

Table 5
Imaging findings.

	All patients (N = 212)	BA (N = 45)	Non-BA (N = 167)	*P*
Abdominal ultrasound performed (%)	192 (90)	45 (100)	147 (88)	NC
Gallbladder absent (%)	15 (8)	14 (31)	1 (1)	<0.001
Gallbladder absent, contracted, or small (%)	123 (64)	38 (84)	85 (58)	0.001
HIDA scan completed (%)	202 (95)	41 (91)	161 (96)	NC
No duodenal drainage seen (%)	82 (41)	41 (100)	41 (25)	<0.001
Percutaneous cholangiogram attempt (%)	47 (22)	19 (42)	28 (17)	<0.001
Percutaneous cholangiogram completed (%)	35 (74)	10 (53)	25 (89)	<0.001
Diagnostic of BA (%)	10/35 (29)	10/10 (100)	0/25 (0)	<0.001

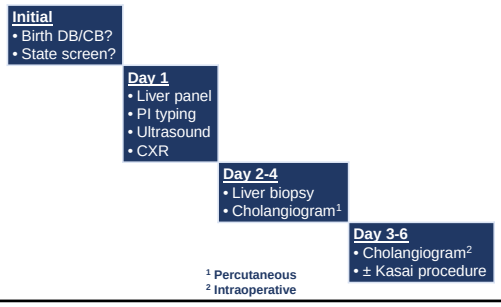
BA – biliary atresia; NC – not calculated, irrelevant; HIDA – hepatobiliary iminodiacetic acid.

Gu et al. (2015) *J Pediatr* 166:e1–902; Hsiao et al. (2008) *Hepatology* 47:1233–40; Jancelewicz et al. (2015) *J Pediatr Surg* 50:363–70.



Mysore et al. (2019) *JPGN* [Epub ahead of print].

Algorithm



What next?

- Labs: AST 43, ALT 32, GGT 453, Direct bili 2.3
- Exam: 50th percentile for weight, yellow stools

A) Follow-up with PCP until labs completely normalize

B) Re-draw liver panel and return to clinic in 1-2 weeks

C) Initiate full cholestatic evaluation, including laboratory tests, imaging, and/or liver biopsy

Summary

1) Identify limitations of commonly-ordered diagnostic tests ***Liver injury vs. Biliary injury***

2) Review new diagnostic tests that may soon be a part of routine clinical care ***MMP-7, Liver stiffness, Genetic testing***

3) Generate an algorithm to efficiently evaluate cholestatic infants, including those less than 30 days old ***Rapidly exclude BA by looking for biliary injury***

Liver Transplant		
Age ≤1 year		
1.	**BA**	**59.0%**
2.	Hepatoblastoma	2.7%
3.	Idiopathic Acute Liver Failure	2.3%
4.	TPN-Associated Liver Disease	2.2%
5.	Alpha-1-Antitrypsin Disease	1.2%
Age 0-17 years		
1.	**BA**	**30.7%**
2.	Hepatoblastoma	6.4%
3.	Idiopathic Acute Liver Failure	4.0%
4.	TPN-Associated Liver Disease	3.1%
5.	Alagille Syndrome	2.9%
All Solid Organ Transplant (Heart, Lung, Liver, Kidney, Small Bowel, Pancreas, Intestine)		
Age ≤1 year		
1.	**BA**	**31.0%**
2.	Congenital Heart Defect†	24.8%
3.	Dilated Cardiomyopathy	13.7%
4.	Hepatoblastoma	1.4%
5.	Idiopathic Acute Liver Failure	1.2%
Age 0-17 years		
1.	Congenital Heart Defect†	9.7%
2.	**BA**	**9.2%**
3.	Dilated Cardiomyopathy	8.4%
4.	Renal Dysgenesis/Agenesis	5.3%
5.	Focal Glomerular Sclerosis	4.5%

*Data collected from United Network for Organ Sharing online publicly-available database.[3]
†Includes all congenital heart defects with or without prior surgery.

Mysore et al. (2019) *JPGN* [Epub ahead of print].

Diagnosis and treatment

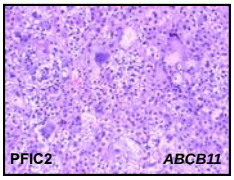
before 30 days of life

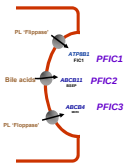
vs.

is <u>possible</u> and <u>attainable</u>

harpavat@bcm.edu

How do I interpret genetic test results?





Saul J. Karpen, M.D., Ph.D.

Raymond F. Schinazi Distinguished Biomedical Chair
Professor of Pediatrics
NASPGHAN Annual Meeting Chicago
October 16, 2019

Disclosures:

Albireo	Consultant
Intercept	Consultant
LogicBio	Consultant
Mirum	Consultant
Retrophin	Consultant
Spruce Bioscience	Consultant

SJK: 7.29.2019

Learning Objectives

1. **Understand the fundamental features of genetic test technologies available to clinicians**
2. **Understand the language common to genetic testing reports—benign, pathogenic, VOUS, etc…**
3. **Avoiding over- & under-interpretation**
4. **Determine when your approach to diagnosis and care may benefit from early incorporation of genetic testing— i.e., genotype before phenotype**

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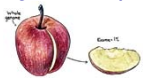
Gene Sequencing Technology

Next Generation Sequencing

- ~~Whole Genome Sequencing~~
- Whole Exome Sequencing
- Gene Panels
- ~~*Single Gene Sequencing*~~



U. Of Washington

- Genome: ~ 6 billion bp
- Exome: ~ 25 million bp (~1 % of genome)
  - Every exon of all 23,000 genes
  - Sequences only the coding regions
  - No need to know to look for individual mutations (e.g. ΔF508 in CFTR)
- Pitfalls:
  - Large deletions can be missed
  - Some regions are poorly covered

Realizing Genomic Medicine

Elizabeth G. Phimister, Ph.D., W. Gregory Feero, M.D., Ph.D., and Alan E. Guttmacher, M.D.

"Current paradigms for providing genetic services,

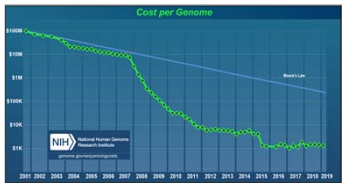
which were developed to handle rare chromosomal and monogenic conditions,

break down in the setting of genomic approaches..."

Or: The technology is far ahead of our analysis

2012

Declining Cost of Genome Sequencing



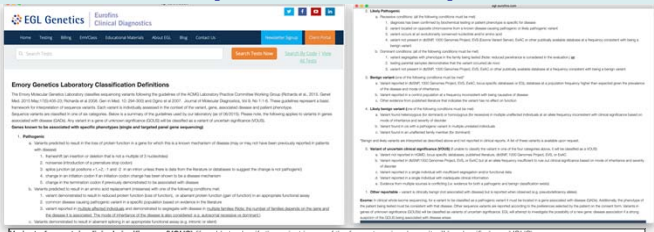
Clinical costs: $500 to $5,000 for WES
2019 lab cost: ~ $250 for WES

NHGRI

Schwarze *Genetic Med* 2018

"Help" from the Report

EGL Genetics



Variant of uncertain clinical significance (VOUS) (if unable to classify the variant in one of the four categories above, it will be classified as a VOUS)

a. Variant not reported in HGMD, locus specific databases, published literature, dbSNP, 1000 Genomes Project, EVS, or ExAC

b. Variant reported in dbSNP,1000 Genomes Project, EVS, or ExAC but at an allele frequency insufficient to rule out clinical significance based on mode of inheritance and severity of disorder

c. Variant reported in a single individual with insufficient segregation and/or functional data

d. Variant reported in a single individual with inadequate clinical information

e. Evidence from multiple sources is conflicting (i.e. evidence for both a pathogenic and benign classification exists)

Pathogenic, Likely Pathogenic, Benign, VOUS

- Average person's genome:
  - 4 x 10^6 variants that differ from the reference genome
  - 300-400 significant variants that change protein function

Labeling of variants:

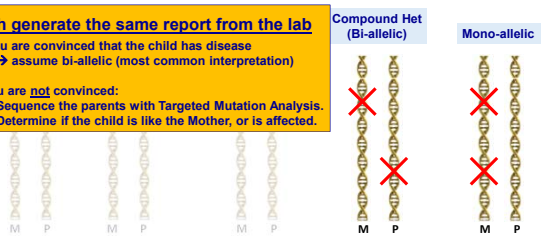
- **Pathogenic:** (e.g., ΔF508 CFTR, A_1AT ZZ)—driven by clinical info
- **Likely Pathogenic:** the change should be relevant, not yet assigned
- **Benign:** Prevalent, not likely to cause disease
- **VOUS (Variant of Unknown Significance):** cannot label

1000 Genomes Project

Variant Definitions

Both generate the same report from the lab

- If you are convinced that the child has disease
  - → assume bi-allelic (most common interpretation)
- If you are not convinced:
  - Sequence the parents with Targeted Mutation Analysis.
  - Determine if the child is like the Mother, or is affected.



Compound Het (Bi-allelic)

Mono-allelic

M: Maternal
P: Paternal

Case 1: Cholestatic infant, seen in Hepatology Clinic on DOL 10

DOL	1	2	3	10
T Bili	8.5	11.4	13.7	9.7
D Bili	**1.0**	**3.0**	**4.4**	**2.9**
AST			48	46
ALT			23	39
INR			1.0	
GGT			537	1,166
25-OH Vit D				

NICU for C Section (Maternal Rickets) & given RHOGAM
Discharged on DOL 4
Pale Yellow Stools

Seen 2 & 4 weeks later – paler stools → liver biopsy

Liver Biopsy at 6 weeks of age:
± bile duct paucity, minimal fibrosis, no BD plugs…

→ Triggered a Gene Test

ECHO: Mild bilateral branch pulmonary artery stenosis

Note: No Cholangiogram
No Surgeon or IR-guided PTC
No HIDA Scan (please …)

Gene	Nucleotide	Amino acid	Zygosity	Type
JAG1	c.2706C>A	p.C902X	Heterozygous	Pathogenic

Comments: Pathogenic variants in the JAG1 gene (MIM # 601920) cause Alagille syndrome. A single pathogenic variant in one copy of the JAG1 gene causes disease. The c.2706C>A (p.C902X) pathogenic variant has been reported in affected individuals from a family with a clinical suspicion of Alagille syndrome [1] and is also of a type expected to cause disease. **Therefore these results are consistent with a diagnosis of Alagille syndrome.**

Case 2: 6 mo, pruritic, organomegaly

Bilirubin Total	3.7 (H)
Bilirubin Direct	2.9 (H)
ALBUMIN	4.5
ALK PHOS	420
AST	179 (H)
ALT	232 (H)
GGT	38
25-OH VIT D	16.4
BILE ACIDS	>180 (H)
INR	Unknown (PT > 120 seconds)

Gene	OMIM#	Disease (Inheritance)	Nucleotide change	Amino acid	Zygosity	Type
ABCB11	603201	Progressive familial intrahepatic cholestasis 2, Benign recurrent intrahepatic cholestasis 2 (AR)	c.2012-8T>G		Apparently Homozygous	Pathogenic[4]
ABCG5	605459	Sitosterolemia (AR)	c.593G>A	p.R198Q	Heterozygous	VOUS[5,6]

Clinically & Genetically, has PFIC2, not BRIC2

What about the variant?

- splice site/chain terminating variant

→ Associated with ↑ risk of HCC.

Care plan changes :

1. Risk of ↑ HCC →
   - Frequent Imaging
   - AFPs
2. List early
3. Don't bother with diversion

Take Homes:
1. **The report did not indicate the variant risk. You need to delve.**
2. **Knowledge of the variant altered the care plan.**
3. **Ignore the *ABCG5* Het.**

Case 3: Cholestatic 10 wo, usual story ("told it would resolve")

Bilirubin Total	9.6 (H)
Bilirubin Direct	8.3 (H)
ALBUMIN	3.0
ALK PHOS	985 (H)
AST	202 (H)
ALT	281 (H)
GGT	1,508 (H)
25-OH Vit D	< 13 (L)
INR	1.4

Light colored stools

Admitted for biopsy (BD Proliferation)

IOC & Kasai HPE the next day

Gene	Nt change	AA change	Zygosity	Type
NPC1	c.67delC		Het	Pathogenic
PEX12	c.452G>A	p.R151H	Het	VOUS

Q: Does this child have BA + Niemann–Pick C?

A: No. Just BA. Treat like BA.

Liver Transplant at 6 m of age.

The Emory 66 Gene Cholestasis Panel

Bile acid synthesis disorders due to single enzyme defects and Cerebrotendinous Xanthomatosis				
AKR1D1	AMACR*	BAAT	CYP7A1	CYP7B1
CYP27A1	DHCR7	HSD3B7	SLC27A5	
Peroxisomal disorders including Zellweger Spectrum Disorders				
PEX1	PEX2	PEX3	PEX5	PEX6
PEX7	PEX10	PEX11B	PEX12	PEX13
PEX14	PEX16	PEX19	PEX26	
Other genetic causes of cholestasis				
ABCB11	ABCB4	ABCC2	ABCG5	ABCG8
ALDOB*	ATP8B1	CC2D2A	CFTR	CLDN1
DCDC2*	DGUOK	EHHADH*	FAH	GPBAR1*
HNF1B	HSD17B4*	INVS	JAG1	LIPA
MKS1	MPV17	NOTCH2	NPC1	NPC2
NPHP1	NPHP3	NPHP4	NR1H4	PKHD1
POLG	SCP2*	SERPINA1	SLC10A1*	SLC10A2*
SLC25A13	SMPD1	TJP2	TMEM216	TRMU
UGT1A1	VIPAS39	VPS33B		

In addition to:

- **Alagille Syndrome**
- **PFIC1, 2, 3**
- **Bile Acid Synthesis Defects**

Made diagnoses of:

- **CF**
- **Niemann-Pick C**
- **PolG & DGUOK**
- **TJP2**
- **FXR Deficiency**
- **Neonatal Scleros. Cholangitis**
- **Many others**

***: Added in 2017.** **Additional ones planned for 2019**

Slide Placeholder

Emory Cholestasis gene panel results from > 2000 subjects

For NASPGHAN Course Reviewers – manuscript submitted & may include a slide if accepted before meeting

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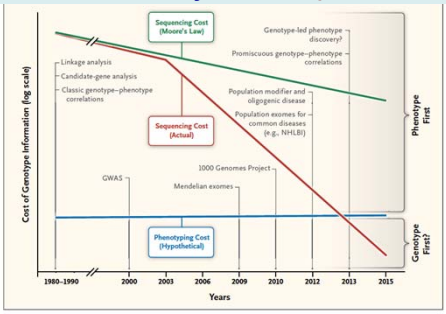
2014 & Beyond: Genotype *or* Phenotype First?



Q: Is it cheaper to perform genetic testing before compete phenotyping?

Lu JT, Campeau PM, Lee BH. Genotype–Phenotype Correlation — Promiscuity in the Era of Next-Generation Sequencing. *N Engl J Med*. 2014 Aug 14;371(7):593–6.

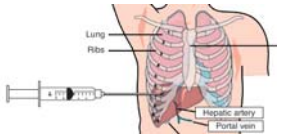
Guideline for the Evaluation of Cholestatic Jaundice in Infants: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition

Sequence first or Biopsy first?

***"Liver biopsy** often remains the cornerstone of the diagnostic workup of infants with cholestatic jaundice …"*

or

*"…current differential diagnostic plans now incorporate consideration of modern broad-based next-generation **DNA sequencing** technologies in the proper clinical context."*



or

JPGN 2017

Dezsőfi JPGN 2014

Exome sequencing – is it cost saving?

Prospective comparison of the cost-effectiveness of clinical whole-exome sequencing with that of usual care overwhelmingly supports early use and reimbursement

Zornitza Stark, MD[1], Deborah Schofield, PhD[1,2], Khurshid Alam, PhD[1,3], William Wilson, PhD[1,3], Nessie Mupfeki, MHIM[1,3], Ivan Macciocca, MHSc[1,3], Rupendra Shrestha, PhD[1], Susan M. White, MD[1,4,5] and Clara Gaff, PhD[1,5]

Diagnostic odyssey: Costs $21,000 vs. WES: $3,000

- Time savings
- Emotional toll
- Diagnostic yields ~ 25-33%

→ **Why wait to send the Genetic test?**

Genetics in Med 2017

Considerations for DNA sequencing prior to biopsy

- **Neonatal cholestasis**
  - Visualized persistently pigmented stools
  - Low GGT
  - Elevated D Bili in Preemies on DOL 1-3
- **Other conditions:**
  - Hepatomegaly → GSD Panel
  - Wilson Disease → Biopsy is preferred over *ATP7B* sequencing
  - Non-obese steatosis → GSD's
  - Small duct PSC → *ABCB4*
  - Multisystem disease → exome sequencing

Utilization of Genetic Testing in Hepatology

- **Modern era of NGS is here**
- **Roles for Panels & Whole Exome Sequencing**
- **VOUS are an expectation → if you believe it is "real" → tell the Lab.**
- **Timely utilization can replace/avoid many aspects of the work-up:**
  - **↓Metabolic studies, Serologies, Single gene tests, Liver Biopsy …**
  - **But be cautious – BA is not a diagnosis of exclusion.**
  - **Human variant databases are open, global & growing.**
  - **New diseases are being discovered through NGS.**
- **Use of NGS can lead to early implementation of effective therapies.**
- **Roles for Genetic Testing are reducing the role for liver biopsy**

What do abnormal liver enzyme levels mean in a tween?

William F. Balistreri, M.D.

Cincinnati Children's

1

What do abnormal liver enzyme levels mean in a tween?

A Common Issue:

- You oversee the care of often complex patients across a wide range of organ systems and chronic diseases
- Challenging to efficiently recognize and evaluate all (liver) test abnormalities, particularly in the early stages of chronic disease:

2

Case

- 12 yo boy - asymptomatic
- Referred for "elevated LFTs"
  - ALT = 93 IU/L
  - AST = 58 IU/L
- Serum Bilirubin, GGT, AP normal

3

What do abnormal liver enzyme levels mean in a tween?

- Serum aminotransferase activity
  - ALT and/or AST
- "liver tests" or "liver chemistries" *(Not LFTs)*
- Guidelines recommend their use to screen for liver disease; example:
  - NAFLD in overweight / obese children
  - Drug-induced injury (DILI)

Vos, JPGN 64:319, 2017

4

What do abnormal liver enzyme levels mean in a tween?

Problems:

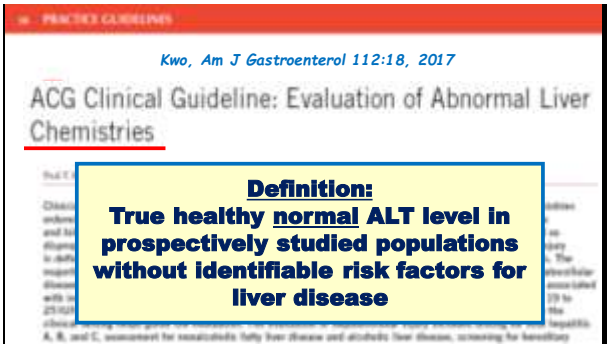
- Threshold value for detecting liver disease in children?
- Variability v/v labs
- Proper interpretation of abnormal values:
  - transient?
  - organ of origin?

5

What do abnormal liver enzyme levels mean in a tween?

1. What is normal?
2. What is abnormal?
3. What is the differential?
4. How do we evaluate?
   - Invasive (biopsy)
   - Non-invasive

6



7

Mean of a healthy ADULT population ± 2SDs*

- Ranges:
  - 29 to 33 IU/L for males
  - 19 to 25 IU/L for females
- *"levels above this should be assessed"*

* = incorporates 95% of subjects, thus 2.5% of population will be >ULN

Kwo, Am J Gastroenterol 112:18, 2017

8

Ask the right Questions:

1. Transient?
2. Clues?
3. Non-hepatic?
4. Degree?
5. Pattern?

9

Assessment - Clues from levels:

1. ALT vs AST
   - AST less liver specific (present in cardiac & skeletal muscle, kidney, brain)
2. Degree of elevation
   - Levels ≥5000, think APAP and ischemia

10

Patterns of Liver Chemistry Test Elevations

Kwo, Am J Gastroenterol 112:18, 2017

- Ratio of AST to ALT levels :
- For most liver conditions (chronic viral hepatitis & NAFLD) ALT > AST
- AST > ALT can be seen in patients with cirrhosis (any etiology)

11

Non-hepatic associations with elevated AST (+/- ALT) levels

- Skeletal muscle injury/rhabdomyolysis
- Cardiac muscle injury
- Strenuous exercise
- Heat stroke
- Hemolysis
- Adrenal insufficiency
- Thyroid disease
- Macro-AST

12

Assessment - Degree of AST and/or ALT elevation:

Kwo, Am J Gastroenterol 112:18, 2017

- "borderline" = <2X ULN
- "mild" 2–5X ULN
- "moderate" 5–15X ULN
- "severe >15X ULN
- "massive" >10,000 IU/L

13

Patterns of Liver Chemistry Test Elevations

Kwo, Am J Gastroenterol 112:18, 2017

1. Hepatocellular injury = disproportionate elevation of AST / ALT levels as compared with alkaline phosphatase level
2. Cholestatic injury = disproportionate elevation in alkaline phosphatase level as compared with AST / ALT levels
3. Mixed pattern

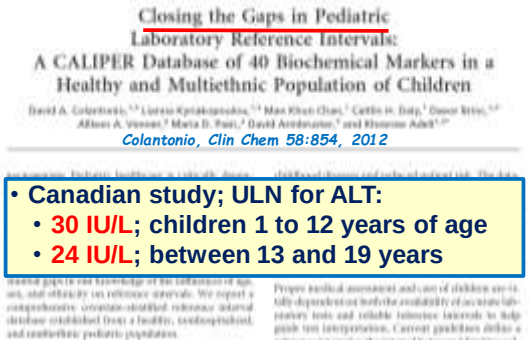
14

SAFETY Study: Alanine Aminotransferase Cutoff Values Are Set Too High for Reliable Detection of Pediatric Chronic Liver Disease

Schwimmer, Gastroenterology 2010;138:1357

- Sex-specific, biology based threshold
- US nationally representative data
  - validated in diverse cohort
- CUTOFFS:
  - 22 IU/L for girls
  - 26 IU/L for boys

15

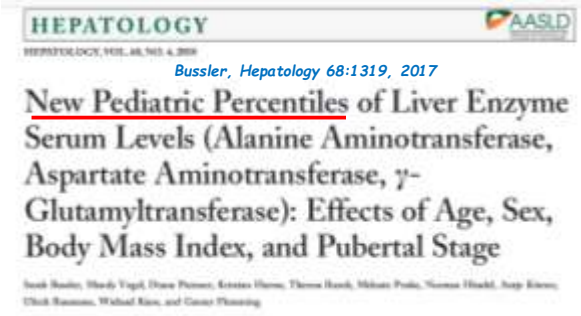


Closing the Gaps in Pediatric Laboratory Reference Intervals: A CALIPER Database of 40 Biochemical Markers in a Healthy and Multiethnic Population of Children

Colantonio, *Clin Chem* 58:854, 2012

- **Canadian study; ULN for ALT:**
  - **30 IU/L; children 1 to 12 years of age**
  - **24 IU/L; between 13 and 19 years**

16



HEPATOLOGY

AASLD

Bussler, *Hepatology* 68:1319, 2017

New Pediatric Percentiles of Liver Enzyme Serum Levels (Alanine Aminotransferase, Aspartate Aminotransferase, γ-Glutamyltransferase): Effects of Age, Sex, Body Mass Index, and Pubertal Stage

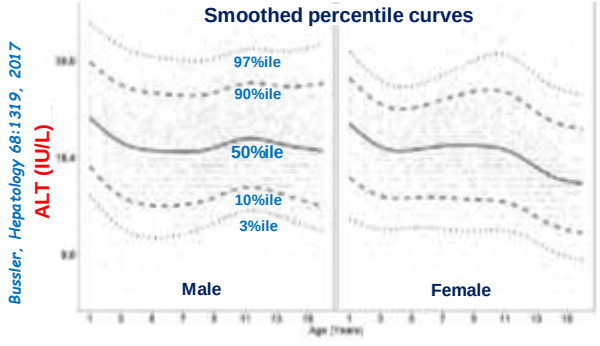
17

New Pediatric Percentiles of Liver Enzyme Serum Levels

Bussler, Hepatology 68:1319, 2017

- Prospective longitudinal, population-based cohort (n= 3,131 cases)
- At all ages and sexes:
  - For ALT/AST - 90% cutoff was ~30 IU/L
  - For GGT - 90% cutoff was ~25 IU/L

18



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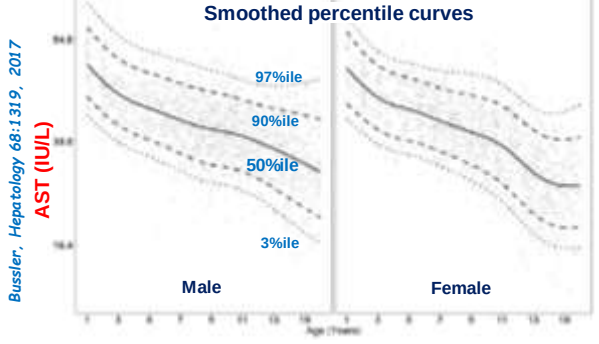


20

What is the differential?

1. Autoimmune Liver Disease
2. Viral Hepatitis
3. Metabolic Liver Disease
4. Systemic Disease
5. DILI
6. Fatty liver

21

Indications for Liver Biopsy

Rockey, HEPATOLOGY, Vol. 49:1017, 2009

1. Diagnosis:
   - Abnormal liver tests of unknown etiology
   - Multiple parenchymal liver diseases?
   - Fever of unknown origin?
   - Focal or diffuse abnormalities on imaging
2. Prognosis:
   - Staging of known parenchymal liver disease
3. Management:
   - Developing treatment plans based on histology

22

Biopsy vs. Non-Invasive

"Much of the interest in noninvasive evaluation of liver disease comes from the known limitations of the biopsy procedure"

Tapper and Lok, N Engl J Med 377:756, 2017

23

Limitations of Liver Biopsy:

Tapper and Lok, N Engl J Med 377:756, 2017

1. Sampling error is common:
   - diseases do not affect the liver uniformly
2. Interpretation is subjective
3. Complications (pain, bleeding, injury to other organs)
4. Costly

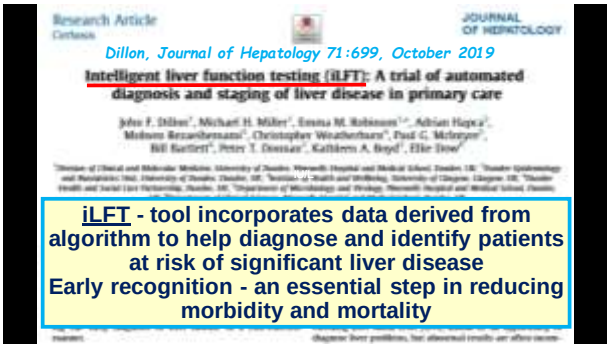
24

Strategies for Noninvasive Diagnosis and Risk Stratification:

Tapper and Lok, N Engl J Med 377:756, 2017

- Goals:
  - "precise" diagnosis
  - categorize patients - low, indeterminate, or high likelihood of advanced disease
- Reserve biopsy for indeterminate
- Incorporate noninvasive indexes - begin with tests that have a high negative likelihood ratio; thus rule out high-risk cases

25



iLFT - tool incorporates data derived from algorithm to help diagnose and identify patients at risk of significant liver disease
Early recognition - an essential step in reducing morbidity and mortality

26

Case

- 12 yo boy - asymptomatic
- Referred for "elevated LFTs"
  - ALT = 93 IU/L
  - AST = 58 IU/L
- Serum Bilirubin, GGT, AP normal

27

Pediatric AIH Diagnostic Score

Mieli-Vergani, JPGN, 66:345, 2018

- Autoantibodies
  - ANA or anti-SMA ≥1:20
  - anti-LKM1 titers ≥1:10
  - anti-SMA or anti-LC1 or anti-SLA
- Hypergammaglobulinemia
- Liver biopsy (histopathology)
  - Interface hepatitis
  - Multilobular collapse
- Exclusion of viral hepatitis
- Exclusion of Wilson's disease

MRCP
ERCP

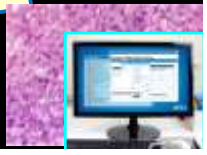
28

What is the differential?

1. **Autoimmune Liver Disease**
2. Viral Hepatitis
3. Metab
4. Systen
5. DILI
6. Fatt

AIH
ASC
PSC

1. Negative serology
2. Normal GGT
3. Normal IgG



29

What is the differential?

1. Autoimmune Liver Disease
2. **Viral Hepatitis**
3. Metabolic Liver Dis
4. Systemic Disea
5. DILI
6. Fatty liver

HAV - HBV- HCV

SCREEN:
1. Anti-HBs +
2. Anti-HAV +
3. Anti-HCV neg

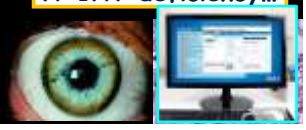
30

1. No clinical features of WD
2. 24 hour urine copper – low
3. A-1-AT phenotype – MM

3. Metabolic Liver Disease

4. Systemic Disease
5. DILI
6. Fatty liver

Wilson disease,
A-1AT deficiency…



31

What is the differential?

1. Autoimmu

1. No clinical features or associations (IBD, celiac disease, cardiac, muscle)
2. IgG, Autoantibodies, TTG – not suggestive

5. Systemic Disease

6. Fatty liver

Celiac
IBD
Ischemia

32

Abnormal Liver Biochemistry is Common in Pediatric IBD:

Valentino, Inflamm Bowel Dis 21:2848, 2015

- 300 children; abnormal AST/ALT = 58%
  - 16% by one mo post-IBD dx
- ? Medication related in some
- Transient - common
- Persistent:
  - 6% prevalence of PSC or ASC

33

Prevalence and causes of abnormal liver tests in patients with Celiac Disease

Casella , Liver Int 33:1128, 2013

- Data from 245 untreated patients:
- 18% had elevated ALT/AST values
- After one year of GFD:
  - normalized in all

34

What is the diff

1. No history of other ingestions (prescribed, OTC, CAM, herbals)
2. Prescribed med – OK by LIVER TOX https://livertox.nih.gov/

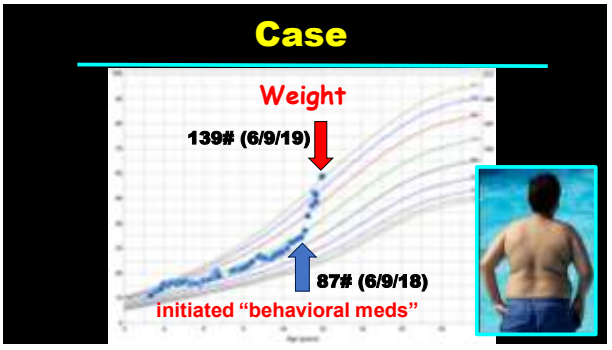
1.
2.
3.
4. [illegible] Disease
5. **DILI** Drugs (APAP), CAMs, et al
6. Fatty liver

35

Case

- 12 yo boy - asymptomatic
- Referred for "elevated LFTs"
  - ALT = 93 IU/L
  - AST = 58 IU/L
- Serum Bilirubin, GGT, AP norm
- One year prior:
  - initiated "ADHD & behavioral medications"
- Recent weight gain

36



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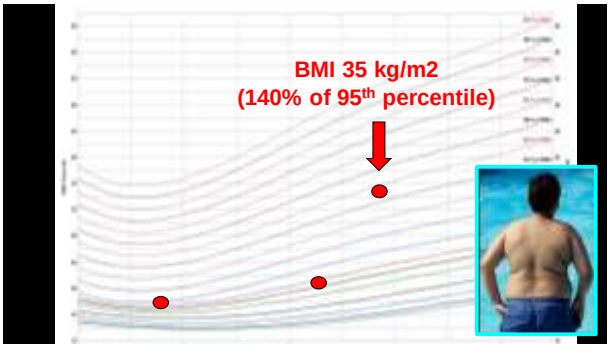

38

Metabolic Effects of Antipsychotics on Adiposity and Insulin Sensitivity in Youths
A Randomized Clinical Trial

Nicol, JAMA Psychiatry. 75:788, 2018

"…clinically significant increases in total and abdominal adiposity and decreased insulin sensitivity during treatment…"

Monitoring
of Adverse Effects in Children and Youngsters
Who Take On-label or Off-label Antipsychotic Medication

39

Psychotropic Medications Are Associated With Increased Liver Disease Severity in Pediatric Nonalcoholic Fatty Liver Disease

[1]Marialuna Mouzaki, [2]Toshifumi Yodoshi, [3]Ana C. Arce-Clachar, [3]Kristin Bramlage, [3]Lin Fei, [3]Sanita L. Ley, and [3]Sharva A. Xanthakos

Mouzaki, JPGN 69:339, 2019

ABSTRACT

Objectives: The aim of the study was to determine whether pediatric patients with nonalcoholic fatty liver disease (NAFLD) exposed to psychotropic medications have more severe liver disease compared to their counterparts who are not on these medications. We hypothesize that use of psychotropic agents is associated with liver disease severity.

Methods: Children and adolescents with biopsy-confirmed NAFLD were included in this study. Histology data, detailed clinical information, and results of serum biochemistries performed within 3 months of the liver biopsy were collected retrospectively. Univariate and multivariate modeling was used to determine differences between the groups and to control for confounders.

What is Known

- The use of psychotropic medications, namely antipsychotics and antidepressants, has been associated with weight gain and the development of metabolic dysregulation, such as insulin resistance.
- Psychotropic medications can also affect lipid handling within the liver and thus predispose patients to nonalcoholic fatty liver disease.

40

History & Physical Examination

- Review of Systems:
  - Snoring
  - Reflux
  - Knee pain
- Exam:
  - Mild elevation of BP
  - Central Adiposity
  - Acanthosis nigricans

41

Key Questions

1. Is it fat or ???
2. Is this “secondary”?
3. NASH?

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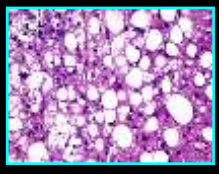
Causes of Secondary Steatosis

Macrovesicular steatosis:

- Medications: MTX, steroids
- Mauriac
- Wilson's disease
- CF
- Lipodystrophy
- Starvation
- TPN
- A-beta-LP
- XS alcohol consumption
- "Syndromic"



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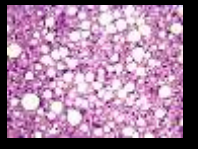
Causes of Secondary Steatosis

Microvesicular steatosis:

- REYE'S SYNDROME
- Meds (valproate)
- Acute fatty liver of pregnancy
- HELLP
- Inborn errors of metabolism:
  - LAL-D
  - CESD
  - Wolman disease
  - LCAT deficiency



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HEPATOLOGY

PRACTICE GUIDANCE

The Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance From the American Association for the Study of Liver Diseases

Preamble.

Chalasani, Hepatology 67:328, 2018

45

Histology = Gold Standard

1. Dx NASH (surrogates are insufficient)
2. Grade & Stage (Pattern of fibrosis and inflammation)
3. Other hepatocellular injury?
4. Choice of & response to intervention

46

Bottom Line: Liver Biopsy

- However:
  - Sampling
  - Clinical indications unclear
  - Biopsies on 1-2 million US children?
- "…justified if effective treatment of NASH"

47

CLINICAL GUIDELINES

NASPGHAN Clinical Practice Guideline for the Diagnosis and Treatment of Nonalcoholic Fatty Liver Disease in Children: Recommendations from the Expert Committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN)

[illegible]

Vos, JPGN 64:319, 2017

48

Consider biopsy for the assessment of NAFLD in children:

Those with an increased risk of NASH and/or advanced fibrosis:

- Splenomegaly
- Higher ALT levels (>80 U/l)
- AST/ALT >1
- Panhypopituitarism
- Type 2 diabetes

Vos, JPGN 64:319, 2017

49

The "ideal test":

1. Simple, easy to use, validated (age-specific), cost-effective
2. Accurate:
   - Dx of NASH
   - Staging of fibrosis
   - Risk stratification
   - Monitoring response to interventions

3. Predicts progression?

50

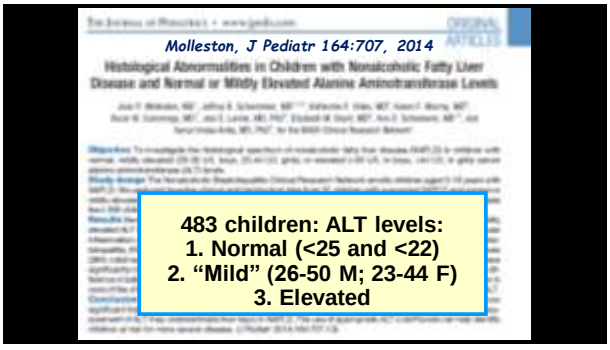
Non-invasive Diagnosis and Monitoring of NASH

1. Markers of Injury (ALT, AST)

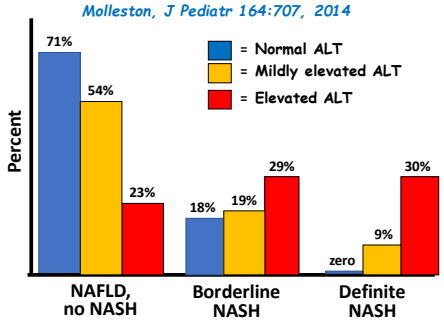
Limitations of AST and ALT:

- Presence, degree, pattern nonspecific
- Poor correlation with histology

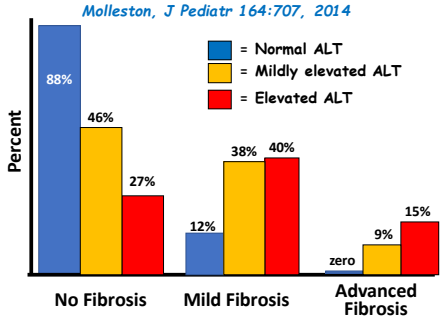
51


Molleston, J Pediatr 164:707, 2014
Histological Abnormalities in Children with Nonalcoholic Fatty Liver Disease and Normal or Mildly Elevated Alanine Aminotransferase Levels
483 children: ALT levels:
1. Normal (<25 and <22)
2. "Mild" (26-50 M; 23-44 F)
3. Elevated

52


Molleston, J Pediatr 164:707, 2014
Percent
= Normal ALT
= Mildly elevated ALT
= Elevated ALT
71%
54%
23%
18%
19%
29%
zero
9%
30%
NAFLD, no NASH
Borderline NASH
Definite NASH

53


Molleston, J Pediatr 164:707, 2014
Percent
= Normal ALT
= Mildly elevated ALT
= Elevated ALT
88%
46%
27%
12%
38%
40%
zero
9%
15%
No Fibrosis
Mild Fibrosis
Advanced Fibrosis

54

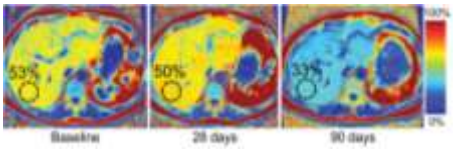
Non-invasive Diagnosis and Monitoring of NASH

1. Markers of Injury (e.g. AST)
2. Markers of Fatty Infiltration:
   - US - Controlled Attenuation Parameter (CAP)
   - MRI-est. proton density fat fraction (MRI-PDFF)

NOTE = MRS the "standard"
correlates with MRI-PDFF

"Fat Map"

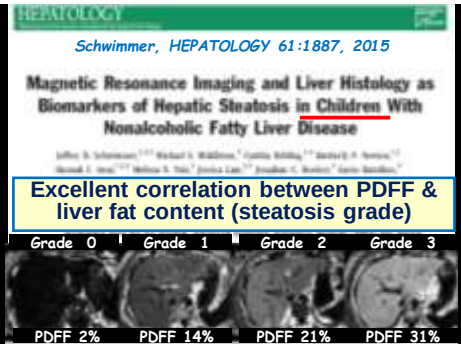
55



- Serial PDFF maps (severe steatosis)
- Treated – decrease in fat content

Reeder, HEPATOLOGY 58:1877, 2013

56



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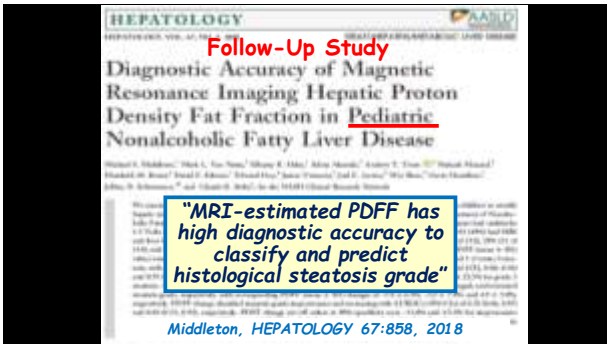
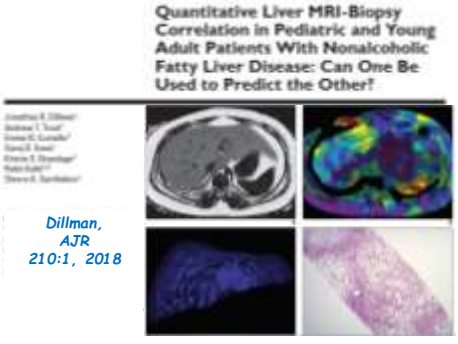
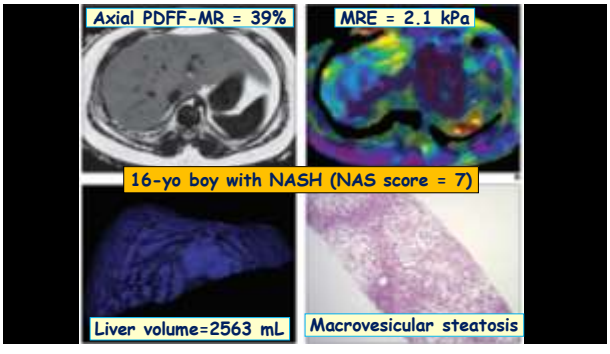

HEPATOLOGY
Follow-Up Study
Diagnostic Accuracy of Magnetic Resonance Imaging Hepatic Proton Density Fat Fraction in Pediatric Nonalcoholic Fatty Liver Disease
"MRI-estimated PDFF has high diagnostic accuracy to classify and predict histological steatosis grade"
Middleton, HEPATOLOGY 67:858, 2018

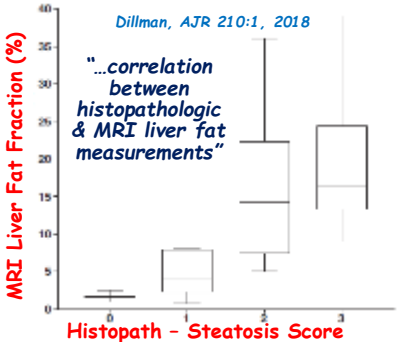
58


Quantitative Liver MRI-Biopsy Correlation in Pediatric and Young Adult Patients With Nonalcoholic Fatty Liver Disease: Can One Be Used to Predict the Other?
Dillman, AJR 210:1, 2018

59


Axial PDFF-MR = 39%
MRE = 2.1 kPa
16-yo boy with NASH (NAS score = 7)
Liver volume=2563 mL
Macrovesicular steatosis

60



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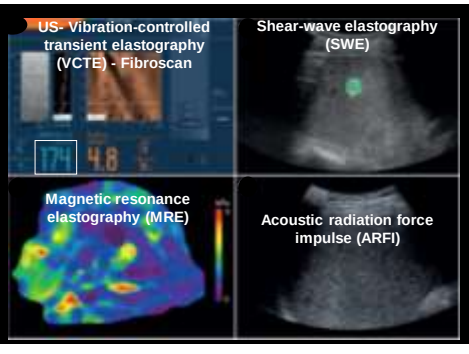
Non-invasive Diagnosis and Monitoring of NASH

1. Markers of Injury (e.g. AST)
2. Markers of Fatty Infiltration:
   - US - Controlled Attenuation Parameter (CAP)
   - MRI-est. proton density fat fraction (MRI-PDFF)
3. Markers of Fibrosis (stiffness):
   - US-based Vibration Controlled Transient Elastography (VCTE) FibroScan®
   - Shear Wave Elastography (SWE)
   - Acoustic Radiation Force Imaging (ARFI)
   - Magnetic Resonance Elastography (MRE)

62



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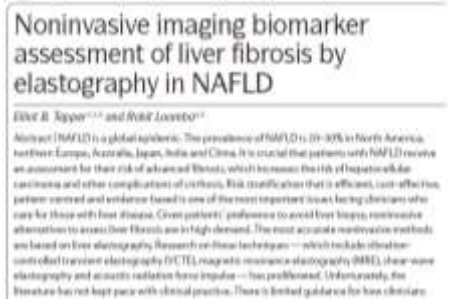

Noninvasive imaging biomarker assessment of liver fibrosis by elastography in NAFLD

Tapper, NATURE REVIEWS; GASTRO & HEPATOL 15:275, 2018

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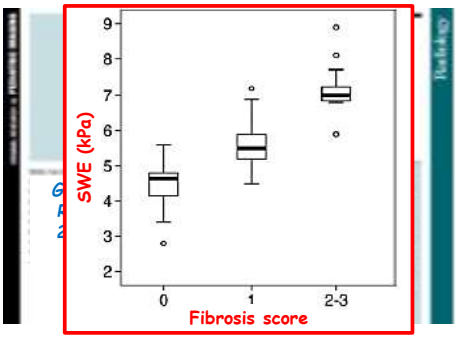

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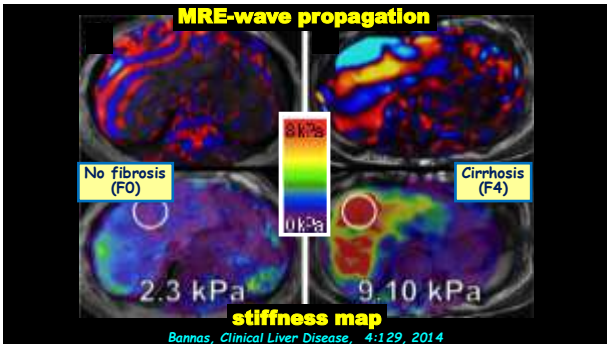
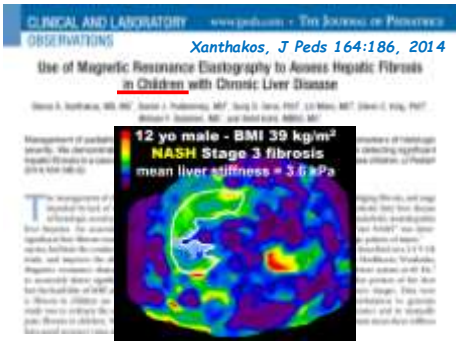


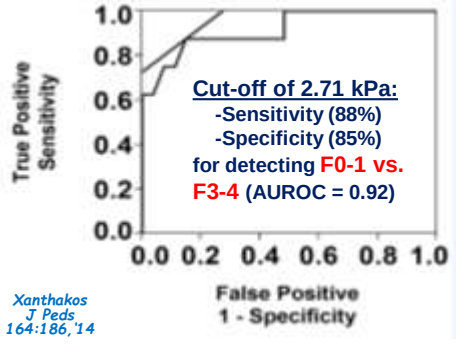
Bannas, Clinical Liver Disease, 4:129, 2014

67



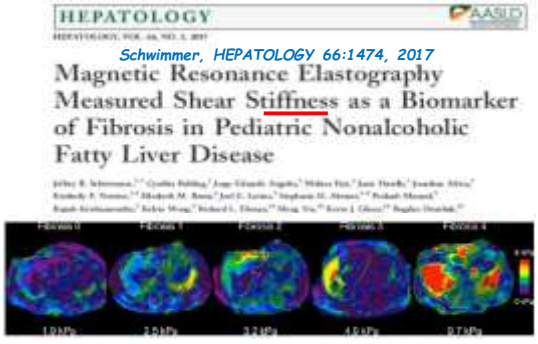
Xanthakos, J Peds 164:186, 2014

68



Xanthakos J Peds 164:186,'14

69



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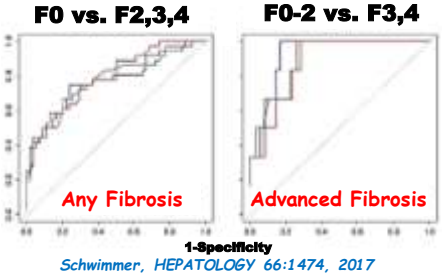
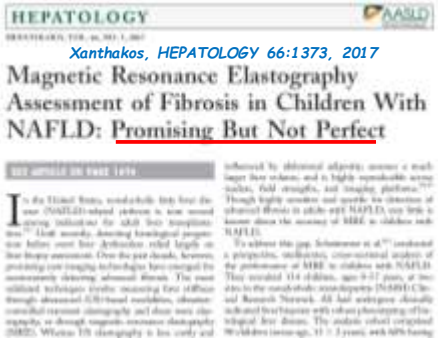
F0-2 vs. F3-4 (AUROC = 0.93)



Schwimmer, HEPATOLOGY 66:1474, 2017

71



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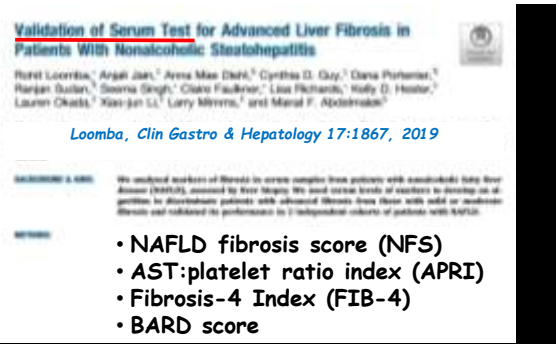
Non-invasive Diagnosis and Monitoring of NASH

4. Clinical Scoring Systems

Serologic markers of fibrosis:

- indirect = ALT, AST
- direct = collagen (ECM) turnover

74



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Non-invasive Diagnosis and Monitoring of NASH

4. Clinical Scoring Systems
5. Markers of Susceptibility (genomics, proteomic, metabolomics)
6. Biomarkers of Pathophysiology:
   a. Insulin Resistance
   b. Oxidative Stress
   c. Inflammation / Cytokines
   d. Fibrogenesis
   e. Apoptosis

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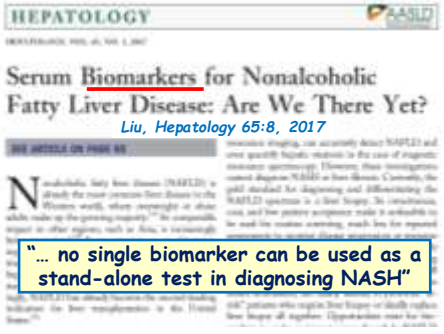

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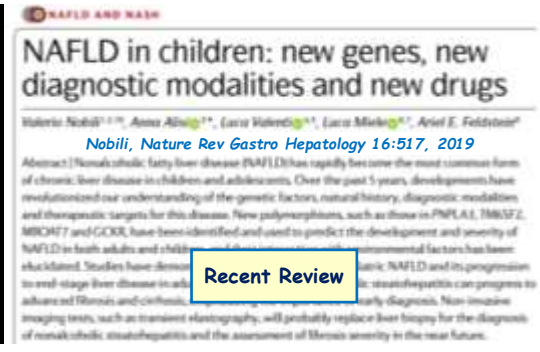

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Bottom Line:

- In most "tweens" with elevated liver enzymes… chronic liver disease can be diagnosed and staged based on:
  - Clinical history and examination
  - Routinely available serum-based and radiologic studies:
    - multiple non-invasive methods to assess for significant fibrosis

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Our Approach to this Patient

80

CCHMC Liver Clinic: Initial Visit

- CBC, CMP, cbili, GGT, PT/INR
- Fasting lipids, insulin; HbA1c
- Auto-antibody panel
- A1AT phenotype
- HBsAg and anti-HBs; Anti-HCV
- U/S (if not done within 12 mos)
- TSH, fT4; TTG, CK, Aldolase
- Nutrition consult

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CCHMC Liver Clinic:
Consider:

- MRE: ? significant fibrosis
- Liver biopsy if:
  - Auto-antibody (≥2+ & ALT>50)
  - Persistent elevation of AST/ALT and self report of adherence to lifestyle modification plan
  - Splenomegaly

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NASPGHAN Single Topic Symposium, October 16, 2019

What Do I Do with this Abnormal Radiology Finding?

Chronic Liver Disease Management for the Gastroenterologist

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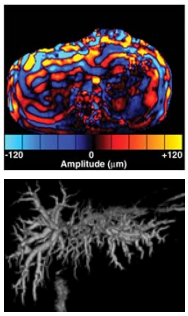
Disclosures

- Research funding from Mirum, Abbvie, Gillead unrelated to this talk
- Research funding from CF foundation, also unrelated
- **I am NOT a radiologist!**



D Boll RadioGraphics 2009
B Yeh RadioGraphics 2009

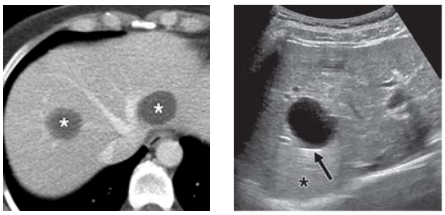
Objectives

- Outline the differential diagnosis and evaluation of focal liver lesions.
- Recognize congenital and acquired vascular abnormalities of the liver.
- Identify appropriate imaging approaches to suspected biliary tract disease.
- *Differentiate various parenchymal liver abnormalities.*

Focal Liver Lesions

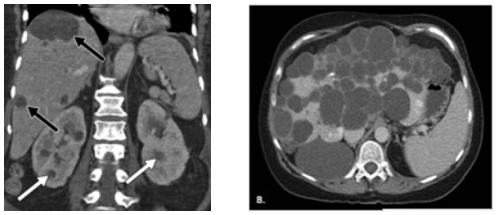
Simple Hepatic Cyst

- 2.5% of the population
- Biliary origin, but no communication with biliary tree



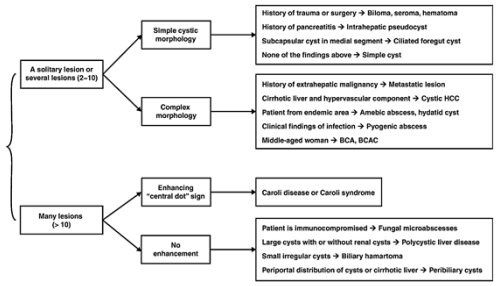
A Bornhani Am J Roentgen 2014

Polycystic Liver Disease: Associated with Polycystic Kidney Disease



A Borhani Am J Roentgen 2014
Mavilia J Clin TranslHepatol 2018

Algorithm for Hepatic Cysts



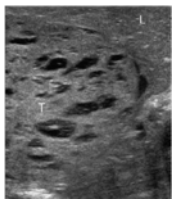
A Borhani Am J Roentgen 2014

Mesenchymal Hamartoma

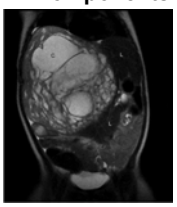
- 8% of pediatric liver tumors (second to hepatoblastoma)
- Usually first 2 years of life, up to age 5
- May be very large, cause mass effect; solid and cystic components
- Myxomatous connective tissue with bland stellate mesenchymal cells and abnormal branching bile ducts
- Benign tumor; malignant transformation is rare

G Talmon Arch of Path and Lab Med 2006

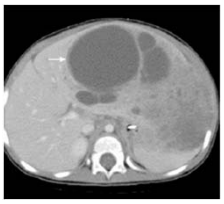
Mesenchymal Hamartoma with Cystic, Septated and Solid Components



Ultrasound, solid and cystic components



MRI T2 coronal image: huge, with cysts, solid, septations

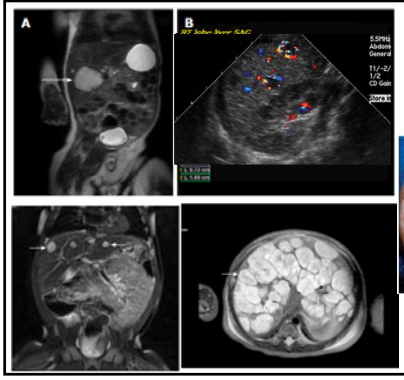


CT with IV contrast

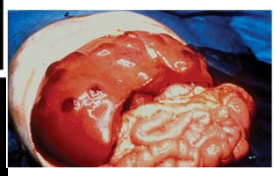
G Anil Br J Radiol, 2010
Gnarra World J Clin Pediatr 2016

Hemangioma

- Often accompanied by cutaneous lesions (60% of multiple)
- GLUT-1 positive
- Complications can include hypothyroidism, AV shunting, heart failure
- Differential diagnosis: hepatoblastoma, mesenchymal hamartoma, cysts, metastases
- Treatment: observation, prednisone, propranolol, (rarely) embolization or transplant



Hepatic Hemangioma: Hyperintense, Vascular

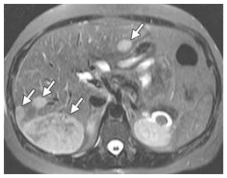


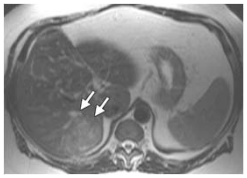
Gnarra World J Clin Pediatr 2016
Chung Radiographics 2010

Hepatic Adenoma

- Benign tumor
- 3 types: inflammatory, HNF mutated, and B-catenin mutated
- 3-4/100,000 women
- Oral contraceptives are a risk, as is GSD
- Complications: bleeding, malignant transformation
- Risk of HCC is 5-10% (especially B-catenin type)

Hepatic Adenoma: No Specific Imaging Pattern





Subtype	T1-weighted Gradient-Echo MR Images	T2-weighted MR Images	Gadolinium-enhanced T1-weighted MR Images
Inflammatory hepatocellular adenoma	Isointense or mildly hyperintense, without signal drop-off with use of chemical shift sequence	Diffusely hyperintense	Intense enhancement during arterial phase that persists in the portal venous and delayed phases
HNF-1α–mutated hepatocellular adenoma	Hypo- or isointense, with diffuse signal drop-off with use of chemical shift sequence	Isointense to slightly hyperintense	Moderate enhancement in the arterial phase, with no persistent enhancement in the portal venous and delayed phases
β-Catenin–mutated hepatocellular adenoma[a]	…	…	…

Katabathina Radiographics 2011

Focal Nodular Hyperplasia (FNH)

- Associated with vascular anomalies
  - absence of PV
  - HV thrombosis
  - AV shunting
- Complications: bleeding in about 2%, usually not cancer

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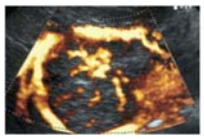
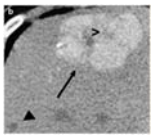
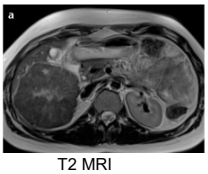
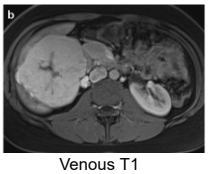
Focal Nodular Hyperplasia: Typical Central Scar



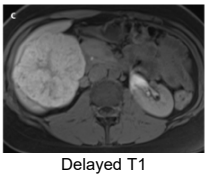




T2 MRI



Venous T1



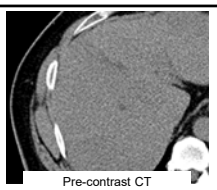
Delayed T1

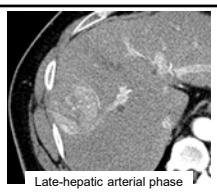
Venturi J Ultrasound 2007
Diagn Interv Radiol 2014 M Thomeer

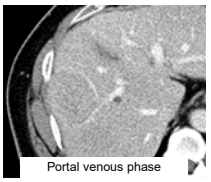
Hepatocellular Carcinoma

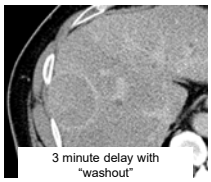
- 3rd most common tumor worldwide; 8/100,000
- Cirrhosis is an important risk factor in adults (80%), esp hep B and C
- Cirrhosis in only 30% of children with HCC
- Risk factors: Hep B/C, tyrosinemia, PFIC2
- Presentation with abdominal mass and pain
- AFP can be elevated (50-70%)
- CT or MRI are best for imaging

D Kelly Clinics in Liver Disease 2015

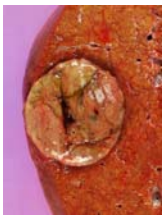

Pre-contrast CT


Late-hepatic arterial phase


Portal venous phase


3 minute delay with "washout"

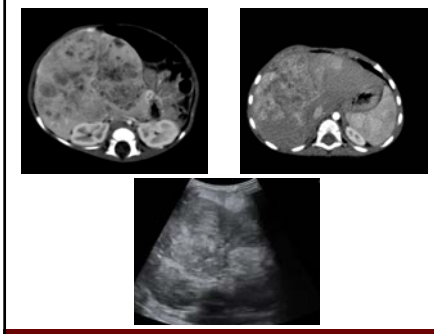
Hepatocellular Carcinoma: "Wash-out"



J Marrero Am G Gastro 2013

Hepatoblastoma

- Most common liver tumor of children
- Associations: Beckwith-Wiedemann, hemihypertrophy, FAP, premies
- Subtypes: epithelial (most common) and mixed type
- Symptoms: abdominal pain, mass
- Labs: AFP
- Imaging: CT/MRI



Hepatoblastoma
Heterogeneous, well defined, necrosis/hemorrhage, calcification

Radiopaedia.org

Vascular Lesions

Portal Vein Thrombosis and Budd-Chiari

- Portal vein thrombosis:
  - Idiopathic (look for hypercoagulable state)
  - Accompanying cirrhosis
  - Anticoagulant if acute
  - Can develop cavernous transformation of the portal vein
- Budd-Chiari: hepatic outflow obstruction due to hepatic vein or IVC obstruction
  - Can present with pain, ascites, liver failure

Portal Vein Thrombosis

F Ponziani World J Gastroenterol 2010

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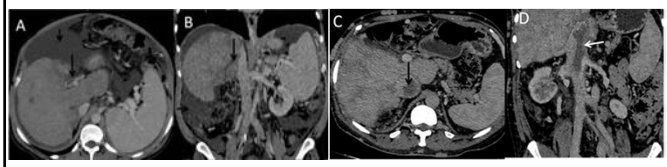
Budd-Chiari Syndrome



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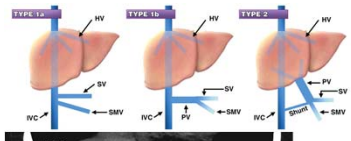
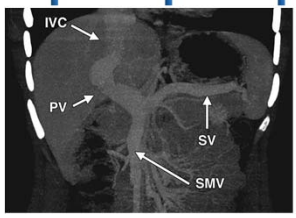
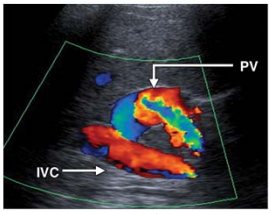


Congenital Portosystemic Shunt
(Abernathy Malformation): Hyperammonemia, Risk of Tumor or Portopulmonary HTN



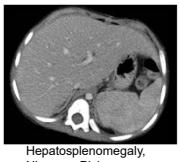


E Alonso-Gamarra Radiographics 2011
L DeLeve Hepatology 2009

Hepatic Parenchymal Changes

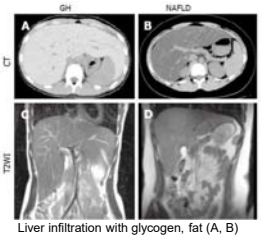
- Hepatomegaly
- Fibrosis/cirrhosis
- Glycogen
- Fat

Liver Parenchyma

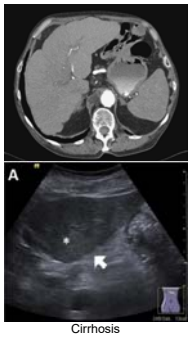


Hepatosplenomegaly, Niemann-Pick

J Sherigar World J Hepatol 2018
Radiopaedia.com
A Huber Eur J Radiol Open 2015

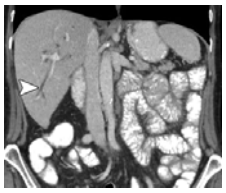


Liver infiltration with glycogen, fat (A, B)

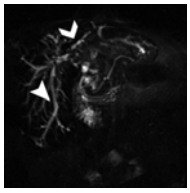


Cirrhosis

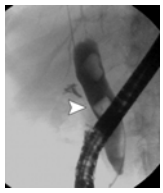
Biliary Imaging



CT: dilated duct



MRCP: beading from PSC



ERCP: stones in CBD

O O'Connor Am J Roentgen 2011

Summary

- Benign lesions

Recognition and Stabilization of the Pediatric Patient with Acute Liver Failure

Robert H. Squires, MD
Professor of Pediatrics
University of Pittsburgh

UPMC CHILDREN'S HOSPITAL OF PITTSBURGH

Disclosures for this Presentation

In the past 12 months, I have had the following relevant financial relationships with the following manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity:

- Up-to-Date: Royalty for chapter contributions on Acute Liver Failure

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Objectives

- Recognize features needed to establish a clinical diagnosis of acute liver failure
- Identify and initiate management of multi-system complications associated with acute liver failure.
- Appreciate age-specific differences in the etiology of acute liver failure
- Know when to make early contact with and/or transfer to a pediatric liver transplant center.

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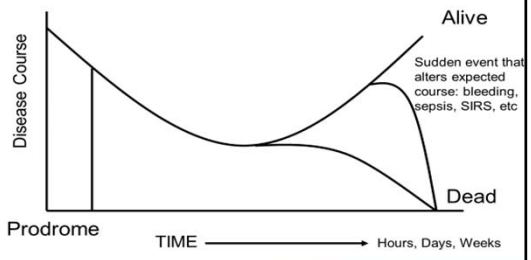
Proposed Model of the Natural Course and Outcome of Acute Liver failure in Children



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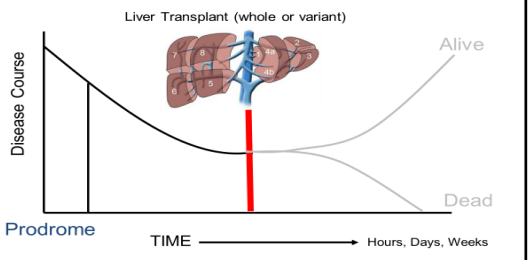
Natural History of Acute Liver Failure in the Liver Transplant Era



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Criteria for Acute Liver Failure in Children

Clinical Parameter	Trey and Davidson 1970	King's Non-APAP O'Grady 1989	King's APAP O'Grady 1989	Infants < 1 yr. Durand P 2001	PALF Study Group Squires RH 2006
Coagulopathy		PT >100 (INR > 6.5); or any 3 below	INR >6.5	PT >17 and Factor V level <50%	INR > 1.5 or PT > 15 sec; not corrected by vitamin K
Coagulopathy		PT >50 (INR 3.5)			
Encephalopahty	Hepatic coma within 8 weeks of illness	Present	Grade III or IV	Regardless of clinical HE	Required if INR 1.5-1.9; Not required if INR ≥2
Evidence of acute liver injury					Within 8 weeks of disease onset
No known evidence of chronic liver diseae	X				X
Age <10 or >40 yr		X			
Etiology		Non-A or B hepatitis; DILI			
Serum bilirubin		17.6 mg;dL / >300 umol/L			
Arterial pH <7.3			X		
Creatinine >3.4 mg/dL			X		

APAP: Acetaminophen; DILI: Drug-Induced Liver Injury; HE: Hepatic Encephalopathy; INR: International Normalized Ratio; PT: Prothrombin Time

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Characterization of PALF

- PALFSG Consensus entry criteria for the PALF study in children
  - No evidence of chronic liver disease
  - Evidence of acute liver injury
  - Coagulopathy unresponsive to Vitamin K
    - PT ≥ 15 sec. or INR ≥ 1.5 with clinical encephalopathy
    - PT ≥ 20 sec. or INR ≥ 2.0 with/without clinical encephalopathy
- Identifies a spectrum that includes severe liver injury to fulminant liver failure
- Meeting these criteria should prompt at least contact with a liver transplant center.

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Biochemical Evidence of Acute Liver Injury in Children

- Suggested parameters indicating evidence of liver injury
  - AST >100 IU/L or,
  - ALT >100 IU/L or,
  - Total bilirubin > 5mg/dL or,
  - Direct or conjugated bilirubin >2.0 mg/dL.
- **PT/INR should always be obtained with evidence of acute liver injury to assess liver function.**
- Acetaminophen toxicity: normal or near normal bilirubin with very high aminotransaminase levels
- Gestational Alloimmune Liver Disease, Tyrosinemia, Galactosemia: normal or near normal aminotransferase levels with high total and direct bilirubin
- Note serum alkaline phosphatase is NOT a lab test traditionally used to determine acute liver injury in children
- These cutoff values were not part of the PALF study criteria.

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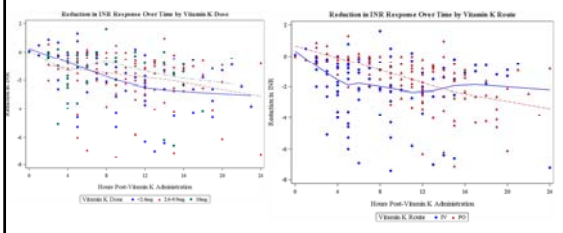
Effect of Vitamin K Administration on Rate of Warfarin Reversal



Polito NB, et.al. Transfusion. 2019

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Hepatic Encephalopathy Grading Scales

HE Grading Scale for Patients Under 3 Years of Age (Whitington/Alonso)

Stage	Clinical	Reflexes	Neurological Signs
Early (I and II)	Inconsolable crying, sleep reversal, inattention to task	Normal or hyperreflexia	Untestable
Mid (III)	Somnolence, stupor, combativeness	Unreliable or hyperreflexia	Most likely untestable
Late (IV)	Comatose, arouses with painful stimuli (IVa), or no response (IVb)	Absent	Decerebrate or decorticate

HE Grading Scale Patients Between 3 and 18 Years of Age (New Haven Criteria)

Stage	Clinical	Reflexes	Neurologic Signs	EEG changes
0	None	Normal	Psych testing only	Normal
I	Confused, mood changes, altered sleep habits, loss of spatial orientation, forgetful	Normal	Tremor, apraxia, impaired handwriting	Normal or diffuse slowing to theta rhythm, triphasic waves
II	Drowsy, in appropriate behavior, decreased inhibitions	Hyperreflexia	Dysarthria, ataxia	Abnormal generalized slowing, triphasic waves
III	Stuporous, obeys simple commands	Hyperreflexia, up going toes (+ Babinski)	Rigidity	Abnormal generalized slowing, triphasic waves
IV	Comatose, arouses with painful stimuli (IVa), or no response (IVb)	Absent	Decerebrate or decorticate	Abnormal, very slow delta activity

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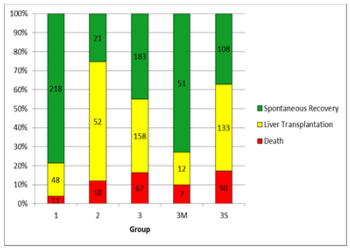
21 day outcomes for 768 PALF Participants based on HE and Coagulopathy



1: No HE in the first 7 days
2: Developed HE
3: HE at enrollment
3M: HE at enrollment and INR ≤2
3S: HE at enrollment and INR >2

Ng VL, et.al. JPGN 2016;63:357-364

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Intensive Care Environment

- If PALF study entry criteria are met
  - Admit to ICU initially for careful biochemical and neurological monitoring
  - Contact pediatric liver transplant center
- Anticipate complications
  - Hypoglycemia
  - Hypophosphatemia
  - Hyperammonemia
  - Neurological deterioration
  - Electrolyte disturbance
  - Cardiopulmonary deterioration
- Avoid sedation
- Maintain oxygenation

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Hematologic Support

- Administer vitamin K parenterally only once
- In the setting of ALF, prolonged INR is a good measure of liver dysfunction, but is not a measure of bleeding risk
- Avoid giving FFP or cryoprecipitate just to correct the INR
- Consider giving blood products if
  - An invasive procedure is planned
  - Significant hemorrhage
  - INR is very high (e.g, >5-6) after parenteral vitamin K

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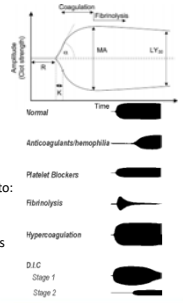
Minimal Effects of Acute Liver Injury / Acute Liver Failure on Hemostasis as Assessed by Thromboelastography (TEG)

- **INR is a measure of liver function and not bleeding risk**
- 51 patients
  - Mean INR 3.4 ± 1.7 (range 1.5-9.6)
  - Mean TEG parameters were normal
  - Factor V and VII (pro-coagulants) were decreased
  - Proportional decreases in anti-coagulant proteins
  - Inversely proportional to elevated Factor VIII levels
- Most patients with ALI/ALF maintain normal hemostasis due to:
  - Increased clot strength
  - Increases Factor VIII and Von Willebrand levels
  - Commensurate decline in pro- and anti-coagulant proteins



Stravitz RT, et.al., Journal of Hepatology 2012;56:129-36

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Metabolic Support

- Maintain glucose between 90-110 mg/dL
  - Dextrose containing fluids, may require D10 or D12.5
- Maintain phosphorus >3.5 mmol/L
- Monitor electrolyte and renal function
- Careful assessment of fluid status
  - Fluid resuscitation if needed
  - Fluid restriction (90-95% of maintenance) preferred
  - Avoid unnecessary use of blood products

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Renal Support

- Renal injury at presentation
  - Shock / hypovolemia
  - Toxic injury (e.g. Acetaminophen or Mushroom toxicity)
- Careful monitoring of I & O
- Avoid over-zealous diuresis
  - Precipitate hepatorenal syndrome
  - Worsen encephalopathy
- Prepare for dialysis / hemofiltration (transplant center only)

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Neurological Support

- Patient should be in a liver transplant center if there is any evidence of encephalopathy
- Minimize stimulation
- If the patient is confused or combative, protect from injury
- Elevate the head of the bed
- Lactulose for hyperammonemia
- Careful fluid management
- CT / continuous EEG

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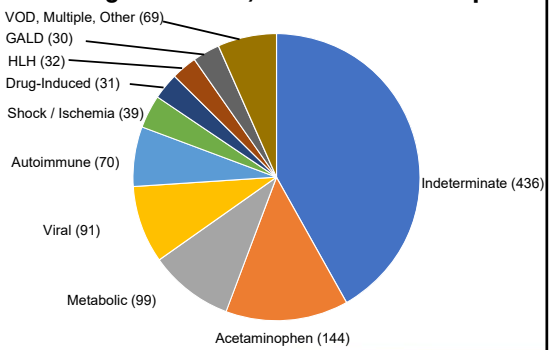
Final Diagnosis in 1,041 PALF Participants



Squires JE, et.al. Hepatology 2019

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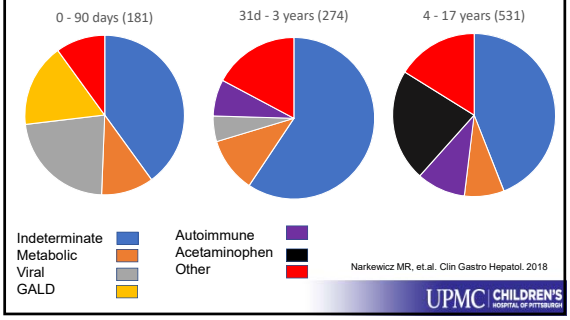
Diagnostic Categories by Age (n=986)



Narkewicz MR, et.al. Clin Gastro Hepatol. 2018

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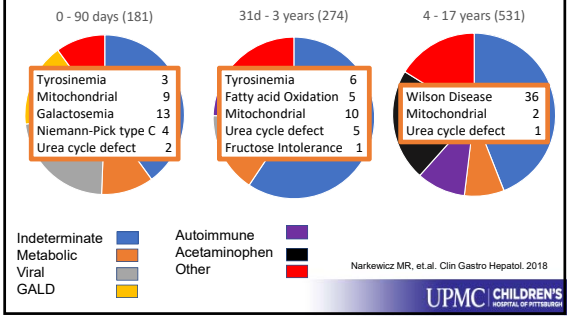
Diagnostic Categories by Age (n=986)



Narkewicz MR, et.al. Clin Gastro Hepatol. 2018

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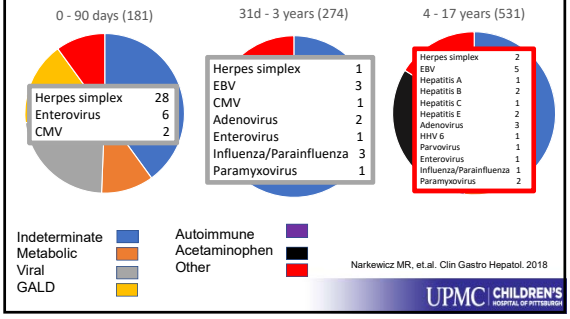
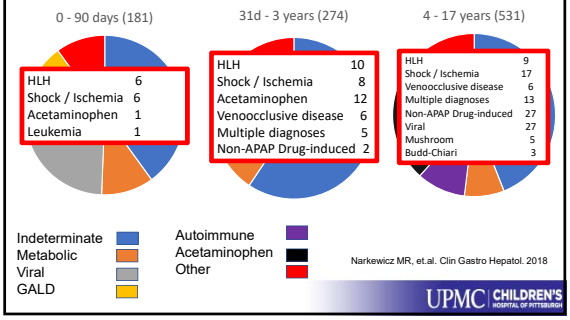
Diagnostic Categories by Age (n=986)



Narkewicz MR, et.al. Clin Gastro Hepatol. 2018

UPMC CHILDREN'S HOSPITAL OF PITTSBURGH

Diagnostic Categories by Age (n=986)



Narkewicz MR, et.al. Clin Gastro Hepatol. 2018

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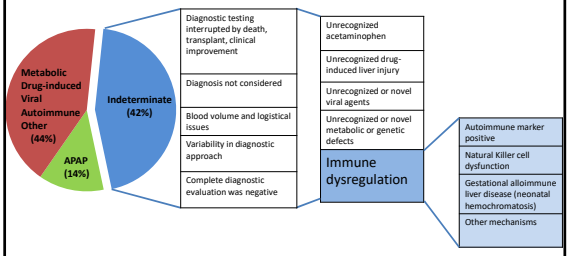
Indeterminate PALF is Heterogeneous



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Summary

- Acute liver failure is a dynamic clinical syndrome characterized by evidence of hepatocellular injury and a liver-based coagulopathy that is often, but not always, associated with clinical encephalopathy.
- Meeting PALF study entry criteria should prompt admission to the ICU and an urgent contact with a pediatric liver transplant center.
- Immediately initiate multi-system monitoring and support
- Age-specific etiologies should prioritize initial diagnostic testing; all infants presenting with ALF should be started on acyclovir.

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Future Direction

- Automate age-specific diagnostic testing.
- Develop effective liver support systems.
- Auxiliary or hepatocyte transplantation to bridge to recovery of the native liver.
- Improve clinical and *in silico* models that predict outcome and inform liver transplant decisions.

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Take Home Message for Patients Meeting PALF Study Entry Criteria

- Admit all patients to the ICU.
- Immediately contact a pediatric liver transplant center.
- Maintain glucose and phosphorous levels; carefully monitor neurological status; avoid overuse of blood products.
- Initiate diagnostic testing, prioritizing potentially treatable conditions; acyclovir should be given to all infants and also be considered in adolescents.

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Board Questions for MOC

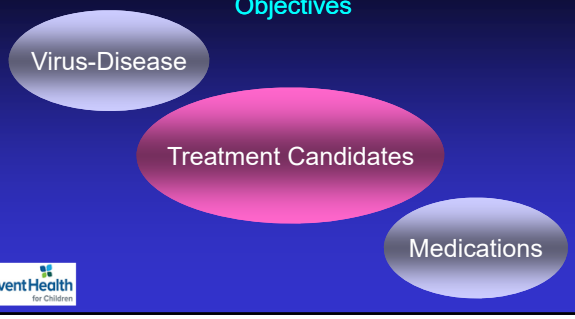
- offer MOC Part II credits as part of the symposium. To this end, please provide 2-3 board style multiple choice questions based on slide content to be submitted along with your slides. These will be used for MOC part II credit for the membership.
-

Disclosures

- Advisory boards: Roche, Alexion, Kadmon
- Grant Support: Gilead, Abbvie, Merck, Alexion
- Discussing UNAPPROVED therapy

What Would Hamlet Do: To Rx or Not to Rx?

Objectives



AdventHealth for Children

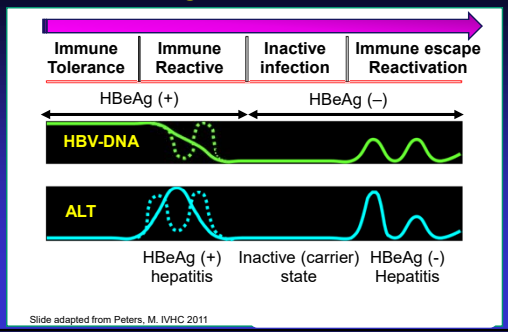
Goal of Treatment

Prevent liver disease

Cirrhosis, Liver Cancer, Stigma

HBV	HCV
HBV DNA suppression HBeAg loss/HBeAb conversion HBsAg loss/HBsAb conversion	Sustained Virologic Response (Loss HCV RNA 12 wks p-Rx)

Phases of Chronic HBV Infection



Slide adapted from Peters, M. IVHC 2011

HBV Treatment: Immune Tolerant

LAM (8 wks)	LAM+ IFN2b (44 wks)	F/U 1 yr

Study Group (n=23)
Vertical transmission
Age: 2.9-16.8 yrs
ALT (<50 IU/ml)
HBV DNA (>100 pg/mL)
Minimal histology

Results	
Completed trial	22 (96%)
HBV DNA loss	18 (78%)
Anti-HBeAb	5 (22%)
Anti-HBsAb	4 (17%)

D'Antiga L, et al. J Pediatrics 2006

HBV Treatment: Immune Tolerant

Sequential Therapy

India (n=62)
Age: 5.9 ± 3.2 yrs
LAM-IFN: F/U 21± 11.9 mo
ALT: <2 ULN
HBV DNA (>10^7 copies/mL)
Histology: normal
Rx: n=28, Obs: n=34

Results	Rx	Obs
HBeAg loss	11 (39%)	2 (6%)
HBsAg loss	6 (21%)	0 (0%)

China (n=69)
Age: 7 yrs
IFN-LAM: F/U 1 yr
ALT: <60 U/L
HBV DNA (>10^7 copies/mL)
Histology: normal
Rx: n=46, Obs: n=23

Results	Rx	Obs
HBeAg loss	15 (33%)	1 (4%)
HBsAg loss	10 (22%)	0 (0%)

Poddar et al. 2013; Zhu et al 2018

HBV Treatment: Immune Tolerant

Sequential Therapy

US (n=60)
Age: 10.9 (3.4-17.9) yrs
Asians: 90%
ETV-PEGIFN: F/U
ALT: <40 U/ml
HBV DNA: 170 x1(

Reasons for discordance
- Population
- Inclusion ALT
- Medications used
- Regimens
- Trial design

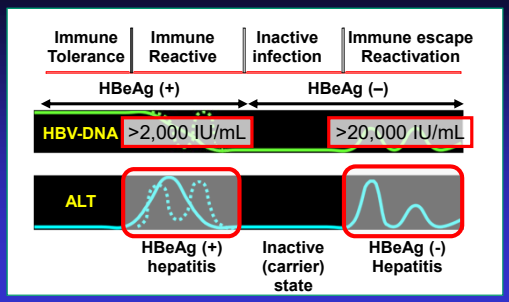
India (n=69)
Age: 7 yrs
13, Obs: n=17
M/TNF-IFN: F/U 1 yr
.5 ULN
NA (>10^7 copies/mL)

Results	
HBeAg loss	2 (3%)
HBsAg loss	0 (0%)

Results	Rx	Obs
HBeAg loss	0 (0%)	2 (12%)
HBsAg loss	0 (0%)	0 (0%)

Rosenthal et al. 2018;Lal et al 2018

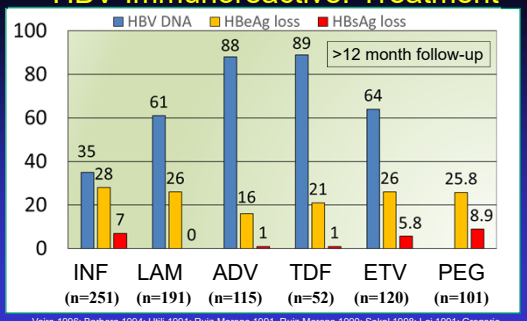
HBV Immunoreactive



Slide adapted from Peters, M. IVHC 2011

AASLD, Hepatology 2018; ESPGHAN, J Hepatol 2017

HBV Immunoreactive: Treatment



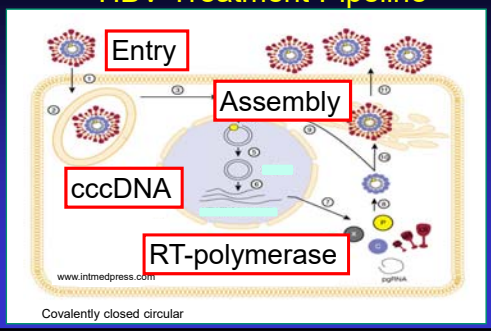
Vajro 1996; Barbera 1994; Utili 1991; Ruiz-Moreno 1991, Ruiz-Moreno 1990; Sokal 1998; Lai 1991; Gregorio 1996; Murray K, 2012; Jonas 2002; Jonas 2008; Jonas 2015;Jonas 2016; Wirth, 2018

Interferon or Nucleos(t)ide Analogues?

Interferon		Nucleos(t)ide Analogues	
Advantages	Disadvantages	Advantages	Disadvantages
▪ Finite course Rx ▪ No resistance ▪ Genotype A	▪ SQ ▪ Frequent AEs ▪ Contraindicated -cirrhosis -pregnancy -immunosupp	▪ PO QD ▪ Rare AEs ▪ Safe -cirrhosis -pregnancy - imunosupp	▪ Long-term or indefinite Rx ▪ Drug resistance

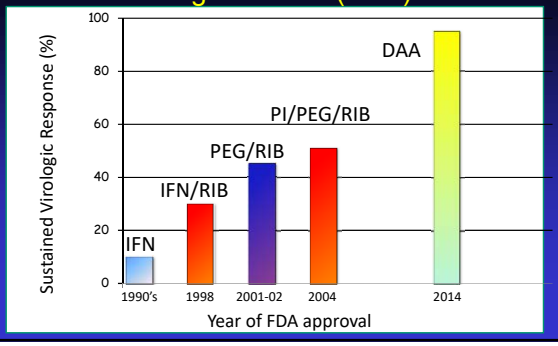
Lok AS. Hepatology. 2010; Buster EH, et al. Gastroenterology. 2008; Lange CM, et al. Hepatology. 2009.

HBV Treatment Pipeline



Hepatitis C

Direct Acting Antivirals (DAA): Adults



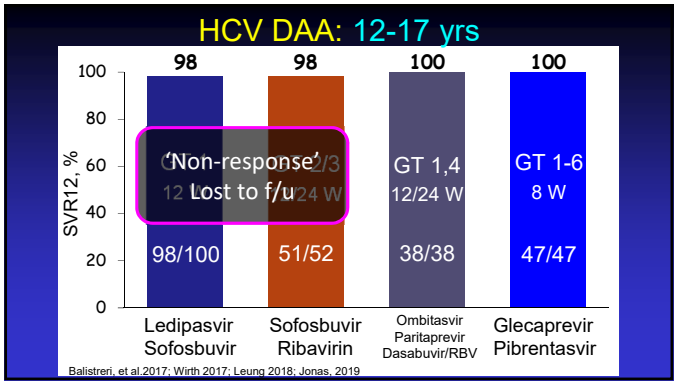
HCV Pediatric DAA Trials

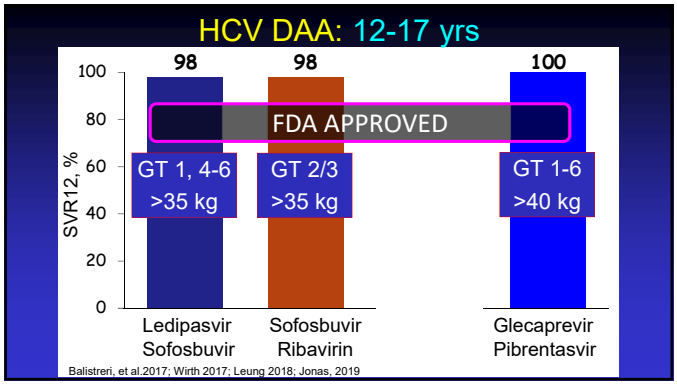
8-24 weeks	SVR 12	F/U 5 yrs

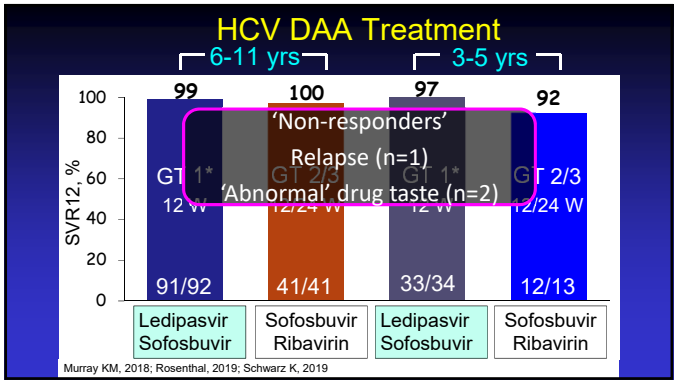
- A
- H
- C
- Al
- IF

DAA
- NS3: -previr
- NS5A: -asvir
- NS5B: -buvir

e


HCV DAA: 12-17 yrs
SVR12, %
100
80
60
40
20
0
98
98
100
100
'Non-response'
Lost to f/u
GT 1,4
12/24 W
GT 1-6
8 W
98/100
51/52
38/38
47/47
Ledipasvir Sofosbuvir
Sofosbuvir Ribavirin
Ombitasvir Paritaprevir Dasabuvir/RBV
Glecaprevir Pibrentasvir
Balistreri, et al.2017; Wirth 2017; Leung 2018; Jonas, 2019


HCV DAA: 12-17 yrs
SVR12, %
100
80
60
40
20
0
98
98
100
FDA APPROVED
GT 1, 4-6
>35 kg
GT 2/3
>35 kg
GT 1-6
>40 kg
Ledipasvir Sofosbuvir
Sofosbuvir Ribavirin
Glecaprevir Pibrentasvir
Balistreri, et al.2017; Wirth 2017; Leung 2018; Jonas, 2019


HCV DAA Treatment
6-11 yrs
3-5 yrs
SVR12, %
100
80
60
40
20
0
99
100
97
92
'Non-responders'
Relapse (n=1)
'Abnormal' drug taste (n=2)
GT 1*
12 W
GT 2/3
12/24 W
GT 1*
12 W
GT 2/3
12/24 W
91/92
41/41
33/34
12/13
Ledipasvir Sofosbuvir
Sofosbuvir Ribavirin
Ledipasvir Sofosbuvir
Sofosbuvir Ribavirin
Murray KM, 2018; Rosenthal, 2019; Schwarz K, 2019

HCV DAA Treatment: Safety

Adverse Effects
Headache
Fatigue
Nausea

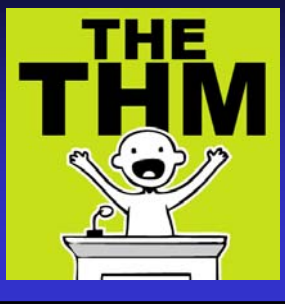
- NO Serious AE
- NO Premature DC

AdventHealth for Children

HCV Treatment: Pediatric Pipeline

DAA	Type	Age	Status
Ledipasvir-Sofosbuvir	1, 4-6	3-11 yrs	Published
Sofosbuvir-Ribavirin	2-3	3-11 yrs	Published
Glecaprevir/Pibrentasvir	1-6	3-11 yrs	Enrolled
Sofosbuvir/Velpatasvir	1-6	3-17 yrs	Enrolled
Elbasvir/Grazoprevir	1, 4	3-17 yrs	Enrolled

What Would Hamlet Do: To Rx or Not to Rx?



What Would Hamlet Do: To Rx or Not to Rx?

HBV

Immunotolerant
Normal ALT
High HBV DNA

Immunoreactive
Elevated ALT
HBV DNA

www.clinicaloptions.com/HepBConsult

Monitor
ALT, HBeAg, HBV DNA

Treat
Exclude other causes
Entecavir, Tenofovir
Pegylated IFN

What Would Hamlet Do: To Rx or Not to Rx?

HCV

>12 yrs
Ledipasvir-SOF (1, 4-6)
Ledipasvir-RBV (2,3)
Glecaprevir-PIB (GT 1-6)

3-12 yrs
Peg-IFN-RBV
DEFER…

<3 yrs
Monitor

AdventHealth for Children

What Would Hamlet Do: To Rx or Not to Rx?

Regino P. Gonzalez-Peralta, MD

Pediatric GI, Hepatology and Liver Transplant

AdventHealth for Children

ARE THERE ANY MEDICAL THERAPIES FOR NASH?

Single Topic Symposium, NASPGHAN 2019

Marialena Mouzaki, MD MSc
Cincinnati Children's Hospital Medical Center

Disclosures

- In the past 12 months, I have had no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.

Learning Objectives

- Present the gaps in the therapeutic armamentarium for pediatric NASH
- Evaluate the preliminary data on the efficacy of novel medications currently being investigated for the treatment of NASH

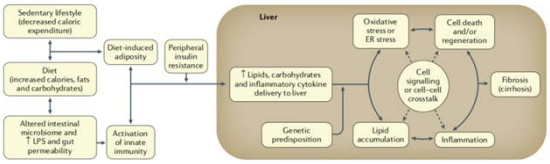
NAFLD: "a growing problem"

Today:
NO DRUG has been specifically approved for the treatment of NAFLD

2025 estimates:
- Drug market worth: $20-35 billion
- >190 products (~150 companies) in the pipeline

Roberts E. J Hepatology 2007
Anderson et al. PLoS One 2015;
Thiagarajan et al. J Clin Experiment Hepatol 2019

Pathogenesis and treatment targets



Sanyal A. Nat Rev Gastroenterol Hep 2019

Recap of NAFLD histology scoring

NAFLD Activity Score (NAS; **0-8**)

- Steatosis: **0-3**
- Lobular inflammation: **0-3**
- Ballooning: **0-2**

Fibrosis stage

- Stage 0: absent
- Stage 1-3: mild-severe
- Stage 4: cirrhosis

Kleiner et al. Hepatol 2005

Medical therapies investigated to date

Successful

- Weight loss
  - Diet and exercise
  - Exact amount is not clear
- Vitamin E
  - 800 IU daily
  - NASH resolution in 58% on vitE vs. 28% on placebo

Not successful

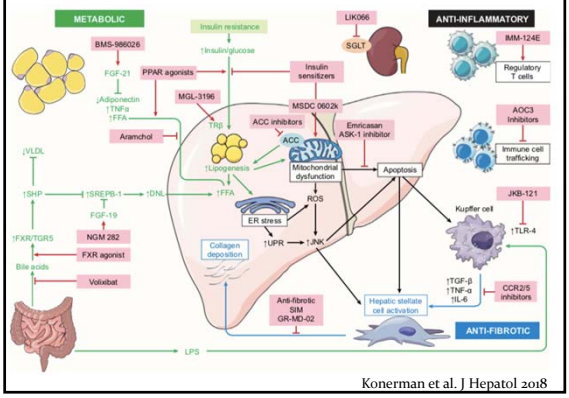
- Metformin
  - 1000 mg daily
- Cysteamine bitartrate
  - 300-450 mg BID

Vos et al. J Pediatr Gastroenterol Nutr 2017;
Lavine et al. JAMA 2011;
Schwimmer et al. Gastroenterol 2016

NASPGHAN guidelines

- Lifestyle changes
  - Limit sugar-sweetened beverages
  - Well-balanced diet
  - Moderate vigorous exercise
  - Limiting screen time <2h per day
- Medications
  - No medications or supplements are currently recommended
- Surgical options
  - Medical weight loss surgery may be considered in select cases

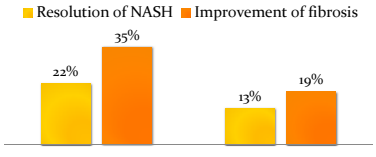
Vos et al. J Pediatr Gastroenterol Nutr 2017



Konerman et al. J Hepatol 2018

Obeticholic acid leads to improved histology

- FXR agonist
  - Improves insulin sensitivity
  - Decreases hepatic steatosis and inflammation
- FLINT trial: RCT 25 mg OCA vs. placebo x72 weeks
  - Primary outcome: ↓NAS by 2 points without worsening of fibrosis

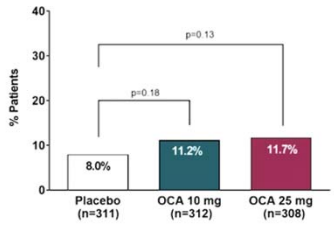


Neuschwander-Tetri et al. Lancet 2014

REGENERATE – Obeticholic acid, phase III

NASH Resolution with No Worsening of Fibrosis

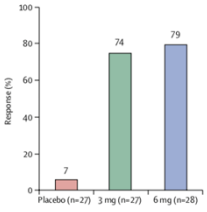
Additional Primary Endpoint: ITT Population, N=931



Younossi et al. Int Liv Congress Austria 2019

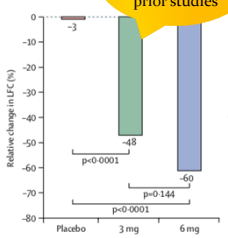
NGM282 ameliorates fat fraction in patients with NASH

- Phase IIa RCT, 12 weeks
- Humanized FGF19 analogue



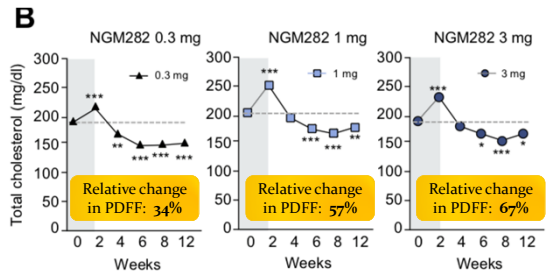
Primary outcome:
≥5% reduction in PDFF

≥30% ↓ in PDFF associated with ≥2 NAS ↓in prior studies

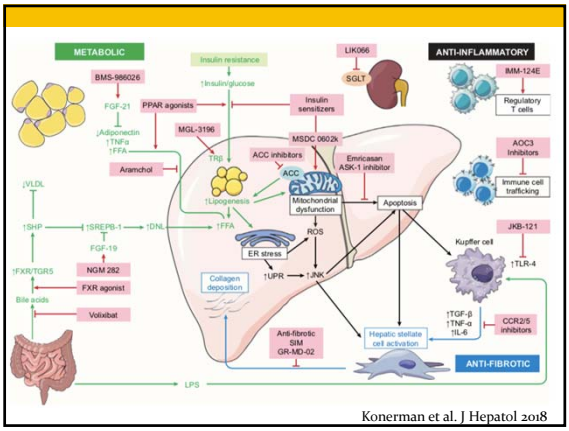


Harrison et al. Lancet 2018;
Patel et al. Therap Adv Gastroenterol 2015

NGM282 also associated with LDL-C increase in patients with NASH



Rinella et al. J Hepatol 2019



Konerman et al. J Hepatol 2018

Elafibranor (dual PPAR-a/δ agonist)

PPARα	• Fatty acid oxidation • Fatty acid transport (↓TG, ↑HDL) • Anti-inflammatory effects
PPARδ	• Fatty acid oxidation • Fatty acid transport (↑HDL) • Improve glucose homeostasis • Anti-inflammatory activities

Ratziu et al. Gastroenterol 2016;
Konerman et al. J Hepatol 2018

Elafibranor

Currently in Phase III trial "RESOLVE-IT"

- Phase II, multicenter RCT, comparing 80 mg vs. 120 mg. vs. placebo x52 weeks
- Primary outcome
  - Protocol – reversal of NASH without fibrosis "worsening"
    - Score=0 in at least one of the NAS components
    - Fibrosis worsening = progression to F3-4 (if <F3 a… progression to cirrhosis if F3 at basline
  - Post hoc – resolution of NASH without any ir…
    - Resolution of ballooning with or without mild (0-1)… on

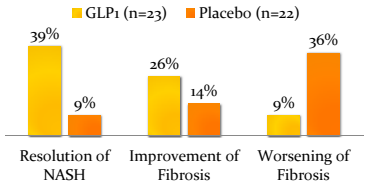
No difference in FIBROSIS compared to placebo

Results: 120 mg reached "post hoc" primary outcome:
- Total cohort (n=274; n=89 on 120 mg): OR=2.3 (p=0.45)
- NAS≥4 (n=234; n=75 on 120 mg): OR=3.5 (p=0.13)
- NAS≥4 and F2-3 (n=118; n=38 on 120 mg): OR=18.5 (p<0.01)

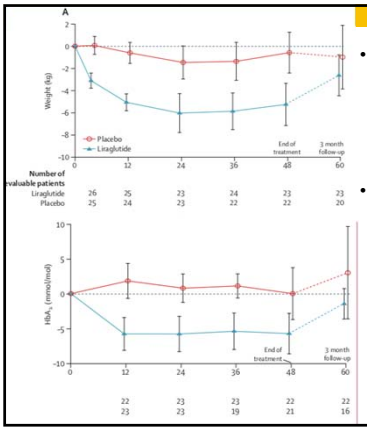
Ratziu et al. Gastroenterol 2016

GLP-1 agonists lead to weight loss and improved histology

- Phase 2, double blind RCT
- SQ liraglutide (1.8 mg daily) x48 weeks
- Primary outcome: resolution of definite NASH

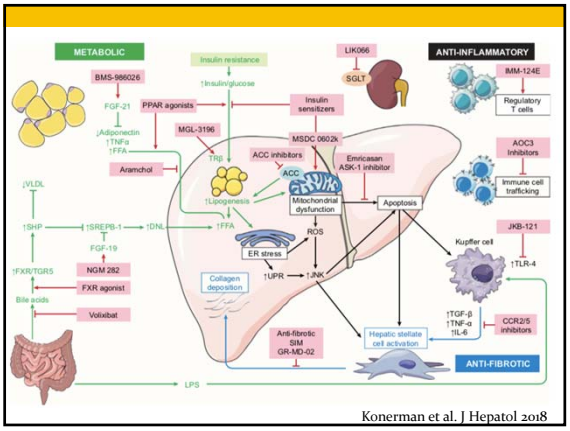


Armstrong et al. Lancet 2016



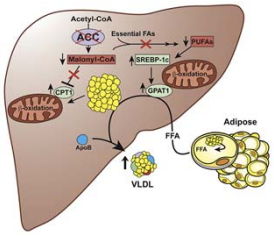
- GLP-1 effects mediated in part through weight and insulin sensitivity improvements
- Other GLP-1 agonists are currently being investigated

Armstrong et al. Lancet 2016



Konerman et al. J Hepatol 2018

Acetyl-coA carboxylase inhibitors

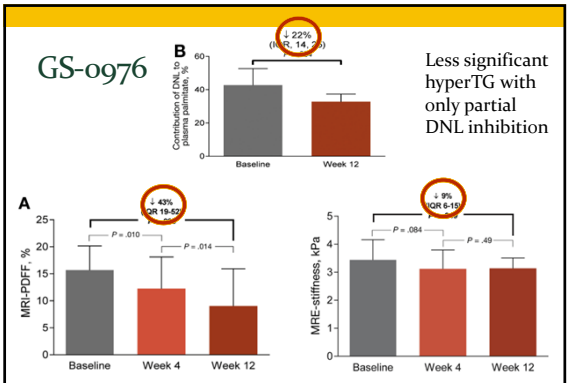


- GS-0976, allosteric inhibitor of ACC1,2
- Open label, 20mg once daily, 12 weeks
- Patients with NAFLD
  - MRI-PDFF>10%
  - MRE≥2.88 kPa
- N=10

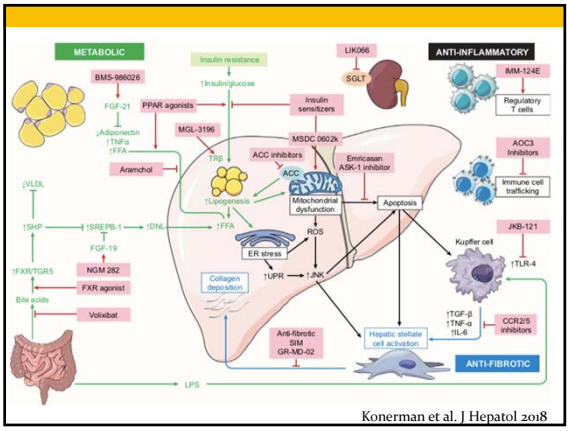
Kim et al. Cell Metab 2017;
Lawitz et al. Clin Gastroenterol Hepatol 2018

GS-0976

Less significant hyperTG with only partial DNL inhibition

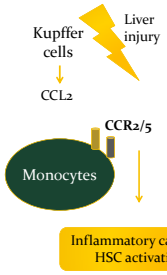


Lawitz et al. Clin Gastroenterol Hepatol 2018



Konerman et al. J Hepatol 2018

Cenicriviroc (CVC; CCR2/5 antagonist)



- Phase IIb RCT, n=282 with NASH
  - NAS≥4, F1-3 AND T2DM/MS
- CVC 150 mg daily vs. placebo x2y
- Primary outcome: ↓NAS by 2 points

- Interim analysis at 1 year:
  - NAS improvement not superior to placebo (16 vs. 19%, p=0.49)
  - **Improvement in fibrosis by ≥1 stage without NASH worsening in 20% on CVC vs. 10% on placebo, p=0.02**

Antifibrotic effect currently investigated in phase III trial

Friedman et al. Hepatol 2017

Summary

- A variety of novel medications with different mechanisms of action are being investigated in phase II and III trials
- Challenging to compare NASH trials
  - Different study design, primary outcome
  - Different patient population
- Steatohepatitis and fibrosis response are not necessarily concurrent

Future Directions

- Address the methodological challenges:

- Population
  - Take into account the phenotypic variability of NAFLD
  - Thoughtful consideration of who actually needs treatment
- Outcome
  - Study the impact of new agents on NASH and fibrosis independently
  - Optimize histology surrogates to be used as outcomes
  - Study combinations of agents

Take Home Messages

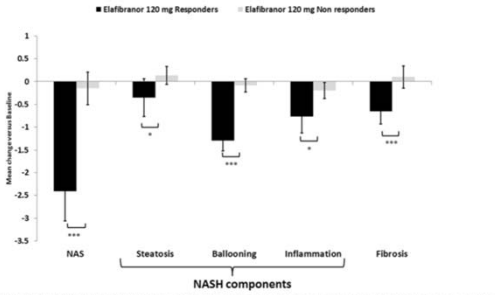
1. No medication is currently approved for the treatment of NAFLD
2. There is a plethora of new agents currently being investigated for the treatment of NAFLD/NASH
3. Careful selection of the patients who need treatment
4. Effective long-term treatment approaches will likely include a combination of agents

Thank you

Other meds trialed

- Recombinant, pegylated FGF21 analogue BMS-986026

Elafibranor - additional



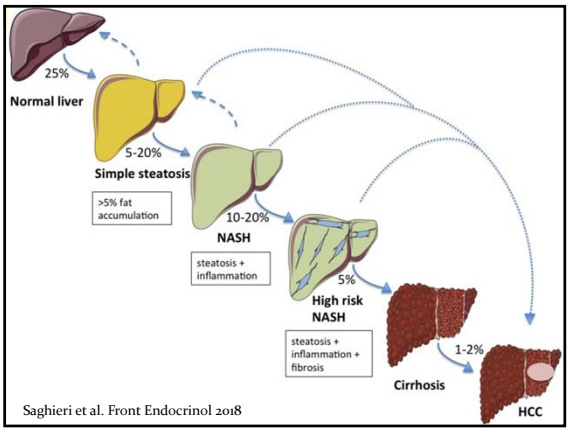
Supplementary Figure 1. Overall improvement in liver histology in patients who achieved the primary outcome according to the modified definition of response in the elafibranor 120-mg arm. Results are expressed as mean values of changes from baseline during treatment in responders (n = 17) and nonresponders (n = 61) to elafibranor 120 mg. Error bars represent 95% CIs. *$P < .05$; **$P < .01$; ***$P < .001$.

Ratziu et al. Gastroenterol 2016

Obeticholic acid also causes dyslipidemia

	Change from baseline to 72 weeks (mean [SD])		Mean changes from baseline* (obeticholic acid vs placebo) (95% CI)	p value*
	Obeticholic acid (n=126)	Placebo (n=131)		
Liver enzymes				
Alanine aminotransferase (U/L)	−38 (47)	−18 (44)	−20 (−28 to −11)	<0·0001
Asparate aminotransferase (U/L)	−27 (37)	−10 (31)	−12 (−18 to −6)	0·0001
Alkaline phosphatase (U/L)	12 (26)	−6 (20)	18 (13 to 24)	<0·0001
γ-glutamyl transpeptidase (U/L)	−37 (70)	−6 (48)	−24 (−35 to −14)	<0·0001
Total bilirubin (μmol/L)	−1·0 (4·1)	0·6 (3·7)	−1·5 (−2·4 to −0·5)	0·002
Lipids				
Total cholesterol (mmol/L)	0·16 (1·07)	−0·19 (0·96)	0·38 (0·16 to 0·60)	0·0009
HDL cholesterol (mmol/L)	−0·02 (0·20)	0·03 (0·19)	−0·06 (−0·10 to −0·01)	0·01
LDL cholesterol (mmol/L)	0·22 (0·90)	−0·22 (0·80)	0·45 (0·26 to 0·65)	<0·0001
Triglycerides (mmol/L)	−0·22 (1·27)	−0·08 (1·74)	−0·02 (−0·35 to 0·30)	0·88

Neuschwander-Tetri et al. Lancet 2014



Saghieri et al. Front Endocrinol 2018

When there is good function but the flow is all wrong; approach to non-cirrhotic portal hypertension

Evelyn Hsu, MD
Seattle Children's Hospital

Learning Objectives

- Know the key aspects of diagnostic evaluation of children with portal hypertension
- Understand the terminology and management of children with non-cirrhotic portal hypertension

Outline

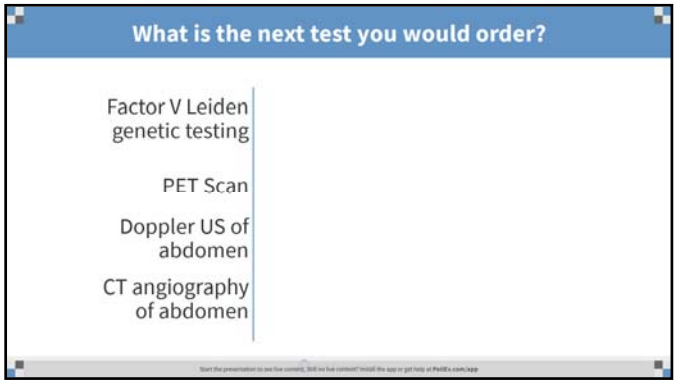
Approach to portal hypertension in a child
Definitions
Epidemiology
Natural History
Management
Future Directions
Extrahepatic portal venous obstruction

Approach to portal hypertension in a child

Case
CC: 8 yo F referred for splenomegaly
HPI: PHC, noted by PMD at routine WCC to have a palpable spleen
No symptoms, no medications
Screening labs → WBC 2.0, Platelets 60K
Bone Marrow Biopsy: trilineage normopoiesis
PMHx: no previous surgeries or hospitalizations
Family history: No family history of thrombosis
Exam: spleen palpable 5 cm from the left costal margin

Approach to portal hypertension in a child

Case (continued)



Imaging modalities

- Doppler US
- CT angiography

Biopsy

- Liver biopsy performed, under IR
- Hepatic Wedge Pressure Gradient ~5 mm Hg
- Results show normal liver histology

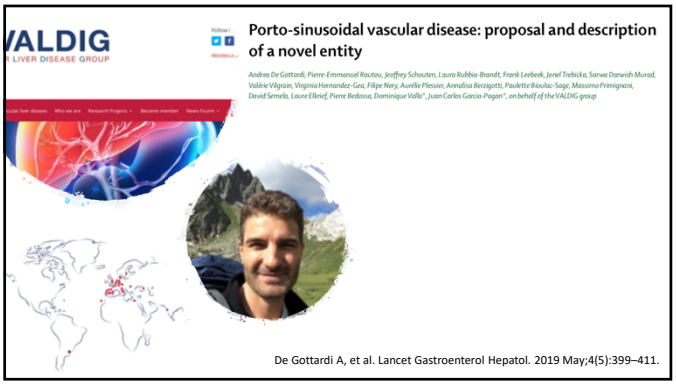
Now what? What do we call this?

- 2011 Recommendations:
- Proposal that Idiopathic non-cirrhotic portal hypertension be viewed as a distinct single entity with various pathological aspects
- **Idiopathic non-cirrhotic portal hypertension**
  - Portal hypertension
  - Absence of cirrhosis as documented histologically in an appropriate liver specimen
  - Absence of obstruction of the extra hepatic portal vein or hepatic vein outflow obstruction
  - Absence of sarcoidosis, schistosomiasis, congenital hepatic fibrosis, or other causes of cirrhosis

Schouten JNL, et al. Hepatology. 2011 Sep 2;54(3):1071–81.

Problems with 2011 recommendations

- Liver lesions observed can be seen in the absence of portal hypertension
- Portal vein thrombosis is a frequent complication during disease course
- Requires exclusion of other causes of liver disease



De Gottardi A, et al. Lancet Gastroenterol Hepatol. 2019 May;4(5):399–411.

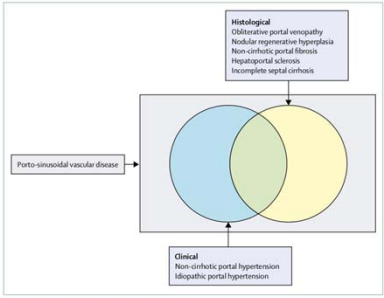


Figure 1: **Elements defining porto-sinusoidal vascular disease**
The term vascular porto-sinusoidal vascular disease encompasses various clinical (highlighted in the blue areas) and histological entities (highlighted in the yellow areas).

De Gottardi A, et al. Lancet Gastroenterol Hepatol. 2019 May;4(5):399–411.

New recommendations as defined by VALDIG

- Porto-sinusoidal vascular disease
- Histological alterations associated with porto-sinusoidal vascular disease with portal hypertension encompass several elementary features that can be observed in isolated or combined fashion

1) Obliterative portal venopathy
2) Nodular regenerative hyperplasia
3) Incomplete septa cirrhosis

- These criteria are specific enough to be regarded as diagnostic for porto-sinusoidal vascular disease, even in the absence of any clinical, imaging, or laboratory features of portal hypertension

Definition of PSVD

Liver biopsy ≥20 mm without cirrhosis	+	1 sign specific for portal hypertension or 1 histological lesion specific for PSVD
OR		
Liver biopsy ≥20 mm without cirrhosis	+	1 sign not specific for portal hypertension and 1 histological lesion not specific for PSVD

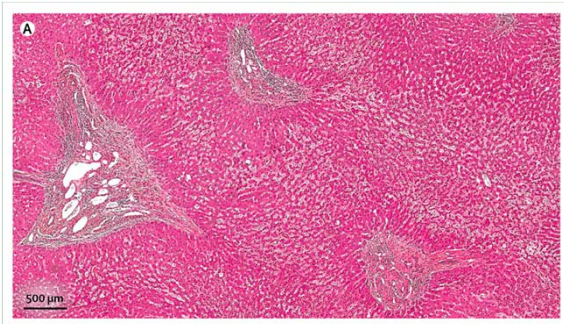
Criteria in the definition of PSVD

	Signs of portal hypertension	Signs of portal hypertension
Specific	Gastric oesophageal, or ectopic varices Portal hypertensive bleeding Porto-systemic collaterals at imaging	Obliterative portal venopathy (thickening of vessel wall, occlusion of the lumen, and vanishing of portal veins) Nodular regenerative hyperplasmia Incomplete septal fibrosis or cirrhosis
Not specific	Ascites Platelet count <150 000 per µL Spleen size ≥13 cm in the largest axis	Portal tract abnormalities (multiplication, dilation of arteries, periportal vascular channels, and aberrant vessels) Architectural disturbance: irregular distribution of the portal tracts and central veins Non-zonal sinusoidal dilation Mild perisinusoidal fibrosis

De Gottardi A, et al. Lancet Gastroenterol Hepatol. 2019 May;4(5):399–411.

Obliterative portal venopathy and hepatoportal sclerosis

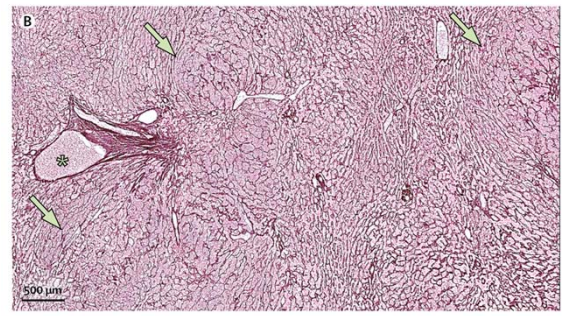
- Affects primarily small and medium branches of the portal vein, with the key feature being phlebosclerosis
- Increased amounts of portal connective tissues around the vessels with irregular wall thickening and eccentric narrowing of the vessel lumen, possibly up to complete occlusion and absence of the vein



De Gottardi A, et al. Lancet Gastroenterol Hepatol. 2019 May;4(5):399–411.

Nodular regenerative hyperplasia

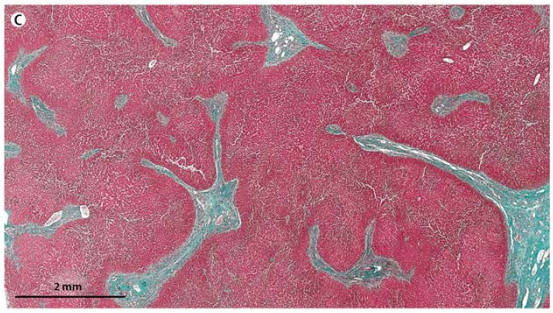
- Transformation of normal hepatic parenchyma into small nodules, mostly 1-3mm, macroscopically paler than normal parenchyma



De Gottardi A, et al. Lancet Gastroenterol Hepatol. 2019 May;4(5):399–411.

Incomplete septal fibrosis

- Presence of incomplete, thin, perforated, or blind-ended septa, and intermittently delimited rudimentary nodules



De Gottardi A, et al. Lancet Gastroenterol Hepatol. 2019 May;4(5):399–411.

Natural history

- Natural history is unknown
- Some patients may develop portal hypertension
- No recognized treatment exists, screening for signs of portal hypertension can be offered
- No data to recommend screening methodology or interval
- Cohort studies show good long-term outcomes following a strategy based upon current management guidelines for cirrhosis- beta blockers, endoscopic band ligation
- TIPS have been used for variceal bleeding/refractory ascites
- Splenectomy or partial splenic embolization can increase platelet count, but benefits have not been demonstrated to outweigh risks
- Liver transplant data is scarce- survival is favorable, there is no defined risk of recurrence but some cases have been reported

Epidemiology

- Terminologies vary worldwide
- Developing countries have higher occurrences that have improved over time, favoring an association with intra-abdominal infection
- 15-34% of cases in India, 3-7% in Europe, US, Canada

Pathogenesis

- Unknown- but relies on the development of vascular changes within the liver
- Associated conditions:
  - Immunity
  - Blood diseases/prothrombotic conditions
  - Infections
  - Congenital or familial defects
  - Drug exposure

Panel 4: Conditions associated with porto-sinusoidal vascular disease

Blood diseases
- Aplastic anaemia
- Myeloproliferative disorder
- Hodgkin's lymphoma
- Multiple myeloma

Prothrombotic conditions
- Protein C or S deficiency
- Factor II or V gene mutation
- Antiphospholipid syndrome
- ADAMTS13 deficiency

Immunological disorders
- Common variable immune deficiency (significant hypogammaglobulinaemia of unknown cause, failure to produce specific antibodies after immunisations, and susceptibility to bacterial infections)
- Autoimmune hepatitis
- Systemic lupus erythematosus
- Scleroderma
- Rheumatoid arthritis
- HIV
- Coeliac disease

Infectious
- Repeated gastrointestinal infections

Drug-induced
- Didanosine
- Azathioprine
- Tioguanine
- Oxaliplatin

Genetic
- Turner's syndrome
- Adams-Oliver syndrome
- *TERT* mutations
- Cystic fibrosis
- Familial cases

De Gottardi A, et al. Lancet Gastroenterol Hepatol. 2019 May;4(5):399–411.

Baveno VI recommendations

"Idiopathic portal hypertension, non-cirrhotic portal fibrosis, and non-cirrhotic portal hypertension indicate the same clinical entity"

Diagnosis requires exclusion of cirrhosis and other causes of non-cirrhotic portal hypertension

Liver biopsy is mandatory and HVPG is recommended for diagnosis

Immunologic diseases and pro-thrombotic disorders should be screened

Insufficient data for what therapy should be preferred for portal hypertension prophylaxis; management according to cirrhosis guidelines recommended

These patients should be screened for development of portal vein thrombosis- every 6 month doppler ultrasounds

Anticoagulation should be started in those who develop PVT

Extrahepatic portal vein obstruction

Evaluation, management, presentation

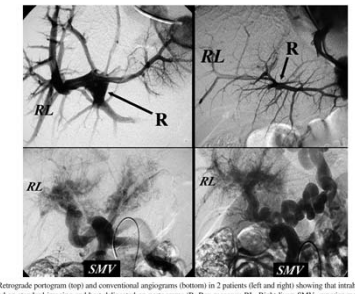


Figure 4 Retrograde portogram (top) and conventional angiograms (bottom) in 2 patients (left and right) showing that intrahepatic portal veins can be ignored on standard imaging and best delineated on portograms (R, Rex recessus; RL, Right liver; SMV, superior mesenteric vein).

Natural history

- Extrahepatic portal vein obstruction is defined by obstruction of extrahepatic portal vein with or without involvement of the intrahepatic portal branches
- Referred with varied manifestations:
  - GI hemorrhage from variceal bleeding
  - Splenomegaly, hypersplenism, less commonly with ascites
- Cavernous transformation: effort to bypass the thrombus and replace physiological portal venous flow or establish a spontaneous portosystemic shut

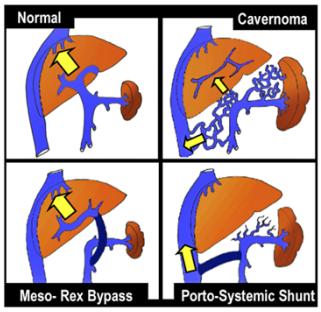
Imaging recommendations

- Doppler US
- CT angiography
- Established protocol for management (Alberti, et al JPBJ 2013 57(5) 619-626)

Conservative management

- Medical therapy
  - Beta-blockers
  - anticoagulation
- Endoscopic therapy
  - Sclerotherapy
  - Endoscopic variceal band ligation

MesoRex Bypass surgery



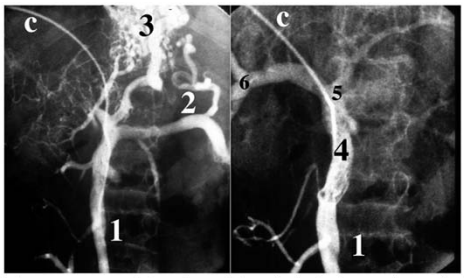
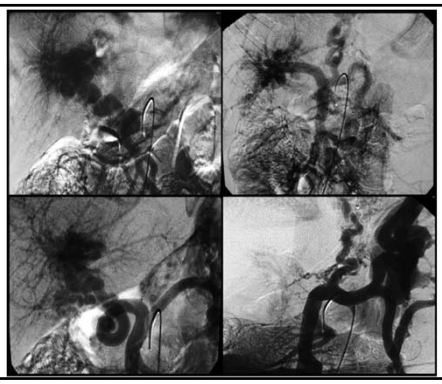


Figure 6 Meso-Rex bypass: percutaneous angioplasty of a stenotic bypass showing that the mesenteric venous flow is diverted into the splenic and gastric routes and feeding the esophageal varices and retroperitoneal collaterals. After plasty of the bypass, the flow is rerouted into the liver. (1, superior mesenteric vein; 2, splenic vein; 3, varices; 4, bypass; 5, left portal vein; 6, right portal vein; c, transhepatic catheter).



TIPS

- Indications for TIPS when rex recessus is obliterated

Reasons for intervention

Table 1. Indications for surgical intervention in EHPVO

Absolute indications
Medically/endoscopically refractory variceal hemorrhage
Severe hypersplenism
Platelet count <10 000
Recurrent complications including non-variceal hemorrhage or infections
Symptomatic and medically refractory porto-systemic encephalopathy
Hepato-pulmonary syndrome*
Porto-pulmonary hypertension*
Relative indications
Symptomatic splenomegaly*
Unacceptable activity restrictions because of splenomegaly*
Large varices and poor access to health care
Neuro-cognitive testing suggestive of porto-systemic encephalopathy*
Portal biliopathy*
Unexplained failure to thrive or delay in sexual development*

*Not acceptable as an indication for DSRS or other non-physiologic surgical approaches to portal hypertension.

What do I do now….
The management of portal hypertensive complications: varices, ascites, and encephalopathy

René Romero, M.D.
Professor of Pediatrics
Clinical Director, Pediatric Hepatology
Medical Director, Pediatric Liver Transplant Program
Children's Healthcare of Atlanta
Emory University School of Medicine

Disclosures

- In the past 12 months, I have had no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.
- I do not intend to discuss an unapproved or investigative use of a commercial product or device in my presentation.

2

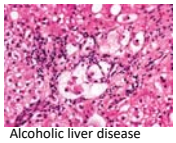
Objectives

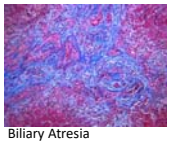
- Understand the appropriate medical management (pharmacologic and endoscopic) of acute variceal hemorrhage.
- Understand dosing and monitoring of diuretics in the management of ascites and the appropriate use of paracentesis.
- Approaches to the recognition and management of encephalopathy in pediatric chronic liver disease.

3

Portal Hypertension in Children

- **Management of complications of portal hypertension in children is challenging**
  - Lack of rigorous clinical studies that inform practice
  - Nature of disease leading to portal hypertension dissimilar to adults
  - Rarity of the condition
  - Limitations of equipment and techniques to study the condition in patient populations at risk
  - Consequences of complications may be different than adults
- **The many controversies surrounding these subjects will not be settled in this presentation**

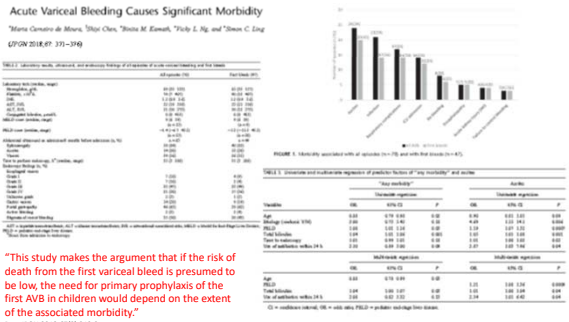

Alcoholic liver disease


Biliary Atresia

Ling et al. JPGN. 2011; 52: 254-261
Shneider et al. Hepatology. 2016; 63 (4): 1368-1380.
Grammatikopoulos et al. Arch Dis Child. 2018; 103: 186-191.
http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/hepatology/alcoholic-liver-disease/
https://childrennetwork.org/For-Physicians/Digital-Liver-Histopathology-Library

4

What do I do…. Why is it important to know which child is at risk for bleeding from varices?

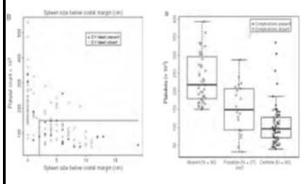

Acute Variceal Bleeding Causes Significant Morbidity

"This study makes the argument that if the risk of death from the first variceal bleed is presumed to be low, the need for primary prophylaxis of the first AVB in children would depend on the extent of the associated morbidity."
Bass JPGN 2018;67(3):312-3

5

What do I do….
Which child is at risk for bleeding from varices?

- How do we identify children who are at risk of developing and bleeding from esophageal varices in childhood?

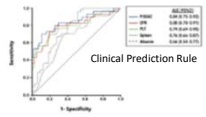


Shneider et al. JPGN 2012; 55: 567-573.
Sutton et al. JPGN 2018; 66:559-569.

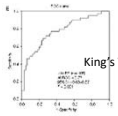
- Gold standard in adults would be HVWPG
  - Not practical
- Clinical findings frequently used
  - not sensitive or specific enough for to predict bleeders
- Imaging or Noninvasive measures of hepatic fibrosis
  - not sensitive or specific enough to predict bleeders
- Scoring systems based on combination of labs and clinical features
  - May be the future

6

What do I do….
Which child is at risk for bleeding from varices?



Clinical Prediction Rule



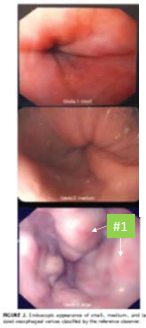
King's Variceal Prediction Score

	Authors	Biomarker	Patients	End point	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUROC	Limitations
Scores	Pash et al	Risk Score (34.2 − 7.1 × log(30) (platelet)+4.2 × log(30) (bilirubin))	63 treatment naive adults with liver fibrosis	HVPG ≥ 10 mmHg	88	86	69	95	0.91	Adults with liver fibrosis only included
	Pash et al	Risk Score (34.2 − 7.1 × log(30) (platelet)+4.2 × log(30) (bilirubin))	63 treatment naive adults with liver fibrosis	EV	82	86	65	92	0.82	Adults with liver fibrosis only included
	Gana et al	Clinical Prediction Rule (0.75 × platelet/ SAZ+5)+ (2.5 × albumin)	308 children with intra/extra hepatic PHT	EV	83	73	87	86	0.80	Only tested for any EV not CSV
	Gana et al	Clinical Prediction Rule (0.75 × platelet/SAZ+ 5)+ (2.5 × albumin)	51 children with intra/extra hepatic PHT	EV	94	81	83	94	0.91	Only tested for any EV not CSV
	Wiltens et al	King variceal prediction score (3 × albumin) − (2 × equivalent adult spleen size)	324 children with CLD	CSV	72	73	82	60	0.77	Only included children with chronic liver disease
	Intel et al	Variceal prediction score (albumin × platelet/1000)	195 infants with BA	CSV	78	73	44	92	0.81	Only included children with biliary atresia

Need prospective validation in larger studies and standard readings from radiologists for spleen size.
App development?

Gana et al. JPGN 2010; 50: 188-193.
Gana et al. Gastroenterology 2011; 141: 2009-2016.
Witters et al. JPGN 2017; 64: 518-523.
Sutton et al. JPGN 2018; 66:559-569.

What do I do…
Varices - recognizing the risk of what we see!



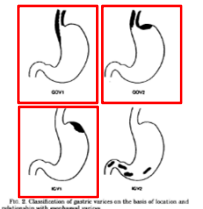
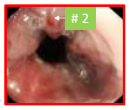


Fig. 2. Classification of gastric varices on the basis of location and relationship with esophageal varices.



<u>Red Signs</u>
1. Cherry red spots- red discrete flat spots on varices
2. Hematocystic spots- red discrete raised spots
3. Red wale markings- longitudinal red streaks on varices

<u>Greatest bleeding risk in children</u>
Large varices +/- red marks
Medium varices with red marks
GOV 1 and GOV 2

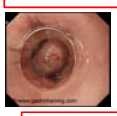
Sarin et al. Hepatology. 1992; 16: 1343-1349.
D'Antiga et al. JPGN 2015; 61: 176-181.
Duché et al. Gastroenterology. 2013;145(4):801-7
Duché et al. Gastroenterology. 2010;139(6):1952-60

What do I do…
Management of acute variceal hemorrhage

Variceal hemorrhage

ABC's
IV access
Labs- CBC, PT/PTT, cultures
Antibiotics- broad coverage
Anti-acid therapy PPI/ H2 blocker
Transfuse to maintain Hb 7-9 g/L
No recommendations re: INR and platelet count

Octreotide 1 mcg/kg over 15 minutes
Infuse 1-4 mcg/kg/hr (max 100 mcg/hr)
Continue 3-5 days with acute hemorrhage



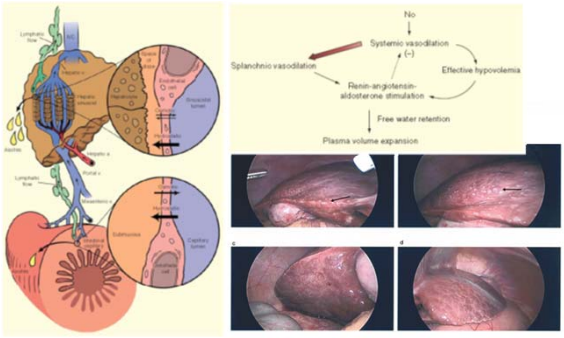
Endoscopic intervention when stable within 24 hours or as indicated by clinical condition.
Band Ligation preferred if size permits.
1- 5 bands no higher than 5 cm above GEJ
Sclerotherapy in small children

Repeat EGD sessions q 2-4 weeks until varices obliterated.
Once obliterated follow up EGD every 6-12 months with additional treatment as needed.

Alternatives for portal hypertensive bleeding using other modalities will be discussed in the following sessions.

Pai et al. Pediatr Clin N Am 2017; 64:543-561
Thomson M et al. JPGN. 2017;64:133-53
Poddar Paediatrics and international child health. 2019;39(1):18-22
Garcia-Tsao et al. Hepatology 2017; 65: 310-335
McKiernan et al. Exp Rev Gastro Hep. 2015; 9: 575-583

What do I do now….
Formation of ascites



Lane et al. Exp Rev Gastroenterol Hep 2015; 9: 1281-1292
Romero R. Clinical Liver Disease. 2013; 2: 210-214

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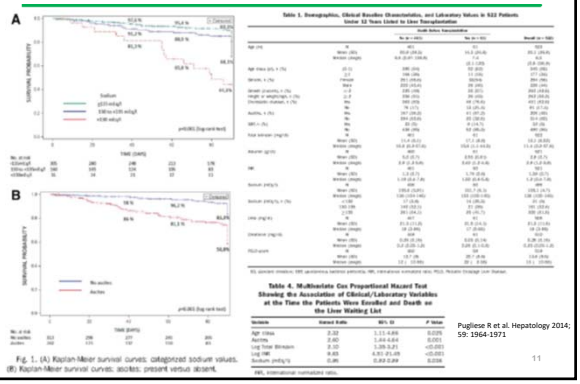
What do I do now….
Why is the formation of ascites important?



Pugliese R et al. Hepatology 2014; 59: 1964-1971

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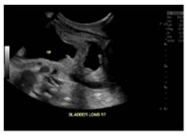
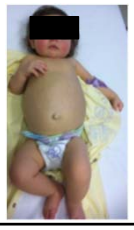
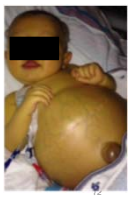
What do I do now…
Recognizing the ascites we see

- Definitions
  - Grade 1 (mild)
    - detectable by US
  - Grade 2 (moderate)
    - Moderate abdominal distension
  - Grade 3 (severe)
    - Tense ascites and/or respiratory distress
  - Resistant
    - Weight loss , 0.8kg and diuresis < intake
  - Refractory
    - No response after 7 d of adequate therapy
  - Intractable
    - Diuretics contraindicated due to adverse effects







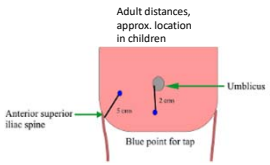
What do I do now…
Treatment of ascites in pediatric liver disease

- Physical Assessment
  - VS, weight, peripheral edema, neuro exam
- Standard testing
  - CBC, CMP, PT/PTT/INR, UA, Ucr, Una, Uosm
  - Abdominal US with Doppler
- Who should be hospitalized
  - Grade 2/3 ascites
  - Suspected infection
  - Electrolyte abnormalities
  - Bleeding
  - Progression of ascites on oral diuretic therapy
- Standard treatment
  - Depends on clinical picture and severity
    - Grade 1
      - Na restriction 1-2 meq/kg/day
    - Grade 2
      - Spironolactone 2-4 mg/kg/d (max 400mg adult)
      - Furosemide 1- 3 mg/kg (max 120 mg adult)
      - 25% albumin infusion?
    - Grade 3
      - Intravenous albumin and IV/oral diuretics especially with peripheral edema or Salb < 2.5-3.0 g/dL
      - Large volume paracentesis
  - Importance of optimizing nutritional status

Runyon BA. Hepatology. 2009;49(6):2087-107
Runyon BA. Hepatology. 2013;57(4):1651-3
Lane et al. Exp Rev Gastroenterol Hep 2015; 9: 1281-1292
Bes et al. Arch Argent Pediatr 2017; 115: 385-390
Bes et al. Arch Argent Pediatr 2017; 115: 505- 511

What do I do now…
The role of paracentesis in ascites management

- Paracentesis
  - Avoid epigastric artery, surgical scars and visible veins
  - US guidance
  - Z-technique
    - Fenestrated paracentesis needle
    - Intravenous catheter
  - No data on coagulation parameters that preclude paracentesis
- Fluid analysis
  - Cell count
  - Culture (10ml in BC bottles)
  - Fluid albumin with simultaneous Salb for SAAG
  - Amylase
  - Triglyceride



SAAG ratio of ≥1.1 g/dl	SAAG ratio of ≤1.1 g/dl
Portal hypertension	Malignancy-related ascites
Budd–Chiari syndrome	Tuberculosis-related ascites
Portal vein thrombosis	Bacterial peritonitis and serositis
Heart failure	Pancreatitis
	Nephrotic syndrome

Serum albumin minus ascites albumin= SAAG

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What do I do now…
Diagnosis of infection & paracentesis in ascites management

- Definitions of infected ascites
  - 250 polys/mm3 without alternative
    - Spontaneous bacterial peritonitis (positive culture)
    - Culture negative neutrocytic ascites
  - Treated the same
- Can patients with infected ascites be identified clinically?

Prospective cohort study of 66 patients with ascites
Undergoing diagnostic paracentesis
Ghobrail et al. Plos one. 2018:13(10):e0203808

Fever, elevated ANC and CRP was associated with infected ascites

- Srivastava et al. JPGN 2017; 64: 194-199
  - Retrospective study 262 Indian children
  - Combination of abdominal pain/tenderness, fever and/or loose stools differentiated infected from non infected ascites
  - A total of 28.6% children with liver disease-related ascites have spontaneous bacterial peritonitis/culture-negative neutrocytic ascites
  - commonly grew gram-negative bacteria
  - These children had a median model for end-stage liver disease/pediatric endstage liver disease [PELD/MELD] of 23)

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What do I do now…
The role of paracentesis in ascites management

- In children, how much fluid is safe to remove in LVP?
- Should 25% albumin be infused at the time of LVP?

Retrospective study of 7 patients

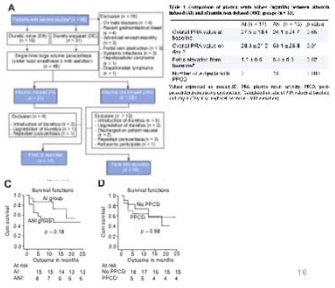
Kramer et al. JPGN. 2001; 33: 245-249

Mean milkg removed per LVP	118 ± 56
Mean duration of drainage (h) per LVP	2.9 ± 1.7
Mean volume removed (n=21) per LVP	3.120 ± 2.052
Percent infused with IV albumin after LVP	95%
Mean dose of albumin given (gm/kg) after LVP	0.6 ± 0.3
Percent treated for SBP after LVP	14%
Percent infused with IV albumin after LVP	95%
Mean dose of albumin given (gm/kg) after LVP	0.6 ± 0.3
PT normal (% of patient)	0%
PT prolonged 1–2 seconds (% of patients)	67%
PT prolonged >5 seconds (% of patients)	25%
Percent of patients infused with FFP within LVP	25%
Complications per LVP	
Hypotension	None
Decreased urine output	1 LVP
Hemorrhage	None
Ascitic leakage	None

PT, prothrombin time; FFP, fresh frozen plasma; LVP, large volume paracentesis; SBP, spontaneous bacterial peritonitis.

Prospective longitudinal observational study in 68 pts

Sarma et al. J Hepatol. 2015; 63: 1126-1132



18

What do I do now…
Does my patient have minimal or chronic encephalopathy?

- Challenges
  - Hard to define HE in pediatrics
  - Paucity of literature
  - Difficult to draw conclusions from Adult experience
- 3 types
  - Type A resulting from ALF
  - Type B resulting predominantly from portosystemic shunting
  - Type C resulting from cirrhosis
- Adult Definition
  - Hepatic encephalopathy is a brain dysfunction caused by liver insufficiency and/or portosystemic shunting
  - Manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma
    - Minimal - only psychometric tests oriented toward attention, working memory (WM), psychomotor speed, and visuospatial ability, as well as electrophysiological and other functional brain measures
    - Overt (5%-25% within 5 years after cirrhosis diagnosis)

Vilstrup et al. Hepatology. 2014;60(2):715-35

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What do I do now…
Does my patient have minimal or chronic encephalopathy?

West Haven / Wilkinson	Type	Description	Suggested Operative Criteria	Comment
Unimpaired		No encephalopathy at all, no history of HE	Tested and proved to be normal	
Minimal	Covert	Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change	Abnormal results of established psychometric or neuropsychological tests without clinical manifestations	No universal criteria for diagnosis. Local standards and expertise required
Grade I	Covert	• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm	Despite oriented in time and space (see below), the patient appears to have some sig nitive/behavioral delay with respect to his or her standard an clinical examination or to the caregivers	Clinical findings usually not reproducible
Grade II	Overt	• Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behavior • Dyspraxia • Asterixis	Disoriented for time (at least three of the following wrongly reported: month, day of the week, month, season, or year); the other mentioned symptoms	Clinical findings variable, but reproducible to some extent
Grade III	Overt	• Somnolence to semistupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behavior	Disoriented also for space (at least three of the following wrongly reported: country, state [or region], city, or place); the other mentioned symptoms	Clinical findings reproducible to some extent
Grade IV	Overt	Coma	Does not respond even to painful stimuli	Comatose state usually reproducible

All conditions are required to be related to liver insufficiency and/or PSS.

In all chronic liver disease patients of any age with a change in behavior or cognition, a precipitating cause needs to be evaluated

Episodic	Recurrent
Infections*	Electrolyte disorder
GI bleeding	Infections
Diuretic overdose	Unidentified
Electrolyte disorder	Constipation
Constipation	Diuretic overdose
Unidentified	GI bleeding

Vilstrup et al. Hepatology. 2014;60(2):715-35

18

What do I do now…

Does my patient have minimal or chronic encephalopathy?

- Can minimal hepatic encephalopathy be identified in children?
  - A variety of psychometric and neurophysiological tests have been utilized, but must be interpreted by experts

Stroop Test Validation to Screen for Minimal Hepatic Encephalopathy in Pediatric Extrahepatic Portal Venous Obstruction

red blue orange purple
orange blue green red
blue purple green red
orange blue red green
purple orange red blue
green red blue purple

- In the absence of functional shunts or other risk factors for neurological injury, minimal hepatic encephalopathy, diagnosed by Revised Amsterdamse Kinder Intelligentie Test, occurs in 18.9% of extrahepatic portal vein obstruction in Indian children in the 7 to 12 years age.
- Computerised Stroop test can screen for minimal hepatic encephalopathy in children and allows selective administration of neuropsychiatric testing in clinical care.

Suresh et al. JPGN. 2018;66(5):802-807

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What do I do now…

Does my patient have minimal or chronic encephalopathy?

- Can minimal hepatic encephalopathy be identified in children?

Minimal hepatic encephalopathy in children with chronic liver disease: Prevalence, pathogenesis and magnetic resonance-based diagnosis

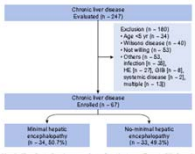

Fig. 2. Flowchart showing overview of patient enrolment. HE, hepatic encephalopathy; GIB, gastrointestinal bleeding.

The objectives of our study were: a) to determine the prevalence of MHE in children with CLD; b) to evaluate the correlation of MHE with changes on brain metabolites on ^{1}HMRS, DTI derived metrics, blood ammonia (BA) and inflammatory cytokines; and c) to determine the potential of ^{1}HMRS and DTI derived metrics for diagnosis of MHE as an objective tool compared to NPT.

Conclusions: In children with CLD, 50% have MHE. There is a significant positive correlation between markers of hyperammonemia, inflammation and brain edema and these correlate negatively with neuropsychological tests. MD on DTI is a reliable tool for diagnosing MHE.

Srivastava et al. J Hepatology. 2017;66(3):528-36

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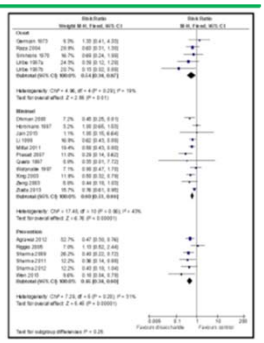
What do I do now…

Treatment for minimal or overt hepatic encephalopathy

- Extremely limited studies in children
  - Non-absorbable disaccharides
  - Rifaximin
  - Metronidazole
  - Probiotics
  - Correction of hypokalemia



Ayra et al. Postgraduate medical journal. 2010;86(1011):34-41
Vilstrup et al. Hepatology. 2014;60(2):715-35
Morgan M. Metab Brain Dis.2016; 31:1361–1364

21

What do I do now….
The management of portal hypertensive complications: varices, ascites, and encephalopathy

- Conclusions
  - The management of portal hypertensive complications in children is challenging due to its rarity and scientific evidence of best practices.
  - Secondary prophylaxis of variceal bleeding with endoscopic therapy is appropriate and should be initiated as soon as is clinically feasible.
  - The development of ascites can be managed with diuretics but is clearly an indicator of liver disease progression.
  - The detection and treatment of all forms of hepatic encephalopathy in children remains problematic and requires specialized testing in the earliest stages.
  - Pediatric Gastroenterologists should utilize frequent consultation with Pediatric Liver Centers for the management of patients with portal hypertensive complications

22

Pediatric Liver Transplant: Indications, Timing and Options

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Medical Director, Pediatric Liver Transplantation
Children's Hospital Colorado

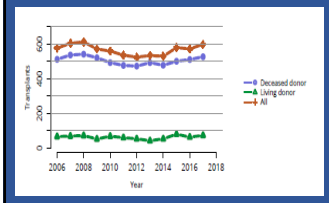
Disclosures

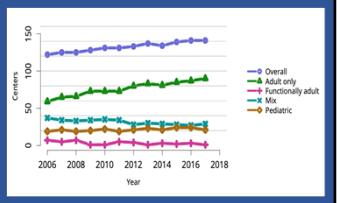
- None

Objectives

- Understand indications/contraindications to liver transplant
- Understand when to refer a patient for transplant evaluation
- Understand the transplant evaluation process
- Understand how to help your patient choose a transplant program
- Understand PELD/MELD scores and limitations

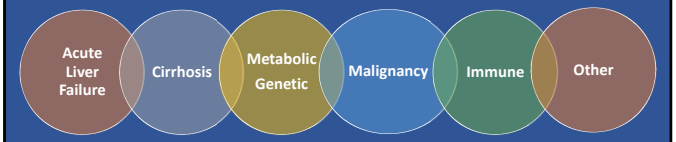
How Common is Pediatric Liver Transplant?





Kim et al, OPTN/SRTR Annual Report AJT 2019

Indications for Pediatric Liver Transplant



Squires RH, Hepatology 2014

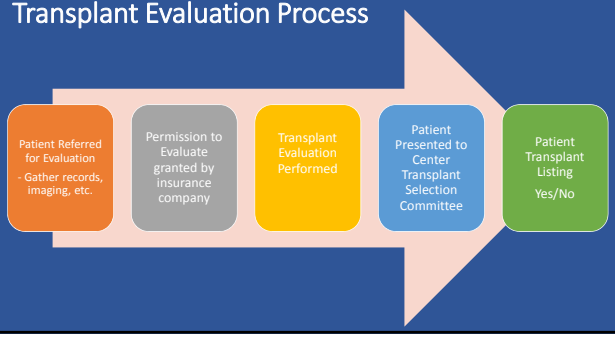
Relative Contraindications	Absolute Contraindications
HCC: venous invasion, rapid progression despite chemotherapy	Extra-hepatic malignancy (except isolated pulmonary metastases with hepatoblastoma)
Hemophagocytic Lymphohistiocytosis	Uncontrolled systemic infection
Non-adherence despite multi-disciplinary support	Severe porto-pulmonary hypertension unresponsive to medical therapy
Social issues not amenable to psychosocial help	Niemann Pick type C
Positive HIV infection	Life-threatening, untreatable, extrahepatic disease
Uncontrolled psychiatric disorder	Severe cardiac or pulmonary dysfunction
Active drug/alcohol use	Inability to comply with or commit to long-term ongoing follow up and medical management

Squires RH, Hepatology 2014

When to Refer for Liver Transplant Evaluation

- Timing: Emergent, Urgent or Anticipatory
  - Emergent
    - Acute Liver Failure
    - Acute decompensation of chronic liver disease
  - Urgent
    - Liver based metabolic crises refractory to medical management
    - Unresectable hepatoblastoma
    - Unresectable hepatocellular carcinoma
  - Anticipatory: chronic liver disease and deterioration of liver function
    - Poor weight gain/growth failure
    - Variceal hemorrhage
    - Intractable ascites
    - Recurrent cholangitis, spontaneous bacterial peritonitis
    - Severe pruritus
    - Encephalopathy
    - Uncorrectable coagulopathy

Transplant Evaluation Process



Purpose of the Transplant Evaluation

- Establish patient meets indications for potential transplant
- Confirm diagnosis, associated systemic manifestations of disease and management plan
  - Identify opportunities for maximizing current medical therapy
  - Assess immunization status, identify plan to complete all needed vaccines
- Confirm finances available
- Determine if non-transplant surgical options exist
- Assess live donor option feasibility
- Anticipate complications (and solutions) following transplant
- Establish trusting relationship between transplant team and patient/family
- Ensure patient/family commitment to long term transplant care

Transplant Evaluation

Medical/Surgical
- Transplant Surgeon
- Transplant Hepatologist
- Transplant Coordinator
- Transplant Anesthesia
- Transplant Infectious Disease

Psychosocial
- Transplant Social Worker
- Transplant Psychologist
- Child Life Specialist
- Physical/Occupational Therapy
- Pastoral Care

Patient
Family

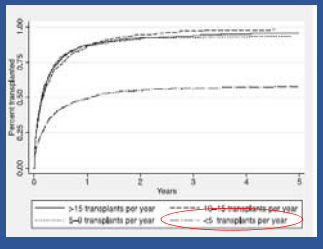
Other
- Nutritionist
- Financial Counseling
- Transplant Pharmacist
- Specialists: Cardiology, Neurology, Oncology, Metabolic, Nephrology, Radiology, ICU

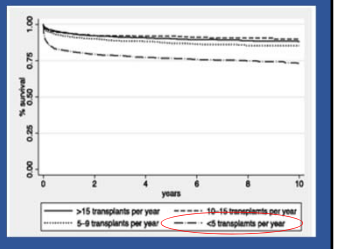
Testing
- Bloodwork
- Immunization titers
- Radiologic exams
- Echocardiogram
- Drug Testing
- Dental Exam

Choosing a Pediatric Liver Transplant Program

- Insurance company may dictate option(s)
- Transplant Team Experience
- Surgical options
  - Living donor (directed or non-directed)
  - ABO incompatible transplant
  - Split liver transplant
- Results
  - Survival on wait list
  - Wait times
  - Graft/Patient Survival
- Patient/Family/Referring provider friendly
- Research

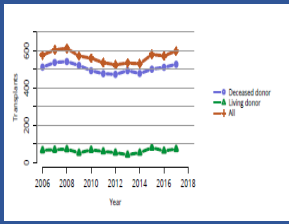
Transplant Team Experience

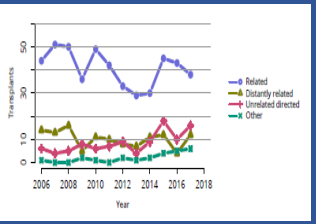




Rana et al. Pediatrics 2015

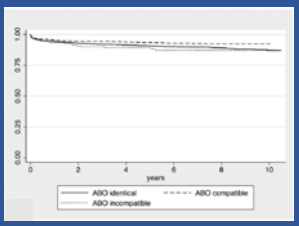
Surgical Options: Living Donor Transplant

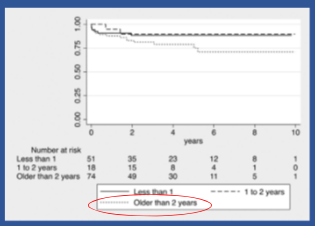




Kim et al, OPTN/SRTR Annual Report AJT 2019

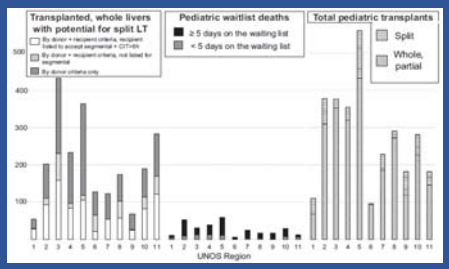
Surgical Options: ABO incompatible Liver TX





Rana J Am Coll Surg 2016

Surgical Options: Split Liver Transplant



E Perito, Transplantation 2019

Using SRTR Data to Guide Center Selection

Compare Each center to the National Rates. Worse Better

Survival On the Waitlist (Deaths Per 100 years of waiting)	NA	9.4	6.5	5.4	2.6
Getting A Deceased Donor Transplant Faster (Transplants Per 100 years of waiting)	42	70.3	96.8	150.7	223.6
1-Year liver Survival (% with functioning transplant at 1 year)	87	88	91	94	96

unos.org

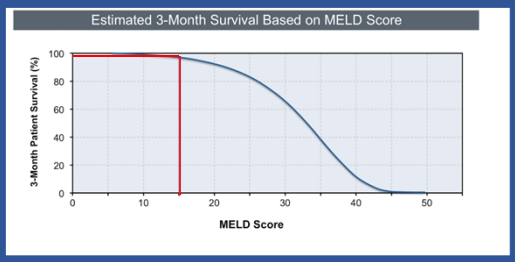
unos.org

MELD and PELD scores

- MELD (Model for End Stage Disease)
  - Developed as a predictor of 3 month mortality
  - Used for children ≥ 12
  - MELD = 3.78×ln[serum bilirubin (mg/dL)] + 11.2×ln[INR] + 9.57×ln[serum creatinine (mg/dL)] + 6.43
- PELD (Pediatric End-Stage Liver Disease)
  - Used for children < 12 years old
  - PELD = 4.80[Ln serum bilirubin (mg/dL)] + 18.57[Ln INR] - 6.87[Ln albumin (g/dL)] + 4.36(<1 year old) + 6.67(growth failure)
  - Growth failure if height or weight < -2 SD
  - If listed at < 12 months of age, added points for age are maintained until 24 months of age

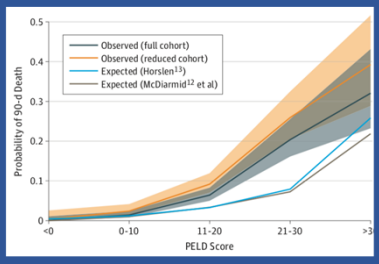
S McDiarmid, Transplantation 2002
unos.org

Estimated 3 Month Survival Based on MELD



Wiesner et al, Gastro 2003

PELD underestimates mortality



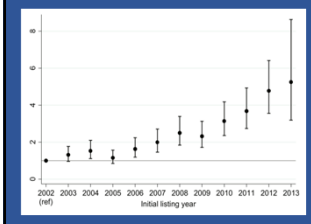
Chang et al JAMA Peds 2018

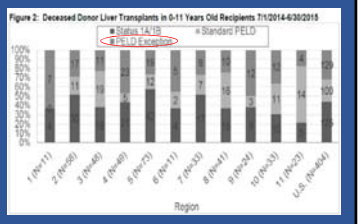
Candidate Listing: UNOS "List"

- Status 1A: Acute Liver Failure
- Status 1B: Chronic Liver Disease with Rapid Decompensation
  - Severe GI Bleed
  - Renal Failure
  - Respiratory Failure
  - Liver tumors
- Calculated MELD/PELD
- Exception MELD/PELD
  - National Liver Review Board
  - Growth failure, infections, complications of portal hypertension encephalopathy
  - Hepatopulmonary syndrome, pruritus metabolic bone disease, vascular complications

unos.org

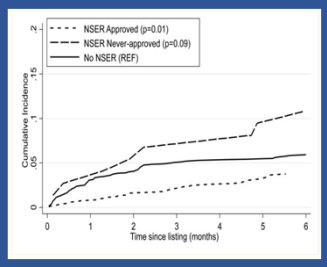
PELD Exceptions





UNOS 2019
Hsu et al AJT 2015

When PELD exceptions are not approved…

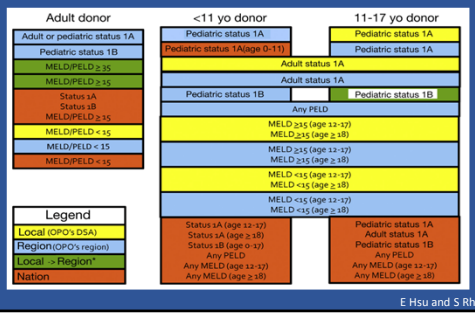


Braun et al AJT 2016

Liver Allocation: Distribution

unos.org

UNOS Liver Allocation Algorithm



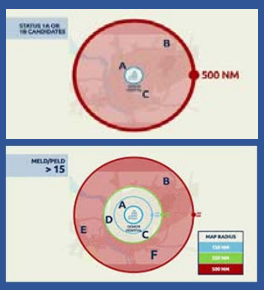
E Hsu and S Rhee, Gastro 2017

Upcoming Changes to Liver Allocation

December 2018:
OPTN/UNOS approved new liver distribution policy to reduce geographic disparities

Spring 2019:
New policy goes into effect
24 hours later: new policy put on hold due to pending lawsuit

September 2019:
Broad Communication to Transplant Programs that "new policy" upheld in courts, no date for implementation



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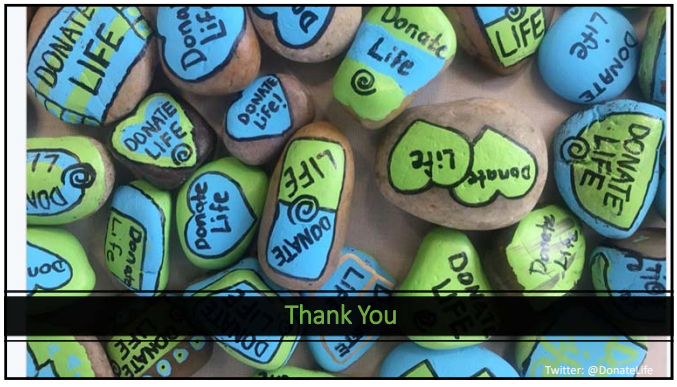

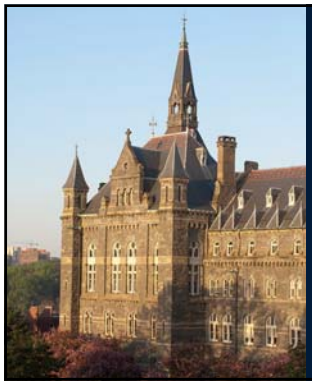

My liver transplant patient has elevated liver tests – *HELP!!!*

Udeme D. Ekong MD MPH FAASLD
Medstar Georgetown Transplant Institute
Washington, DC.

NASPGHAN Single Topic Symposium
October 16, 2019

GEORGETOWN UNIVERSITY

Disclosure slide

- In the past 12-months, I have had no relevant financial relationships with manufacturers of any commercial product, and/or provider of commercial services discussed in this CME activity.
- I do not intend to discuss an unapproved or investigative use of a commercial product or device in my presentation.

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Case 1.

- 10 -year old boy
- DDLT for Congenital Hepatic Fibrosis ~4-years previously
- Routine post transplant care labs
- TB/DB: 0.4/0.2
- ALT 72
- AST 66
- GGT 17
- Tacrolimus level 5
- Reported URI symptoms

- Repeat labs 2-weeks later
- TB/DB: 0.4/0.3
- ALT 168
- AST 144
- GGT 21
- Tacrolimus level 2
- CMV PCR – none detected
- EBV PCR – none detected
- DUS: no intrahepatic biliary ductal dilatation, normal hepatic vasculature.

3

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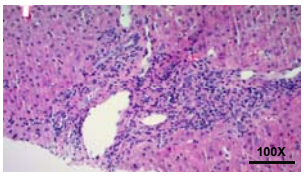
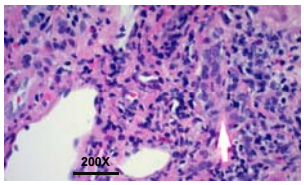
Diagnosis?





a) Normal liver biopsy
b) CMV hepatitis
c) Acute cellular rejection

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Definition of Acute cellular rejection

- "Inflammation of allograft elicited by antigenic disparity between donor and recipient primarily affecting interlobulary bile ducts and vascular endothelia, including portal vein and hepatic venules, and occasionally the hepatic artery and its branches."

International Working Party Terminology for hepatic allograft rejection. Hepatology 1995.

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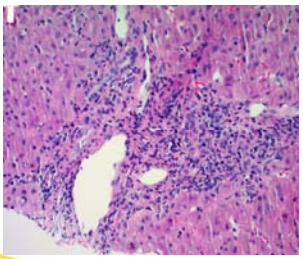
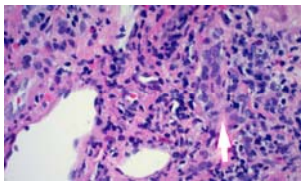
Acute cellular rejection (*T cell mediated rejection*)





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Acute cellular rejection

- Incidence of early acute cellular rejection after primary LT in children is ~50% - 60%.
- Early recognition is paramount as easily reversed with a response rate of 75%.
- Those who fail to respond or have recurrent episodes have a higher risk of progression to chronic rejection.

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Clinical symptoms

- Due to baseline immunosuppression (IS), *clinical symptoms are preceded by liver serological abnormalities*.
- *Clinical symptoms are uncommon* and are related to graft swelling (abdominal pain and hepatomegaly) due to inflammation, and cytokine release (fever, malaise).
- Due to the subtle clinical features or absence thereof, *diagnosis of acute rejection is made by liver biopsy*.

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Mechanisms of rejection

- Acute rejection is initiated by the large number of recipient T cells that recognize donor alloantigens (mostly those encoded by the major histocompatibility complex [MHC]).
- Donor alloantigens are processed by antigen presenting cells (APC).
- Donor MHC molecules are internalized by donor and recipient antigen presenting cells; following intracellular processing, MHC peptide fragments are presented to the recipient's T cells.

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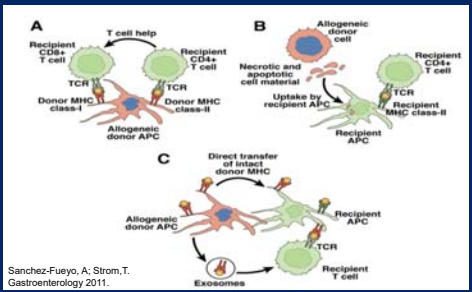
Pathways of alloantigen presentation



Sanchez-Fueyo, A; Strom,T. Gastroenterology 2011.

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Acute cellular rejection

Mechanisms of rejection (contd)

- $CD4^+$ and $CD8^+$ T cells participate in acute cellular rejection, although the rejection response is mediated primarily by $CD4^+$ T cells.

Anti-rejection therapy

- Corticosteroids – reverses 60% - 75% of all rejection episodes.
- Solumedrol 10 mg/kg daily X3-days, max 1 g daily.
- Adjust Tacrolimus 12-hour trough level to goal of 8 – 12.
- Restart prednisone at 0.3 mg/kg/day.

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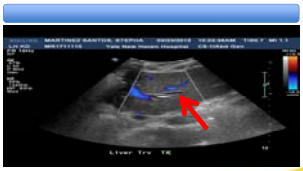
Case 2.

- 9-year old girl
- LDLT for Biliary Atresia ~9-years previously
- Routine clinic follow-up
- TB/DB 0.3/0.1
- AST 93 ALT 106 GGT 344
- Tacrolimus level 3
- EBV and CMV PCR – none detected

Dilated Intrahepatic Bile Ducts



Ultrasound with doppler

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What next?

- A) Ursodeoxycholic acid and watch
- B) Percutaneous Transhepatic Biliary Drainage (PTBD)
- C) Liver patients have *wayyyyy too* much drama!!!!

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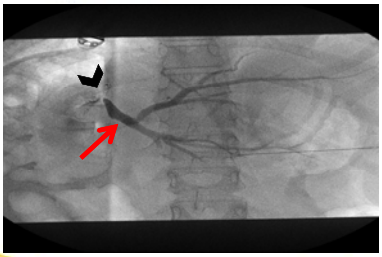

Brian Dillon MD

Percutaneous Transhepatic Cholangiogram

- The red arrow depicts the dilated intrahepatic bile ducts.
- The black arrow head depicts the markedly delayed, and very minimal drainage to the bowel.

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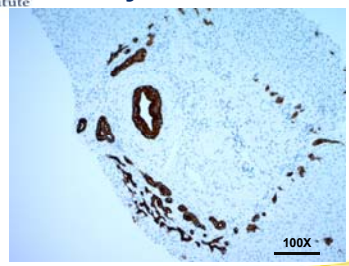
Biliary obstruction



CK7

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Biliary complications following pediatric liver transplantation

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- Biliary complications after LT remain frequent despite improvements/innovations in surgical techniques.
- These complications occasionally lead to graft failure or even death.
- The reported incidence of biliary complications after LDLT is 10% - 35% in pediatric recipients.
- Suggested risk factors for biliary complications include:
  - Hepatic arterial thrombosis
  - Acute cellular rejection
  - Prolonged cold ischemia time
  - Older age of donor
  - LDLT
  - ABO-incompatible LT

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Biliary obstruction following pediatric liver transplantation

- 2 major therapeutic options for post-transplant biliary strictures:
  - Surgical – biliary reconstruction (Roux-en-Y hepaticojejunostomy)
  - Nonsurgical – PTBD
    - In cases of post-transplant biliary strictures in duct-to-duct biliary reconstruction, conventional endoscopic intervention is the first-line Rx

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Biliary obstruction following pediatric liver transplantation

- In biliary reconstruction at pediatric LT, Roux-en-Y hepaticojejunostomy is a standard procedure because the most common original disease is biliary atresia.
- In cases of post-transplant biliary strictures in hepaticojejunal biliary reconstruction, conventional endoscopy cannot approach the hepaticojejunal anastomotic site*
- Therefore PTBD is the first-line Rx for pediatric post-transplant biliary strictures.

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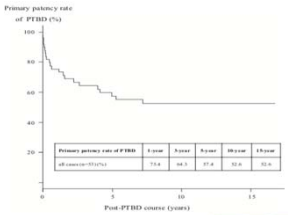
Biliary obstruction following pediatric liver transplantation

Sanada et al.
Clinical Transplantation 2019.

- Retrospective analysis of their experience on long-term outcome of PTBD for post-transplant biliary strictures.
- Success rate of PTBD – 90.6%
- 15-year primary patency rate of PTBD – 52.6%
- The recurrence rate of biliary strictures after PTBD - 18.8%



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Outcomes of PTBD for pediatric post-transplant biliary strictures

TABLE 1 The outcomes of PTBD treatment for pediatric post-transplant biliary strictures

Institutions	Number of cases (PTBDs)	Successful rate of PTBD	Recurrence rate after PTBD	Primary patency rate of PTBD (observation period)	Clinical success
Colombia, 2017[9] Fundación Valle del Lili	40 (61)	88%	44%	56% (mean 40 mo)	83%
Brazil, 2017[10] Universidade Federal de São Paulo	7 (21)	86%	100%	–	100%
Japan, 2015[11] Kyoto University	52	–	25%	68% (10-y)	83%
Italy, 2015[12] University of Torino	13	100%	54%	46% (mean 2364 d)	69%
Germany, 2014[13] University Medical Center Regensburg	16 (23)	100%	6%	–	75%
Brazil, 2014[5] Sírio Libanês Hospital	43	100%	20%	77% (median 54 mo)	–
Brazil, 2010[14] São Paulo University Medical School	64	93%	34%	61% (mean 5.5 y)	–
Italy, 2008[15] IsMeTT	27	100%	20%	75% (mean 15 mo)	56%
USA, 2006[16] Northwestern University	35	100%	66%	34% (mean 4.5 y)	60%
Israel, 2004[17] Rabin Medical Center	7 (9)	100%	0%	100% (mean 27 mo)	100%
USA, 2001[18] University of Chicago	76 (120)	91%	–	–	–
Our institution	41 (53)	91%	19%	53% (15-y)	85%

Abbreviation: PTBD, percutaneous transhepatic biliary drainage.

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Case 3.

- 16-year old F
- DDLT 15 ½-years previously for ESLD secondary to Biliary Atresia
- Routine clinic visit
- IS: Last four Tacrolimus levels: 9, 2, 8, 9
- PE: no peripheral adenopathy
- Tonsils 2+ bilaterally, no exudates
- BP 50% for age, height, and gender
- Liver not palpable or percussed beneath SCM, span 6 cm. No splenomegaly, no ascites.
- TB/DB: 0.6/0.1
- ALT: 127
- AST: 140
- GGT: 255
- EBV PCR – none detected
- CMV PCR – none detected
- DUS: no intrahepatic biliary ductal dilatation, patent hepatic vasculature.

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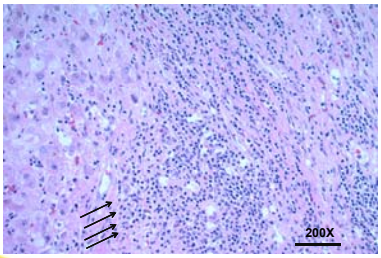

H&E Raffaella Morotti MD

Lymphoplasmacytic portal inflammation extending into the lobule (arrows) and interface hepatitis.

Additional labs obtained:

- **ANA 1:320**
- **IgG elevated**
- Anti-smooth muscle Ab, anti-LKM Ab, SLA all normal.

Clinical parameters used for diagnosing dnAIH (Kerkar, Vergani. J. Autoimmunity 2018).

Clinical parameters used for diagnosing de novo AIH.

1	Indication for liver transplantation not autoimmune hepatitis
2	Graft dysfunction with elevated serum aminotransferases and/or bilirubin
3.	Presence of serological features of autoimmune hepatitis Elevated serum immunoglobulin G Positive anti-nuclear antibody, smooth muscle antibody and/or liver kidney microsomal antibody (typical or atypical)
4	Histology characteristic of autoimmune hepatitis Interface hepatitis, lymphoplasmacytic infiltration, bridging collapse Fibrosis ranging from minimal to cirrhosis, classically bridging fibrosis
5	Response to therapy used to treat autoimmune hepatitis Prednisone – slow taper over weeks rather than days as is done in rejection Addition of Azathioprine or Mycophenolate Mofetil
6	Scoring of probable or definite AIH using the revised International autoimmune hepatitis scoring system Probable AIH (score 10–15) Definite AIH (score > 15)
7	Exclusion of other known causes of graft dysfunction, classical cellular rejection, vascular, biliary or infectious etiologies and PTLD

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Reports of dnAIH in pediatrics from around the world

Reports of de novo AIH in pediatrics from around the world.

Year	Author Location	Number (%)	Median time (years) to de novo AIH (median)	Outcomes
1998	Kerkar et al., London, UK [1]	7/180 (4%)	2	1 relapse 6 of 7 in remission at 283 days
2001	Hernandez et al., Chicago, USA [13]	5/155 (3.2%)	5.1	2 of 5 developed rejection within a year,1 death.
2001	Gupta et al., Chicago, USA [14]	6/115 (5.2%)	8.5	1 death (3rd transplant) and 1 re-transplant
2001	Andries et al., Brussels, Belgium [15]	11/471 (2.4%)	4.0	Three had mild to moderate relapse within a year
2001	Spada et al., Bergamo, Italy [16]	5/116 (4.3%)	2.4	Three had recurrence during steroid taper
2002	Pote et al., Bergamo, Italy [17]	18/155 (11%)	2.5	Stable at median follow-up of 14 months
2004	Miyagawa-hayashino et al. Kyoto, Japan [18]	13/633 (2.1%)	3.1	Three re-transplants, 8 with persistent histological abnormalities, median 3.5 years
2006	Gibelli et al., Sao Paulo, Brazil [19]	2/205 (1%)	3.5	1 stable 9 years post-transplant, 1 N/A
2007	Venick et al., Los Angeles, USA [20]	41/619 (6.6%)	7 ± 1.2 (mean)	2 deaths, 3 re-transplants at mean follow-up of 4 years
2011	Cho et al., Seoul, Korea [21]	4/148 (2.7%)	12.4	N/A
2017	Ekong et al., USA, Canada and UK [23]	31/1833 (1.7%)	5.3 (1.2–14.9)	Follow-up of 7.1yrs- no deaths, 2 re-transplants and 4 with cirrhosis and portal hypertension

Kerkar, Vergani. J Autoimmunity 2018.

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De novo Autoimmune hepatitis (dnAIH)

- Characterized by chronic liver damage with interface hepatitis, high transaminase levels, high IgG levels and positive autoantibodies.
- Occurs in LT recipients transplanted for non-autoimmune liver disorders.
- The possibility that an antibody directed to a drug-metabolizing enzyme expressed at high levels within the liver and kidneys – namely glutathione-S-transferase T1 (GSTT1)is instrumental to the development of dnAIH has been suggested.

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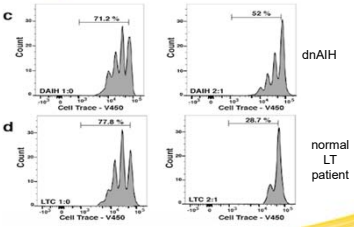
Immune pathogenesis of dnAIH



Regulatory T cells (Tregs) of these patients are dysfunctional; and produce the pro-inflammatory cytokines – IFN-γ & IL-17A

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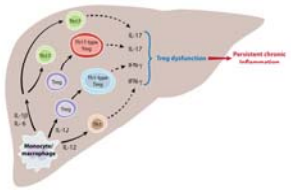
Immune pathogenesis of dnAIH

Arterbery, Ekong et al.
J. Immunology 2016.



- Monocytes/Macrophages seem to be key in promoting an inflammatory milieu that subsequently leads to the observed functional impairment of Tregs.

Immunc pathogenesis of dnAIH

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frontiers in Immunology

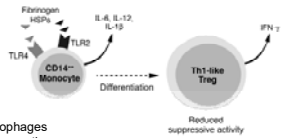
Inflammasome Priming Mediated *via* Toll-Like Receptors 2 and 4, Induces Th1-Like Regulatory T Cells in *De Novo* Autoimmune Hepatitis

Adam S. Arterbery[1], Jie Yao[1], Andrew Ling[1], Yaron Avitzur[1], Mercedes Martinez[1], Steven Lobritto[1], Yanhong Deng[1], Gan Gelang[1], Sameet Mehta[2], Guilin Wang[1], James Knight[3] and Udeme O. Ekong[1]*

The inflammasome is highly activated within monocytes of patients with dnAIH but not in those liver transplanted patients without dnAIH.

The highly activated monocytes are able to induce Tregs to assume an effector phenotype, thus becoming themselves effectors of damage.

Model of Reduced Suppressive Function of Tregs and Th1-like Treg Development after TLR2/4 Stimulation



Autoimmunity in dnAIH is promoted by monocytes/macrophages predominantly through activation of inflammatory signaling pathways.

Arterbery, Ekong et al. Frontiers In Immunology 2018.

Case 4.

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- 7-year old boy underwent DDLT.
- Homozygous mutation in the *ATP8B1* gene: C.1587_1589delCTT(p.F529del), predictive of Progressive Familial Intrahepatic Cholestasis Type 1.
- 7-months post LT he developed refractory diarrhea
- 13-months post LT, fluctuating serum aminotransferases
- ~18-months later, persistent aminotransferase elevation
- AST 342 ALT 309 GGT 30
- EBV and CMV PCR – none detected
- DUS - no intrahepatic biliary ductal dilatation, normal hepatic vasculature.

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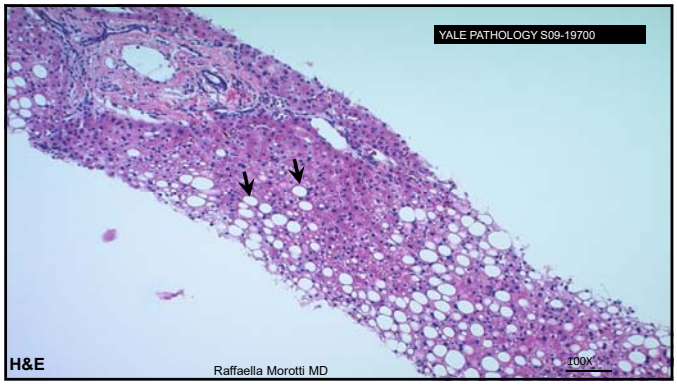
What next?

- A) watchful waiting
- B) percutaneous liver biopsy
- C) methylprednisolone bolus
- D) see what I was talking about – Liver patients and *DRAMA!!!!*



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Pathogenesis of allograft steatosis

- The pathogenesis of liver steatosis after LT is unclear
  - malfunction of FIC1 gene product in native bowel with disordered enterohepatic interaction, including pertubations of bile salt and lipid transport and metabolism contribute to the development of steatosis
  - a combination of increased bile salt pool after LT with continued intestinal FIC1 dysfunction could cause steatosis.
- Speculation on the role of malnutrition secondary to refractory diarrhoea and pancreatitis as possible causes of graft steatosis

Knowledge and Compassion **Focused on You**

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Pathogenesis of allograft steatosis

- *ATP8B1* mutations appear to affect sites of more functional importance in patients who develop post transplant steatosis
  - greater protein dysfunction at sites of secretion and absorption in the body

Knowledge and Compassion **Focused on You**

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Pathogenesis of intractable diarrhoea

- *ATP8B1* is expressed in liver, small intestines, pancreas and kidneys
- Several functions have been proposed for FIC1, including a role in intestinal bile acid reabsorption or its regulation
- Reinforced by the fact that diarrhea is exacerbated and becomes more evident after successful LT

Knowledge and Compassion **Focused on You**

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Pathogenesis of intractable diarrhoea

- Following LT, there is continuous restoration of intestinal bile flow and biliary bile acid secretion, however, FIC1 gene product dysfunction remains on the intestinal side
- Consistent with this hypothesis is the fact that intractable diarrhea in transplanted patients with PFIC1 is associated with increased concentration of stool bile acids and is improved by bile adsorptive resin treatment.

Knowledge and Compassion **Focused on You**

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Take home points PFIC1

Counseling of families about LT for PFIC1

- Extrahepatic symptomatology:
  - is not corrected by LT
  - may be aggravated following LT
- Appearance of graft steatosis following LT

Rx strategies proposed

- Bile adsorptive resin therapy
- Pancreatic enzyme supplementation
- Long-term biliary diversion

Knowledge and Compassion **Focused on You**

Ann & Robert H. Lurie Children's Hospital of Chicago

What is a "normal" childhood after liver transplantation

Estella M. Alonso, M.D.
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NORTHWESTERN UNIVERSITY FEINBERG SCHOOL OF MEDICINE

Disclosures

- In the past 12 months, I have had no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.

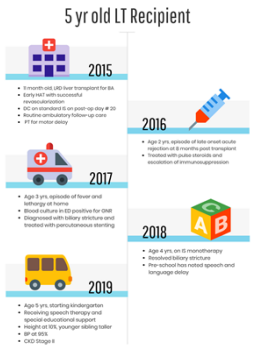
Objectives

- Identify the common physical and psychosocial challenges children experience after LT
- Review risk factors for lower than expected physical function and school performance after LT
- Discuss screening strategies to implement in a post-transplant ambulatory setting to identify high risk patients

Expectations

What is a "normal" life?

- Normal physical health
  - No signs of chronic liver disease and no chronic or life-threatening infections
  - No chronic complications of immunosuppression
- Normal growth and lack of physical limitations
- Normal energy level
- Ability to attend school regularly and participate in age-appropriate activities
- Average or above average school performance
- Average psychosocial health and family function
- Ability to become an independent adult

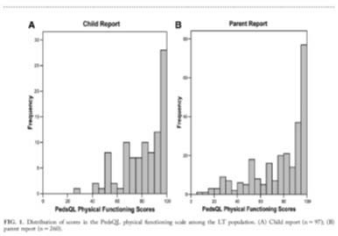


Timeline of Events

What is the toll?

- Hospital Days
- Ambulance Ride
- ED visits
- Ambulatory Visits
- Lab Draws
- Imaging
- Days of Physical Therapy
- Missed School Days

Physical Function at One Year Post-LT



- Lower physical function scores compared to matched health group ($p<0.01$)
- 35.0% with physical function score >1 SD below the healthy mean
- Physical function scores higher in survivors with optimal health ($p<0.01$)

Predictors of Lower Physical Function

- Primary disease
- Height Z score<-1.64
- ≥4 days of hospitalization
- Not listed as Status 1

Liver Trans 2016;22:495-504

Common Medical Complications

- Rejection
  - 40-60% of recipients with at least one episode in the first year
  - 2-3% per year after the first year
    - Consider non-adherence
- Vascular stenosis or thrombosis < 10%
  - Hepatic artery
    - Progressive scarring versus immune phenomenon
  - Portal Vein
    - External compression versus scarring
- Biliary strictures up to 30%
  - Any interval from transplant
  - Anastomotic versus intra-hepatic
  - Re-admission/ Long-term drain placement

Problematic Post-Transplant Infections

- More severe community acquired viral infections
  - Norovirus
  - Adenovirus
- Chronic upper respiratory infections
  - Otitis Media
  - EBV driven tonsillar hypertrophy
- Opportunistic infection rare, but real
- Bacteremia/Sepsis
  - Invasive Pneumococcal Disease
  - Enteric bacteria associated with biliary obstruction
  - Ischemic abscess

What to do about a fever?

Number and timing of bacterial infections in children post liver transplantation hospitalized for fever

Post-transplantation period	Febrile hospitalizations	Bacterial infection n (%), of febrile hospitalizations
<1 month	3	1 (33)
1 month–1 year	39	13 (33)
1–5 years	58	38 (66)
>5 years	33	21 (64)

Transpl Infect Dis 2016;18:333-40

Post-transplantation period	Febrile hospitalizations *n*	Bacterial infection *n* (%), of febrile hospitalizations
<1 month	3	1 (33)
1 month–1 year	39	13 (33)
1–5 years	58	38 (66)
>5 years	33	21 (64)

Risk of Blood Stream Infection

- 29/340 (9%) LT recipients > 6 Months
- 42 organisms
  - 9 GPC
  - 33 GNR
- Intraabdominal infection most frequent source (47%)
  - 39% episodes with no apparent focus.
- Risk factors in multivariate analysis
  - Operative time > 12 hours (odds ratio [OR] = 3.55; P = 0.04)
  - Biliary stenosis (OR = 4.60; P = 0.006)

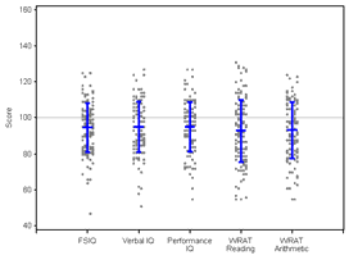
Pediatr Infect Dis J 2018;37:263-8

School Readiness

- Language delay (>1 SD below norms) in infants awaiting LT
  - 40% with receptive language delay
  - 67% with expressive language delay
- Diagnosis of ADHD approximately double
- 15% sensorineural hearing loss after transplant
- 25% LT recipients have mild to moderate developmental delay at age 5-7 yrs
  - Cognitive and math deficits tend to persist up to age 9
  - Reading may improve
  - Predictors of lower FSIQ include single parent household (P < .002), parent education (P < .01), weight z-score at liver transplantation (P < .03), and transfusion volume during liver transplantation (P < .0001)

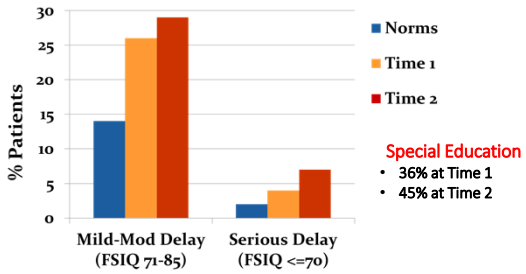
J Pediatr 2010;156:936-40
Pediatr Transplantation 2003: 7: 265–269
J Pediatr 2014;165:65-72

Distribution of IQ and Achievement Scores Following LT



Sorensen LG et al, Am J Transplant 2011;11:303-11

Cognitive Delay

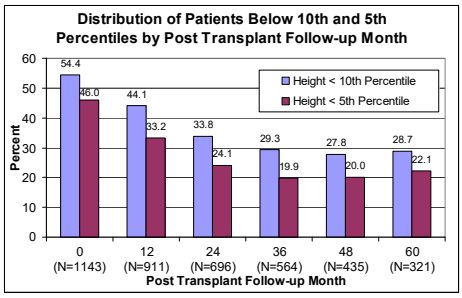


Special Education
- 36% at Time 1
- 45% at Time 2

J Pediatr 2014;165:65-72

Physical Growth

- 60% of children malnourished at transplant
- Usually achieve nutritional rehabilitation within 12-24 months
  - Complete catch-up for weight within 12-24 months
  - Catch-up linear growth not achieved until after 12-24 months
- Sub-optimal linear growth continues into long-term follow-up
  - Pre-transplant nutritional status
  - Post-transplant complications and medications



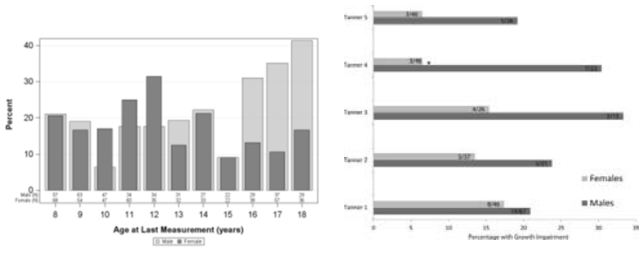
AJT 2009; 9:1389-97

Multivariate Analysis for Growth Impairment at 2 Years

Factor	Comparison	Reference	OR	95% CI	p-value
Primary disease overall p=0.0146	Other Cholestatic ALF **Metabolic Disease** Other	Biliary atresia	1.40 1.10 **4.40** 2.16	0.64, 3.04 0.38, 3.17 **1.83,10.59** 0.95, 4.91	0.4028 0.8556 **0.0009** 0.0675
Prednisone use up to 24 months overall p=0.0046	6-17.9 months **18+ months**	<6 months	1.42 **3.02**	0.70, 2.90 **1.39, 6.55**	0.3350 **0.0053**
Weight z score at transplant	continuous		**0.80**	**0.65, 0.99**	**0.0385**
Height z score at transplant	continuous		**0.62**	**0.51, 0.77**	**<0.0001**
Total Bilirubin at transplant	continuous		**1.05**	**1.02, 1.07**	**0.0010**
GGTP at 12 months	continuous		**1.002**	**1.000, 1.004**	**0.0328**

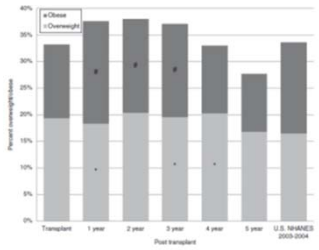
AJT 2009; 9:1389-97

Linear Growth in 353 Post-Pubertal Children



J Pediatr 2103; 163:1354–60

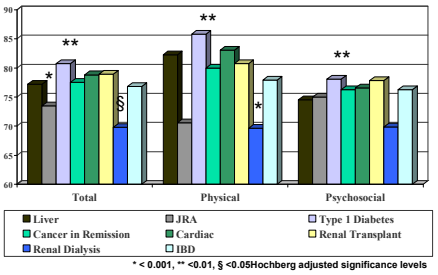
Obesity



JPGN 2012;55:657-62

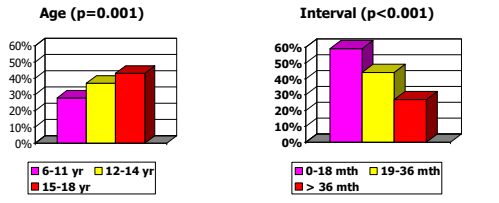
PedsQL™ Scores for LT Compared to 6 Chronic Disease Groups

Pediatr Transpl 2011: 15: 245–253



* < 0.001, ** <0.01, § <0.05Hochberg adjusted significance levels

Absent > 10 days/year



Liver Transpl 2010;16:1041-48

PedsQL 4.0 Parent Proxy-Report

30.6% scored > 1 SD below mean for healthy sample

Scales	LT Sample (Mean±SD) n=869	Healthy Children (Mean±SD) n=3869	Effect Size
Total Score	77.26±17.58***	84.12±13.74	0.47
Physical Health	79.33±22.07***	86.87±17.05	0.42
Psychosocial Health	75.72±17.33***	82.53±14.09	0.46
Emotional Functioning	73.27±19.28***	81.02±15.93	0.47
Social Functioning	78.99±20.63***	85.93±16.98	0.39
School Functioning	67.42±22.43***	79.34±18.37	0.62

*** p<0.001

J Pediatr 2010;156:270-6

PedsQL 4.0 Child Self-Report

31.1% scored > 1 SD below mean for healthy sample

Scales	LT Sample (Mean±SD) n=363	Healthy Children (Mean±SD) n=1844	Effect Size
Total Score	77.21±14.28***	83.68±12.26	0.51
Physical Health	82.29±15.62***	88.07±12.30	0.45
Psychosocial Health	74.51±15.83***	81.33±14.04	0.48
Emotional Functioning	74.00±19.90***	78.56±18.29	0.25
Social Functioning	80.95±19.09***	85.50±16.93	0.26
School Functioning	68.53±18.56***	79.83±16.33	0.68

*** p<0.001

Sub-analysis of School Function

School Functioning Scale Components			
Parent Report	LT n=746 Mean (±SD)	Healthy n=3215 Mean (±SD)	Effect Size
School Functioning	67.4±22.4	79.3±18.4	-0.62*
Cognitive	67.2±27.1	74.1±24.4	-0.28*
Missing School	67.7±23.8	84.0±17.8	-0.85*

* p < 0.001

PedsQL™ Multidimensional Fatigue Scale

	iWITH Baseline		Healthy Controls				
	Mean	SD	n	Mean	SD	Adjusted Significance Level	Effect Size
Child Report n=81							
Total Fatigue	74.9	17.75	157	82.19	12.27	0.0012	0.51
General Fatigue	80.2	18.89	157	86.36	13.11	0.0144	0.40
Sleep/Rest Fatigue	71.3	20.42	157	77.44	15.41	0.04	0.36
Cognitive Fatigue	73.4	22.15	157	82.78	16.26	0.0012	0.51
Parent Proxy-Report n=87							
Total Fatigue	78.0	16.11	157	87.24	10.91	0.0004	0.71
General Fatigue	80.1	16.28	157	88.40	11.67	0.0004	0.62
Sleep/Rest Fatigue	81.4	16.57	157	86.70	12.63	0.022	0.38
Cognitive Fatigue	72.4	24.00	157	86.62	16.36	0.0004	0.74

iWITH Unpublished Data

Health-Related Quality of Life and Cognitive Functioning in Liver Transplant Recipients During a 10-year Time Span

Objectives

- Determine if early developmental assessment at time of school entry predicts cognitive function in adolescence
- Determine if HRQOL changes as a function of time since transplant in long-term survivors

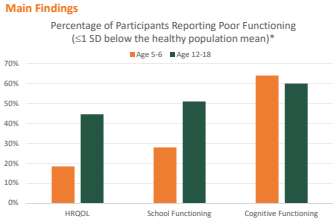
Methods

- Longitudinal neurocognitive assessment cohort study age 5-6, 7-8 and in adolescence (age 12 up to 18)
- Adolescent assessment; online surveys regarding perceived cognitive functioning and HRQOL

Conclusions

- HRQOL does not appear to improve in adolescence. Over half of adolescent LT recipients appear to be at risk for lower cognitive and school function

Main Findings



*On parent-report PedsQL™ 4.0 Generic Core Scale Total Score, School Functioning Scale, and PedsQL™ Cognitive Functioning Scale

AASLD 2018

Is early childhood assessment predictive of functioning in adolescence?

- Early childhood PedsQL™ (Parent Report) showed excellent predictive value for poor functioning in adolescence

	Poor Function at T1 (n)	Poor Function at T1 and T3 (n)	Positive Predictive Value
PedsQL™ 4.0 Total Score	19	14	74%
PedsQL™ School Functioning	21	18	86%
PedsQL™ Cognitive Functioning	31	22	71%

- BRIEF scores at T1 predict PedsQL™ Cognitive Function scores at T3
  - BRIEF Metacognition Index ($p = 0.0298$)
  - BRIEF Working Memory ($p < 0.0001$)

461 LT Survivors at 5 Years

- Immunosuppression requirements
  - 97% on CNI
  - 25% still on prednisone at 5 years
- Liver function preserved
  - Bilirubin and albumin normal in > 90%
  - 30-50% had abnormal transaminases

PTLD in 6%

- Chronic rejection in 5%
- 13% with cGFR <90 ml/min/1.73 m^2
  - None required renal transplant
- 12% with BMI > 95th percentile
- 29% with height < 10th percentile

Pediatrics 2008;122:e1128-e1135

167 LT Survivors at 10 years

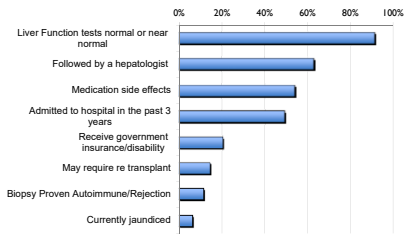
Table IV. The ideal SPLIT 10-year survivor of pediatric LT

Medical variable: result reported at 10-year visit	Patient data available, n	Patients who answered "yes" to variable as phrased, n (%)	Patients missing data, n (%)
Sustainability of allograft			
1 No retransplantation	167	147 (88%)	0
2 No chronic rejection; confirmed diagnosis previously/presently	167	152 (91%)	0
3 Serum ALT normal	166	148 (89%)	1 (1%)
4 Serum TB normal	165	161 (98%)	2 (2%)
5 Serum albumin normal	162	160 (99%)	5 (3%)
6 Serum GGT normal	149	126 (85%)	18 (11%)
Absence of immunosuppression-induced comorbid conditions			
7 No PTLD; previous diagnosis of tissue-confirmed PTLD	167	158 (94%)	0
8 No renal dysfunction; cGFR <90 mL/min/1.73 m^2	118	107 (91%)	49 (29%)
9 Acceptable linear growth; >−2 SD for healthy population	121	112 (93%)	46 (27%)
10 No diabetes	167	165 (99%)	0
Absence of need for additional medications			
11 No ongoing use of prednisone	167	135 (81%)	0
12 No use of antihypertensive agent	167	146 (87%)	0
13 No use of anticonvulsant medication	167	167 (100%)	0

J Pediatr 2012;160:820-6

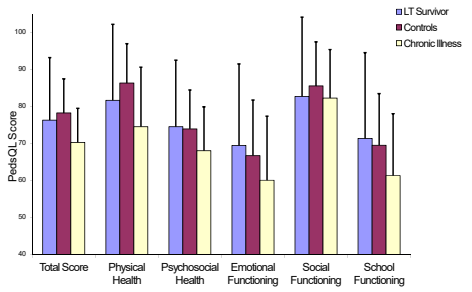
Health Status at 20 Years

Young adults transplanted 1988-92

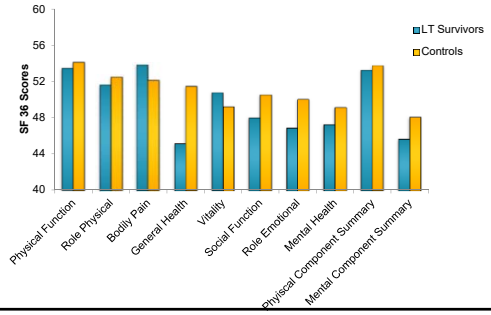


AJT 2012;12:1486–95

PedsQL 4.0 Generic Core Scale



SF 36 Scores



Health screening

- Assess for Liver Injury and Dysfunction
  - Liver enzymes
  - US with doppler and elastography
  - Surveillance liver biopsy
- Screen for co-morbidities
  - Skilled BP measurement
  - Insulin level, Hgb A1c, Lipid Profile
  - Cystatin-C
- Assessment of Growth, Development and Wellness
  - Growth percentiles and puberty status
  - School function
  - HRQOL screening

Summary

- Medical complications following Pediatric LT are not uncommon
  - Interval from transplant impacts type of problems
- Functional outcomes are good, but lower than healthy peers
  - Especially in the area of school function
    - Missed school days are important
  - LT survivors may have more fatigue
- Cognitive function maybe impaired
  - Recovery versus adaptation in early adulthood