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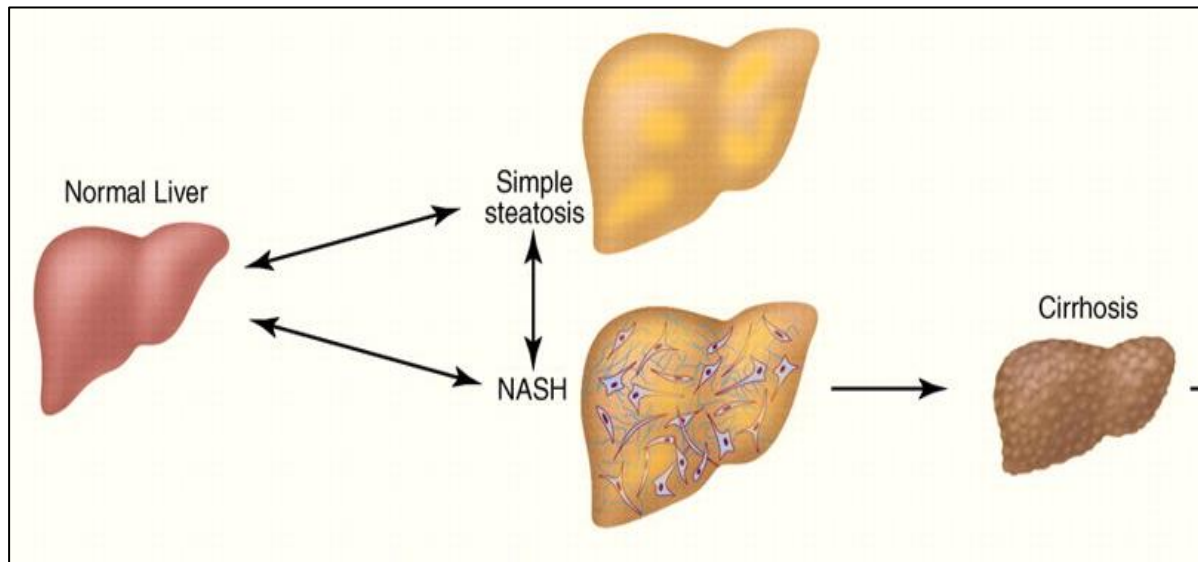
Session VI

Key Information Needed to Track
Disease Progression in
Pediatric Studies

www.hivforum.org

Liver Forum:
Pediatric Issues Working Group
March, 2017

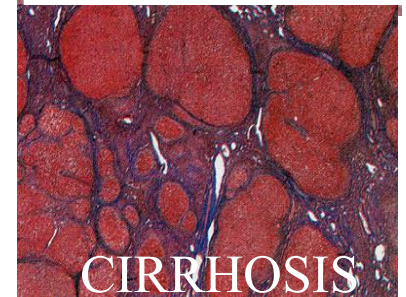
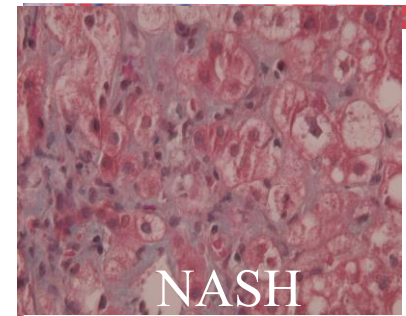
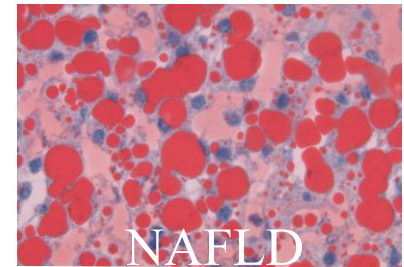
Key Information to Track Disease Progression
in Pediatric Trials



Joel E. Lavine, MDPhD
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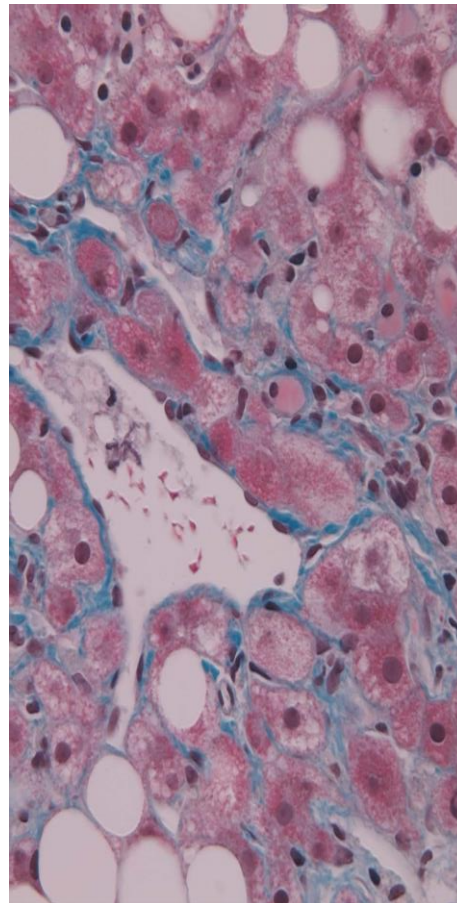
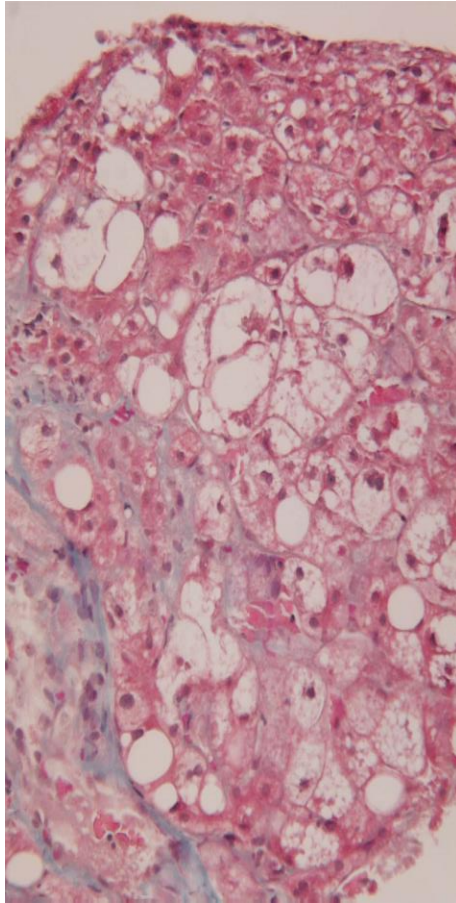
Why is Pediatric NAFLD Important?

- Obesity prevalence increased rapidly
- Most common pediatric liver disease
- Ethnic predisposition and severity
- Differs significantly from adult NASH
- Genetic penetrance
- Cirrhosis in childhood and beyond
- Liver disease co-morbidity
- Association with CV morbidity risk
- Limited treatment

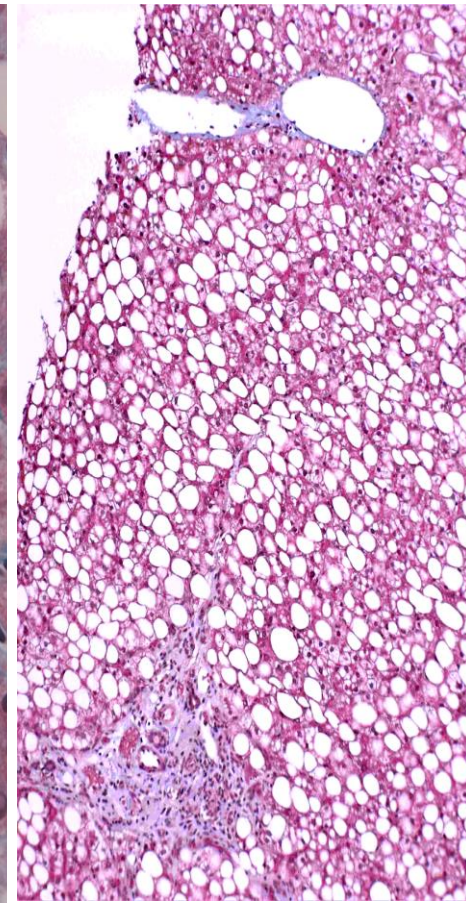


What is Pediatric NASH? N=100

Type 1

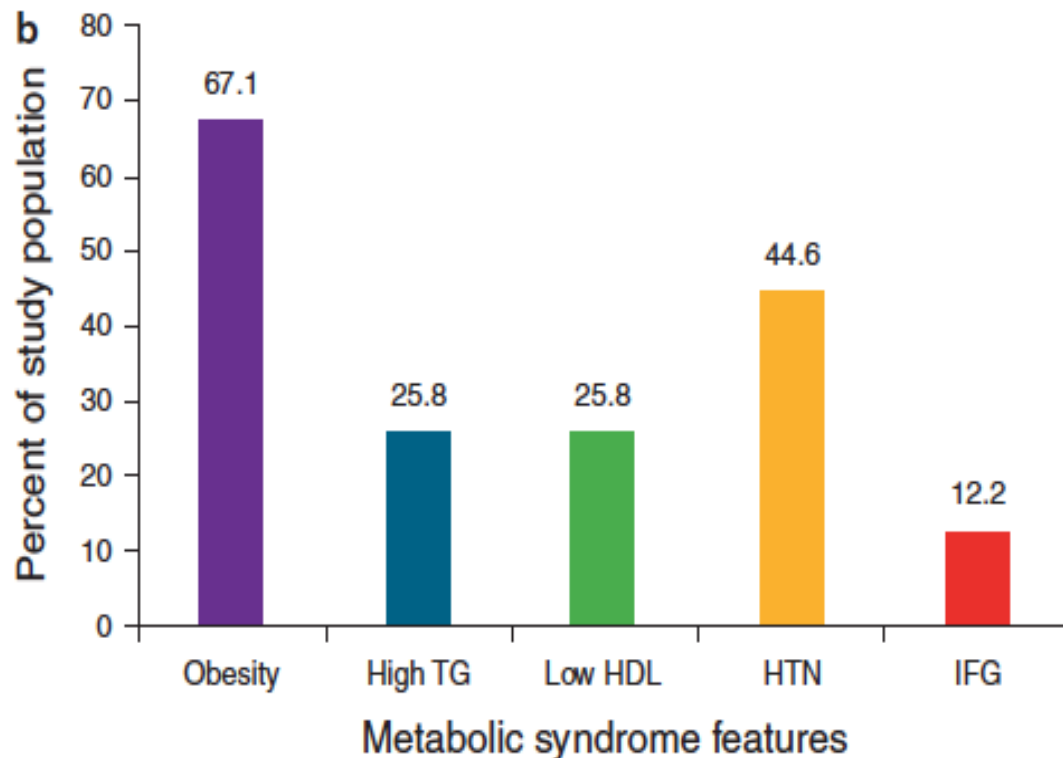


Type 2/BZ1



Association Between Metabolic Syndrome and Liver Histology Among Children With Nonalcoholic Fatty Liver Disease

Heather M. Patton, MD¹, Katherine Yates², Aynur Unalp-Arida, MD, PhD², Cynthia A. Behling, MD, PhD³, Terry T.-K. Huang, PhD, MPH⁴, Philip Rosenthal, MD⁵, Arun J. Sanyal, MD⁶, Jeffrey B. Schwimmer, MD¹, Joel E. Lavine, MD, PhD¹ and the NASH CRN



Clinical Correlates of Histopathology in Pediatric Nonalcoholic Steatohepatitis

HEATHER M. PATTON,* JOEL E. LAVINE,[‡] MARK L. VAN NATTA,[§] JEFFREY B. SCHWIMMER,[‡] DAVID KLEINER,^{||} JEAN MOLLESTON,[¶] and the Nonalcoholic Steatohepatitis Clinical Research Network

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Table 4. Predictors of Fibrosis Stage

	None (n = 46)	Mild (n = 77)	Moderate (n = 29)	Bridging (n = 24)	P trend
Demographics					
Male (%)	72	79	72	88	.26
Mean age (y)	13.1	12.1	13.0	11.5	.05
White race (%)	74	71	76	74	.89
Hispanic ethnicity (%)	63	69	31	54	.05
Clinic site: UCSD (%)	52	53	38	46	.33
Laboratory data, median values					
ALT (U/L)	84	82	96	126	.01
AST (U/L)	48	52	56	76	.0003
Alkaline phosphatase (U/L)	202	250	218	263	.02
GGT (U/L)	38	32	52	54	.001
Albumin (g/dL)	4.5	4.3	4.2	4.4	.01
White blood cell count (1000/mm ³)	7.2	7.6	7.8	8.3	.004
Hematocrit (%)	42	41	40	40	.002
Fasting insulin (mU/mL)	30	24	33	33	.17
HOMA-IR	6.7	5.2	7.5	7.6	.14
QUICKI	0.291	0.301	0.287	0.287	.14
ANA (% positive)	20	19	24	4	.26
ASMA (% positive)	27	32	37	32	.54
Anthropometric, median values					
BMI (kg/m ²)	34	32	34	32	.99
BMI percentile	99.0	99.1	99.0	99.2	.31
Percentage of body fat	41	44	45	44	.02
Clinical					
Tanner stage (mean)	3.0	2.3	2.7	2.0	.03
Histologic					
Median biopsy length (mm)	14	15	13	15	.75
<10 mm (%)	17	6	17	17	.79
Definite NASH (%)	22	26	72	54	<.0001
NAS (mean)	4.1	4.2	5.0	5.1	.0006

Increased Risks for Pediatric NAFLD

- Obesity
- Boys
- Hispanics
- “Adult onset” diabetes
- Dyslipidemia
- Family history of NAFLD
- Obstructive sleep apnea
- Hypopituitarism



Pediatric NAFLD Natural History

No prior prospective studies in children



NAFL

NASH

Cirrhosis

Lifestyle Factors Associated with Pediatric NAFLD



- Modern diets/Fast food
 - Too many calories
 - Decreased antioxidants
 - Certain types of fat
 - Too much fructose
- Insufficient activity/play
- Obstructive sleep apnea
- Alteration of gut bacteria
- Some medications

What Information Should We Collect?

Key Historical Variables

- Essential
 - How and why diagnosis made (symptoms, screening, incidental?)
 - Alcohol ingestion
 - Past use of medications associated with fatty liver
 - Past use of medications potentially to treat fatty liver
 - Use of drugs to treat hypertension, diabetes or dyslipidemia
 - Sleep pattern (hours, snoring problems, hx sleep apnea)
- Desirable but not essential
 - Family member's BMI or BMI z-score
 - Birth weight
 - Gestational age at birth
 - Mode of delivery
 - Weight gain and medications of mother during pregnancy
 - Others in family with known liver disease/type
 - Antibiotics prior to age 2
 - Breast feeding yes/no and duration

So What Information Should We Collect?

Key Demographic Variables

- Essential
 - Age at diagnosis
 - Age at entry of natural history study
 - Race/ethnicity (using ?criteria)
 - Location (country/state/city)
- Desirable
 - Socioeconomic status

So What Information Should We Collect?

Key Anthropometric Variables

- Essential
 - Height and height percentile for age/gender
 - Weight and weight percentile for age/gender
 - BMI z-score
 - Waist circumference
- Desirable
 - Percent body fat by BIE
 - Localization of fat by DXA
 - Body composition profile by MR

What Information Should We Collect?

Key Physical Exam Variables

- Essential
 - Blood pressure and percentile for age/gender
 - Liver span
 - Splenic enlargement
 - Acanthosis nigricans
 - Signs of liver disease
 - Telangiectasia, clubbing, abdominal venous pattern, ascites, jaundice, excoriation from pruritus
- Desirable
 - Tanner stage

What Information Should We Collect?

Key Laboratory Variables

- Essential
 - LFTs (ALT, AST, GGT, alkaline phosphatase, T/D bili)
 - History of anti-SMA, ANA, anti LKM1 if done
 - History of A1AT, ceruloplasmin, HCV/HBV labs
 - Fasting glucose and insulin (HOMA)
 - Fasting triglycerides, cholesterol total, HDL, LDL
- Desirable
 - PT, albumin, platelets, WBC, Hgb

What Information Should We Collect?

Key Imaging Variables

- Essential (if done)
 - Ultrasound result with or without doppler
 - CAP/TE result
 - MR/MR PDFF/MRE
 - CT Scan of liver

What Information Should We Collect?

Key Histology Variables

- Essential
 - When liver biopsy done or repeated
 - NAFLD pattern (definite NASH, BZ1 or 3, NAFL)
 - Grade of:
 - Steatosis
 - Inflammation (portal and lobular)
 - Cell injury (mallory and ballooning)
 - NAS score
 - Stage of:
 - Fibrosis (with location)

What Information Should We Collect?

Key Life Variables

- Essential
 - Hospitalizations/reason
 - Grade in school
 - New medications
- Desirable
 - Quality of Life questionnaire
 - Dietary questionnaire
 - Exercise questionnaire