Nonalcoholic Fatty Liver Disease and Other Liver Disorders

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The Spring Course BEST OF DDW 2019

Case 1

- 54 year old woman
- BMI 34, DM2, HTN
- No alcohol, no tobacco, exposures
- AST 54, ALT 78, AP 88,
- PE: no significant findings
- Next step?

NAFLD: Diagnostic Updates

- Noninvasive assessments
  - Calculators: NFS, FIB-4, APRI
  - VCTE:
    - CAP score useful for
    - LSM: good at distinguishing between minimal fibrosis and cirrhosis
  - MRI/MRE (best noninvasive estimate of fibrosis)

Performance of LSM for Assessing Fibrosis

Fibrosis Stage	Cross-Validated AUROC (95% CI)	Sensitivity fixed at 0.90			Specificity fixed at 0.90		
		Cut-off (kPa)	PPV	NPV	Cut-off (kPa)	PPV	NPV
0 vs 1-4	0.74 (0.68, 0.79)	4.9	0.80	0.48	9.4	0.93	0.34
0-1 vs 2-4	0.79 (0.74, 0.83)	5.6	0.62	0.80	11.9	0.80	0.59
0-2 vs 3-4	0.83 (0.79, 0.87)	6.5	0.45	0.91	12.1	0.71	0.80
0-3 vs 4	0.93 (0.90, 0.97)	12.1	0.34	0.99	14.9	0.41	0.97

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AASLD 2017; from NAFLD/NASH Diagnostic, R. Sterling

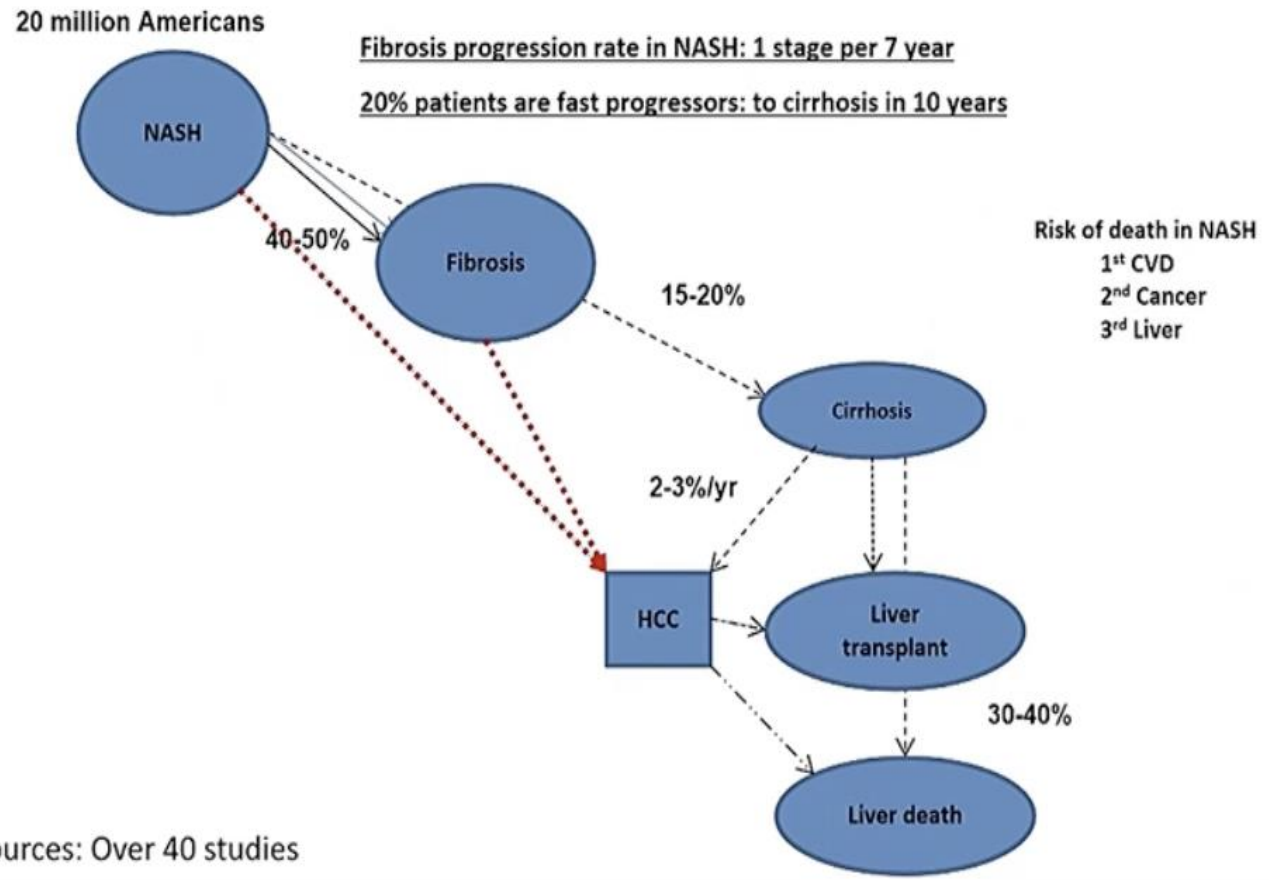
NAFLD/NASH Phase III Studies

Agent	Mechanism	Trial (N)	Primary Endpoint
Obeticholic acid	FXR agonist	REGENERATE[1] (2370)	≥ 1 stage fibrosis improvement with no NASH worsening; resolution of NASH with no fibrosis worsening (18 mos)
		REVERSE[2] (540)	≥ 1 stage fibrosis improvement with no NASH worsening (12 mos)
Elafibranor	PPARα/δ agonist	RESOLVE-IT[3] (2000)	Resolution of NASH with no fibrosis worsening (72 wks)
Cenicriviroc	CCR2/5 antagonist	AURORA[4] (2000)	≥ 1 stage fibrosis improvement with no NASH worsening (12 mos)
Selonsertib	ASK1 inhibitor	STELLAR 3[5] (808) STELLAR 4[6] (883)	≥ 1 stage fibrosis improvement with no NASH worsening (48 wks)

[1]NCT02548351; [2]NCT03439254; [3]NCT02704403; [4]NCT03028740; [5]NCT03053050; [6]NCT03053063

Courtesy Jennifer Price, MD, PhD

Natural history of NASH



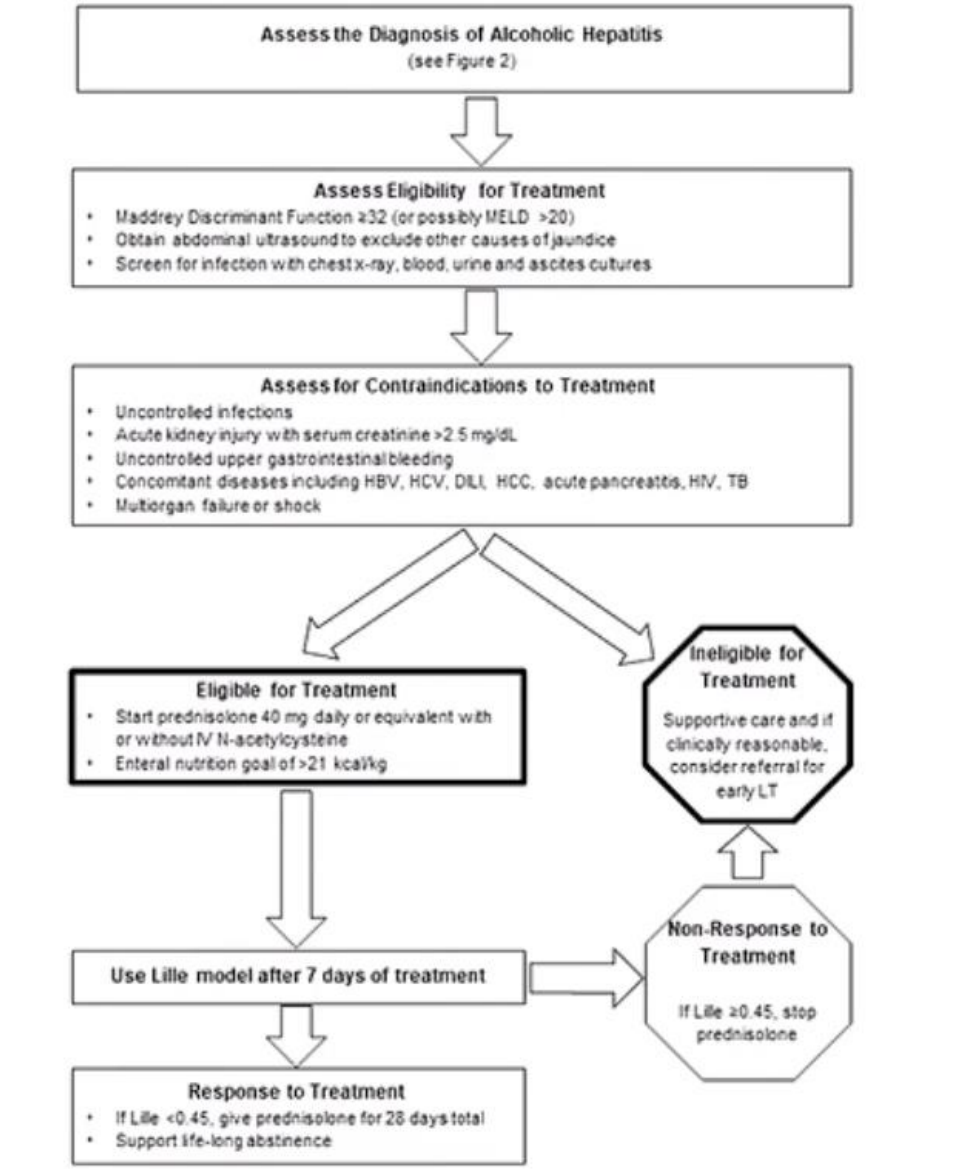
R. Loomba, #3235, Novel Advances in Noninvasive Imaging in NAFLD

Case 2

- 38 year old man, started drinking in law school, drinks daily, with recent rise after birth of child
- Called by ED with nausea, vomiting
- Tb 6, AST 110, ALT 156, AP 90, Alb 2.8
- What is best prognostic score to use?

Lab-based Prognostic Scores in Alcoholic Hepatitis

	Advantages	Disadvantages
MDF	Decades of experience in AH Key inclusion criterion in most AH trials	False positives can lead to excess corticosteroid treatment
MELD	Extensive experience in hepatology	Uncertain threshold for initiating corticosteroids
ABIC	3-tiered stratification	Uncertain threshold for initiating corticosteroids and not verified outside of Spain
GAHS	Improves specificity of MDF>32 patients needing corticosteroids	Not verified outside of UK
Lille	Allows early cessation of corticosteroids	Uncertain decision-making with partial response (Lille 0.46-0.56)



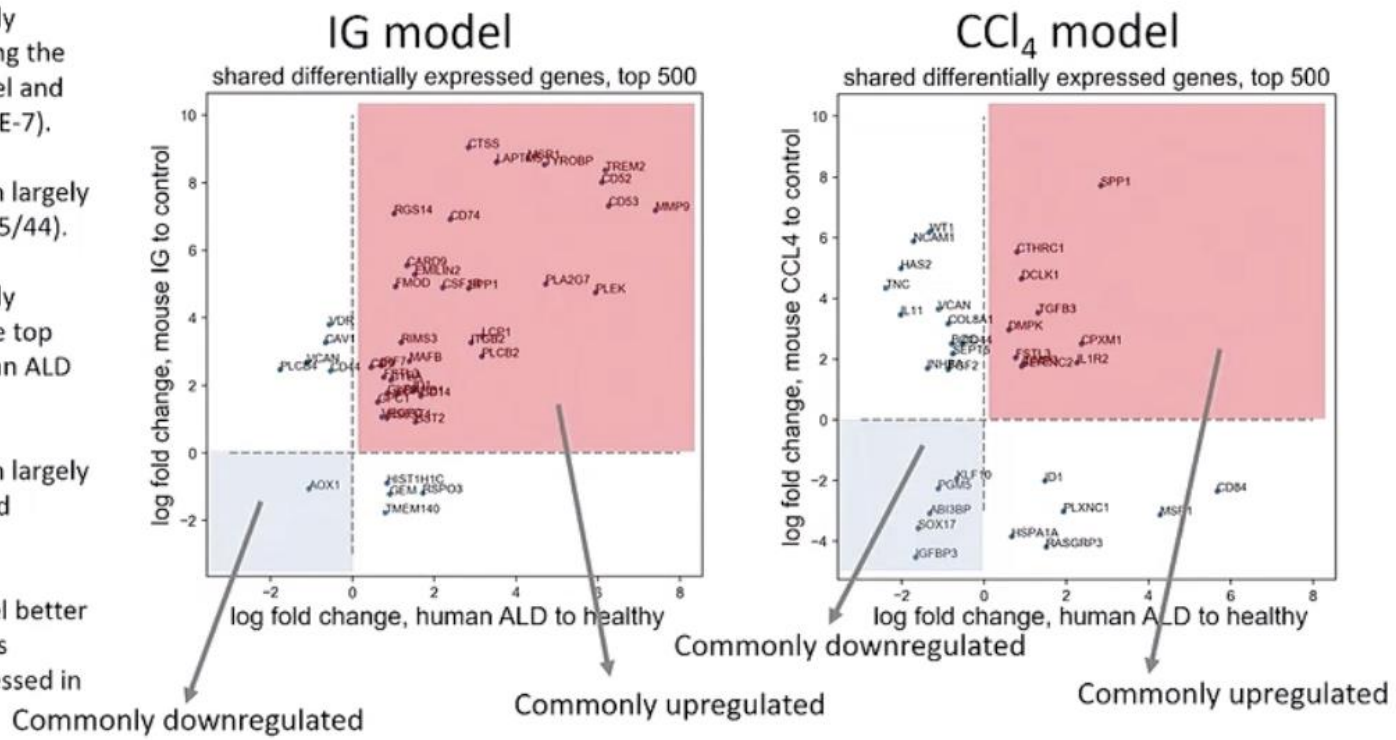
Courtesy M. Lucey; #3700 'Alcoholic Hepatitis 'Are Steroids Still in Vogue?

Treatment

- Prednisolone with or without NAC used
- Pentoxifylline no longer recommended for AH (STOPAH trial)
- Other agents being studied

Human ALD differentially expressed genes shared in mouse models

- 44 genes commonly dysregulated among the top 500 in IG model and human ALD (p=3.9E-7).
  - Direction of dysregulation largely conserved (35/44).
- 33 genes commonly dysregulated in the top 500 CCl_4 and human ALD genes (p=0.002).
  - Direction of dysregulation largely not preserved (15/33).
- → mouse IG model better recapitulates genes differentially expressed in human ALD



S. Rosenthal, #3700 Comparative Analysis of Gene Expression Profile in Primary Human Normal and Alcohol Injured HSCs…

Case 3

- 28 year old with PSC listed for OLT with exception points for recurrent cholangitis
- Now stent free, no episodes x 3 years
- HCC/Cholangio surveillance negative
- EGD last year normal
- In the last 2 minutes of your visit, she mentions a new partner and inquires re: family planning

Pregnancy in Advanced Liver Disease

- Overall fertility rate in CLD unknown
  - Appears to be preserved in AIH, PBC, PSC
  - Amenorrhea in half of patients with CLD, increased with more advanced disease
  - **Corrects 2-6 mos post transplant**
- Consider waiting one year after OLT before attempting conception

Type of Contraception	Considerations	CDC Category
IUDs (Copper-T, Progestin)	More effective Can cause irregular bleeding	Category 2
Depot medroxyprogesterone acetate	Very effective Irregular bleeding Cholestasis?	Category 2
Combined oral contraceptive pill, contraceptive patch, vaginal ring	Contraindicated with active liver disease Contraindicated in those with h/o MI, stroke, DVT, uncontrolled HTN	Category 2 (uncomplicated) Category 4 (complicated)
Progestin-only pill	Less effective than combined pill	Category 2

Category 4: having an unacceptable risk for use in those with increased risk of graft failure, rejection or vasculopathy

Courtesy: Kymberly Watt #3070 (see slides for additional acknowledgements)

Pregnancy in Advanced Liver Disease

- High risk OB!
- Maternal mortality 1.8-7.8%
- Perinatal mortality 11-18%
- 30-50% pregnancies with complications
  - EVH (18-32%; 75% with varices bleed during pregnancy; highest risk in trimesters 2-3)
    - Mortality: 18-50% if cirrhotic, 2-6% if non-cirrhotic
  - Liver/renal failure
  - HE, ascites, SBP
- Post partum hemorrhage
- MELD ≥ 10 or portal hypertension considered very high risk

Chronic Liver Disease Meds to Avoid in Pregnancy

- Spironolactone – associated with feminization of male fetus
- Terlipressin with oxytocic effect

MAYO CLINIC

Immunosuppression Issues

Immunosuppression	Historical FDA Classification	Observations
Prednisone	B	No teratogenicity
Tacrolimus	C	Preeclampsia, preterm birth, hyperkalemia, kidney impairment, ⇧DM
Cyclosporine	C	LBW, Preeclampsia, HTN
Everolimus/Sirolimus	C	Limited knowledge! Antiproliferative effects potentially detrimental in pregnancy
Azathioprine	D	Premature birth, LBW Neonatal leukopenia, thrombocytopenia, [illegible]
My[illegible] mo[illegible]		[illegible] ffecting ears, heart, esophagus, kidney and limbs

Eliminate mycophenolate mofetil, sirolimus and everolimus 6 weeks pre-conception

Trough levels can decrease in the 1st trimester due to increased plasma volume

Courtesy of Carla Brady, MD

Thank you