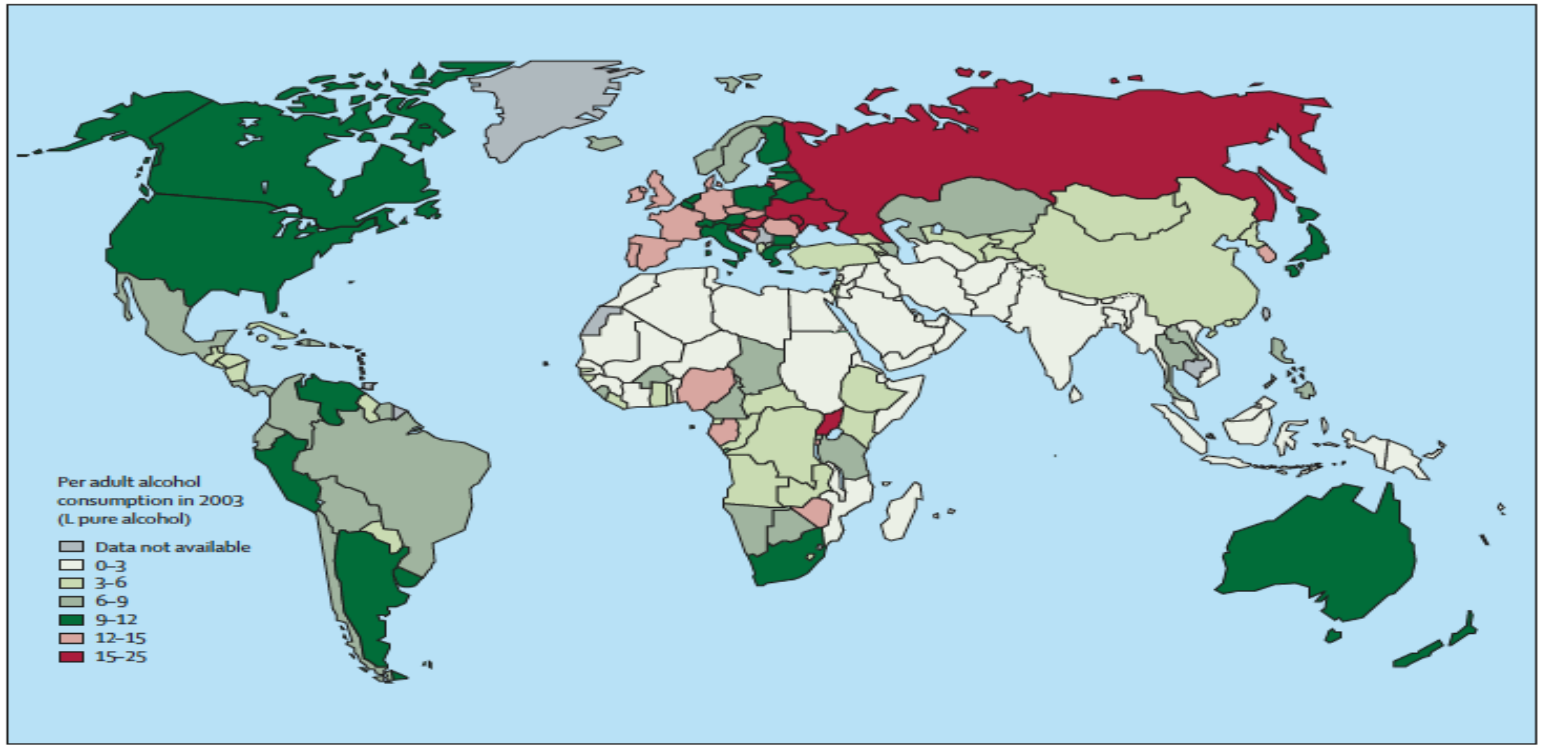
Alcoholic Hepatitis: Routine Screening for Early Recognition and Management

Juan Guerrero, MD

Texas Liver Institute

UT Health San Antonio School of Medicine

Global Problem



- 1% of GNP of medium/high income countries
- Additional societal costs
- Disproportionately affects low SES/marginalized populations
- 48% of cirrhosis-related deaths in US

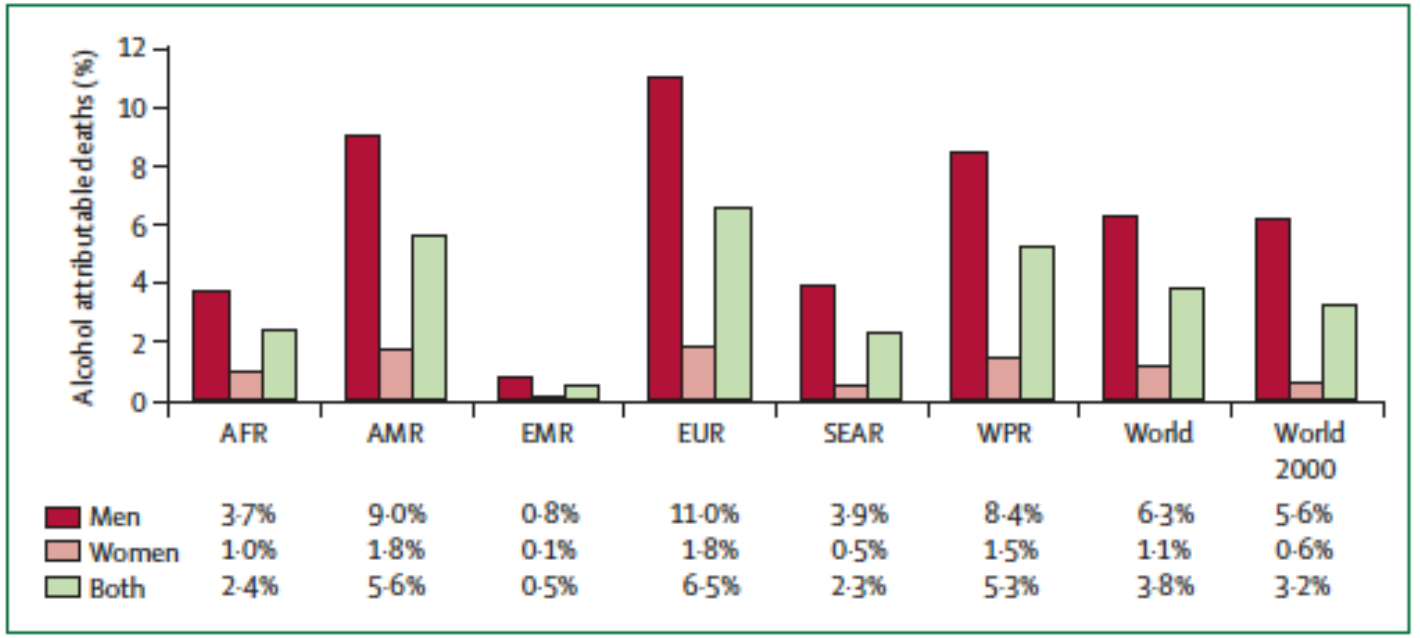
Rehm Lancet 2009.

Texas Liver Institute

UT Health San Antonio School of Medicine

Alcohol is a Major Burden

- 3.8% of **ALL** deaths worldwide in 2004
  - 6.3% for men vs. 1.1% for women
  - In population <70 yo: 15 per 10,000 men vs 3.5 per 10,000 women in Europe

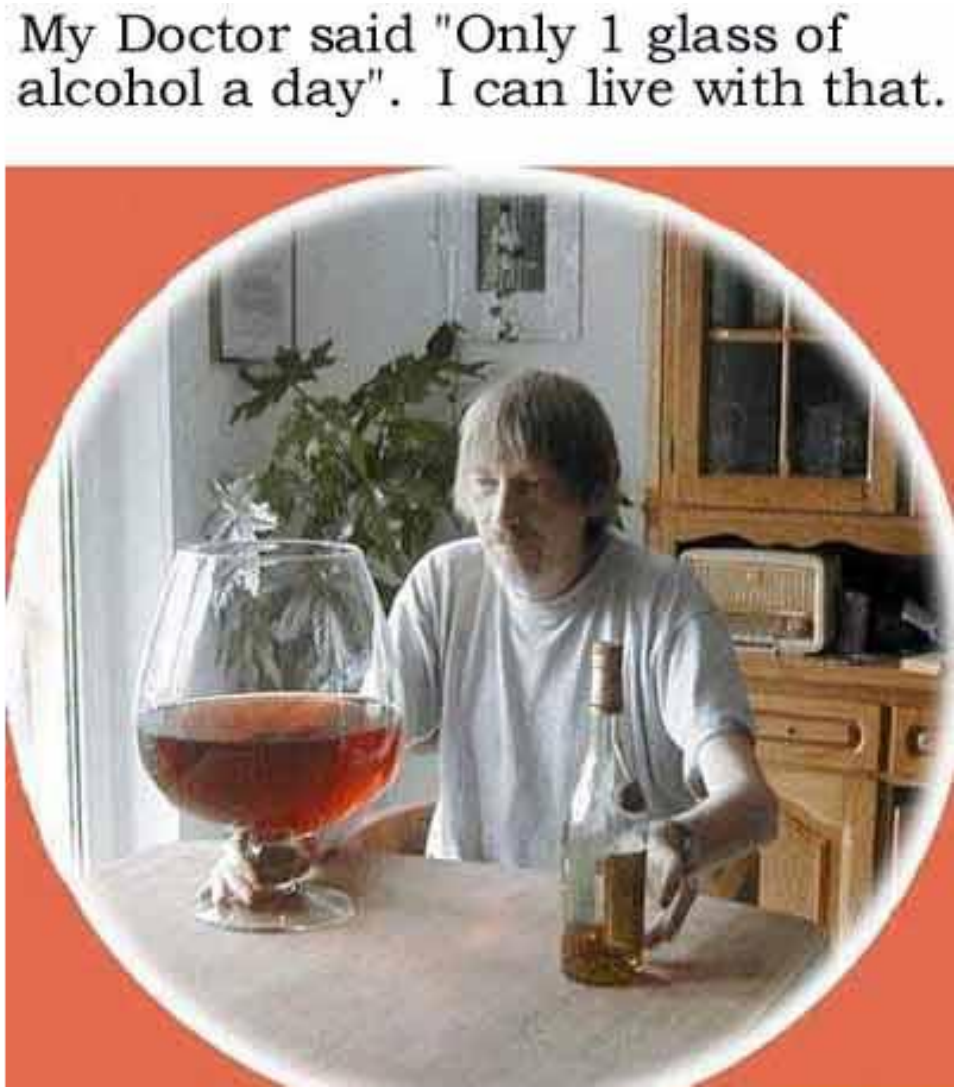


Rehm Lancet 2009.

Texas Liver Institute

UT Health San Antonio School of Medicine

How Much is Too Much?



Texas Liver Institute

UT Health San Antonio School of Medicine

Standard Drinks

10-12 g ETOH

Regular	Bud	= 1 drink
Light	Miller Lite	= .8 drink
Ice	Ice House	= 1.2 drink
Specialty / Micro-Brews	Sam Adams	= 1.3 drink
Malt Liquor		= 1.3 to 2 drinks
Tequila	40%, 80 proof	= 1 drink
Rum	75.5%, 151 proof	= 1.9 drinks
Vodka	40%, 80 proof	= 1 drink
Wine Coolers 12 oz.	6-8%, 12-16 proof	= 1 to 1.5 drinks
Everclear	95%, 190 proof	= 2 drinks

Texas Liver Institute

UT Health San Antonio School of Medicine

Long-term Consequences

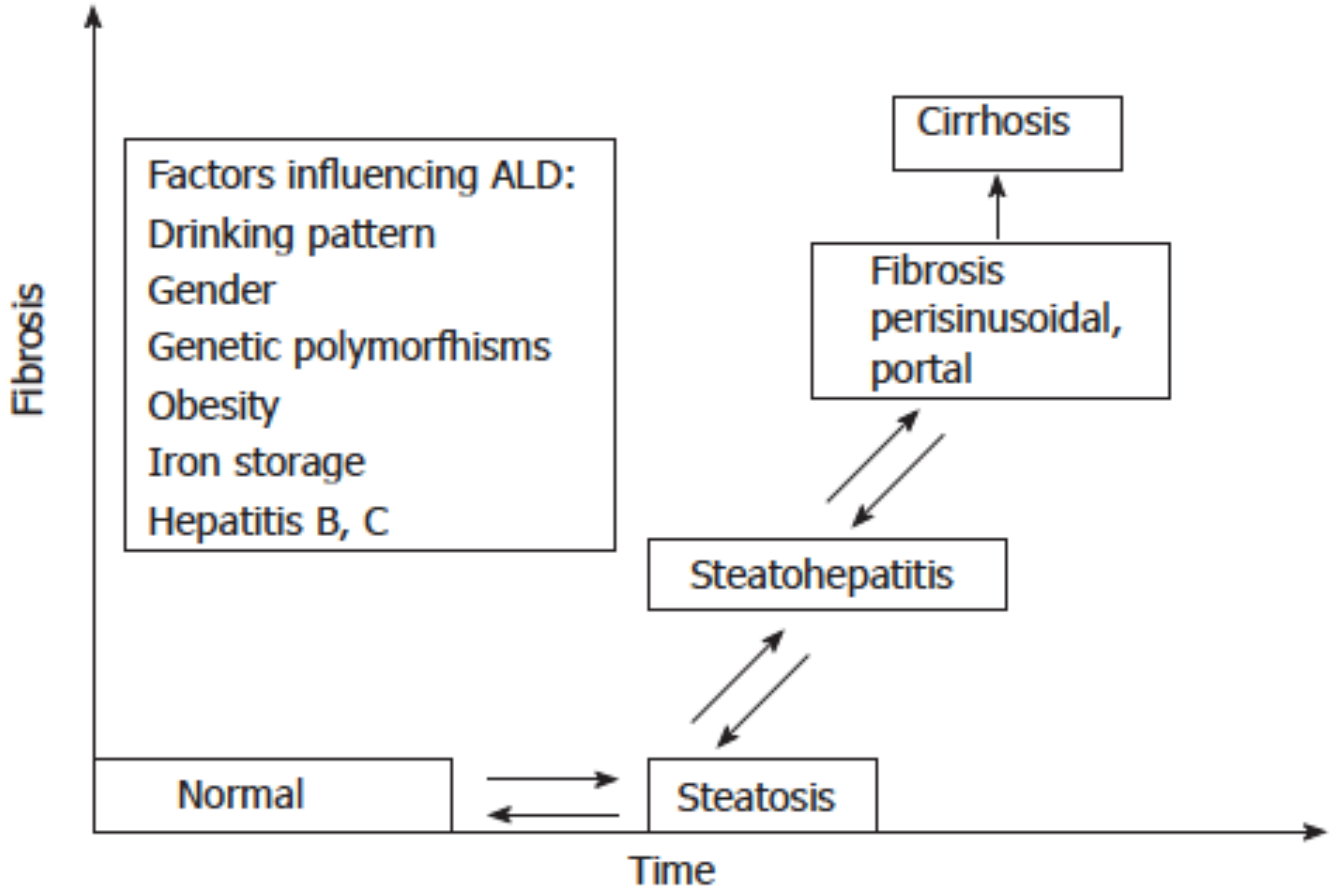
- How much causes problems?
  - Men: 60-80 grams/day x 10 years
  - Women: 20-40 grams/day x 10 years
- How many alcoholics develop cirrhosis?
  - Only 15-20% of chronic alcoholics develop chronic liver disease
  - Genetics clearly important but poorly understood

Texas Liver Institute
UT Health San Antonio School of Medicine

Other Risk Factors

- Sex
  - Females increased risk
- Drinking pattern
  - Daily drinking from a young age > binge/episodic
- Genetics
  - PNPLA3
- Co-factors
  - Obesity – NASH – or malnutrition (common)
  - Chronic liver disease – HCV/HBV
  - Fe overload
  - Smoking

Only a Minority Progress



Reversal with abstinence

Texas Liver Institute

UT Health San Antonio School of Medicine

Clinical Features
Acute Alcoholic Hepatitis

- History
  - Alcohol intake – usually binge, usually honest (not always)
  - Fever
  - Weight loss – malnutrition
- Exam
  - Toxic looking, fever, tachycardia
  - Tender hepatomegaly +/- bruit
  - Signs of CLD & MALNUTRTION – often severe

Acute alcoholic hepatitis vs decompensated alcoholic cirrhosis?
No reliable indicator aside from recent alcohol intake

Texas Liver Institute

UT Health San Antonio School of Medicine

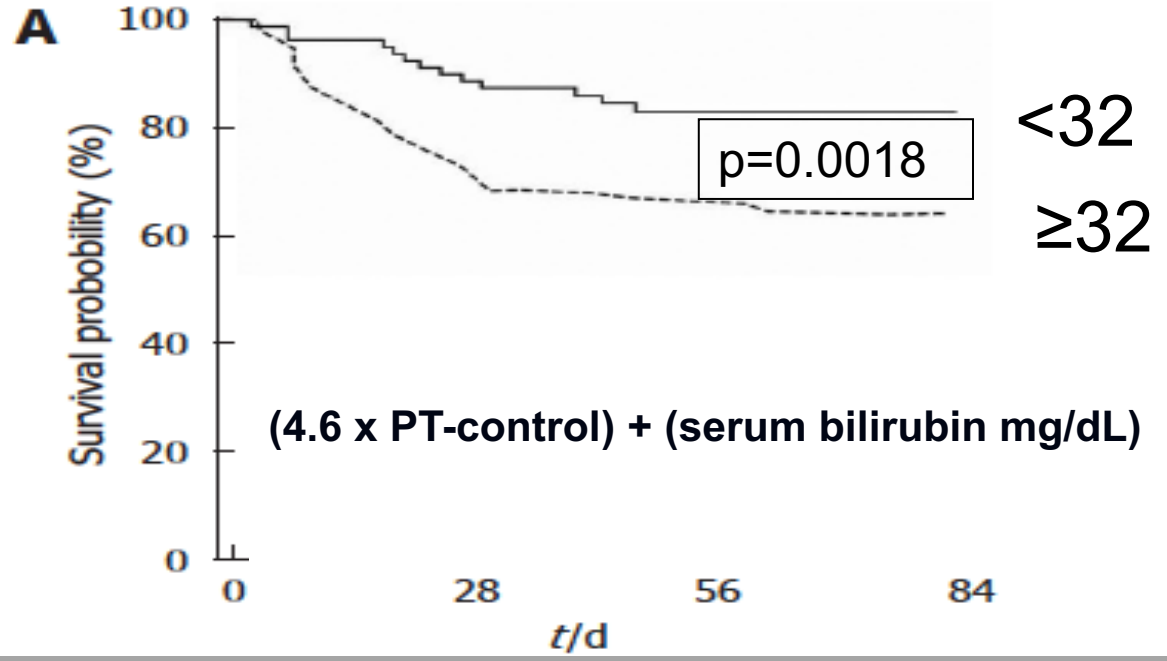
Lab Features

- Liver Tests
  - AST:ALT>2:1
    - Rarely above 300 (never above 500 IU/L)
    - AST increased due to mitochondrial damage
  - GGT +/- ALP elevation – may appear very cholestatic
  - Bilirubin & INR increased, Albumin depressed
- CBC
  - WBC elevation with PMNs → but may be infection
  - Low plt → direct BM suppression vs portal HTN
  - Low Hb → nutritional deficiency, bleeding
- Creatinine
  - Predictor of outcome – very important

Texas Liver Institute
UT Health San Antonio School of Medicine

Discriminant Function

Maddrey's (modified) discriminant function



(4.6 x PT-control) + (serum bilirubin mg/dL)

mDF ≥ 32
With encephalopathy 45% mortality
Without encephalopathy 35% mortality

More recent data → up to 100% survival <32 & 34% 28d mortality untreated cohorts

Maddrey, et al. *Gastroenterology*. 1978; Mathurin. *J Hep*. 2012; Kulkarni. *J Clin Gastro*. 2004.

Texas Liver Institute

UT Health San Antonio School of Medicine

Glasgow Alcoholic Hepatitis Score

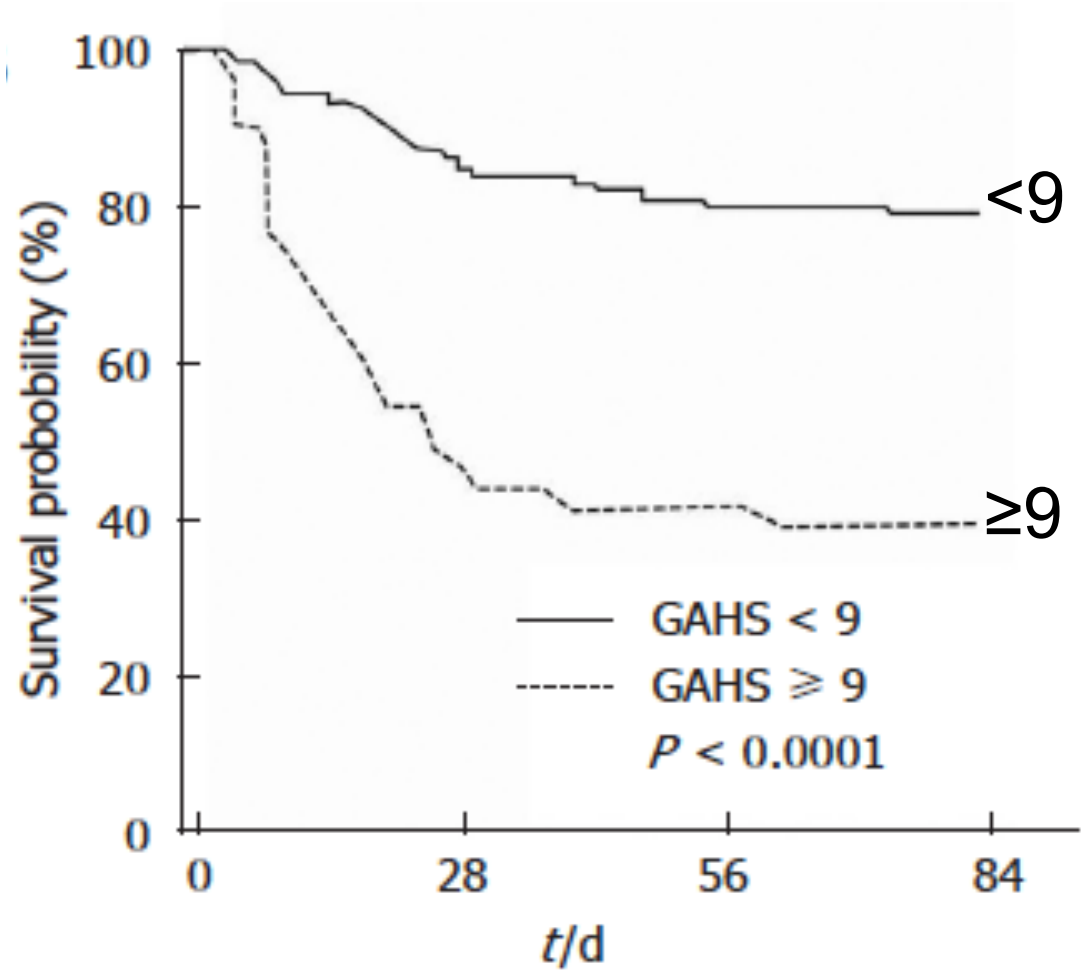


Table 1 Glasgow alcoholic hepatitis score[44]

Parameter/score	1	2	3
Age (yr)	< 50	⩾ 50	-
Leucocytes (10^9/L)	< 15	⩾ 15	-
Urea (mmol/L)	< 5	⩾ 5	-
INR	< 1.5	1.5-2	> 2
Bilirubin (μmol/L)	< 125	125-250	> 250

- Range 5 - 12 points
- ≥ 9 = bad prognosis

Forrest. *Gut*. 2005.

Texas Liver Institute

UT Health San Antonio School of Medicine

MELD Works Too

- MELD factors include: INR>creatinine> bilirubin
- MELD>21 associated with higher mortality
  - Particularly those with ascites and/or encephalopathy
- 30 day mortality
  - MELD sensitivity 75%, specificity 75%
  - DF sensitivity sensitivity 75%, specificity 69%
- 90 day mortality
  - MELD sensitivity 75%, specificity 75%
  - DF sensitivity sensitivity 88%, specificity 65%
- Similar data other studies

Dunn, et al. *Hepatology*. 2005.

Texas Liver Institute

UT Health San Antonio School of Medicine

Lille Score

- Formula allows predicting improved mortality after 7 days of steroid therapy
- Heavily weighted on change in bilirubin
- A score of >0.45 associated with ~25% 6 month survival vs 85% if <0.45
- Allows for decision making of steroid discontinuation and/or exploration of alternative txs

Texas Liver Institute
UT Health San Antonio School of Medicine

Treatment

Texas Liver Institute
UT Health San Antonio School of Medicine

Resuscitation

- Sick patients!
- Address other issues:
  - Ascites → tap to r/o SBP
  - Infection → very low threshold for antibiotics, culture often
  - Renal function → make sure fluid replete, no NSAIDs, careful with diuretics and contrast dye, albumin, albumin, albumin
  - Encephalopathy → lactulose, Xifaxan
  - Alcohol withdrawal → benzodiazepines
  - Nutrition
    - Vitamins B complex (Wernicke's)
    - Protein
    - Calories

Texas Liver Institute
UT Health San Antonio School of Medicine

Nutrition – CRITICAL!!

- 71 patients randomized:
  Prednisone 40 mg/d x 30 d vs
  Total Enteral Nutrition 2000 Kcal/d x 30 d
- Similar 30 d mortality – 9/36 vs 11/35
- 1 year mortality HIGHER with steroids
  - 10 of 27 vs 2 of 24 (p=0.025)
  - 9 of 10 steroid deaths due to infection

Nutrition comparable to steroids

Cabre. *Hepatology*. 2000.

Texas Liver Institute

UT Health San Antonio School of Medicine

Specific Therapies

- Lots of things evaluated…
  - Anabolic steroids
  - Insulin/glucagon
  - Colchicine
  - PTU
  - SAMe
  - Anti-TNF (infliximab/etanercept)

} No benefit

- Nutrition
- Steroids
- Pentoxyfilline
  - Both

} Let's discuss…

Texas Liver Institute

UT Health San Antonio School of Medicine

What About Steroids?

- Lots of trials
- Meta-analysis…15 RCTs (but ? good ones)
  - Mortality benefit if DF>32 or encephalopathy
    - RR 0.37 (0.16-0.86)
- 5 most recent RCTs…
  - N=418 → 80% vs 66% 28-day survival
- Prednisone 40 mg/day x 30 d
- Exclude: Active GI bleed,
  Renal failure
  Coma
  Active uncontrolled infection

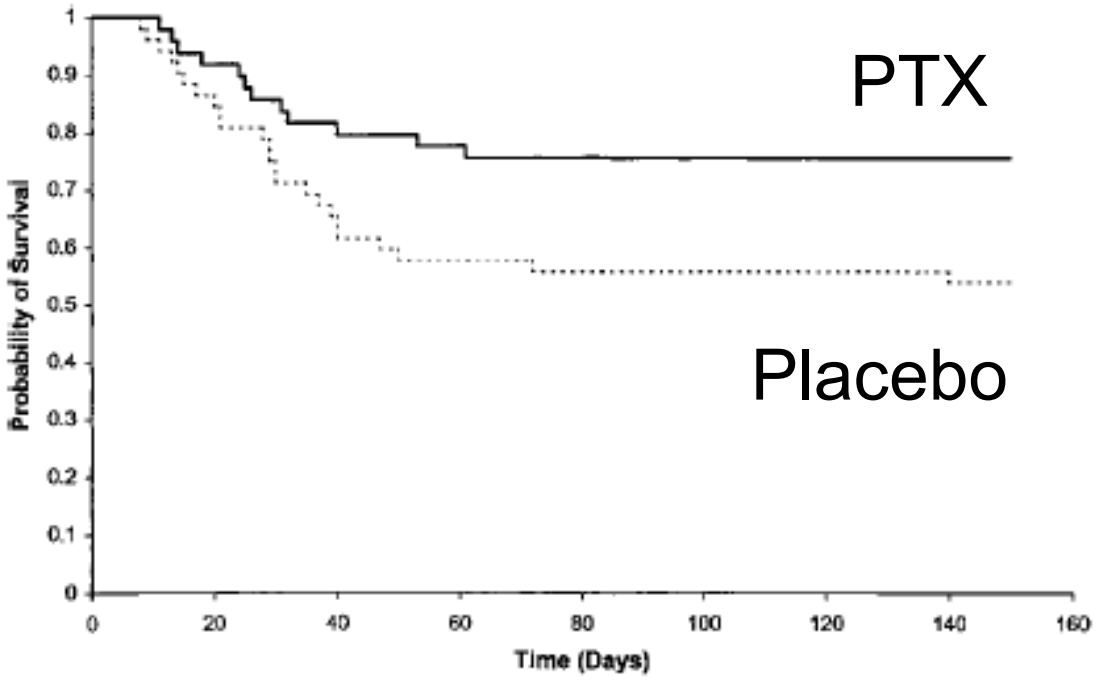
Reynolds. *Hepatology.* 1990; Mathurin P. *J Hep.* 2012; Louvet. *J Hep*. 2008.

Texas Liver Institute

UT Health San Antonio School of Medicine

Pentoxyfilline

Pentoxyfilline 400 mg PO TID vs placebo



- Deaths – 25% vs 46%
- Main benefit in reduction in mortality due to HRS
- Fairly well tolerated

This single study led to widespread adoption of PTX!

Akriviadis. *Gastro*. 2000.

Texas Liver Institute

UT Health San Antonio School of Medicine

ORIGINAL ARTICLE

Prednisolone or Pentoxifylline for Alcoholic Hepatitis

Mark R. Thursz, M.D., Paul Richardson, M.D., Michael Allison, Ph.D., Andrew Austin, M.D., Megan Bowers, M.Sc., Christopher P. Day, M.D., Ph.D., Nichola Downs, P.G. Cert., Dermot Gleeson, M.D., Alastair MacGilchrist, M.D., Allister Grant, Ph.D., Steven Hood, M.D., Steven Masson, M.A., Anne McCune, M.D., Jane Mellor, M.Sc., John O'Grady, M.D., David Patch, M.D., Ian Ratcliffe, M.Sc., Paul Roderick, Ph.D., Louise Stanton, M.Sc., Nikhil Vergis, M.B., B.S., Mark Wright, Ph.D., Stephen Ryder, D.M., and Ewan H. Forrest, M.D., for the STOPAH Trial*

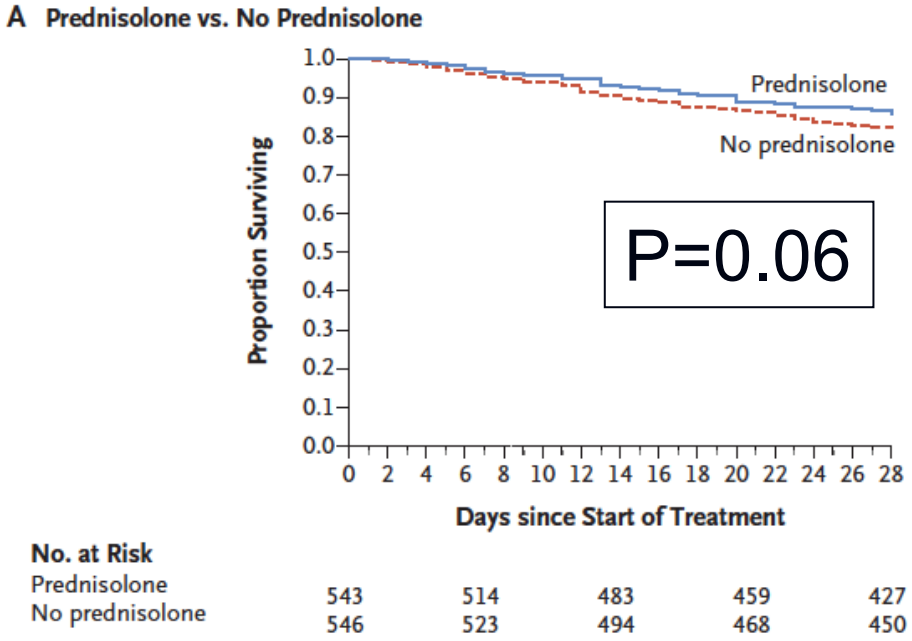
- Alc hep with DF>32, bili>4 with no active GI bleed or untreated infection
  - Prednisone – n=277
  - PTX – n=276
  - Pred + PTX – n=274
  - Placebo – n=276

Texas Liver Institute

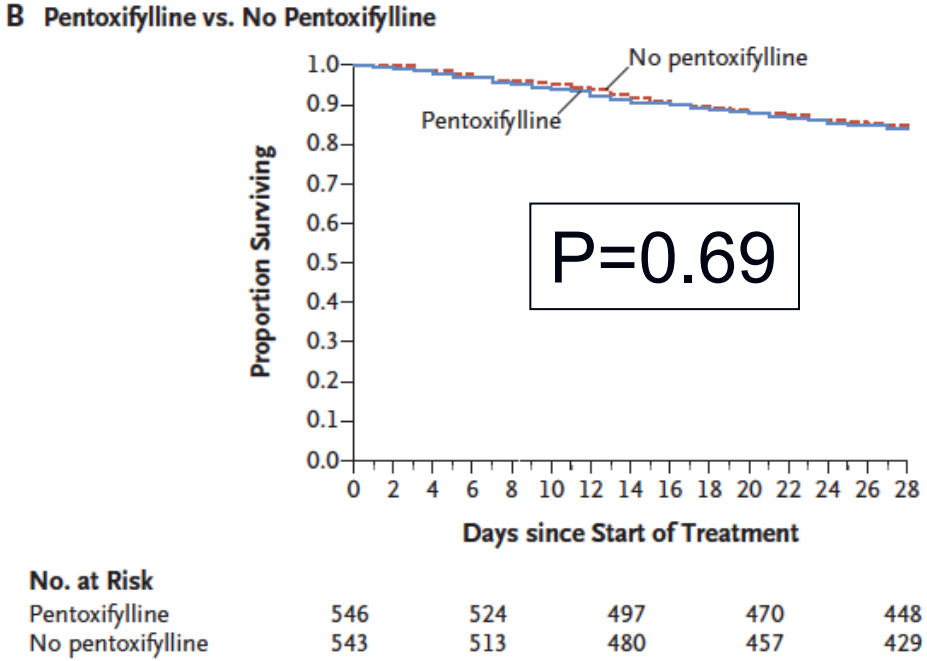
UT Health San Antonio School of Medicine

28 Day Survival – Primary Endpoint

Pred vs no Pred



PTX vs no PTX



- Trend toward benefit for prednisone
- No benefit of PTX
- Lower mortality than expected in placebo arm (17%)

Thursz. *NEJM*. 2015.

Texas Liver Institute

UT Health San Antonio School of Medicine

Short-term Benefit to Prednisone

Table 3. Analysis of Factors Associated with Mortality at 28 Days.*

Variable	Univariate Analysis†		Multivariate Analysis‡	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Prednisolone vs. no prednisolone			0.61 (0.41–0.91)	0.02
Pentoxifylline vs. no pentoxifylline			1.10 (0.74–1.64)	0.62
Discriminant function	1.02 (1.02–1.03)	<0.001		
GAHS	2.17 (1.86–2.53)	<0.001		
MELD	1.15 (1.12–1.18)	<0.001		
Lille§	1.03 (1.02–1.03)	<0.001		
Prothrombin ratio or INR	1.38 (1.10–1.73)	0.005	1.38 (1.13–1.69)	0.002
Age	1.05 (1.03–1.07)	<0.001	1.05 (1.03–1.07)	<0.001
White cells	1.06 (1.03–1.08)	<0.001	1.03 (1.00–1.06)	0.04
Urea	1.14 (1.10–1.18)	<0.001	1.06 (1.01–1.12)	0.01
Creatinine	3.07 (2.32–4.08)	<0.001	1.56 (1.05–2.33)	0.03
Pyrexia	0.66 (0.37–1.16)	0.15		
Hypotension	1.20 (0.79–1.83)	0.39		
Tachycardia	1.09 (0.71–1.65)	0.70		
Alcohol intake	1.00 (1.00–1.00)	0.37		
Albumin	0.99 (0.96–1.02)	0.41		
Alkaline phosphate	1.00 (1.00–1.00)	0.07		
Bilirubin	1.07 (1.05–1.09)	<0.001	1.03 (1.01–1.06)	0.003
Hepatic encephalopathy	3.70 (2.59–5.29)	<0.001	3.07 (2.05–4.60)	<0.001

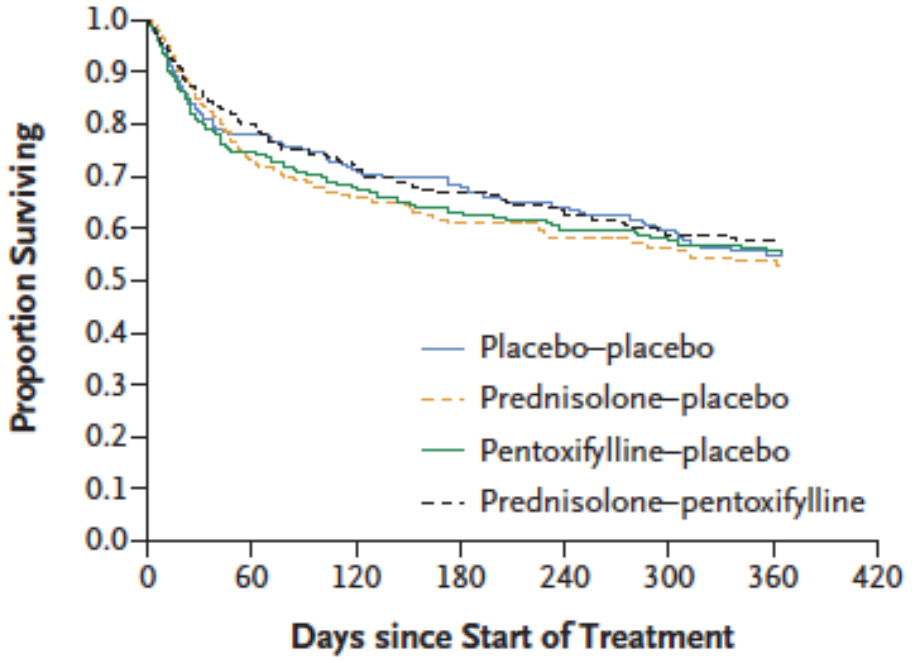
Adjusting for baseline factors – modest benefit to steroids

Texas Liver Institute

UT Health San Antonio School of Medicine

No Long-term Benefit

C One-Year Survival in All Groups



No. at Risk

Placebo–placebo	272	199	159	142	121	104	89
Prednisolone–placebo	274	182	139	116	102	91	84
Pentoxifylline–placebo	271	178	133	119	104	95	83
Prednisolone–pentoxifylline	272	201	157	137	115	101	84

Beyond 28 d, only abstinence associated with survival

Texas Liver Institute

UT Health San Antonio School of Medicine

Take Home Messages

- PTX of no benefit
- Prednisone likely has a modest EARLY benefit but no long-term benefit
- ABSTINENCE is key (and the only thing that probably matters)

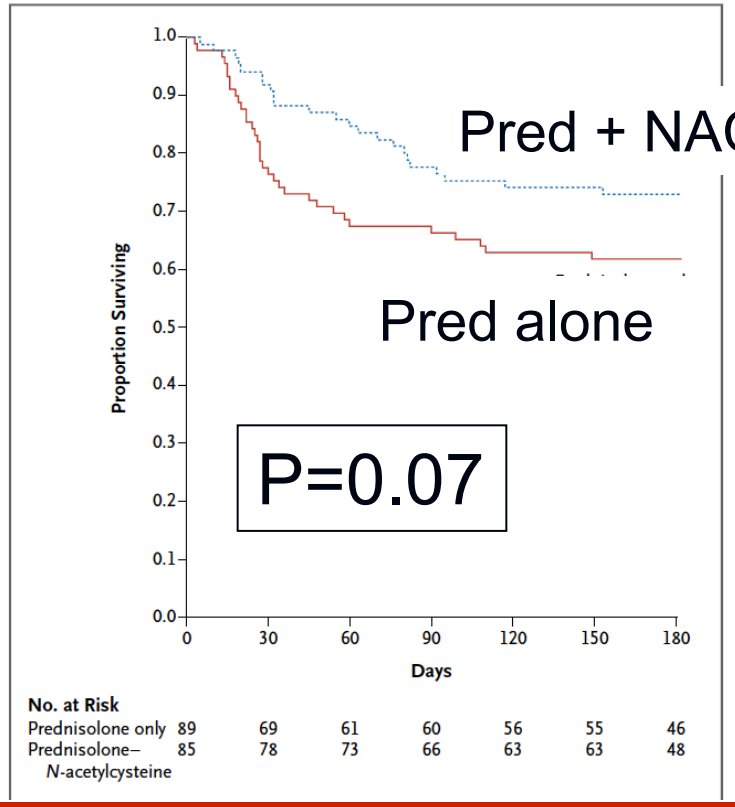
Consider using prednisone because you need to get them through the first month to give them a chance to be abstinent!

Texas Liver Institute

UT Health San Antonio School of Medicine

Would NAC help?

Alc Hep with DF>32 → Pred + NAC vs Pred alone x 30 d



- Fewer infections in Pred + NAC group
- Improved bilirubin at day 7 = 90% 6 m survival vs 10% with no change!

Nguyen. *NEJM*. 2011.

Texas Liver Institute

UT Health San Antonio School of Medicine

Summary

- Alcoholic liver disease causes a huge burden of illness worldwide
- Only a minority of heavy drinkers develop cirrhosis
- Acute alcoholic hepatitis has a poor prognosis
- Multiple scoring systems – all useful
  - mDF most widely used
  - Lille helps guide therapy
- Treatment: NUTRITION, supportive care, steroids, +/- NAC → ABSTINENCE!
- Assess response at day 7 and stop if no response
- Long-term – abstinence is EVERYTHING!

Roundtable/Q&A

Drs. Poordad, Alkhouri and Guerrero

Texas Liver Institute

UT Health San Antonio School of Medicine