II CURSO DE HEPATOLOGÍA CLÍNICA

"Lo Mejor de ALEH, AASLD, APASL y EASL"
II ALEH Clinical Course on Hepatology
"The Best of ALEH, AASLD, APASL & EASL"
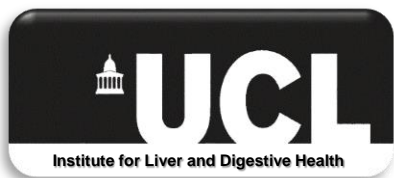
2 Y 3 DE MAYO, 2019
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Alcoholic hepatitis

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UCL
Institute for Liver and Digestive Health

Royal Free London NHS
NHS Foundation Trust

Summary

- Epidemiological data

- Clinical and laboratory findings

- Prognostic scores

- Treatment

- Liver transplantation

Deaths due to alcohol

Rehm Lancet 2009
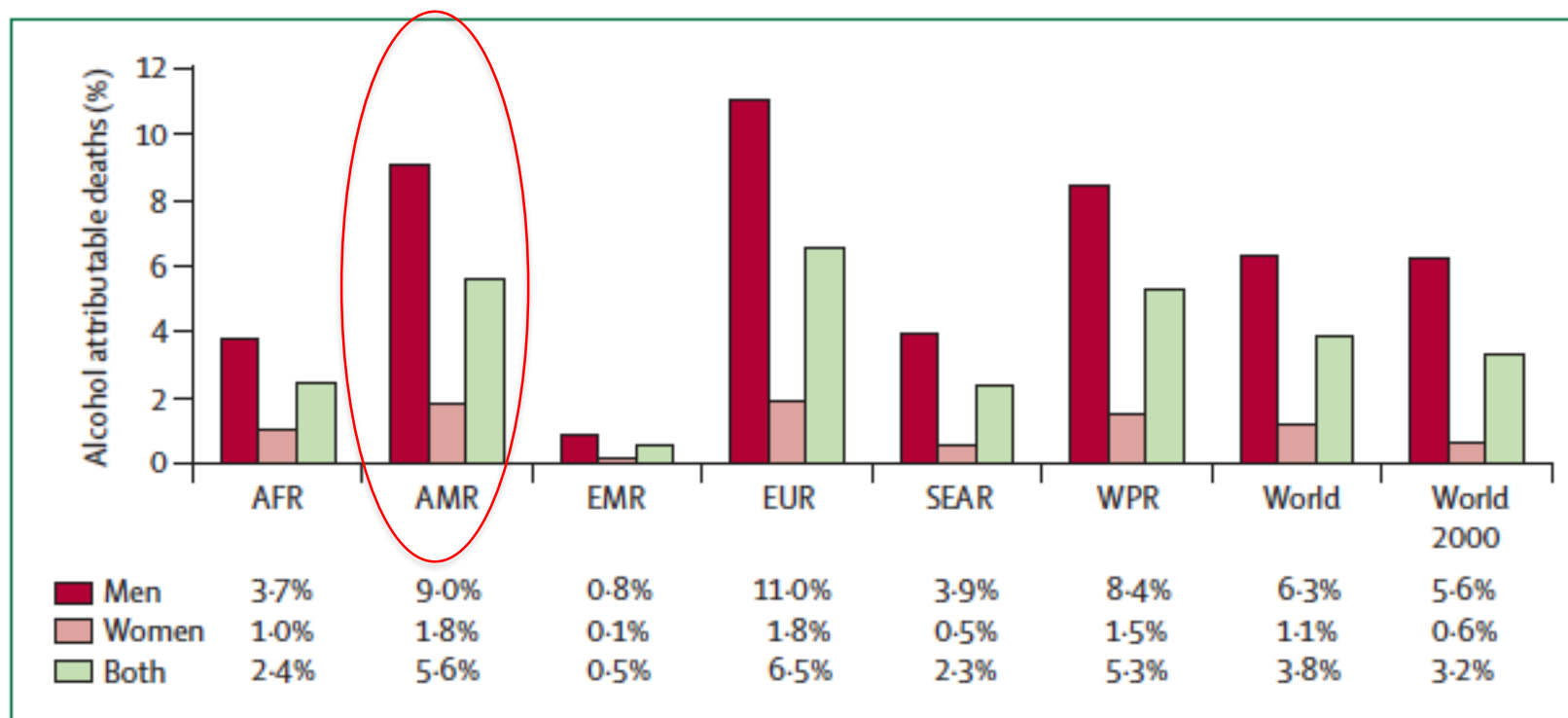
Global burden of alcohol consumption

Table 3. Global burden of alcohol consumption.

	Liters per capita 2005	Liters per capita 2010	Prevalence of alcohol use disorders, 2010 (%)	Prevalence of alcohol dependence, 2010 (%)
Africa	6.2	6.0	3.3	1.4
Americas	9.2	8.4	6.0	3.4
South-East Asia	2.9	3.5	2.2	1.7
Europe	9.1	10.9	7.5	4.0
Eastern Mediterranean	0.7	0.7	0.3	0.2
Western Pacific	5.4	6.8	4.6	2.3
(WHO) Global	5.6	6.2	4.1	2.9

Data available from Global Status Report on Alcohol and Health 2014, Geneva, World Health Organization; 2014.

Progression of ALD

Normal liver

$\downarrow$ 90-100%

Fatty liver

10-35%   8-20%

Alcoholic hepatitis → Cirrhosis

?40%
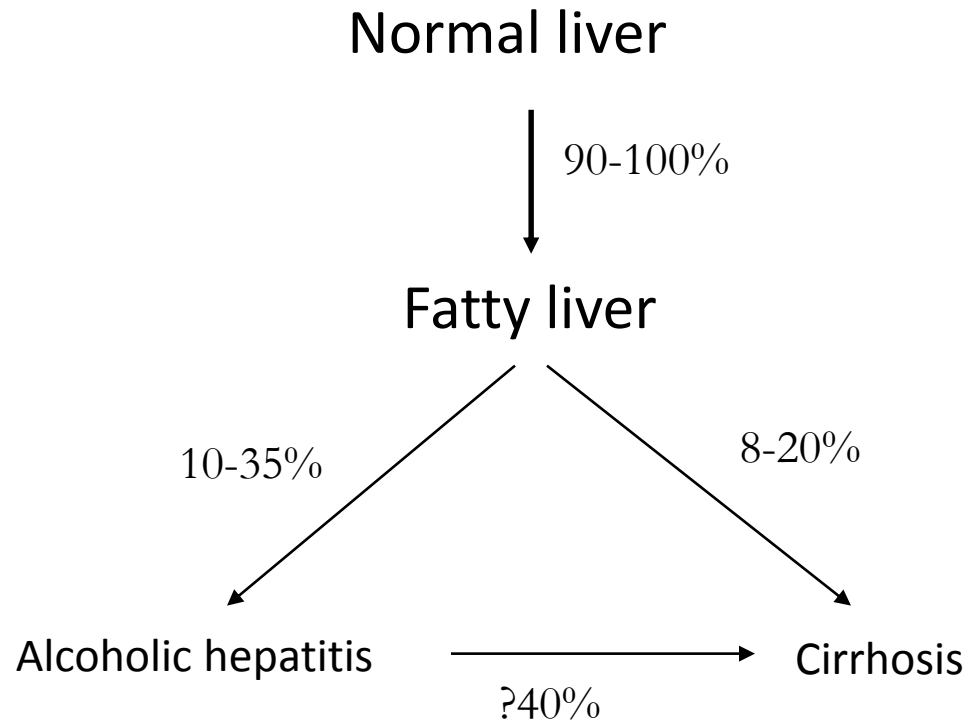
Symptoms of AH

- **Sudden onset of jaundice**

- History of significant alcohol consumption

- Sometimes alcohol cessation 1-2 months before

- Often first presentation of liver disease

- Ascites and/or encephalopathy

Clinical findings

- Hepatomegaly

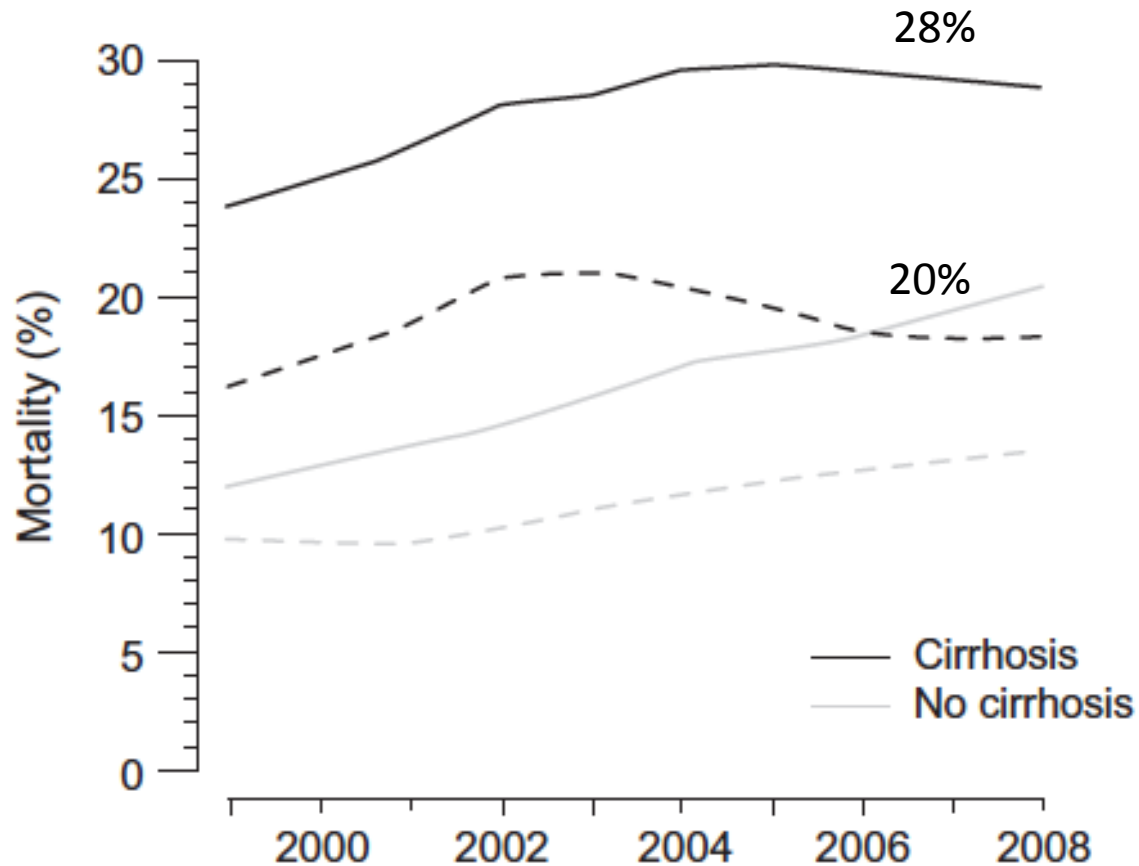- Hepatic bruit

- SIRS

- Loss of muscle mass

- Ascites

Laboratory findings

- Leukocytosis

- Abnormal transaminases but <300-400 IU/ml

  (alternative/additional diagnosis if higher)

- AST>ALT

- Prolonged prothrombin time (but administer vit K)
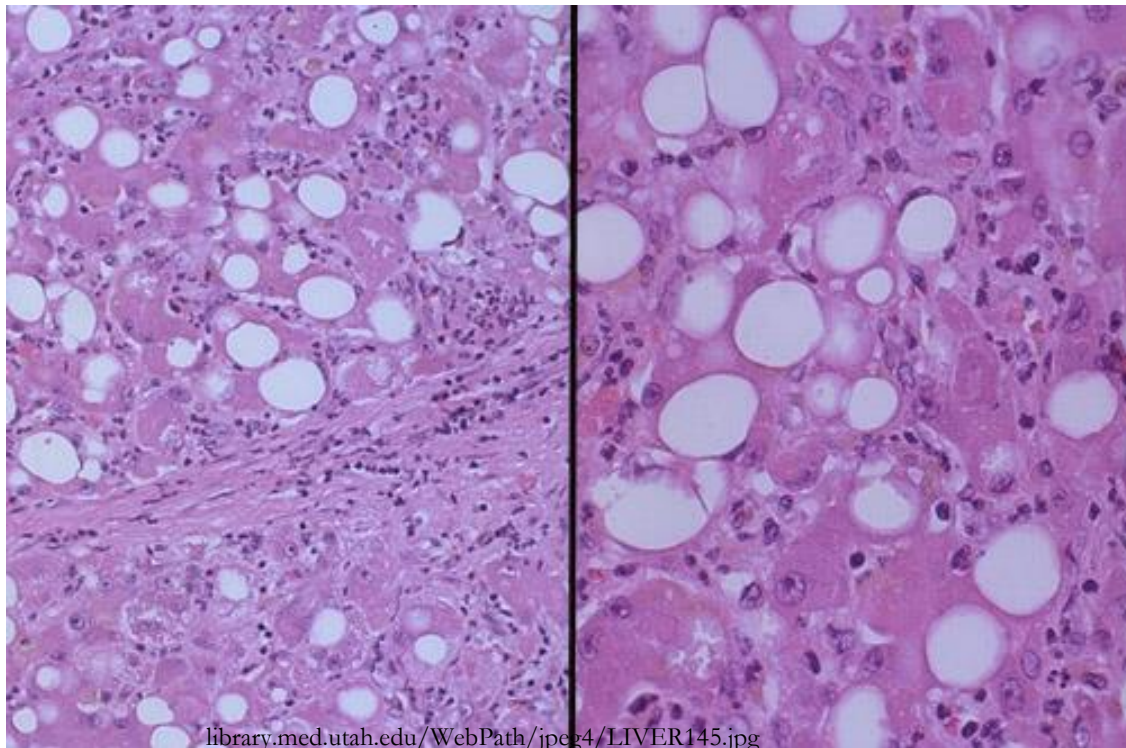
- Renal dysfunction poor prognostic marker

Mortality

28- and 84- day mortality

Denmark 1999-2008
1951 patients with AAH

Sandahl J Hepatol 2011

Histological findings

Neutrophilic infiltrate and hepatocyte necrosis

neutrophils, necrosis of hepatocytes, collagen deposition, and fatty change. These findings are typical for acute alcoholic hepatitis

library.med.utah.edu/WebPath/jpeg4/LIVER145.jpg

Disease severity and prognosis

- **Maddrey DF = (4.6xPT) + serum bilirubin (mg/dl)**

- **MELD = 3.8xloge(bili mg/dl) +1.2xloge(INR)+9.6xloge(creat mg/dl)**

- **Glasgow Acute Hepatitis Score (GAHS)**

- **Lille model** (response to steroids in day 7)

Prognostic scores

	Bilirubin	INR	Creatinine	WCC	Age	Albumin	ΔBil (0-7)
Maddrey	+	+					
MELD	+	+	+				
GHAS	+	+	+	+	+		
Lille	+	+	+		+	+	+

Maddrey's Discriminant Function

4.6 x (patient's PT-control PT) + bilirubin (mg/dl)

- Developed in 1978, modified in 1989 (mDF)

- mDF≥32 identifies severe AH (50% mortality at 1mo): threshold for Tx
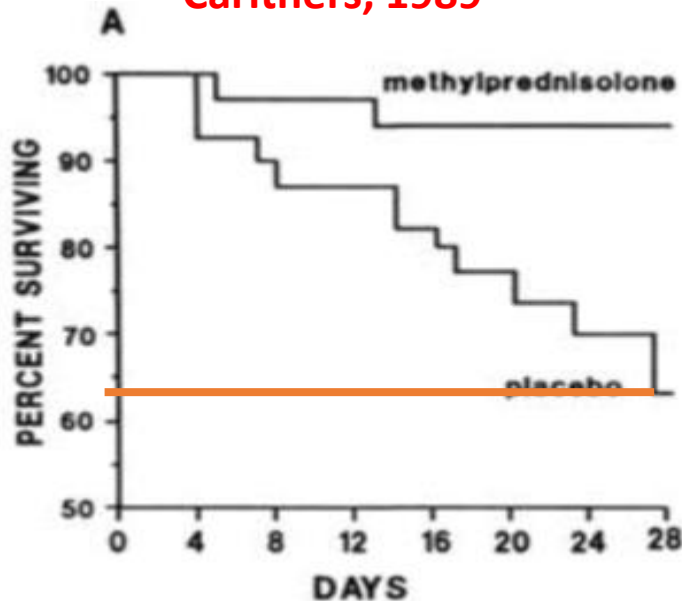
- mDF<32: <10-20% mortality at 1mo
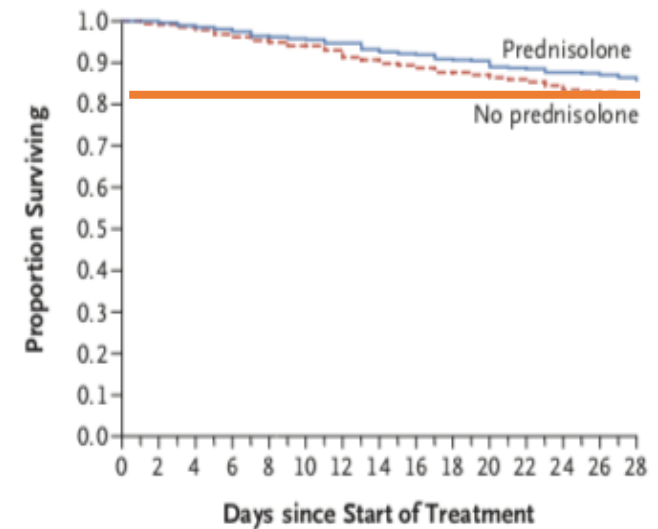
PROS

- Best validated model
- Easy to calculate

CONS

- Poor standardization of PT
- Does not incorporate Creatinine
- Lacks specificity (overtreatment?)
- 32 cut-off may be obsolete

Maddrey, Gastroenterology, 1978
Carithers, Ann Intern Med, 1989
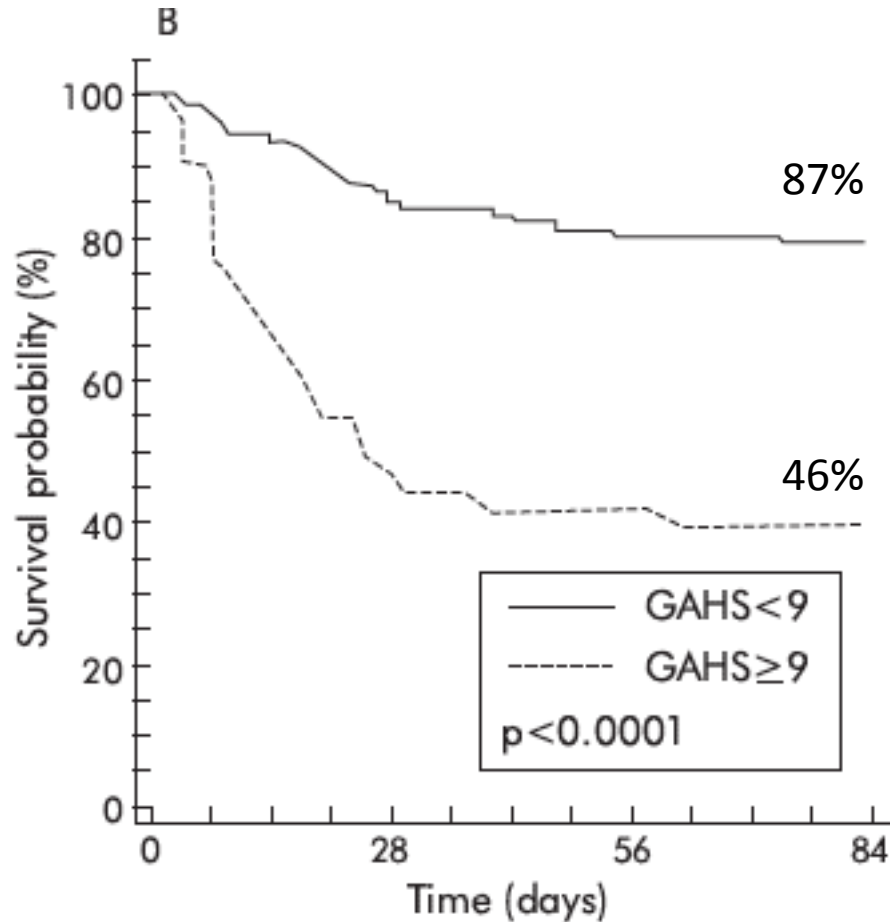
Carithers, 1989

Thursz, 2015 (STOPAH)

- Survival of untreated pts with sAH has improved over the years!!! (advances in supportive care?)
- **Do we need to re-calibrate mDF?**

Author/Journal/year	Optimal mDF cut-off
Dunn/Hepatology/2005	37
Sheth/BMC Gastroenterol/2002	42
Papastergiou/APT/2014	44

Glasgow acute hepatitis score (GAHS)

	1	2	3
Age	<50	>50	
WBC	<15	>15	
Urea	<5	>5	
INR	<1.5	1.5-2.0	>2.0
Bilirubin	<125	125-250	>250

Forrest Gut 2005

Glasgow acute hepatitis score

87%

46%

	Sens	Spec
GAHS	54	89
DF	82	39

Forrest Gut 2005

A — GAHS <9

- P=n.s. — Day 28: Corticosteroid 80%, No treatment 84%
- P=n.s. — Day 84: Corticosteroid 68%, No treatment 73%

n=81/225 (36%)

B — GAHS ≥9

- P=0.002 — Day 28: Corticosteroid #78%, No treatment #52%
- P=0.02 — Day 84: Corticosteroid *59%, No treatment *38%
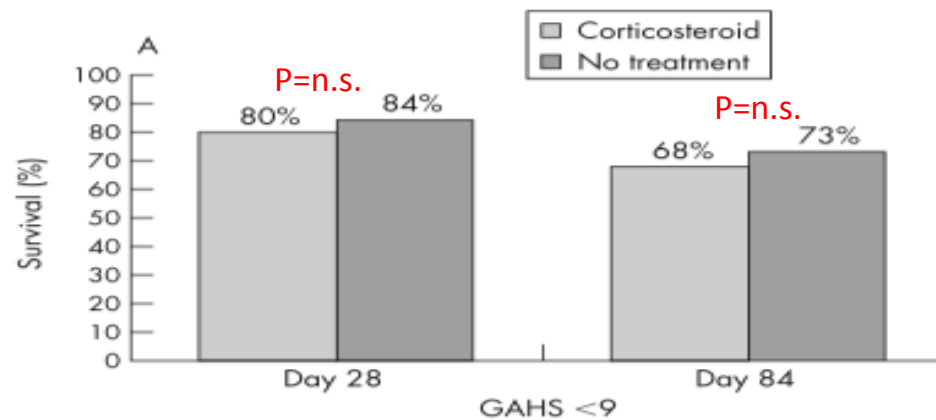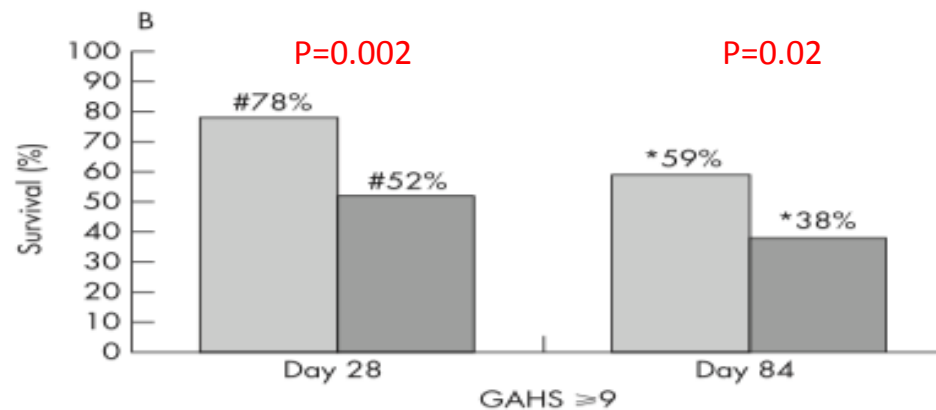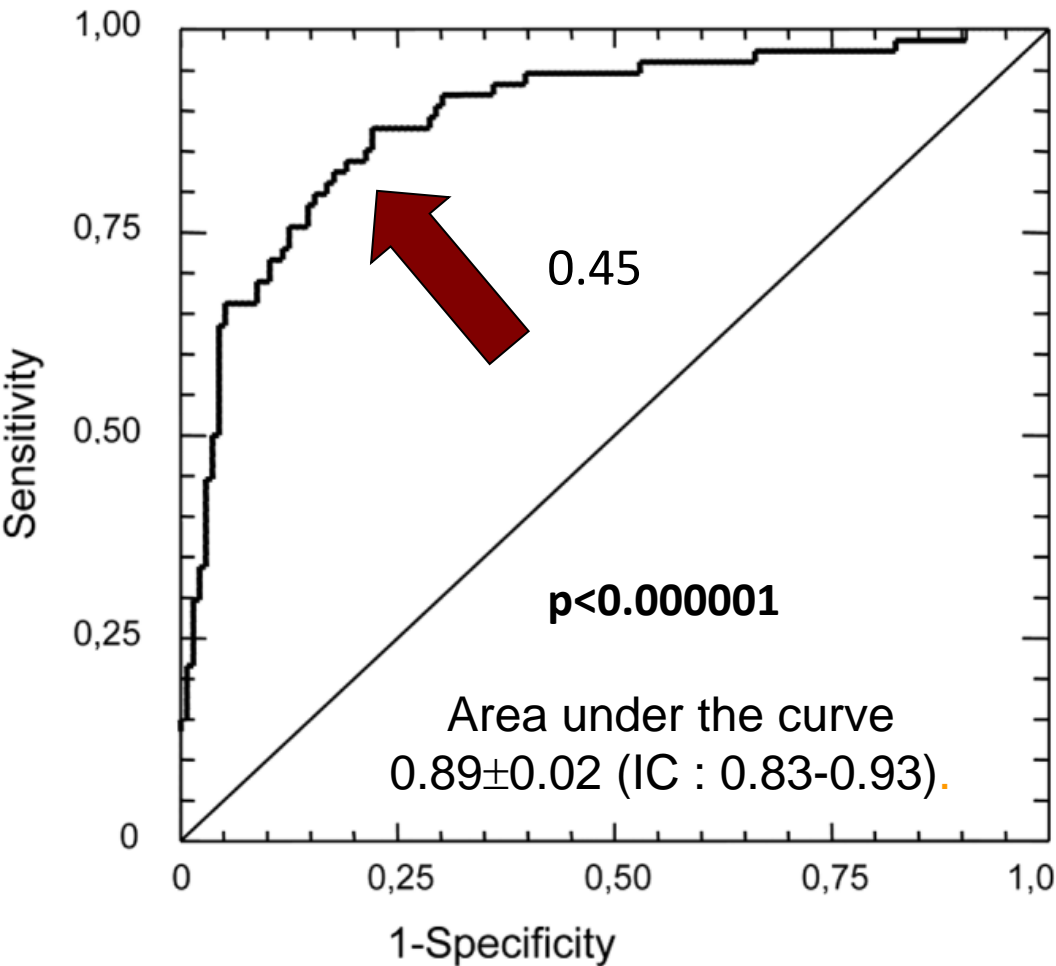
n=144/225 (64%)

- **Among Pts with mDF≥32, GAHS identifies those with extremely poor prognosis who will benefit from Tx**

Forrest, Gut, 2007
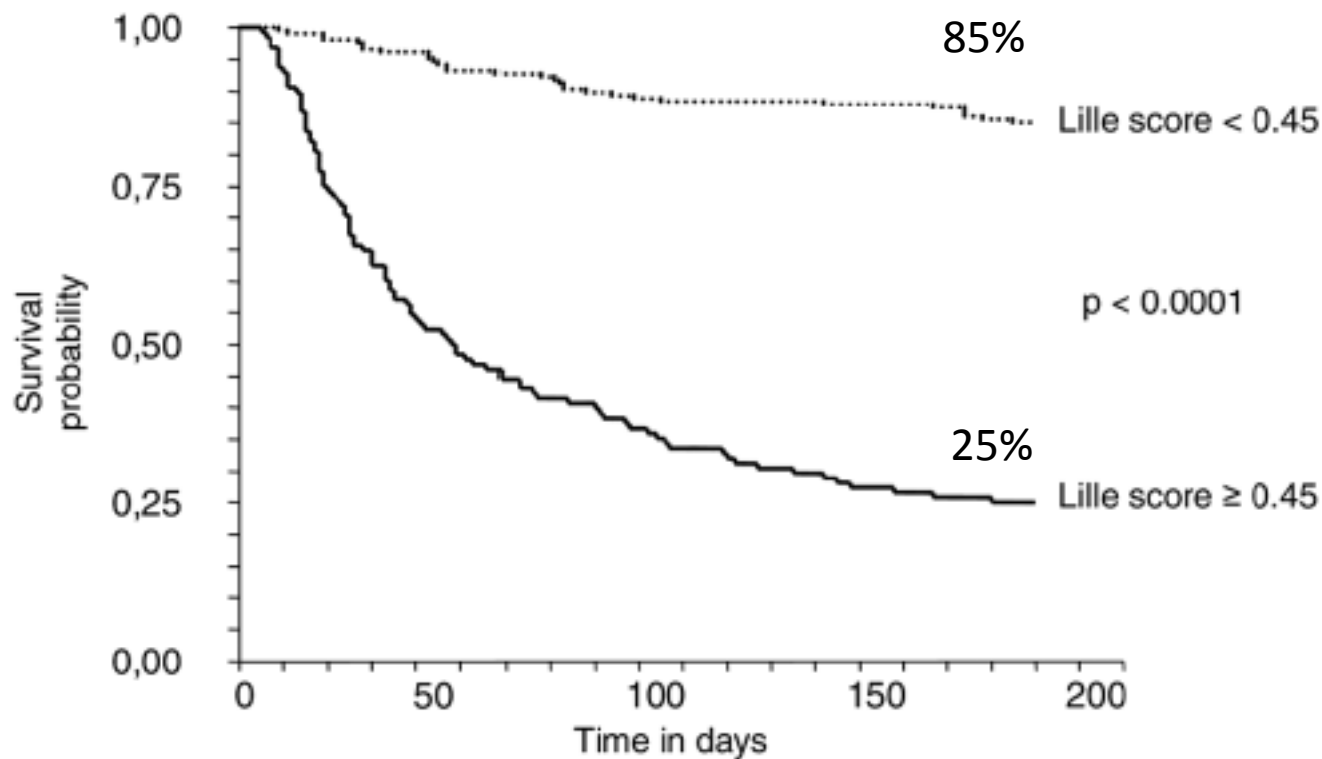
Prognostic models in severe alcoholic hepatitis
Lille Model

0.45

p<0.000001

Area under the curve
0.89±0.02 (IC : 0.83-0.93).

Sensitivity

1-Specificity

Assessment of steroid treatment response at day 7

www.lillemodel.com

Louvet, Hepatology 2007

Prognostic models in severe alcoholic hepatitis
Lille Model

85%

Lille score < 0.45

p < 0.0001

25%

Lille score ≥ 0.45

Survival probability — Time in days

Better than change from day 0-7 in DF, GAHS, MELD

Louvet, Hepatology 2007

Treatment

- Supportive measures

- Lifelong alcohol abstinence

- Specific treatment in those with poor prognosis

  (DF≥32 and/or encephalopathy)

Supportive measures

- Vitamin B complex and thiamine

- Vitamin K stat dose IV

- Prevention of withdrawal symptoms

  - chlomethiazole   (Heminevrin)

  - chlordiazepoxide (Librium)

- **Risk stratification**

Alcohol withdrawal syndrome

- Mild/moderate (6-24hrs): nausea/vomiting, hypertension, tachycardia, tremors, irritability, anxiety, headache

- Severe: **delirium tremens**, seizures, coma, death (5-15%)

❏ **TREAT if CIWAA≥8**
❏ **Patients with moderate/severe AWS should be monitored in the ICU**

Appendix. Clinical Institute Withdrawal Assessment for Alcohol.*

Category	Range of Scores	Examples
Agitation	0–7	0=normal activity 7=constantly thrashes about
Anxiety	0–7	0=no anxiety, at ease 7=acute panic states
Auditory disturbances	0–7	0=not present 7=continuous hallucinations
Clouding of sensorium	0–4	0=oriented, can do serial additions 4=disoriented as to place, person, or both
Headache	0–7	0=not present 7=extremely severe
Nausea or vomiting	0–7	0=no nausea, no vomiting 7=constant nausea, frequent dry heaves and vomiting
Paroxysmal sweats	0–7	0=no sweat visible 7=drenching sweats
Tactile disturbances	0–7	0=none 7=continuous hallucinations
Tremor	0–7	0=no tremor 7=severe, even with arms not extended
Visual disturbances	0–7	0=not present 7=continuous hallucinations

* The Clinical Institute Withdrawal Assessment for Alcohol measures 10 categories of symptoms, with a range of scores in each. The maximal score is 67. Minimal-to-mild withdrawal symptoms result in a total score below 8; moderate withdrawal symptoms (marked autonomic arousal), in a total score of 8 to 15; and severe withdrawal symptoms, in a total score of more than 15. High scores are predictive of seizures and delirium.

Kosten, NEJM, 2003
ACG CPG, 2018

Nutrition

- Malnutrition central feature in severe AH and associated with poor prognosis

- Daily calorie intake <21.5kcal/kg/day: increased 6-mo mortality (65.8% vs 33.1, p<0.001)

- Recommended energy intake: 35-40 kcal/kg (protein: 1.1-1.5 gr/kg)

- Replace: Thiamine, B complex vitamins, zinc other trace elements

- **ENT>PNT** ($\downarrow$ bacterial translocation, line sepsis)

- NGT strongly recommended (premature withdrawal: 48.5%)

- Steroids+intensive* ENT=steroids (6mo mortality: 44 vs 52%, p=0.4)

*Fresubin HP Energy® via NGT for 14days: 1500-3000 Kcal based on BW

EASL CPG, 2018
Moreno, Gastroenterology, 2015

Pharmacotherapy

- Consider in patients with DF≥32 and/or encephalopathy

- Steroids

- Screen for infection

  (Chest XR, blood, urine and ascitic fluid cultures)

Pentoxifylline (PTX) for severe AH

- Oral non-selective phosphodiesterase inhibitor (approved for intermittent claudication)
- Inhibition of TNF-a
- Reno-protective effect ??? (action on renal microcirculation/haemodynamics)

➢ Landmark RCT: PTX Vs Placebo for 28 days (n=101) ➔improvement in 28d survival (76% vs 54%, p=0.03) attributed to prevention of HRS (50% vs 92%, p=0.009)

Akriviadis, Gastroenterology, 2000

➢ Systematic Review (10 trials, 884 pts) ➔↓Incidence of fatal HRS (RR:0.47), but...NO IMPACT ON 1-mo SURVIVAL
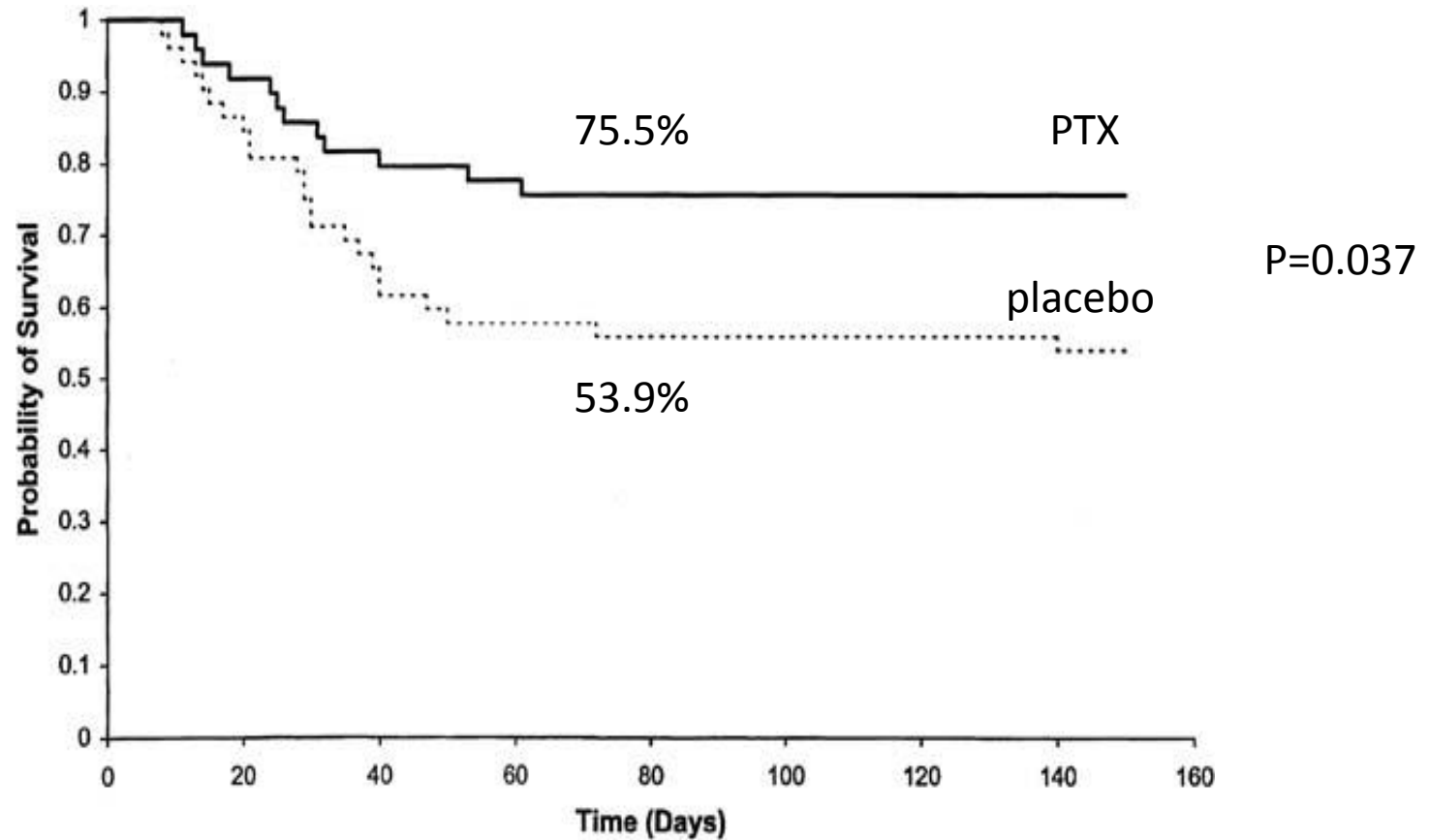
Parker, APT, 2012

➢ Steroids + PTX=Steroids alone

Sidhu, DDS, 2012
Mathurin, JAMA, 2013

➢ No benefit from early switch to PTX in steroid non-responders

Louvet, J Hep, 2008

Pentoxifylline

101 ασθενείς

Steroids for severe AH

Potential mechanisms

- ↓ circulating cytokines (TNF-a, IL-8, ICAM-1)
- ↓ formation acetaldehyde products
- Restoration PMN function (anti-inflammatory)
- Inhibition collagen production (anti-fibrotic)

**Pros**

- Improve short-term survival (marginally)

Cons

- No impact on medium/long-term survival
- Increased risk of sepsis
- Contraindications (avoid in active infection, GI bleed, severe kidney injury, acute pancreatitis, HBV, TB)
- 30-40% of pts with sAH will not respond to Tx

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*

❑**RCT** with **2x2 factorial design** (4 randomization groups)

❑**1103 pts with severe (mDF≥32) AH** from **65 UK hospitals** (2011-2014)

Placebo + Placebo	Prednisolone + Placebo	PTX + Placebo	Prednisolone + PTX
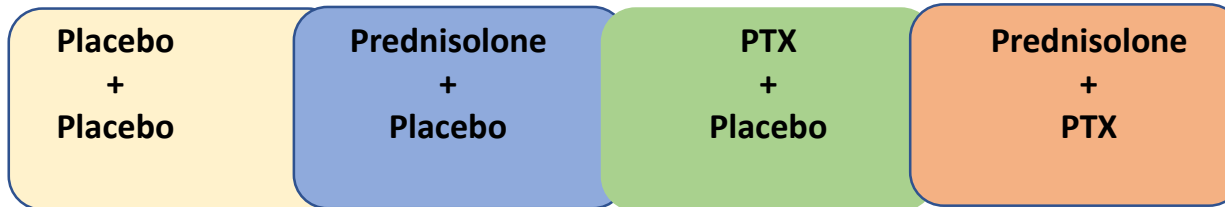
Thursz, NEJM, 2015
(STOPAH)

STOPAH trial: Survival at 28 days

A Prednisolone vs. No Prednisolone

Proportion Surviving vs. Days since Start of Treatment

Prednisolone
No prednisolone
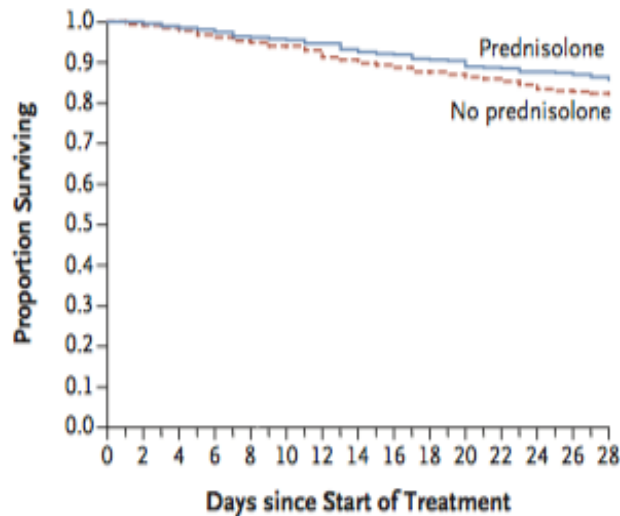
No. at Risk

Prednisolone	543	514	483	459	427
No prednisolone	546	523	494	468	450

OR: 0.72 (95%CI: 0.52-1.01; P=0.06)

B Pentoxifylline vs. No Pentoxifylline

Proportion Surviving vs. Days since Start of Treatment

No pentoxifylline
Pentoxifylline
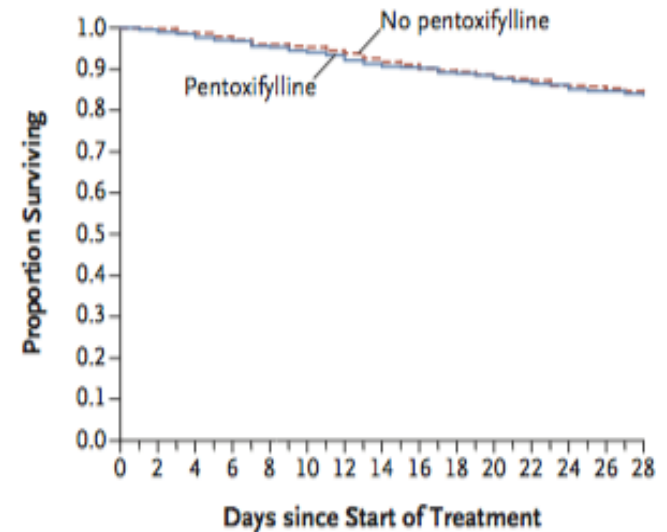
No. at Risk

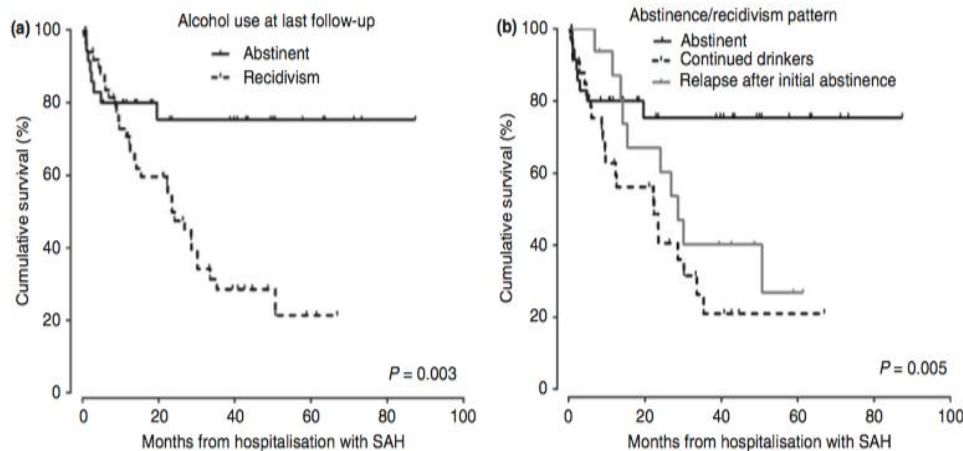|					
Pentoxifylline	546	524	497	470	448
No pentoxifylline	543	513	480	457	429

OR: 1.07 (95%CI: 0.77-1.49; P=0.69)

Thursz, NEJM, 2015

Predictors of medium/long-term outcomes in AH

❑Steroids do not improve survival beyond 1 month
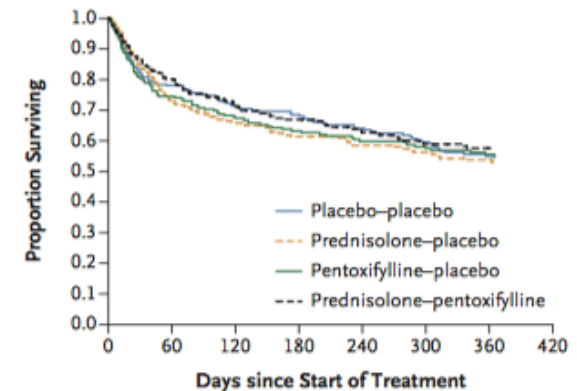❑Abstinence is the only predictor of long-term survival in AH

J. R. Potts et al.

(a) Cumulative survival (%) — Alcohol use at last follow-up
- Abstinent
- Recidivism

P = 0.003
Months from hospitalisation with SAH

(b) Cumulative survival (%) — Abstinence/recidivism pattern
- Abstinent
- Continued drinkers
- Relapse after initial abstinence

P = 0.005
Months from hospitalisation with SAH

Table 5 | Multivariable analysis of parameters associated with death in those surviving index hospitalisation with severe alcoholic hepatitis (n = 87)

Variable	B	S.E.	Wald	df	P value	Hazard ratio	95% CI Lower	Upper
Paracetamol use	0.503	0.352	2.035	1	0.154	1.653	0.829	3.298
Abstinence at last follow-up	−0.993	0.404	6.037	1	0.014	0.370	0.168	0.818

C One-Year Survival in All Groups

Proportion Surviving vs Days since Start of Treatment
- Placebo–placebo
- Prednisolone–placebo
- Pentoxifylline–placebo
- Prednisolone–pentoxifylline

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

Thursz, NEJM, 2015
(STOPAH)
Potts, APT, 2013
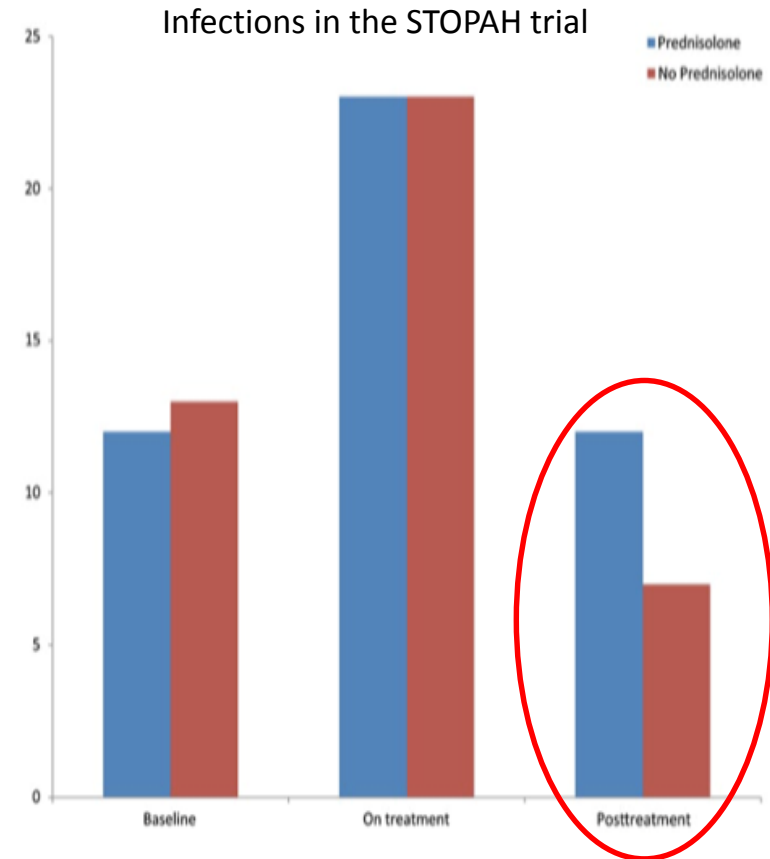
Steroids
Individual patient meta-analysis from 5 RCTs

Mathurin Gut 2011

Steroids
Individual patient meta-analysis from 5 RCTs

Mathurin Gut 2011
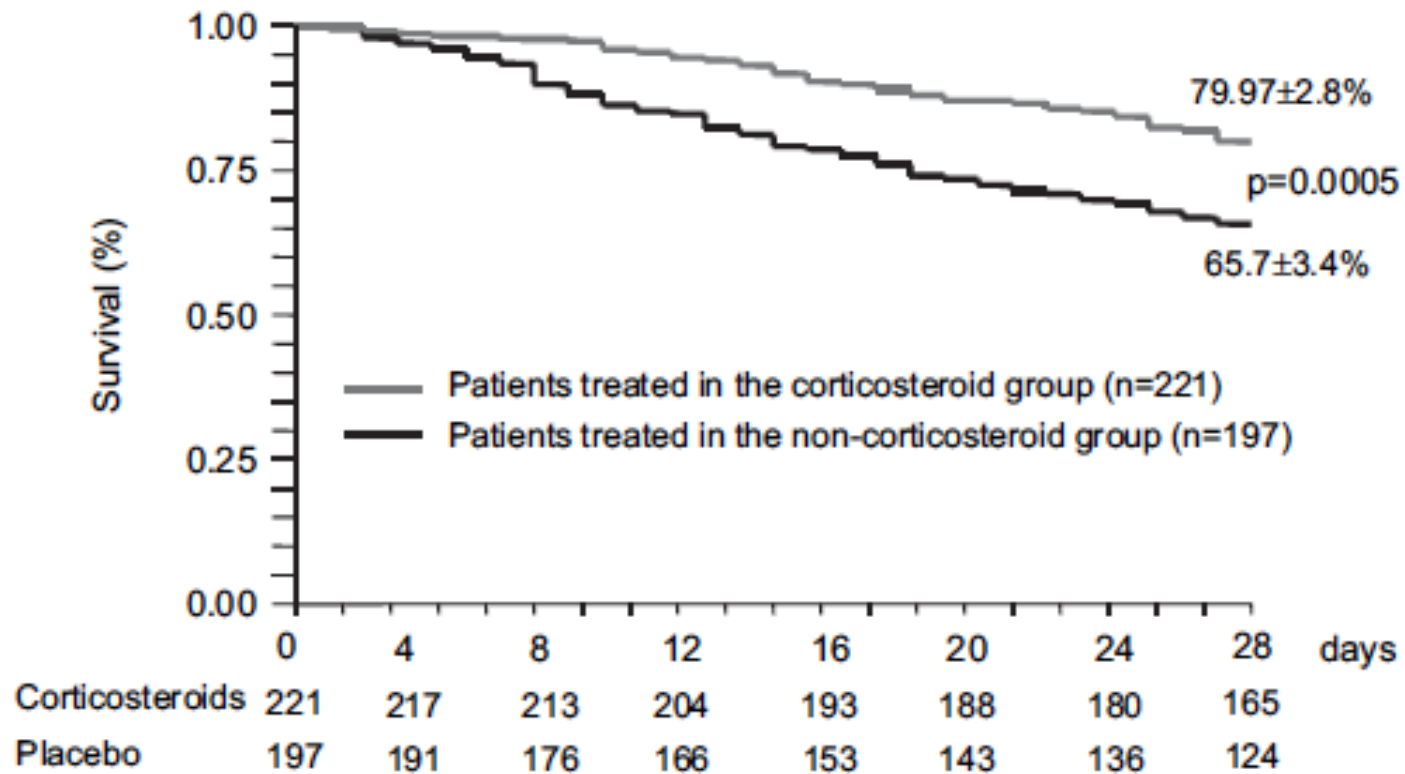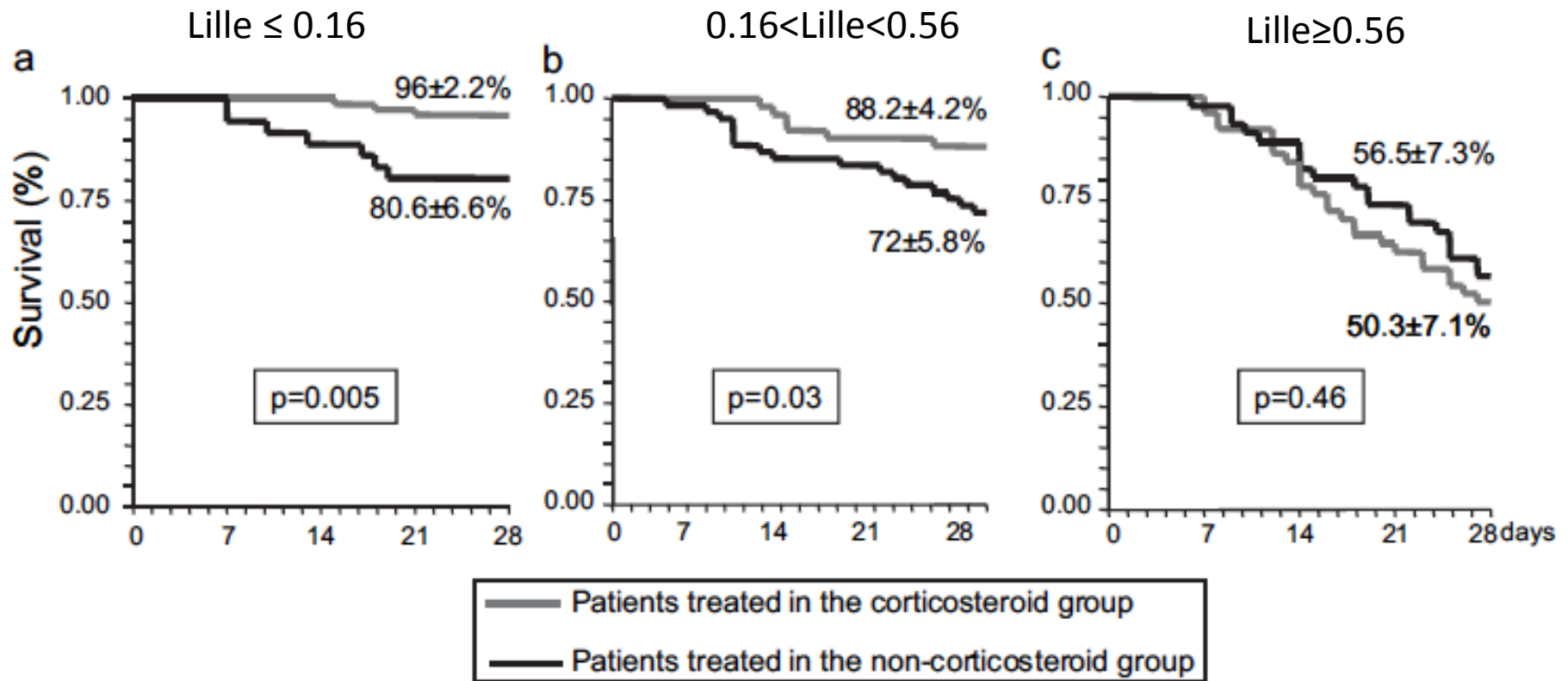
Infection: a key determinant of outcome in AH

- **25% of deaths** in sAH are attributed to infection
- Approximately **25% of patients with sAH have infection** at admission (mostly SBP, bacteremia, UTI)
- **10-24% of patients with sAH** will experience infections (mostly respiratory tract) **during or after treatment with steroids**
- **Steroid Tx** is associated with an **increased risk of (serious) infection**
- Patients **infected during steroids** have significantly **lower 2mo survival** (46% vs 77%)

Infections in the STOPAH trial

■ Prednisolone
■ No Prednisolone

Baseline   On treatment   Posttreatment

FIG 2 Treatment with prednisolone is associated with an increased rate of posttreatment, but not on-treatment, infections.

Louvet, Gastroenterology, 2009
Thursz, NEJM, 2015
Vergis, Gastroenterology, 2017

Fungal infections in AH

- Invasive Aspergilosis developed in 15.8% (15/94) pts with sAH
- Lungs (n=11), CNS (n=2), disseminated (n=2)
- Predictors of IA: baseline MELD >24, ICU admission
- IA was associated with higher mortality
- Systematic screening for IA should be recommended
- Serum galactomannan (cut-off: ≥0.5, ELISA) may be a good screening test (Se: 89%, Sp: 84%).

Gustot, J Hep, 2014
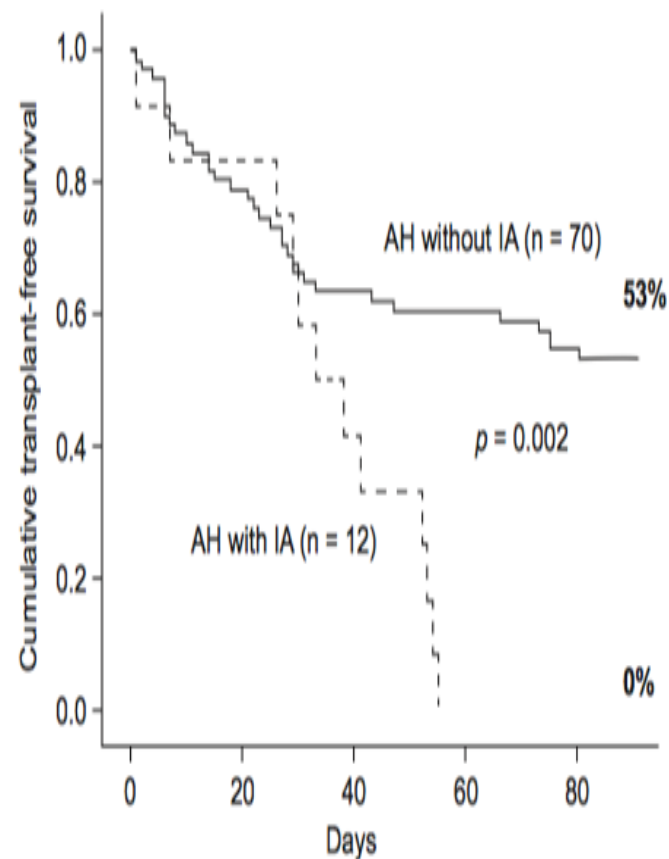
Infections in patients receiving steroids
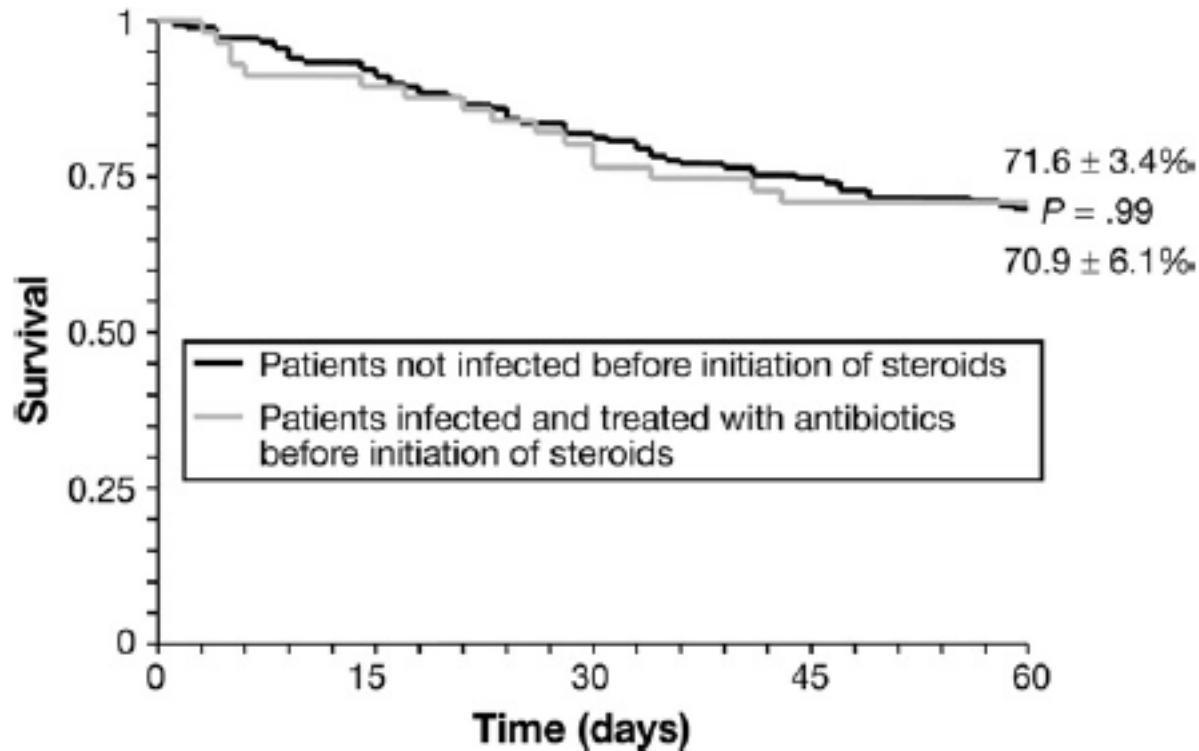
246 patients with severe alcoholic hepatitis
63 episodes of infection after first presentation
Steroid initiation after treatment of infection

Louvet Gastro 2009

Infections in patients receiving steroids

- 57 patients developed an infection after starting steroids (median time 14 days)

- Response to steroids according to Lille model only factor associated with infection

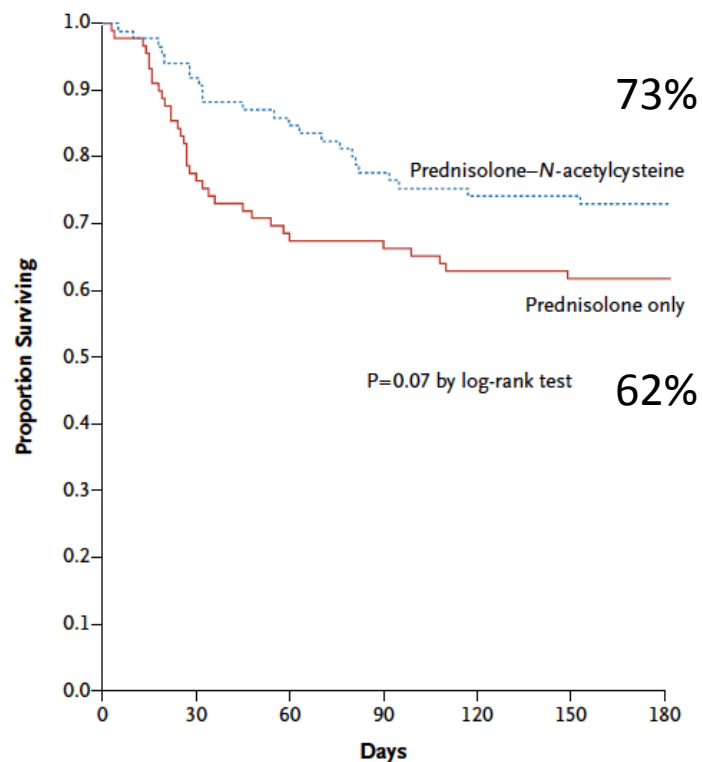- Incidence 11.1% vs. 42.5% in responders vs. non-responders
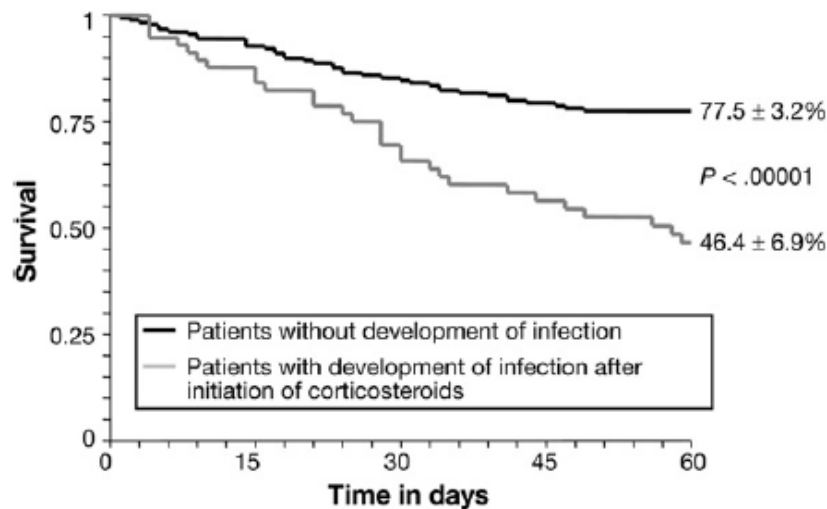
Louvet Gastro 2009

Infections in patients receiving steroids
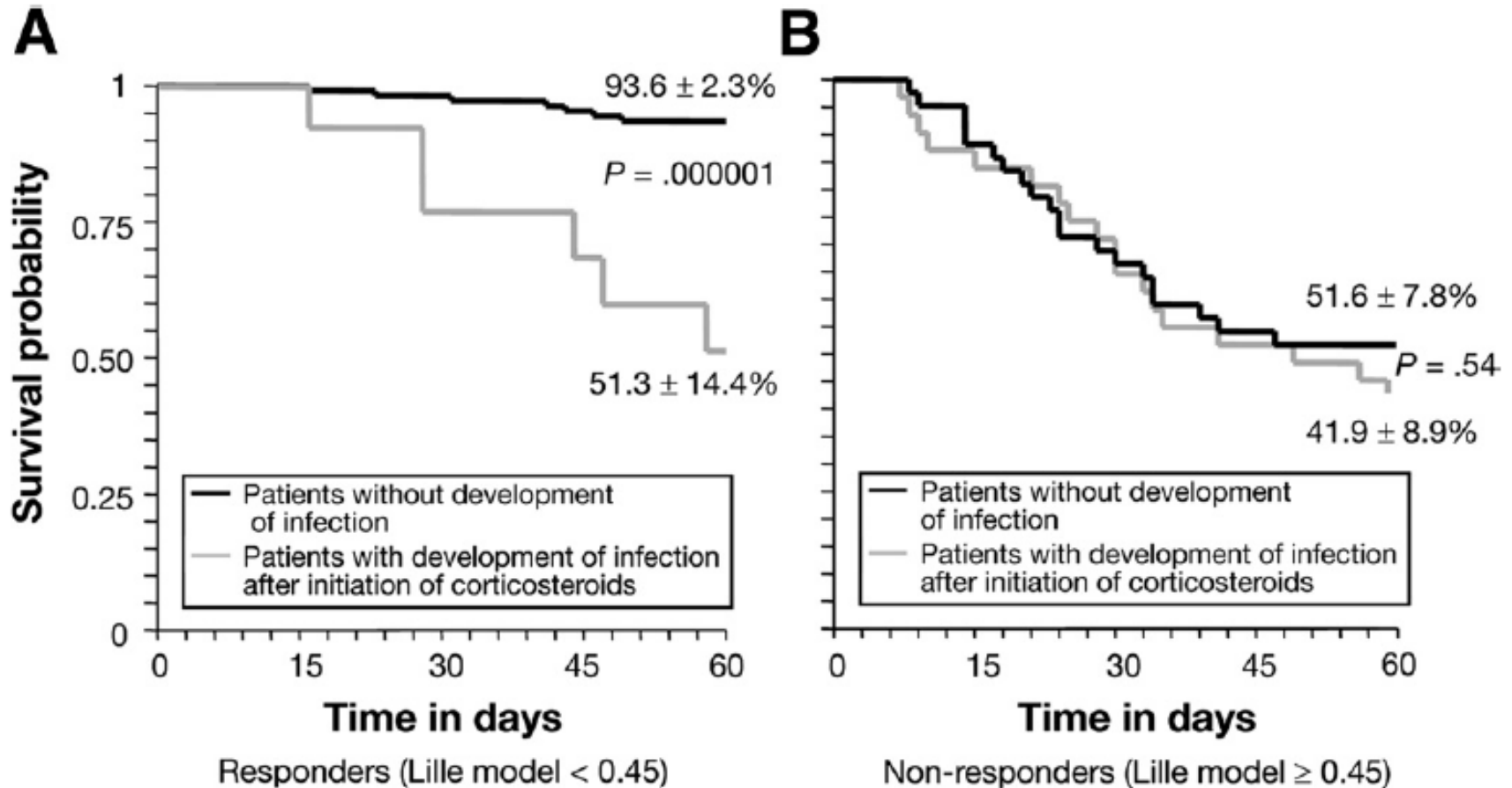
Pre-emptive antibiotics in responders?

Louvet Gastro 2009

Combination of steroids and NAC

73%

62%

IV NAC days 1-5
Survival benefit at 1 months (8% vs. 24%)
Trend for benefit at 3 and 6 months

Nguyen-Khac NEJM 2012

Liver Transplantation for ALD

- "6-mo abstinence rule" adopted by most countries/centers

- Fear of recidivism (10%-60%)

- Ethical persuasions (self-inflected disease with negative social impact)

- Organ shortage/Overload of transplant systems (ALD: 15%-20% of LTs; 3rd most common indication after HCV, NASH)

Best with Northern Ireland in 1976

Early Liver Transplantation for Severe Alcoholic Hepatitis

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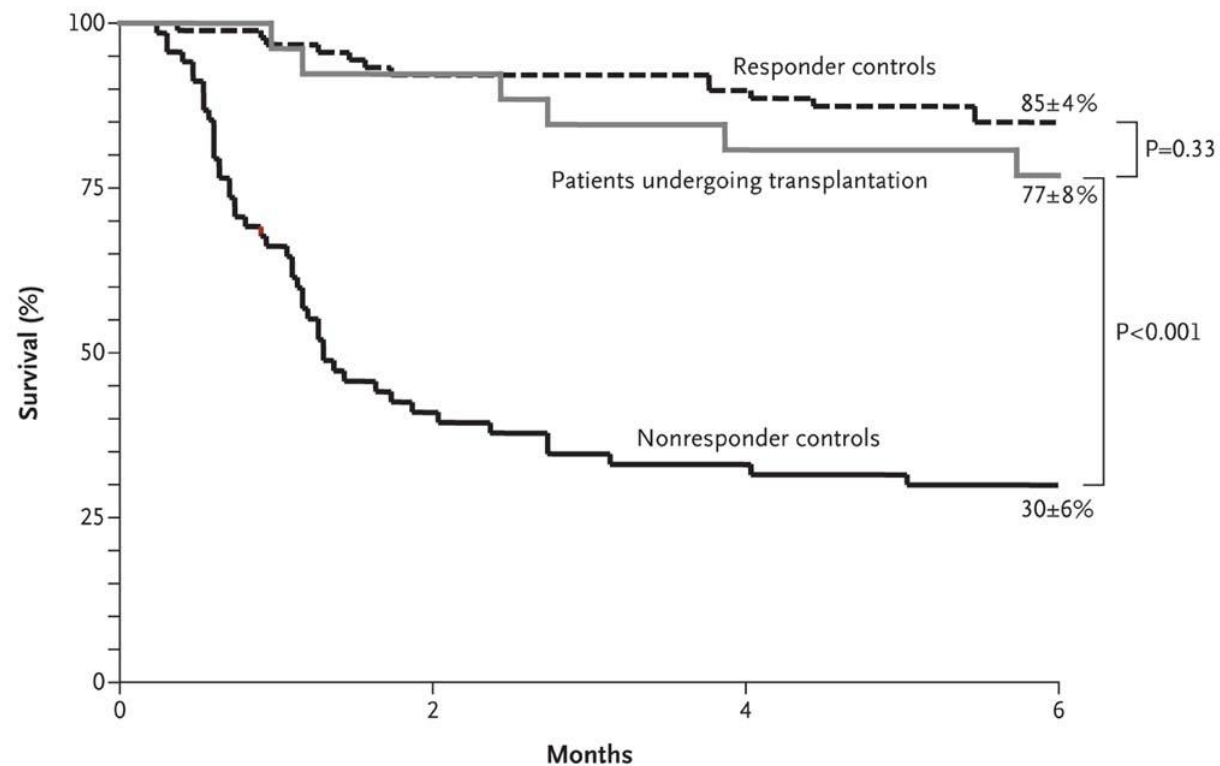
Inclusion criteria

- Severe alcoholic hepatitis not responding to steroids

- Lille score > 0.45 after 7 days of steroids

- First presentation of liver disease

- Multiple meetings of medical team with family members

- Full agreement of all team members required

After liver transplantation

- 5/6 deaths due to infection in the first two weeks

- Invasive aspergillosis in 4/5

- Three patients had an alcohol relapse

Impact on waiting list

- 315/891 liver transplants due to ALD during that period

- 26/891 (2.9%) for alcoholic hepatitis

- 233 patients presented with severe alcoholic hepatitis

- 18/233 had a liver transplant (1.8%)

Dilemmas

- Only available treatment if no response to steroids

- ?Impact on organ donation

- Need for objective listing criteria

Future treatments

Pathology	Therapeutic target	Therapy	Trial ID:clinicaltrials.gov, EudraCT, PMID
Portal translocation of gut microbiota	Intestinal dysbiosis	Rifaximin	NCT02116556, EudraCT 2014-002264-33
		Oral vancomycin, gentamycin, meropenem	NCT03157388
		Faecal microbiota transplant	NCT03091010 NCT02458079
		Probiotics *Lactobacillus spp.*	NCT01922895
			NCT02335632
	Intestinal mucosal integrity	Zinc	NCT01809132
		Obeticholic acid,	NCT02039219
		Canakinumab,	NCT03775109
		Anakinra	
Enterohepatic circulation of bile acids	Farnesoid receptor	Obeticholic acid	NCT02039219
Hepatic inflammation	IL-1β	Anakinra	NCT01809132
		Canakinumab	NCT03775109
	TLR-4	Anti-LPS IgG	NCT01968382
	Non-specific	Bovine colostrum	NCT02473341
Hepatocellular injury and repair	Oxidative stress	Metadoxine	NCT02019056
			NCT02161653
			PMID 24756009
		N-acetylcysteine	NCT00863785 PMID 22070475
		S-Adenosyl methionine	NCT00851981 NCT02024295
		Omega 5	NCT03732586
	Hepatocyte regeneration	IL-22	NCT02655510
		G-CSF	NCT01820208 NCT02971306 NCT02442180 NCT01341951 NCT02776059 NCT03703674
Complications	Infection	Co-amoxiclav	NCT02281929

Anakinra plus pentoxifylline and zinc

- 53 patients IL-1RA
- 50 patients steroids
- Mortality at 30, 90, 180 d
- No significant difference in survival (66.8% IL-1RA vs. 52.3% steroids)

Szabo AASLD 2018
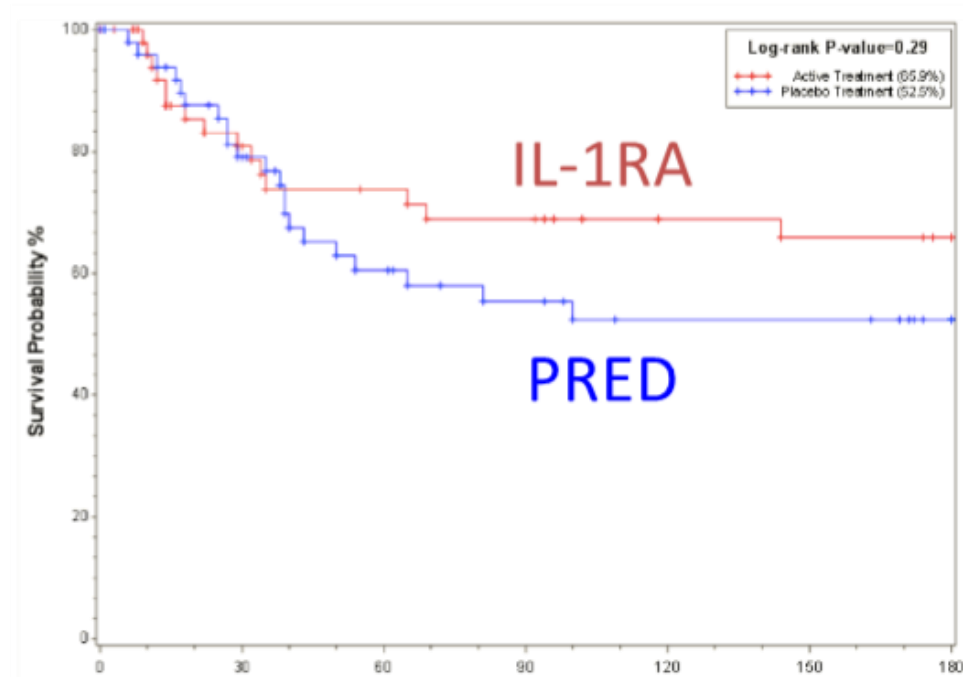
Conclusions

- High mortality

- Use prognostic scores

- Thorough screening for infections

- Steroids in severe AH

- ? Liver transplantation