

Alcoholic Liver Disease: What are the treatment options?

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Outline

- Spectrum of alcoholic liver disease (ALD)
- Current treatment options based on evidence

Forms of ALD

Parameter	Fatty Liver	Alcoholic Hepatitis	Cirrhosis
Histologic specificity for alcoholic cause	No	No	No
Prognosis	Excellent	Variable	Guarded
Reversible?	Yes	Variable	Generally No

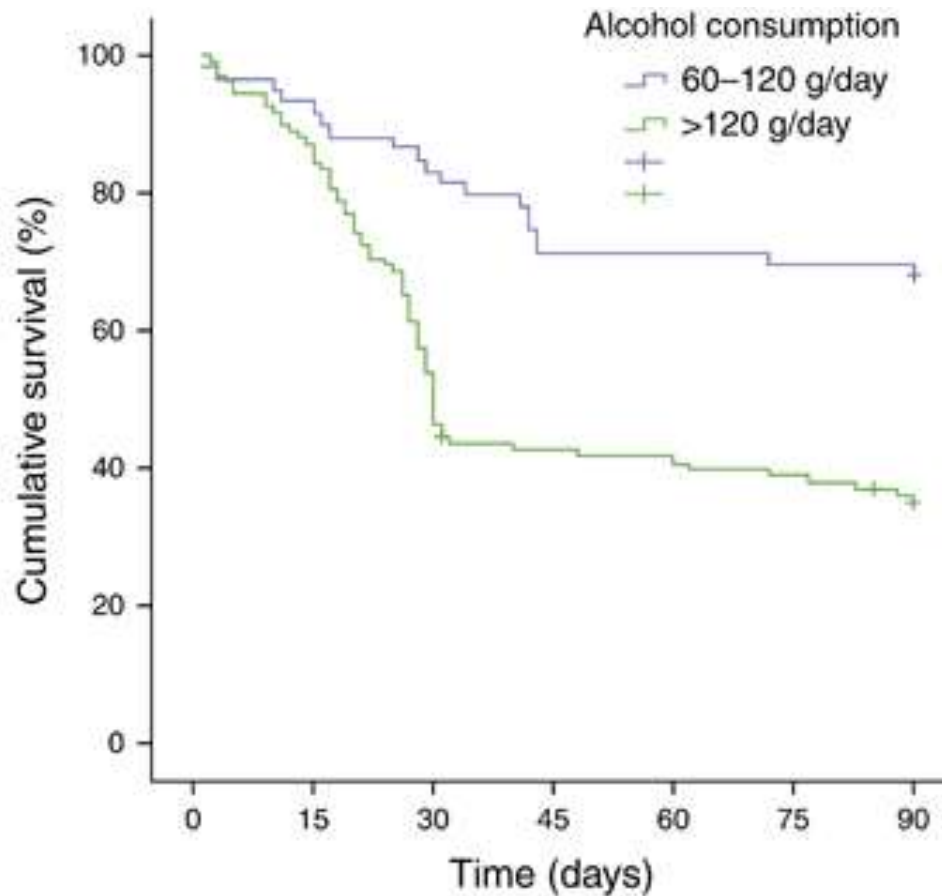
Alcohol Content of Some Common Beverages

Drink	Amount (ml)	Absolute Alcohol (g)
Beer	330	16.5
Wine	100	13.5
Liquor (80 proof)	30	12

Prevalence

- Fatty liver
 - 40% of modest alcohol intake (20g/day)
- Alcoholic hepatitis
 - Threshold daily alcohol intake of 40g – pathologic changes
 - 80g/day – increase in severity
- Cirrhosis
 - Daily intake of >60g and >20g in m/w – increases risk

Amount of Alcohol Consumption Negatively Impacts Short-Term Mortality in Alcoholic Hepatitis (AH)

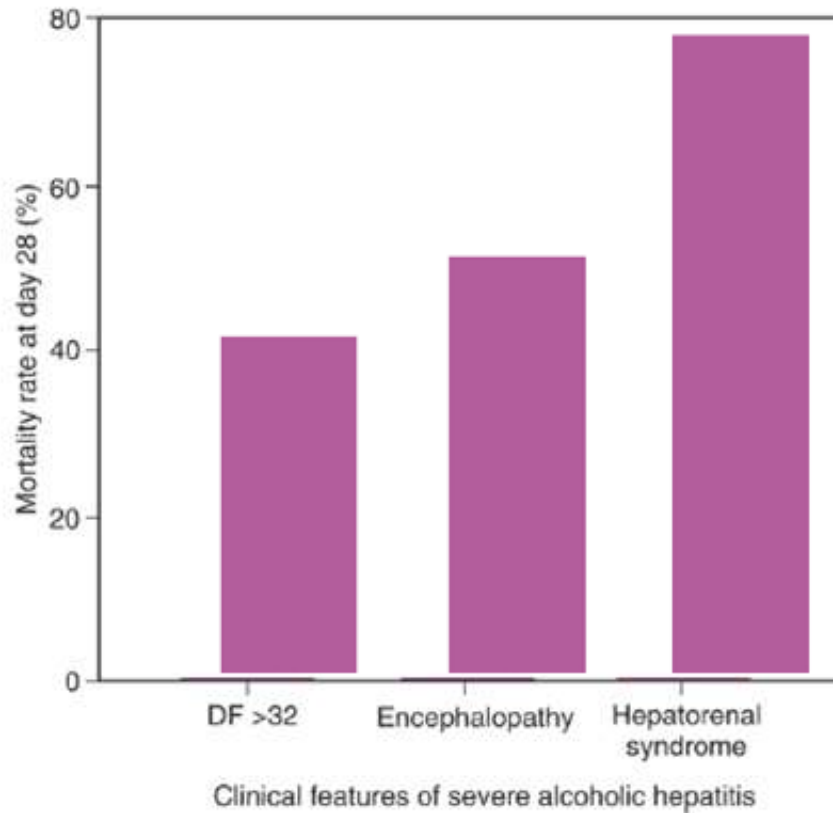


Current alcohol consumption							
60–120 g/day	67	62	54	50	49	48	47
>120 g/day	108	91	50	46	44	42	39

Clinical and Diagnostic Features

	Fatty Liver	Alcoholic Hepatitis	Cirrhosis
Symptoms	Asymptomatic or nonspecific	Spectrum of manifestations	Nonspecific
Signs	Enlarged, smooth rarely tender liver	Hepatomegaly, jaundice, ascites, fever, encephalopathy	Complications of portal hypertension, jaundice
Diagnostics	ALT < 2x ULN Hyperechoic or bright liver by sonography	AST/ALT: 2 Levels < 300	Thrombocytopenia, hypoalbuminemia, coagulopathy Nodular liver by sonography
Liver biopsy	Not necessary	Occasionally necessary	Not necessary

Discriminant function (DF) score: for alcoholic hepatitis



- Calculated as:
[4.6 x
prothrombin
time – control
value (seconds)]
+ serum
bilirubin
(mg/dL)

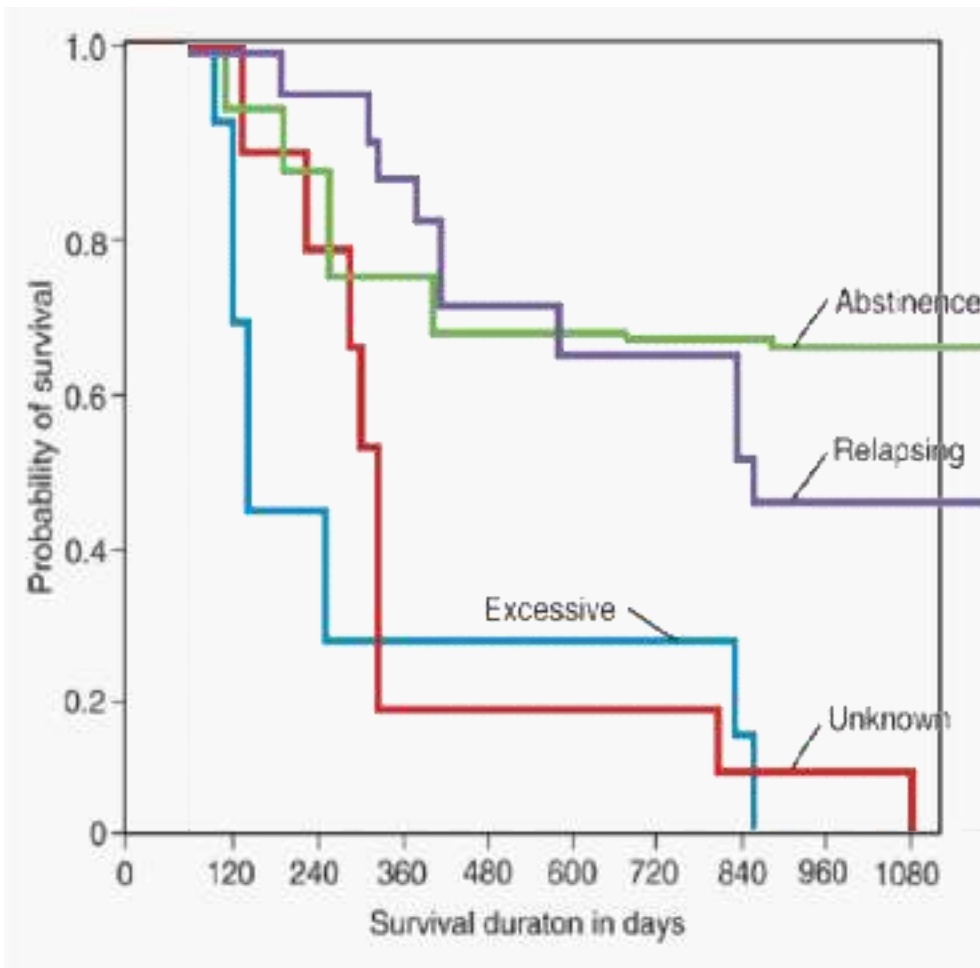
Lille Model for AH

- Age
- Creatinine
- Albumin
- PT
- Bilirubin
- Evolution of bilirubin on day 7
- > 0.45 (www.lillemodel.com)

Treatment of ALD

- Alcohol abstinence
 - Beneficial effects on patient survival (even in decompensated cirrhosis)
 - Reduction in consumption also improves survival
 - Causes resolution of hepatic steatosis
 - Prevents ongoing injury and fibrosis

Impact of alcohol abstinence



- Survival differed significantly between abstinent and excessively drinking patients

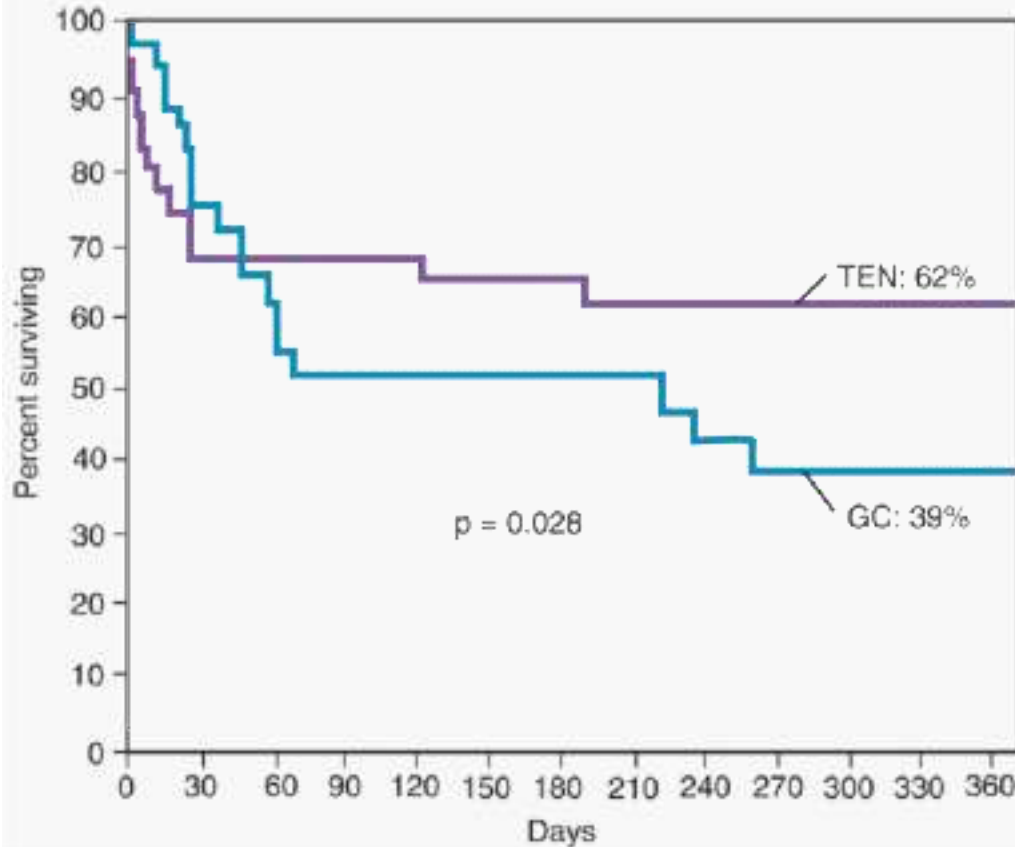
($P < .001$).

Treatment of ALD

- Nutrition

- High frequency of malnutrition in alcoholic hepatitis patients
- In one study, patients derived ~50% of energy requirements from alcohol
- Malnutrition correlates with mortality
- Enteral nutrition is preferable
- Protein should not be routinely restricted

Impact of nutrition on ALD



- Similar 1-month mortality rates
- Significantly lower 1-year mortality rate in the TEN group

TEN = total enteral nutrition
GC = glucocorticoids

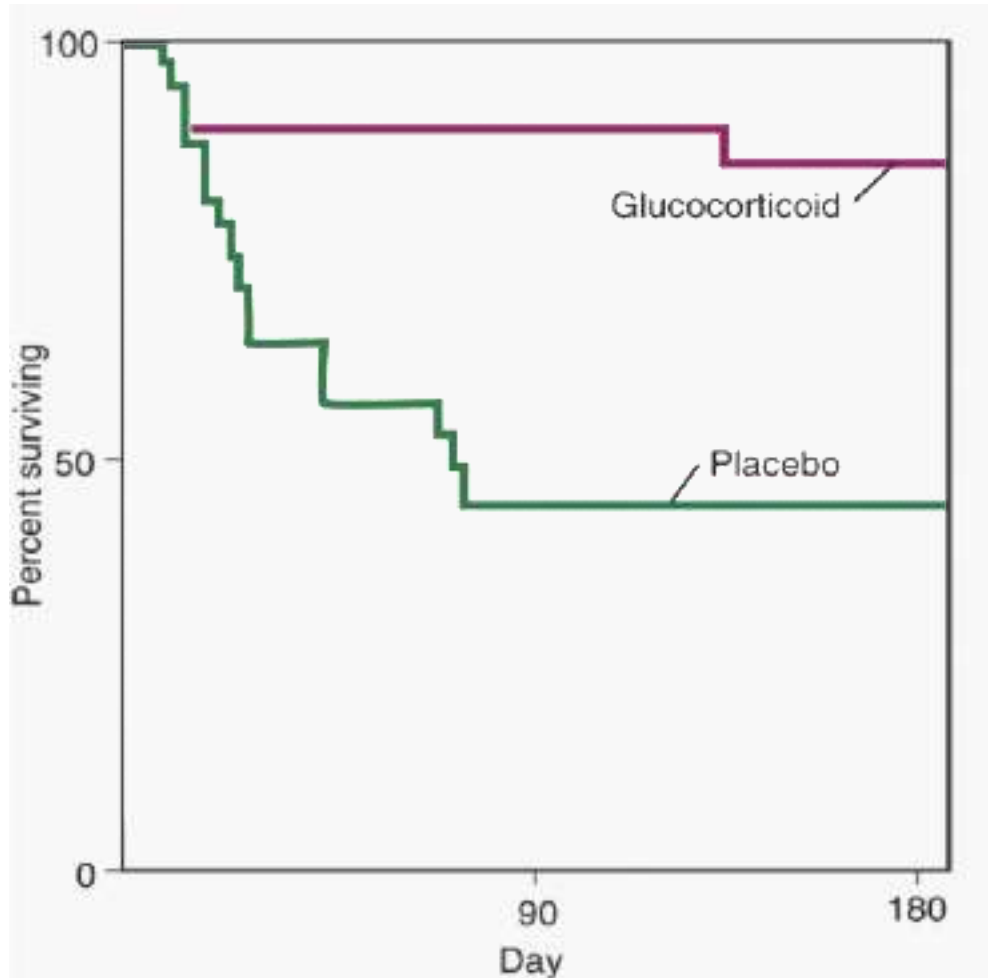
Recommended Nutritional Treatment for Alcoholic Hepatitis

Calories	35-40 cal/kg/day
Protein	1.2-1.5 g/kg/day
Sodium	2 g/day
Meals	4 or 5 meals per day, including an evening snack
Multivitamins, minerals	Thiamine, B2, B12, folate, Magnesium, zinc, selenium

Glucocorticoids

- Extensively studied
- Remains controversial
- Analysis of published data shows improved survival in:
 - Severe alcoholic hepatitis
 - With hepatic encephalopathy

Glucocorticoids in acute alcoholic hepatitis

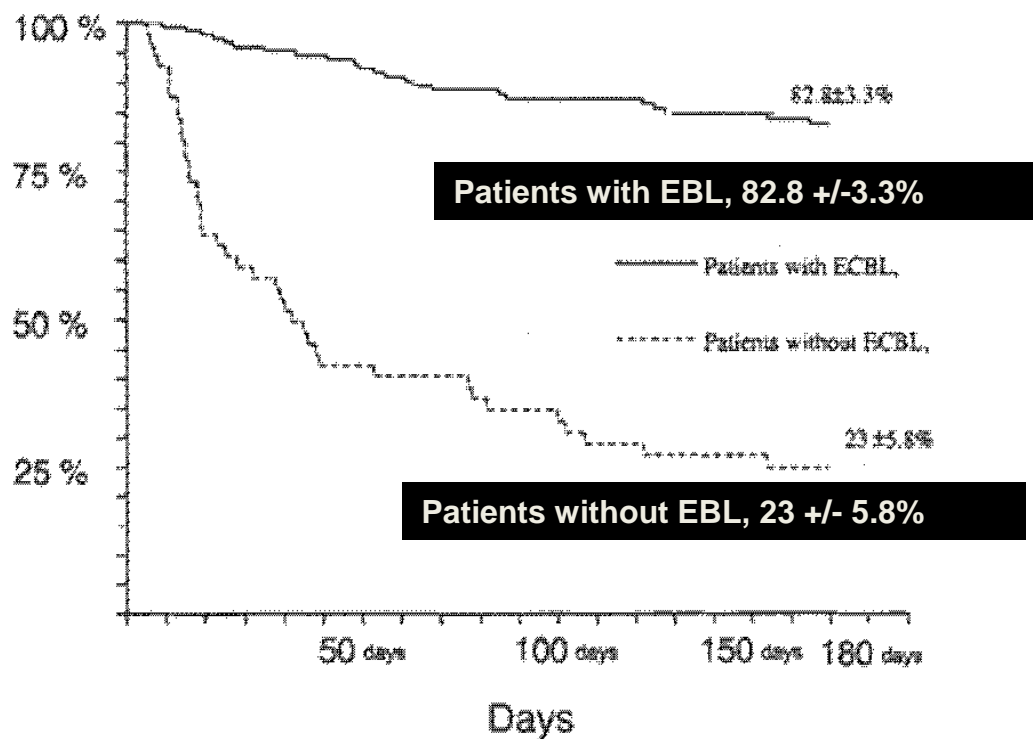


Survival rates at 6 months:

- Prednisone group : 84% \pm 6%
- Placebo group: 45% \pm 9%
- $P = .002$

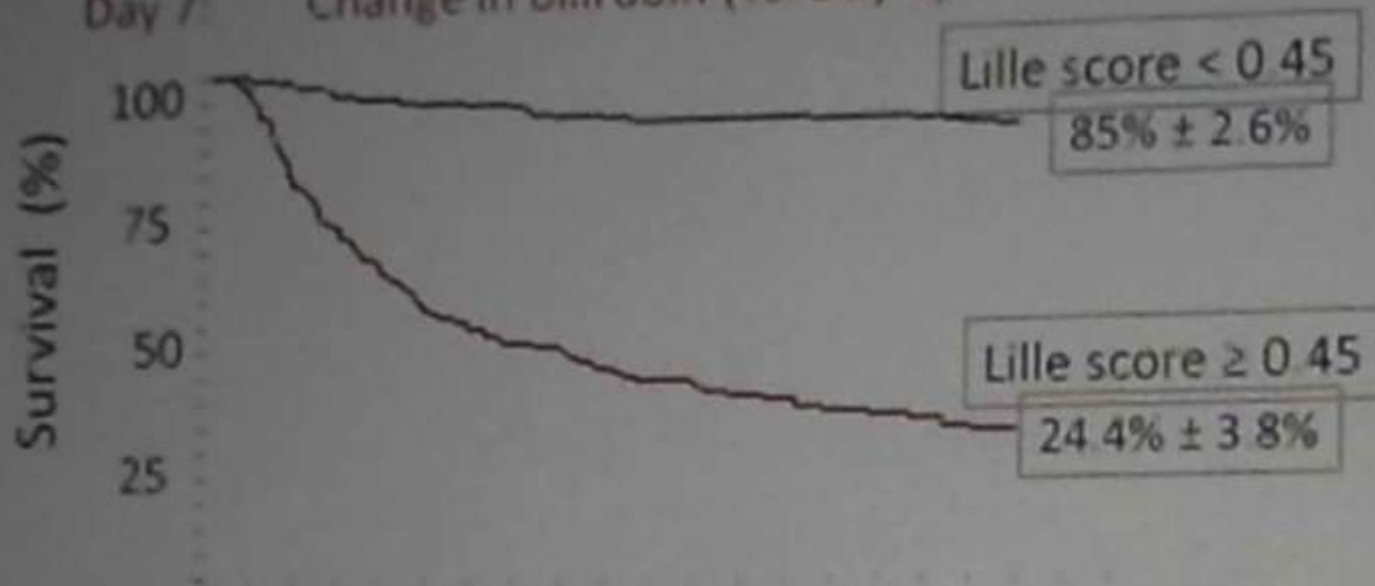
Early biological response (EBR) determines whether steroids should be continued or discontinued

- In best trials, 40% of patients don't respond to steroids
- If bilirubin does not improve by 1 week of therapy then steroid response is unlikely and can be discontinued for consideration of alternatives

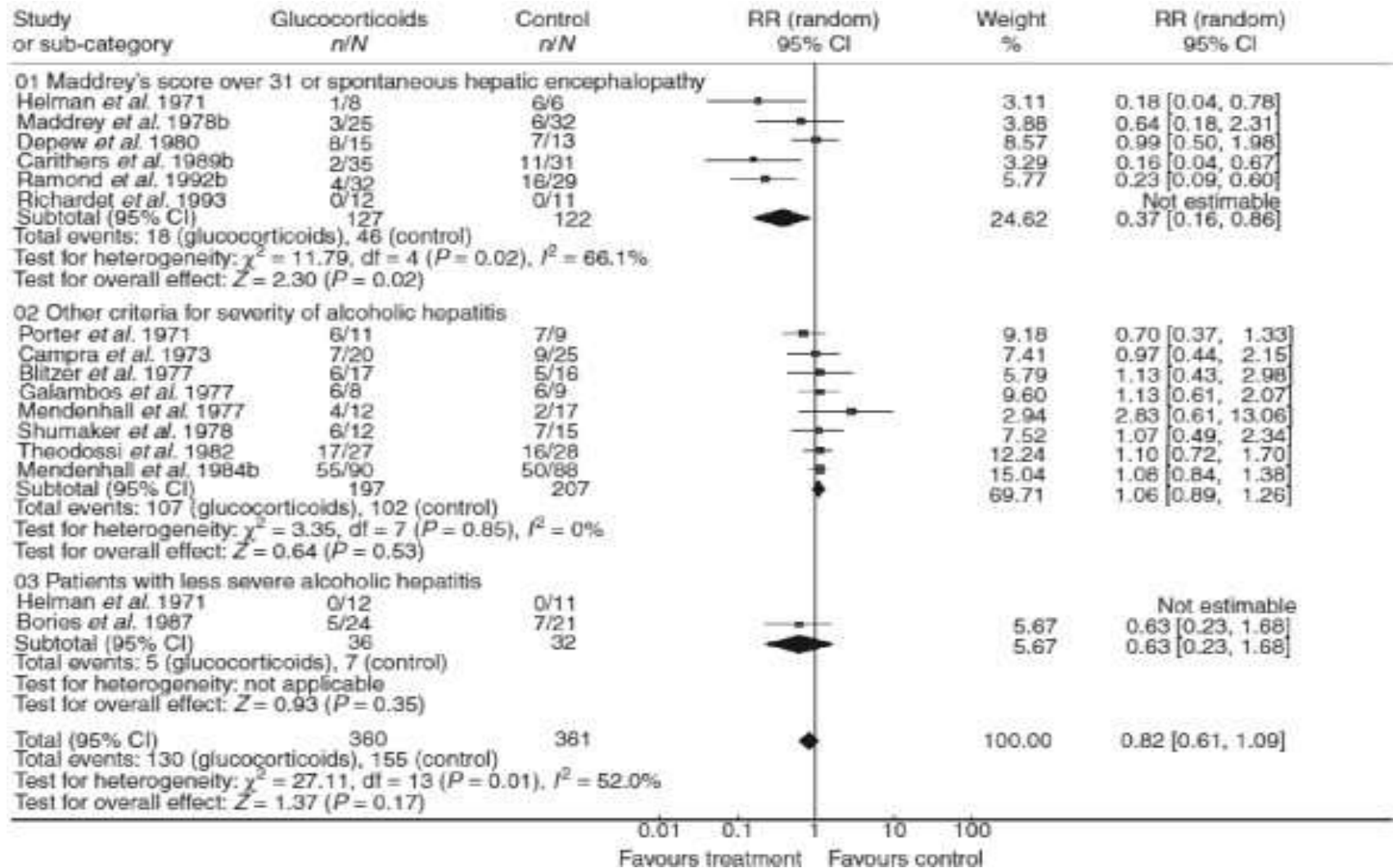


Lille Score Predicts 6-Month Survival in Alcoholic Hepatitis, with Prednisolone

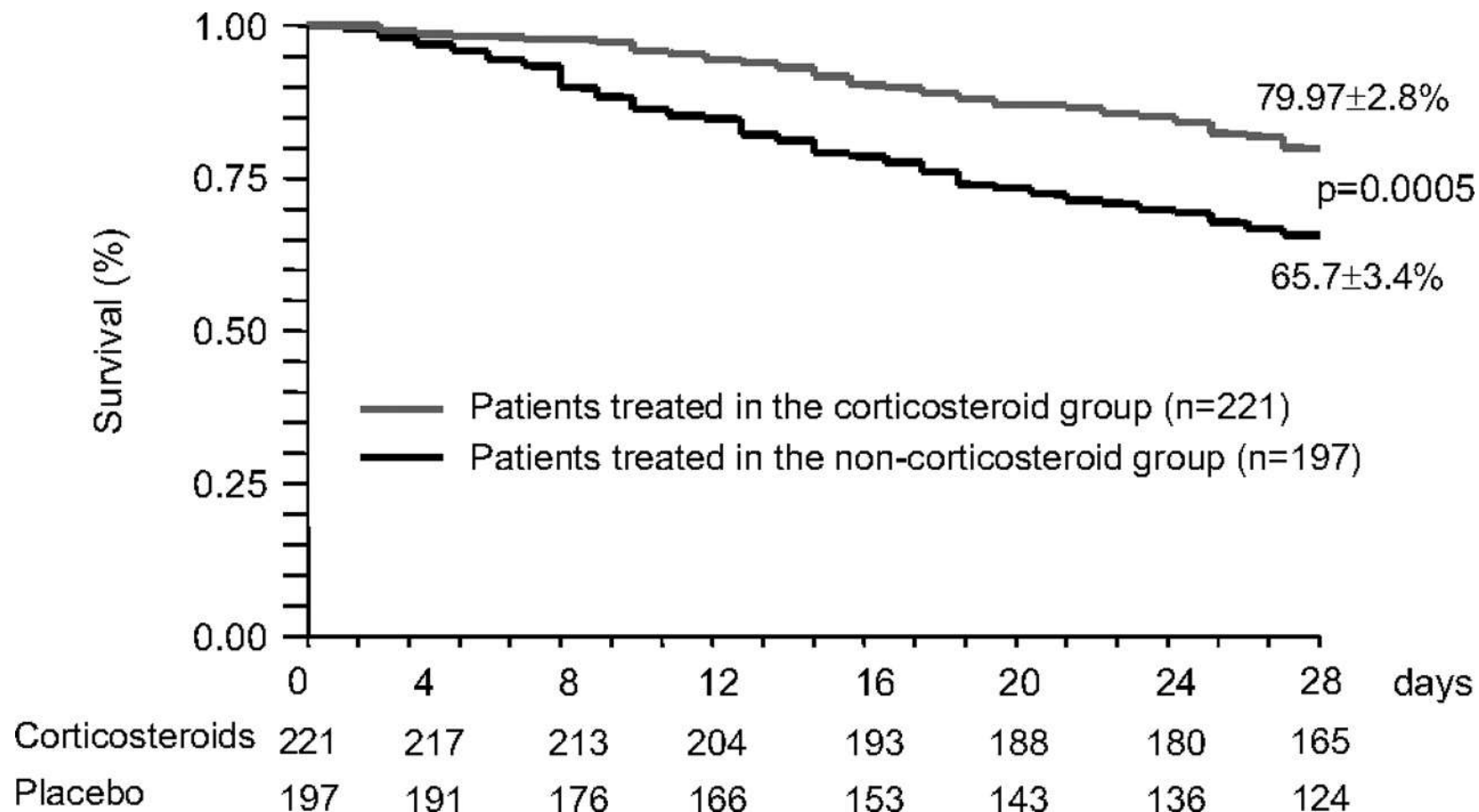
Baseline: Age, albumin, bilirubin, creatinine, protime
Day 7: Change in bilirubin (vs. Day 1)



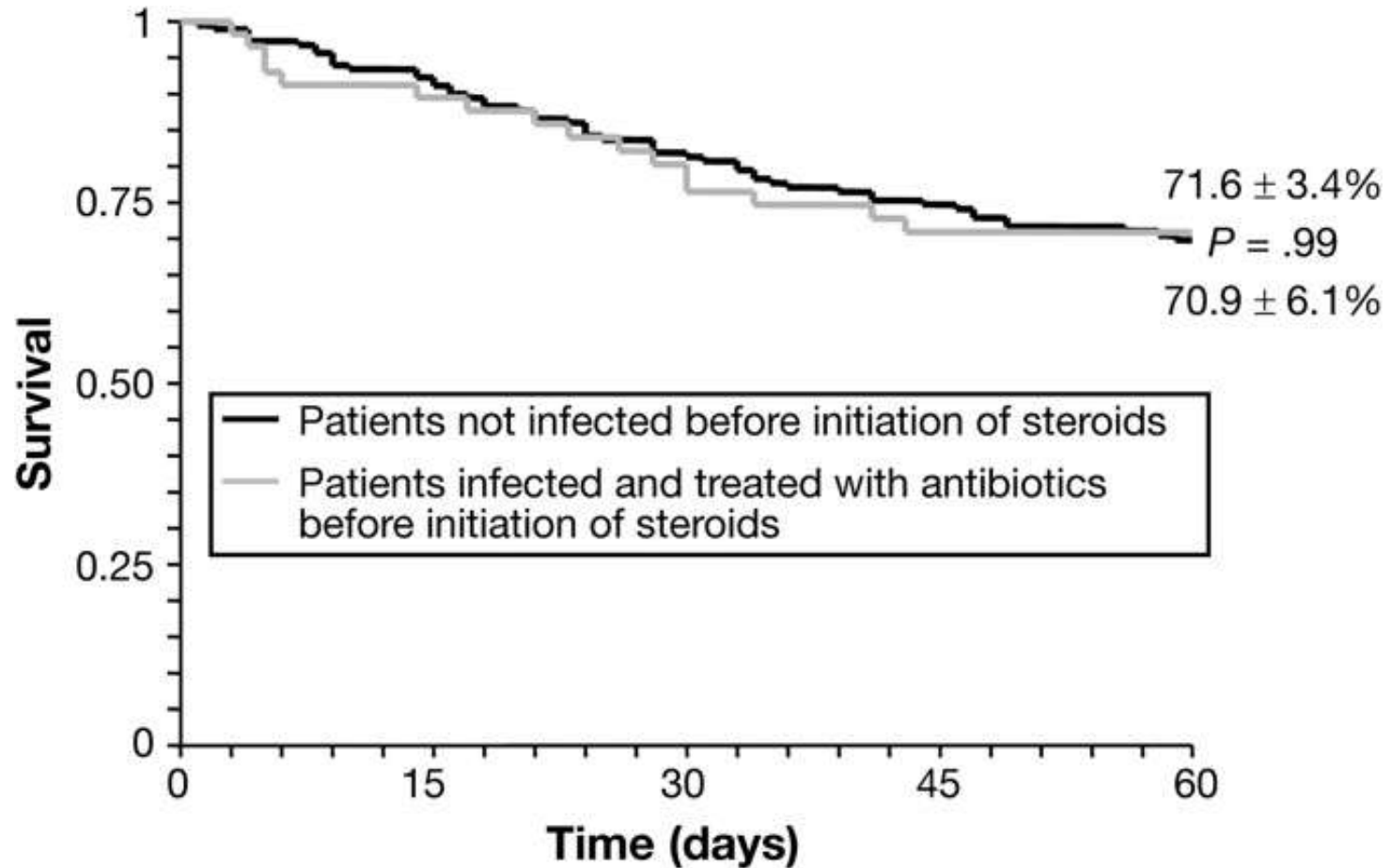
Treatment of Alcoholic Hepatitis



Probability of 28-day survival according to treatment with corticosteroids or non-corticosteroids



Steroids can be used after treatment of active infections...



Objective pros and cons of steroids

Pros

- Several positive RCT's and meta-analyses support its utility in patients with $DF > 32$ and/or patients with encephalopathy
- 1 study shows a survival benefit at 1 year

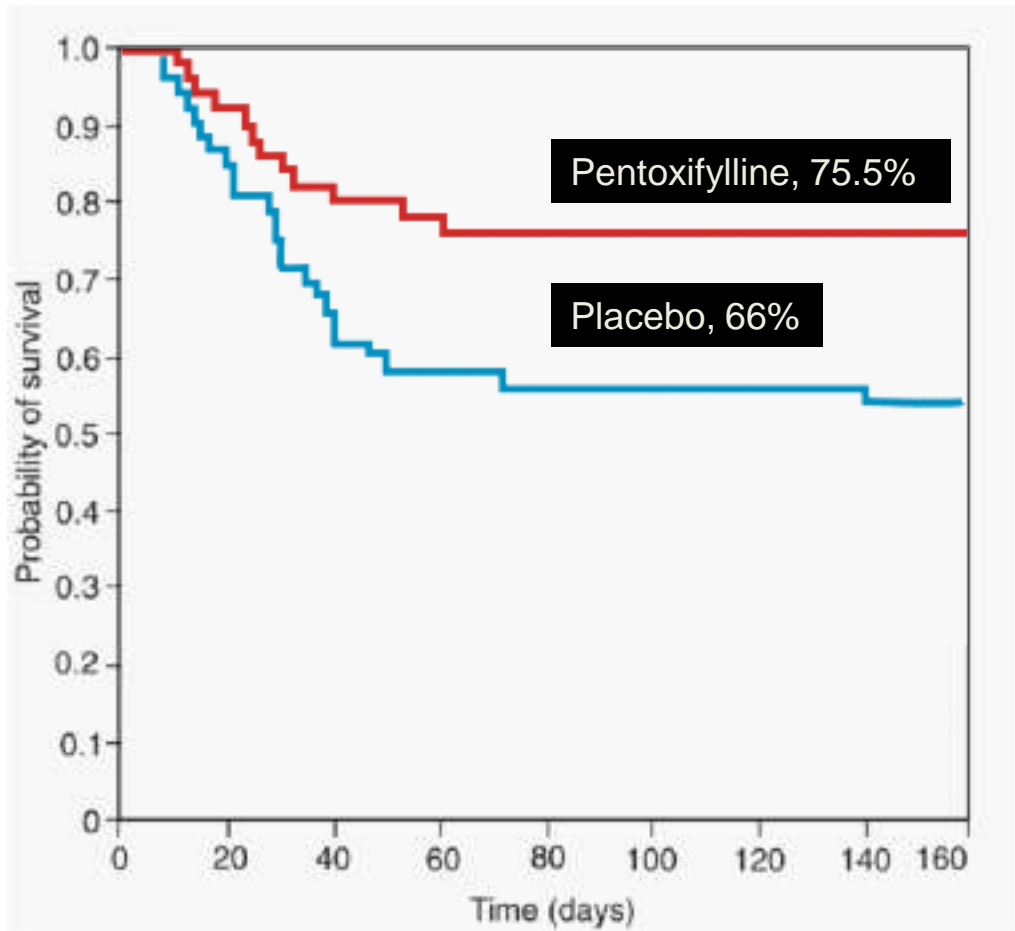
Cons

- Efficacy is still debated
- Need to treat 5 patients to save one
- Infectious sequelae
- Long term survival benefit not as well established
- Alternative tx has no major adverse effects

Pentoxifylline

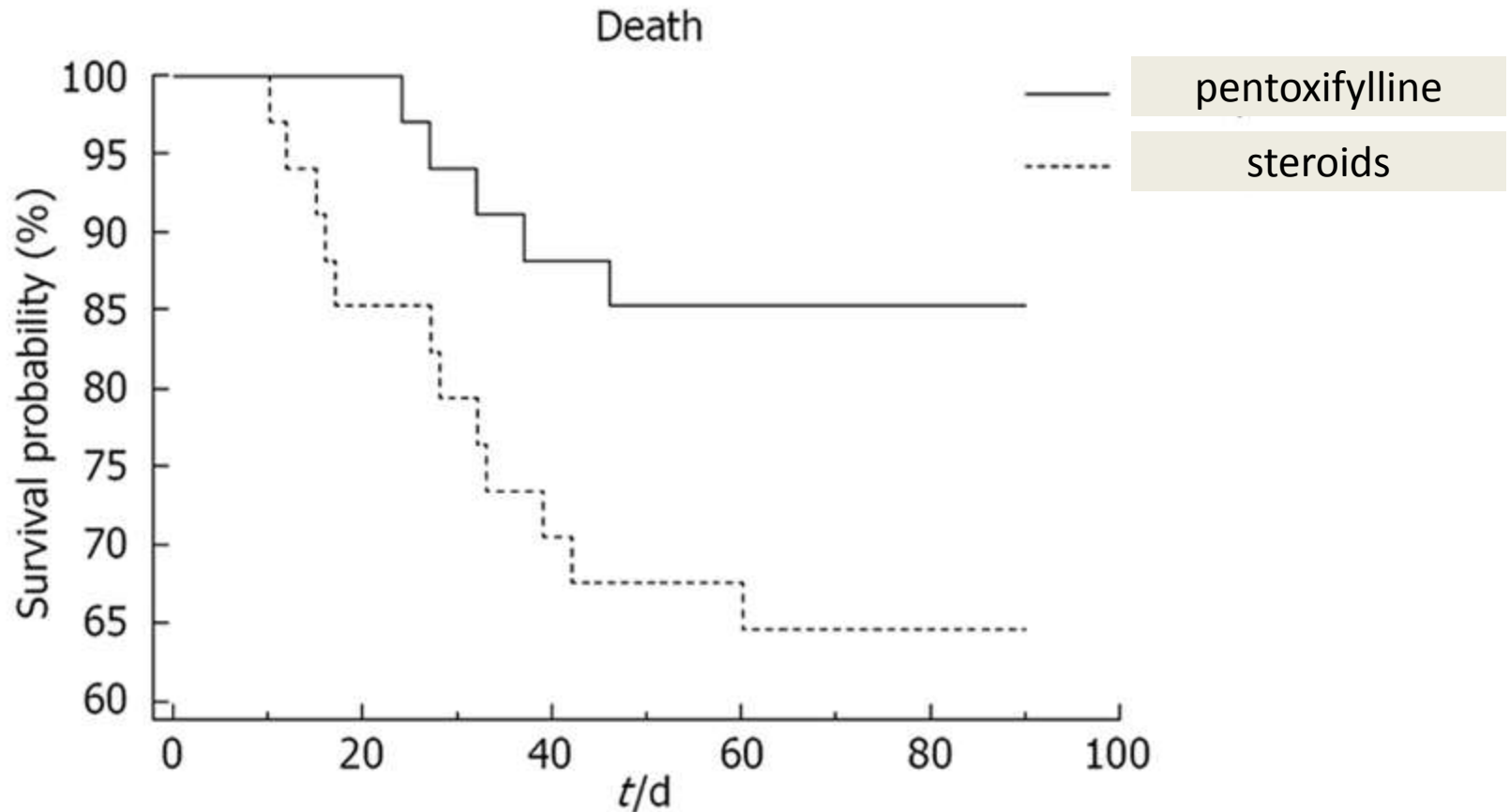
- Non-selective phosphodiesterase inhibitor
- Increases cellular cAMP and cGMP to inhibit TNF production
- Inhibition of chemokine/cytokine production
- Reduces fibroblast proliferation and collagen secretion

Pentoxifylline in acute alcoholic hepatitis



- 101 patients with severe alcoholic hepatitis treated with pentoxifylline (400 TID) or placebo for 28 days
- Significant decrease in the incidence of hepatorenal syndrome
- Well-tolerated

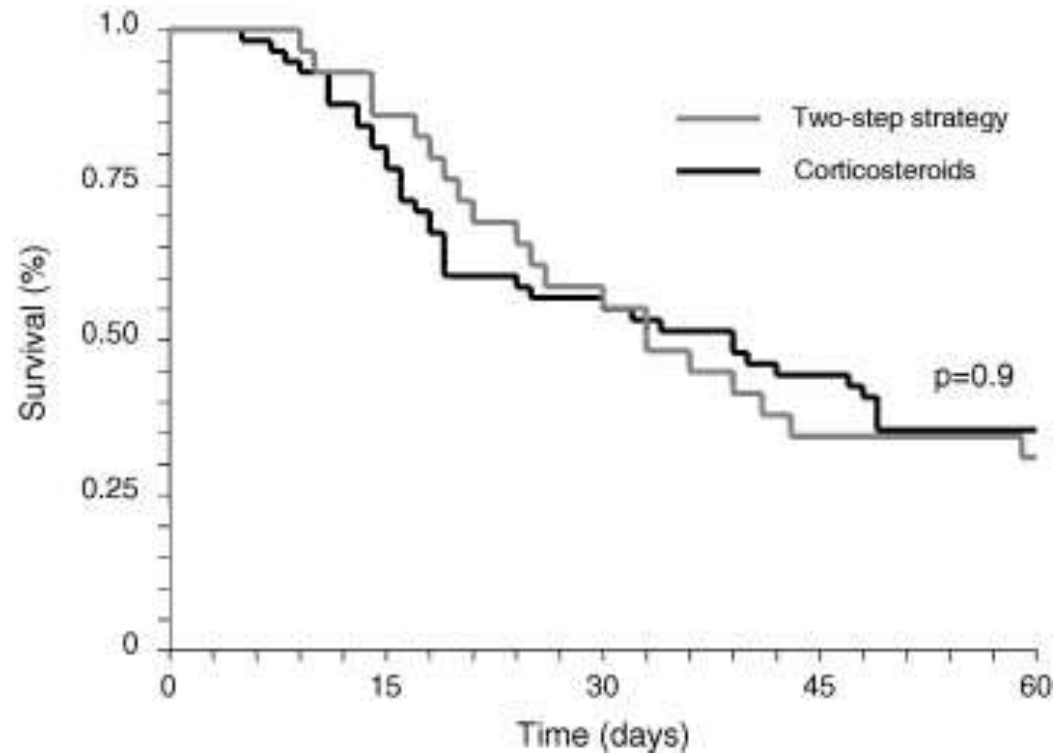
Steroids vs Pentoxifylline



Pentoxifylline treated patients had much better survival than patients receiving steroids

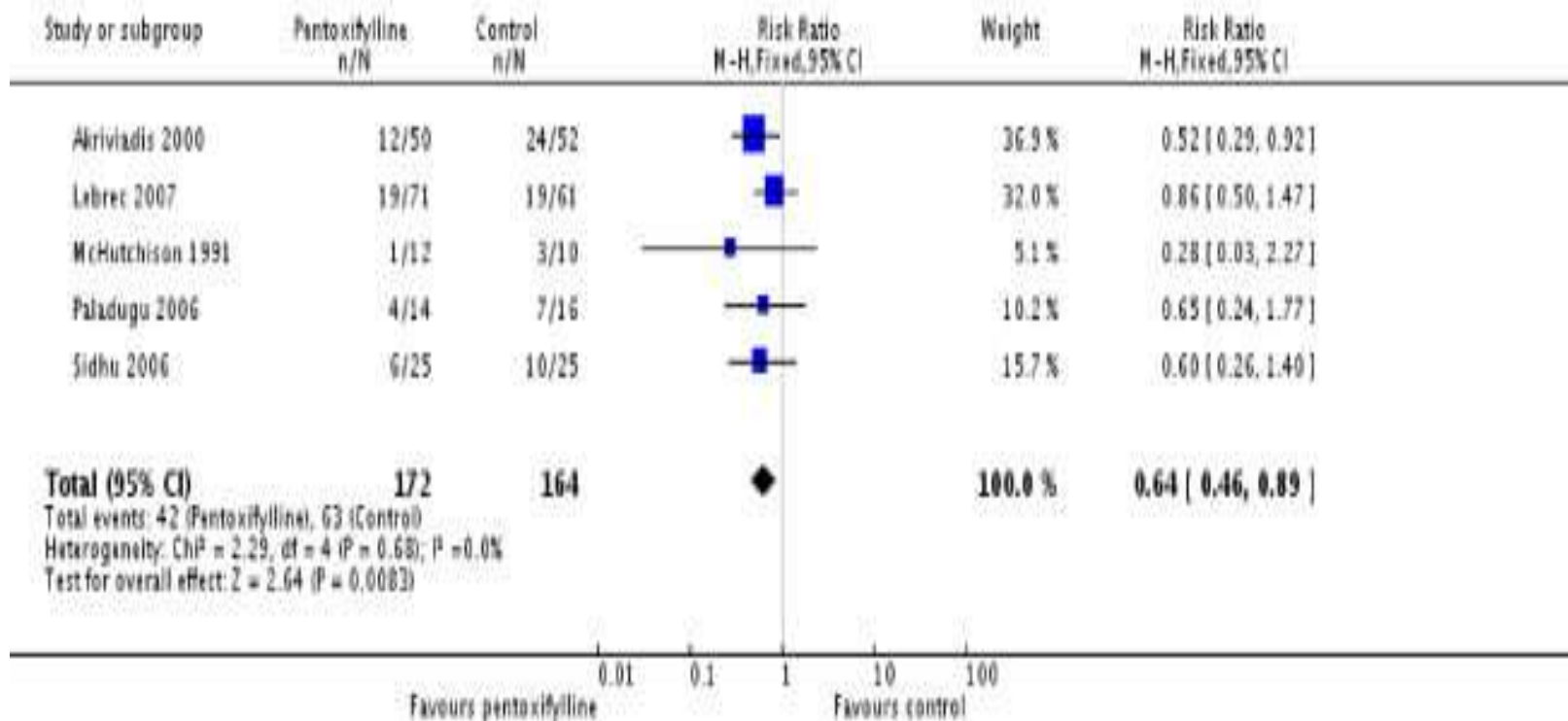
Conversion of steroid non-responders to pentoxifylline is not effective

- Patients who did not show improvement in bilirubin at 1 week were converted to pentoxifylline but there was no benefit
- Possible reasons:
 - Historical control group
 - Nonresponders are too sick
 - Pentoxifylline is not so great

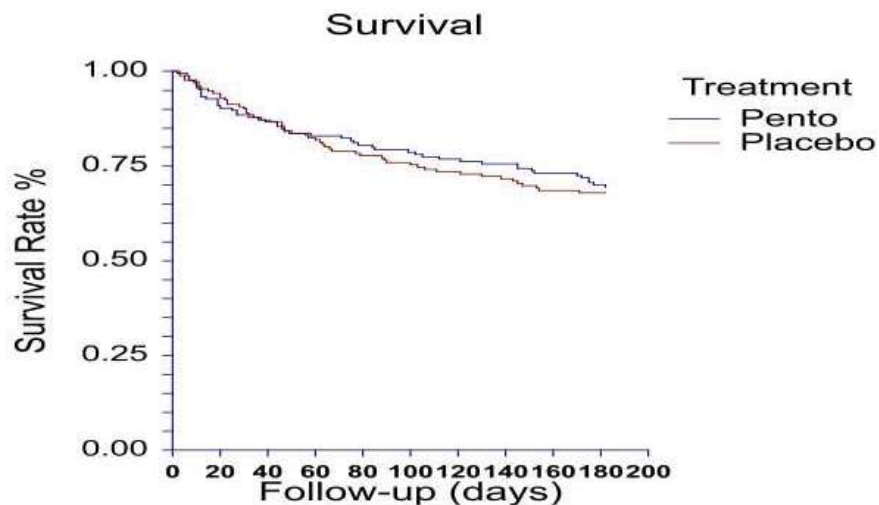


Treatment of alcoholic hepatitis

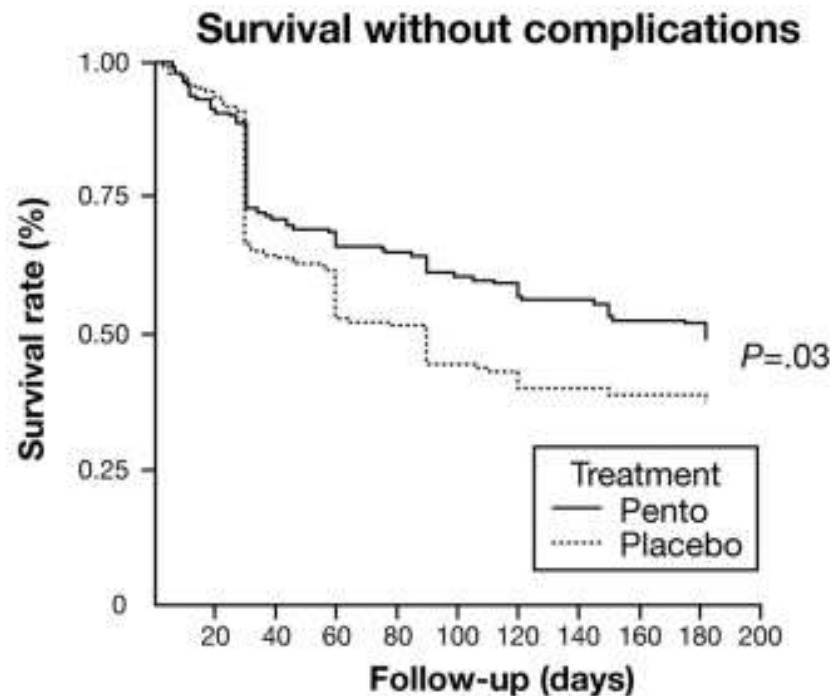
Review: Pentoxifylline for alcoholic hepatitis
 Comparison: 1 All-cause mortality, pentoxifylline versus control
 Outcome: 1 Mortality using the fixed effect model



Pentoxifylline does not improve survival in alcoholic hepatitis/cirrhosis but may reduce complications



Patients at risk	Baseline	60 days	180 days
Pentoxifylline	164	135	113
Placebo	171	139	108



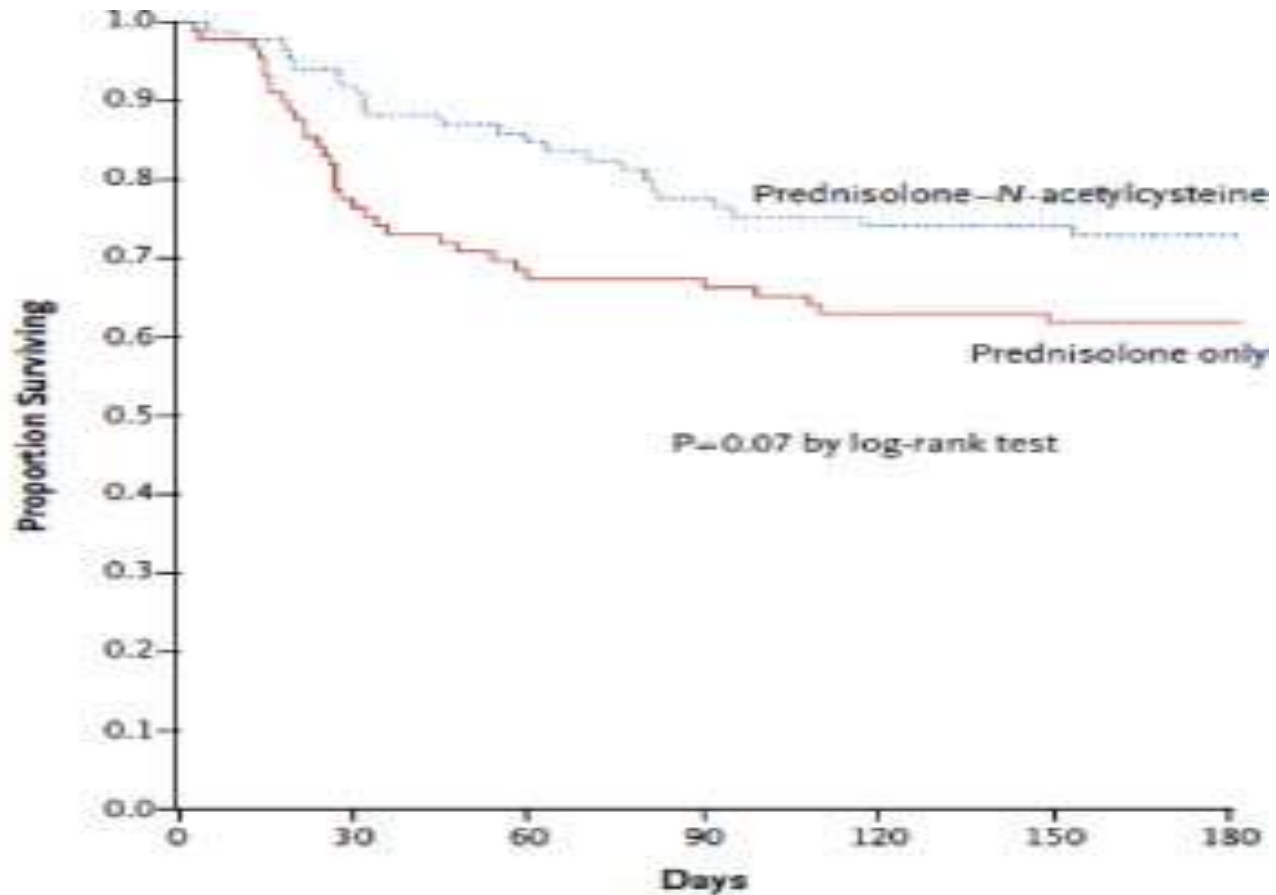
Patients at risk	Baseline	60 days	180 days
Pentoxifylline	164	111	83
Placebo	171	104	62

Less liver related complications in patients receiving pentoxifylline but this was not a primary endpoint

Does pentoxifylline really work?

- French RCT aimed to determine if PTX in combination with steroids was more effective than steroids alone
- Survival curves were interchangeable; there was no beneficial effects of combination therapy on survival, steroid response, or renal function

Treatment of alcoholic hepatitis with N-acetylcysteine



No. at Risk

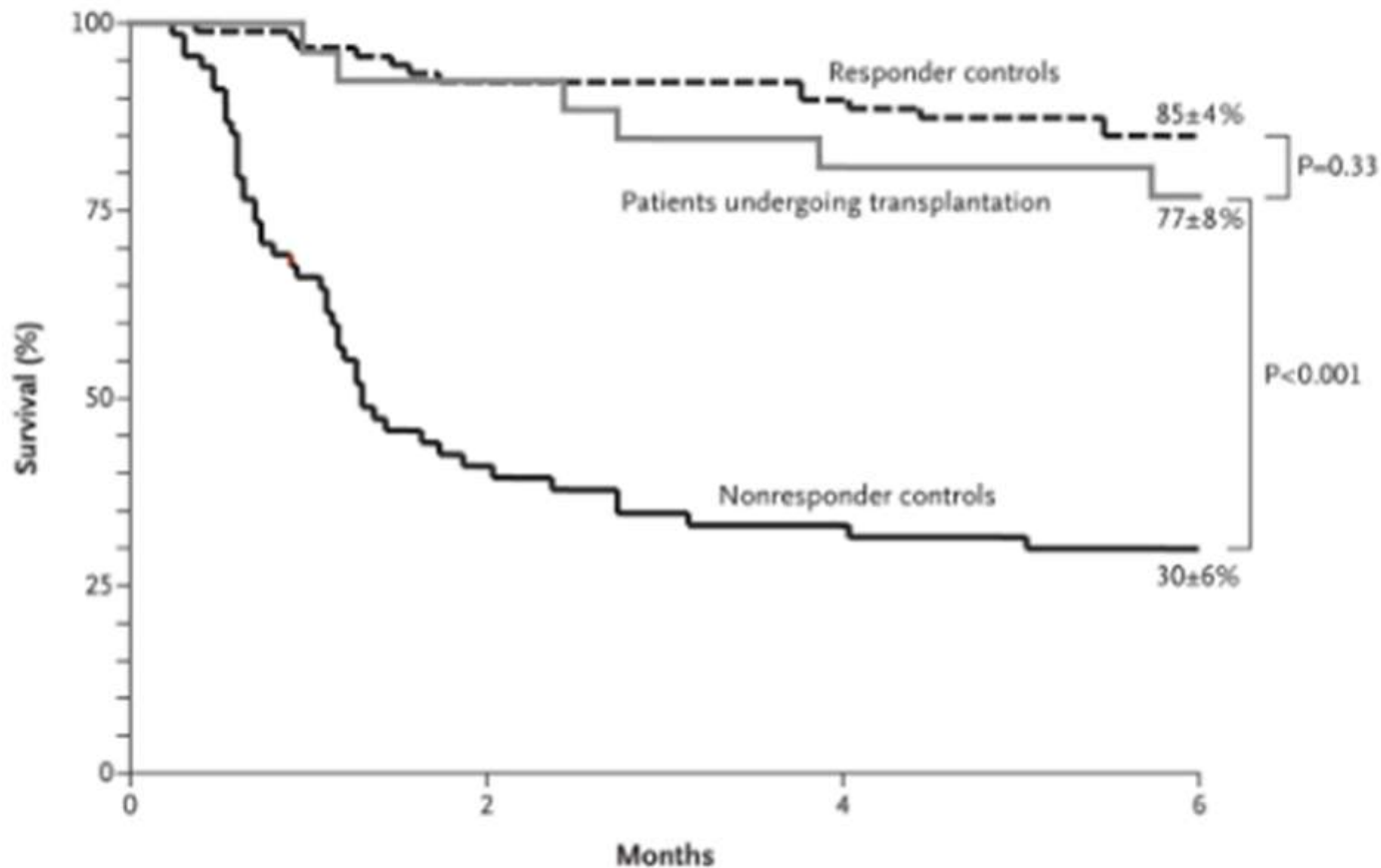
	0	30	60	90	120	150	180
Prednisolone only	89	69	61	60	56	55	46
Prednisolone-N-acetylcysteine	85	78	73	66	63	63	48

Liver Transplantation for AH

A Pilot Study in 26 patients

- Non-response to prednisolone (Lille>0.45)
- First episode of alcohol problems
- Supportive family members
- Absence of severe co-morbidities/psychiatric
- Agreement by patient and family for abstinence
- Agreement by four medical teams

Liver transplant for alcoholic hepatitis



No. at Risk

Responder controls	92	77	75	71
Patients undergoing transplantation	26	21	21	20
Nonresponder controls	69	21	21	19

Liver Transplantation for AH

- 5 of 6 deaths were due to infection
 - 4 were due to invasive aspergillus
- 233 patients admitted with AH
 - 4 (1.8%) received LT
 - 14 additional patients referred for LT
- 891 transplants performed during study
 - 26 (2.9%) were for AH
- 3 patients returned to drinking (one harmful)

Alcoholic Hepatitis Trials in Progress

- STOPAH (UK)
 - placebo vs Pred/placebo vs PTX/placebo vs Pred/PTX
 - 1200 patients
- Prednisolone vs Prednisolone + NAC (France)
- LT for AH (France)
- NIAAA consortia
 - Pilot clinical trials of new agents for AH

Summary

- ALD carries a high mortality and morbidity rate if left undiagnosed or untreated
- Alcohol abstinence remains a cornerstone in the treatment of ALD
- Prednisolone and Pentoxifylline are effective treatments for alcoholic hepatitis
- Prednisolone can be used after an infection is controlled
- LT for patients who failed prednisolone improved survival in a pilot study and deserves further investigation

Thank You