Clinical considerations on the management of alcoholic liver disease

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Topics for discussion

Burden of ALD

Assessment of ALD

Management of Alcoholic Steatohepatitis

Management of Alcoholic Cirrhosis

Burden of alcohol-related disease

- In Europe, 6.5% of all deaths and 11.6% of DALYs (disability adjusted life years) are attributable to alcohol
- Large sex differences: deaths attributable to alcohol 11% in men, 1.8% in women
- Alcohol associated mortality in young: 25% male, 10% female

Burden of ALD in Europe

- Alcohol abuse accounts for up to 30% of liver cirrhosis in France (Gut 2010).
- Mortality rates from liver cirrhosis vary considerably among European countries. Eastern European countries have higher rates.
- Time trends over past 30 years: increasing rates (Finland, Ireland, UK, most Eastern

Risk factors for disease progression

Amount of alcohol and likelihood of developing ALD

- in persons drinking >60g/d, steatosis found in 60%
- risk of developing cirrhosis highest with consumption >120g/d *Hepatology 1997, Gut 1997*
- consumption >40g/d increases risk of progression to liver cirrhosis in uncomplicated steatosis (to 30%) and in established alcoholic fibrosis (ro 37%) *Lancet 1995*

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Morphological spectrum of ALD in liver biopsy

1. steatosis with a predominant feature of macro-vesicles, associated or not with micro-vesicles (the earliest pattern)
2. hepatocyte damage often described as ballooning
3. inflammatory infiltrate which predominates in the lobules
4. a variable degree of fibrosis and lobular distortion which may progress to cirrhosis

Assessment of ALD with liver biopsy

- Presence of ALD can be suspected based on clinical, biological, and ultrasound parameters. Nevertheless, histology is required for confirmation of the diagnosis and evaluation of the severity of ALD.
- Liver biopsy should be considered in patients with aggressive forms of ALD requiring specific interventions, in patients with cofactors suspected to contribute to liver disease and in the setting of clinical studies.

Prevalence of histological lesions among heavy drinkers

In a large series of 1407 patients admitted for alcoholism or ALD undergoing a liver biopsy:

- 14% of patients had normal liver
- 28% pure steatosis
- 20% fibrosis (with or without steatosis)
- 8.5% alcoholic hepatitis
- 29% cirrhosis

Naveau et al, Hepatology 1997

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Alcoholic steatohepatitis. Definition.

- Mainly a clinical syndrome: recent onset of jaundice and/or ascites in a heavily drinking patient.
- Exacerbation of an underlying chronic liver disease (term *acute* not recommended)
- The syndrome may also result from infection, massive steatosis, drug-induced liver injury.
- Histology: coexistence of steatosis, hepatocyte ballooning and inflammatory infiltrate with PMN cells

Alcoholic steatohepatitis. Diagnosis.

- progressive jaundice
- fever (+/- infection)
- weight loss, malnutrition
- large and tender liver
- AST 2-6X, AST/ALT >2, neutrophilia, low albumin, prolonged PT, high INR

Prognostic models in alc. steatohepatitis

- Maddrey discriminant function (MDF)
- MELD (model for end-stage liver disease)
- GAHS (Glasgow alcoholic hepatitis score)
- ECBL (early change in bilirubin levels)
- Lille model

Repeated testing in prognostic models

- early improvement in liver function has a major impact on short-term mortality
- ECBL (early change in bilirubin levels)
- score changes in MELD predict in-hospital mortality
- Lille model

Maddrey's Discriminant Function

- Most commonly used predictive model; developed to facilitate assessment of response to steroids in 1978; modified in 1989

  Discriminant function =

  (4.6 x [PT -control PT]) + (total bilirubin in mg/dl)

- MDF ≥ 32 in the presence of hepatic encephalopathy (severe form) predicts > 50% mortality at 28 days (in the absence of therapy); one month survival > 90% if MDF < 32

Ramond et al, N Engl J Med 1992

Model for End-Stage Liver Disease (MELD)

- MELD score has been shown in multiple studies to predict short term mortality in pts with ASH
- MELD >11 is roughly equivalent to MDF >32
- MELD score on admission ≥ 18, MELD at 1 week ≥ 20 or rise in MELD ≥ 2 have been shown in a retrospective study to be more sensitive (91%) and specific (85%) than MDF or Child-Pugh score in predicting mortality

Dunn et al, Hepatology 2005

Srikureja et al, J Hepatol 2005

Glasgow Alcoholic Hepatitis Score

Score	1	2	3
Age	<50	≥ 50	
WCC(10^9/l)	<15	≥15	
Urea (mmol/l)	<5	≥5	
PT ratio	<1.5	1.5-2.0	>2.0
Bili (μmol/l)	<125	125-250	>250

- Derived in 2005 to identify variables related to one- and three-month survival after hospital admission in pts with ASH
- In patients with MDF ≥ 32 and GAHS < 9, no difference in survival noted with steroids
- With MDF ≥ 32 and GAHS ≥ 9, the 24 day (78 vs 52%) and 84 day (59 vs 38%) survival better with steroids

Forrest EH et al. Gut 2005; 54: 1174-9

ECBL (early change in bilirubin levels)

- Derived to determine which patients with severe (MDF ≥ 32) and biopsy-proven ASH do not respond to corticosteroids
- An early change in bilirubin levels (ECBL), defined as bilirubin level at 7 days lower than bilirubin level on the first day of treatment, identified 95% of pts with continued improvement in liver function on steroids
- At 6 months, patients with ECBL had 83% survival compared to 23% without drop in bilirubin at day 7

Mathurin et al, Hepatology 2003

Lille Model

- Model generated using 6 variables to identify patients with severe ASH (MDF ≥ 32) not responding to steroids

Lille score formula (on line computation http:/www.lillemodel.com):

3.19–0.101×age (years) +0.147×albumin on day 0 (g/L) +0.0165×evolution in bilirubin level (μmol/L) −0.206× renal insufficiency −0.0065× bilirubin on day 0 (μmol/L) −0.0096×PT (seconds)

- A score of > 0.45 identifies 75% of deaths
- A score of > 0.45 predicts a 6-month survival of 25%, versus a 85% survival when the score is <45%
- Better than Child Pugh, MDF, GAHS, and MELD at predicting prognosis

Louvet et al, Hepatology 2007

Table 1. Components of Scoring Systems Used to Assess Prognosis in Alcoholic Hepatitis.*

Scoring System	Components							
	Bilirubin	Prothrombin Time or INR	Creatinine	Age	White-Cell Count	Urea Nitrogen	Albumin	Change in Bilirubin between Day 0 and Day 7
Maddrey's discriminant function†	Yes	Yes	No	No	No	No	No	No
MELD score‡	Yes	Yes	Yes	No	No	No	No	No
Glasgow score§	Yes	Yes	No	Yes	Yes	Yes	No	No
Lille score¶	Yes	Yes	Yes	Yes	No	No	Yes	Yes

Lucey et al, N Engl J Med 2009

Management. General measures

- alcohol abstinence
- compensation of vitB and liposoluble vitamins deficiencies
- treat malnutrition - daily protein intake: 1.5 g/kg body weight
- prevent renal failure (volume expansion, early treatment of hepatorenal syndrome)
- infection screening at admission

Corticosteroid therapy

- Most intensely studied, most sharply debated
- Blocks cytotoxic and inflammatory pathways, inhibition of leucocyte activation
- Consider only in severe ASH (MDF>32 or hepatic encephalopathy). Predn 40mg/d for 4w and taper (provided ECBL)
- Stop early in non-responders (after 7 days consider poor response)
- Contraindications: mild cases, GI bleeding, active infection (allowed after appropriate antibiotic treatment), renal insufficiency

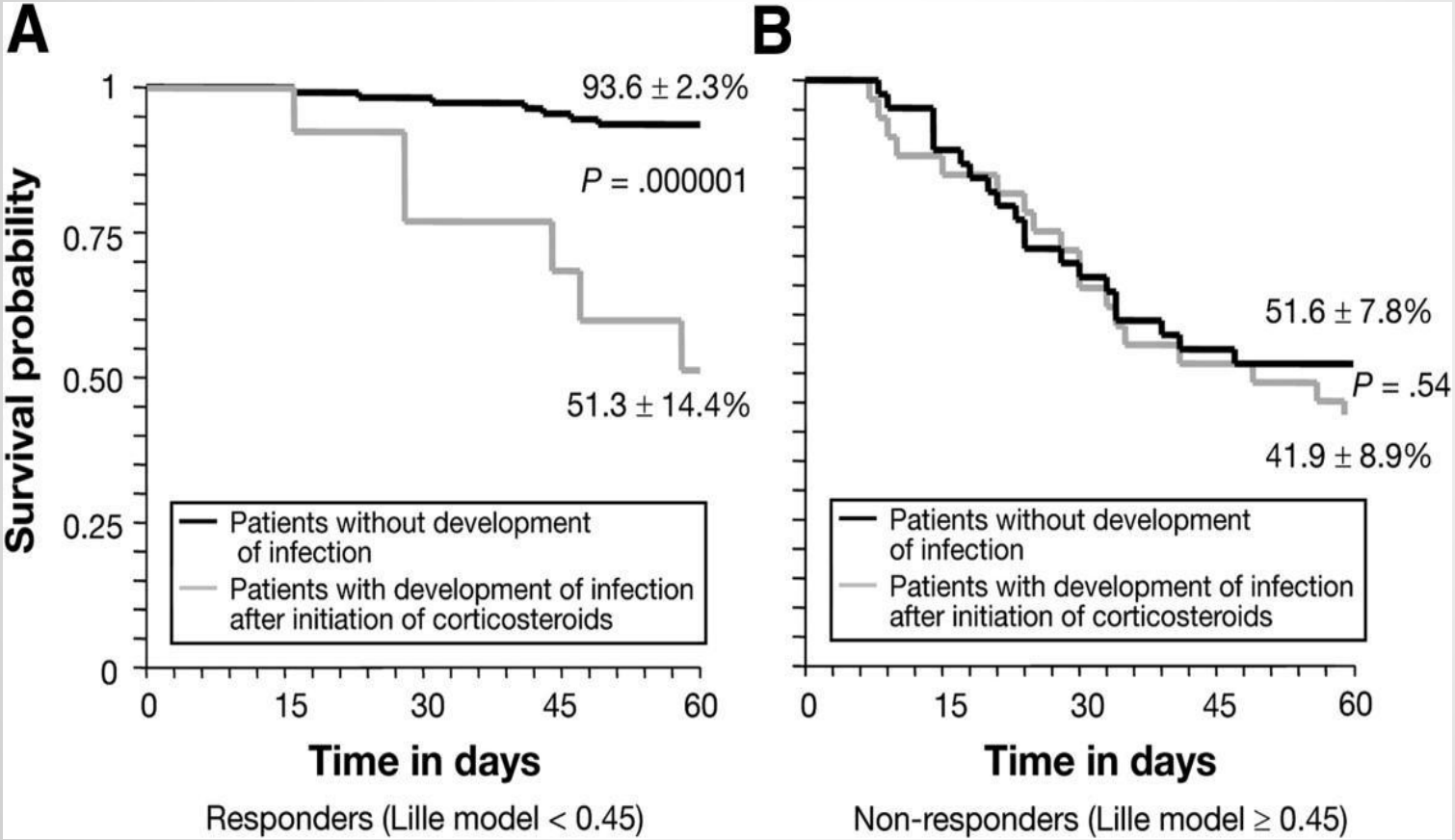
Steroids for ASH

- Data from the 3 largest trials of Prednisolone vs placebo analyzed patients with MDF ≥ 32
- 28 day survival was 85% vs 65%, **NNT 5**
- The 5 largest trials were re-analyzed in Cochrane review which confirmed the survival benefit in patients with MDF ≥ 32 or hepatic encephalopathy
- ~40% pts with ASH are unresponsive to steroids

Mathurin et al, Hepatology 2003, 2008

Rambaldi et al, Aliment Pharmacol Ther 2008

Steroids, infection and early response



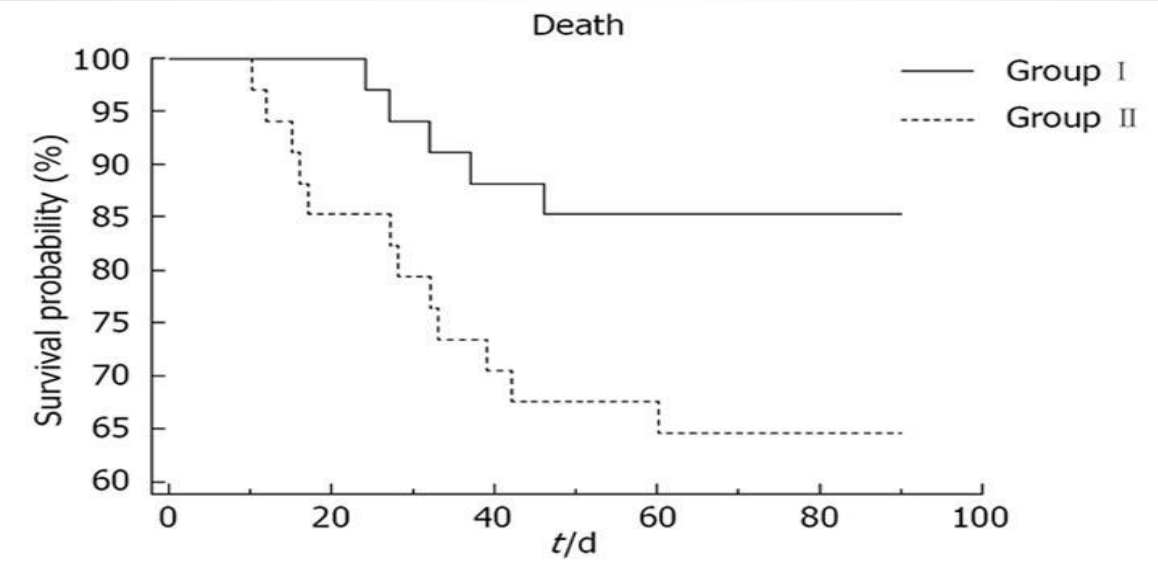
Louvet et al. Gastro 2009

Pentoxifylline on ASH

- A non-selective phosphodiesterase inhibitor and TNF-α suppressor.
- RCT of 101 patients with severe ASH (MDF ≥ 32) receiving 4 weeks pentoxifylline 400mg TID versus placebo: lower hospital mortality in PTX group (24.5%) versus placebo group (46.1%)-Hepatorenal syndrome was the cause of death in 50% PTX pts and 92% of placebo group.
- TNF-α levels were not predictive of survival but were increased markedly in non-survivors vs survivors.

Akriviadis et al, Gastroenterology 2000

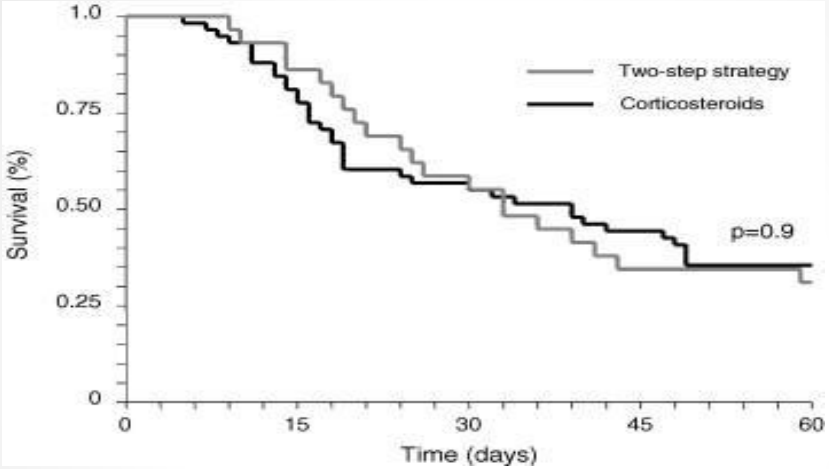
Pentoxifylline vs Prednisone



- RCT of 68 pts with severe ASH (MDF ≥ 32) receiving Prednisolone (Gr I) vs Pentoxifylline (Gr II)
- 3-month mortality was 35% in steroid group vs 14.7% in PTX; more pts in steroid group developed hepatorenal syndrome

Krishna De et al, World J Gastroenterol 2009

Pentoxifylline in Steroid Non-Responders



- 121 pts with severe AH were treated with steroids; of 87 non-responders (using ECBL), 29 were switched to PTX and 58 kept on steroids
- There was no survival benefit at 2 months in pts switched to PTX (35.5 versus 31%)

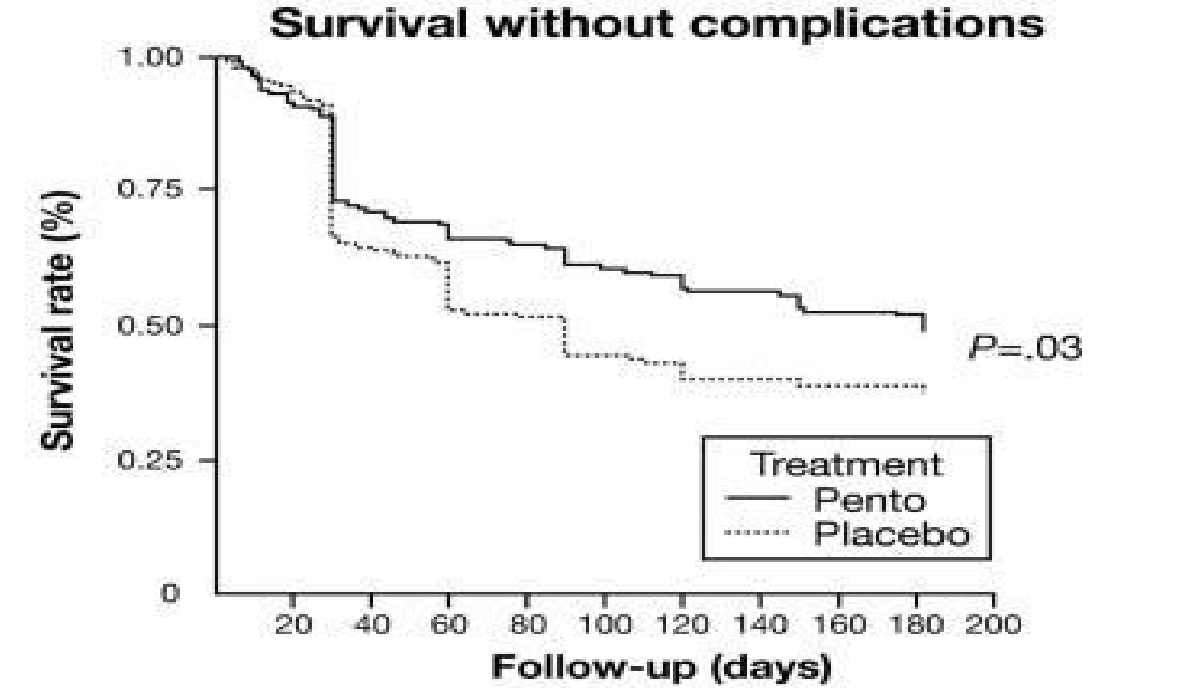
Louvet et al, Hepatology 2008

Pentoxifylline in advanced cirrhosis

- 335 patients with cirrhosis (Child Pugh C) were given pentox or placebo for 6 months. **Mortality was no different** at 2 or 6 months in either group (6 month mortality 30% in pentox group and 31.5% in placebo group)
- **Pentox reduced complication rates**: the proportion of patients without complications (infection, renal insufficiency, hepatic encephalopathy, or GI bleeding) was higher in the pentox group than in the placebo group at 2 months (78.6% vs 63.4%) and 6 months (66.8% vs 49.7%).
- 133 pts had ASH. 55 pts had MDF ≥ 32 and got steroids along with pentox vs placebo-there was **no difference in 2 and 6 month mortality** between these groups

Lebrec et al, Gastroenterology 2010

Pentoxifylline in advanced cirrhosis



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

Anti TNF-a treatment in ASH

- Infliximab and Etanercept have been studied for severe ASH
- Infliximab showed a positive effect in small studies; RCT comparing Infliximab and Prednisolone was stopped early due to increased rates of infections and death
- Etanercept was studied in 48 patients with MELD ≥ 15 versus placebo x 3 weeks; 6 month mortality was higher in Etanercept group (58 versus 23%); infection rates were also higher (35 versus 9%)
- Speculation: excessive TNF blockade negatively affects liver regeneration

Naveau et al, Hepatology 2004

Boetticher et al. Gastroenterology 2008

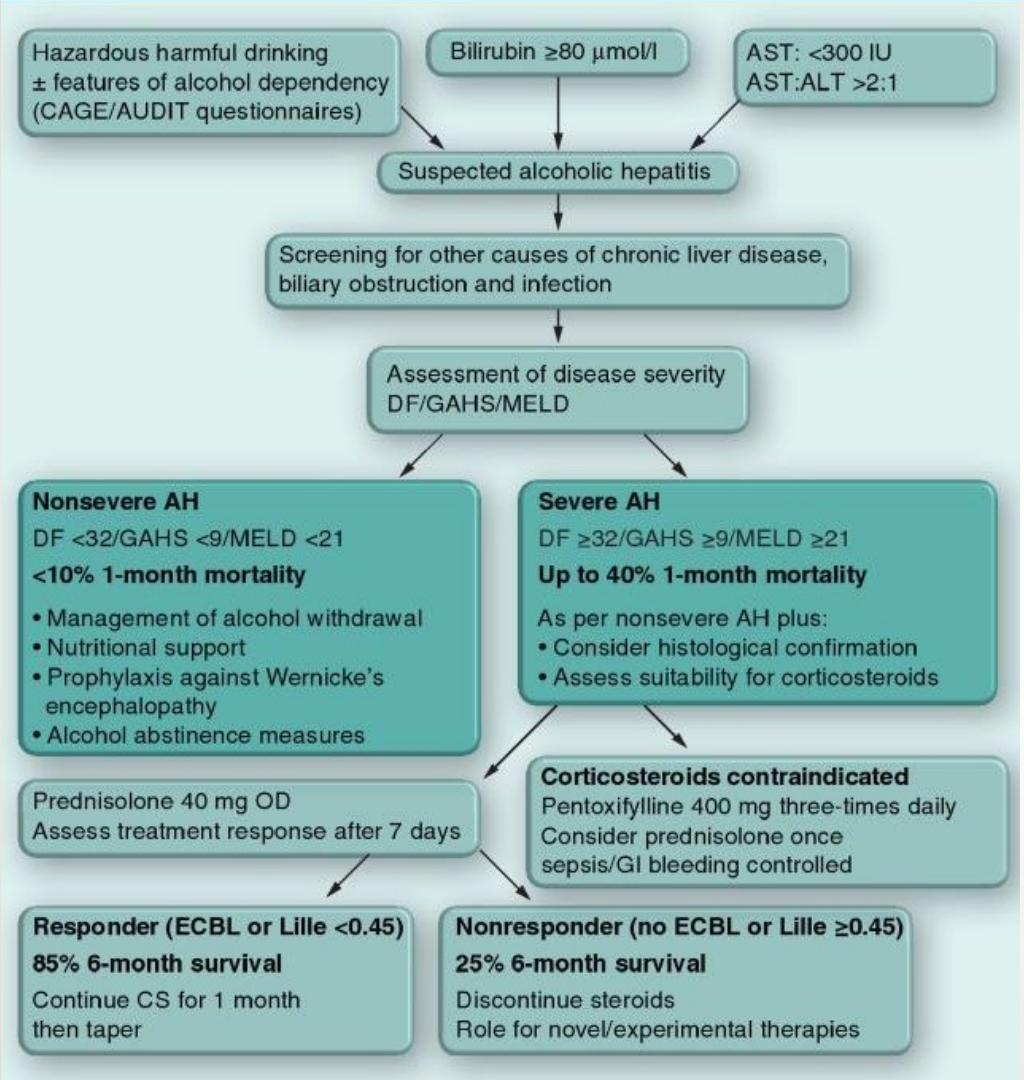
Nutrition in ASH

- Mortality in ASH is closely correlated with degree of malnutrition
- RCT comparing enteral tube feeding (2000 kcal/day) vs Prednisolone in 71 pts with severe ASH revealed similar 1-month and 1-yr survival in both groups highlighting the effects of nutritional support

Cabre et al, Hepatology 2000

Other therapies

- N-acetylcysteine. No evidence of a significant effect. May have synergistic effects with steroids
- Propylthiouracil. No significant effect. Not recommended
- Colchicine. No effect on short-term survival. Not recommended



ECBL: early change in bilirubin

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Clinical course of alcoholic cirrhosis

- Only 30% of pts with AC are hospitalized before decompensation
- Risk, first year after hospitalization: 20% ascites, 6% variceal bleeding, 4% hepatic encephalopathy
- HCC in AC: 7-16% after 5y, 29% after 5y

Jepsen et al, Hepatology 2010

N'Kontchou et al, Clin Gastro Hepatol 2006

Screening in pts with alcoholic cirrhosis

- HCC
- alcoholic myocardiopathy
- IgA-induced nephropathy
- central and peripheral CNS involvement
- chronic pancreatitis
- evaluation of nutritional status
- pts with impaired cognitive function: alcoholic dementia, Wernicke’s encephalopathy, withdrawal syndrome

Factors increasing death risk

- persistence of alcohol use
- superimposed episodes of ASH - bad prognosis
- smoking
- comorbidity

Bell et al, Scand J Gastro 2004

Pessione et al, Liver Int 2003

Jepsen et al, Hepatology 2008

Treatment goals in alcoholic cirrhosis

- alcohol abstinence (motivational therapy, anti-craving drugs, use of disulfiram not recommended - hepatotoxicity, baclofen useful)
- aggressive nutrition therapy rich in proteins
- prophylaxis of cirrhosis complications

Addolorato et al, Lancet 2007

Conclusions

- Alcoholic liver disease is the most prevalent cause of advanced liver disease in Europe.
- ALD is a complex disease. An interdisciplinary approach is recommended: public health, addiction medicine, alcohol-induced organ injury.
- ALD may have several aspects: steatosis, steatohepatitis and cirrhosis.