Alcoholic hepatitis

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Bible Class Gastroenterolgy

Definitions

A) Alcohol use disorder

B) Alcohol-related liver disease (ALD)

C) Cirrhosis due to ALD

D) Steatohepatitis due to ALD

E) Fibrosis due to ALD

F) Alcoholic hepatitis (AH)

Previous term	Current term	Abbreviation
Alcoholic	Alcohol use disorder	AUD
Alcoholic liver disease	Alcohol-related liver disease	ALD
Alcoholic cirrhosis	Cirrhosis due to alcohol-related liver disease	ALD cirrhosis
Alcoholic steatohepatitis (histologically-defined lesion)	Steatohepatitis due to ALD	ASH
Alcoholic fibrosis	Fibrosis due to ALD	ALD fibrosis
Alcoholic hepatitis	Alcoholic hepatitis*	AH

Clinical presentation of alcoholic hepatitis?

Cardinal sign of AH:

- Progressive jaundice in patients with ongoing alcohol abuse.
- It is not uncommon for patients to have ceased alcohol consumption days or weeks before the onset of symptoms.

Other signs of AH:

- Fever (even in the absence of infection)
- Malaise, weight loss and malnutrition

Lab presentation of alcoholic hepatitis

Laboratory profile:

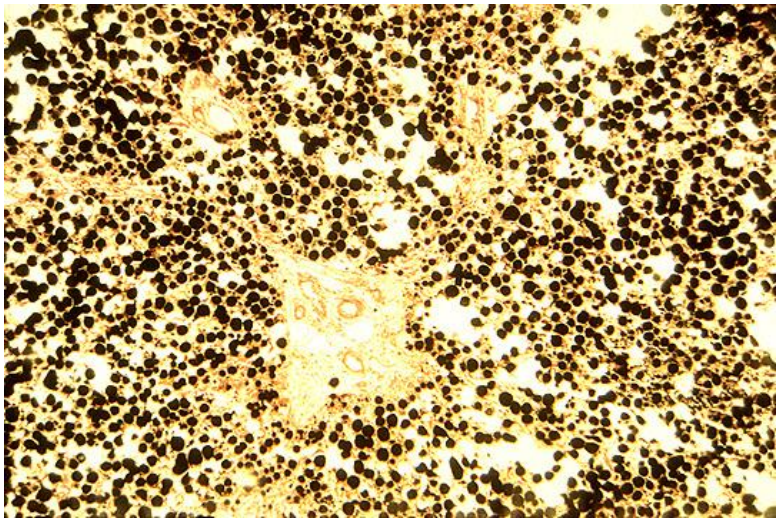
- Hyperbilirubinemia (>50 µmol/L)
- AST greater than twice the upper limit of normal (although rarely above 300 U/L)
- AST/ALT ratio typically greater than 1.5–2.0
- Neutrophilia

Severe forms:

- Prolonged prothrombin time
- Hypoalbuminemia
- Decreased platelet count

Histological features of the underlying steatohepatitis due to ALD?

Steatohepatitis



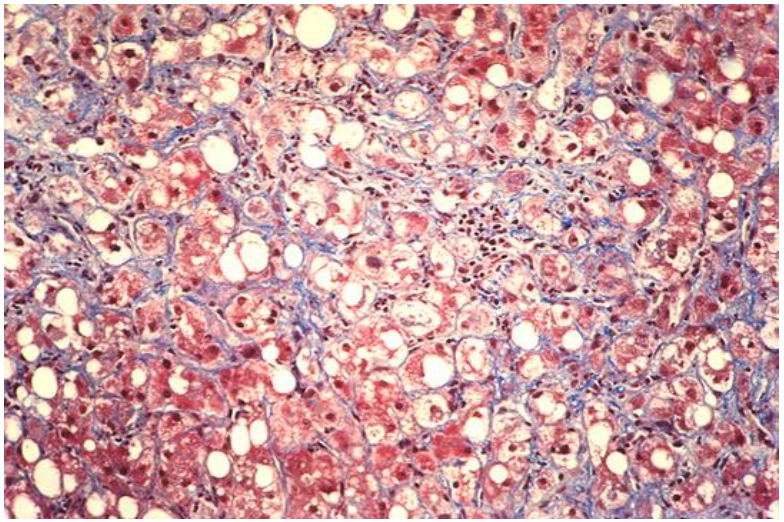
Fatty change

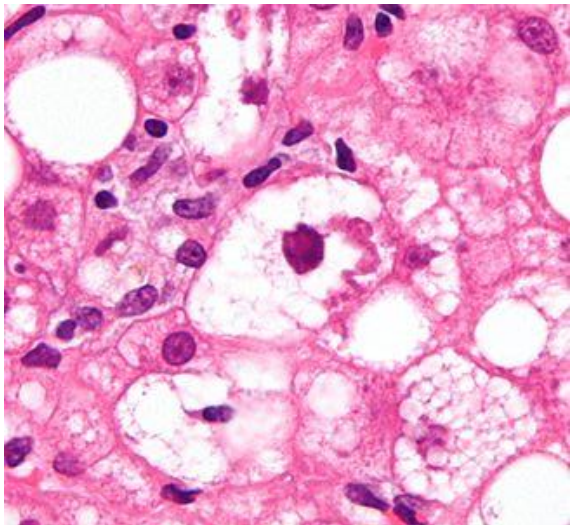
Pericellular fibrosis

Mallory's hyaline

Hepatocyte ballooning

PMN infiltrate





www.meddean.luc.edu

Histological features of alcoholic hepatitis?

Gastroenterology 2014;146:1231–1239

CLINICAL—LIVER

A Histologic Scoring System for Prognosis of Patients With Alcoholic Hepatitis

José Altamirano,[1] Rosa Miquel,[2] Aezam Katoonizadeh,[3] Juan G. Abraldes,[4,5] Andrés Duarte–Rojo,[6,7] Alexandre Louvet,[8] Salvador Augustin,[9] Rajeshwar P. Mookerjee,[10] Javier Michelena,[1] Thomas C. Smyrk,[11] David Buob,[12] Emmanuelle Leteurtre,[12] Diego Rincón,[13] Pablo Ruiz,[1] Juan Carlos García–Pagán,[1,5] Carmen Guerrero–Marquez,[14] Patricia D. Jones,[15] A. Sidney Barritt IV,[15] Vicente Arroyo,[1] Miquel Bruguera,[1] Rafael Bañares,[13] Pere Ginès,[1] Juan Caballería,[1] Tania Roskams,[3] Frederik Nevens,[16] Rajiv Jalan,[10] Philippe Mathurin,[8] Vijay H. Shah,[6] and Ramón Bataller[1,15]

Table 3. AHHS for Prognostic Stratification of AH

	Points
Stage of fibrosis	
No fibrosis or portal fibrosis	0
Expansive fibrosis	0
Bridging fibrosis or cirrhosis	+3
Bilirubinostasis	
No	0
Hepatocellular only	0
Canalicular or ductular	+1
Canalicular or ductular plus hepatocellular	+2
PMN infiltration	
No/Mild	+2
Severe	0
Megamitochondria	
No megamitochondria	+2
Megamitochondria	0

NOTE. The AHHS categories are as follows: mild, 0–3; intermediate, 4–5; severe, 6–9. Histologic features included in the AHHS were the product of the multivariate logistic regression analysis (Table 2). Weighting of each histologic feature was based on the odds ratio of the updated model (training plus test set samples). See Supplementary Methods for information on model building.

Which are the most useful scores in alcoholic hepatitis?

Based on which parameters are they calculated?

Table 6. Variables incorporated in the five prognostic scores most commonly used in alcoholic hepatitis.

Score	Bilirubin	PT/INR	Creatinine/urea	Leucocytes	Age	Albumin	Change in bilirubin from day 0 to day 7
Maddrey	+	+	–	–	–	–	–
MELD	+	+	+	–	–	–	–
GAHS	+	+	+	+	+	–	–
ABIC	+	+	+	–	+	–	–
Lille	+	+	+	–	+	+	+

Maddrey, Maddrey discriminant function; MELD, model for end-stage liver disease; GAHS, Glasgow alcoholic hepatitis score; ABIC, age, serum bilirubin, INR, and serum creatinine score.

Maddrey DF was originally developed in 1978, and then modified (mDF) in 1989.

How to evaluate the severity of alcoholic hepatitis?

mDF: In its modified version, a cut-off value of 32 identifies patients with severe AH and is usually the threshold used for initiating specific therapy.

MELD: Retrospective studies suggest that patients with an MELD score above 20 are at a high risk of 90-day mortality

GAHS: Five variables independently associated with outcome (age, serum bilirubin, blood urea, prothrombin time, and peripheral blood white blood cell count) and identifies patients at greatest risk of death in the absence of treatment. The GAHS ranges from 5 to 12 and patients with an mDF ≥32 and a GAHS ≥9 have a poor prognosis and an 84-day survival benefit when treated with corticosteroid.

The **ABIC** score classified patients with AH according to low, intermediate and high risk of death at 90 days.

These different scoring systems often incorporate the same variables and appear to have similar efficacy in predicting short-term survival.

How to treat patients with alcoholic hepatitis?

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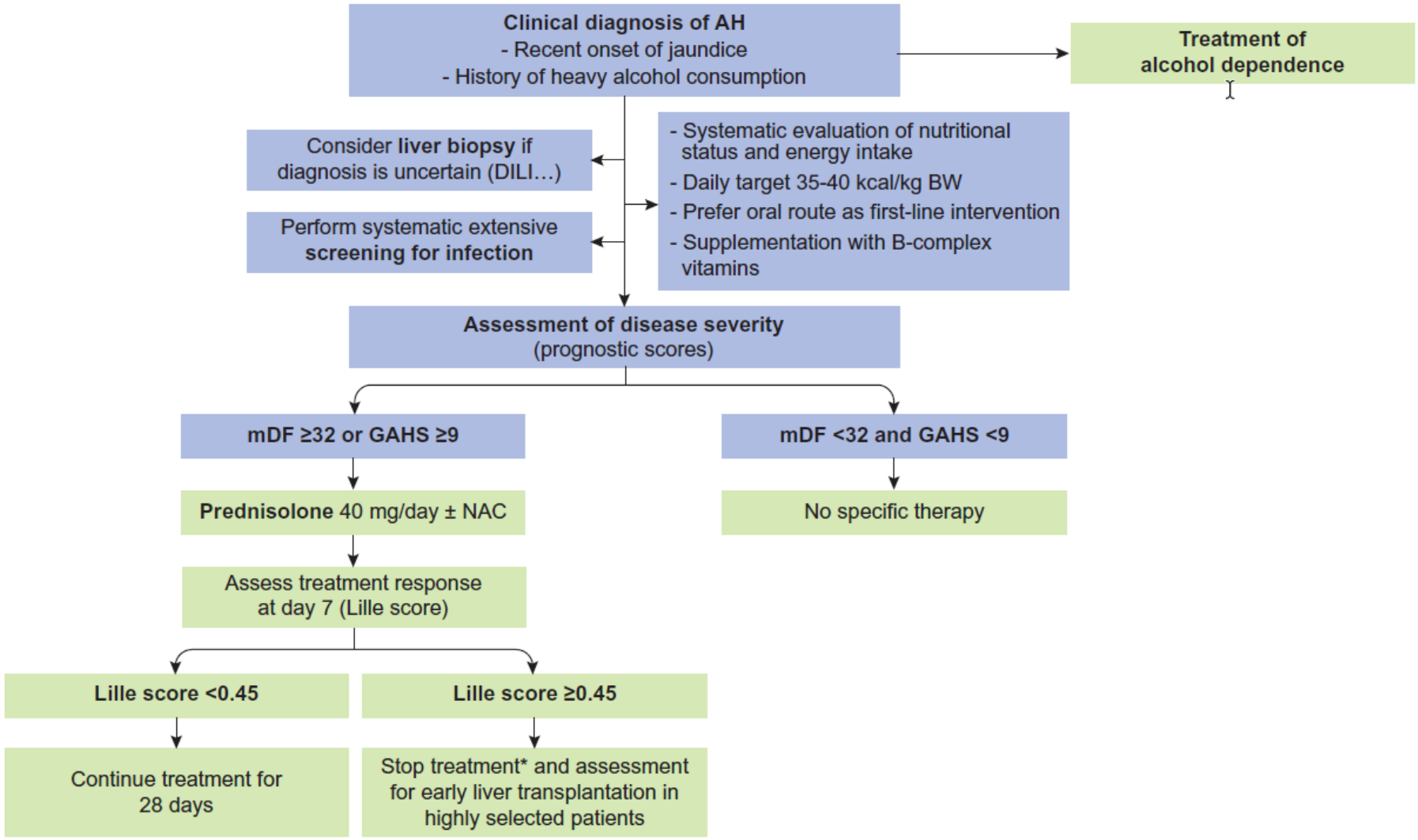

How to evaluate response to steroids?


Lillemodel.com
Introduction
Lille Model
MELD Score
Child-Pugh Score
Maddrey Score
Glasgow Score
ABIC Score
Alcoholic Hepatitis in General
Contact
Lille Model
This model has been developed by the hepatology unit of the CHRU Lille with the collaboration of 4 other French centers.
In the following model, survival probability at 6 months is defined by the 0.45-cutoff: 6-month survival probability of patients with a Lille model above 0.45 is about 25% contrary to patients with a Lille model below this cutoff (85%).
See for more details the manuscript published in Hepatology 2007.
Day 0 23 / 2 / 2016 (dd/mm/yyyy)
Date of Birth / / (dd/mm/yyyy)
Bilirubin µmol/L (at Day 0)
µmol/L (at Day 7)
Creatinine µmol/L (at Day 0)
Albumin* g/L (at Day 0)
Patient's prothrombin time sec (at Day 0)
Compute
Reset all fields

What about nutrition in patients with alcoholic hepatitis?

- Malnutrition is commonly associated with cirrhosis and its severity.
- Several studies have highlighted that protein energy malnutrition is present in almost every patient with severe AH, and is associated with poor prognosis.
- The European Society for Clinical Nutrition and Metabolism (ESPEN) recommend a daily energy intake of 35–40 kcal/kg of body weight (BW) and a daily protein intake of 1.2–1.5 g/kg of BW in patients with AH.
- Patients with a daily calorie intake below 21.5 kcal/kg of BW had a significantly higher risk of one- and six-month mortality and infections. (post-hoc analysis)

Is extracorporeal liver support a treatment option?

Extracorporeal liver support procedures can remove some potentially damaging circulating molecules, and are therefore of potential interest in patients with severe AH.

Some encouraging preliminary data with albumin dialysis were reported in patients with severe AH.

However, to date, no clear benefit has been demonstrated using these extracorporeal liver support devices.

Are patients with AH candidates for liver transplantation?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early Liver Transplantation for Severe Alcoholic Hepatitis

Philippe Mathurin, M.D., Ph.D., Christophe Moreno, M.D., Ph.D.,

N Engl J Med 2011;365:1790-1800.

CONCLUSIONS

Early liver transplantation can improve survival in patients with a first episode of severe alcoholic hepatitis not responding to medical therapy. (Funded by Société Nationale Française de Gastroentérologie.)

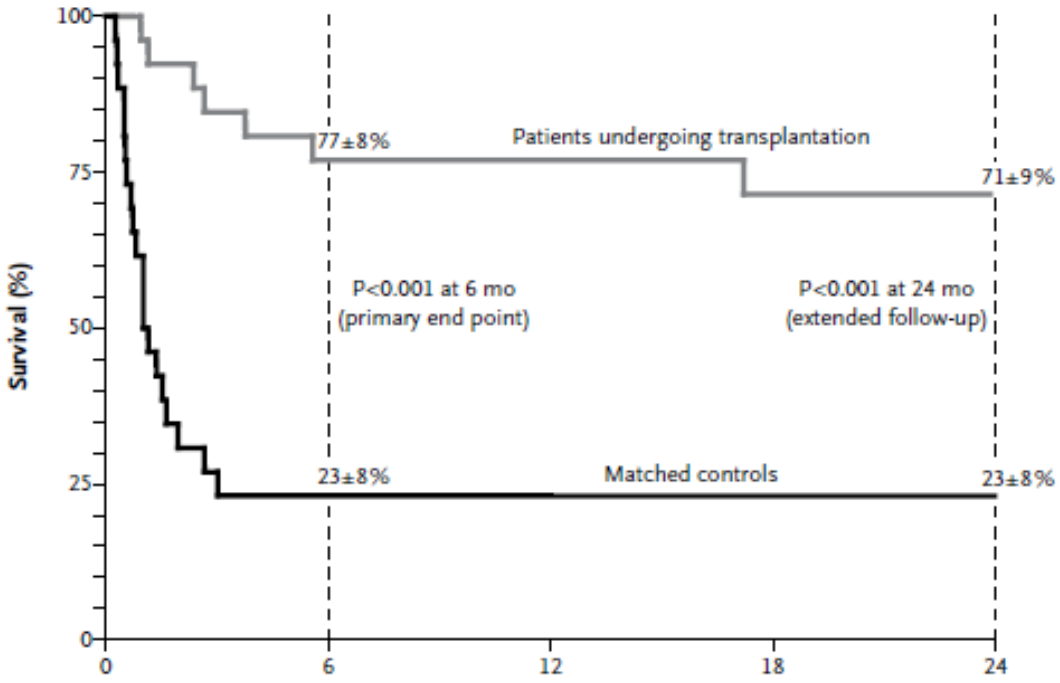

Figure 1. Kaplan–Meier Estimates of Survival in the 26 Study Patients and the 26 Best-Fit Matched Controls.

N ENGL J MED 365;19 NEJM.ORG NOVEMBER 10, 2011

Future treatment strategies?

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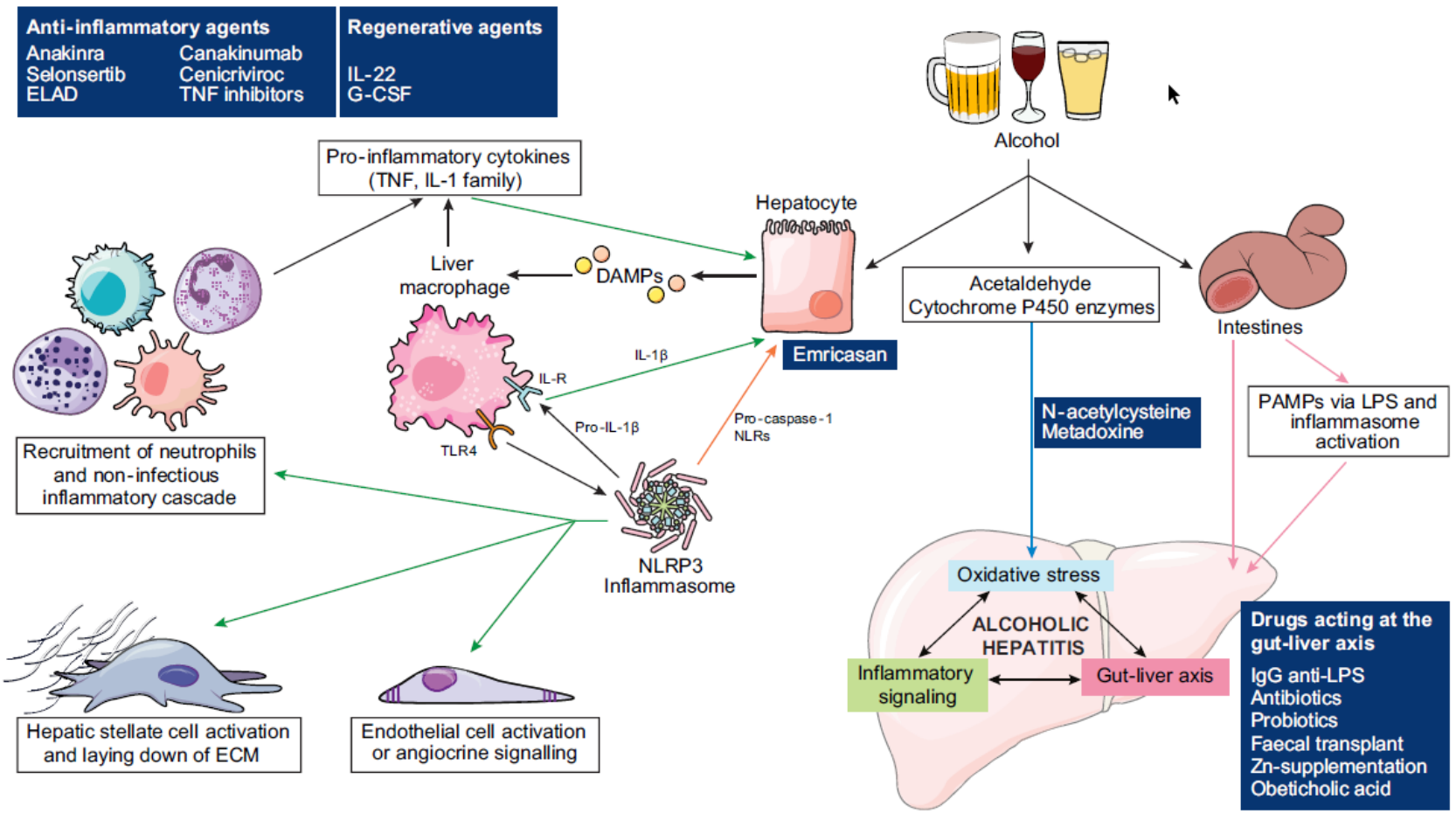

Singal et al. Journal of Hepatology 2019 vol. 70 | 305–313

Table 1. Current clinical trials with novel therapeutic agents for treatment of alcoholic hepatitis.

Pharmaceutical agent	Mechanism of action	Study design [N]	Main inclusion	Primary endpoint	Status
Bovine colostrum (IMM-124E)	IgG to LPS and reduces bacterial translocation	Placebo controlled RCT	MELD score ≥20 but ≤28	Decrease in serum endotoxin levels at 7 months	Phase II, active, not recruiting
Lactobacillus rhamnosus GG	Change in gut microbiome	Placebo controlled RCT	MELD score <21	Change in MELD score at 30 days	Phase II, active and recruiting
Augmentin	Antibiotic amoxicillin plus clavulanic acid	Placebo controlled RCT with CS	MELD score ≥21	Survival at 2 months	Phase III, active and recruiting
Faecal transplant	Change in gut microbiome	RCT FMT *vs.* CS[42]	Eligible for CS treatment	Survival at 3 months	Active and recruiting
Anakinra	Antagonist to IL-1 receptor	RCT Anakinra + Zn + PTX *vs.* CS[42]	MELD score ≥20 and Madre DF ≥32	Survival at 6 months	Phase II, active and recruiting
Obeticholic acid [INT-747]	FXR activation, bile acid agonist, and anti-inflammatory	Placebo controlled RCT	MELD score >11 and <20	Change in MELD score at 6 weeks	Phase II, completed
Selonsertib [GS-4997]	ASK-1 antagonist to inhibit MAPK, JNK, p38	Placebo controlled RCT with CS	Maddrey DF score ≥32	Safety and SAE at 28 days plus 30 days	Phase II, completed
Emricasan [IDN-6556]	Pan caspase inhibitor	Placebo controlled RCT[42]	MELD score >20 but <35 or 35–40 if SOFA score <10	Survival at 28 days	Phase II, terminated after 5 patients
Metadoxine	Antioxidant and promotes abstinence	Placebo controlled RCT with CS[42]	Severe alcoholic hepatitis	Survival at 30 days	Phase IV, completed
IL-22 [F-652]	Anti-inflammatory and hepatic regeneration	Open label	MELD score 11–28	Safety and SAE at 42 days	Phase I completed Phase II planned
G-CSF [Filgrastim]	Increase neutrophils, hepatic regeneration	Placebo controlled RCT with CS in partial responder and without CS in null responder	Maddrey DF score ≥32	Survival at 2 months in null responder to CS and at 6 months in partial responder	Phase IV, active and recruiting

CS, corticosteroid; MELD, model for end-stage liver disease; PTX, pentoxifylline; RCT, randomised controlled trial; SAE, serious adverse event; SOFA, sequential organ failure assessment.

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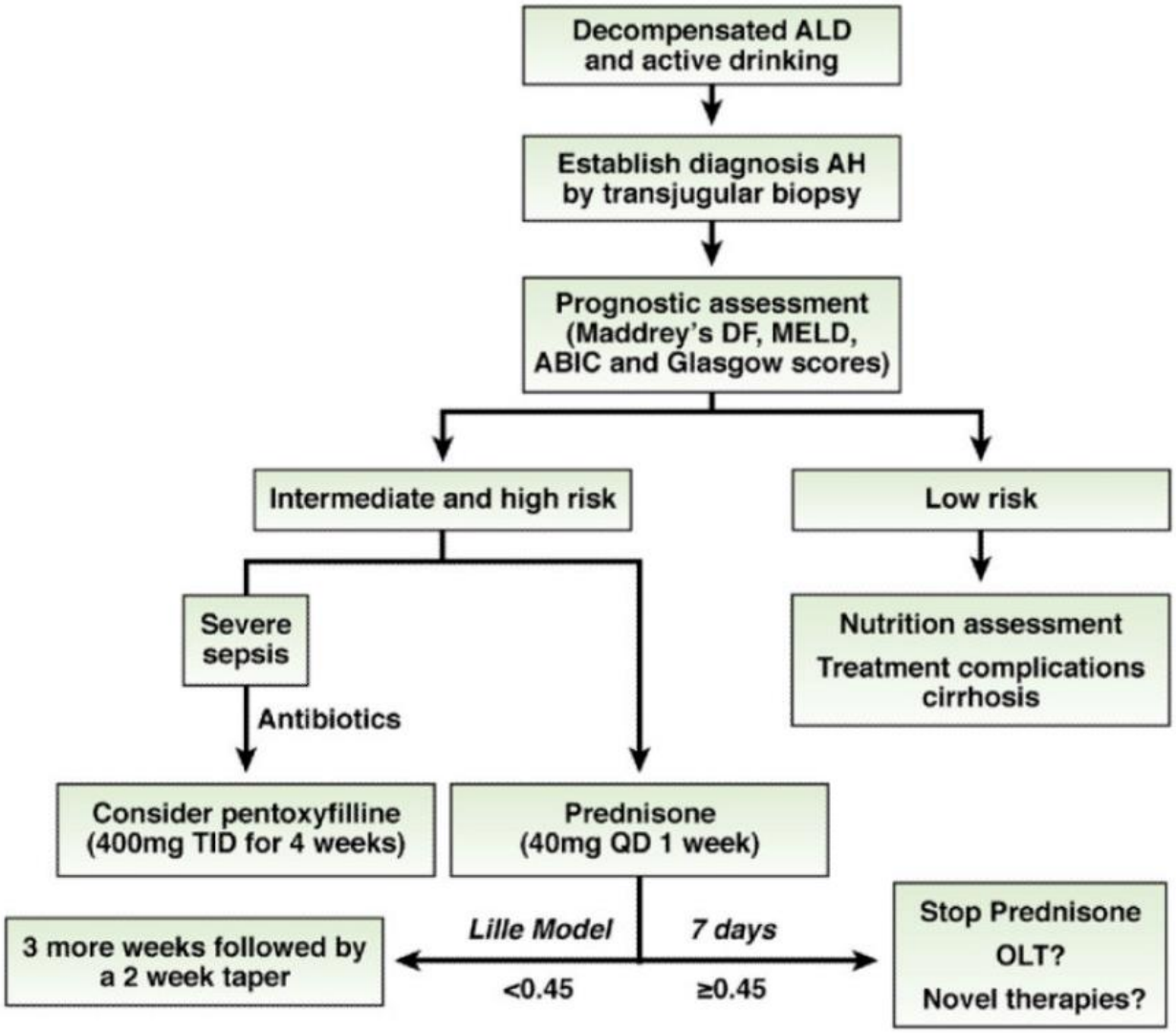
Is pentoxyfilline still a treatment option?

Pentoxyfilline is a phosphodiesterase inhibitor with the ability to inhibit production of tumour necrosis factor (TNF).



Gao. Gastroenterology 2012

IL-1 receptor antagonist in combination with pentoxifylline and zinc for severe alcoholic hepatitis: A multicenter randomized double-bind placebo-controlled clinical trial

Aims: This study evaluated the safety and efficacy of the combination of recombinant human interleukin-1 receptor antagonist (anakinra), pentoxifylline (PTX), and zinc (Zn) sulfate in patients with AH. We targeted critical pathogenic elements of AH: inflammation (anakinra), protection from cellular injury (PTX), and gut leakiness (Zn).

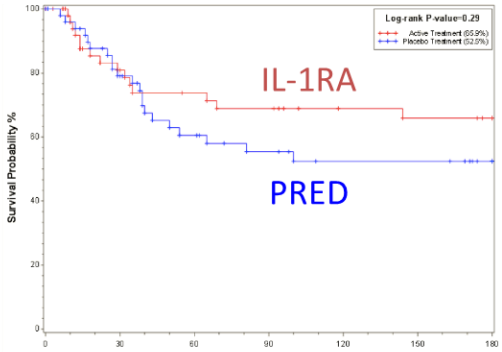
Methods: Subjects with clinical diagnosis of severe AH (MELD >20, MDF >32) were randomized to methyl prednisolone, 32 mg orally daily for 28 days (PRED) or a combination of anakinra, 100 mg daily subcutaneously for 14 days plus PTX 400 mg orally 3 times daily for 28 days plus Zn 220 mg orally daily for 180 days (IL-1RA). Endpoints included mortality at 30, 90, and 180 days. A Cox proportional regression analysis was used to identify variables associated with mortality.

Results:

- Fifty-three patients were randomized into the IL-1RA and 50 to the PRED arms.
- Baseline characteristics were comparable between treatment groups.
- Survival probability at 180-day post randomization, the primary outcome was 66.8% in the IL-1RA and 52.8% in the PRED group (HR=0.69; *p*=0.26).
- In Cox regression analysis, higher baseline MELD score was independently associated with mortality (*p*=0.003).
- No unexpected treatment-related severe adverse events were noted in either group. The incidence of infection was comparable in both groups.
- Survival at 180 days in subjects with initial MELD 20-25 (72.6%) was significantly higher than those with initial MELD 26-31 (45.2%) (HR=2.9, *p*=0.003).
- Both MELD strata (MELD 21-25; MELD 26-31) showed non-significant treatment effects in favor of IL-1RA.

Szabo G, et al., Abstract LB-1 (U01 AA0021893 DASH Consortium)

Kaplan-Meier survival curves through 180 days by treatment group



Conclusions: A combination of anakinra, PTX, and Zn provides comparable short-term and may provide long-term survival benefits compared to currently used PRED therapy in severe AH. Initial MELD is an important predictor of survival at 30, 90, and 180 days.

The End