ALCOHOLIC LIVER DISEASE (ALD)

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Objectives

- Spectrum of alcoholic liver disease
  - Focus on Alcoholic Hepatitis (AH)
- Pathophysiology and role of inflammation in AH
- Scoring systems to assess severity
- Treatment algorithm
- Role of corticosteroids and pentoxifylline (PTX)

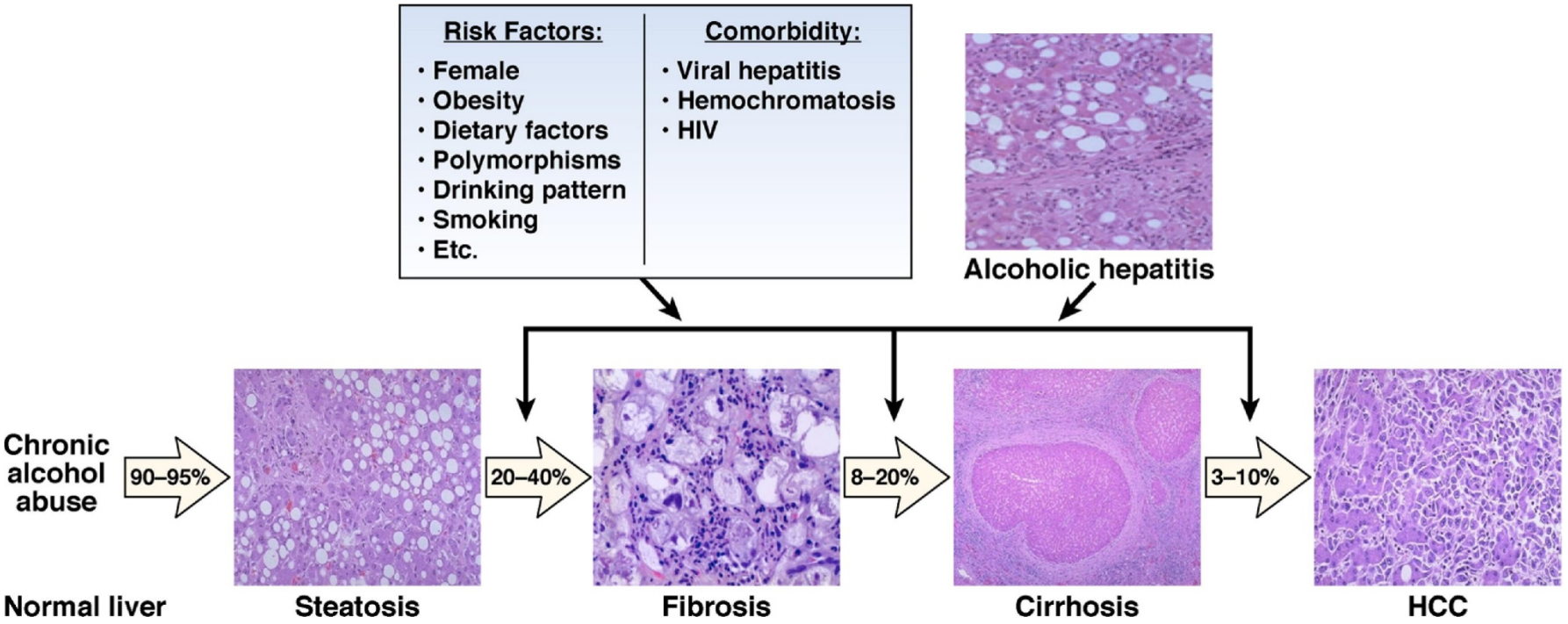
Epidemiology

- In the U.S., approximately 67% of people drink alcohol
- Majority drink small or moderate amounts
  - No evidence of clinical disease
- Alcohol dependence - drink excessively, develop physical tolerance and withdrawal (3.8%)
- Alcohol abusers and problem drinkers (4.5%)
  - those who engage in harmful use of alcohol, defined by the development of negative social and health consequences of drinking (e.g., repeated absences or poor work performance, recurrent legal problems, neglect of family or children, organ damage, accidental injury, or death)

Epidemiology

- Alcoholic cirrhosis – 8th leading cause of death in US
- 40% of deaths from cirrhosis
- 30% of deaths from HCC

Spectrum of Disease

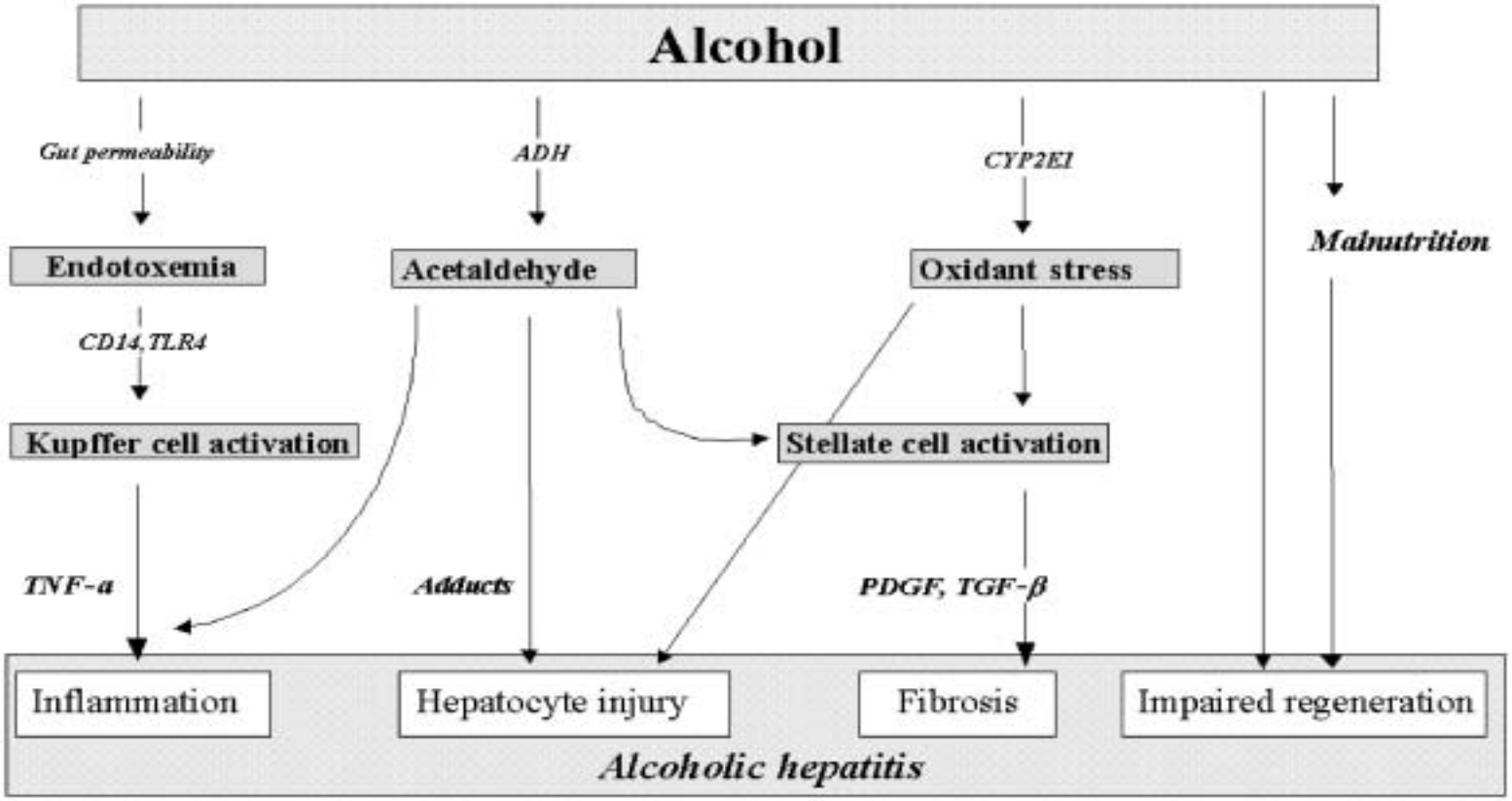


ALD

- Development of liver injury
  - the dose, duration, drinking patterns, sex, ethnicity;
  - associated risk factors including obesity, iron overload, concomitant infection with viral hepatitis, and genetic factors
- **The amount of alcohol ingested (independent of the form in which it is ingested) is the most important risk factor for the development of ALD**
- Risk of cirrhosis
  - Men >60-80grams/day
  - Women >20grams/day
- One drink (12 oz beer, 4 oz wine, 1-1.5 oz spirit) =10-12 grams

ALD

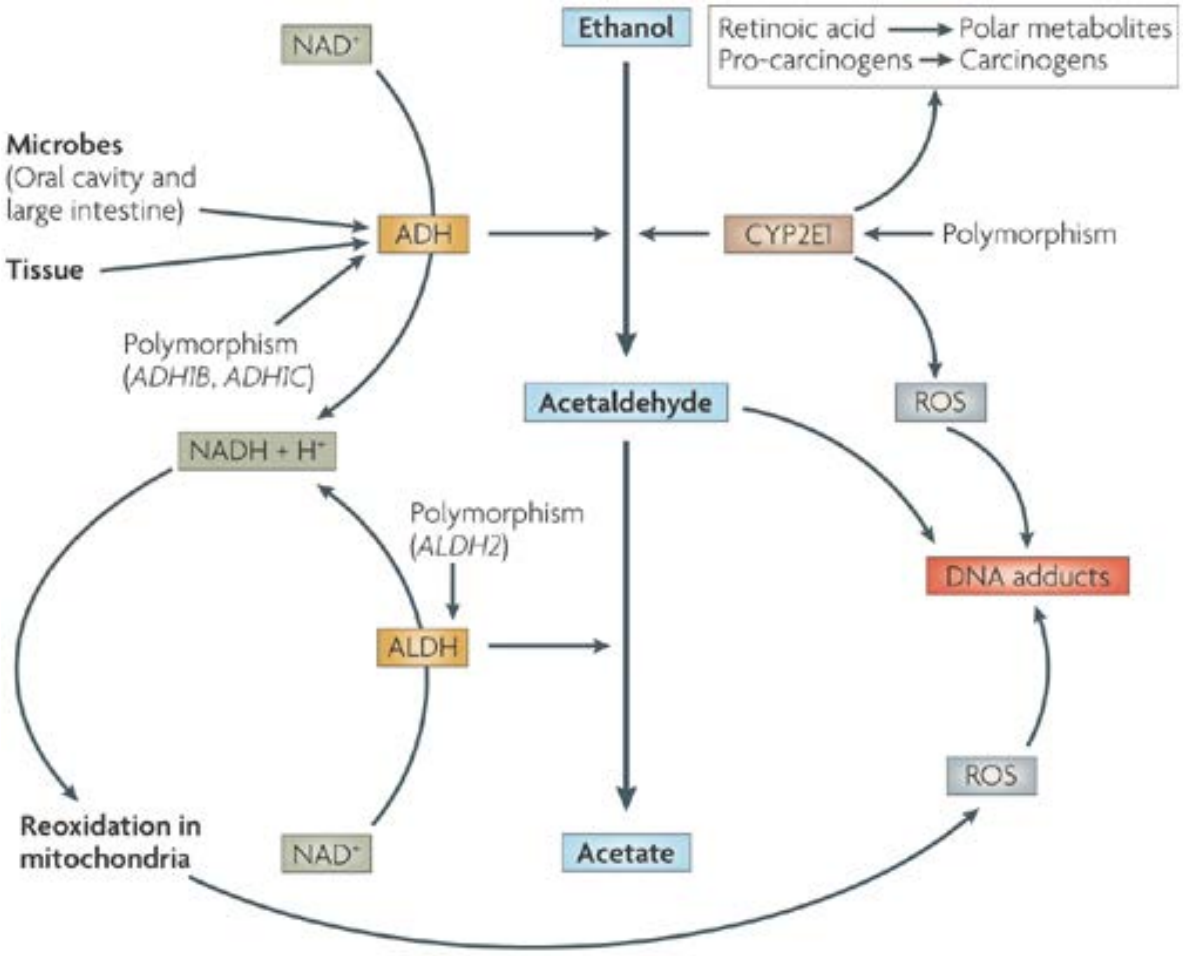
BEVERAGE	ALCOHOL CONTENT	SERVING SIZE	AMOUNT OF ALCOHOL	Daily Intake Needed to Exceed Threshold for Alcoholic Liver Disease*	
				MEN	WOMEN
Beer	5%	12 oz	13.85 g	3-6 cans	1.5-3 cans
Wine	12%	4 oz	10.7 g	4-8 glasses	2-4 glasses
Fortified wine	20%	4 oz	17.8 g	2-4 glasses	1-2 glasses
Hard liquor	40%	1.5 oz	13.4 g	3-6 drinks	1.5-3 drinks


Alcohol
Gut permeability
ADH
CYP2EI
Malnutrition
Endotoxemia
Acetaldehyde
Oxidant stress
CD14,TLR4
Kupffer cell activation
Stellate cell activation
TNF-a
Adducts
PDGF, TGF-β
Inflammation
Hepatocyte injury
Fibrosis
Impaired regeneration
Alcoholic hepatitis

Ethanol Metabolism

- Alcohol dehydrogenase (ADH),
- Cytochrome P450 2E1 (CYP2E1),
- Catalase (less important)

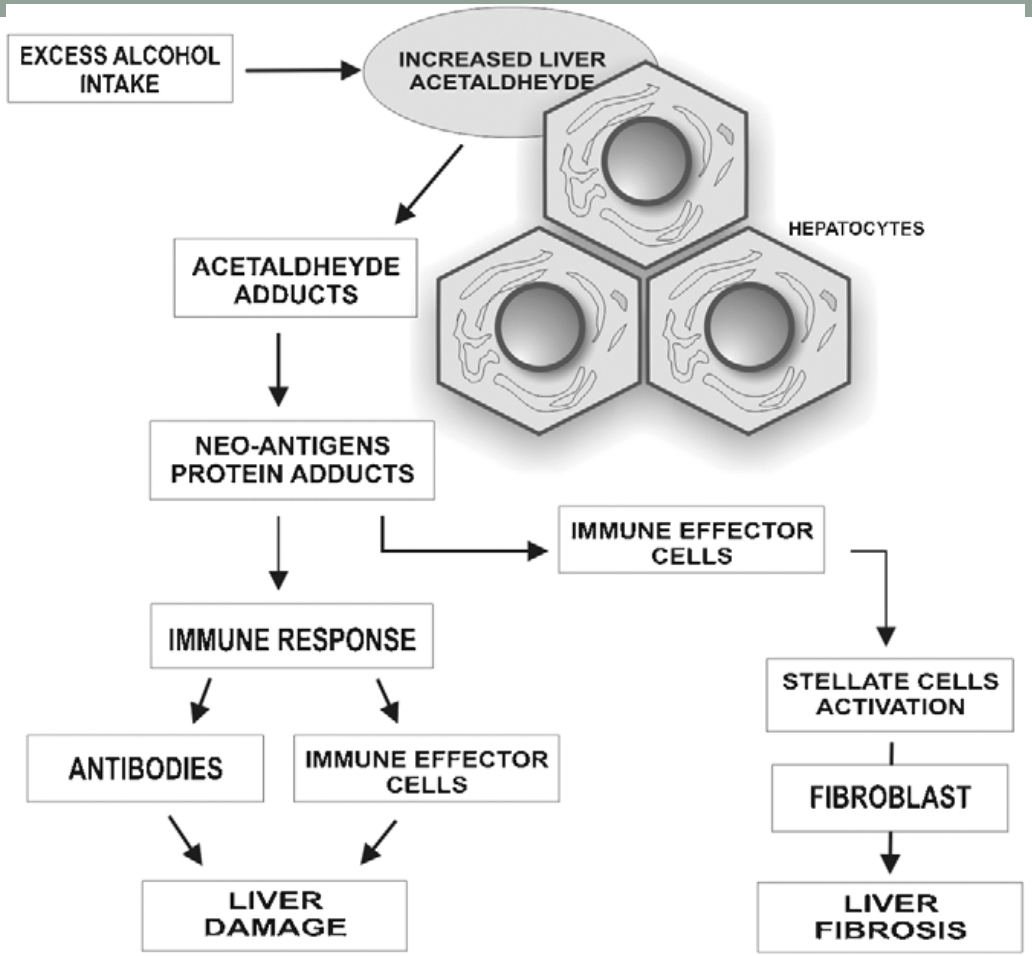
- ADH is the primary enzyme system responsible for metabolism of ethanol at low concentrations,
- CYP2E1 contributes at higher concentrations of ethanol and is **induced** by exposure to ethanol
  - Influences drug metabolism (acetaminophen/isoniazid toxicity)



Nature Reviews | Cancer

Liver Injury

- **Acetaldehyde**: highly reactive and potentially toxic compound that is responsible for many of the systemic toxic effects of alcohol, such as nausea, headaches, and flushing
- Increased levels in blood and liver tissue in alcoholic liver disease



Effect of increased acetaldehyde (triggered by heavy drinking): production of protein adducts and immune response leading to liver damage. Activation of stellate cells and fibroblasts, leading to liver fibrosis.

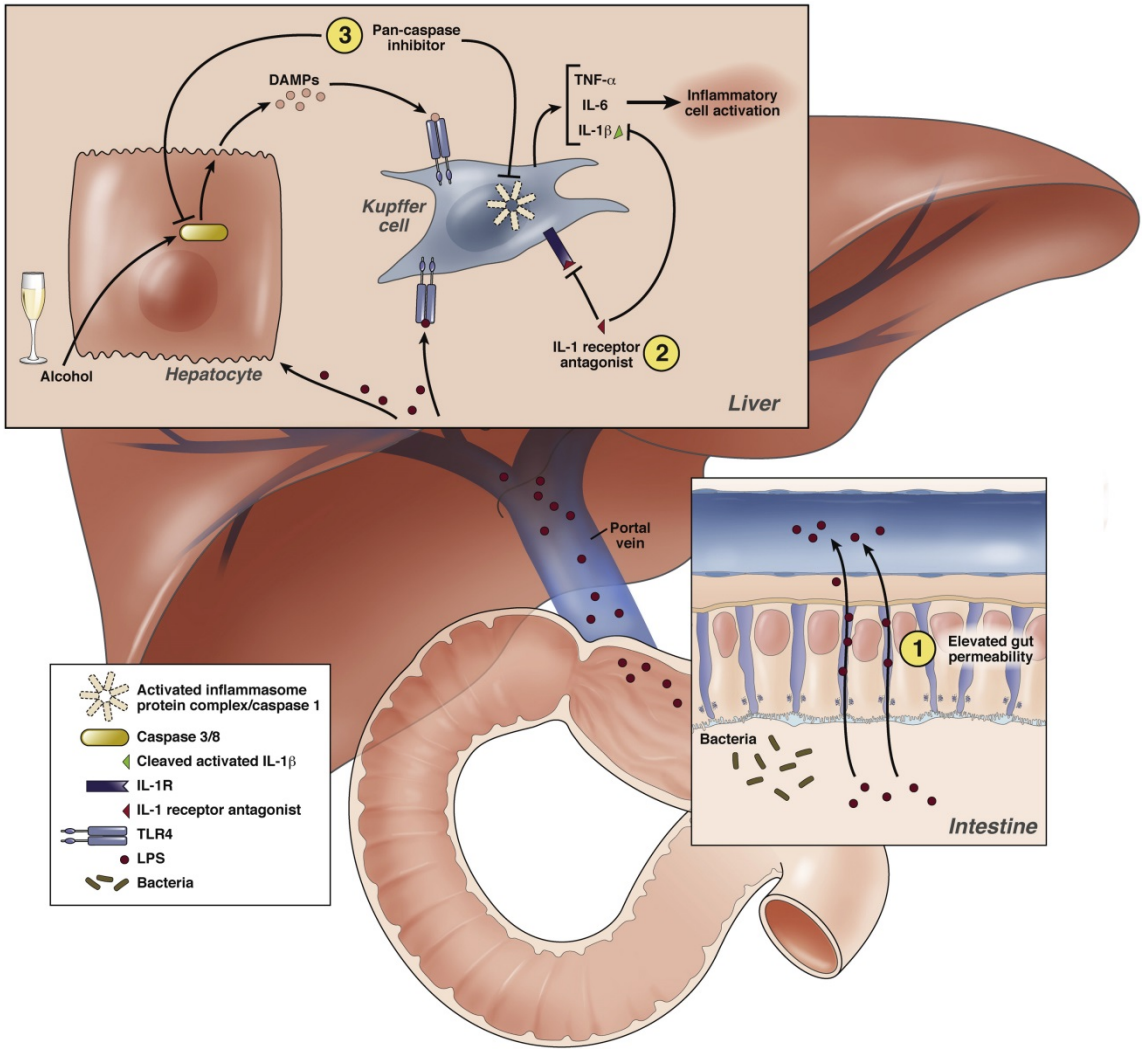
Liver Injury – Oxidant Stress

- Induction of CYP2E1 by alcohol intake stimulates the formation of reactive oxygen species (ROS) during ethanol oxidation
- Overproduction of ROS, or inadequate antioxidant defenses (e.g., low levels of vitamins, selenium, mitochondrial glutathione),can lead to liver injury
- Oxidant stress also leads to stellate cell activation causing steatosis and fibrosis

Liver Injury - Endotoxins

- Bacterial endotoxin is a toxic lipopolysaccharide (LPS) present in the cell wall of some intestinal bacteria
- When bacteria die, the endotoxin is released and enters the portal and systemic circulation
- Excess EtOH leads to increased intestinal permeability (disruption of the mucosal barrier) and increased endotoxemia

- Ultimately leads to upregulation of proinflammatory cytokines **(notably TNF α)**



Alcoholic Hepatitis

- Acute hepatic inflammation associated with significant morbidity and mortality that occurs in a subset of patients who consume excessive amounts of alcohol
- Clinical syndrome of jaundice and liver failure that generally occurs after decades of heavy alcohol use (mean intake, approximately 100 g per day)
  - Can occur several weeks after alcohol abstinence
  - Usually age 40-60,
  - Female sex an independent risk factor for AH
  - Cardinal sign is rapid onset of jaundice

Alcoholic Hepatitis

- Severe cases, mortality 30-50%
- Spectrum from mild to severe
- Often times on background of cirrhosis

Presentation

- Fever, tachycardia
- Encephalopathy
- Physical Exam: jaundice, enlarged and tender liver, hepatic bruit, parotid enlargement, Dupuytren contracture, spider nevi, ascites
- Labs: ↑AST > 2x ALT (usually <300 IU/ml), Tbili > 5, Leukocytosis, thrombocytopenia, elevated INR,
  - Hypokalemia, hypomagnesemia, hyperuricemia, elevated ferritin hypertriglyceridemia, low zinc level, hypoalbuminemia, elevated MCV.
  - Elevated Cr (ominous)

TABLE 84-2 Symptoms and Signs in Hospitalized Patients with Alcoholic Liver Disease*

Data from Mendenhall CL. Alcoholic hepatitis. Clin Gastroenterol 1981; 10:417-41.

SYMPTOM OR SIGN	Patients Affected (%)			
	MILD DISEASE (*n* = 89)	MODERATE DISEASE (*n* = 58)	SEVERE DISEASE (*n* = 37)	OVERALL
Hepatomegaly	84.3	94.7	79.4	86.7
Jaundice	17.4	100	100	60.1
Ascites	30.3	79.3	86.5	57.1
Hepatic encephalopathy	27.3	55.2	70.3	44.6
Splenomegaly	18.0	30.9	39.4	26.0
Fever	18.0	31.0	21.6	22.8

Differential Diagnosis

- Decompensated cirrhosis,
- Acute or chronic viral hepatitis,
- Drug-induced liver injury,
- Fulminant Wilson’s disease,
- Autoimmune liver disease,
- Alpha-1 antitrypsin deficiency,
- Pyogenic hepatic abscess,
- Ascending cholangitis,
- Decompensation associated with hepatocellular carcinoma

Work-up

- Screen for bacterial infections
  - Blood culture, CXR, spontaneous bacterial peritonitis, and urinary tract infection
- Hepatic ultrasonography
  - hepatic abscess, clandestine hepatocellular carcinoma, and biliary obstruction, each of which may mimic alcoholic hepatitis.

Assessing Disease Severity

Table 1. Scoring Systems to Assess Severity of AH

Scoring system	Variables	Severe disease	Advantages	Limitations
mDF[24]	4.6 × (patient's PT-control PT in seconds) + serum bilirubin	32	Simple to use, validated internationally, and guides treatment initiation	Does not guide treatment response
MELD[29]	SB, INR, serum creatinine Web site: www.mayoclinic.org/meld/mayomodel6.html	21	Validated internationally	Variable cutoff across studies
GAHS[32]	Age, BUN, WBC, SB, and INR each scored 1-3	9	Simple to use and stratifies DF >32 patients for treatment	Not validated worldwide and needs day 7 laboratory values
ABIC[33]	Age, SB, INR, serum creatinine	9	Stratifies patients to low, intermediate, and high risk	Only validated in Spain
Lille[35]	Age, SB, serum albumin, PT, change in SB at day 7 Web site: gihep.com/calculators/hepatology/lille-model	0.45	Identifies nonresponders to steroids	Complex to use and does not guide treatment initiation

BUN, blood urea nitrogen; PT, prothrombin time; SB, serum bilirubin.

Maddrey's Discriminant Function

- – DF: 4.6 (PT-control)+TB
- – DF >32 indicates a poor prognosis
- – Mortality up to 44-62%

- Limitations
  - Not used to guide therapy. DF < 32 are still at risk for mortality
- Results can vary among laboratory

MELD Score

- MELD Score = 3.8 * $\log_e$(bilirubin in mg/dL) 11.2 * $\log_e$(INR) 9.6 * $\log_e$(creatinine mg/dL) 6.4

- MELD ≥21, estimated 90 day mortality of 20%
- Increase in MELD ≥ 2 in first week has been shown to predict in hospital mortality

Glasgow Alcoholic Hepatitis Score

- age, leukocyte count, serum urea level, PT ratio (ratio of patient-to-control PT), and serum bilirubin level
- A score > 8 predicts poor prognosis
- Score > 9
  - 78% 28- day survival with corticosteroids vs. 52% without
  - 59% vs. 38%, 84 day survival
- Rarely used clinically

ABIC

- most recent scoring system, includes age, serum bilirubin, INR, and serum creatinine.
- It stratifies risk of mortality from AH as low (score < 6.71), intermediate (score:6.71-8.99), and high (score ≥ 9.0), with 90 d mortality at 0%, 30%, and 75%, respectively (*P* < 0.0001)
- Rarely used clinically & Not validated externally

Treatment - Abstinence

- Current therapy focuses on supportive care & complete EtOH abstinence
- AH may persist for months after cessation, and may worsen during the first weeks of abstinence.
- Inpatient: measures for decompensated cirrhosis in many cases
- Thiamine, MVI, folate, pyridoxine
- Watch for DTs and EtOH withdrawal

Treatment - Nutrition

- Protein calorie malnutrition
- Vitamin deficiencies
- Risk of death correlated with malnutrition

Treatment - Nutrition

- Randomized, controlled clinical trial compared enteral tube feeding (2000 kcal per day) with prednisolone therapy (40 mg of prednisolone per day) for 28 days in 71 patients with severe alcoholic hepatitis.
- The survival rate in the two groups was similar at 28 days
- Overall lower mortality in nutrition group at 1 year (p=ns)
- Nutritional support may be as effective as corticosteroids in some patients

Treatment - Corticosteroids

- Rationale is to decrease the immune and pro-inflammatory cytokine response.
- There have been 13 randomized, controlled trials evaluating corticosteroids in alcoholic hepatitis
  - Inconsistent results with 5 showing reduction in mortality, and the remainder showing no benefit

Table 2 Meta-analyses of randomized controlled trials of corticosteroid therapy *vs* placebo for severe alcoholic hepatitis

Ref.	Inclusion criteria	Number of RCTs (total number of patients)	Endpoint parameters (primary endpoint listed on first line of each entry)	RR, HR or OR for primary endpoint	95%CI	Comments
Imperiale *et al*[122], 1990	RCTs of patients with acute AH receiving corticosteroids *vs* placebo	11 (562)	Mortality Hepatic encephalopathy	RR = 0.63	0.5-0.8	Positive study ($P = 0.025$)
Christensen *et al*[123], 1995	RCTs evaluating short term effect on survival of treatment with glucocorticoids *vs* placebo for AH	13 (659)	Mortality Age Serum bilirubin Ascites Male gender Hepatic encephalopathy	RR = 0.78	0.51-1.18	Negative study ($P = 0.2$)
Mathurin *et al*[89], 2002	RCTs during 1984-1992 of patients receiving glucocorticoids *vs* placebo	3 (215)	Survival Age Liver function tests DF Hepatic encephalopathy Gender Serum creatinine Ascites Leukocyte count	OR = 0.39	0.22-0.71	Positive study ($P = 0.002$) Used individual patient data analysis to increase statistical rigor for the meta-analysis
Rambaldi *et al*[100], 2008	RCTs of patients with severe, clinically overt AH diagnosed by clinical and biochemical criteria, treated with glucocorticoids *vs* placebo (or no intervention)	15 (721)	Mortality Liver-related mortality Symptoms and complications Liver function tests Liver histology Adverse events	RR = 0.83	0.63-1.11	Negative study ($P = 0.21$)
Mathurin *et al*[99], 2011	RCTs from 1984 to 2006 with specific data on DF ≥ 32 or hepatic encephalopathy, of corticosteroids *vs* placebo, enteral nutrition or antioxidants	5 (418)	Survival DF Lille score Liver function tests	Complete responder: HR = 0.18	Complete responder: 0.05-0.71	Positive study Complete responders ($P = 0.005$)
			Serum creatinine Ascites	Partial responder: HR = 0.38	Partial responder: 0.17-0.87	Partial responders ($P = 0.03$)
			Hepatic encephalopathy Age	Null responder: HR = 0.81	Null responder: 0.45-1.45	Null responders ($P = 0.46$)
			Gender Leukocyte count			Used individual patient data analysis to increase statistical rigor for the meta-analysis

RCT: Randomized controlled trials; AH: Alcoholic hepatitis; DF: Discriminant function.

-significant increase in short-term survival among treated patients compared to control patients: 84.6% versus 65%.

-30% relative risk reduction, and translates into a number needed to treat of 5,

Treatment - Corticosteroids

- Active infections, gastrointestinal bleeding, pancreatitis, renal failure, and non-compliance are excluded, because corticosteroids treatment may adversely affect these conditions
  - Prednisolone 40mg/d for 4 weeks then tapered over 2-4 weeks
  - Active form of prednisone, and not metabolized by liver
- Still, 40% of patients unresponsive

Lille Score

- Predicts 6 months survival in patients treated with corticosteroids
- based on pretreatment data plus the response of serum levels of bilirubin to a 7-day course of corticosteroid therapy
- A score < 0.45 predicts 15% mortality, whereas a score ≥0.45 predicts 75% mortality ($P < 0.0001$).
- Alternative therapies should be considered when the score is ≥ 0.45 at day 7 of corticosteroid therapy

Treatment – TNF α inhibitors

- Pentoxifylline (PTX), a nonselective phosphodiesterase inhibitor that inhibits TNF synthesis
- One prospective, randomized, double blind clinical trial in 101 patients who had severe alcoholic hepatitis (mDF score ≥ 32)
  - PTX 400mg PO TID vs placebo
  - In-hospital mortality lower (24.5% vs 46.1%)

Treatment – TNF α inhibitors

- The survival benefit of PTX seemed to result from a significant decrease in the risk of death from hepatorenal syndrome
  - PTX group 6 of 12 deaths (50%)
  - Placebo group 22 of 24 deaths (92%)
- The mechanism by which PTX decreased the development of hepatorenal syndrome is not clearly explained in this study
- Most authorities advocate PTX for patients with contraindications to using corticosteroids

Jaurigue MM *et al*. Therapy for ALD

Table 3 Published randomized controlled trials of pentoxifylline *vs* placebo for severe alcoholic hepatitis *n* (%)

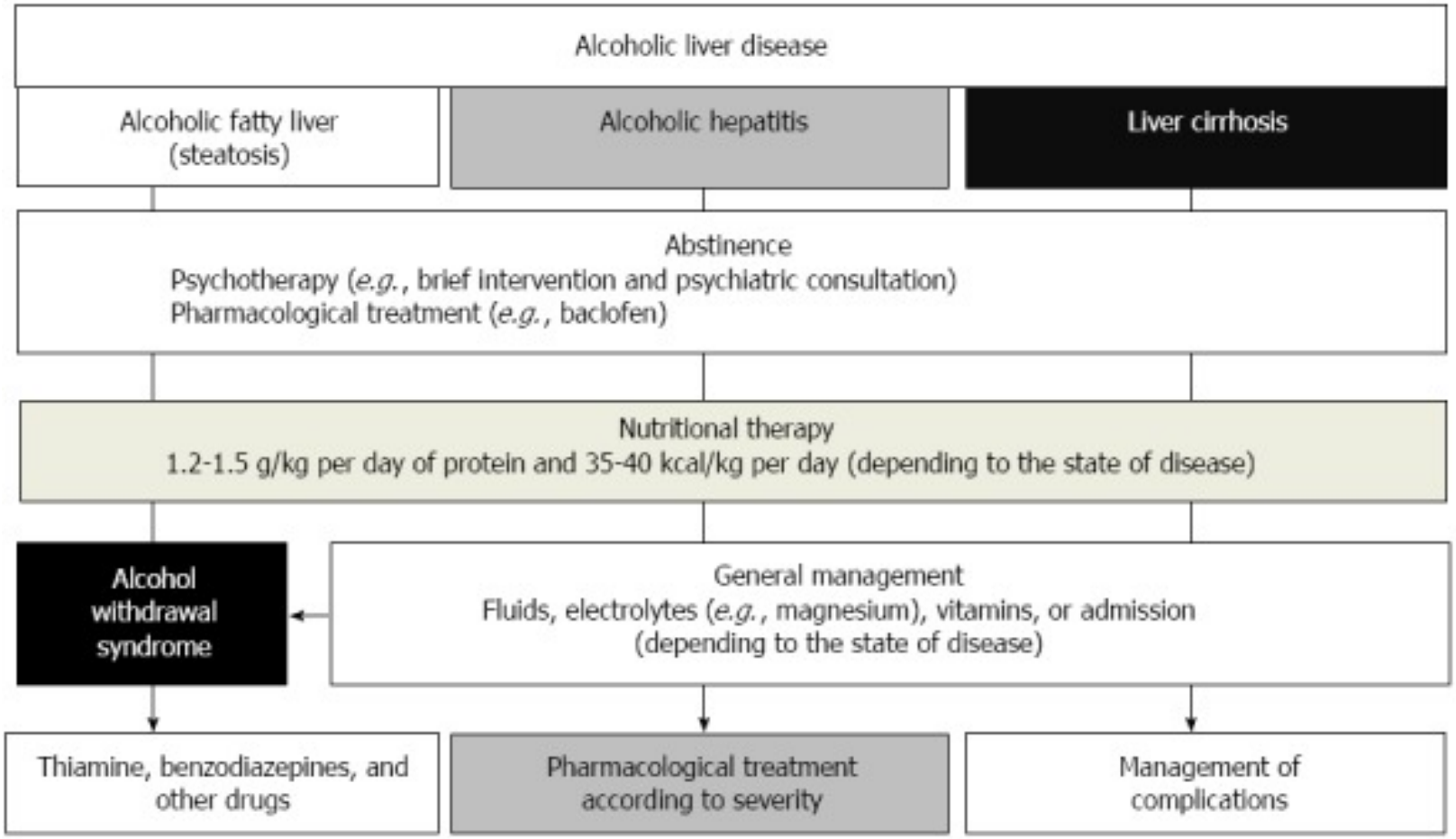
Ref.	*n*	Duration of treatment with pentoxifylline 400 mg PO *tid*	Mortality in placebo	Mortality in pentoxifylline	Relative risk or hazard ratio	95%CI	Comments
Akriviadis *et al*[110], 2000	101	28 d	24/52 (46)	12/49 (24)	RR = 0.59	0.35-0.97	Positive study (P = 0.037)
Fernández-Rodríguez *et al*[112], 2008	24	28 d	Not reported[1]	Not reported[1]	HR = 1.46	0.5-4.28	Negative study (P = 0.48)
Tyagi *et al*[107], 2011	61[2]	6 mo	2/31 (6)	1/30 (3)	Not reported	Not reported	Negative study[2] (P = 0.15)
Sidhu *et al*[109], 2012	50	28 d	10/25 (40)	5/25 (20)	RR = 0.5	0.19-1.25	Negative study (P = 0.216)

[1]Fernandez-Rodriguez *et al*[112] reported no statistically significant difference in short-term or long-term survival based on actuarial survival curve; [2]Tyagi *et al*[107] randomized 70 patients, but only 61 completed follow-up and were included in the analysis. The study did not show a significant difference in mortality, but showed a significant difference in the occurrence of hepatorenal syndrome. PO: Per overall survival; RR: Relative risk; HR: Hazard ratio.

Treatment – TNF α inhibitors

- Infliximab (chimeric human/mouse TNF α antibody) infusion
  - Trials with no benefit, one with no survival advantage
  - Another with infliximab + prednisolone vs prednisolone alone stopped prematurely because of higher death rate related to severe infections
- Etanercept (p75-soluble TNF receptor:FC fusion protein)
  - RCT, mod-sev AH
  - Compared with placebo, etanercept was associated with significantly higher mortality (mainly due to infections) after six months (58 versus 23 percent)

Management Algorithm



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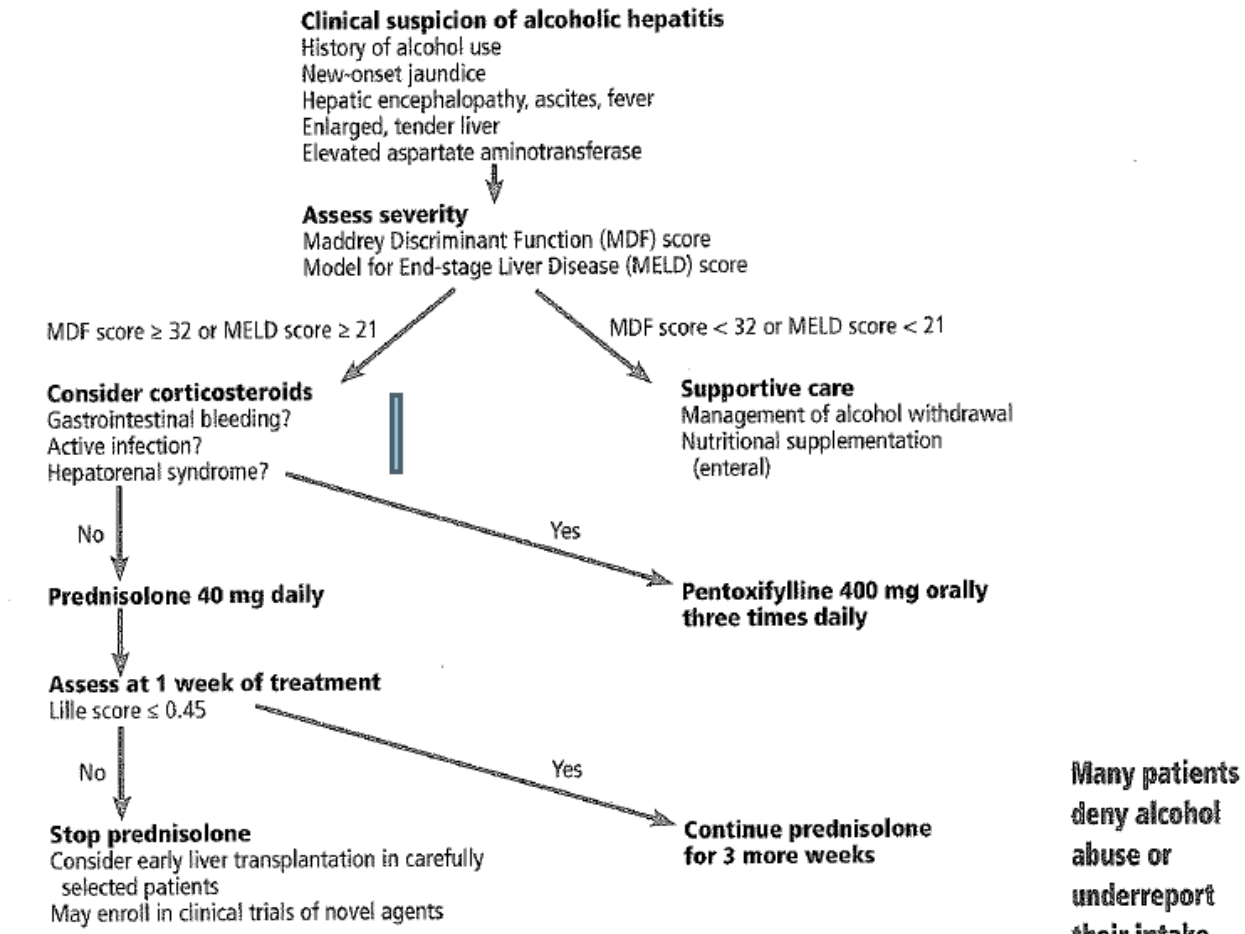

FIGURE 2. Management algorithm for alcoholic hepatitis.

ADAPTED FROM THE GUIDELINES OF THE AASLD AND EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER.

The NEW ENGLAND JOURNAL 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*

-1103 patients with severe acute alcoholic hepatitis DF >32
-randomized to placebo, Prednisolone, PTX, or combination
-28 day mortality
-Prednisolone decreased mortality at 28 days (14% vs 17%, ns)
-PTX similar to placebo

References

- AASLD
- CGH 2014

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