Published in final edited form as:

Dig Dis. 2016 ; 34(4): 347–355. doi:10.1159/000444545.

PATHOGENESIS AND MANAGEMENT OF ALCOHOLIC LIVER DISEASE

M. Omar Farooq and **Ramon Bataller**

Division of Gastroenterology and Hepatology, Department of Medicine and Nutrition, University of North Carolina at Chapel Hill, NC.

Abstract

Alcoholic liver disease (ALD) is a leading cause of liver-related morbidity and mortality. ALD encompasses a spectrum of disorders ranging from asymptomatic steatosis, alcoholic steatohepatitis (ASH), fibrosis, cirrhosis and its related complications. Moreover, patients can develop an acute-on-chronic form of liver failure called alcoholic hepatitis (AH). Most patients are diagnosed at advanced stages of the disease with higher rates of complications and mortality. The mainstream of therapy of ALD patients, regardless of the disease stage, is prolonged alcohol abstinence. The current therapeutic regimens for AH (i.e. prednisolone) have limited efficacy and targeted therapies are urgently needed. The development of such therapies requires translational studies in human samples and suitable animal models that reproduce clinical and histological features of AH. In recent years, new animal models that simulate some of the features of human AH have been developed, and translational studies using human samples have identified potential pathogenic factors and histological parameters that predict survival. In this review, we discuss the pathogenesis and management of ALD, focusing on AH, its current therapies and potential treatment targets.

1. ALCOHOLIC LIVER DISEASE: GENERAL CONCEPTS

Alcohol use disorders account for a significant cause of preventable disease worldwide, with resultant alcoholic liver disease (ALD) causing significant liver-related morbidity and mortality among adults with prolonged alcohol abuse[1]. ALD represents half of the cases of liver cirrhosis, therefore, making it the dominant cause of advanced liver disease globally[2]. The diagnosis of ALD is usually made at advanced stages of disease with higher rates of complications and mortality[1]. Early detection of initial forms of ALD in the primary care setting and subsequent behavioral interventions should be encouraged. However, there is a lack of characterization of the early stages of ALD in humans. Moreover, there is a clear need to define the natural history and prognostic factors as well as to develop reliable non-invasive markers for ALD.

Address for correspondence: Ramon Bataller, M.D. PhD., 7340.A Medical Biomolecular Research Building, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, Tel 919-966-4812, bataller@med.unc.edu.

Disclosure Statement

The authors have nothing to disclose

The management of patients with ALD has evolved little due to many factors including difficulties of conducting clinical trials in patients with an active alcohol addiction, the lack of interest from drug companies, public funding for research and the drawbacks of existing experimental models. As a consequence, there are not approved targeted therapies to treat patients with severe ALD[3]. The development of such therapies requires translational studies in human samples and suitable animal models that reproduce clinical and histological features of alcoholic hepatitis (AH). In recent years, new animal models that simulate some of the features of human AH have been developed, and translational studies using human samples have identified potential pathogenic factors and histological parameters that predict survival[3, 4].

2. ENVIRONMENTAL AND GENETIC FACTORS

The susceptibility to develop ALD among heavy drinkers depends on genetic and environmental factors. At similar levels of ethanol consumption, some patients only develop macrovesicular steatosis, while others develop progressive fibrosis and cirrhosis. Although a positive correlation between cumulative alcohol intake and degrees of liver fibrosis has been reported, extensive variability in the histological response to alcohol abuse exists in individuals[5]. The environmental risk factors identified as promoters for the progression of ALD in patients with alcohol abuse include sex, obesity, drinking patterns, dietary factors, non-sex-linked genetic factors, and cigarette smoking[6-8].

Epidemiological studies suggest that several genetic factors influence the severity of steatosis and oxidative stress, and that the cytokine milieu, the magnitude of immune response and the severity of fibrosis also modulate an individual's propensity to progress to advanced ALD[9]. Genes encoding the main alcohol metabolizing enzymes and proteins involved in the toxic effects of alcohol and its metabolites on the liver, such as antioxidants and pro-inflammatory cytokines, have been the focus of investigation[8]. Genetic factors that influence the activity of these enzymes and the rate of alcohol metabolism have been studied. Variations in the rate of generation of acetaldehyde, a promoter of fibrogenesis, could explain the differences in the susceptibility of individuals to ALD from alcohol abuse. Although polymorphisms in the genes encoding the main alcohol-metabolizing enzymes such as ADH, ALDH and CYP2E1 are accepted to be involved in an individual's susceptibility to alcoholism, their role in the progression of ALD remains controversial[10]. Recent studies indicate that variations in the patatin-like phospholipase domain-containing protein 3 (PNPLA3) are strongly associated with increased risk of ALD. PNPLA3 polymorphisms can be considered as the only confirmed and replicated genetic risk factor for ALD. Future studies would clarify the role of PNPLA3 and identify it as a target for therapy[11-13]. Despite the large number of studies that have assessed the role of genetic variation in susceptibility to ALD, a large-scale, well-designed, genome wide association study of factors associated with ALD remains to be performed. Consequently, a genetic test capable of identifying which patients are susceptible to advanced ALD is yet to be developed[3].

3. DISEASE SPECTRUM AND PATHOGENESIS

ALD comprises different stages of liver disease as a result of susceptibility factors and duration of alcohol abuse. These stages include steatosis, alcoholic steatohepatitis (ASH), progressive fibrosis, cirrhosis, decompensated cirrhosis and superimposed hepatocellular carcinoma (HCC) (**Figure 1**). Patients with underlying cirrhosis and ongoing alcohol abuse are predisposed to developing AH[14, 15]. With a mortality rate of 30-50% at 3 months[15], AH represents one of the deadliest diseases in clinical hepatology.

Steatosis is defined histologically as the deposition of fat in hepatocytes. Alcohol intake increases NADH/NAD+ in hepatocytes, thereby disrupting fatty acid oxidation[16]. Increased fatty acid and triglyceride synthesis, hepatic influx of free fatty acids from adipose tissue and chylomicrons from the intestinal mucosa, results in increased hepatic lipogenesis, decreased lipolysis, and mitochondrial and microtubule damage[17]. Up to 90% of patients with heavy alcohol intake have some degree of steatosis[18], which is usually asymptomatic and rapidly reversible with abstinence.

Continued heavy alcohol consumption leads to ASH, characterized by polymorphonuclear (PMN) cell infiltration and hepatocellular damage. Acetaldehyde, a byproduct of alcohol metabolism, is implicated for the hepatocellular injury. It binds proteins and DNA, forming adducts that promote glutathione depletion, lipid peroxidation and mitochondrial damage[19, 20].

Sustained alcohol misuse causes progression to liver fibrosis and cirrhosis, which leads to a high risk of complications (such as ascites, variceal bleeding, hepatic encephalopathy, renal failure and bacterial infections)[21, 22]. Acetaldehyde promotes fibrogenesis directly by increasing the expression of collagen in hepatic stellate cells (HSC)[23, 24]. HSCs can also be activated by neutrophils, damaged hepatocytes, and activated Kupffer cells through various pro-fibrogenic mediators including transforming growth factor β, platelet-derived growth factor, IL-8, angiotensin II and leptin[25]. The activation and biological actions of these mediators are largely due to reactive oxygen species (ROS)[26]. Alcohol abuse contributes to dysbiosis and inflammation of the intestinal tract with resulting translocation of microbial products such as lipopolysaccharide (LPS) to the liver[27]. LPS targets toll-like receptor-4 (TLR4) signaling in HSCs and sinusoidal endothelial cells, resulting in HSC activation and promotion of fibrogenesis through regulation of angiogenesis[28].

4. ALCOHOLIC HEPATITIS

AH is a *clinical syndrome* characterized by new onset jaundice and/or ascites in the setting of ongoing alcohol abuse and underlying ALD[14]. Patients typically present with *rapidly progressive jaundice*, which can be accompanied by fever, abdominal pain, anorexia, and weight loss. In some cases, portal hypertension is severe, and the patient presents with ascites, encephalopathy, or variceal bleeding. Alcohol use history can be quite variable. Often, there is a history of daily heavy alcohol use, which may have escalated in the weeks and months prior to presentation. Alternatively, as patients begin feeling ill, they may reduce or discontinue alcohol use in the preceding days or even weeks. Physical exam findings are

nonspecific, and may include fever, tender hepatomegaly, ascites, muscle wasting, and other stigmata of chronic liver disease.

The diagnosis of AH is made on clinical grounds, based on a history of excessive alcohol use with the typical physical exam and laboratory findings. Other potential causes of Acute Hepatitis such as viral, drug-induced liver injury, spontaneous bacterial peritonitis (SBP) or other infections should be considered and ruled out. Imaging is important to exclude biliary or vascular disorders and to evaluate for co-existing hepatocellular carcinoma. In many patients with ALD and clinical complications, the presence of a superimposed AH is not explored and therefore its real incidence is unknown. Population based studies using administrative data estimate approximately 4.5 hospitalizations for AH per 100,000 persons each year, with a slight male predominance[29]. Prospective studies assessing the incidence, risk factors and clinical features of AH are clearly needed.

The Maddrey's discriminant function (DF) is one of several models that have been developed to help predict outcomes of patients with AH and to guide therapy. A DF value ≥ 32 is indicative of a high risk of short-term mortality (35% at 1 month) and is the basis for patient selection for specific therapy with corticosteroids. Additional predictive models include the Model for End-Stage Liver Disease (MELD), the Glasgow AH score, the ABIC score, and the Lille model.

Patients that develop severe AH usually require hospitalization for initial management. Primary prevention is aimed at alcohol abstinence; active management of alcohol use disorders is critical to achieving continued abstinence. For the successful management of these patients, a multidisciplinary team composed of hepatologists, psychologists, psychiatrists and social workers is highly recommended[29]. Significant protein calorie malnutrition and vitamin and mineral deficiencies including vitamin A, vitamin D, thiamine, folate, pyridoxine, and zinc is common[6, 30, 31]. Nutritional support improves liver function and short-term follow-up studies suggest that improved nutrition might improve survival times and histological findings in patients with AH[32]. Most patients improve spontaneously with abstinence and supportive care. Medical treatment is considered for patients who present with a very severe clinical picture or continue to deteriorate.

The management of AH depends on the severity of the episode (Fig. 2). Severe AH requiring medical intervention is defined as a Maddrey's discriminant function >32, MELD >21, ABIC >6.9 or Glasgow >8[3]. Both the AASLD and EASL practice guidelines recommend the use of corticosteroids (i.e. prednisolone 40 mg daily for 4 weeks) for patients with severe AH[6, 33]. Moreover, clinical practice guidelines recommend stopping corticosteroids after one week in those with an unfavorable Lille score, as the risks of continued therapy likely outweigh the benefits. When considering treatment with corticosteroids, patients require careful monitoring for evidence of present or developing infections and/or active GI bleeding.

Pentoxifylline is a phosphodiesterase inhibitor that inhibits the synthesis of tumor necrosis factor, which is increased in patients with AH. In practice, pentoxifylline was typically reserved as a second-line agent for patients with contraindications to corticosteroid therapy.

The recent STOPAH trial, comparing prednisolone and pentoxifylline, has proven to be a definitive study for assessing the efficacy of these drugs for AH[34]. Current consensus regarding pentoxifylline is that it is not effective rescue therapy in patients who do not respond to corticosteroids.

The anti-TNF agents, Infliximab and etanercept, were also investigated as potential therapies for patients with AH. TNF alpha was theorized as a key culprit in potentiating hepatocyte inflammation. Studies did not support the hypothesis[35] and instead demonstrated adverse side effects such as increased rates of infection and increased mortality. Presently anti-TNF-α agents are not recommended for treatment of AH[36].

N-acetylcysteine replenishes glutathione in damaged hepatocytes and prevents cell death in ALD. A recent randomized trial performed using a combination of N-acetylcysteine with prednisolone showed a clear trend to improve survival, with decreased 1-month mortality (8% vs. 24%) and reduced incidence of hepatorenal syndrome and infection. The study, however, was underpowered to reach statistical significance and was found to have no effect on six-month survival and primary outcome[37]. Its favorable safety profile renders N-acetylcysteine a potential option, in combination with corticosteroids, for patients with severe disease.

5. NEW MOLECULAR TARGETS TO TREAT ALCOHOLIC HEPATITIS

Cell death via apoptosis

Alcoholic hepatitis results in massive hepatocyte cell death and apoptosis is a prominent feature of many of the preceding stages of alcoholic liver disease. Since caspase inhibitors are known to inhibit apoptosis, animal studies, in models of chronic liver injury from viral hepatitis secondary to hepatitis C infection, and non-alcoholic steatohepatitis, using caspase inhibitors and have shown promising results in ameliorating liver injury and impeding progression to fibrosis[38-40]. It is reasonable to think such an approach would work in alcoholic liver disease, in particular in alcoholic hepatitis.

Role of Innate Immune System

Following activation, neutrophils undergo transmigration into the liver parenchyma where they destroy damaged hepatocytes through the release of ROS and proteases, supporting their prominent role in ALD[41]. IL-17 is increased in patients with alcoholic hepatitis and directly induces neutrophil recruitment, but also indirectly promotes neutrophil recruitment by stimulating HSCs to secrete IL-8 and CXCL1[42, 43]. This suggests that the modification of these chemokines, or their precursors or activators, may mediate neutrophil infiltration and perhaps attenuate alcoholic hepatitis. The role of CXCL family of chemokines has been examined in translational studies, and discovered that elevated levels correlate with severity of disease, degree of portal hypertension, and patient survival[35, 44]. Given these promising findings, therapeutic agents that target CXC chemokines may be considered in the treatment of AH. Osteopontin is an extracellular matrix protein that is markedly upregulated in alcoholic hepatitis, similar to other CXCL chemokines[45]. Osteopontin inhibitors, therefore,

are also attractive potential new therapeutic agents. The redundancy of chemokines and their receptors makes the development of targeted therapeutics challenging.

Instigators of inflammation are also thought to play an important role. Sources of inflammatory mediators can be classified as sterile, originating from intracellular sources, or microbiological, from bacterial translocation in the gut. Damage-associated molecular patterns (DAMPs) are intracellular molecules released by dying cells that trigger the innate immune system[46]. Among the DAMPs, high mobility group box-1 (HMGB-1) has been implicated in the development of alcoholic steatohepatitis[45], and likely also has a role in alcoholic hepatitis. Gut-derived bacterial products belong to the class of pathogen-associated molecular patterns (PAMPs). These PAMPs circulate through the portal circulation and induce an inflammatory response through activation of HSCs and Kupffer cells[47, 48]. Protecting against gut leakage could be a potential target for therapy aimed at preventing the initiation of the innate immune response in alcoholic hepatitis.

Role of the Adaptive Immune System

It is well-known that the adaptive immune system responds to oxidative stress and peroxidation adducts, but its role in hepatocellular damage and inflammation in alcoholic hepatitis remains unknown. As previously described, increased alcohol consumption generates ROS through multiple mechanisms and leads to adduct formation; protein adducts have altered conformation and function, and are relatively immunogenic. Patients with alcoholic hepatitis have been found to have circulating T cells with antibodies to these adducts, enforcing that the adaptive immune response likely plays a large, yet undiscovered role in AH[49-52].

Targeting dysbiosis

Alterations in the gut microbiome has unique implications on the development of alcoholic hepatitis, this was first suggested in the intragastric mouse feeding model in which elevated serum ethanol levels were maintained, treated mouse populations were observed to have both microbial translocation and dysbiosis[53]. In studies involving patients with chronic alcoholic liver disease, administration of probiotics appeared to improve liver function in this patient group, further supporting that the intestinal bacterial milieu is of great importance[54]. Work examining the applicability of probiotics in patients with alcoholic hepatitis is still underway. Other genomic and metabolomic analyses of intestinal bacteria revealed low levels of lactobacilli and reduced production of saturated long chain fatty acids (LCFA). In this model, supplementation with LCFA restored eubiosis, intestinal barrier function, and reduced liver injury in mice[55], suggesting a role for potential supplementation of LCFA in this patient group.

The role of hepatocyte proliferation and regeneration

Hepatic regeneration in the healthy liver results from expansion of the remaining healthy hepatocytes. In the diseased state, in which hepatocyte proliferation is inhibited, pluripotent liver progenitor cells, also referred to as oval cells, or ductal hepatocytes, proliferate and differentiate to repopulate hepatocytes or biliary epithelial cells[56]. In the rodent model, alcohol attenuates regeneration of hepatocytes following partial surgical hepatectomy[57], so

despite a lack of human studies, it is reasonable to hypothesize that alcohol not only causes hepatocellular injury and death, but also prevents regeneration. While histologically, the presence of bilirubinostasis and severe fibrosis are associated with a poorer prognosis in alcoholic hepatitis, the presence of proliferating hepatocytes is associated with better prognosis[58]. In addition, intense neutrophilic infiltrate was also associated with better prognosis[56], suggesting that cytokines released by neutrophils likely play a role in hepatic regeneration following cessation of alcohol, and that resolving inflammation may actually have a beneficial, rather than detrimental role in alcoholic liver disease, contributing to hepatic regeneration (Table 1). Severe alcoholic hepatitis is marked by a failure of liver progenitor cells to progress past massive proliferation to maturation into mature hepatocytes[59], the mechanism for which remains to be elucidated (Figure 3). Potential therapeutic agents to promote hepatic regeneration are being explored.

6. CONCLUSIONS AND PROSPECTS FOR FUTURE

Alcohol consumption is a leading cause of global morbidity and mortality, with much of its negative impact as a result of ALD. The lack of characterization of the early stages of ALD accounts for diagnoses being made at advanced stages of disease with higher rates of complications and mortality. Emphasis on better defining the natural history and prognostic factors and developing reliable non-invasive markers for ALD is required. Early detection of initial forms of ALD in the primary care setting and subsequent behavioral interventions would address this need.

Despite some important advances in our understanding of the pathogenesis and clinical characteristics of ALD, there have been no significant advances in therapy in the last 40 years. The mainstream of therapy for patients with ALD, regardless of the disease stage, is prolonged alcohol abstinence. Abstinence is associated with improved clinical outcomes throughout the spectrum of ALD, from the asymptomatic early to the complicated severe cases. Clinical endpoints depend on the stage of ALD. In compensated patients, the endpoints consist of normalization of abnormal lab tests and reduction of liver fibrosis. These endpoints can be monitored non-invasively. The incidence of AH, one of the deadliest diseases, is unknown. Supportive therapy is the mainstay of treatment and current medical interventions are largely limited and ineffective. In patients with AH and decompensated cirrhosis, the clinical endpoints are survival and compensation of the liver disease. The molecular and cellular factors that influence AH are not completely known. Recent translational work using human liver tissue has been informative in identifying some potential therapeutic targets for severe AH. However, translation of these findings into novel therapies has been lacking. Additional detailed studies of these potential targets in humans and animal models are urgently needed to improve outcomes in this patient population.

Acknowledgement

This work was supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) (1U01AA021908-01) and P30 DK34987.

Abbreviations

ALD	alcoholic liver disease
ASH	alcoholic steatohepatitis
AH	alcoholic hepatitis
ADH	alcohol dehydrogenase
ALDH	acetaldehyde dehydrogenase
CYP2E1	Cytochrome P450 2E1
PNPLA3	patatin-like phospholipase domain-containing protein 3
HCC	hepatocellular carcinoma
NADH	Nicotinamide adenine dinucleotide
PMN	Polymorphonuclear leukocytes
HSCs	hepatic stellate cells
ROS	reactive oxygen species
LPS	lipopolysaccharide
TLR4	toll-like receptor-4
SBP	spontaneous bacterial peritonitis
DF	Maddrey Discriminant Function
MELD	model for end-stage liver disease
GAHS	Glasgow Alcoholic Hepatitis Score
ABIC	Age, Bilirubin, INR, Creatinine
AASLD	American association for the Study of Liver Disease
EASL	European Association for the Study of the Liver
TNF	tumor necrosis factor
IL	interleukin
CXCL1	chemokine (C-X-C motif) ligand 1
DAMP	damage-associated molecular pattern
HMGB1	high mobility group box-1
PAMP	pathogen-associated molecular pattern
LCFA	long chain fatty acids

References

1. Gao B, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. Gastroenterology. 2011; 141:1572–85. [PubMed: 21920463]
2. WHO.. Alcohol. World Health Organization;
3. Altamirano J, Bataller R. Alcoholic liver disease: pathogenesis and new targets for therapy. Nat Rev Gastroenterol Hepatol. 2011; 8:491–501. [PubMed: 21826088]
4. Bertola A, Mathews S, Ki SH, et al. Mouse model of chronic and binge ethanol feeding (the NIAAA model). Nat Protoc. 2013; 8:627–37. [PubMed: 23449255]
5. Bataller R, North KE, Brenner DA. Genetic polymorphisms and the progression of liver fibrosis: a critical appraisal. Hepatology. 2003; 37:493–503. [PubMed: 12601343]
6. O'Shea RS, Dasarathy S, McCullough AJ. Alcoholic liver disease. Hepatology. 2010; 51:307–28. [PubMed: 20034030]
7. Tsukamoto H, Machida K, Dynnyk A, et al. "Second hit" models of alcoholic liver disease. Semin Liver Dis. 2009; 29:178–87. [PubMed: 19387917]
8. Wilfred de Alwis NM, Day CP. Genetics of alcoholic liver disease and nonalcoholic fatty liver disease. Semin Liver Dis. 2007; 27:44–54. [PubMed: 17295176]
9. Druesne-Pecollo N, Tehard B, Mallet Y, et al. Alcohol and genetic polymorphisms: effect on risk of alcohol-related cancer. Lancet Oncol. 2009; 10:173–80. [PubMed: 19185835]
10. Zintzaras E, Stefanidis I, Santos M, et al. Do alcohol-metabolizing enzyme gene polymorphisms increase the risk of alcoholism and alcoholic liver disease? Hepatology. 2006; 43:352–61. [PubMed: 16440362]
11. Salameh H, Raff E, Erwin A, et al. PNPLA3 Gene Polymorphism Is Associated With Predisposition to and Severity of Alcoholic Liver Disease. Am J Gastroenterol. 2015; 110:846–856. [PubMed: 25964223]
12. Anstee QM, Daly AK, Day CP. Genetics of Alcoholic Liver Disease. Semin Liver Dis. 2015; 35:361–74. [PubMed: 26676812]
13. Friedrich K, Wannhoff A, Kattner S, et al. PNPLA3 in end-stage liver disease: alcohol consumption, hepatocellular carcinoma development, and transplantation-free survival. J Gastroenterol Hepatol. 2014; 29:1477–84. [PubMed: 25273282]
14. Lucey MR, Mathurin P, Morgan TR. Alcoholic hepatitis. N Engl J Med. 2009; 360:2758–69. [PubMed: 19553649]
15. Mathurin P, Bataller R. Trends in the management and burden of alcoholic liver disease. J Hepatol. 2015; 62:S38–46. [PubMed: 25920088]
16. Ji C, Deng Q, Kaplowitz N. Role of TNF-alpha in ethanol-induced hyperhomocysteinemia and murine alcoholic liver injury. Hepatology. 2004; 40:442–51. [PubMed: 15368449]
17. Baraona E, Lieber CS. Effects of ethanol on lipid metabolism. J Lipid Res. 1979; 20:289–315. [PubMed: 87483]
18. Lefkowitch JH. Morphology of alcoholic liver disease. Clin Liver Dis. 2005; 9:37–53. [PubMed: 15763228]
19. Ronis MJ, Korourian S, Blackburn ML, et al. The role of ethanol metabolism in development of alcoholic steatohepatitis in the rat. Alcohol. 2010; 44:157–69. [PubMed: 20116195]
20. Crabb DW, Matsumoto M, Chang D, et al. Overview of the role of alcohol dehydrogenase and aldehyde dehydrogenase and their variants in the genesis of alcohol-related pathology. Proc Nutr Soc. 2004; 63:49–63. [PubMed: 15099407]
21. Adachi M, Brenner DA. Clinical syndromes of alcoholic liver disease. Dig Dis. 2005; 23:255–63. [PubMed: 16508290]
22. Bataller RG. Bin. Liver fibrosis in alcoholic liver disease. Seminars in Liver Disease. 35:146–156. [PubMed: 25974900]
23. Lindros KO, Jokelainen K, Nanji AA. Acetaldehyde prevents nuclear factor-kappa B activation and hepatic inflammation in ethanol-fed rats. Lab Invest. 1999; 79:799–806. [PubMed: 10418820]
24. Setshedi M, Wands JR, Monte SM. Acetaldehyde adducts in alcoholic liver disease. Oxid Med Cell Longev. 2010; 3:178–85. [PubMed: 20716942]

25. Bataller R, Brenner DA. Liver fibrosis. Journal of Clinical Investigation. 2005; 115:209–218. [PubMed: 15690074]
26. Zhu H, Jia Z, Misra H, et al. Oxidative stress and redox signaling mechanisms of alcoholic liver disease: updated experimental and clinical evidence. J Dig Dis. 2012; 13:133–42. [PubMed: 22356308]
27. Schnabl B, Brenner DA. Interactions between the intestinal microbiome and liver diseases. Gastroenterology. 2014; 146:1513–24. [PubMed: 24440671]
28. Paik YH, Schwabe RF, Bataller R, et al. Toll-like receptor 4 mediates inflammatory signaling by bacterial lipopolysaccharide in human hepatic stellate cells. Hepatology. 2003; 37:1043–55. [PubMed: 12717385]
29. Sandahl TD, Jepsen P, Thomsen KL, et al. Incidence and mortality of alcoholic hepatitis in Denmark 1999-2008: a nationwide population based cohort study. J Hepatol. 2011; 54:760–4. [PubMed: 21126790]
30. Singal AK, Charlton MR. Nutrition in alcoholic liver disease. Clin Liver Dis. 2012; 16:805–26. [PubMed: 23101983]
31. Rambaldi A, Iaquinto G, Gluud C. Anabolic-androgenic steroids for alcoholic liver disease: a Cochrane review. Am J Gastroenterol. 2002; 97:1674–81. [PubMed: 12135017]
32. Cabre E, Rodriguez-Iglesias P, Caballeria J, et al. Short- and long-term outcome of severe alcohol-induced hepatitis treated with steroids or enteral nutrition: a multicenter randomized trial. Hepatology. 2000; 32:36–42. [PubMed: 10869286]
33. European Association for the Study of L. EASL clinical practical guidelines: management of alcoholic liver disease. J Hepatol. 2012; 57:399–420. [PubMed: 22633836]
34. Thursz M, Forrest E, Roderick P, et al. The clinical effectiveness and costeffectiveness of STeroids Or Pentoxifylline for Alcoholic Hepatitis (STOPAH): a 2 × 2 factorial randomised controlled trial. Health Technol Assess. 2015; 19:1–104. [PubMed: 26691209]
35. Colmenero J, Bataller R, Sancho-Bru P, et al. Hepatic expression of candidate genes in patients with alcoholic hepatitis: correlation with disease severity. Gastroenterology. 2007; 132:687–97. [PubMed: 17258719]
36. Boetticher NC, Peine CJ, Kwo P, et al. A randomized, double-blinded, placebocontrolled multicenter trial of etanercept in the treatment of alcoholic hepatitis. Gastroenterology. 2008; 135:1953–60. [PubMed: 18848937]
37. Nguyen-Khac E, Thevenot T, Piquet MA, et al. Glucocorticoids plus N-acetylcysteine in severe alcoholic hepatitis. N Engl J Med. 2011; 365:1781–9. [PubMed: 22070475]
38. Pockros PJ, Schiff ER, Shiffman ML, et al. Oral IDN-6556, an antiapoptotic caspase inhibitor, may lower aminotransferase activity in patients with chronic hepatitis C. Hepatology. 2007; 46:324–9. [PubMed: 17654603]
39. Shiffman ML, Pockros P, McHutchison JG, et al. Clinical trial: the efficacy and safety of oral PF-03491390, a pancaspase inhibitor - a randomized placebo-controlled study in patients with chronic hepatitis C. Aliment Pharmacol Ther. 2010; 31:969–78. [PubMed: 20163376]
40. Ratziu V, Sheikh MY, Sanyal AJ, et al. A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of GS-9450 in Subjects With Nonalcoholic Steatohepatitis. Hepatology (Baltimore, Md.). 2012; 55:419–428.
41. Ramaiah SK, Jaeschke H. Hepatic neutrophil infiltration in the pathogenesis of alcohol-induced liver injury. Toxicol Mech Methods. 2007; 17:431–40. [PubMed: 20020946]
42. Maltby J, Wright S, Bird G, et al. Chemokine levels in human liver homogenates: associations between GRO alpha and histopathological evidence of alcoholic hepatitis. Hepatology. 1996; 24:1156–60. [PubMed: 8903391]
43. Lemmers A, Moreno C, Gustot T, et al. The interleukin-17 pathway is involved in human alcoholic liver disease. Hepatology. 2009; 49:646–57. [PubMed: 19177575]
44. Dominguez M, Miquel R, Colmenero J, et al. Hepatic expression of CXC chemokines predicts portal hypertension and survival in patients with alcoholic hepatitis. Gastroenterology. 2009; 136:1639–50. [PubMed: 19208360]
45. Seth D, Gorrell MD, Cordoba S, et al. Intrahepatic gene expression in human alcoholic hepatitis. J Hepatol. 2006; 45:306–20. [PubMed: 16797773]

46. Kubes P, Mehal WZ. Sterile inflammation in the liver. Gastroenterology. 2012; 143:1158–72. [PubMed: 22982943]
47. Ge X, Antoine DJ, Lu Y, et al. High Mobility Group Box-1 (HMGB1) Participates in the Pathogenesis of Alcoholic Liver Disease (ALD). J Biol Chem. 2014; 289:22672–91. [PubMed: 24928512]
48. Szabo G, Bala S, Petrasek J, et al. Gut-liver axis and sensing microbes. Dig Dis. 2010; 28:737–44. [PubMed: 21525758]
49. Albano E, Vidali M. Immune mechanisms in alcoholic liver disease. Genes Nutr. 2010; 5:141–7. [PubMed: 19809845]
50. Mottaran E, Stewart SF, Rolla R, et al. Lipid peroxidation contributes to immune reactions associated with alcoholic liver disease. Free Radic Biol Med. 2002; 32:38–45. [PubMed: 11755315]
51. Thiele GM, Duryee MJ, Willis MS, et al. Autoimmune hepatitis induced by syngeneic liver cytosolic proteins biotransformed by alcohol metabolites. Alcohol Clin Exp Res. 2010; 34:2126–36. [PubMed: 20860619]
52. Thiele GM, Freeman TL, Klassen LW. Immunologic mechanisms of alcoholic liver injury. Semin Liver Dis. 2004; 24:273–87. [PubMed: 15349805]
53. Yan AW, Fouts DE, Brandl J, et al. Enteric dysbiosis associated with a mouse model of alcoholic liver disease. Hepatology. 2011; 53:96–105. [PubMed: 21254165]
54. Kirpich IA, Solovieva NV, Leikhter SN, et al. Probiotics restore bowel flora and improve liver enzymes in human alcohol-induced liver injury: a pilot study. Alcohol. 2008; 42:675–82. [PubMed: 19038698]
55. Chen P, Torralba M, Tan J, et al. Supplementation of saturated long-chain fatty acids maintains intestinal eubiosis and reduces ethanol-induced liver injury in mice. Gastroenterology. 2015; 148:203–214. [PubMed: 25239591]
56. Altamirano J, Miquel R, Katoonizadeh A, et al. A Histologic Scoring System for Prognosis of Patients With Alcoholic Hepatitis. Gastroenterology. 2014
57. Dubuquoy L, Louvet A, Lassailly G, et al. Progenitor cell expansion and impaired hepatocyte regeneration in explanted livers from alcoholic hepatitis. Gut. 2015; 64:1949–60. [PubMed: 25731872]
58. Lanthier N, Rubbia-Brandt L, Lin-Marq N, et al. Hepatic cell proliferation plays a pivotal role in the prognosis of alcoholic hepatitis. J Hepatol. 2015; 63:609–21. [PubMed: 25872168]
59. Sancho-Bru P, Altamirano J, Rodrigo-Torres D, et al. Liver progenitor cell markers correlate with liver damage and predict short-term mortality in patients with alcoholic hepatitis. Hepatology. 2012; 55:1931–41. [PubMed: 22278680]

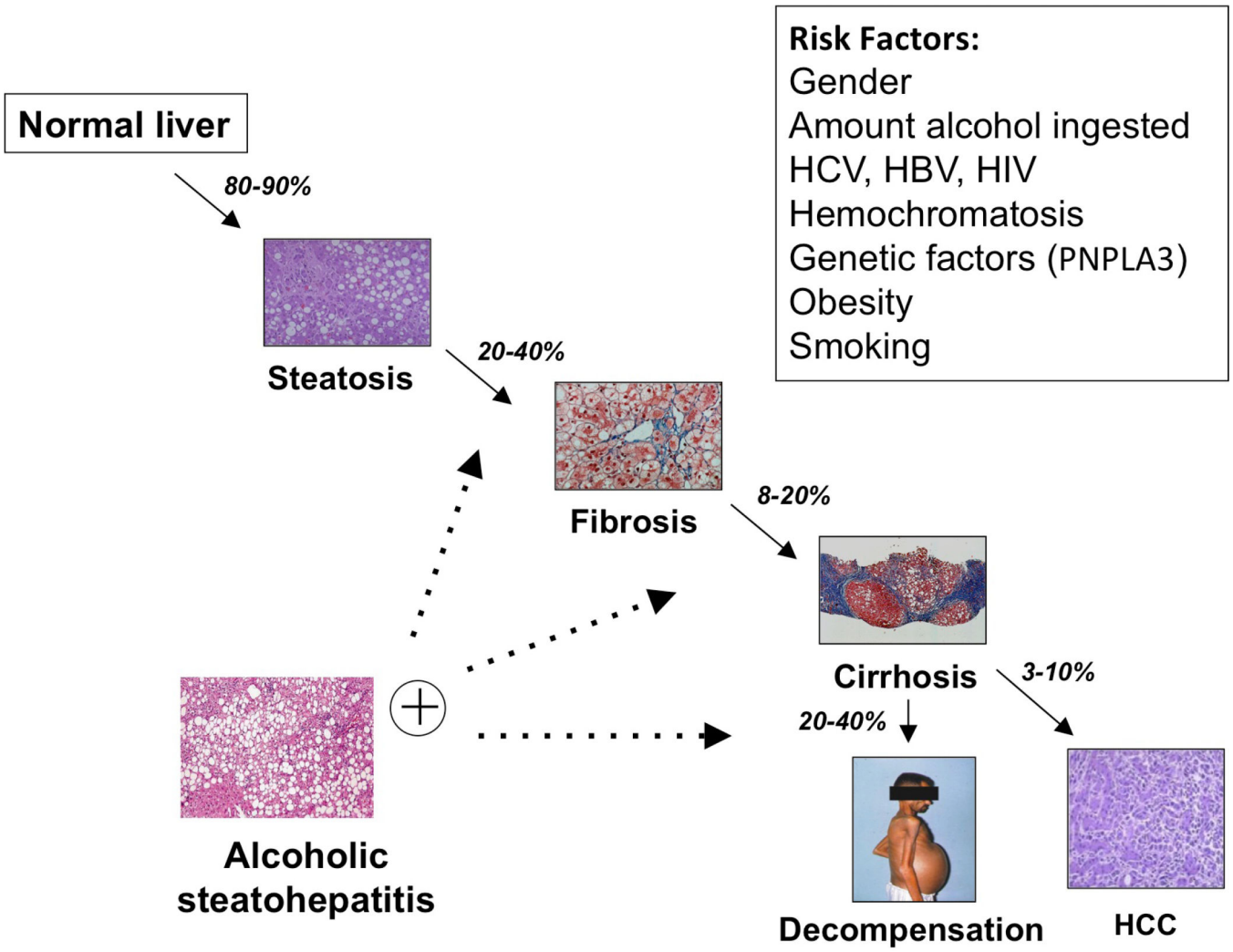


Figure 1.

Natural progression along the spectrum of ALD, from steatosis, to the inflammatory state of steatohepatitis, to progressive fibrosis and cirrhosis, and finally, to decompensated cirrhosis and hepatocellular carcinoma (HCC). Exacerbations of alcoholic hepatitis (AH) occur at many of the later stages of disease. Predisposing risk factors to accelerated progression are listed.

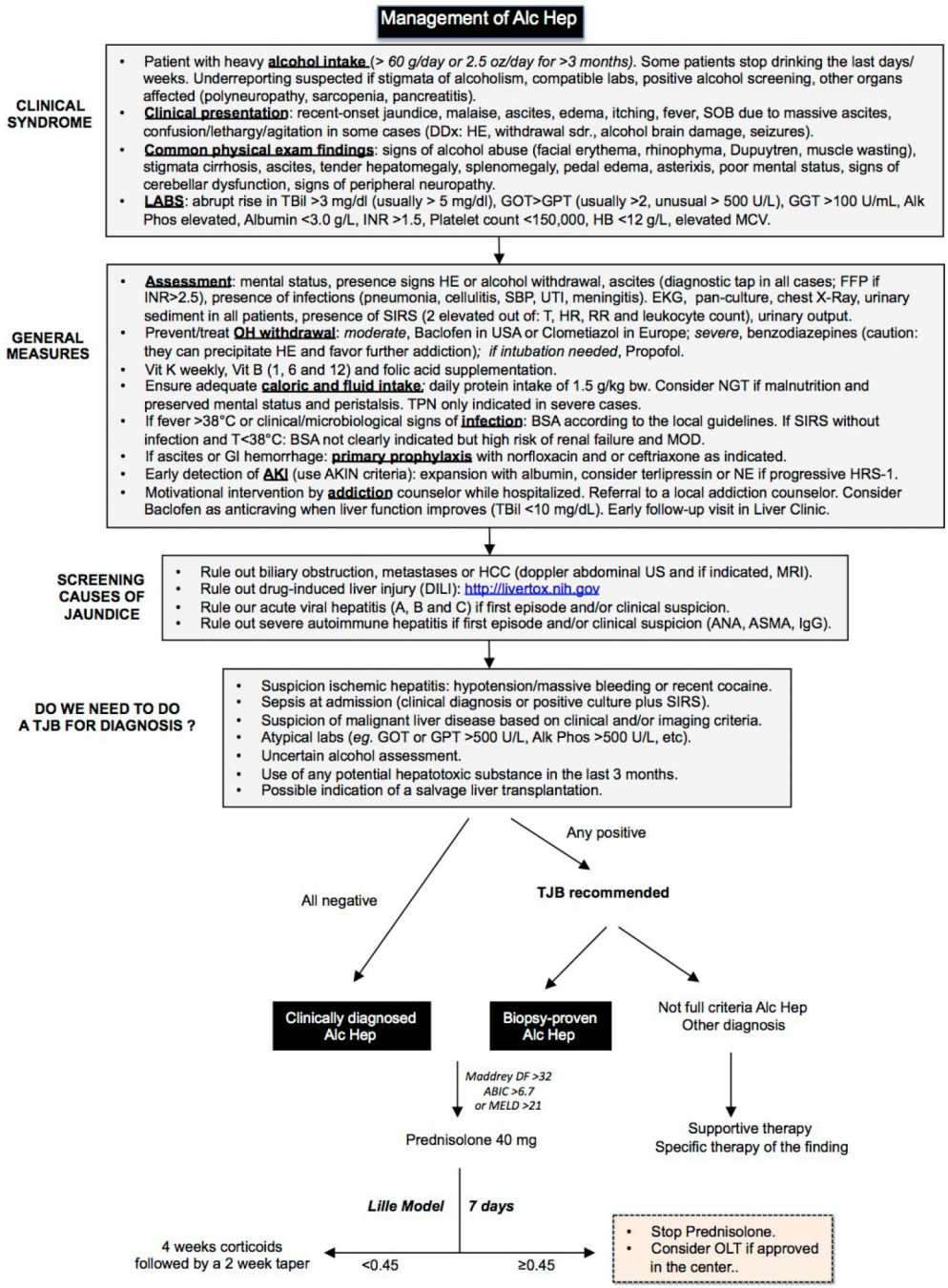
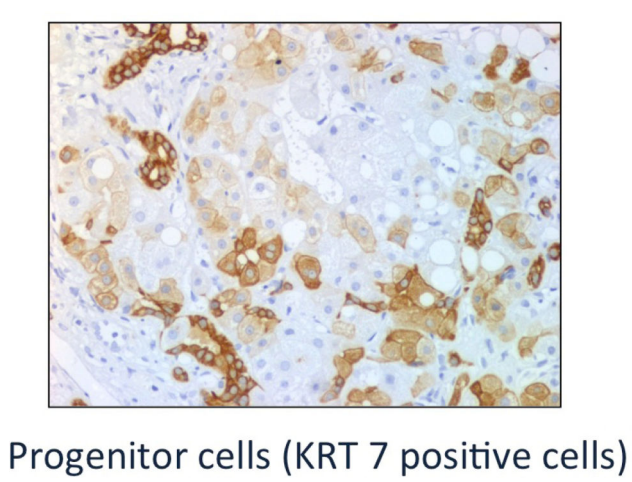


Figure 2.

Clinical evaluation for a patient with high suspicion of alcoholic hepatitis (AH) involves ruling out precipitating factors of decompensated liver disease and confounding illnesses. Role of transjugular liver biopsy is dependent on the availability in the center and the presence of potential confounding factors. Besides general measures, patients with severe episodes of AH should be treated with prednisolone (40 mg/day for 4 weeks). At week 1 the efficacy of prednisolone therapy should be evaluated using the Lille Score (www.Lillescore.com).



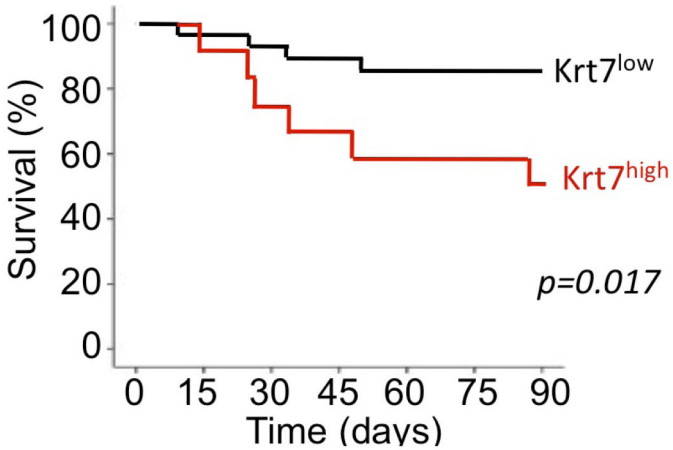


Figure 3.

Prognostic role of the accumulation of progenitors cells (cytokeratin-7 postive ductular cells) in patients with alcoholic hepatitis (AH). With permission from Sancho-Bru et al[59].

Table 1

Alcoholic Hepatitis Histological Score (AHHS) for Prognostic Stratification of Alcoholic Hepatitis[56].

	Points	
Fibrosis stage		**AHHS categories (0-9 points)**
None Fibrosis or Portal fibrosis	0	Mild : 0-3
Expansive fibrosis	0	Intermediate: 4-5
Bridging fibrosis or Cirrhosis	+3	Severe: 6-9
Bilirubinostasis		
None	0	
Hepatocellular only	0	
Canalicular or ductular	+1	
Canalicular or ductular plus Hepatocellular	+2	
PMN infiltration		
Mild PMN Infiltration	+2	
Severe PMN Infiltration	0	
Megamitochondria		
No Megamitochondria	+2	
Megamitochondria	0	