Journal of Nutrition & Food Sciences
ISSN: 2155-9600

Sevastianos, J Nutr Food Sci 2016, 6:3
DOI: 10.4172/2155-9600.1000508

Commentary Open Access

Alcoholic Liver Disease: A Clinical Review

Vassilios A Sevastianos[1*] **and Spyros P Dourakis**[2]

[1]*Internal Medicine and Hepatology, 4th Department of Internal Medicine, Evangelismos General Hospital, Athens, Greece*

[2]*Internal Medicine and Hepatology, 2nd Academic Department of Internal Medicine, Hippokratio General Hospital, Athens, Greece*

[*]**Corresponding author:** Vassilios A Sevastianos, Physician in Internal Medicine and Hepatology, Evangelismos General Hospital, Athens, Greece, Tel: 302106919912; E-mail: vsevastianos@gmail.com

Received date: May 11, 2016; **Accepted date:** May 27, 2016; **Published date:** May 31, 2016

Abstract

Liver disease is responsible for more than 55% of deaths resulting from alcohol abuse, and the prevalence of alcoholic liver disease (ALD) is closely correlated with per capita alcohol consumption. ALD represents a broad range of histological changes ranging from simple steatosis to heavier forms of liver injury, including alcoholic hepatitis (AH), cirrhosis, or the parallel development of hepatocellular carcinoma (HCC). These alterations of the hepatic parenchyma are not necessary to reflect distinct stages of the liver disease progression but rather a continuum relating histological changes that may be observed simultaneously in the same patient.

The fact that only 35% of patients with substantial alcohol abuse develop advanced stages of liver disease suggests that the pathogenesis of ALD involves many other factors that include gender, obesity, drinking patterns, dietary factors, non-sex-linked genetic factors, and smoking. Also, long-term drinking can affect synergistically with hepatitis B or C or the human immunodeficiency virus, the non-alcoholic fatty liver disease, and hepatic disorders such as hemochromatosis.

The diagnosis of ALD is based on a combination of findings, including the history of significant alcohol consumption, the clinical evidence of the concomitant liver injury, and the support of the clinical case from the resultant histological, imaging, and laboratory findings.

The beneficial effect of treating AH with corticosteroids occurs in patients with encephalopathy or with poor prognosis, based on the various grading and prognostic systems of gravity, while its harmful effect is evident in patients with milder disease as they manifest an increased risk of infections compared with those not receiving corticosteroids. In patients with alcoholic hepatitis, who cannot take corticosteroids for various reasons and in those with the onset of functional renal failure (hepatorenal syndrome), the use of pentoxifylline is recommended.

Keywords: Alcohol; Liver disease; Hepatitis; Clinical picture; Diagnosis; Treatment

Abbreviations:

ALD: Alcoholic Liver Disease; DALYs: Disability-Adjusted Life Years Cases; AH: Alcoholic Hepatitis; HCC: Hepatocellular Carcinoma; ERCP: Endoscopic Retrograde Cholangiopancreatography; CDT: Carbohydrate-Deficient Transferrin; EtG: Ethyl Glucuronide; CRP: C-Reactive Protein; NAFLD: Non-Alcoholic Fatty Liver Disease; NASH: Steatohepatitis; MELD: Model for End-stage Liver Disease; INR: International Normalized Ratio; FSR: Fibrin Split Products; CT: Computed Tomography; MRI: Magnetic Resonance Imaging

Introduction

Humans have been drinking alcoholic beverages since at least the Neolithic period. For more than 10,000 years, beverages that have undergone alcoholic fermentation (alcohol concentration of less than 16%) have represented a source of fluids and energy for Western civilization, particularly during those periods when consuming water from nature was unsafe and the practice of boiling water had not yet prevailed. However, the morbidity of alcohol use or abuse sharply rose when the production of wine and distilled spirits received a broad acceptance in Europe around the sixteenth century AD [1].

Alcoholic liver disease (ALD) represents the oldest form of liver damage known to humans [2]. It includes a broad spectrum of liver parenchyma lesions, ranging from simple steatosis to severe cirrhosis and hepatocellular carcinoma. Alcohol abuse represents a significant background for morbidity development from organic systems or organs other than the liver that are often co-expressed in the same patient [1,3]. Today, alcohol toxicity is ranked as the third most frequent cause of morbidity and mortality from a potentially preventable and socially acceptable harmful agent. It accounts for 3.8% of deaths worldwide and 4.6% of disability-adjusted life years cases (DALYs) [4].

So, based on the fact that liver disease and other complications related to alcohol consumption are entirely consequences of human behavior, any intervention aimed to inform and raise awareness of the nature and risks of abuse is imperative, beneficial, and can yield significant scientific and social benefits.

Epidemiology

The actual prevalence of ALD is tough to assess in the general population. Recently, with the use of liver elastography as a screening tool, alcohol emerged as an underlying cause for a third of the cases with advanced hepatic fibrosis in the general population [5].

It seems that liver disease is responsible for more than 55% of deaths from alcohol abuse while the prevalence of ALD appears closely correlated with per capita alcohol consumption [1]. It estimated that for every 1 lit. increase in per capita use of alcohol, the incidence of cirrhosis grew by 14% in men and 8% in women [6].

The highest prevalence of alcoholic liver disease in Europe is recorded in the United Kingdom in parallel with the eastern and southern European countries. It is interesting that the largest differences in consumption between these countries are more pronounced at ages over 45 years and the incidence occurs two to three times more often in men than women [4,7].

However, a study that included 13,000 Danish women showed a greater chance of developing cirrhosis compared with males for a given consumption of ethyl alcohol [8]. However, the published epidemiological evidence of alcoholic disease in Europe probably underestimates the actual burden of the problem. Data from the European Liver Transplant Registry highlights that the number of transplants due to alcoholic disease today follow an increasing trend. At the same time, alcohol abuse is the second leading cause for liver transplantation and is related to the one-third of cirrhosis cases that led to transplantation in the European continent [9].

There are significant differences in the prevalence and the mortality associated with ALD between different ethnological groups. Countries with large Muslim communities have lower alcohol consumption rates and ALD [1,10]. Therefore, the literature data show differences in alcohol consumption between different ethnological or social groups [11]. However, it remains unclear whether the differences in the percentage of alcoholic cirrhosis and ALD recorded represent genetic peculiarities, differences in the amount and type of alcohol consumed, or characteristics of socioeconomic status and accessibility of medical services in each country.

Despite the strong association between alcohol consumption and the incidence of liver disease, severe alcohol liver disease develops in only a small minority of patients with abuse. In the Dionysus study, the possibility of alcohol-related liver toxicity was significant with the consumption of more than 30 g/day while those who consumed more than 120 g experienced more frequent cirrhosis. However, only 2.2% of the high-risk individuals had liver cirrhosis in this study [12], which underlines the idiosyncratic nature of the liver damage or presence differences of other natures in the alcohol receptiveness.

On the other hand, mortality from liver cirrhosis in France between 1925 and 1964 was estimated in 14 per 100,000 individuals who consumed less than 80 g of alcohol per day and 357 per 100,000 among those who drank more than 160 g per day. It seems, therefore, that those who consume between 80 and 160 g of alcohol a day pose a significant risk of developing progressive liver diseases, including alcoholic hepatitis and cirrhosis [1,13]. However, a more recent meta-analysis found an increased likelihood of loss of life from liver cirrhosis among men and women who consumed between 12 g and 24 g of alcohol daily [14].

Therefore, it is shown that there is probably a lower limit on alcohol consumption beyond which the risk of the development and progression of liver disease is significant [14]. This threshold is likely to be very humble and probably difficult to document because of the difficulties of recording in the general population's consumption of 10-12 g of alcohol per day [4]. The effects of binge drinking on the organism in general (drinking five or more drinks for men and four or more for women in a period of two hours) are still unknown [15].

Natural History of Alcoholic Liver Disease and Risk Factors

ALD represents a broad variety of disorders ranging from simple steatosis to more severe liver injury, including alcoholic hepatitis (AH), cirrhosis, or the parallel development of hepatocellular carcinoma (HCC) [16]. These lesions of the hepatic parenchyma are not necessary to reflect distinct stages of liver disease progression but, rather, involve a continuous spectrum of parenchymal changes that can be observed simultaneously in the same patient (Figure 1) [17]. Indeed, the advanced stages of the progression of the liver disease are associated with the presence of more specific histological findings, including Mallory bodies, megamitochondria or perivenular and perisinusoidal fibrosis [18].

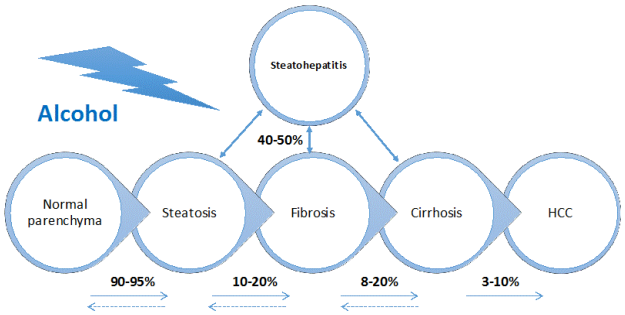

Figure 1: Natural history of alcoholic liver disease [2-4,12,19,20].

Fatty liver characterizes an early organ response to alcohol hits observed in more than 90% of substance abusers with the presence of mild hepatocyte steatosis in Zone 3 (perivenular). It can also affect Zone 2 or even Zone 1 (periportal) in the cases with more significant liver damage. Interestingly, only one-third of people with severe abuse develop more severe forms of ALD such as advanced fibrosis and cirrhosis. In patients with underlying ALD and heavy alcohol consumption that can be observed at the clinical level, recurrent episodes of alcoholic hepatitis (AH) can lead to the development of portal hypertension and liver failure with high rates of short-term mortality [16].

The fact that only 35% of patients with severe alcohol abuse develop advanced stages of liver disease suggests that in the pathogenesis of ALD, other factors are involved (Figure 2) [16]. Several risk factors have identified, and these include gender, obesity, drinking patterns, dietary factors, non-sex-linked genetic factors, and smoking. The female sex is one of the well-documented risks factors for ALD development, which can be attributed to the lower levels of alcoholic dehydrogenase in the gastric fluids, the higher percentage of body fat, and the presence of estrogen, which characterizes the female gender. Obesity is another important factor that accelerates the development of both fibrosis and cirrhosis.

- Consumption:
  - Men > 60-80 gr/d
  - Woman > 20 gr/d
- Everyday use
- Alcohol outside meals
- Binge drinking
- No wine
- Female gender
- Race
- Concurrent viral hepatitis (hepatitis C)
- HIV infection
- Increased body weight and insulin resistance
- Smoking
- Hemochromatosis
- Genetic factors

Gene	Existing evidence
Genes involved in alcohol metabolism	
ADH1B	Conflicting results for all variants; data from meta-analysis suggest no association with ALD
ADH1C	
CYP2E1	
CYP1A1	
ALDH2	
Genes related to oxidative stress	
GSTM1	Mostly negative studies; positive associations challenged by failure to replicate in subsequent studies; MnSOD variation may be associated with hepatocellular carcinoma (to be confirmed independently)
GSTP1	
GSTT1	
MnSOD	
NAT	
HFE	
Genes implicated in immune reactions	
TNFa	All conflicting or yet unconfirmed except for TNFα −238A allele which was found to be associated with ALD in several independent studies and by meta-analysis; and CD14 variation which was linked to ALD in three studies
Interleukin (IL)-10	
IL-1R antagonist	
IL-1b	
CD14 receptor	
CTLA-4	
TLR4	
Genes coding for fibrosis-associated factors	
TGFb1	No association in sufficiently powered genetic case–control studies
MMP3	
Genes involved in the modulation of steatosis	
PPARg	As yet unconfirmed single studies of *PPARg* and *MTP* variants with low sample sizes showing significant association with ALD; *ApoE* with conflicting data from two very small studies
MTP	
ApoE	
Miscellaneous	
NFkB1	Single study showing association of *NFkB1* variant −94 ins/del with fibrosis; *DRD2* and *SLC6A4* negative
DRD2	
SLC6A4	

Figure 2: Risk factors for the development of alcoholic related cirrhosis [19].

Experimental studies show that the synergistic effects of obesity and alcohol abuse include, among others, the response of the endoplasmic reticulum system to stress, the type I macrophage activation, and the resistance to adiponectin [3,16,21,22].

Daily or almost daily heavy drinking that starts at an early age increases the risk of serious ALD development compared with episodic or binge drinking. Some genetic factors appear to influence the development of ALD, but currently, little data are available in the literature. Changes in the genes that encode antioxidant enzymes, cytokines, other inflammatory mediators, and enzymes that metabolize alcohol may play a role in pathogenesis [22]. Indeed, recent studies show that changes in the polymorphism of TNF-238A [23] and PNPLA3 protein (patatin-like, phospholipase, domain-containing protein 3) [19] may influence the development of alcoholic cirrhosis in Caucasian patients who abuse alcohol, but these data require more literature documentation.

Also, long-term drinking can interfere synergistically with viral hepatitis B or C and human immunodeficiency virus, non-alcoholic fatty liver disease, and disorders such as hemochromatosis that accelerate the progression of liver disease at more advanced stages, probably through activation of multiple mechanisms [16,24]. Specifically, it appears that in patients with hepatitis C who consume more than 30-50 g of alcohol per day, the risk of liver fibrosis development is increased by four times while those who drink excessive alcohol have a 30 times greater risk of developing cirrhosis [4].

On the other hand, the presence of iron in the liver biopsy specimens has also been associated with the development of fibrosis in ALD and with increased mortality in alcoholic cirrhosis. Elevated levels of iron in serum are not uncommon in patients with ALD compared with alcoholics without underlying liver disease. However, while there are studies that have described a liver disease correlation with the mutation H63D, there is no a respective de nite correlation with mutations in the C282Y HFE gene. Of course, alcohol and iron may act synergistically in producing oxidative stress and thus accelerate the progressive liver damage [25].

Diagnosis of ALD

The diagnosis of ALD is based on a combination of findings, including the history of significant alcohol consumption and the evidence of the related liver injury. Furthermore, the clinical suspicion may support the corresponding histological, imaging, and laboratory findings. Alcohol abuse is usually refused by the patients while semiological features of abuse are present. Physicians often underestimate the problem with the result, rarely seeing alcohol abuse revealed as reality by the consequences and complications.

Both clinical and laboratory findings of ALD may be non-diagnostic, especially in patients with mild ALD or early stages of alcoholic cirrhosis. Therefore, the clinician should be sensitized in detecting ALD resorting to the search for accurate information from other family members or even through questionnaires combined with the laboratory evidence that can support the clinical feeling.

Clinical picture

The findings on a physical examination in ALD patients vary considerably and have low sensitivity even in detecting advanced disease or cirrhosis. Although particular clinical findings are observed more frequently among people with ALD, such as swelling of the parotid, the contraction of the palmar fascia, and signs of male feminizing, even those are not specific [3]. On the other hand, the detection of hepatic encephalopathy, dilated veins in the anterior abdominal wall, ascites, presence of spider nevi, and the feeling of weakness have associated with an increased risk of life loss during the next year [26].

Alcoholic hepatitis is manifested clinically by anorexia, fever, and jaundice. On physical examination are found tender hepatomegaly (due to the deposition of fat and protein in hepatocytes) [27], having relatively small spleen enlargement (the opposite happens in cirrhosis on the grounds of hepatitis), ascites, and loss of proximal muscle mass. Hepatic encephalopathy can coexist with renal failure of functional type ("hepatorenal syndrome"). In the right hypochondrium often sounds (50%) a murmur (suggesting enhanced hepatic arterial perfusion). Indeed, in a reference study including 101 patients with alcoholic hepatitis, the murmur was verified in 58% of the case-patients [28]. The fever (38-38.5°C) could be attributed to the alcoholic disease after having ruled out the presence of infection that often coexists. The clinical picture of alcoholic hepatitis mimics an acute cholecystitis with fever, jaundice, and leukocytosis added on a preexisted hepatomegaly.

The simultaneous presence of fever and lymphocytosis can frustrate the clinician towards the septic syndrome, especially if the patient's history is unclear. On the other hand, malnutrition and comorbidities often coexist in the same patient with an advanced liver disease, predisposing him or her to the development of infections; impose at least the necessity of taking (blood and urine cultures), performing chest a radiograph, and an evaluation of ascitic fluid if present [29].

Also, one can often observe unexplained intrahepatic and extrahepatic cholestasis due to the obstruction of the lower third of the bile duct from fibrosis owing to the accompanying chronic pancreatitis. This finding should be evaluated carefully on the basis that if endoscopic retrograde cholangiopancreatography (ERCP) is performed in these cases, it implies a significant risk for the development of severe necrotizing pancreatitis and, therefore, should not be carried out for purely diagnostic reasons [29].

It is worth noting that the clinician must take into account that ALD often coexists with manifestations from other organs or systems including malnutrition and muscle mass loss, alcoholic cardiomyopathy, pancreatic dysfunction, and neurotoxicity from alcohol abuse [3].

Laboratory findings

Currently, there is no specific biological marker to associate alcohol with the underlying cause of liver damage. Several laboratory parameters used in clinical practices have been linked with chronic alcohol consumption and alcoholic liver damage. Indeed, the sensitivity of carbohydrate-deficient transferrin (CDT) and γGT to evaluate the drinking of greater than 50 g per day is 69% and 73%, respectively. These rates are significantly higher than that of AST (50%), ALT (35%), and MCV (52%) [30] while the combination of CDT and GGT shows much greater sensitivity, reaching near 90% (Figure 3) [31].

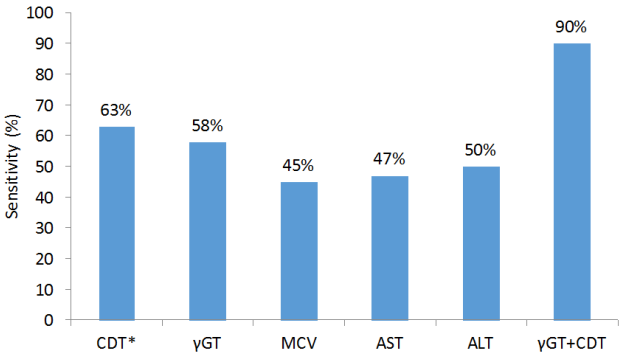

Figure 3: Sensitivity of biochemical markers to detect severe alcohol abuse [31].

The γGT is usually higher in ALD patients compared to those who suffer from other liver diseases. Given the lower cost of the assay, the remains the laboratory test are most commonly used in clinical practice. However, 1/3 of individuals with heavy alcohol use have γGT values within the normal limits in serum even in cases of excessive consumption [32]. Additionally, the γGT serum activity loses its sensitivity in more advanced liver diseases because the activity is often increased in patients with extensive fibrosis regardless of the underlying etiology. Recently, it was found that the γGT levels in serum are affected not only by the amount of alcohol consumed but also by the body mass index and gender [33]. Lower γGT levels of <100 IU/L or the ratio of total bilirubin/γGT>1 have been proposed as predictors of increased mortality rates within one year in patients with alcoholic cirrhosis [34]. Also, direct metabolites of alcohol have been studied and used as biological markers of abuse, such as the

determination of ethyl glucuronide (EtG) showing sensitivity and specificity of 92% and 91% respectively [35].

Alcoholic hepatitis, characterized by increased aminotransferase (transaminase), is greater than twice the upper limit of normal (>2 XULN). But, always remain <300 U/L with the ratio of AST (aspartate aminotransferase or glutamic oxaloacetic transaminase SGOT) to ALT (alanine aminotransferase or glutamic pyruvate transaminase SGPT), typically >2 in more than 70% of cases [36-38]. The above typical picture is attributed to a lack of pyridoxine (vitamin 6) that is a cofactor for the ALT enzyme activity and to the increased mitochondrial AST [39,40].

ALT levels >500 U/L exclude the diagnosis of alcoholic hepatitis [41]. Higher values should raise the suspicion of concurrence with alcohol abuse of viral, ischemic, or drug-related (e.g., by taking a relatively large amount of paracetamol) hepatitis. Attention is required for the interpretation of the increases in serum transaminases levels owing to an extrahepatic origin (rhabdomyolysis, myocardial infarction, etc.).

With the above mentioned may coexist increasing IgA, leukocytosis with neutrophilia (maybe at levels leukemoid reaction: >40.000/mm^3), increased C-reactive protein (CRP), and hyperbilirubinemia (>5 mg/dl) with the predominance of the direct type. The last one typically increases more with the coexistence of renal failure or hemolytic anemia. Note that γGT was often found to be significantly increased (70%) due to its activation. Also observed were macrocytosis (MCV >100 fl), owing to B12 and folate deficiencies, alcohol toxicity on maturating erythrocytes, and impaired lipids on the membranes of erythrocytes (red cells "as spurs"-spur-cell). Often, thrombocytopenia was present as a result of bone marrow suppression from ethanol toxicity or sequestration of platelets in the splenic reservoir due to portal hypertension and splenomegaly (hypersplenism). There may be an extension of prothrombin time because of liver failure that cannot be corrected despite the parenteral administration of vitamin K. Also, hyperuricemia often coexists (in severe hepatic impairment that shows hypouricemia), as does hypokalemia of multifactorial etiology (vomiting, but mostly from the toxic effect of ethanol on urinary tubules). Serum ferritin can increase, consequential to its release from the hepatocytes as a result of inflammation but related to the extent of liver fibrosis [42,43]. The ferritin levels in the serum, normalized after a few months of abstinence from alcohol, and the inflammatory activity in the liver showed improvement [44]. The rate of erythrocyte sedimentation can increase because of the presence of polyclonal hypergammaglobulinemia typically seen in chronic liver disease and the increased CRP levels in the serum. The serological markers of hepatotropic viral infections and the absence of autoantibodies could exclude concurrent viral or autoimmune liver diseases. Autoantibodies (antinuclear and against smooth muscle fibers) are often found in low titers (<1/160) but not accompanied by a significant increase of gamma globulins. If higher titles of these autoantibodies are found in serum or hypergammaglobulinemia, histological examination is essential for establishing the diagnosis and the marginalization of coexisting autoimmune liver disease [2-4].

An increase in the creatinine >1.5 mg/dl and the reduction of the creatinine clearance <40 ml/min are indications of hepatorenal syndrome representing an adverse prognostic marker for the disease progression [45]. However, in cirrhotic patients, creatinine and urea in serum underestimate the severity of the renal impairment. The latter may be attributed to the presence of hyperbilirubinemia (technical problems in the biochemical measurement), the blood volume increase due to the concomitant dilution, the hypo-protein feeding, and the reduced urea synthesis from a dysfunctional liver parenchyma. Furthermore, the malnutrition may play a significant role typically observed in these individuals with the parallel decrease in muscle mass and consequently declining endogenous creatinine production. Because of the above, it requires a much greater reduction in the glomerular filtration rate for the corresponding increase in urea and creatinine to become apparent. In contrast, the increase in blood urea could be attributable to gastrointestinal bleeding, intense catabolism, or corticosteroids.

Imaging studies

Imaging studies provide valuable information. Ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) can be used as tools for the presymptomatic detection of fatty liver but do not contribute to the determination of the exact etiology of the underlying liver disease. However, they can decisively support the exclusion of other causes of the impaired liver biochemistry such as the obstructive biliary lesions or the presence of invasive liver neoplasms [3,4].

The liver ultrasound usually shows diffuse echogenic liver parenchyma. The infiltration of the liver parenchyma with fat reduces hepatic attenuation compared with the spleen on non-contrast imaging. Indeed, in the CT study of the liver without intravenous contrast, the liver appears enlarged and hypodense in contrast to the corresponding picture of the spleen and kidney while intrahepatic branches of portal and hepatic veins are more conspicuous than those of the healthy liver. The findings are similar to those observed in non-alcoholic fatty liver disease/steatohepatitis (NAFLD/NASH). Focal fat concentration in the liver parenchyma presented on CT imaging as a hypodense area ("pseudo-tumor") and may be confused with certain liver tumors while for the differential diagnosis, an MRI must performed. The findings, as mentioned earlier, could coexist with those of liver cirrhosis (irregularity of the external contour of the liver, enlarged caudate lobe, thickening of the gallbladder wall, ascites, splenomegaly, and portosystemic shunts). An additional Doppler ultrasound study shows an increment in the speed of hepatic artery blood flow or a rise in its diameter [46].

Among these methods, ultrasound probably has the lower sensitivity and specificity, particularly when steatosis on the histologic level does not exceed the limit of 20-30% of the hepatic parenchyma. MRI and MR spectroscopy are reliable tools for assessing the degree of steatosis, but the lack of standardization of these methods and their high costs limit their use and availability [4].

The position of the transient elastography in ALD

Measuring liver stiffness appears to be a valuable tool for the assessment of hepatic fibrosis in patients with ALD. However, in studies that did not take into account the coexistence of alcoholic steatohepatitis, the lower value of the stiffness index corresponding to F3 and F4 fibrosis stage in histological level was significantly higher compared to that verified in patients with viral related liver diseases. Also, several studies have shown that patients with alcoholic cirrhosis had significantly higher stiffness values compared to those who suffered from cirrhosis secondary to viral infection, underscoring the fact that the causative agent can greatly affect the extent and the progression of fibrosis in the liver [4].

Therefore, the liver stiffness index can be correlated with the stage of fibrosis in ALD, but the diagnosis of advanced-stage liver disease, severe fibrosis, or cirrhosis probably requires a higher lower limit of the index as compared with other liver diseases. Increased liver stiffness index can also be observed in cases of alcoholic disease and concomitant increase aminotransferase levels on or above 100 IU/L, but in these cases, it should be interpreted with caution [47]. Possibly, the different distribution of fibrosis in the liver and the cholestasis, the liver enlargement, the inflammation, and hepatocytes necrosis as the result of acute hepatocellular injury could give a satisfactory explanation of this phenomenon [48]. As a result, the heavy alcohol abusers with or without the presence of alcoholic hepatitis can experience an increased liver stiffness index, leading to an inaccurate estimate of fibrosis, a datum that should be noticed by the clinical hepatologist as the liver stiffness index in ALD has not yet been standardized.

Liver histology in ALD

Although liver biopsy does not significantly contribute to the management of patients with ALD, in some cases, it is useful considering that more than 20% of patients with a history of alcohol abuse have a secondary or other coexisting cause of liver damage. Also, on a well-compensated liver disease, the biopsy can capture the stage and the severity of liver disease [3].

Alcoholic liver disease is associated with three main histological lesions in the liver that often coexist (steatosis, steatohepatitis, cirrhosis). Of the patients with alcohol abuse, 80% present with histological liposis, 10-35% with steatohepatitis, and 10% with cirrhosis. On hematoxylin and eosin staining, many hepatocytes are formed with fat droplets in the protoplasm and vacuolar nuclei displaced to the cell membrane [49]. The lesions are most pronounced around portal spaces (zone 1 of the hepatic lobules). The droplets of fat are stained with oil red O in the cryostat sections. During the fixation of the liver biopsy specimens, in a formalin solution, the fat droplets dissolve and, thus, are shown as empty areas within the hepatocytes. There is also liposis in the liver parenchyma, expressed as ballooning degeneration of the hepatocytes, containing the nucleus near amorphous eosinophilic Mallory bodies, with the presence of giant mitochondria; an infiltration of parenchyma by polymorphonuclear neutrophils can also be seen [17]. The degree of polymorphonuclear cell infiltration has a poor predictive value and can coexist with mononuclear cells. Pericentral (around the central vein, in zone 3 of the hepatic lobules) and perisinusoidal fibrosis (in the space of Disse) are typically present [50]. Fibrosis can extend into the portal areas or other central vessels, forming central-central and central-portal bridges. Fibrosis represents the result of connective tissue production by cells of Ito (stellate cells) and may be followed by the accumulation of material, similar to the composition of the basement membrane of capillaries, culminating in sinusoidal capitalization in the case of micronodular liver cirrhosis [51]. The histological features of NASH may be identical to those observed in alcoholic hepatitis [52].

Differential diagnosis

Diagnosis is based on clinical presentation (jaundice, ascites, tender hepatomegaly, increased transaminase <300 U/L, the ratio AST/ALT>2, leukocytosis with polymorphonucleates) in an individual with alcohol abuse. In some cases, you may need an interaction with family members or the working environment to confirm the abuse. Histology studies may be useful in a diagnostic and prognostic basis, but it is not necessary for the diagnosis.

Differential diagnosis includes NAFLD/NASH, acute or chronic viral hepatitis, acute drug-induced hepatitis, fulminant Wilson disease, autoimmune hepatitis, acute cholecystitis, hepatic abscess, and hepatocellular carcinoma. Caution is also needed in the differential diagnosis of the liver manifestations of the alcoholic cardiomyopathy that can exist or co-exist with alcoholic hepatitis/cirrhosis. The differential diagnosis of the ethanol withdrawal syndrome by hepatic encephalopathy complicating alcoholic hepatitis is of great importance for treatment management while being based primarily on semiology of the sympathetic system stimulation. H alcoholic hepatitis is a febrile illness with concomitant leukocytosis with polymorphonucleates elevation in parallel with an increase in CRP levels and needs a careful differential diagnosis of possibly concurrent bacterial infections that may worsen with the therapeutic management (corticosteroids). It has been suggested that procalcitonin in the serum that rises in infections but not in alcoholic hepatitis could help in the differential diagnosis [53].

ALD Prognosis

The prognosis depends primarily on the patient's decision to stop alcohol use. However, avoiding alcohol use is often manifested by a temporary worsening of the clinical condition in spite of the abstinence. Patients with alcoholic hepatitis exhibit a mortality rate of 40% even with the best treatment [54]. Poor prognostic factors include leukocytosis, severe fibrosis, ascites, encephalopathy, functional renal failure ("hepatorenal syndrome"), and coagulopathy. In most patients with less severe forms of alcoholic hepatitis who abstain from alcohol use, we can see a clinical and laboratory improvement in a few months.

Various systems have been proposed for the assessment of alcoholic hepatitis clinical severity (Maddrey index, Glasgow score Table 1, MELD (Model for End-stage Liver Disease), Lille model score) to select the appropriate patients who benefit from treatment with corticosteroids (Tables 2 and 3). These systems include common parameters (bilirubin and prothrombin time). The known prognostic classification score Child-Turcotte-Pugh used for staging the severity of cirrhosis is not accurate for alcoholic hepatitis.

Grade			
	1	2	3
Age	<50	≥50	-
WCC (109/L)	<15	≥15	-
Urea (mmol/L)	<5	>5	-
INR	<1,5	1,5-2	>2,0
Bilirubin (μmol/L)	<125	125-250	>250

Table 1: Glasgow scoring system [55].

	Grade	28 days survival
Maddrey score	<32	93%
	>32	68%

Glascow alcoholic hepatitis score	<9	87%
	>9	46%
Model for end stage liver disease (MELD) score	<11	96%
	>11	45%

Table 2: Prognostic systems of short term survival in alcoholic hepatitis [55-57].

Markers	Mortality
Hepatic encephalopathy	>50% at 3 months
Maddrey score	>35% at 2 months when >32
MELD score	>50% at 3 months when >25

Table 3: Prognostic systems for three months survival in alcoholic hepatitis [2-4].

The Maddrey discriminant function (4, 6 Xprolongation of prothrombin time in seconds+bilirubin in mg/dl) is the oldest and most widely used [58]. Although, it includes the measurement of prothrombin time in seconds compared to the control but not the INR (International Normalized Ratio) that is the modern way of evaluation internationally (it was devised to standardize the results between laboratories). The survival in those with Maddrey index <32 is about 90%, so the side effects of using steroids exceed the expected benefit from the treatment intervention.

The Glasgow alcoholic hepatitis score (not to be confused with the Glasgow coma scale) is based on five parameters: age, white blood cells, urea, bilirubin, and prothrombin time (Table 1) [59]. The score helps in predicting and distinguishing those with Maddrey index patients >32 who will benefit most from the use of corticosteroids. A Glasgow score value >9 correlated with poor prognosis in 1 and 3 months. Those who had Maddrey index >32 and Glasgow score >9 but received corticosteroids had a three-month survival of 60% versus 40% of those on only conservative treatment.

The MELD score [3.8 (10 log serum bilirubin (mg/dL))]+11.2 [10 log INR]+9.6 [10 log serum creatinine (mg/dL)]+6.4, [www.mayoclinic.org/meld/mayomodel7.htm, www.unos.org/resources/MeldPeldCalculator.asp?index=98] is a statistical model used to predict survival in patients with cirrhosis while on the waiting list for a liver transplantation in the US. Several studies showed that the MELD score is as good or better than the Maddrey score for assessing the severity of alcoholic hepatitis [60]. Scores >11 were associated with increased mortality from alcoholic hepatitis and value >21 with a 3-month mortality rate of 20%, putting the indication for corticosteroid therapy. Additionally, the score could be assessed during the patient's hospital admission and after one week to determine the prognosis.

The Lille score (www.lillemodel.com) takes into account six variables: bilirubin, creatinine, prothrombin time in INR, age, albumin change, and bilirubin change as a response to one-week corticosteroid treatment. If there is no response to treatment, corticosteroids can be stopped since they outweigh their potential side effects (particularly infections) [61].

A study from the Second University Department of Medicine at the University of Athens, including 34 patients with alcoholic hepatitis, the total mortality at 30 days and 90 days was 6% and 15%, respectively, confirmed the accuracy of the survival prediction models Maddrey and MELD. Also, the AST levels, fibrin split products (FSR), and CRP values in serum showed a significant correlation with survival [62].

Alcoholic hepatitis represents a poor prognostic factor in patients with cirrhosis because when they coexist in the same patient, the total annual mortality rate is 26% compared to 7% in cirrhosis without steatohepatitis [2-4].

Treatment

The immediate cessation of alcohol use is recommended with the support of the family, the social service, and the specialized psychiatrist. Complete cessation of alcohol leads to a regression of fatty infiltration (in 4 weeks-6 weeks), to inflammation, and possibly to connective tissue that had developed, which is crucial for reducing the portal system pressure.

The position of corticosteroids in the treatment of alcoholic hepatitis was controversial for a long time [63-65]. The beneficial effect manifested in the groups of patients with severe disease, namely, in patients with encephalopathy or poor prognosis according to different scoring systems of severity. On the other hand, the deleterious effect is significant in patients with a milder form of the disease as they undergo to an increased risk of infection compared to patients who do not receive corticosteroids. A recent systematic review yielded an overall negative result but was positive for the use of corticosteroids for those with a Maddrey score >32 or hepatic encephalopathy. It is now accepted for patients with alcoholic hepatitis and hepatic encephalopathy, with a Maddrey index >32 or MELD score >21, to be administered corticosteroids (prednisolone 40 mg/day for four weeks) if the patient does not exhibit gastrointestinal bleeding or infection. Corticosteroids should not apply to patients with Maddrey index <32 or MELD <21 [66]. Patients who experience a decrease in bilirubin levels after six to nine days of treatment show significant and sustained response in parallel with a good prognosis [67]. The mortality rate in the group of patients who have not demonstrated a drop in bilirubin levels in the same period was 36.8% and 57.9% at 28 and 56 days; for those who achieved a bilirubin decline of 25%, the corresponding mortality rate was 0% and 11.1% [68]. Forty percent of cases of alcoholic hepatitis do not respond to treatment with corticosteroids. One must treat five patients to save only one. A Lille score >0.45 indicates non-response to corticosteroids, resulting in a six-month survival rate <25%. Prednisolone is preferred because it does not need to metabolize in the liver, such as prednisone does. In patients with pancreatitis, gastrointestinal bleeding, or renal impairment, the use of corticosteroids has not been studied [69]. The risk of infections developing during steroid treatment is critical, and close clinical monitoring is required [70].

The increased disposal price of anti-TNF-a compounds in patients with alcoholic hepatitis has led the medical community toward the use of pentoxifylline. Pentoxifylline is an anti-TNF agent but may act through another mechanism because it does not change the levels of the cytokines. It is administered as Tarontal, in tablets, per os, at a dose of 400 mg, three times daily for 28 days. Is recommended for patients that cannot take steroids and in patients with functional renal failure events ("hepatorenal syndrome"). Patients who did not respond to corticosteroids and pentoxifylline administration had unhelpful

results. The concomitant use of corticosteroids and pentoxifylline does not increase the effectiveness of the intervention [28,71].

Is the treatment of alcoholic disease complications such as ethanol withdrawal syndrome, gastrointestinal bleeding, infections, ascites or hepatic encephalopathy necessary? Patients with ascites were granted unsalted diets and diuretics, those with hepatic encephalopathy lactulose were given antibiotics against endogenous gut flora (rifaximin), and those with hepatorenal syndrome were given albumin and terlipressin. Also, H2 receptors antagonists or proton pump inhibitors were administered for preventing upper gastrointestinal bleeding.

Usually, patients with ALD are cachectic in a hypercatabolic condition, which worsens the prognosis. Good nutrition is essential. In anorectic patients, enteral feeding can be administered with 2000 kcal/day with an albumin content of 1.5 g/kg even in those with hepatic encephalopathy events. Survival can be similar to the observed in the treatment with corticosteroids. B complex vitamins were also administered (before the administration of carbohydrates to prevent Korsakoff syndrome) and folic acid (to address possible shortcomings).

Patients with alcoholic hepatitis exhibit susceptibility to infections since their polymorphonuclear cells are numerous but functionally inferior. Patients should frequently be examined for the presence of bacterial infection (pneumonia, spontaneous bacterial peritonitis, urinary tract infection) with the appropriate investigations (blood cultures, urine, ascites fluid, chest X-ray).

In patients with severe liver disease and withdrawal syndrome, granted chlormethiazole (Hemineurin or Distaneurin), midazolam (Dormicum), or lorazepam (Tavor) should be used due to is short half-life time. When there are prevailing psychotic manifestations, administer neuroleptic drugs (haloperidol or "atypical" as olanzapine, etc.). The long-term administration of baclofen can help without clinically significant adverse effects [2-4].

The Position of the Liver Transplantation in the Treatment of ALD

After a long period of reluctance to join the liver transplant list, patients with ALD worldwide are beginning to see that transplantation offers an excellent survival advantage in appropriately selected patients similar to that observed for other liver transplant indications. The different visions are mainly based on the fact that the ALD is a self-inflicted disease in parallel with the increased likelihood of significant damage with alcohol use to organs other than the liver. Furthermore, in the medical community, there is a dominant lack of compliance of these patients to the instructions in the postoperative period and the recurrence of abuse that can lead to early graft failure [72,73].

In fact, initially, alcohol use was considered a contraindication for liver transplantation [74,75]. However, in patients who develop end-stage liver failure, transplantation can be attempted after a complete abstinence from alcohol use for at least six months [76]. During this time, some patients will die while others delist. Those who have not improved within three months of stopping alcohol use are not expected to improve later and can be estimated as potential transplantations [77]. Recurrent abuse after transplantation is frequent (10.8%) [78-80].

The first primary liver transplant experience in patients with alcoholic cirrhosis is detailed in Pittsburgh, wherein survival among 42 patients transplanted was similar to that of other forms of liver disease [81]. Currently, similar data has been published by other centers. Indeed, the relative survival of patient and graft, in another study that included 123 patients, was 84% and 81% for the first year, 72% and 66% for the fifth, and 63% and 59% for the seventh year after transplantation, respectively [82]. Without liver transplantation, five-years survival appears to be less than 23% [83].

Clinicians who treat patients with end-stage liver disease due to alcohol abuse contribute decisively to the success of transplantation when they promptly examine this possibility as a potential option and refer their patients to the appropriate transplant centers for evaluation. A period of six months of abstinence from alcohol is widely used to prevent recurrence while allowing recovery of the hepatic parenchyma by the toxicity of abuse. However, this time-limit cannot be used to distinguish the group of patients who will continue to abstain [3]. In a study including 40 patients with ALD admitted to assessing the likelihood of liver transplantation, it was found that 38% had a positive urine test for alcohol and 30% for illicit drugs [84].

However, a French study of 26 patients with alcoholic hepatitis with a high risk of life loss underwent liver transplantation after failure to respond to the conservative treatment. The patients were selected by the existence of a real socially supportive environment, no previous episodes of alcoholic liver disease, and no past history of severe psychiatric illness. These patients compared with 26 patients who were randomized as the control group. The cumulative percentage of six-month survival was significantly higher in the patients transplanted (77 compared to 23%). The two-year survival was also significantly higher (71 compared with 23%). Three of the patients who underwent transplantation were exposed again in the use of alcohol, one 720 days, one 740 days, and one 1140 days after liver transplantation [85].

In conclusion, liver transplantation represents an alternative for treating selected patients with an alcoholic liver disease despite the fact that both transplantation from cadaveric and much more from a living liver donor raise important social and ethical questions.

References

1. Schwartz JM, Reinus JF (2012) Prevalence and natural history of alcoholic liver disease. Clin Liver Dis 16: 659-666.
2. O'Shea RS, Dasarathy S, McCullough AJ (2010) Alcoholic liver disease. Am J Gastroenterol 105: 14-32.
3. O'Shea RS, Dasarathy S, McCullough AJ (2010) Practice Guideline Committee of the American Association for the Study of Liver D, Practice Parameters Committee of the American College of G. Alcoholic liver disease. Hepatology 51: 307-328.
4. European Association for the Study of Liver (2012) EASL Clinical practical guidelines: management of alcoholic liver disease. Journal of Hepatology 57: 399-420.
5. Roulot D, Costes JL, Buyck JF, Warzocha U, Gambier N, et al. (2011) Transient elastography as a screening tool for liver fibrosis and cirrhosis in a community-based population aged over 45 years. Gut 60: 977-984.
6. Corrao G, Ferrari P, Zambon A, Torchio P (1997) Are the recent trends in liver cirrhosis mortality affected by the changes in alcohol consumption? Analysis of latency period in European countries. J Stud Alcohol 58: 486-494.
7. WHO (2010) European Staus Report on Alcohol and Health.
8. Becker U, Deis A, Sorensen TI, Gronbaek M, Borch-Johnsen K, et al. (1996) Prediction of risk of liver disease by alcohol intake, sex, and age: a prospective population study. Hepatology 23: 1025-1029.
9. Burra P, Senzolo M, Adam R, Delvart V, Karam V, et al. (2010) Liver transplantation for alcoholic liver disease in Europe: a study from the ELTR (European Liver Transplant Registry). American journal of Transplantation: Official Journal of the American Society of

Transplantation and the American Society of Transplant Surgeons 10: 138-148.

10. Stinson FS, Grant BF, Dufour MC (2001) The critical dimension of ethnicity in liver cirrhosis mortality statistics. Alcoholism, Clinical and Experimental Research 25: 1181-1187.
11. Caetano R, Kaskutas LA (1995) Changes in drinking patterns among whites, blacks and Hispanics, 1984-1992. J Stud Alcohol 56: 558-565.
12. Bellentani S, Saccoccio G, Costa G, Tiribelli C, Manenti F, et al. (1997) Drinking habits as cofactors of risk for alcohol induced liver damage. The Dionysos Study Group. Gut 41: 845-850.
13. Pageaux GP, Bismuth M, Perney P, Costes V, Jaber S, et al. (2003) Alcohol relapse after liver transplantation for alcoholic liver disease: does it matter? J Hepatol 38: 629-634.
14. Rehm J, Taylor B, Mohapatra S, Irving H, Baliunas D, et al. (2010) Alcohol as a risk factor for liver cirrhosis: a systematic review and meta-analysis. Drug and Alcohol Review 29: 437-445.
15. Zakhari S, Li TK (2007) Determinants of alcohol use and abuse: Impact of quantity and frequency patterns on liver disease. Hepatology 46: 2032-2039.
16. Gao B, Bataller R (2011) Alcoholic liver disease: pathogenesis and new therapeutic targets. Gastroenterology 141: 1572-1585.
17. MacSween RN, Burt AD (1986) Histologic spectrum of alcoholic liver disease. Semin Liver Dis 6: 221-232.
18. Lefkowitch JH (2005) Morphology of alcoholic liver disease. Clin Liver Dis 9: 37-53.
19. Stickel F, Hampe J (2012) Genetic determinants of alcoholic liver disease. Gut 61: 150-159.
20. Fattovich G, Stroffolini T, Zagni I, Donato F (2004) Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology 127: S35-S50.
21. Tsukamoto H, Machida K, Dynnyk A, Mkrtchyan H (2009) "Second hit" models of alcoholic liver disease. Semin Liver Dis 29: 178-187
22. Wilfred de Alwis NM, Day CP (2007) Genetics of alcoholic liver disease and nonalcoholic fatty liver disease. Semin Liver Dis 27: 44-54.
23. Marcos M, Gómez-Munuera M, Pastor I, González-Sarmiento R, Laso FJ (2009) Tumor necrosis factor polymorphisms and alcoholic liver disease: a HuGE review and meta-analysis. Am J Epidemiol 170: 948-956.
24. Siu L, Foont J, Wands JR (2009) Hepatitis C virus and alcohol. Semin Liver Dis 29: 188-199.
25. Gleeson D, Evans S, Bradley M, Jones J, Peck RJ, et al. (2006) HFE genotypes in decompensated alcoholic liver disease: phenotypic expression and comparison with heavy drinking and with normal controls. Am J Gastroenterol 101: 304-310.
26. Orrego H, Israel Y, Blake JE, Medline A (1983) Assessment of prognostic factors in alcoholic liver disease: toward a global quantitative expression of severity. Hepatology 3: 896-905.
27. Baraona E, Leo MA, Borowsky SA, Lieber CS (1975) Alcoholic hepatomegaly: accumulation of protein in the liver. Science 190: 794-795.
28. Akriviadis E, Botla R, Briggs W, Han S, Reynolds T, et al. (2000) Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. Gastroenterology 119: 1637-1648.
29. Choi G, Runyon BA (2012) Alcoholic hepatitis: a clinician's guide. Clin Liver Dis 16: 371-385.
30. Bell H, Tallaksen CM, Try K, Haug E (1994) Carbohydrate-deficient transferrin and other markers of high alcohol consumption: a study of 502 patients admitted consecutively to a medical department. Alcoholism, Clinical and Experimental Research 18: 1103-1108.
31. Niemelä O (2007) Biomarkers in alcoholism. Clin Chim Acta 377: 39-49.
32. Moseley RH (1996) Evaluation of abnormal liver function tests. Med Clin North Am 80: 887-906.
33. Puukka K, Hietala J, Koivisto H, Anttila P, Bloigu R, et al. (2006) Additive effects of moderate drinking and obesity on serum gamma-glutamyl transferase activity. The American Journal of Clinical Nutrition 83: 1351-1354.
34. Poynard T, Zourabichvili O, Hilpert G, Naveau S, Poitrine A, et al. (1984) Prognostic value of total serum bilirubin/gamma-glutamyl transpeptidase ratio in cirrhotic patients. Hepatology 4: 324-327.
35. Sohail U, Satapathy SK (2012) Diagnosis and management of alcoholic hepatitis. Clin Liver Dis 16: 717-736.
36. Cohen JA, Kaplan MM (1979) The SGOT/SGPT ratio--an indicator of alcoholic liver disease. Dig Dis Sci 24: 835-838.
37. Sorbi D, Boynton J, Lindor KD (1999) The ratio of aspartate aminotransferase to alanine aminotransferase: potential value in differentiating nonalcoholic steatohepatitis from alcoholic liver disease. Am J Gastroenterol 94: 1018-1022.
38. Williams AL, Hoofnagle JH (1988) Ratio of serum aspartate to alanine aminotransferase in chronic hepatitis. Relationship to cirrhosis. Gastroenterology 95: 734-739.
39. Ludwig S, Kaplowitz N (1980) Effect of pyridoxine deficiency on serum and liver transaminases in experimental liver injury in the rat. Gastroenterology 79: 545-549.
40. Vech RL, Lumeng L, Li TK (1975) Vitamin B6 metabolism in chronic alcohol abuse The effect of ethanol oxidation on hepatic pyridoxal 5'-phosphate metabolism. The Journal of Clinical Investigation 55: 1026-1032.
41. Matloff DS, Selinger MJ, Kaplan MM (1980) Hepatic transaminase activity in alocholic liver disease. Gastroenterology 78: 1389-1392.
42. Bugianesi E, Manzini P, D'Antico S, Vanni E, Longo F, et al. (2004) Relative contribution of iron burden, HFE mutations, and insulin resistance to fibrosis in nonalcoholic fatty liver. Hepatology 39: 179-187.
43. Trombini P, Piperno A (2007) Ferritin, metabolic syndrome and NAFLD: elective attractions and dangerous liaisons. J Hepatol 46: 549-552.
44. Milman N, Graudal N (1984) Serum ferritin in acute viral hepatitis. Scand J Gastroenterol 19: 38-40.
45. Mutimer DJ, Burra P, Neuberger JM, Hubscher S, Buckels JA, et al. (1993) Managing severe alcoholic hepatitis complicated by renal failure. Q J Med 86: 649-656.
46. Han SH, Rice S, Cohen SM, Reynolds TB, Fong TL (2002) Duplex Doppler ultrasound of the hepatic artery in patients with acute alcoholic hepatitis. J Clin Gastroenterol 34: 573-577.
47. Mueller S, Millonig G, Sarovska L, Friedrich S, Reimann FM, et al. (2010) Increased liver stiffness in alcoholic liver disease: differentiating fibrosis from steatohepatitis. World Journal of Gastroenterology 16: 966-972.
48. Bardou-Jacquet E, Legros L, Soro D, Latournerie M, Guillygomarc'h A, et al. (2013) Effect of alcohol consumption on liver stiffness measured by transient elastography. World Journal of Gastroenterology 19: 516-522.
49. French SW, Nash J, Shitabata P, Kachi K, Hara C, et al. (1993) Pathology of alcoholic liver disease. VA Cooperative Study Group 119. Semin Liver Dis 13: 154-169.
50. Levitsky J, Mailliard ME (2004) Diagnosis and therapy of alcoholic liver disease. Semin Liver Dis 24: 233-247.
51. Van Ness MM, Diehl AM (1989) Is liver biopsy useful in the evaluation of patients with chronically elevated liver enzymes? Ann Intern Med 111: 473-478.
52. Vuppalanchi R, Chalasani N (2009) Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: Selected practical issues in their evaluation and management. Hepatology 49: 306-317.
53. Elefsiniotis IS, Skounakis M, Vezali E, Pantazis KD, Petrocheilou A, et al. (2006) Clinical significance of serum procalcitonin levels in patients with acute or chronic liver disease. European Journal of Gastroenterology and Hepatology 18: 525-530.
54. Alexander JF, Lischner MW, Galambos JT (1971) Natural history of alcoholic hepatitis. II. The long-term prognosis. Am J Gastroenterol 56: 515-525.
55. Tilg H, Kaser A (2005) Predicting mortality by the Glasgow alcoholic hepatitis score: the long awaited progress? Gut 54: 1057-1059.
56. Carithers RL, Herlong HF, Diehl AM, Shaw EW, Combes B, et al. (1989) Methylprednisolone therapy in patients with severe alcoholic hepatitis. A randomized multicenter trial. Annals of Internal Medicine 110: 685-690.

57. Sheth M, Riggs M, Patel T (2002) Utility of the Mayo End-Stage Liver Disease (MELD) score in assessing prognosis of patients with alcoholic hepatitis. BMC Gastroenterology 2: 2.
58. Maddrey WC, Boitnott JK, Bedine MS, Weber FL, Mezey E, et al. (1978) Corticosteroid therapy of alcoholic hepatitis. Gastroenterology 75: 193-199.
59. Forrest EH, Evans CD, Stewart S, Phillips M, Oo YH, et al. (2005) Analysis of factors predictive of mortality in alcoholic hepatitis and derivation and validation of the Glasgow alcoholic hepatitis score. Gut 54: 1174-1179.
60. Dunn W, Jamil LH, Brown LS, Wiesner RH, Kim WR, et al. (2005) MELD accurately predicts mortality in patients with alcoholic hepatitis. Hepatology 41: 353-358.
61. Louvet A, Naveau S, Abdelnour M, Ramond MJ, Diaz E, et al. (2007) The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. Hepatology 45: 1348-1354.
62. Soultati AS, Dourakis SP, Alexopoulou A, Deutsch M, Vasilieva L, et al. (2006) Predicting utility of a model for end stage liver disease in alcoholic liver disease. World J Gastroenterol 12: 4020-4025.
63. Christensen E, Gluud C (1999) Glucocorticosteroids are not effective in alcoholic hepatitis. Am J Gastroenterol 94: 3065-3066.
64. Imperiale TF, McCullough AJ (1990) Do corticosteroids reduce mortality from alcoholic hepatitis? A meta-analysis of the randomized trials. Ann Intern Med 113: 299-307.
65. Imperiale TF, O'Connor JB, McCullough AJ (1999) Corticosteroids are effective in patients with severe alcoholic hepatitis. Am J Gastroenterol 94: 3066-3068.
66. Rambaldi A, Saconato HH, Christensen E, Thorlund K, Wetterslev J, et al. (2008) Systematic review: glucocorticosteroids for alcoholic hepatitis--a Cochrane Hepato-Biliary Group systematic review with meta-analyses and trial sequential analyses of randomized clinical trials. Alimentary Pharmacology and Therapeutics 27: 1167-1178.
67. Mathurin P, Abdelnour M, Ramond MJ, Carbonell N, Fartoux L, et al. (2003) Early change in bilirubin levels is an important prognostic factor in severe alcoholic hepatitis treated with prednisolone. Hepatology 38: 1363-1369.
68. Morris JM, Forrest EH (2005) Bilirubin response to corticosteroids in severe alcoholic hepatitis. Eur J Gastroenterol Hepatol 17: 759-762.
69. Mathurin P, O'Grady J, Carithers RL, Phillips M, Louvet A, et al. (2011) Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis: meta-analysis of individual patient data. Gut 60: 255-260.
70. Louvet A, Wartel F, Castel H, Dharancy S, Hollebecque A, et al. (2009) Infection in patients with severe alcoholic hepatitis treated with steroids: early response to therapy is the key factor. Gastroenterology 137: 541-548.
71. Louvet A, Diaz E, Dharancy S, Coevoet H, Texier F, et al. (2008) Early switch to pentoxifylline in patients with severe alcoholic hepatitis is inefficient in non-responders to corticosteroids. J Hepatol 48: 465-470.
72. Lucey MR (2011) Liver transplantation in patients with alcoholic liver disease. Liver transplantation: official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 17: 751-759.
73. Moss AH, Siegler M (1991) Should alcoholics compete equally for liver transplantation? The Journal of the American Medical Association 265: 1295-1298.
74. Lucey MR (2007) Liver transplantation for alcoholic liver disease: past, present, and future. Liver transplantation: official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 13: 190-192.
75. Lucey MR, Brown KA, Everson GT, Fung JJ, Gish R, et al. (1997) Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. Liver transplantation and surgery: official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 3: 628-637.
76. Everhart JE, Beresford TP (1997) Liver transplantation for alcoholic liver disease: a survey of transplantation programs in the United States. Liver transplantation and surgery: official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 3: 220-226.
77. Veldt BJ, Lainé F, Guillygomarc'h A, Lauvin L, Boudjema K, et al. (2002) Indication of liver transplantation in severe alcoholic liver cirrhosis: quantitative evaluation and optimal timing. J Hepatol 36: 93-98.
78. De Gottardi A, Spahr L, Gelez P, Morard I, Mentha G, et al. (2007) A simple score for predicting alcohol relapse after liver transplantation: results from 387 patients over 15 years. Arch Intern Med 167: 1183-1188.
79. Dew MA, DiMartini AF, Steel J, De Vito Dabbs A, Myaskovsky L, et al. (2008) Meta-analysis of risk for relapse to substance use after transplantation of the liver or other solid organs. Liver Transpl 14: 159-172.
80. Kelly M, Chick J, Gribble R, Gleeson M, Holton M, et al. (2006) Predictors of relapse to harmful alcohol after orthotopic liver transplantation. Alcohol and Alcoholism 41: 278-283.
81. Starzl TE, Van Thiel D, Tzakis AG, Iwatsuki S, Todo S, et al. (1988) Orthotopic liver transplantation for alcoholic cirrhosis. The Journal of the American Medical Association 260: 2542-2544.
82. Bellamy CO, DiMartini AM, Ruppert K, Jain A, Dodson F, et al. (2001) Liver transplantation for alcoholic cirrhosis: long term follow-up and impact of disease recurrence. Transplantation 72: 619-626.
83. Cowling T, Jennings LW, Goldstein RM, Sanchez EQ, Chinnakotla S, et al. (2004) Societal reintegration after liver transplantation: findings in alcohol-related and non-alcohol-related transplant recipients. Ann Surg 239: 93-98.
84. Webzell I, Ball D, Bell J, Sherwood RA, Marsh A, et al. (2011) Substance use by liver transplant candidates: an anonymous urinalysis study. Liver transplantation: official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. Liver Transpl 17: 1200-1204.
85. Mathurin P, Moreno C, Samuel D, Dumortier J, Salleron J, et al. (2011) Early liver transplantation for severe alcoholic hepatitis. N Engl J Med 365: 1790-1800.