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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (10): Alcoholic liver disease

Focus on alcoholic liver disease: From nosography to treatment

Letiția Adela Maria Streba, Cristin Constantin Vere, Costin Teodor Streba, Marius Eugen Ciurea

Letiția Adela Maria Streba, Cristin Constantin Vere, Internal Medicine-Medical Semiology, University of Medicine and Pharmacy of Craiova, 200639 Craiova, Romania
Cristin Constantin Vere, Costin Teodor Streba, Research Center of Gastroenterology and Hepatology of Craiova, University of Medicine and Pharmacy of Craiova, 200639 Craiova, Romania
Marius Eugen Ciurea, University of Medicine and Pharmacy of Craiova, 200639 Craiova, Romania
Author contributions: Streba LAM and Vere CC contributed equally to this manuscript and share first authorship; Streba LAM, Vere CC, Streba CT and Ciurea ME wrote this paper; Streba CT and Vere CC critically revised the text; Ciurea ME supervised the literature research and critically revised the text.
Correspondence to: Costin Teodor Streba, MD, PhD, MSc, Research Center of Gastroenterology and Hepatology of Craiova, University of Medicine and Pharmacy of Craiova, 1 Mai 66, 200639 Craiova, Romania. costinstreba@gmail.com
Telephone: +40-722-389906 Fax: +40-351-401376
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Abstract

Abusive alcohol intake currently ranks as a major cause of liver disease, and is associated with significant mortality worldwide. Alcoholic liver disease (ALD) generically defines liver abnormalities ranging from liver steatosis to the end-stages of disease such as liver cirrhosis. Information regarding the precise incidence and prevalence of ALD is still limited by a lack of large population-based studies and by the absence of large systematic reviews of all epidemiological data available. However, existing collected data show an overall increase in the number of alcohol abusers and alcohol-related liver disease. The burden exerted on medical systems worldwide is significant, with hospitalization and management costs rising constantly over the years. A great number of all cirrhosis-related deaths in Europe and a significant percentage worldwide are associated with alcohol consumption. The main possible risk factors for ALD are the amount and duration of alcohol abuse, patterns of drinking and the type of alcoholic beverage consumed. However, ALD does not progress to cirrhosis in all patients, therefore a series of additional factors are implicated. Even though insufficiently studied, genetic factors are generally regarded as highly important, and the presence of comorbidities and dietary habits seem to play a role in disease onset and progression. This lack of clear pathophysiological data further translates in the absence of definite treatment for ALD and shall prove challenging in the coming years. In this article, we aimed to briefly review epidemiologic data on the burden of ALD, risk factors, clinical and nosographic as well as therapeutic aspects of this disease. Without attempting to be exhaustive, this short topic highlight emphasizes each point and may serve as a general guidance tool in the complicated literature related to ALD.

Key words: Alcoholic liver disease; Epidemiology; Risk factors; Diagnosis; Treatment

Core tip: Alcoholic liver disease (ALD) generically defines liver abnormalities ranging from liver steatosis to the end-stages of disease such as liver cirrhosis. The burden exerted on medical systems worldwide is significant, with hospitalization and management costs rising constantly over the years. In this article, we aimed to briefly review epidemiologic data on the burden of ALD, risk factors, clinical and nosographic as well as therapeutic aspects of this disease. Without attempting to be exhaustive, this short topic highlight emphasizes each point and may serve as a general guidance tool in the complicated literature related to ALD. For each point, the areas of uncertainty were emphasized.

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INTRODUCTION

Excessive and chronic alcohol intake is a major avoidable cause of liver disease, and is associated with high mortality worldwide. The liver is one of the most important targets of alcohol toxicity, as it is the principal site of alcohol metabolism[1-3]. Alcoholic liver disease (ALD) encompasses a varied spectrum of liver abnormalities that range from simple steatosis to alcoholic hepatitis, progressive fibrosis and cirrhosis[4]. ALD is one of the oldest liver diseases known, and its health burden and economic impact are internationally recognized, ALD research investments are much lower than those for other chronic liver diseases[5]. The lack of research on ALD is confirmed by the ETOh score (the ratio of the estimated death rate of different liver diseases to the number of trials focused on these diseases). The disparity is evident, given that a high ETOh score reveals few studies on a relatively morbid condition. For example, the ETOh score of ALD is 358 (only 34 registered clinical trials and 12185 deaths per 100000 population), compared with 1.4 for hepatitis B (850 registered clinical trials and 1100 deaths per 100000 population) or with 15.2 for primary biliary cirrhosis (32 registered clinical trials and 485 deaths per 100000 population)[6]. As a result, the pathogenesis of ALD is still not entirely understood, human gene expression profiles of disease susceptibility have not been sufficiently investigated and there are no accurate detection methods for individual susceptibility in ALD[7,8]. Additionally, few studies on quantity, duration, frequency and pattern of alcohol consumption in ALD patients have been conducted[9]. These aspects explain why no new drug has been widely introduced in the last few decades[8].

EPIDEMIOLOGY AND GLOBAL BURDEN OF ALD

Precise incidence and prevalence measurements for ALD have been limited by a lack of large population-based studies and by the absence of large systematic reviews of all epidemiological data available[10,11]. Globally, important variations in ALD incidence and prevalence in different regions of the world have been observed. In the United States, alcoholic hepatitis occurs in 35%-40% of alcohol abusers and approximately 20%-25% of all cases of liver cirrhosis are alcohol-related[12]. Taking into account the prevalence of alcohol abusers in the United States, the estimated number of patients with alcoholic hepatitis may be approximately 5 million[13]. In European countries the burden of ALD is significant compared to other etiologies of liver disease[14]. According to a nationwide population based cohort study, the annual incidence rate of alcoholic hepatitis in the Danish population has increased from 37 to 46 per 100000 for men and from 24 to 34 per 100000 for women from 1999 to 2008[15]. A total of 16745 patients were diagnosed with alcoholic cirrhosis in Denmark between 1988 and 2005 and an increasing trend in alcoholic cirrhosis prevalence from 1988 to 2005 was observed. Between 2001 and 2005, the alcoholic cirrhosis incidence rates were higher for men (26.5 per 100000 per year for men and 11.8 per 100000 per year for women) in the Danish population[16]. According to a nationwide survey performed in Japan, alcoholic cirrhosis represents 13.6% of all cases of cirrhosis[17]. ALD involves a huge burden in terms of mortality, disability, functional decline, health-related quality of life, social and healthcare costs[3,14]. In Germany, ALD was the most common cause of death of all liver cirrhosis deaths (8.9 deaths per 100000 population) in 2009[18]. In the United Kingdom there was a 36% increase in ALD deaths between 2001 and 2008[19]. In the United States, the age-standardized death rate for ALD was 4.5 deaths per 100000 in 2009[20]. Globally, alcohol-attributable cirrhosis deaths accounted for 47.9% of all liver cirrhosis deaths and 14544000 disability adjusted life years (DALYs), representing 46.9% of all liver cirrhosis DALYs in 2010. The highest proportion of alcoholic cirrhosis deaths was recorded in Central Europe (72.3% of all liver cirrhosis deaths). Worldwide, the alcohol-attributable cirrhosis death rate was 7.2 deaths per 100000 population in 2010. Central Asia recorded the highest alcoholic cirrhosis death rate (17.5 deaths per 100000 population), followed by Central Latin America (15.8 deaths per 100000 population)[21]. On the other hand, ALD contributes significantly to rising health care costs. In the United Kingdom, alcoholic cirrhosis was the main indication for liver transplantation between 1996 and 2000 (468 liver transplants at an estimated total cost of £23.5 million)[22]. The burden of alcoholic liver cirrhosis on the Danish healthcare system has increased from 1988 to 2005, following the increased prevalence of alcoholic cirrhosis and the subsequent growing number of hospitalizations[16]. However, there are limitations in estimating the epidemiology and the entire magnitude of the ALD burden[11].

FROM STEATOSIS TO CIRRHOSIS: SPECTRUM AND RISK FACTORS

Schematically, the ALD spectrum includes fatty liver (simple steatosis), alcoholic hepatitis, progressive fibrosis and alcoholic cirrhosis. This classification does not always reflect a chronological progression, especially as these lesions are often associated[4]. On the other hand, chronic alcohol consumption is linked with an increased risk of hepatocellular carcinoma (HCC), especially in patients with alcoholic cirrhosis[5,23,24]. However, a recent epidemiologic population-based study from Denmark showed a low incidence and mortality for HCC in pure alcoholic

cirrhosis[25].

Macrovesicular steatosis, the most common morphological feature of alcoholic steatosis, is generally reversible after alcohol abstinence[26]. However, it is estimated that the progression from steatosis to fibrosis and cirrhosis occurs in 5%-15% of patients despite alcohol abstinence[4]. While alcoholic steatosis develops in more than 90% of heavy drinkers, only 10%-35% of them will develop alcoholic hepatitis, which may be mild and asymptomatic or severe with profound liver damage and worse short-term prognosis[27,28]. Histological features of alcoholic hepatitis may vary depending on the disease severity (*e.g.*, ballooning degeneration of hepatocytes, megamitochondria, neutrophil infiltration, Mallory hyaline inclusions, intrasinusoidal fibrosis, as well as areas of microvesicular steatosis and acute sclerosing hyaline necrosis). Perivenular fibrosis and periportal fibrosis, characteristic lesions of alcoholic fibrosis, may coexist with alcoholic hepatitis findings[13,29]. The end-stage of alcoholic hepatic fibrosis is micro-nodular cirrhosis[5].

The main possible environmental risk factors that may contribute to ALD development and progression include the amount and duration of alcohol abuse, the type of alcoholic drink consumed and the patterns of drinking[4,5,9]. Most retrospective studies have shown that a daily intake of pure alcohol, exceeding 40-80 g/d for males and 20-40 g/d for females during 10-12 years, will lead to ALD[30,31]. However, significant liver damage was observed in individuals with a lower daily alcohol consumption. Therefore, the threshold daily alcohol intake to produce liver damage is difficult to establish, according to current knowledge[5]. Results from a meta-analysis of daily consumption levels in relation to cirrhosis, suggest a higher risk of cirrhosis in patients who consumed 25 g pure alcohol per day than in non-drinkers[32]. Yet, only 10%-20% of drinkers who consume more than 80 g alcohol per day and 40% of patients with persistent alcohol abuse after a positive diagnosis of ALD develop alcoholic cirrhosis[33,34].

The type of alcoholic drink consumed may influence the risk for ALD development[5]. A lower risk for alcoholic cirrhosis in wine drinkers than beer or spirits drinkers was demonstrated by a Danish cohort study that included 30630 individuals (14335 women and 16295 men)[35]. On the other hand, the results of a French case-control study (42 cirrhotic and 60 non-cirrhotic patients) show that for heavy drinkers, the risk of developing cirrhosis is equal, independent of the type of alcoholic drink consumed[36]. Unfortunately, very few studies have researched the association between alcoholic beverage types and the risk for ALD. As a result, the relationship between ALD and the type of alcoholic drink consumed is still unclear[4,5].

Pattern of drinking is another possible risk factor for ALD[4]. Results of a prospective survey conducted in the United Kingdom show that daily or near-daily heavy drinking, as opposed to weekly binge drinking, increases the risk for ALD, as well as liver-related mortality[37]. Other studies have shown that binge drinking increases the risk for alcoholic hepatitis[38].

Gender-dependent differences on the hepatotoxic effects of alcohol have been observed. Compared to men, women develop more severe liver damage at lower levels of consumption over a shorter period of time[39,40]. This phenomenon is poorly understood, but several hypotheses have been postulated[41]. Some studies have suggested that lower gastric alcohol dehydrogenase (ADH) activity in women is responsible for a slower first pass of alcohol metabolism, resulting in increased bioavailability of alcohol[42,43]. However, no differences in gastric ADH activity between men and women were found in other studies[44-46]. Factors such as a higher body fat content and a lower proportion of total body water in which to distribute alcohol, may also contribute to an increased risk of ALD in women[47]. The involvement of sex hormones may contribute to the vulnerability of females to alcohol consumption. Although the exact role of female hormones in ALD development is not yet fully understood, evidence from both human studies and animal models have indicated their involvement in increasing gut permeability and portal endotoxin levels[48].

Other risk factors for the development and progression of ALD are obesity and insulin resistance[49,50] malnutrition[51], viral hepatitis[52], ethnicity[53], iron overload, and cigarette smoking[4,5]. Genetic factors such as a change in a region of the DNA encoding human CD14 protein has been linked to the development of fibrosis[54]. Polymorphisms of genes involved in alcohol-metabolizing enzymes, in oxidative stress and in those which regulate the release of proinflammatory and anti-inflammatory cytokines were reported in ALD[55,56]. An important association between genotype PNPLA3 rs738409 (G/G) and severe liver cirrhosis was recently found in alcoholic Caucasians[57].

DIAGNOSIS OF ALD

The diagnosis of ALD is established by a history of habitual alcohol intake, physical signs and laboratory abnormalities suggestive of liver disease, including elevated serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels[4,58]. Suggestive signs of chronic alcoholism (Dupuytren contracture of the palmar fascia, bilateral parotid gland hypertrophy, peripheral neuropathy, malnutrition, spider angiomata) are often seen in ALD. An increase in serum gamma glutamyl-transferase (GGT) level may indicate heavy alcohol use and liver injury[4,5]. Carbohydrate-deficient transferrin (CDT) seems a sensitive biomarker for previous alcohol abuse, with a specificity and a sensitivity greater than GGT[59,60]. However, false-positive and false-negative results have been reported[61]. Using both GGT and CDT tends to produce a higher sensitivity[62]. Mean corpuscular volume, has also been considered a biomarker of alcohol intake[4]. A severe stage of ALD is suspected in the presence of portal hypertension complications and laboratory abnormalities such as hypoalbuminemia, thrombocytopenia, prolonged

Table 1 Prognostic scoring systems in alcoholic hepatitis

Scoring system	Year	Formula			
Maddrey DF (initial)[65]	1978	4.63 × PT (s) + serum bilirubin (mg/dL)			
Maddrey DF (modified)[66]	1989	4.6 (patient's PT - control PT) + serum bilirubin (mg/dL)			
MELD (initial)[69]	2000	10 × [0.957 × $\log_e$(creatinine mg/dL) + 0.378 × $\log_e$(bilirubin mg/dL) +1.120 x $\log_e$(INR) + 0.643 × cause of cirrhosis[1]]			
MELD (modified)[70]	2001	9.6 × $\log_e$(creatinine mg/dL) + 3.8 × $\log_e$(bilirubin mg/dL) +11.2 × $\log_e$(INR) + 6.4			
GAHS[68]	2005	Score given[2]	1	2	3
		Age (yr)	< 50	⩾ 50	
		WCC	15 × 10^9/L	⩾ 15 × 10^9/L	
		Urea (mmol/L)	< 5	⩾ 5	
		INR	< 1.5	1.5-2	> 2
		Bilirubin (μmol/L)	125	125-250	> 250
Lille[72]	2007	3.19 - 0.101 × (age in years) + 0.147 × (albumin day 0 in g/L) + 0.0165 × (bilirubin day 1 in μmol/L - bilirubin day 7 in μmol/L) - (0.206 × renal insufficiency[3]) - 0.0065 × (bilirubin day 0 in μmol/L) - 0.0096 × PT (s)			
ABIC[73]	2008	(age × 0.1) + (serum bilirubin × 0.08) + (serum creatinine × 0.3) + (INR × 0.8)			

[1]Cause of cirrhosis: 0 = alcohol or cholestasis; 1 = other etiology; [2]GAHS: a score is given for each variable, producing a combined score of between 5 and 12; [3]Renal insufficiency = 1 if creatinine ⩾ 115 μmol/L; Renal insufficiency = 0 if creatinine < 115 μmol/L. DF: Discriminant Function; MELD: Model for End-Stage Liver Disease; GAHS: Glasgow alcoholic hepatitis score; ABIC: Age, bilirubin, INR and creatinine; PT: Prothrombin time; WCC: White cell count; INR: International normalized ratio.

prothrombin time and elevated bilirubin level[5,26].

Alcoholic steatosis

Patients with alcoholic steatosis and moderate forms of ALD are often asymptomatic[5,58]. Hepatomegaly is present in 70% of patients with alcoholic steatosis[63] and two-thirds of patients have normal laboratory tests[26].

Alcoholic hepatitis

The diagnosis of alcoholic hepatitis is based on a medical history of significant alcohol use, rapid and recent onset of jaundice, physical signs of liver damage and abnormal liver function tests including an elevated level of AST (below 300 IU/mL), a ratio of AST/ALT greater than 2, elevated total serum bilirubin, neutrophilia and thrombocytopenia[29,64]. Severe cases are characterized by ascites, encephalopathy, gastrointestinal bleeding, alterations of kidney function, low serum albumin levels, prolonged prothrombin time and elevated international normalized ratio (INR)[4,5,26]. The risk-benefit ratio of liver biopsy should be considered in patients with alcoholic hepatitis. Although the precise indications of liver biopsy are not well established in routine practice, this procedure may be indicated in severe alcoholic hepatitis that requires specific therapies and if comorbidities are suspected[4,5].

Prognostic scoring systems in alcoholic hepatitis

Over time, several individual clinical and laboratory features have been tested as measures of disease prognosis and various prognostic models have been used to assess the severity of alcoholic hepatitis and to help guide treatment[4,29].

The Maddrey discriminant function (DF) was the first disease-specific score for alcoholic hepatitis, originally developed by Maddrey *et al*[65] in 1978 and then modified (mDF) in 1989[66]. A DF value greater than or equal to 32 indicates severe disease[66] and is the threshold for initiating corticosteroid treatment[29]. Although mDF was validated and used for a long time, it has some drawbacks, including a low specificity and an inherent inaccuracy in its values due to the use of the prothrombin time (PT), a variable with significant measurement variations between laboratories[67,68]. Novel prognostic models (Table 1) such as MELD (Model for End-Stage Liver Disease)[69,70], modified MELD including serum sodium (MELD-Na)[71], the GAHS (Glasgow Alcoholic Hepatitis Score)[68], the Lille model[72] and the ABIC score[73] (age, serum bilirubin, INR, and serum creatinine) are now available in the setting of alcoholic hepatitis. Usually, a MELD score > 18 indicates a poor prognosis[4]. The GAHS score ranges from 5 to 12 and patients with a GAHS greater than or equal to 9 have a poor prognosis and require corticosteroid treatment[74]. The Lille score ranges from 0 to 1: a Lille score ⩾ 0.45 indicates poor responders, and a Lille score < 0.45 indicates responders to corticosteroids[72]. A recent study that re-evaluated the Lille score as a predictor of response to corticosteroids, identified three patterns of response to corticosteroid therapy: complete responders (Lille score ⩽ 0.16), partial responders (Lille score 0.16-0.56) and null responders (Lille score ⩾ 0.56)[75].

A recent analysis of the MELD score, MELD-Na score, GAHS, Lille model and the ABIC score in a Danish study, showed no major differences between them in predicting the 28-, 84- and 180-d mortality in patients with alcoholic hepatitis[76].

Alcoholic cirrhosis

Alcoholic cirrhosis, the end stage of ALD, is characterized by extensive liver fibrosis and regenerative nodules[77]. Early stage alcoholic cirrhosis may be asymptomatic[78]. The occurrence of decompensation is characterized by the presence of complications of portal hypertension including ascites, variceal bleeding, and hepatic encephalopathy, as well as laboratory abnormalities such as hypoalbuminemia, thrombocytopenia, prolonged prothrombin

time and elevated bilirubin level[26,78]. Continued alcohol consumption can lead to superimposed alcoholic hepatitis, while prolonged abstinence improves disease evolution[5].

TREATMENT OF ALCOHOLIC LIVER DISEASE

General measures

General measures in ALD include abstinence from alcohol, lifestyle modifications and the correction of nutritional deficiencies[4,5,26].

Alcohol abstinence is one of the most important measures in managing ALD, since it leads to a decrease in the severity of liver lesions and improves survival even in advanced stages of ALD[4,26,79]. Behavioral and psychosocial interventions such as cognitive-behavioral therapy, psychodynamic approaches, therapeutic communities or vocational rehabilitation may be useful[80]. Most of the proposed treatments for promoting alcohol abstinence in ALD patients were tested within small trials and no large multicenter studies have been conducted.

In alcoholic cirrhosis, cessation of alcohol intake remains the most important measure to prevent decompensation and no other management strategies exist, as is the case with other causes of cirrhosis[8].

Nutritional status should be balanced in the case of malnutrition. A daily protein intake of 1.5 g/kg and 35-40 kcal/kg of body weight per day are recommended in ALD patients[33]. Supplementation with folate, pyridoxine, vitamin A and thiamine is required if these deficits are observed[5,26]. The usage of some antioxidants such as vitamin E[81] or silymarin[82] has not been proved to be effective.

Alcoholic hepatitis

Despite the fact that corticosteroids have been the most extensively studied therapy for alcoholic hepatitis, their role remains controversial. Multiple differences in trial design with a high risk of bias may explain the variability of meta-analyses results. The most recent Cochrane meta-analysis which included 15 trials reported that corticosteroids significantly reduced mortality in the subgroup of trials that enrolled patients with a Maddrey's DF $\geqslant$ 32 or hepatic encephalopathy[83]. The main contraindications to using corticosteroids in severe alcoholic hepatitis (DF $\geqslant$ 32) are sepsis, hepatorenal syndrome, chronic hepatitis B, gastrointestinal bleeding and other clear contraindications to steroids[4,29].

Pentoxifylline, a phosphodiesterase with anti-TNF properties, antifibrotic and antioxidant effects, can be used to treat patients with severe alcoholic hepatitis when corticosteroid therapy is contraindicated[4,5,29]. The survival benefit of pentoxifylline *vs* corticosteroids appears to be linked to the lower occurrence of gastrointestinal bleeding[84], and to a marked reduction in the incidence of the hepatorenal syndrome[85].

Two anti-TNF-α agents have been studied as therapy for alcoholic hepatitis (infliximab and etanercept), but clinical trials showed that these drugs are associated with severe infections and deaths[5,8].

N-acetylcysteine, an antioxidant substance, used in combination with corticosteroids decreases the rate of hepatorenal syndrome and infections[5].

S-adenosylmethionine (SAMe) is a major methylating agent that influences oxidative stress, mitochondrial function and hepatocellular apoptosis. Although SAMe may offer clinical benefits in ALD, very few large and high-quality clinical trials have been performed[86].

Probiotics influence the gut-liver axis and have been shown to be efficacious in numerous studies[8,87].

Liver transplantation is currently the only definitive treatment for hepatic failure associated with ALD. Previous expert opinions considering alcoholic hepatitis as a contraindication for liver transplantation have recently been reconsidered by a case controlled study which showed a clear improvement of survival in patients who underwent early liver transplantation[5].

New targets for ALD therapy includes CXC chemokines (GROα, IL-8)[88], Interleukin-22 and the complement system[8].

CONCLUSION

The relationship between alcohol consumption and liver disease needs to be researched further. Study design and size should be taken further in order to strengthen the quality and quantity of information in this field of research.

Data collection should be improved and coordinated at an international level, possibly through multicenter research studies aimed at identifying the relationship between liver disease and alcohol intake. All scientific data should be put to use in information campaigns aimed at vulnerable population groups. Further studies should identify whether genetic susceptibilities increase the chance of developing alcoholic hepatitis and cirrhosis.

Novel therapies are already underway; the basis of this research exists, however, it requires further development, possibly supported by new relevant clinical and basic scientific data.

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