Digestive and Liver Disease xxx (2020) xxx–xxx

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Guidelines

Alcohol associated liver disease 2020: A clinical practice guideline by the Italian Association for the Study of the Liver (AISF)

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ARTICLE INFO

Article history:
Received 29 May 2019
Accepted 17 December 2019
Available online xxx

Keywords:
Alcohol abstinence
Alcohol associated liver disease
Alcoholic hepatitis
Alcohol use disorder
Binge drinking
Liver damage
Liver transplantation
Psychosocial interventions
Treatment

ABSTRACT

Alcohol use disorder which includes alcohol abuse and dependence represents one of the leading risk factors for premature mortality in Europe and it is responsible of over 200 conditions, including neuropsychiatric disorders, chronic diseases, cancers and accidents leading to permanent disability. Alcohol use disorder represents the most common cause of liver damage in the Western world, with a wide spectrum of diseases ranging from steatosis, steatohepatitis, fibrosis, cirrhosis and cancer. The present clinical practice guidelines by the Italian Association for the Study of the Liver (AISF) are focused on the current knowledge about epidemiology, pathophysiology, clinical features, diagnosis and treatment of alcohol associated liver disease, aiming to provide practical recommendations on the management of this complex pathological condition.

The evidence and recommendations in these guidelines have been graded according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system (Table 1). The quality of the evidence in these clinical practical guidelines (CPGs) has been classified into one of three levels: high (A), moderate (B) or low (C). The GRADE system specify two grades of recommendation: strong (1) or weak (2) (Table 1). The CPGs thus consider the quality of evidence: the higher the quality of evidence, the more likely a strong recommendation is warranted; the greater the variability in values and preferences, or the greater the uncertainty, the more likely a weaker recommendation is warranted.

1. Epidemiology of alcohol consumption in Italy

Question 1 How frequent is alcohol intake end/or alcohol use disorder (AUD)?

P (Population/patient): Italian general population
I (Intervention/Indicator): alcohol intake
C (Comparator/Control): non-drinkers
O (Outcome): Prevalence of alcohol intake

Question 2 Is there a gender difference in alcohol intake?

P (Population/patient): drinkers (Italian)
I (Intervention/Indicator): alcohol intake
C (Comparator/Control): male/female
O (Outcome): gender difference in alcohol intake

Alcohol use, along with other risk-taking behaviors, continues to be a major cause of health concern in western countries. The burden of alcohol use on public health accounts for 5.1% of the global

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https://doi.org/10.1016/j.dld.2019.12.008
1590-8658/

Table 1
Grading of evidence and recommendations.

Grading of evidence	Notes	Symbol
High quality	Further research is very unlikely to change our confidence in the estimate of effect	A
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	B
Low or very low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain	C

Grading of recommendation	Notes	Symbol
Strong recommendation warranted	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost	1
Weaker recommendation	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted Recommendation is made with less certainty; higher cost or resource consumption	2

Adapted from Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. Br Med J 2008;336:1049–1051.

burden of disease. Alcohol associated liver disease (AALD) is one of the 30 most frequent causes of death in the world and liver-related death rates correlate with alcohol consumption [1].

Alcohol use disorder (AUD) is a chronic, relapsing disease affecting about 10% of the general population in western countries. Despite the high global burden of mortality due to AALD (both in terms of number of deaths and of years of life lost), there is the problem of the possible underestimation of the true burden of disease. In fact much of the information about alcohol-related mortality relies on the coding of death certificates and patients tend to under-report alcohol addiction with a consequent under-reporting of alcohol-related disease.

The International Classification of Diseases 11th revision (ICD-11) issued in May 2019 reports over 200 conditions for which alcohol consumption is an evitable risk factor, including neuropsychiatric disorders, chronic diseases, tumours and accidents leading to permanent disability [2–5].

Europe has the negative record of the highest levels of alcohol use in the world. Alcohol consumption is the third most common risk factor for morbidity in European countries, after cigarette smoking and hypertension [6,7].

Moreover, alcohol has been reported to be one of the leading risk factors for premature mortality in Europe. In 2016, alcohol consumption accounted for 10.1% of all deaths in Europe. Drinking patterns show large variations across Europe. Typically, Mediterranean countries are characterized by more frequent but moderate drinking, while less regular but heavier drinking is more frequent in northern European countries [8].

Drinking patterns are also influenced by different types of alcoholic drinks: beer and spirits are more likely associated with binge drinking, while wine is less likely to be consumed excessively [9,10].

There has been a trend towards a decrease of alcohol consumption in the last decades in Europe, but alcohol-related disease remains a major health threat.

Italy, which was historically one of the countries with a medium to high average alcohol consumption, managed to decrease its rates and in 2010 was the European country with the lowest reported average alcohol consumption (7 L/person). However, in the following years, average consumption started to rise again and in 2014 was 7.6 L/person [11].

In the 2014 World Health Organization (WHO) report on alcohol, total per capita annual alcohol consumption was reported to be 7–8 L in Italy, compared to 10 L/adult in the United States (US), 12–13 L in France, 11–12 L in the United Kingdom (UK), 11–13 L in Eastern Europe, while only 0-2 L in North Africa/Middle East [6,7].

The 2014 WHO survey to monitor health behaviors, health outcomes and social environments of adolescents reports one of the highest rates of weekly alcohol drinking in Italy for both adolescent males (31%) and females (17%) among European countries [12].

1.1. Gender difference in alcohol consumption in Italy

Overall Italian people who reported no alcohol consumption in the year 2016 were 21.7% of men and 46.2% of women, for a total of 18.500.000 people. In the same year Italian people over the age of 11 year who reported at least one alcoholic beverage were 64.7%, corresponding to over 35 million people, with a highest prevalence for men (77.3%) rather than women (52.9%).

The prevalence of wine consumers who are males is higher than females for all age classes [13].

Over 26 millions of people aged 11 or older in Italy reported beer consumption in the year 2016, with significantly higher rates for males rather than females (62.5% vs 34,0% respectively). Beer consumption has been on the rise in recent years (+1.2% for males and 1.6% for females in comparison with 2015), in particular in the age class 18–64 for women and over 64 (+1.6%) for both genders (+4%).

In the same report spirits and liquors were consumed by over 13 million 500 thousand people aged over 11, corresponding to 37.3% of men and 14.5% of women, with no significant variations compared to previous years. Prevalence was stable for adolescents, while showed a significant increase for people aged over 18 compared to 2007.

In 2016 14.8% of males and 6.2% of women aged over 11, for a total of 5.600.000 million people, reported unhealthy drinking, defined as more than 7 drinks per week for women and more than 14 drinks per week for men [14]. The highest rates of unhealthy drinking were found in adolescents aged 16–17 years (M = 49.3%; F = 40.0%) and in over 65, and the lowest rates in the 18–24 age group. The prevalence of unhealthy drinkers had decreased of 5.7% in 2016 compared to 2007, more consistently among men, but from 2012 on rates have been stable for both genders.

Over the last 4 years there has been a constant increase in the rates of binge drinkers for both genders (+0.6% compared to 2015) [11]. Currently in Italy there are an estimated 8.600.000 individuals with an unhealthy drinking pattern (M = 6.100.000 [23.2%], F = 2.500.000 [9.1%]) [11].

There is a regional variability in unhealthy drinking in Italy, with a north to south gradient [15]. In 2014 the number of deaths due to alcohol-related disease in people aged 15 or older in Italy has been 1174, of which 965 (82.2%) males and 209 (17.8%) females. This

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corresponds to about 38 deaths/million people among men and 1 death/million people among women with a standardized national average rate of 2.2/100.000. Alcohol-related mortality shows a regional variability, with the highest rates mostly in Northern regions such as Trentino Alto Adige (5.49/100.000) Friuli Venezia Giulia (3.79/100.000) and Piemonte (2.71/100.000), but also Calabria (3.01/100.000) and Sardinia (3.26/100.000). The regions with the lowest rates of alcohol-related deaths are Lazio (1.75/100.000) and Tuscany (1.32/100.000) [11].

The two most frequent alcohol-related pathologies, both for men and women, are AALD and alcohol induced psychosis, which, on the whole, causes 94.3% of alcohol-related death among men and 94.8% among women. In 2014 the standardized mortality rate for directly alcohol-related disease in people over the age of 15 was 3.89/100.000 people for men and 0.73/100.000 for women. Alcohol-related mortality is higher in older age groups; in people over the age of 55 years the standardized mortality rate is 7.3/100.000 for men and 1.34/100.000 for women [11].

1.2. How much alcohol is too much?

Studies on the safe levels of alcohol consumption, are actually not conclusive to exactly define health and risks benefits. A recent large study, including data from 333,247 participants, reported that high alcohol consumption is linked to a variety of health issues. To the contrary moderate alcohol consumption is widely recommended for protective effects against cardiovascular disease [16]. A most recent study to report on alcohol use and health risk published by the Global Burden of Disease 2016 Alcohol Collaborators, estimates alcohol use, attributed deaths, and disability-adjusted life years (DALYs) in 195 locations from 1990 through 2016, including for both sexes and for ages 15 through 95 and older [17]. This study used 694 data sources of individual and population-level consumption, and 592 prospective and retrospective studies on the risk of alcohol use. The Authors found that alcohol use was the seventh leading risk factor for both deaths and DALYs in 2016 and concluded that alcohol use is a leading risk factor for disease burden globally, accounting for almost 10% of deaths among populations aged 15–49. The study also reported that the safest level of drinking is none, conflicting with most health guidelines that report up to two drinks per day produces health benefits. In this context, the National Institute on Alcohol Abuse and Alcoholism (NIAAA), according to the "Dietary Guidelines for Americans 2015–2020" U.S. Department of Health and Human Services and U.S. Department of Agriculture, define moderate drinking as a up to 1 drink per day for women, and up to 2 drinks per day for men. In general, for healthy adults drinking more than 4 drinks on any day or 14 per week for men, and more than 3 drinks on any day or 7 per week for women, is considered "at-risk" or "heavy" drinking [14].

1.3. Binge drinking

Question 1 How is the most diffused pattern of alcohol intake among adolescent?

P (Population/patient): Adolescent
I (Intervention/Indicator): Pattern of alcohol intake
C (Comparator/Control): Adults
O (Outcome): Prevalence of binge drinking behavior

Question 2 Is alcohol abstinence mandatory in adolescent?

P (Population/patient): Adolescent
I (Intervention/Indicator): Alcohol intake
C (Comparator/Control): Non-drinker adolescents
O (Outcome): Prevalence of alcohol related damage

Binge drinking (BD) is actually the most widespread pattern of drinking among adolescents. Binge drinking is defined as the consumption of alcoholic beverages (more frequently beer and cocktails) greater than five drinks in males and four drinks in females within two hours. This amount of alcohol is able to determine an ethanol blood concentration higher than 80 mg/dL, in particular in people under 18 years old [18]. A recent cross-sectional study was conducted among Italian adolescents, aged between 13 and 20 years, attending high school [19]. Primary outcome measures were the prevalence of BD and relationship between BD and AUD among adolescents. A high rates of alcohol consumption and a very high prevalence of BD behavior were found. Moreover this study firstly reported a significant association between BD and the presence of AUD, including alcohol dependence according to AUDIT criteria (see page 8). This means a major risk of alcohol-related disease given that adolescents are more susceptible to alcohol-related injury than adults; in adolescent liver enzymes are not completely expressed to adequately metabolize alcohol [20] so total alcohol abstinence is mandatory.

BD represents an emerging serious public health problem, both for social and socio-economic associated costs and for its high impact on systemic organ damage.

BD affects liver function. In particular, high risk of liver damage was described in subjects who consume alcohol with BD behavior [21], and this risk increase in relation to the frequency of BD episodes. BD is able to increase gut permeability, bacterial translocation from the gut and serum endotoxin levels, which contribute to liver toxicity [22]. Moreover BD is associated with increased fasting plasma glucose in non-diabetic subjects [23] and it seems to be able to induce fat accumulation by cumulative gene expression changes [24]. Finally, in human a single episode of BD induces changes in immune system, with an early and transient pro-inflammatory state followed by an anti-inflammatory state [25]. All these factors could contribute to the onset and/or progression of liver damage.

In addition, BD leads to premature dysfunction of the brain, cardiovascular and gastrointestinal systems. BD affect prefrontal cortex and limbic system function, with cognitive and memory impairment, in particular in adolescents whose central nervous system is developing [26,27]. BD is also associated with a high risk of cardiovascular events, such as stroke, sudden cardiac death and ischemic heart disease [28]. Binge drinking is also associated with qualitative and quantitative changes in LDL (correlated with the progression of atherosclerosis), coagulation abnormalities and risk of arrhythmia predisposition. These mechanisms may explain the peak of hospital visits for arrhythmic and ischemic heart diseases, mainly on weekends or on Monday [27]. Finally, BD is also associated with an increased risk of acute pancreatitis, infertility and fetal alcohol syndrome.

In conclusion, alcohol consumption and abuse among adolescents is very alarming and BD is becoming increasingly frequent among Italian adolescents. BD behavior could represent a gateway to AUDs, including alcohol dependence with severe health consequences, increased burden of disease and related high socio-economic costs.

At present the Ministry of Health reports the Drinking guidelines for Italy at http://www.salute.gov.it/portale/salute/p1_5.jsp?lingua=italiano&id=81&area=Vivi_sano setting to zero alcohol consumption for people under the age of 18.

Appropriate public health policies are necessary to prevent an increase of alcohol related problems in the future adulthood. Current public programs to prevent alcohol consumption among adolescents have failed their scopes [29]. For this reason, novel approaches to prevent alcohol consumption among students are strongly needed. Peer-based approaches, defined as 'the teaching or sharing of health information" and involving people of the same age or older peers in informal settings, may be effective [29]. Policy makers might consider focusing on this information in their Inter-

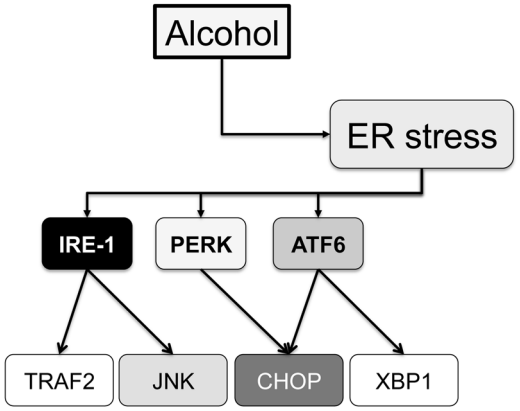

Fig. 1. ER stress pathways. Alcohol determines ER stress, which may trigger apoptotic and inflammatory pathways. IRE-1 (ERN1), PERK (EIF2AK3), and ATF6 are three major downstream mediators of ER stress and regulate the expression of proapoptotic genes. TRAF2, a protein of the TNF receptor superfamily, JNK, CHOP and XBP1 are downstream targets.

ventions and social policies to effectively modify alcohol use and its consequences on young peoples.

Recommendations

- Total alcohol abstinence during adolescence is mandatory because adolescents are more susceptible to alcohol-related injury than adults (**Grade A, Level 1**)

2. Pathophysiology of alcohol-induced organ injury

Question 1: What kind of damage does alcohol induce?

P (Population/patients): Patients with alcohol use disorder

I (Intervention/indicator): inflammation, steatosis, fibrosis

C (Comparator/control): abstinent subjects or healthy subjects with low/moderate alcohol intake (up to 2 Alcohol Unit per day if male or 1 Alcohol Unit per day if female)

O (Outcomes): evidence of morphological and functional organ injury.

2.1. Molecular mechanisms of alcohol-induced injury

2.1.1. Oxidative stress and lipid peroxidation

Oxidative stress represents an imbalance between reactive oxygen species (ROS) production and anti-oxidant defense mechanisms [30,31]. Lipid peroxidation is a process by which oxidants determine damage to specific lipids (particularly polyunsaturated fatty acids) [32]. Under excessive alcohol intake, oxidative damage overcomes cell repair ability with consequent apoptosis [33]. In case of chronic alcohol intake, microsomal cytochrome P450 becomes activated and produces large amounts of aldehyde, 1-hydroxyethyl radical and other free radicals [34]. Free radicals interact with polyunsaturated fatty acids generating lipid peroxidation end-products and protein adducts leading to cell necrosis [35].

2.1.2. Organelle damage

Alcohol causes accumulation of misfolded and/or unfolded proteins in cellular organelles favoring both stress status and cell death [36,37]. Alcohol determines activation of endoplasmic reticulum (ER)-specific sensor molecules that detect altered protein homeostasis and initiate stress signaling from ER to nucleus, possibly resulting in cell death. The ER stress response comprises ER chaperones, three ER resident sensors, and transcription factors (Fig. 1) [38].

Alcohol damages Golgi apparatus of many tissues such as the mammary gland, sexual organs, secretory epithelia [36] and neuronal dendrites [39]. When alcohol-induced protein modification and secretion exceed the Golgi capacity, the unfolded protein response (UPR) develops, with consequent increased expression of glycosylation enzymes and vesicular transportation [40,41].

Alcohol also causes quantitative and qualitative modifications of lysosomal enzymes with reduced myocardial protein synthesis and relevant impact on the patients' mortality risk [42,43].

2.1.3. MicroRNAs

Ethanol alters expression of a wide variety of microRNAs [44–47]. In patients with chronic alcohol intake, 35 microRNAs, including miR-34c, miR-146a, miR-194, miR-203, and miR-369, were up regulated [48], while other microRNAs involved in cell cycle, differentiation, signaling and nervous system development were down regulated [48,49].

In the pancreas, chronic ethanol treatment increased miR-21, miR-199a-3p and miR-211 and reduced miR-148a and miR-802 [50,51].

2.1.4. Autophagy

Both beneficial and detrimental consequences of autophagy have been described in alcohol-induced tissue damage. Autophagy might be beneficial removing damaged mitochondria and lipid droplets. Conversely, it appears to be harmful for alcohol-induced myocardial dysfunction, and skeletal muscle atrophy [52,53].

2.2. Specific mechanisms of liver injury

2.2.1. Fatty liver

Alcohol use increases NADH/NAD+, distracting fatty acid oxidation with consequent progressive fat accumulation [54–56]. Ethanol increases fatty acid and triglyceride synthesis, rises the hepatic influx of free fatty acids and chylomicrons from adipose tissue and intestinal mucosa, increases hepatic lipogenesis, reduces lipolysis, and causes mitochondrial and microtubular injury, resulting in elevation of very-low-density lipoprotein [57–59].

2.2.2. Inflammatory pathways

The inflammatory state of AALD requires a cross-talk involving inflammatory cells, hepatocytes and non-parenchymal liver cells, and the contribution of damage-associated molecular patterns (DAMPs) and pathogen associated molecular patterns (PAMPs) [60].

Infiltration of neutrophils represents a hallmark of alcoholic steatohepatitis (ASH) [60–62].

Cytokines and chemokines such as interleukin (IL)-1, IL-8, IL-17, chemokine ligand (CXCL)1, CXCL5, mediate neutrophil infiltration [63–65].

Surprisingly, Altamirano et al. [63] reported that infiltration of neutrophils is correlated with good prognosis in ASH, possibly via promotion of wound healing, secretion of growth factors, and/or control of bacterial infections [66].

In patients with AALD, hepatic infiltration and activation of CD3 + T cells and increased expression of activation markers (CD69, CD38) in circulating T cells has been reported [67]. Liaskou et al. [68] identified the oligoclonal nature of T cells in AALD, suggesting the presence of neoantigen-specific T cell responses. These neoantigens could originate from protein adducts formed with acetaldehyde and/or aldehydic products of lipid peroxidation [69].

In ethanol-induced injury, complement initiation leads to amplified expression of inflammatory cytokines and chemokines, and plays an important role in wound healing, and response to tissue damage [70].

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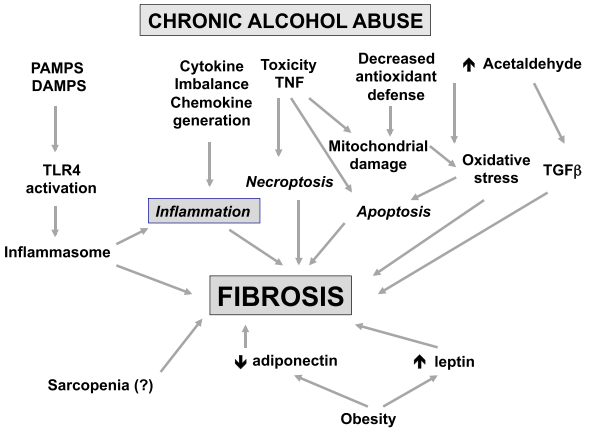

Fig. 2. Pathways of alcohol-induced inflammation and fibrogenesis. The mechanisms leading to inflammation and fibrogenesis upon prolonged alcohol exposure are schematically depicted.

After ethanol intake, Kupffer cells are sensitized to toll-like receptors (TLR)-4 induced signaling [71]. Kupffer cells and infiltrating macrophages activated by lipopolysaccharide (LPS) are polarized toward a so-called M1 phenotype and produce high levels of cytokines such as IL-1beta, tumor necrosis factor, IL-12, IL-18 and IL-23 [71]. On the contrary, M2-polarized macrophages secrete large amounts of IL-10, IL-1R antagonist and transforming growth factor beta, decreasing inflammation and promoting tissue repair [72].

Activation of the immune system alters many soluble mediators, in particular cytokines and chemokines [73]. IL-8 and CXCL1 play a pivotal role in supporting liver inflammation and damage via induction of neutrophil infiltration [64]. In addition, the chemokine CCL20 has been indicated as a critical factor promoting both inflammation and the development of fibrosis, targeting hepatic stellate cells (HSC) [74].

Intestinal dysbiosis and increased intestinal permeability have a key role in the ASH pathogenesis [75]. Alcohol significantly increases gut permeability to endotoxin/LPS [75,76]. AALD is associated with reduced synthesis of long-chain fatty acids that support growth of commensal Lactobacilli and integrity of ut barrier [77]. Alcohol-induced dysbiosis increases intestinal concentration of unconjugated bile acids due to overexpression of bacterial cholylglycine hydrolase, resulting in the down regulation of farnesoid X receptor [77].

LPS belongs to the group of PAMPs, which derive from gut microbes and result in activation of different toll-like receptors [78]. This signaling pathway is at least partially shared by DAMPs (mediators of "sterile" inflammation) [79].

Ethanol influences metabolic and immune functions of adipose tissue, altering lipid metabolism and increasing the delivery of fatty acids to the liver [80]. Adipose tissue becomes inflamed in response to ethanol, increasing the expression of inflammatory cytokines, which in turn reduce the release of anti-inflammatory adipokine such as adiponectin [81].

2.2.3. Fibrogenesis

The mechanisms of fibrogenesis in AALD are partially in common with other forms of chronic liver disease, but several pathways are specifically activated (Fig. 2). Both alcohol and acetaldehyde–induced hepatocellular injury can initiate the release of Hedgehog ligands, that induce genes promoting HSCs activation, expression of extracellular matrix and establishment of perisinusoidal and pericellular fibrosis [82]. Activation of Kupffer cells and other inflammatory cells play a pivotal role in triggering HSC activation, via secretion of growth factors and chemokines [83].

3. Clinical presentation of AALD

AALD can appear through different types of histopathological manifestations that range from steatosis to steatohepatitis up to fibrosis, cirrhosis and hepatocellular carcinoma (HCC) and at the same time it can show various clinical manifestations [54,84] (Table 2). It is necessary to specify that strongly typical clinical manifestations for AALD don't exist and that this pathology in its stages of histological presentations can progress for long period without symptoms. In this way it is possible to suspect the diagnosis only after a detection of laboratory modified parameters and compatible information obtained from the patient and his relatives. Indeed, a lot of symptoms and signs of the disease are not a direct consequence of alcohol consumption, but rather a consequence of the progression of the pathology to more severe stages, showing the clinical signs of advanced liver disease.

Episodes of tremors, morning vomiting, amnesia, asthenia, dyspeptic symptoms, traffic accidents or at work could be reported by the patient and/or collected by physician. The objective examination should not leave out among the various assessments to look for the characteristics of the breath (alcoholic halitosis) as a sign of recent ingestion of alcoholic beverage, the state of nutrition, the eventual testicular atrophy, gynecomastia, loss of skin hair, the presence of spider nevi, hepato/splenomegaly, edema, clubbing of fingers, palmar erythema, white nails, symptoms of alcohol abstinence (i.e. tremors, sweating, anxiety, tactile, auditory and visual disturbances, arterial hypertension, tachycardia) may also be present (see below).

The history of AALD is also influenced by many host factors, as overweight and obesity, female gender, viral co-infection, iron overload: all these factors are well known to increase the risk of liver damage. Moreover, a lot of drug, as antibiotics, paracetamol, non-steroidal anti-inflammatory, anti-depressants, cause an increased risk of alcohol-related damage through their interaction with ethanol metabolism.

3.1. Acute presentation

Question: How is the clinical manifestation of acute AALD?

P (Population/patients): subjects with alcohol abuse

I (Intervention/indicator): clinical features of acute alcohol abuse

C (Comparator/control): patients affected by other acute liver disease

O (Outcomes): timing of jaundice development after acute alcohol intoxication

Acute alcohol intoxication may occur with various clinical aspects including digestive symptoms (gastric pains and repeated vomiting), and impaired state of vigilance up to coma. Acute presentation of AALD could include also acute alcoholic hepatitis (AAH) symptoms, a particular condition characterized by a fast development of jaundice in patients who consume alcohol in harmful way. The presence of tremors feeds the diagnostic suspicion and information collected by patient and/or relative, i.e. recent intake of large amount of alcohol, could support the diagnosis. In this context, jaundice represents the predominant clinical sign and it can be or not associated to typical manifestations of hepatic decompensation, including hepatic encephalopathy (HE) and/or ascites [85,86]. Concomitantly, the patient can have fever in absence of infections. The risk of infections is particularly high in these patients so a broad-spectrum antibiotic prophylaxis is indicated and a screening for possible superimposed infections in case of admission for AH is recommended [87]. This clinical picture, especially in a chronic alcohol consumption can be often associated to a state of malnutrition and sarcopenia,

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Table 2
Clinical presentation of AALD.

Clinical presentation		Clinical signs and symptoms
Acute	Alcohol intoxication	Gastric pains Impaired state of vigilance Repeated vomiting Hepatic decompensation (encephalopathy and/or ascites)
	Hepatitis (on health liver, on alcoholic or other chronic liver diseases)	Jaundice Malnutrition Sarcopenia Temperature Tremors
	Liver failure	Coagulopathy Coma Encephalopathy Jaundice
	On chronic liver failure	Gastrointestinal bleeding Jaundice
	Withdrawal syndrome	Cardiac failure Coma Delirium tremens Headache High blood pressure and/or pulse rate Hyperreflexia Irritability, anxiety Nausea and vomiting Tremors
Chronic	Steatosis/steatohepatitis	a/oligosymptomatic Hepatomegaly
	Fibrosis/cirrhosis	Abdominal pain hepato/splenomegaly Alopecia and body hair loss Clubbing of fingers Edema Epistaxis Gonadal atrophy Intermittent mild fever Palmar erythema Spider nevi angiomas White nails
	Wernicke–Korsakoff syndrome	Ataxia, cognitive alterations, ocular abnormalities
	Peripheral neuropathy	Alterations or abolition of osteotendinous reflexes, dysmotility, neuropathic pain, numbness and impaired vibration sensation paresthesia.
Extrahepatic injury	Cerebellar degeneration	Ataxia, tremor
	Myocardial involvement	Dilated cardiomyopathy
	Acute and chronic pancreatitis	Abdominal pain
	Esophagitis	Barrett esophagus, Mallory–Weiss syndrome
	Hyperestrogenic syndrome	Hypogonadism and infertility

that make the patient extremely fragile from a medical point of view. Hematochemical investigation of a patient with AH often reveals high neutrophil count, hyperbilirubinemia, increase of serum aspartate aminotransferase (AST), an AST/alanine aminotransferase (ALT) ratio greater than 2.0 and prolonged prothrombin time, low albumin level, decreased platelet count in more severe forms.

As underlined, the histology of this manifestation is represented by a hepatocyte inflammation that can associate to an extended hepatic necrosis with concomitant loss of protidosynthetic and detoxifying functions carried out by the organ.

If the patient develops a coma, the alcoholic genesis can be suspected only on the basis of the anamnesis by relatives, taking into account that the coma in an alcohol use disorders (AUD) patient can be also caused by other factors associated to alcohol intake (hypoglycemia, ketoacidose, post-traumatic event, mixed). Independently from the possibility to develop acute on chronic liver failure (ACLF), another possible emergency condition in a patient with advanced AALD is represented by the chance that the pathology occurs through the onset of gastrointestinal bleeding due to break of esophageal/gastric varices or other types of injuries [88].

3.2. Alcohol withdrawal syndrome

Question: Are there typical clinical condition related to the abrupt suspension or reduction of alcohol intake in AUD patients?

P (Population/patients): alcohol abusers

I (Intervention/indicator): clinical manifestation of alcohol withdrawal

C (Comparator/control): healthy non-AUD subjects

O (Outcomes): prevalence of clinical manifestation of alcoholic withdrawal syndrome

Alcohol withdrawal syndrome (AWS) is characterized by symptoms related to the abrupt suspension or decrease of alcohol intake; it could be one of the clinical picture developing in patients with AALD which try to achieve and maintain total alcohol abstinence.

AWS need to be managed as potential medical emergency. Symptoms can appear after 6–24 h from the suspension/reduction of alcohol intake and usually include high blood pressure and/or pulse rate, irritability, anxiety, tremors, hyperreflexia, headache, nausea and vomiting. Later, the patient can develop more severe forms of AWS showing itself with delirium tremens, coma, cardiac failure until to the death [89]. The severity of clinical manifestations and therefore an urgent intervention with a suitable therapeu-

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tic approach (see the below specific treatment section) can be evaluated by the Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar) scale, a scoring system for quantitative evaluation of physical symptoms of AWS [90]. Scores of <8 indicate mild withdrawal, 8–15 indicate moderate withdrawal (marked autonomic arousal) and >15 indicate severe withdrawal and are also predictive of the development of seizures and delirium

3.3. Chronic liver damage

Question: Are AUD patients with chronic liver damage more exposed to liver-related complications?

P (Population/patients): AUD patients with chronic liver damage
I (Intervention/indicator): liver-related complications
C (Comparator/control): non-alcoholic chronic liver damage
O (Outcomes): prevalence of liver-related complications

Frequently AALD occurs as a condition of chronic damage following a silent evolution to advanced stages of disease. Liver steatosis and steatohepatitis are present in 80% of habitual users of more than 30 g of ethanol/day and 90% of consumers over 60 g/day. Clinically they are asymptomatic; on the target examination there may be no painful hepatomegaly, with rounded edges, slightly increased consistency and smooth surface. Ultrasound detects a bright liver. Biochemical parameters that differentiate the two forms are not known. However, the two pathologies have different prognosis: the simple steatosis is completely reversible after 4–6 weeks of abstinence, while the steatohepatitis has a 40% chance of developing cirrhosis in 5 years. Progression to severe fibrosis and cirrhosis is more common in drinkers over 40 g/day for periods of at least 20–25 years.

As previously described, obesity, female gender, drugs, hepatitis virus infection, iron, are all cofactors that contribute to the onset and the progression of liver damage.

The clinical presentation of the patient with alcoholic cirrhosis is similar to that of patients with cirrhosis from another etiology; it is often asymptomatic or oligosymptomatic. Only the anamnesis allows to distinguish between the various causes of liver disease.

Signs and symptoms associated with this condition can be vague as: intermittent mild fever, epistaxis, spider naevi angiomas, palmar erythema, edema, abdominal pain, hepato/splenomegaly, peripheral edemas [58]. Moreover other signs could be mild fever that becomes continuous, clubbing of fingers, white nails, alopecia and body hair loss, gonadal atrophy [58].

Patients with AALD can also present different level of hepatic decompensation including, jaundice, ascites, variceal bleeding, HE and infections, conditions that worse prognosis of patient drastically and need an immediate intervention that should follow the recommendation of cirrhosis complication management, independently from the etiology of chronic liver disease [91].

In a study based on 466 patients with a diagnosis of alcoholic cirrhosis between 1993–2005, 24% of patients presented with no complications at the time of diagnosis, whereas 76% of patients with complications of liver disease [92,93].

Moreover, it has been shown that patients with alcoholic cirrhosis presents a significantly higher prevalence of variceal bleeding compared to patients with virus-related cirrhosis [94].

Amongst patients with no initial complications 1-year mortality rate has been reported of 17%, progressively increasing according to the development of complications (20% following variceal bleeding, 29% following ascites, and 64% following HE) [92,93].

The presence and type of complications at diagnosis has been identified as predictors of mortality in patients with AALD [95], but also age and more importantly, alcohol consumption of more than 10 g ethanol per day (RR 2.9; 95%CI 1.4–5) are independent and significant predictors of mortality [95].

Alcohol consumption can definitively worsen the portal hypertensive syndrome by increasing portal vein pressure and portal-collateral blood flow [96], with the increase in hepatic venous pressure gradient being maximum at 15 min after ethanol intake [97]. Considering the development of infections, these represent one of the most frequent complications and cause of death in hospitalized patients with decompensated AALD and in patients with AAH. However, alcoholic etiology of liver disease seems not to be related to the occurrence of more frequent infection after adjustment for confounders as shown in a retrospective study [98]. Conversely, the risk of infection is significantly higher in patients with active alcohol consumption at the moment of hospital admission, and alcohol consumption has been identified as a significant risk factor for infection patients usually considered at low-risk (Child–Turcotte-Pugh A) [99]. In terms of screening strategies at time of admission pan-cultures, chest-Xray and analysis of ascites if it is present should be performed in all patients [99].

Patients with advanced AALD usually presents with a degree of sarcopenia and poor nutritional status which is significantly more severe compared to other etiology of liver disease. This also contribute to the increases risk of developing infections amongst patients with AALD [100].

Higher prevalence of psychiatric comorbidity such as anxiety disorders, affective disorders, and schizophrenia have been described in AUD patients [101,102]. Particularly, anxiety and affective disorders could induce relief and/or reward craving and consequently increase consumption of alcohol, nicotine and other drugs that could have a synergic effect on HCC development [103].

Thiamine deficit derived from chronic alcohol consumption could underlie the development of neuropsychiatric syndromes such as Wernicke encephalopathy (WE) and Korsakoff psychosis (KP), together named Wernicke–Korsakoff syndrome (WKS) [104,105]. WE requires 4/6 weeks after the development of thiamine deficit to show itself [106]. It clinically occurs with the classical triad:

- cognitive alterations: attention deficit disorder, lethargy, apathy and drowsiness, whereas in more severe cases the alteration can be clinically similar delirium tremens reaching coma;
- ataxia: slow and uncertain gait and frequent falls;
- ocular abnormalities: nystagmus, double vision, palpebral ptosis.

However, often this symptomatic triad could not show, therefore the diagnosis of the pathology is difficult and it acquires a wide range of clinical manifestations that are not typically associated to WE [107]. WKS affects the patient's working memory. Patients who suffer from it have difficulty in acquiring new information, short-term memories to long-term memories due to alterations of diencephalon-hippocampal circuit. These patients are unable to carry out tasks that don't belong to the normal routine [108].

The involvement of nervous system for chronic ethanol consumption can be also evident through the participation of large and/or small (including autonomic) fibers, showing itself in heterogenous way [109,110]. The pathogenesis of this type of damage is very discussed and probably it involves more etiological factors (i.e. direct alcohol toxicity, liver cirrhosis, nutritional/vitamin deficit, etc.) that act together determining a neuronal dysfunction that over the time becomes irreversible [109,111,112]. From a clinical point of view, the onset of alcohol-related neuropathy is sneaky and requires different years before the complete manifestation [113–115]. The first manifestations are paresthesia, numbness and impaired vibration sensation [113–115]. Later, dismotility with alterations or abolition of osteotendinous reflexes and neuropathic pain can occur, whereas proprioception is rarely involved [113–115].

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In addition to nervous central system, chronic ethanol consumption can involve the myocardial tissue causing a ventricular dysfunction named alcoholic cardiomyopathy, which clinically occurs as dilated cardiomyopathy, with important differences in terms of histological features if compared to other types of dilated cardiomyopathy with alternative etiology [116–118].

For acute pancreatitis, the risk increase is directly proportional to the importance of alcohol consumption, reaching a staggering correlation when more than 5 alcoholic beverages per day are ingested. The risk depends on the quantity of ingested alcohol in a single moment.

The continuous use of ethanol can lead to the passage from acute pancreatitis to chronic one, as well as acute episodes of relapses. The risk of acute pancreatitis relapse is significantly higher in male patients aged <40 with an annual rate of relapse of 5.3%. It is high within the first 4 years after the first episode particularly in patients who generally consume large amounts of ethanol.

Recommendations

The evaluation and the management of liver-related complications in patients with AALD is the same as in patients with liver disease due to other etiologies (**Grade A, Level 1**).

A screening for possible infections is recommended in patients with AALD in case of hospital admission (**Grade A, Level 1**).

Patients with AALD should be always screened for psychiatric comorbidity and addiction of other substance of abuse (**Grade A, Level 1**).

Patients with AALD must be evaluated for the possibility to develop alcohol withdrawal syndrome (**Grade A, Level 1**).

A fast development of jaundice in patients with recent intake of large amount of alcohol could indicate the presence of AAH, a severe condition with high mortality rate which require inpatient management (**Grade A, Level 1**)

4. Diagnosis of AALD

Question 1: What is the effectiveness of screening to identify patients with a dangerous drinking habits?

P (Population/patients): Health care setting.

I (Intervention/indicator): Quantity-frequency questionnaires

C (Comparator/control): No intervention, usual care

O (Outcomes): Alcohol consumption risk patterns, alcohol related harm, mortality

Question 2: Are non-invasive tests most accurately to identify AALD?

P (Population/patients): People with AALD.

I (Intervention/indicator): Non-invasive tests to determine which patients have liver damage including biochemical markers, surrogate scores and various imaging techniques.

C (Comparator/control): Liver biopsy.

O (Outcomes): Sensitivity, specificity, ROC curve or area under the curve

4.1. Clinical diagnosis

The diagnosis AALD can be made based on laboratory abnormalities suggestive of liver injury in a subject with a history of chronic alcohol intake. However, it is often difficult to obtain exact information on alcohol consumption, for the low compliance of patients to provide an adequate medical history. In this context, physicians may underestimate the presence of alcohol-related diseases, especially in the early stage. For this reason can be useful to define in grams the intake of alcohol and/or the number of drinks per day or week. A standard alcohol unit is a term referring to a specific amount of pure alcohol, expressed in the form of a specific measure of a certain beverage product. There is no international consensus on how much pure alcohol is contained in a standard alcohol unit. The Dietary Guidelines for Americans, establish for one standard drink as a 14 g of pure ethanol, instead for EU Member States, the most frequent value is 10 g of, followed to 12 g [119].

Moderate alcohol consumption is defined as having up to one drink per day for women and up to two drinks per day for men [120]. The following beverages corresponding to one alcohol unit: regular beer (5% alcohol), glass of table wine (12% alcohol), or shot of distilled spirits (40% alcohol).

The use of anonymous quantity-frequency questionnaires can be helpful, to identify patients with a dangerous drinking habits. The Alcohol Use Disorders Identification Test (AUDIT) is the gold standard in many international guidelines. AUDIT, that is developed by the World Health Organization, is a simple screening tool to detect the early signs of hazardous and harmful drinking and identify mild dependence, with a good sensitivity and specificity [121]. It explores consumption, dependence, and alcohol-related problems by ten questions, with two cut-off points, one for dependence and one for risky drinking. A shorter version of AUDIT, called AUDIT-concise (AUDIT-C), has been developed and it includes the first three questions of the AUDIT, and is reliable to screen the risky drinking [122]. Screening tools have also been developed for special populations, as a adolescents, older adults, and pregnant women. For adolescents, the NIAAA recommends two screening questions, about friends' and patient's drinking, as a powerful predictors of current and future alcohol problems [123]. The NIAAA also developed the related Brief Screener for Tobacco, Alcohol, and other Drugs (BSTAD) to use this approach to assess alcohol, tobacco, and drug use [124]. To assess the risk of drinking in older people, was developed the Comorbidity Alcohol Risk Evaluation Tool (CARET), an updated and revised version of the Short Alcohol-Related Problems Survey (ShARPS) [125]. Four instruments have been developed to screen the abuse of alcohol in pregnant. In particular Tolerance, Worried, Eye-openers, Amnesia, Cut down (TWEAK), Tolerance-Annoyed, Cut down, Eye opener (T-ACE), Past use, Pregnancy, use by Parents and Partners (4P's Plus), and Normal drinker, Eye opener, Tolerance (NET) [126]. Finally, the World Health Organization (WHO) developed the Alcohol Smoking and Substance Involvement Screening Test (ASSIST), a comprehensive instrument that screens for nine substances abuse, including alcohol [127].

The diagnosis of AALD is usually suspected after documentation of regular alcohol consumption more than 20 g/die in females, and more than 30 g/d in males, with the presence of clinical and/or biological abnormalities suggestive of liver injury [128]. There is not a single specific laboratory marker helpful to identify AALD. Aminotransferase serum levels are five to eight times the normal range, with aspartate/alanine transaminase ratio typically greater than 2, in 70–80% of patients [54]. A screening for AALD is recommended in high-risk populations, such as harmful drinkers identified by general practitioners, subjects in alcohol rehabilitations clinics, patients with extra-hepatic manifestation of alcohol abuse or admitted in emergency department [129].

No individual laboratory markers can identify AALD. Gamma-glutamyl transferase (GGT), has a high sensitivity to detect ethanol consumption more than 50 g/die, and it is also useful to define alcohol abuse. Unfortunately it loses its specificity in case of obesity and in advanced form of AALD [130]. Carbohydrate-deficient transferrin (CDT), is a biomarker with high specificity to detect chronic alcohol consumption, and if combined with GGT, its sensitivity increases to 90% for men and 75% for women. Another biomarker is the ethyl glucuronide, an alcohol metabolite, detectable in urine until 4–5 days after the last use of alcohol, and in the hairs for a month.

In clinical practice, it is mandatory to exclude other causes of liver disease, including viral and auto-immune hepatitis, drug-induced liver injury, iron and copper overload, and α1-antitrypsin deficiency. It is also important to take in the account the possibility that liver disease can be related to a drug induced liver injury. In

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Table 3
Diagnostic non-invasive test for diagnosis of fibrosis in patients with AALD.

Test	Including parameters
Fibrotest	Alpha-2-macroglobulin, haptoglobin, GGT, ApoA1, bilirubin, age, gender
Enhanced liver fibrosis (ELF) test	Hyaluronic acid (HA), N-terminal pro-peptide of collagen type III (PIIINP), tissue inhibitor of metalloproteinase-1 (TIMP-1)
FibroMeter	Prothrombin time, alpha-2-macroglobulin, hyaluronic acid, age
Fibrosis-4 (FIB-4) index	Serum aspartate aminotransferase, alanine aminotransferase, platelets, age
AshTest	Alpha-2-macroglobulin, haptoglobin, GGT, ApoA1, bilirubin, serum aspartate aminotransferase, age, gender

case of suspected severe fibrosis or cirrhosis, should be determined also serum albumin, prothrombin levels, platelet and white blood cell counts, in order to evaluate liver function and laboratoristic signs of portal hypertension.

During the follow-up for patients with alcoholic cirrhosis, an upper gastrointestinal endoscopy should be performed, in order to screen the presence of oesophageal varices. Clinical, laboratory and ultrasound surveillance is also indicated.

4.2. Liver biopsy

Liver biopsy has been proposed for a long time as a gold standard to evaluate liver disease. However, this diagnostic technique is invasive, expensive, and associated with some potential complications. In clinical practice, in the absence of decompensated liver disease, liver biopsy is suitable to establish the diagnosis of AALD, to assess the stage and prognosis, and to exclude concomitant and/or other causes of damage. Three different guidelines, the American Association for the Study of Liver Diseases (AASLD) guidelines [54], the European Association for the Study of Liver Diseases (EASL) guidelines [128], and the American College of Gastroenterology guidelines (ACG) [129], report that biopsy is not routinely recommended for all suspected AALD patients, but it is useful in case of aggressive forms of AALD, taking in account the risks, the benefits and the therapeutic consequences. According to EASL and ACG recommendations, liver biopsy should be considered for those patients included in clinical trials or for candidates to specific pharmacological interventions. In these cases the histology assessment of disease severity is the better predictor of long-term prognosis and/or mortality. Percutaneous biopsy may be performed in most patients; however if a possible presence of ascites and/or coagulopathy have been considered, transjugular route represents the first route choice.

4.2.1. Histologic features

The typical histological features in patients with AALD, includes steatosis which develops up to 90% of heavy drinkers, ballooning and/or Mallory-Denk bodies in the hepatocites, lobular inflammation with basically polymorphonuclear cells infiltration [131]. Some patients develop a variable degree of fibrosis (20–40%), and lobular changes that may progress to cirrhosis [132]. The first manifestation of AALD is a centrilobular microvesicular steatosis, also called foamy degeneration [133]. Lipid droplets which accumulated within hepatocytes are about 1–2 μm in diameter with high surface/volume ratio. The overload with ethanol in hepatocytes, induces the conversion of it into acetate, and hence into fatty acids and triglycerides synthesis. In case of steatosis progression, small-droplets coalesce achieve size exceeding 20 mm in diameter, and cause nuclear displacement to the periphery of the cell. They are characterized to a low surface/volume ratio, which minimizes the effects of cytoplasmic lipases. Commonly, histological pattern over time may contain both forms of steatosis at the same time [85]. Liver cell injury is also a significant feature of alcoholic steato-hepatitis and depending on liver cell types death, it can manifest as ballooning or acidophilic degeneration. Hepatocellular ballooning is a severe cell injury, with cellular enlargement, related to loss of osmotic regulation of cell size [134]. Hepatocytes may contain Mallory–Denk bodies, eosinophilic intracytoplasmic inclusions proteins, which are a characteristic finding in zone 3 ballooned hepatocytes and in areas of perisinusoidal fibrosis, in case of alcoholic steato-hepatitis [135,136]. In case of alcoholic steato-hepatitis, Mallory–Denk bodies are well formed, existing in large quantities and detected usually when immunohistochemistry with keratin antibodies used.

Inflammation is variable, and ranges from scant/mild, lobular rather than portal and predominantly with mononuclear infiltration of the portal tracts and hepatic parenchyma at neutrophilic predominance. Neutrophil infiltration contributes significantly to damage the progression of AALD [137]. Other microscopic findings in histologic pattern, include megamitochondria, lipogranulomas and glycogenated nuclei, but are not always required to establish the diagnosis [138].

The pivotal events in hepatic fibrogenesis involve activation of perisinusoidal stellate cells, deposition of extracellular matrix, and degeneration of parenchymal microvasculature. Perivenular fibrosis that extends outward along the sinusoids with initial accumulation of extracellular matrix in the space of Disse, has been well documented in the early stages of liver injury from alcohol, and is accompanied by a decrease in sinusoidal density in the perivenular region.

Several histological classifications for the most common liver disease are been described. However, AALD is perhaps the only common liver disease for which there is no validated histological classification that would ensure an adequate level of predictive and clinically relevant data [139]. On the basis of the wide morphological overlap, many study groups propose to practice for AALD the grading used for non-alcoholic fatty liver disease. In this context, histological scoring system has been proposed for predicting short-term (90-day) mortality in patients with AAH. The resulting Alcoholic Hepatitis Histological Score (AHHS), comprises four parameters independently associated with survival: fibrosis degree, polymorphonuclear infiltration, type of bilirubinostasis, and presence of megamitochondria. This histological score identifies patients with a low (0–3 points), moderate (4–5 points), or high (6–9 points) risk of death within 90 days, combining these parameters in a semiquantitative manner [140].

4.3. Non-invasive tests

The evaluation of AALD presents clinical implications. Considering the limits of liver biopsy, it is mandatory to introduce new useful noninvasive tools in clinical practice. In this way, several noninvasive laboratory tests for diagnosis of AALD have been proposed (Table 3). These tests reveale an excellent diagnostic accuracy to detect advanced fibrosis stages. In particular, Fibrotest®, a marker panel analyses alpha-2-macroglobulin, haptoglobin, GGT, ApoA1 and bilirubin and it is corrected for age and gender, ranging from 0 to 0.10 have 100% negative predictive value (NPV) for the absence of liver fibrosis, while scores ranging from 0.60 to 1.0 have more than 90% positive predictive value (PPV) for significant fibrosis [141]. The enhanced liver fibro-

sis (ELF) test, was found to have a similar diagnostic accuracy to detect advance fibrosis as a FibroTest, with NPV of 94 an PPV of 71 [142]. Another non-invasive test called FibroMeter®, present NPV 98.9% and PPV 53.7% for diagnosis of cirrhosis [143]. The diagnostic value of Hepascore® combining bilirubin, GGT, hyaluronic acid, alpha-2-macroglobulin, age and gender, do not differ from previous scores to detect advanced fibrosis secondary to AALD, with a NPV of 0.78 and PPV of 0.71, using the cut-off 0.5–0.55 [144]. The Fibrosis-4 (FIB-4) index is also a non-invasive panel to evaluate underlying hepatic fibrosis. FIB-4 values <1.45 and ≥3.25 were reported to have a NPV of 90% and PPV of 65% for advanced fibrosis [145]. Finally, the AshTest, combining the five components of FibroTest and serum AST adjusted by age and gender, shows a high diagnostic potential for detection of alcoholic steatohepatitis in patients with AALD. The score of AshTest ranges from 0 to 1.0, with NPV of 0.89 and PPV of 0.72, to predict AAH [146].

While the topics of non-invasive diagnosis of AALD have been the focus of many clinical and translational trials, reliable and validated approaches in general practice are still awaited. However, the combination of any of these tests does not improve diagnostic accuracy. Therefore, the use of surrogate scores may reduce the use of liver biopsy, and permit an earlier treatment and an easy follow-up of liver disease.

4.4. Imaging techniques

Ultrasound, computerized tomography and magnetic resonance detect the presence of liver steatosis and/or signs of cirrhosis and portal hypertension, with poor identification of patients with less advanced stages of fibrosis. However, these imaging techniques do not have a role in establishing the specific aetiology of alcohol induced liver disease. Among these methods, ultrasound probably has the lowest sensitivity and specificity, especially when steatosis is below a threshold of 20–30%. Magnetic resonance, magnetic resonance spectroscopy, are reliable tools to assess the amount of steatosis and can detect 5–10% of steatosis [147]. However, the use of standard sequences is not well established. Finally, magnetic resonance elastography, demonstrates high accuracy in the detection of advanced fibrosis than elastography in liver diseases. Moreover, the utility of this method has not been extensively evaluated.

New techniques have been recently applied in this disease. Transient elastography (TE), is an ultrasound-based technique that uses an ultrasonic transducer probe (5 MHz), which emits low frequency vibrations into the liver creating a propagating shear wave [148]. The latter is detected by a pulse-echo acquisition, which then calculates its velocity. The results that are obtained from ten valid measurement, with a success rate more than 60%, and an interquartile range under 30% were considered successful. The final value is the median of these measurement expressed in Kilopascals (kPa) and represents the resistance of material to deformation. TE measures the stiffness in 1 cm in diameter and 4 cm in length, about 1/500 of the liver volume, 100 times larger than the volume of the liver biopsy specimen. TE is useful in clinical practice to identify and to follow patients with different degrees of fibrosis, and is directly related to AST and bilirubin concentrations [149]. Inflammation, cholestasis, liver congestion can influence the results, independently to fibrosis. In addition, alcohol consumption may also modify liver stiffness measurement, as a shown by its decrease in abstainers and the increase in relapsers [150]. TE shows an excellent diagnostic accuracy for diagnosis of advanced fibrosis and cirrhosis, with an AUROC values close to 0.90 for stages of diseases [151]. In addition, the combined use of TE and Fibrotest® does not improve the performance of TE.

Recently, controlled attenuation parameter (CAP), a new technique specifically focused on steatosis, based on elastography method, has been described [152]. However, the aetiology of liver disease, and presence of co-morbities and evaluation of body mass index, have to be considered in the correct interpretation of CAP values.

Other techniques as acoustic radio force impulse, supersonic shear imaging, and magnetic resonance elastography, have been recently introduced to study liver fibrosis, also in AALD. However, there are still undergoing validation and are not used routinely.

4.5. Diagnosis and evaluation of severity

AAH is a clinical picture characterized by recent onset of jaundice with or without other signs of liver decompensation, in alcohol abuse subjects [153]. The main sign of AH is a progressive jaundice, often associated with fever without infection, malaise, weight loss and malnutrition [154]. In this context, the decision to undertake a specific pharmacotherapy is based on the assessment of the prognosis. In fact mild and moderate forms of AH, simply respond to abstinence, whereas patients with severe AH, with a mortality up to 40% within 6 months, should be considered for steroid therapy [155]. Several scoring system are available to assess the severity and the prognosis of liver disease. If Child-Turcotte-Pugh (CTP) score and Model for End-stage Liver Disease (MELD) are applicable to all aetiologies, to the contrary While Maddrey's Discriminant Function (MDF), Glasgow Alcoholic Hepatitis Score (GAHS) and Age-Bilirubin-INR-Creatinin (ABIC) score, have been proposed exclusively in the setting of AH [156–159].

MELD score, including serum bilirubin level, creatinine level and international normalization ratio (INR), is relatively accurate in predicting 3 months mortality and it is also used to prioritize liver transplantation candidates. MDF, which includes only prothrombin time and serum bilirubin, is validated as a reproducible criterion to predict early mortality and select AH patients likely to benefit from corticosteroids therapy. Severe forms of AH are defined as MDF ≥ 32 or MELD ≥ 18, with mortality ranging between 30–60% without therapy. These different scoring systems often incorporate the same variables, and appear to present similar efficacy in predicting short-term survival. During the hospitalization, a change equal or more than 2 points in the MELD score, or a reduction in serum bilirubin, evaluated by Lille score in the first week, are good predictor of mortality. GAHS and ABIC have been tested versus MDF and CTP, demonstrating a higher diagnostic accuracy in predicting 28 days and 90 days outcome. The combination of MELD and the Lille model is suitable to be an effective algorithm to predict short-term mortality in clinical practice.

Recommendations

- AUDIT or AUDIT-C should be used to evaluate patients with alcohol use disorder and dependence (**Grade A, level 1**)
- Screening for alcohol consumption and/or abuse should be performed in high-risk population groups (**Grade A, level 2**)
- Aspartate/alanine transaminase ratio greater than 1.5–2 is tipically associated with AALD (**Grade A, level 1**)
- Liver biopsy is required when the diagnosis is uncertain, severity staging is required, or in candidates to specific pharmacological treatment (**Grade A, level 1**)
- TE showed an excellent diagnostic accuracy to detect steatosis, and to detect advanced fibrosis and cirrhosis (**Grade A, Level 1**)
- A recent onset of jaundice in patients with alcohol abuse is suggestive of AH (**Grade A, Level 1**)
- Prognostic scores should be used to detect severe forms of AH, defined by Maddrey's discriminant function score >32, or MELD score >20 (**Grade A, Level 1**)
- The combination of MELD and Lille score is effective to predict short-term mortality in AH patients (**Grade A, Level 1**)

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5. Treatment

5.1. General measures

Question 1: Is total alcohol abstinence strictly indicated in AALD?

P (Population/patient): Adults affect by AALD
I (Intervention/Indicator): alcohol abstinence
C (Comparator/Control): alcohol consumption
O (Outcome): clinical and biochemical improvement

Question 2: Are corticosteroid therapy and total alcohol abstinence strictly indicated in AAH?

P (Population/patient): Adults affect by AAH
I (Intervention/Indicator): corticosteroid therapy
C (Comparator/Control): no drugs
O (Outcome): short- and long-term survival

Question 3: How can liver function response to corticosteroid therapy in AAH be evaluated?

P (Population/patient): Adults affect by AAH
I (Intervention/Indicator): corticosteroid therapy
C (Comparator/Control): no corticosteroid therapy
O (Outcome): Lille score at 7 days

The goal in the treatment of AALD is to reduce the severity of the clinical and biochemical manifestations and to prevent the progression to severe forms and its complications. In the early stage of AALD, alcohol discontinuation can improve liver histology. Although definite results are lacking, the use of non-specific antioxidants, as a vitamin E, *N*-acetylcysteine, and other natural antioxidants as a silymarin, could be useful to reduce alcohol-induced oxidative stress. Metadoxine, a drug able to enhance alcohol metabolism by increasing acetaldehyde dehydrogenase activity, showed efficacy in reducing laboratory signs of hepatic necrosis and cholestasis, when compared to vitamins or placebo [160].

Chronic alcohol abuse leads pathological changes in gut microbiota composition, that is characterized by small intestine bacterial overgrowth [161]. Bacterial species associated with the AALD included increase of Bacteroides phylum as well as Bilophila, Alistipes, Butyricimonas, Clostridium, Proteus and *Escherichia coli* [162] This disequilibrium produce intestinal mucosal inflammation and increased gut permeability, with bacterial translocation from the lumen to portal blood flux, and consequent endotoxin mediated oxidative stress and liver damage. Different approaches of gut microbiota modulation in patients with AALD, and in particular the administration of antibiotics, probiotics, prebiotics and synbiotics, have been recently proposed.

AALD is often complicated by malnutrition, whose severity is linearly related with the severity of the hepatic involvement [163]. Malnutrition in AALD is multifactorial process and include a poor dietary intake due to the anorexia and dysgeusia exacerbated by micronutrients deficiency, disproportionate amount of calories from alcohol, impairment mucosal absorption related to alcohol, hyper-metabolic/catabolic state due to the metabolism of alcohol, and increased cytokines production. Although, a severe malnutrition can lead to serious complications of liver disease. AALD patients frequently present nutritional deficiencies, including fat-soluble vitamins A, D, E and K, folate, thiamine, vitamin B6, vitamin B12 and elements as zinc and magnesium [100]. These nutritional deficiencies may develop specific extrahepatic manifestations and complications, as a Wernicke's encephalopathy or peripheral neuropathy in thiamine deficit and anemia in folate deficit. Therefore, appropriate supplementations of mineral and vitamin must be provided.

AAH requires a specific treatment (Tables 4 and 5). In severe AAH (MADDREY discriminant function up to 32 points) corticosteroid treatment is recommended [128]. Practically, prednisolone at a dose of 40 mg per day or methylprednisolone at a dose of 32 mg per day is prescribed for 28 days. The applicability of corticosteroid therapy is limited because of the increased risk of sepsis and gastrointestinal bleeding. In the absence of active infection, corticosteroids should be considered in patients with severe AH to reduce short term mortality [128]. For these reasons, a systematic screening for infection should be performed before initiating therapy, during corticosteroid treatment, and during the follow-up period. Therefore, early identification of non-responders to corticosteroids (Lille score at day seven up to 0.45) is important because in these cases the cessation of therapy should be applied. In case of non-response to corticosteroids, highly selected patients should be considered for early liver transplantation. Patients that response to corticosteroid treatment (Lille score less than 0.45) have to continue this therapy for 28 days and at the end of treatment, the prednisolone or methylprednisolone can be stopped all at once, or the dose can be gradually tapered over a period of three weeks [128].

In addition to corticosteroid therapy, *N*-acetylcysteine (for five days, intravenously, limiting oxidative stress) may be added in patients with severe AH [128] and a careful evaluation of nutritional status should be performed to achieve a daily energy intake ≥35–40 kcal/kg BW and 1.2–1.5 g/kg protein, and to adopt the oral route as first-line intervention [128].

Total alcohol abstinence and early management of AUD is mandatory in patients with AH [128]. The severity of liver injury seems to determine short-term survival while alcohol abstinence is the main determinant of long-term prognosis [164].

In particular, the efficacy of medical (and surgical) treatments for AALD, including AAH, is limited when drinking continues [165]. Thus, the cornerstone for the treatment of AALD is the treatment of AUD to achieve total alcohol abstinence and relapse prevention.

Recommendations

- The goal in the treatment of AALD is to prevent the progression to severe forms and its complications and total alcohol abstinence is recommended (**Grade A, level 1**)

In severe AAH (MADDREY discriminant function up to 32 points) corticosteroid treatment is recommended (**Grade A, Level 1**). A screening for infection should be performed before initiating therapy, during corticosteroid treatment, and during the follow-up period (**Grade A, Level 1**).
Early identification of non-responders to corticosteroids (Lille score at day seven up to 0.45) is mandatory because in these cases the cessation of therapy must be applied (**Grade A, Level 1**)

5.2. Treatment of alcohol withdrawal syndrome

Question: How alcohol withdrawal syndrome should be treated?

P (Population/patient): Adults
I (Intervention/Indicator): pharmacological treatment
C (Comparator/Control): no pharmacological treatment
O (Outcome): reduction/ disappearance of clinical symptoms of AWS

Symptoms of AWS may develop within 6–24 h after the abrupt discontinuation or decrease of alcohol consumption. In the moderate to severe forms of AWS (CIWA-Ar score up to 8 points), pharmacological treatment is recommended [128].

Other than the normalization of fluids, electrolytes and glycemia imbalance, as well as vitamin administration (in particular thiamine), benzodiazepines (BZDs) are the gold standard for the treatment of AWS. Diazepam (10 mg intravenous or orally 4 times per day for 1 day, then 5 mg 4 times per day for 2 days, then tapering off) or chlordiazepoxide (50–100 mg intravenous or orally 4 times per day for 1 day, then 25–50 mg 4 times per day for 2 days, with subsequent tapering off) are the most widely used drugs on the basis of their long half-lives. However most of BZDs undergo an extensive metabolism in the liver with production of active

Table 4
Common scoring formulas to define severity of acute alcoholic hepatitis.

Maddrey's Discriminant Function (MDF)	4.6 (patient prothrombin time – control prothrombin time [seconds]) + total bilirubin (mg/dL)			
Model for End-Stage Liver Disease (MELD) score	9.57 × ln creatinine (mg/dL) + 3.78 × ln total bilirubin (mg/dL) + 11.20 × ln INR + 6.43			
MELD-Na score	MELD score + 1.32 × (137-Na) – [0.033 × MELD × (137-Na)]			
		1	2	3
	Age	<50	≥50	–
Glasgow Alcoholic Hepatitis Score (GAHS)	WBC (109/L)	<15	≥15	–
	Urea (mmol/L)	<5	≥5	–
	PT ratio	<1.5	1.5–2.0	>2.0
	Bilirubin (μmol/L)	<125	125–250	>250
Age serum Bilirubin INR and serum Creatinine (ABIC) score	(age × 0.1) + (serum bilirubin in mg/dL × 0.08) + (serum creatinine in mg/dL × 0.3) + (INR × 0.8)			
Lille Model score	(Exp[-R]/[1 + Exp(-R)]) R = 3.19–0.101 age (years) + 0.147 albumin (g/L) + 0.0165 × change in bilirubin (total bilirubin at day 0 mmol/L – total bilirubin at day 7 in mmol/L) – 0.206 renal insufficiency (0 or 1) – 0.0065 total bilirubin at day 0 (mmol/L) – 0.0096 prothrombin time (seconds) Renal insufficiency is rated as 1 if creatinine level at day 0 is ≥ 1.3 mg/dL, and as 0 if creatinine level is <1.3 mg/dL			

Table 5
Treatment considerations of severe alcoholic hepatitis.

Treatment	Options	Comments
Corticosteroids	Prednisolone	If MDF ≥32: 40 mg daily orally for 28 days followed by a 2/4-week taper
Phosphodiesterase inibitors	Ppentoxyfilline	400 mg orally 3 times daily for 4 weeks
Anti TNF-α	Infliximab	Infliximab 5 mg/kg i.v. at day 0 and prednisone 40 mg/day for 28 days
Nutrition	Eating, tube feeding	Diet rich in carbohydrate- and protein-derived calories; potassium replacement; vitamin supplementation
Antioxidant	Metadoxine	1500 mg/day orally for 3 months
Antioxidant	*S*-Adenosylmethionine	1200 mg/day orally in ambulatory patients
Alcohol abstinence	Rehabilitation program; baclofen (?)[a]	Reduce alcohol withdrawal symptoms, alcohol craving and intake, promote abstinence, evaluation for OLT program

[a] Only a retrospective case series; Yamini D, Lee SH, Avanesyan A, et al. Utilization of baclofen in maintenance of alcohol abstinence in patients with alcohol dependence and alcoholic hepatitis with or without cirrhosis. Alcohol Alcohol. 2014; 49:453–6.

metabolites. In patients with reduced liver metabolism the use of short-acting agents may be preferred in order to prevent excessive sedation and respiratory depression [166,167]. In particular in patients affected by advanced liver disease, BDZs like oxazepam (15–30 mg orally, 3 or 4 times per day) or lorazepam (1 mg intravenous or 2 mg orally 4–6 times per day) are preferable because of their shorter half-life and the absence of active hepatic metabolite products [166,167].

BDZs should be used to treat AWS but should not be prescribed beyond 10–14 days because of the potential for abuse and/or encephalopathy [128].

Other non-BZD drugs like baclofen have been tested in AWS showing an efficacy comparable to benzodiazepines [167,168].

Recommendations

- In patients with AWS benzodiazepines [Diazepam (10 mg 4 times per day for 1 day, then 5 mg 4 times per day for 2 days, then tapering off) or chlordiazepoxide (50–100 mg 4 times per day for 1 day, then 25–50 mg 4 times per day for 2 days, with subsequent tapering off)] are the treatment of choice (**Grade A, Level 1**).
- In patients with AWS and advanced liver disease benzodiazepines with short half-life [oxazepam (15–30 mg orally, 3 or 4 times per day) or lorazepam (1 mg intravenous or 2 mg orally 4–6 times per day)] should be used (**Grade A, Level 1**)
- In AWS, BDZs should not be prescribed beyond 10–14 days because of the potential for abuse and/or encephalopathy (**Grade A, Level 1**).

5.3. Treatment of alcohol use disorder (AUD) in patients without liver disease

Question: How alcohol use disorder should be treated?

P (Population/patient): Adults affect by AUD

I (Intervention/Indicator): combination between medications and psychosocial interventions

C (Comparator/Control): no treatment for AUD

O (Outcome): reduction of alcohol intake or total alcohol abstinence

The goal of the treatment is to achieve total alcohol abstinence or, alternatively, the reduction of alcohol intake, on the basis of patient's requirement and according to harm reduction policy. The most effective management strategy is the combination of psychosocial interventions and pharmacological therapy [169].

The most frequently used psychosocial interventions for AUD treatment include twelve-step facilitation therapy, motivational enhancement therapy (MET) and cognitive-behavioral therapy (CBT). They represent the backbone of AUD treatment.

Disulfiram, naltrexone, nalmefene and acamprosate represent the approved drugs in most of the world countries, even if a large number of pharmacological agents have been tested for the treatment of AUD [170] (Table 6).

Disulfiram, that is the first drug approved for the treatment of AUD, inhibits acetaldehyde dehydrogenase enzyme action, developing distressing and alcohol-deterrent symptoms when disulfiram and alcohol are consumed together. All symptoms including nausea, vomiting, flushing, hypotension, headache and

Table 6
Anticraving drugs approved for the treatment of alcohol use disorder.

Anticraving drug	Approved country	Mechanism of action	Dose	Available data on efficacy and safety in AUD patients with ALD
ACAMPROSATE	US and EU	Glutamate receptor modulation	1.3 g/day (weight <60 kg) and 2 g/day (weight >60 kg) in three daily administrations	Only one day administration study in Child A-B liver cirrhosis[a]
BACLOFEN	France	GABA-B agonist	10 mg t.i.d. in patients with liver disease	In Child A-C liver cirrhosis and in AAH (see Ref [175])
DISULFIRAM	US and EU	Inhibitor of aldehyde dehydrogenase	800-1200 mg/day for 3–4 days, then 400 mg/day until the 7th day, after 200 mg/day	NO
NALMEFENE	EU	Selective opioid receptor ligand with antagonist activity at the μ and δ receptors and partial agonist activity at the κ receptor	18 mg per day "on demand"	NO
NALTREXONE	US and EU	Opiate antagonist with the highest affintiy for the μ receptor	50–100 mg/day	NO
SODIUM OXIBATE (GHB)	Italy Austria	GABA-B/ GHB receptor agonist	50 mg/kg divided into three or six daily administrations	Only one case report[b]

[a] Delgrange, T, Khater J, Capron D, et al. Effect of acute administration of acamprosate on the risk of encephalopathy and on arterial pressure in patients with alcoholic cirrhosis. Gastroenterol Clin Biol 1992; 16: 687–91.
[b] Caputo F, Bernardi M, Zoli G. Efficacy and Safety of Gamma-Hydroxybutyrate in treating alcohol withdrawal syndrome in an alcohol-dependent inpatient with decompensated liver cirrhosis: a case report. J Clin Psychopharmacol. 2011; 31: 140–1.

diarrhea are termed "acetaldehyde syndrome". However, some possible serious adverse events, such as liver failure, neuropathy and psychosis do not support its use in patients affected by liver disease, peripheral neuropathy and psychosis [128,171,172].

Naltrexone, l and k-opioid receptor antagonist, reduces alcohol-related dopamine release in the nucleus accumbens with a reduction of alcohol related reward sensation. In this way, patients are less motivated to drink alcohol (as called "extinction mechanism"). Naltrexone has been approved in the USA by FDA in 1994 for the treatment of AUD [for review see Ref. [170]]. The most common side effects are headache, nausea, dyspepsia and sedation.

Nalmefene, l and d-opiod antagonist and k-opioid partial-agonist, is effective to reduce alcohol intake, in particular to reduce heavy drinking in AUD patients. With this indication, it was recently approved in Europe by the European Medicines Agency. Nalmefene is prescribed 'as needed' and it is indicated particularly in patients who have as main objective the reduction of alcohol intake, not the total abstinence [173].

Acamprosate, that is a *N*-metil-D-aspartate glutamate receptor antagonist, reduces alcohol intake and maintains alcohol abstinence, at least in mild to moderate forms of AUD. Acamprosate was approved in the USA by Food and Drug Administration (FDA) in 2004 for the treatment of alcohol dependence [for review see Ref. [170]].

In the last decades, a number of additional drugs (currently approved for other indications or used as off-label) have been tested [170] (Table 6).

Sodium oxybate (SMO) is a GABAB agonist approved in US for the treatment of narcolepsy and in some EU countries for the treatment of AUD. A Cochrane evaluation confirmed the efficacy of this drug to promote total alcohol abstinence and to prevent relapse [174]. This drug is approved in Italy and in Austria for the treatment of withdrawal syndrome and for relapse prevention.

Topiramate facilitates GABA transmission and reduces glutamatergic activity with the goal of reducing dopamine release in the limbic system. This drug is approved for the treatment of seizures and migraine. The administration of topiramate in RCTs with a dose escalation design was effective in reducing daily alcohol intake and heavy drinking days, and in increasing abstinence rate [for review see Ref. [170]].

Ondansetron, a 5-HT3 receptor antagonist, leads to a dopaminergic downregulation, and consequently it reduces the reward-related alcohol intake. This drug is currently approved for the treatment of emesis [for review see Ref. [170]].

Baclofen is a selective GABAB receptor agonist that inhibits the dopamine-mediated alcohol reinforced behaviors. This drug is currently approved to control spasticity. Preclinical and clinical studies demonstrated that baclofen may represent an effective mediation to reduce alcohol withdrawal symptoms, as well as to reduce alcohol craving and intake, and to promote alcohol abstinence [175]. A recent consensus statement on the use of baclofen in AUD patients, was developed by an international panel of experts [176].

Gabapentin, a drug structurally similar to GABA, is presently approved for the treatment of seizures and neuropathic pain. Gabapentin, at a dose of 600 mg/day twice per day, was superior to placebo in reducing alcohol consumption in AUD patients with post-traumatic stress disorder who were resistant to selective serotonin re-uptake inhibitors, and in AUD patients with insomnia [177].

Recommendations

- In AUD patients without advanced liver disease, the combination between medications and psychosocial interventions reduce alcohol consumption and prevent relapse (**Grade A, Level 1**)

5.4. Treatment of AUD in patients with AALD

Question: How can we treat alcohol use disorder in patients affected by AALD?

P (Population/patient): Adults affect by AUD and AALD

I (Intervention/Indicator): combination between selected medications and psychosocial interventions

C (Comparator/Control): no treatment for AUD

O (Outcome): total alcohol abstinence

At present AUD represents the main risk factor for liver diseases. More than 60% of liver cirrhosis both in Europe and in North America are related to alcohol [178]. AALD ranging from steatosis and AAH to liver cirrhosis and its complications (varices, ascites, hepatic encephalopathy, hepatopulmonary hypertension, hepatocellular carcinoma, hepatorenal syndrome, spontaneous bacterial peritonitis, and coagulation disorders). Amount of alcohol intake, duration and pattern of drinking (e.g., episodic, binge, continuous) play the major role in alcohol-induced liver damage [179].

The cornerstone of treatment for AALD is achieving total alcohol abstinence. Medical and surgical treatments for AALD have limited success when drinking continues [165]. AUD patients with advanced liver disease represent a special population. In particular AALD should be considered as a dual pathology including both a liver and an addiction disease. For this reason these patients should be treated by a team of specialists, including hepatologist and providers (i.e. psychiatrist and psychologist) with a mandatory expertise in addiction medicine who could manage anti-craving drugs and psychosocial support and which should work within the Liver Unit or, alternatively, by hepatologists with a mandatory expertise in addiction medicine [165]. In particular integrating alcohol interventions with medical care, AALD patients who would not accept an external consultant for alcoholism treatment might be engaged in the Liver Unit as they are usually willing to return for medical appointments [165].

As concern psychosocial management, a recent meta-analysis showed that a single psychosocial intervention is useful only for AUD patients without LD while in AUD patients affected by LD only integrated combination between psychotherapy with CBT, MET and comprehensive medical care is effective [180]. These data underline that AUD patients with LD need intensive behavioral approaches integrated within medical care.

The anti-alcohol medication previously described are useful to improve abstinence and to reduce relapse. However their use is limited to AUD patients without advanced liver disease and/or with early stage of liver disease (and in this case liver function must be monitored) because most of these medications have not been tested in AUD patients with advanced liver disease (Table 6). In particular, to date, only baclofen has been formally evaluated in randomized clinical trials in AUD patients affected by liver cirrhosis. The safety and efficacy of the drug to increase total alcohol abstinence and to prevent relapse firstly showed in this subset of AUD patients [181] have been recently replicated both in RCT [182] and in prospective cohort studies [for review see Ref. [183]].

Recommendations

- In AUD patients with liver disease total alcohol abstinence is recommended (**Grade A, Level 1**)
- AUD patients with advanced liver disease represent a special population and should be treated by a team of specialists, including hepatologist and providers (i.e. psychiatrist or psychologist) with a mandatory expertise in addiction medicine or, alternatively, by hepatologists with a mandatory expertise in addiction medicine (**Grade A, Level 1**). It would be advisable that each Liver Unit which manage AALD patients has the specialist in addiction medicine within the staff rather than to utilize external consultant (**Grade B, Level 2**)
- Most of anticraving medications should be used with caution in patients with early stage of liver disease and should not be administered to AUD patients with advanced liver disease (**Grade B, Level 1**); in these patients baclofen (10 mg 3 times per day) proved safety and efficacy to prevent alcohol relapse and to increase total alcohol abstinence rate (**Grade B, Level 2**)

5.5. Liver transplantation

Question 1: When is recommend to refer patients with end-stage AALD to a liver transplant center?

P (Population/patient): Adults with end-stage AALD

I (Intervention/Indicator): alcohol abstinence for more than 6 month

C (Comparator/Control): alcohol abstinence for less than 6 month

O (Outcome): long-term survival

Question 2: What are the benefits of liver transplantation in AUD patients with advanced liver disease?

P (Population/patient): Adults with end-stage liver disease

I (Intervention/Indicator): patients underwent to LT

C (Comparator/Control): only medical support

O (Outcome): short- and long-term survival

When liver function does not improve after an adequate abstinence or when the severity of disease does not allow waiting for improvement, liver transplantation (LT) represents the gold standard treatment for patients with advanced AALD [128,171].

It is mandatory to reduce the risk of alcohol relapse after transplantation in order to reduce the probability of graft loss and the liver damage related to alcohol relapse. An abstinence period of 6 months before LT – the so-called "6-months rule" – is usually required mainly because a recovery of liver function after a prolonged alcohol abstinence could avoid unnecessary LT. However the role of the "6-month rule," as a specific time point predicting post-transplantation abstinence is questionable and not evidence based. Decisions on LT candidacy should not be made solely on length of sobriety criterion according to the International Liver Transplant Society Guideline [184]. In particular, when medical urgency does not allow a 6-month waiting time, the LT evaluation may proceed in selected patients. In this regard, early LT should be proposed to a very selected patients with severe AH not responding to medical therapy [185].

Patients with AUD on the transplant waiting list should be checked for alcohol use by regular clinical interviews and use of laboratory tests to confirm abstinence.

A multidisciplinary approach evaluating not only medical but also psychological suitability for transplantation is mandatory before and after LT and the integration of an addiction specialist may decrease the risk of relapse in heavy drinking individuals [186].

After liver transplantation low and occasional drinking could be tolerated, but considering the risk of craving/loss of control consuming alcohol in these category of patients, total alcohol abstinence is promoted and recommended [128,171].

Considering patients with AH, despite the high mortality rates especially in patients not responding to medical therapy, AH is still considered an absolute contraindication to liver transplantation in most liver transplant centres. This is mainly due to the fact that patients are actively drinking at the time of evaluation and therefore the so called 6 month rule, is not fulfilled, although it is not evidence based and not required by the International Guidelines [184].

In particular Mathurin et al. [187] performed a multicenter study demonstrating that liver transplantation can represents a therapeutic option for patients with severe AAH not responding to steroids, when strict selection criteria are applied. Patient survival at 6 months after LT was significantly higher in liver transplanted patients compared to matched control patients with severe AAH not responding to steroids but who did not undergo LT (77% vs 23%). Alcohol relapse was diagnosed in 11% of patients, a percentage comparable with the alcohol relapse rate usually diagnosed in patients transplanted for alcoholic liver cirrhosis [187].

Please cite this article in press as: Addolorato G, et al. Alcohol associated liver disease 2020: A clinical practice guideline from the Italian Association for the Study of the Liver (AISF). Dig Liver Dis (2020), https://doi.org/10.1016/j.dld.2019.12.008

Following these results, other single centre studies have been published with similar results, but with lower number of included patients [188,189]. More recently, a multicentre retrospective study evaluated the outcomes in terms of survival and alcohol relapse amongst 147 patients who underwent liver transplantation for severe AH. Interestingly, amongst the 146 patients with available explant histology records 140 (96%) had cirrhosis, and amongst these 83/140 (59%) presented cirrhosis with steatohepatitis, whereas 57/140 (41%) cirrhosis alone without concurrent steatohepatitis. One and 3-year survival rates after LT were 94% and 84% respectively, and the cumulative incidence of any alcohol use was 25% and 34% at 1 and 3 years respectively. When authors performed the multivariate analysis sustained alcohol use after LT was associated with a four fold increase in the risk of death, and only younger age was associated with alcohol relapse after LT [190].

Similarly, Weeks et al. [191] evaluated 46 liver transplanted patients for severe AH (October 2012–July 2017) and compared them with 34 patients with alcoholic cirrhosis who underwent LT under standard protocols. Amongst patients with AH, 96% had cirrhosis on explant pathology and 52% demonstrated histologic changes consistent with AAH. At a median follow-up time of 532 days there were no significant differences between groups in terms of patient and graft survival or alcohol recidivism.

Although data on good survival after liver transplantation for AH are consistent across different studies, data on post-transplant alcohol relapse rate are still controversial. This is mainly due to different follow-up in terms of duration and methodology in assessing alcohol relapse amongst studies and different definition of alcohol relapse. Moreover the comparison between patients transplanted for AH and patients transplanted for alcohol-related cirrhosis, with a pre-transplant 6 month abstinence period – is emerging as the true parameter to assess the role of early LT in this specific subset of patients. Data form a multicentre French-Belgian Study are awaited to demonstrate that alcohol relapse within the 2-year follow-up period in patients selected for early liver transplantation for severe AH is not inferior to that of patients transplanted for alcoholic cirrhosis using the 6-month sobriety period [192].

The initial experience of liver transplantation for patients with AH has raised several ethical and social issues, in particular regarding the risk for a loss of confidence from the public to the transplant practitioners, with potential negative impacts on organ donation. This is mainly due to the fact that AALD is considered a "self-inflicted" disease, and that patients transplanted for AH are actively drinking at the time of evaluation. However, to date fulminant hepatic failure due to acetaminophen overdose or cirrhosis due to HCV in patients with previous i.v. drug use are well recognized indications for LT with no concern from the public. Moreover, in a recent study, an online survey was performed on 503 participants in order to evaluate attitudes on liver transplantation generally and on early transplantation for patients with AH. Nearly 82% of respondents was at neutral toward early transplantation for patients AH. Middle-aged patients, with good social support and financial stability were viewed most favorably [193].

Another important aspects is that to date there is a strong variability in terms of access to liver transplantation for patients with AH, not only internationally, but also at a national level, with a consequent marked inequity, and a potential "postcode lottery" scenario where the likelihood of being listed for transplantation is related to the place you live and the policy of the local transplant center. Therefore there is a strong need for international and national consensus on criteria for listing patients with AH [194].

In Italy, a position paper has been recently published stating that patients with AAH, as a first episode of decompensation in chronic liver disease, and not responding to steroid therapy can only be considered for LT if specific and strict criteria are met These criteria include the presence of absolute consensus of paramedical and medical staff, the absence of co-morbidities, a good social integration with supportive family members, and a favorable psychiatric evaluation and addictive profile. Patients not suitable for steroid therapy can be considered for transplantation only if these criteria are satisfied [185].

Recommendations

- LT represents the gold standard treatment for patients with advanced AALD (**Grade A, Level 1**)
- AUD patients listed for LT should be checked for alcohol use by regular clinical interviews and use of laboratory tests to confirm abstinence (**Grade A, Level 1**)
- Decisions on LT candidacy should not be made solely on length of sobriety criterion (**Grade A, Level 1**). When medical urgency does not allow a 6-month abstinence waiting time, the LT evaluation may proceed in selected patients (**Grade C, Level 1**).
- Early LT should be proposed to a very selected patients with severe AAH not responding to medical therapy (**Grade A, Level 1**)
- A multidisciplinary approach evaluating medical and psychological suitability for transplantation is mandatory before and after LT (**Grade A, Level 1**).

Conflict of interest

None declared.

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Please cite this article in press as: Addolorato G, et al. Alcohol associated liver disease 2020: A clinical practice guideline by the European Association for the Study of the Liver (AISF). Dig Liver Dis (2020), https://doi.org/10.1016/j.dld.2019.12.008

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Please cite this article in press as: Addolorato G, et al. Alcohol associated liver disease 2020: A clinical practice guideline from the European Association for the Study of the Liver (AISF). Dig Liver Dis (2020), https://doi.org/10.1016/j.dld.2019.12.008