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EASL Clinical Practical Guidelines: Management of Alcoholic Liver Disease

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Introduction

Alcoholic liver disease (ALD) is the most prevalent cause of advanced liver disease in Europe. However, there has been limited research investment into ALD despite its significant burden on the health of Europeans. This disparity is reflected by the ETOh score – the ratio of the estimated population mortality rate to the number of trials focused on a particular disease. The ETOh score for ALD is 358, compared with 1.4 for hepatitis B, 4.9 for hepatitis C, and 15.2 for primary biliary cirrhosis [1].

In recent years however, the mechanisms driving disease progression and the natural history of ALD have been better defined and novel targets for therapy have been identified [2]. In addition, significant clinical research has produced a clear framework for the evaluation of new therapies in particular in patients with alcoholic steatohepatitis (ASH).

ALD is a complex disease, the successful management of which hinges on the integration of all the competences in public health, epidemiology, addiction behavior and alcohol-induced organ injury. Both primary intervention to reduce alcohol abuse and secondary intervention to prevent alcohol-associated morbidity and mortality rely on the coordinated action of multidisciplinary teams established at local, national, and international levels.

These guidelines are largely based on the issues raised during the EASL monothematic conference on ALD held in Athens in 2010. The guidelines have three main aims: (1) to provide physicians with clinical recommendations; (2) to emphasize the fact that alcohol can cause several liver diseases (steatosis, steatohepatitis, cirrhosis), all of which may coexist in the same patient; (3) to identify areas of interest for future research, including clinical trials.

The evidence and recommendations in these guidelines have been graded according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system [3]. The strength of recommendations thus reflects the quality of underlying evidence. The principles of the GRADE system have been enunciated. 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 offers 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.

Burden of ALD

Burden of alcohol-related disease and injury

Alcohol consumption is responsible for 3.8% of global mortality and 4.6% of disability-adjusted life-years (DALYs) lost due to premature death [4]. The attributable burden in Europe, with 6.5% of all deaths and 11.6% of DALYs attributable to alcohol, is the highest proportion of total ill health and premature deaths due to alcohol of all WHO regions [4,5]. Europe shows particularly large sex differences in burden: the deaths attributable to alcohol being 11.0% and 1.8% for men and women, respectively. The young account for a disproportionate amount of this disease burden, with an alcohol-associated mortality over 10% and 25% of female and male youth, respectively [6].

Burden of ALD in Europe

The burden of compensated alcohol cirrhosis among the general population and heavy drinkers is not well known. The development of non-invasive methods to detect significant liver fibrosis (e.g., elastography, serum markers) should help in elucidating this issue. A recent study in France indicates that alcohol abuse accounts for up to one third of liver fibrosis cases [7]. The best comparative proxy for the burden of ALD is mortality from liver cirrhosis as a whole, although as discussed later this has its limitations. Mortality rates from liver cirrhosis vary considerably between European countries [8] with a 15-fold variation between the highest and lowest national rates [9]. However, Europe is essentially divided into two, with Eastern European states tending to have higher rates than the others [8].

Time trends in liver cirrhosis mortality over the past 30 years show very heterogeneous patterns between countries. About half

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Table 1. Grading of evidence and recommendations (adapted from the GRADE system).

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

the countries of Europe, including Austria, France, Germany, Italy, Portugal, and Spain as well as two Eastern European countries (Hungary and Romania) have experienced sharp declines in liver cirrhosis mortality [9], whereas the Western countries of Finland, Ireland, and the United Kingdom [10], as well as a larger number of Eastern European countries including Estonia [11], Lithuania, Poland, and Russia have increasing rates. In terms of alcohol-related hospital admissions, for example, parallel to the upward trend in liver cirrhosis mortality, general hospital admissions [12], and admissions to intensive care units with ALD have risen sharply in the United Kingdom [13].

Limitations to estimate the burden of ALD

The extent of international variation and trends in ALD is difficult to determine. Mortality data from liver disease is available for most countries, and to this extent liver cirrhosis mortality is frequently used as the indicator of choice. However, it is not possible to reliably separate out alcoholic from non-alcoholic cirrhosis mortality. In an undetermined proportion of deaths in which alcohol is the key factor, the certifying doctor may choose not to explicitly mention alcohol on the death certificate [14]. The extent of this bias is unknown, but it is likely to vary by country, sex, age, and era. For this reason, emphasis is usually given to analyzing mortality from liver cirrhosis regardless of whether it is specified as alcoholic or not [15]. These factors, taken together, mean that at the present time our best estimates about the international variation in the burden of ALD, based on mortality from liver cirrhosis as a whole, need to be interpreted with caution. There is a clear need to perform large-scale epidemiological studies to determine the prevalence of compensated ALD in the general population and the weight of ALD as a cause of cirrhosis.

Types of alcohol and patterns of consumption

European countries vary considerably in terms of *per capita* alcohol consumption, predominant beverage type, and the extent to which drinkers imbibe substantial quantities on single occasions (binge drinking) [6]. In order to propose a consensual definition, the National Institute of Alcohol Abuse and Alcoholism defines binge drinking episodes as consumption of five or more drinks (male) or four or more drinks (female) in the space of about 2 h [16]. These differences in type and pattern of consumption tend to fall along an East–West divide [17]. While *per capita* alcohol consumption is strongly correlated with liver cirrhosis mortality rates across countries [18], there remains uncertainty about whether these other dimensions of drinking behavior in a population are related to risk [19,20]. There are several aspects to this. Firstly, does beverage type matter above and beyond volume of ethanol consumed [21]? Secondly, does drinking to intoxication (sometimes referred to as binge drinking) confer a particular risk? Thirdly, what is the contribution to the burden of ALD induced by the consumption of substances that may contain hepatotoxic substances in addition to ethanol [20,22,23]? This latter class of drink includes fruit brandies, which are frequently consumed in Hungary, for example [24] as well as home brewed alcohols that are drunk in Russia [25] and other parts of the former Soviet Union [26].

Risk threshold of alcohol consumption for liver cirrhosis

An important aspect of public health policy concerning alcohol has been the attempt to establish a safe threshold for consumption. This revolves primarily around the extent to which moderate alcohol consumption is cardioprotective [27,28]. This positive effect of alcohol, if real, can then offset the large array of negative health consequences of even moderate alcohol consumption. For many individual diseases such as liver cirrhosis; however, there is no *a priori* reason to believe a threshold effect exists, as risk appears to increase steeply with the amount of alcohol consumed. In a meta-analysis of daily consumption levels in relation to cirrhosis, patients taking 25 g of ethanol a day were at higher risk of cirrhosis than non-drinkers [29]. A more recent meta-analysis found increased risks of mortality from liver cirrhosis among men and women drinking 12–24 g of ethanol per day [30]. Indeed, among women, a significant increase was also seen for those drinking up to 12 g/day. These levels of consumption (<25 g/day) are appreciably lower than most public health recommendations for overall safe levels of consumption. The human evidence to date therefore suggests that if a threshold exists, it is very low, and may in fact be difficult to detect because of limitations in measuring consumption below 10–12 g per day.

It should be noted that neither meta-analysis was able to distinguish between the effects of daily consumption from the effects of "binge" drinking. To this extent little is known about

thresholds as applied to "binge" drinking. Further clinical and experimental studies are required to define the role of "binge" in the pathogenesis of ALD and the underlying mechanisms. Finally, risk of cirrhosis is almost certainly related to the length of time over which an individual has drunk regularly and not simply to the usual amount consumed.

Conversely, there is some clinical evidence that cessation of drinking at any point in the natural history of the disease reduces the risks of disease progression and occurrence of complications from cirrhosis.

Public health implications

Even though there remain uncertainties about the precise burden of and trends in ALD in Europe, there is no doubt that in many countries it is very substantial and or increasing. While improvements in treatment are essential, developing population-based policies to reduce levels of harmful and hazardous consumption are a priority. More broadly, there is increasing recognition of the heavy social, health, and economic burdens imposed by heavy alcohol drinking and the policies to reduce harm caused by alcohol, need to be urgently implemented [31]. Several meta-analyses have evaluated the efficacy and cost efficacy of different policy targeted areas [32]. The most cost-effective policies are those that reduce availability of alcohol, either through the pricing policies or the hours and places of sale, as well as implementation of minimum age purchase laws.

Statements

(1) Alcohol abuse is a major cause of preventable liver disease worldwide.
(2) *Per capita* alcohol consumption is strongly correlated with liver cirrhosis mortality rates across countries. Any evidence based policy in Europe need to implement preventive measures aimed at reducing alcohol consumption at the population level.
(3) The binge drinking pattern is becoming increasingly prevalent, mainly among young individuals, but its impact on liver disease is unknown.

Recommendations

- Excess alcohol consumption should be addressed using pricing-based policies (**Recommendation A1**)
- Restrictions on the number of alcohol vendors should be used to control alcohol consumption (**Recommendation A1**)
- Advertising of alcohol either directly or indirectly should be banned (**Recommendation A1**)
- Primary care facilities for managing alcohol use disorders need to be made widely available (**Recommendation A1**)

Suggestions for future studies

(1) Large epidemiological studies using non-invasive methods should establish the prevalence of all forms of alcoholic liver disease in the general population.
(2) Studies evaluating the short and long-term impact of binge drinking in the development and severity of ALD are particularly needed.

Management of alcohol abuse and alcohol dependence

A large number of European citizens drink alcohol. Europe has the highest *per capita* alcohol consumption (11 L of pure alcohol per year in population $\geqslant$15 years old). Fifteen percent of Europeans (58 million citizens) drink excessively (>40 g per day in men, and >20 g per day in women), with a higher proportion among males and young people.

Alcohol abuse and alcohol dependence must be seen as different forms of the same disorder, as it is recognized in the new DSM-V draft. Alcohol abuse is not recognized as a disorder in the ICD-10, and in fact the WHO uses the terms hazardous and harmful alcohol use instead of alcohol abuse. The term 'risky drinker' is commonly used to define people who drink excessively.

Drinking habits of patients need to be routinely screened in patients with liver diseases, and this must be done with tools that have proven its reliability [16]. There is a common trend to measure alcohol intake in grams per day or grams per week. Calculations are usually made counting standard drink units [33]. The content of a standard drink may differ from country to country, but in Europe most of the countries have fixed their standard drink unit to an ethanol content of 8–10 g. Even though measurements in standard drinks may lose accuracy, they are reliable, save time, and are particularly useful in busy clinical settings.

Screening tools to detect alcohol abuse and dependence

Quantity-frequency questionnaires and retrospective diaries (time-line follow back) can be used to calculate patients' drinking habits. The former are usually preferred for their simplicity, but they must include data on both working and weekend days. A good alternative to quantity frequency questionnaires is the use of screening instruments to screen risky drinking and alcohol dependence. There are many tools that have been validated and translated into many languages, but the AUDIT (Alcohol Use Disorders Inventory Test) remains the 'gold standard'. Developed by the WHO in 1982, it has proven to have good sensitivity and specificity in clinical settings across different countries [34]. The AUDIT has 10 questions that explore consumption (1–3), dependence (4–6), and alcohol related problems (7–10) (Table 2). There are two cut-off points, one for dependence and one for risky drinking. Shorter versions have been developed. The AUDIT C includes just the first three questions of the AUDIT and is reliable for the screening of 'risky drinking' [35,36]. The NIAAA (National Institute of Alcohol Abuse and Alcoholism) recommends using the third question of the AUDIT (How often do you have six or more drinks in one occasion?) as a single screening question, which should be followed by the whole AUDIT in case the answer is rated positive [16].

Table 2. AUDIT questionnaire [36]. To score the AUDIT questionnaire, sum the scores for each of the 10 questions. A total ⩾8 for men up to age 60, or ⩾4 for women, adolescents, or men over age 60 is considered a positive screening test.

Questions	0	1	2	3	4
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2 to 4 times a month	2 to 3 times a week	4 or more times a week
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more
3. How often do you have 5 or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
4. How often during the last year you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
9. Have you or someone else been injured because of your drinking?	No		Yes, but not in the last year		Yes, during the last year
10. Has a relative, friend, doctor or other health care worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, during the last year

Screening of patients with psychiatric disorders

Alcoholics have a high psychiatric co-morbidity. In general, population surveys of alcoholics show high prevalence of anxiety disorders, affective disorders, and schizophrenia [37]. Anxiety and affective disorders may be independent or concurrent with alcohol dependence. Independent disorders will need specific treatment, while concurrent disorders may disappear once the patient is weaned off alcohol.

Alcoholics have a higher risk of developing other addictions, including nicotine. Alcoholics tend to be heavier smokers and the treatment of nicotine dependence requires more intensive support [38]. Alcoholics who are polydrug users are difficult to manage and should be systematically referred to specialized treatment.

Data suggest that alcohol dependence appears within 5 years before the patient is referred to specialist treatment. Special attention should be paid to the coordination between hepatologists and addiction specialists (psychiatrists, psychologists, and social workers) in order to reduce the gap between the signs of alcohol dependence appearing and referral. Because cigarette smoking and alcohol abuse are synergistic in causing cardiovascular diseases and cancer, including HCC, hepatologists are encouraged to promote and assist smoking cessation among patients with ALD [39].

Management of alcohol withdrawal syndrome

Alcohol withdrawal syndrome (AWS) is a severe medical condition affecting alcohol-dependent patients who suddenly discontinue or decrease alcohol consumption. Light or moderate AWS usually develops within 6–24 h after the last drink and symptoms may include increase in blood pressure and pulse rate, tremors, hyperreflexia, irritability, anxiety, headache, nausea, and vomiting. These symptoms may progress to more severe forms of AWS, characterized by delirium tremens, seizures, coma, cardiac arrest, and death [40]. Severity scores for AWS are potentially useful in the management of patients. However, these scores are insufficiently validated at this time, especially in the setting of ALD.

Benzodiazepines are considered the 'gold standard' treatment for AWS, given their efficacy to reduce both withdrawal symptoms and the risk of seizures and/or delirium tremens [41,42]. Long-acting benzodiazepines (e.g. diazepam, chlordiazepoxide) provide more protection against seizures and delirium, but short and intermediate-acting benzodiazepines (e.g. lorazepam, oxazepam) are safer in elderly patients and those with hepatic dysfunction [43]. In Europe, clomethiazole is also used to treat AWS [44].

Given the side-effects of benzodiazepines in patients with advanced liver disease and potential for abuse, preliminary research has been conducted to identify new medications for AWS, such as clonidine, atenolol, carbamazepine, valproic acid, gamma-hydroxybutyrate, topiramate, baclofen, gabapentin, and pregabalin [45]. Whilst sufficient evidence in favor of their use is lacking, topiramate and baclofen have promise given their potential to be used for AWS first [46,47], and then to prevent relapse.

Medical therapy of alcohol dependence in patients with ALD

Alcohol abstinence represents a critical goal in patients with ALD since abstinence improves the clinical outcomes of all stages of ALD. In the past, disulfiram was the only drug available for

alcoholism. Disulfiram represents an effective alcohol pharmacotherapy [48]; however, disulfiram should be avoided in patients with severe ALD because of possible hepatotoxicity [49]. More recently, the growing understanding of the neurobiology of alcoholism has led to the development of effective pharmacologic agents that can complement psychosocial treatments, in particular naltrexone [50] and acamprosate [51]. Both naltrexone and acamprosate are approved to treat alcoholism; however, these drugs have not been tested in patients with cirrhosis. The opioid antagonist naltrexone has been intensively evaluated, especially the oral formulation [52]. A large trial also showed the efficacy of an intramuscular formulation of naltrexone in alcoholism [53]. Given the potential for hepatotoxicity, naltrexone has not been tested in patients with ALD, and its use in this population is not recommended. Acamprosate is a modulator of the glutamatergic receptor system and a meta-analysis of 24 randomized controlled trials confirmed its efficacy as an alcohol pharmacotherapy [54]. Based on some clinical trials, gamma-hydroxybutyric acid was approved in some European countries (Italy and Austria) to treat alcoholism, but more research is needed, considering the risk of gamma-hydroxybutyric acid abuse [55].

Amongst other compounds, topiramate, ondansetron, and baclofen seem the most promising pharmacotherapies for alcoholism [56]. Topiramate is an anticonvulsant medication, which has demonstrated safety and efficacy in reducing heavy drinking [57]. There was also a decrease in liver enzyme levels in patients treated with topiramate [58]; however, topiramate has not been tested in patients with ALD. The 5-HT3 antagonist ondansetron has been shown to reduce drinking, but this effect was limited to 'early onset' alcoholics [59]. Some studies suggest that baclofen, a $GABA_B$ receptor agonist, increases abstinence rate and prevents relapse in alcohol-dependent patients [60]. Moreover, to date, baclofen represents the only alcohol pharmacotherapy tested in alcoholics with significant liver disease. Baclofen may represent a promising pharmacotherapy for alcohol-dependent patients with ALD. A clinical trial demonstrated the safety and efficacy of baclofen in promoting alcohol abstinence in alcoholic cirrhotics patients [61], but confirmatory studies in cirrhotic patients are warranted.

The effect of brief interventions

Brief interventions are often performed through motivational interviewing [62]. Motivational interviewing is a technique, which aims to be both non-judgmental and non-confrontational. Its success depends largely on the presentation of objective feedback based on information provided by the physician. The technique involves acknowledgement that individuals who attend a counseling session, assessment or prevention program may be at different levels of readiness to change their alcohol consumption patterns. The technique attempts to increase a patient's awareness of the potential problems caused, consequences experienced, and risks faced as a result of patterns of alcohol consumption. A meta-analysis found evidence for the positive impact of brief interventions on alcohol consumption and alcohol related morbidity and mortality [62]. The most recent Cochrane review shows that brief interventions are effective to reduce drinking by an average of 57 g per week in men [63]. Evidence is less conclusive in women and populations under 16 years of age. A brief intervention should at least have the components defined in the five As' model: Ask about use, Advice to quit or reduce, Assess willingness, Assist to quit or reduce and Arrange follow-up.

When a motivational component is added to brief interventions its efficacy improves [64]. Essential components of a motivational approach are an empathic attitude and a collaborative approach that respects the patients' autonomy and evoques from them ways to reach the goals agreed.

Recommendations

- Drinking habits of patients need to be routinely screened by physicians with tools which have proven their reliability
(**Recommendation A1**)
The AUDIT is the 'gold standard' screening test for alcohol abuse and dependence
(**Recommendation B1**)
- In patients with acute withdrawal syndrome and ALD, benzodiazepines are the treatment of choice
(**Recommendation A1**)
- In patients with ALD, persistent alcohol intake is associated with disease progression; therefore the most effective recommendation for these individuals is total alcohol abstinence
(**Recommendation A1**)
- Brief motivational interventions should be routinely used in the medical management of alcohol use disorders
(**Recommendation A1**)
- In alcohol-dependent patients without advanced ALD, disulfiram, naltrexone and acamprosate, combined with counseling, reduce alcohol consumption and prevent relapse
(**Recommendation A1**)
These drugs cannot be recommended in patients with advanced ALD because of the potential side-effets
(**Recommendation B1**)
- In patients with advanced ALD, recent studies suggest that baclofen is safe and effective to prevent alcohol relapse
(**Recommendation B2**)

Suggestions for futures studies

(1) Collaborative studies by multidisciplinary teams composed of epidemiologists, addiction specialists, and hepatologists are strongly encouraged.
(2) The impact of brief interventions on the prognosis of advanced ALD should be evaluated.
(3) More studies testing anti-craving drugs in the setting of advanced ALD are required.

Pathogenesis of ALD

The spectrum of ALD includes simple steatosis, alcoholic steatohepatitis (ASH), progressive fibrosis, cirrhosis, and the development of hepatocellular cancer (HCC). Although many individuals consuming more than 60 g of alcohol per day (e.g. 1/2 a bottle of wine or more than 1 L of beer) develop steatosis,

only a minority of the patients with steatosis progress to ASH and 10–20% eventually develop cirrhosis [65]. Genetic and non-genetic factors modify both the individual susceptibility and the clinical course of ALD [2]. The mechanisms of ALD are not completely understood. Most studies have been performed in rodents with chronic alcohol intake (e.g. Tsukamoto-French model or Lieber–DiCarli diet). However, these models basically induce moderate liver disease and non-severe fibrosis or liver damage develops. Few studies have been performed so far in livers from patients with ALD. These translational studies are needed to develop novel targeted therapies for these patients [2]. The pathogenesis varies in different stages of the disease.

Alcoholic fatty liver

There are four main pathogenic factors: (1) Increased generation of NADH caused by alcohol oxidation, favouring fatty acid and triglyceride synthesis, and inhibiting mitochondrial β-oxidation of fatty acids [66]. (2) Enhanced hepatic influx of free fatty acids from adipose tissue and of chylomicrons from the intestinal mucosa [66]. (3) Ethanol-mediated inhibition of adenosine monophosphate activated kinase (AMPK) activity [67] resulting in increased lipogenesis and decreased lipolysis by inhibiting peroxisome proliferating-activated receptor α (PPARa) [68] and stimulating sterol regulatory element binding protein 1c (SREBP1c) [69]. (4) Damage to mitochondria and microtubules by acetaldehyde, results in a reduction of NADH oxidation and the accumulation of VLDL, respectively [66].

Alcoholic steatohepatitis

Alcoholic fatty livers can develop parenchymal inflammation (mainly by PMN cells) and hepatocellular damage, a prerequisite for progress to fibrosis and cirrhosis. In cases of severe ASH episodes in patients with an advanced disease, ASH may cause profound liver damage, increased resistance to blood flow and it is also associated with a poor prognosis [70]. Various factors may contribute to the development of ASH (1) Acetaldehyde-induced toxic effects. It binds to proteins [71] and to DNA [72] resulting in functional alterations and protein adducts, which activate the immune system by forming autoantigens. It also induces mitochondria damage and impairs glutathione function, leading to oxidative stress and apoptosis [73]. (2) Reactive oxygen species (ROS) generation and the resulting lipid peroxidation with DNA adduct formation [74]. Main sources of ROS include CYP2E1-dependent MEOS, mitochondrial electron transport system of the respiratory chain, NADH-dependent cytochrome reductase, and xanthine oxidase [75,76]. Moreover, chronic alcohol intake markedly up-regulates CYP2E1, which metabolizes ethanol to acetaldehyde and parallels the generation of ROS and hydroxyl–ethyl radicals [77]. (3) Pro-inflammatory cytokines. Alcohol metabolites and ROS stimulate signaling pathways such as NFκB, STAT-JAK, and JNK in hepatic resident cells, leading to the local synthesis of inflammatory mediators such as TNFα and CXC chemokines (e.g. interleukin-8), as well as osteopontin [78]. Alcohol abuse also results in changes in the colonic microbiota and increased intestinal permeability, leading to elevated serum levels of lipopolysaccharides [79] that induce inflammatory actions in Kupffer cells via CD14/TLR4 [80]. The resulting inflammatory milieu in the alcoholic liver leads to PMN infiltration, ROS formation and hepatocellular damage. (4) Impaired ubiquitin–proteasome pathway leading to hepatocellular injury and hepatic inclusions of aggregated cytokeratins (i.e. Mallory–Denk bodies) [81].

Fibrosis progression

Patients with ASH may develop progressive fibrosis [82]. In ALD, the fibrotic tissue is typically located in pericentral and perisinusoidal areas. In advanced stages, collagen bands are evident and bridging fibrosis develops. This condition precedes the development of regeneration nodules and liver cirrhosis. The cellular and molecular mechanisms of fibrosis in ALD are not completely understood [83]. Alcohol metabolites such as acetaldehyde can directly activate hepatic stellate cells (HSC), the main collagen-producing cells in the injured liver. HSC can also be activated paracrinally by damaged hepatocytes, activated Kupffer cells and infiltrating PMN cells. These cells release fibrogenic mediators such as growth factors (TGFβ1, PDGF), cytokines (leptin, angiotensin II, interleukin-8, and TNFα), soluble mediators (nitric oxide), and ROS. Importantly, ROS stimulate pro-fibrogenic intracellular signaling pathways in HSC including ERK, PI3K/AKT, and JNK [84]. They also up-regulate TIMP-1 and decrease the actions of metalloproteinases, thereby promoting collagen accumulation. Cells other than HSC can also synthesize collagen in ALD. They include portal fibroblasts and bone-marrow derived cells. Whether other novel mechanisms such as epithelia-to-mesenchymal transition of hepatocytes also play a role in liver fibrosis is under investigation [85].

Suggestions for futures studies

(1) Experimental models of severe ALD with hepatocellular damage and fibrosis are needed.
(2) Translational studies with human samples of patients at different stages of ALD are required to identify new therapeutic targets.
(3) Studies assessing liver regeneration in severe ALD should be performed.

Risk factors for disease progression in alcoholic liver disease

Risk factors for fibrosis progression in ALD have been evaluated in two types of approaches: (1) comparisons of the prevalence of risk factors in patients with and without fibrotic ALD; (2) longitudinal evaluation using sequential histology. Risk factors for fibrosis progression can be thought of as host and environmental or genetic and non-genetic. Non-genetic or environmental factors that potentially modulate the development of ALD include the amount and type of alcoholic beverage, the duration of abuse and patterns of drinking. Gender, ethnicity, coexisting conditions such as metabolic syndrome, iron overload, and infection with chronic hepatitis viruses are important genetic or host factors, respectively (Fig. 1). Increasingly, the contribution of host genetic factors to the risk of ALD is being acknowledged.

There is a clear dose-relationship between the amount of alcohol and the likelihood of developing ALD. Alcoholic steatosis can be found in 60% of individuals who drink >60 g of alcohol per day and the risk of developing cirrhosis is highest in those with a daily consumption of above 120 g of alcohol per day [86,87]. However, lower daily amounts of alcohol may also lead to significant liver injury in some individuals. The consumption of >40 g

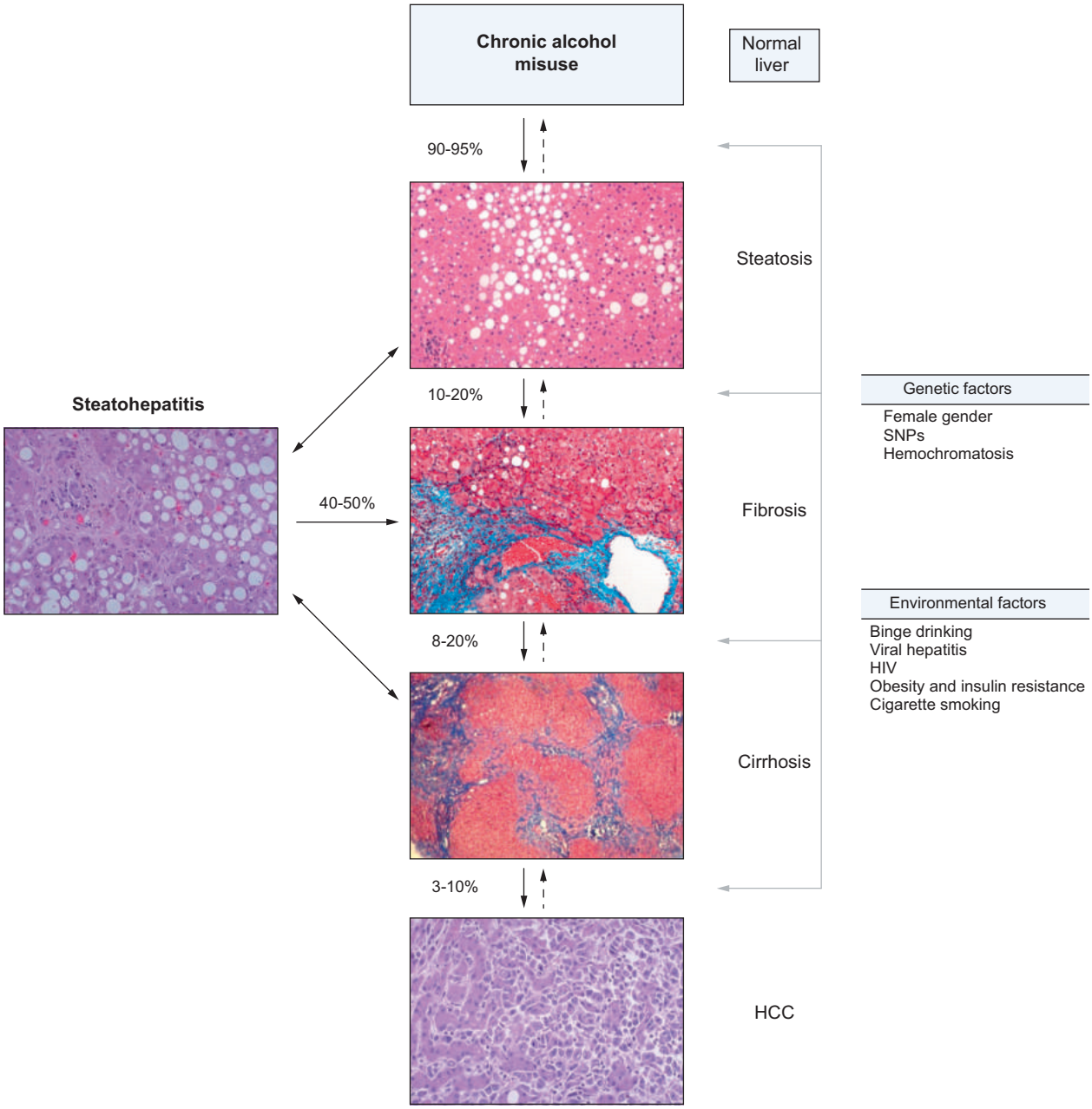

Fig. 1. Natural history of alcoholic liver disease (ALD). The spectrum of ALD is comprised of steatosis, steatohepatitis, fibrosis, cirrhosis, and superimposed hepatocellular carcinoma. Both environmental and genetic factors are known to modify the progression of ALD (adapted from [2] with permission from the American Gastroenterological Association).

of alcohol per day increases the risk of progression to liver cirrhosis to 30% in patients with uncomplicated alcoholic fatty liver, and to 37% in those with established alcoholic fibrosis [65]. Whether the type of alcoholic drink consumed, e.g. wine as opposed to beer or hard liquor, impacts the risk of ALD is still debated [88,89] and it is unclear whether the effect of different beverages on disease risk is direct or related to confounding factors, such as diet. Patterns of drinking vary substantially among patients with ALD and may influence the risk of ALD. While earlier studies indicated that binge drinking increases the risk of ALD [90,91], data from a recent prospective, single-center study suggested that recent increases in liver-related mortality in the UK are the result of daily or regular heavy drinking rather than due to episodic or binge drinking [92]. Drinking outside meals increases the risk of ALD compared to drinking only together with meals [87,93]. However, data on whether drinking patterns affect the likelihood of ALD evolution are sparse and information on alcohol consumption is largely restricted to total amounts [16]. A number of studies have also shown that caffeine intake appears to protect against cirrhosis in heavy drinkers, with a clear inverse dose–response effect [94–96]. However, the mechanism behind this correlation is unknown.

Studies in humans have demonstrated that women are more susceptible towards the hepatotoxic effects of alcohol, and

develop ALD more quickly than men when daily alcohol consumption is equal [86,97–100]. The pathophysiology behind this increased sensitivity to alcohol is not yet fully understood, but is probably related to oestrogens and their synergistic impact on oxidative stress and inflammation [101]. In addition, women drinking equal amounts of alcohol exhibit higher blood ethanol levels than men. This difference is possibly due to higher gastric alcohol dehydrogenase levels resulting in a faster first-pass metabolism of alcohol in men [102] or to a lower volume of distribution for alcohol in women compared with men.

There are notable differences in the prevalence of ALD and associated mortality among different ethnic groups [103–105]. The highest mortality rates of alcoholic cirrhotics for men are found in white Hispanics, followed by black non-Hispanics, white non-Hispanics, and black Hispanics. In women, the order is black non-Hispanics, white Hispanics, white non-Hispanics, black Hispanics [106]. However, it remains unclear whether ethnic differences in rates of alcoholic cirrhosis and ALD are due to genetic differences or differences in the amount and type of alcohol consumed or related to differences in socioeconomic status and access to medical care.

The most significant, diet-related risk factor for fibrosis progression appears to be obesity, with several studies showing that obesity is the single most important risk factor determining the risk of cirrhosis in heavy drinkers [107,108]. The synergy between obesity and heavy alcohol intake presumably reflects similar mechanisms of disease for both ALD and non-alcoholic fatty liver disease, along with the direct fibrogenic effects of expanded larger mass of adipose tissue (via high levels of noradrenaline, angiotensin II and leptin, and low levels of adiponectin).

Numerous case-control, cross-sectional, and cohort studies have unequivocally shown that coexistence of alcohol misuse and chronic hepatitis C virus infection leads to an acceleration of liver injury [109–113]. From these data it can be concluded that individuals with chronic hepatitis C who drink more than 30–50 g per day increase their risk of developing fibrosis approximately 4-fold. However, one study has even quantified the risk of cirrhosis as 30 times greater in patients with hepatitis C who consume alcohol to excess [114].

Iron in liver biopsies has also been associated with fibrosis in ALD [108] and increased mortality in alcoholic cirrhosis [115]. Elevated serum iron indices are not uncommon in ALD patients, more so than in alcohol misusers without liver disease [115]. However, there is no clear association with the C282Y *HFE* gene mutation. Some studies have described an association with the H63D mutation [116,117]. Certainly alcohol and iron can act synergistically to produce oxidative stress and thus potentiate progressive liver damage.

Studies of twins have indicated the importance of genetic susceptibility to ALD, demonstrating that monozygotic twins have a higher concordance rate for alcohol-related cirrhosis than dizygotic twins [118,119]. Such studies suggest that genetic factors may represent up to 50% of an individual's susceptibility to ALD. In an attempt to identify possible genetic modifiers of the risk of ALD, a large number of hypothesis-driven, candidate gene case control studies have been performed. These compared the allelic and/or genotypic frequencies of certain genetic variants (i.e. single nucleotide polymorphisms; SNP) between alcoholic cirrhosis and alcoholics without liver disease or healthy controls. In the majority of publications, chosen candidate genes were those associated with alcohol metabolism, fibrogenesis/fibrolysis, or with the inflammatory response. A meta-analysis reviewed studies on associations between SNPs in genes coding for alcohol and aldehyde dehydrogenases, and cytochrome P450 2E1 and retrieved 50 case control studies between 1990 and 2004 [120]. While there were significant associations between certain genetic variants and the risk of alcoholism, no overall association of any of the tested SNPs with alcoholic cirrhosis was detected. Studies on a possible association between ALD and genetic variation of the antioxidant response, cytokines, and others also failed to robustly confirm any of the genetic variants as risk factors for ALD in independent cohorts [121]. However, recently, two candidate gene case control studies in alcoholics found a significant association between the risk of alcoholic cirrhosis and carriage of genotype *PNPLA3* rs738409 (GG) in Mestizo subjects [122] and Caucasians [123].

Suggestions for future studies

(1) Large genome-wide association studies should identify the genetic determinants implicated in individual susceptibility to develop ALD.
(2) The interaction between environmental and genetic factors should be investigated.
(3) Additional studies are required to identify the factors influencing disease regression after drinking cessation and long-term outcome in abstinent patients.

Diagnosis of ALD

Histological features of ALD

The morphological spectrum of ALD encompasses four groups of elementary lesions: (a) steatosis with a predominant future of macro-vesicles, associated or not with a variable blend of macro- and micro-vesicles, (b) hepatocyte damage often described as ballooning, (c) an inflammatory infiltrate which predominates in the lobules, and (d), a variable degree of fibrosis and lobular distortion which may progress to cirrhosis. [124]. In a given individual, a single lesion or any other combination of the other elementary lesions may be found [125,126].

The prevalence and distribution of histological lesions among heavy drinkers is not well known. In a large series of 1407 patients admitted for alcoholism or ALD undergoing a liver biopsy, 14% of patients had normal liver, 28% pure steatosis, 20% fibrosis (with or without steatosis), 8.5% alcoholic hepatitis, and 29% cirrhosis [107]. Further studies among asymptomatic heavy drinkers should be performed.

Among the histological lesions of ALD, macrovesicular steatosis is the earliest and most frequently seen pattern of alcohol-induced liver injury [127]. Whether simple steatosis is a benign condition or can progress to more severe forms of ALD is a matter of debate. Some studies suggest that steatosis should no longer be considered a benign condition since cirrhosis may occur after a median of 10.5 years in 10% of patients with a histological diagnosis of simple steatosis without evidence of fibrosis or alcoholic steatohepatitis [128]. Other studies also suggested that steatosis, a common finding in active drinkers, is associated with more rapid progression of fibrosis.

Alcoholic steatohepatitis is defined by the coexistence of steatosis, hepatocyte ballooning and an inflammatory infiltrate with polymorphonuclear neutrophils. The presence of Mallory–Denk's bodies, and mega-mitochondria, although not specific to alcoholic steatohepatitis, are often associated with the elementary lesions described above. However, the presence of these lesions in a patient with ALD suggests active drinking.

The development of fibrosis is a key event in ALD since it is a prerequisite for the progression to cirrhosis. Fibrosis progression varies according to the histological lesions of ALD [128–131,99,132]. Alcoholic hepatitis, steatosis, and the extent of fibrosis are independent, predictive factors of fibrosis progression. Among those lesions, patients with ASH exhibited the highest risk of fibrosis progression leading to the development of cirrhosis in at least 40% of cases [129,130,99,133–135]. The persistence of ASH over a long period may accelerate the progression of fibrosis [135]. The ultimate stage of fibrosis is micro-nodular cirrhosis, which may occasionally be mixed micronodular and macronodular [126]. The assessment of the degree of fibrosis should be performed using special techniques, such as trichromic or Sirus red staining. Reticulin staining is advisable to assess both the extent of fibrosis and lobular architecture. Although semi-quantitative methods such as the Metavir scale are encountered, they are not validated in the setting of ALD.

Histological diagnosis of ALD requires a liver biopsy. It can be done percutaneously in most patients and requires a transjugular approach in patients with a low platelet count and/or a prolonged prothrombin time. However, liver biopsy is an invasive procedure with significant morbidity. Therefore, it is not recommended for all patients with suspected ALD. The precise indications of liver biopsy are not well established in routine practice. However, it is indicated in patients with aggressive forms of ALD such as severe steatohepatitis requiring specific therapies (e.g. corticosteroids and/or pentoxiphylline) and in patients with other cofactors suspected of contributing to liver disease. In the setting of clinical trials, the assessment of liver histology by performing a liver biopsy is recommended. Importantly, the assessment of liver histology allows a better prediction of the patient's outcome. Thus, it allows the risk of long-term mortality prognosis of patients with ALD to be classified according to the severity of the histological lesions [136]. An increase in mortality of at least 50% is observed in patients with histological diagnosis of ASH or cirrhosis as compared to those with only alcoholic steatosis [137].

Clinical diagnosis of ALD

Most patients with moderate forms of ALD are asymptomatic and it can only be detected by appropriate screening methods. Some patients can show signs suggestive of harmful alcohol drinking such as bilateral parotid gland hypertrophy, muscle wasting, malnutrition, Dupuytren's sign, and signs of symmetric peripheral neuropathy. In patients with cirrhosis, most physical findings are not specific of the etiology. However, some signs such gynecomastia and extensive spider angiomas may be more frequently seen in those with alcohol as the main cause of liver disease.

The diagnosis of ALD is frequently suspected upon documentation of excess alcohol consumption >30 g/d and the presence of clinical and/or biological abnormalities suggestive of liver injury. However, screening of ALD is difficult as significant proportions of patients with histological features of ALD do not show any clinical symptoms. Routine blood tests such as mean corpuscular volume (MCV), gamma glutamyl transpeptidase (GGT), glutamic oxaloacetic transaminase (GOT), and glutamic pyruvic transaminase (GPT) can indicate early ALD whereas advanced ALD is suspected if there is decreased albumin, prolonged prothombin time, increased bilirubin level or thrombocytopenia.

Although no single laboratory marker definitely establishes chronic alcohol consumption, carbohydrate deficient transferrin (CDT) and GGT are the most frequently used markers to detect previous alcohol consumption [138]. Indeed, the sensitivity for detection of daily ethanol consumption >50 g of CDT (69%), and GGT (73%) are higher than those of AST (50%), ALT (35%), and MCV (52%) [139]. The specificity of CDT was 92%, compared with 75%, 82%, 86%, and 85% for GGT, AST, ALT, and MCV, respectively [139]. As the measurement of GGT is easy and inexpensive, it remains the most frequently used marker for early detection of chronic alcohol misuse [140]. GGT is usually higher in ALD patients compared with those who have other liver diseases. However, serum GGT activity loses its specificity for alcohol in more advanced liver disease because its activity is elevated in patients with extensive fibrosis regardless of the cause [141,142]. More recently, it has been shown that serum GGT activity is influenced not only by the amount of alcohol consumed but also by body mass index (BMI) and sex [143].

Elevation of aspartate amino transferase (AST) may be observed in all forms of ALD with a sensitivity of 50% and a specificity of around 80%. AST levels are rarely above 300 IU/ml, while serum alanine aminotransferase (ALT) levels are commonly lower. The AST/ALT ratio typically is greater than 1 [144,145], although this finding is neither specific nor sensitive and it has also been shown to be an indirect marker of advanced fibrosis [146].

Non-invasive tests to estimate liver fibrosis

Serum markers

Several new blood tests combining different biomarkers of fibrosis are now available. Although these tests were initially designed for patients with hepatitis C, some of them seem to be efficient in patients with ALD. However, different cut-offs may have to be considered when using such biomarkers for ALD instead of hepatitis C.

Aspartate aminotransferase (AST) to platelet ratio index (APRI) has been evaluated in heavy drinkers. A total of 1308 subjects from two studies of ALD were evaluated, with a liver biopsy available from 781 non-cirrhotic patients and a history of decompensation in 527 patients [147]. In 507 patients with biopsy-confirmed fibrosis, the sensitivity of APRI for significant fibrosis was 13.2% and the specificity was 77.6%. Twenty percent were misclassified. Thus, APRI may be of limited use in the diagnosis of fibrosis in many patients.

FibroTest® is a serum biomarker of fibrosis combining alpha-2-macroglobulin, haptoglobin, GGT, ApoA1, and bilirubin, corrected for age and sex [141]. It seems to have high diagnostic potential for the detection of significant fibrosis in patients with ALD. In a study of 221 consecutive patients with biopsy-proven ALD, the mean FibroTest® value ranged from 0.29 in those without fibrosis to 0.88 in those with cirrhosis and its AUROC for the diagnosis of cirrhosis was at 0.95 [148]. FibrometerA®, combining PT, alpha-2-macroglobulin, hyaluronic acid, and age has similar diagnostic accuracy in ALD [149]. In the validating step, the

Fibrometer® AUROC curve was 0.892 in overall patients and 0.962 in patients with ALD. Hepascore® combines bilirubin, GGT, hyaluronic acid, alpha-2-macroglobulin, age, and sex. The diagnostic accuracies of Fibrotest®, Fibrometer®, and Hepascore® were compared in patients with ALD [136]. The diagnostic values of FibrometerA® and Hepascore® did not differ from that of FibroTest® for advanced fibrosis (AUROCs around 0.80) and cirrhosis (AUROCs around 0.90), and were significantly greater than those of non-patented biomarkers (APRI, Forns, FIB4). The combination of any of these tests was useless in improving diagnostic performance [136].

In addition to their diagnostic performance in the screening of fibrosis, non-invasive tests may be useful in predicting liver-related mortality as shown in a study of patients with ALD followed-up for more than 8 years, where survival was correlated with baseline non-invasive fibrosis score [136]. ELF®, a panel of sensitive automated immunoassays to detect matrix constituents and mediators of matrix remodeling in serum [150] may also predict clinical outcomes in patients with chronic liver disease on long term follow-up [151]. However, its utility has not been fully evaluated in large cohorts of alcoholic patients.

Transient elastography (Fibroscan®)

Liver stiffness measurement (LSM) has been demonstrated to be a reliable tool for assessing hepatic fibrosis in patients with ALD [152–157]. In patients with ALD, liver stiffness correlates with the degree of fibrosis. In the studies that did not consider the presence of ASH as a potential confounding factor, the cut off values for F3 and F4 fibrosis were considerably higher as compared to patients with viral hepatitis. In this regard, several studies have shown that patients with alcoholic cirrhosis had significantly higher values of liver stiffness than patients with viral cirrhosis, suggesting that the etiology may strongly affect the amount of fibrosis at the same stage. However, a recent study indicated that coexisting ASH markedly increases LSM in patients with ALD independent of fibrosis stage [152,158].

The existence of inflammation, cholestasis or liver congestion may interfere with LSM, independently of fibrosis [159]. Since all these conditions may occur during ALD, LSM should always be interpreted in the context of clinical, imaging and laboratory findings. A decision tree, taking into account those parameters has been proposed for the use of transient elastography in heavy drinkers [158]. Importantly, elevated liver stiffness values in patients with ALD and ASAT serum levels >100 U/L should be interpreted with caution because of the possibility of falsely elevated liver stiffness as a result of superimposed ASH [152]. In addition, alcohol consumption may also modify LSM as shown by the decrease in liver stiffness among abstainers and the increase in relapsers [152,160].

Hepatic imaging techniques

Imaging techniques such as ultrasonography, MRI, and CT may allow the detection of fatty liver, help exclude other causes of chronic liver disease and contribute to the assessment of advanced liver disease and its complications independent of the etiology [161]. However, imaging studies do not have a role in establishing alcohol as the specific etiology of liver disease.

Steatosis may be screened using ultrasonography, CT, and MRI. Among those methods, ultrasound probably has the lowest sensitivity and specificity, especially when steatosis is below a threshold of 20–30%. MRI and MR spectroscopy are reliable tools for assessing the amount of steatosis but the standardization of sequence characteristics are not established and their cost and availability are limiting [162,163].

In clinical practice, ultrasonography may be proposed in heavy drinkers as a screening procedure for steatosis [164]. Ultrasonography can also be useful in detecting signs of advanced stages of ALD such as liver dysmorphy, portal-systemic collaterals and splenomegaly.

Recommendations

- Presence of ALD can be suspected based on clinical, biological, and ultrasound parameters. Nevertheless, histology is required for confirmation of the diagnosis and evaluation of the severity of ALD (**Recommendation B1**)
- Liver biopsy should be considered in patients with aggressive forms of ALD requiring specific interventions, in patients with cofactors suspected to contribute to liver disease and in the setting of clinical studies (**Recommendation B1**)

Suggestions for future studies

(1) Longitudinal studies using non-invasive tools should evaluate disease progression both in persistent heavy drinkers and after abstinence.
(2) New histological scoring systems integrating steatosis, steatohepatitis, and fibrosis should be specifically developed for patients with ALD.
(3) Future studies are warranted to propose and validate diagnostic algorithm including liver biopsy and non-invasive tests.

Alcoholic hepatitis (alcoholic steatohepatitis)

Definition, incidence, and diagnosis

Alcoholic hepatitis is a clinical syndrome, i.e. recent onset of jaundice and/or ascites in a patient with ongoing alcohol misuse. Historically, it was referred to as ''acute alcoholic hepatitis''. Although the clinical presentation may present abruptly, the term ''acute'' is not recommended, since it is an exacerbation of an underlying chronic liver disease and usually follows an extended course. ASH, a disease defined histologically, is the predominant cause of this syndrome, which can also result from infection, massive micro-vesicular steatosis, stone migration, drug-induced liver injury, etc. ASH is defined by the coexistence of steatosis, hepatocyte ballooning, and an inflammatory infiltrate with PMNs. The lesions defining alcoholic steatohepatitis do not differ in essence from those described in non-alcoholic steatohepatitis. ASH, however, is usually associated with more severe clinical course and histological lesions than NASH.

The annual incidence of ASH remains largely unknown. A retrospective Danish study based on diagnosis codes estimated the incidence to range from 24 to 46 per million in women and

men, respectively [165]. Concerning its prevalence, a large study using systematic biopsies in 1604 alcoholic patients, symptomatic or not, showed the prevalence of ASH to be 20% of cases [107]. In symptomatic patients including those with decompensated liver disease, the prevalence of ASH is not well known, partly because most centers rely on clinical criteria and do not consider transjugular liver biopsy as a routine practice in the management of patients with decompensated ALD. Relying only on clinical criteria carries a 10–50% risk of wrongly classifying patients with or without ASH [166–168]. In a recent prospective cohort study of 250 patients, histological proven severe ASH was observed in 6% of the patients with a chronic hepatic decompensation and in 25% of the patients who developed an acute-on-chronic liver failure during admission [169].

Progressive jaundice is the main presenting feature of symptomatic ASH. It may be associated with fever with or without infection, weight loss and malnutrition, and a large tender liver. In severe cases, ASH may induce liver decompensation with ascites, encephalopathy, and gastrointestinal bleeding. With respect to biological tests, AST levels are typically elevated to 2–6 times the upper limit of the normal range with AST/ALT ratio greater than 2 and increased bilirubinemia and neutrophilia are also frequently observed. Depending upon the severity, serum albumin may be decreased, prothombin time prolonged and the international normalized ratio (INR) may be elevated. Patients with severe forms of ASH are prone to develop bacterial infection and acute renal failure due to Type 1 hepatorenal syndrome [170].

Prognostic models in alcoholic steatohepatitis

Prognostic models have been designed to identify patients with ASH at high risk of early death 1–2 months after hospitalization. The Maddrey discriminant function (DF) was the first score to be developed and remains the most widely used. Severe forms of ASH are defined as DF $\geqslant$32 [171,172]. In the absence of treatment, the 1-month spontaneous survival of patients with a DF $\geqslant$32 has fluctuated between 50% and 65% [172,173].

Other prognostic scores such the MELD (Model for End-Stage Liver Disease), the GAHS (Glasgow ASHScore) and the ABIC score (age, serum Bilirubin, INR, and serum Creatinine score) have been proposed in the setting of ASH. The initial studies testing those scores suggest higher diagnostic accuracy in predicting 28-day and 90-day outcome than DF, but external validation is still required and the proposed cut-off of those scores need to be tested outside the initial population of their development [174–177].

It is important to stress that actual definition of severe forms is only based on two categories (severe versus non-severe) and early mortality risk. However, a proportion patients classified as having "non-severe ASH" die at later time points (i.e. up to 6 months). The ABIC score classified patients according to low, intermediate and high risk of death [174]. Such classification will permit the evaluation of drugs and help to calculate the sample size for such purpose.

Early improvement in liver function has a major impact on short-term mortality [254]. Several studies have demonstrated the utility of repeated testing and calculation of prognostic scores [175–177]. For example, a $\geqslant$2 points change in the MELD score in the first week has been shown to predict in-hospital mortality [177]. A similar observation was obtained with the Lille score which includes the reduction in serum bilirubin at day 7 [178]. Based on a recent meta-analysis of individual patient data using 2 new cut-offs of the Lille score, three prognostic groups predicting the 6-month survival could be defined [179].

Management of ASH

General measures

Regardless of the severity, abstinence is the cornerstone of therapy and early management of alcohol abuse or dependence is warranted in all patients with ASH. Malnutrition is frequent and nutrition status should be evaluated. Considering the potential risk of Wernicke's encephalopathy, supplementation with B-complex vitamins is recommended. Independent from hepatic encephalopathy, a daily protein intake of 1.5 g/kg of body weight should be ensured. Liposoluble vitamins deficiency should be compensated.

Patients with symptomatic forms of ASH often develop acute renal failure which negatively impacts survival [170]. The most frequent causes of acute renal failure are Type 1 hepatorenal syndrome and tubular necrosis whereas glomerulonephritis or interstitial nephritis are uncommon [180]. Severe forms of ASH should be considered as a risk factor of radiocontrast-induced nephropathy. Measures aimed at preventing the development of renal failure are recommended. They include volume expansion if needed and early treatment of hepatorenal syndrome.

Infections are frequent and difficult to diagnose in these patients since SIRS criteria is common at admission and could reflect either the inflammatory state associated with the ASH episode or an ongoing bacterial infection. Systematic body fluid sampling and close clinical monitoring are advised for early detection of infection. In the absence of scientific evidence, criteria for initiating empirical antibiotic administration, although it is widely used, remain debated. In patients with severe ASH, infection screening at admission is particularly warranted because a quarter of them are infected at admission [181]. Patients with severe ASH and clinical or biological deterioration during their hospital stay disclose a even higher risk of infection and should be screened repeatedly.

Specific therapy in severe forms of alcoholic steatohepatitis

The following recommendations apply only to severe forms of ASH, as defined using the above prognostic scores predicting a high risk of early death (Table 3, Fig. 2).

Corticosteroids

Meta-analyses of the literature yielded inconsistent results than can be mainly attributed to the wide variations in disease severity [182]. Three meta-analyses concluded that the survival effect of corticosteroids was restricted to severe disease [183–185], whereas Cochrane meta-analyses questioned the efficacy of corticosteroids in AH [186,187]. The most recent Cochrane meta-analysis reported that corticosteroids significantly reduced mortality in the subgroup of trials that enrolled patients with a DF of at least 32 or hepatic encephalopathy [187]. Analysis of individual data from the five most recent randomized controlled trials [168,172,173,188,189] showed that patients allocated to corticosteroid treatment had higher 28-day survival than patients allocated to non-corticosteroid treatment [179].

Most studies indicate that only a limited proportion of patients with severe forms of ASH benefit from corticosteroids.

Table 3. Comparison of the elements that constitute 5 prognostic instruments in alcoholic hepatitis (adapted from [254]).

	Bilirubin	PT/INR	Creatinine/ urea	Leucocytes	Age	Albumin	Change in bilirubin from day 0 to day 7
Maddrey score	+	+	-	-	-	-	-
MELD score	+	+	+	-	-	-	-
GAHS score	+	+	+	+	+	-	-
ABIC score	+	+	+	-	+	+	-
Lille score	+	+	+	-	+	+	+

Maddrey score, Maddrey discriminant function; GAHS, Glasgow Alcoholic Hepatitis Score; ABIC score, age, serum Bilirubin, INR, and serum Creatinine (ABIC) score; MELD score, Model-for-End-Stage-Liver-Disease score.

Thus, early identification of non-responders to corticosteroids is important to define stopping rules [190] and limit unnecessary exposure [178]. For example, after 7 days on corticosteroids, a Lille score above 0.45 predicts poor response [178]. In poor responders, the interruption of corticosteroids is recommended particularly in those classified as null responders (Lille score >0.56) [179]. In poor responders, an early switch to pentoxifylline [191] or the use of a molecular adsorbent recirculating system (MARS) appears not to modify the outcome. Novel therapies are urgently needed for poor responders. In these patients, early liver transplantation may be considered after a careful selection process [192].

The applicability of corticosteroid therapy is limited by concerns about heightened risks of sepsis and gastrointestinal hemorrhage. Patients with gastrointestinal bleeding [184] or hepatorenal syndrome may be less responsive to steroid treatment than patients without these complications. In such circumstances, the outcome of patients may be related to these complications rather than to ASH itself. Up to now, in severe AH, infection has classically been viewed as a contraindication for corticosteroid treatment, although specific data are lacking. In patients with sepsis, pentoxifylline can be considered as a first line therapy. However, a recent study suggests that corticosteroid treatment may not be precluded in patients with infection after appropriate antibiotic therapy [181].

Pentoxifylline

Pentoxifylline has been evaluated in patients with ASH for its antioxidant and anti-TNF properties. When compared to placebo, patients with severe AH (DF $\geqslant$32) treated with pentoxifylline exhibited a higher 6-month survival. This survival benefit was not accompanied by significant changes in liver function but related to a marked reduction in the incidence of hepatorenal syndrome [193]. One subsequent randomized controlled trial in patients with cirrhosis related or not with ALD also supported the preventive effect of pentoxifylline on hepatorenal syndrome [194]. However, a sensitivity analysis restricted to the subgroup of patients with severe AH (DF $\geqslant$32), failed to show a significant difference in survival between the pentoxifylline and placebo treated patients.

One study comparing pentoxifylline to corticosteroids observed better outcome in pentoxifylline-treated patients, which was related to prevention of hepatorenal syndrome [195]. A recent, large randomized controlled trial of 270 patients with severe AH testing the combination of prednisolone and pentoxifylline (PTX) failed to show any benefit over corticosteroids alone [196].

Anti-TNF agents

A pilot randomized study in patients with severe ASH showed that single dose infliximab in combination with corticosteroids was well tolerated and associated with a significant improvement in Maddrey's score at day 28 [197]. However, the size of this study did not allow comparison with a control group [198]. However, the effectiveness of anti-TNFα was not confirmed in two randomized controlled trials testing multiple doses of infliximab [199] or etanercept [200]. In fact, anti-TNFα treatment was associated with a higher probability of severe infections and deaths. It may be speculated that repeated or excessive TNF blockade negatively affects liver regeneration.

N-acetylcysteine

N-acetylcysteine is an antioxidant substance and replenishes glutathione stores in hepatocytes. In a randomized controlled trial of N-acetylcysteine alone versus placebo there was no evidence of a significant effect [201]. In another randomized trial, N-acetylcysteine alone was inferior to corticosteroids in terms of short-term survival [173]. More recently, a randomized controlled trial observed that patients treated with combination therapy (corticosteroids and N-acetylcysteine) had better 1-month survival than patients treated with corticosteroids alone [202]. The rates of hepatorenal syndrome and of infection were lower in patients treated with corticosteroids and N-acetylcysteine. However, there was no significant difference in survival between the two groups at 6-months, the primary planned end point. Therefore, corticosteroids and N-acetylcysteine may have synergistic effects. This strategy and the question of optimal duration of N-acetylcysteine administration should be evaluated in additional studies.

Enteral nutrition

Malnutrition due to impaired caloric intake and increased catabolism is frequent in patients with ASH. The recommended protein-caloric intake is often difficult to achieve orally in a significant proportion of patients with ASH.

A randomized controlled trial comparing enteral nutrition versus corticosteroids did not show any difference in 28-day mortality rate [203]. However, deaths occurred earlier with enteral nutrition whereas steroid therapy was associated with a higher mortality rate in the weeks following the treatment period. Enteral nutrition probably deserves to be tested in combination with corticosteroids.

Other therapies

There are no randomized studies evaluating extracorporeal liver supports, although pilot studies reported improvement in

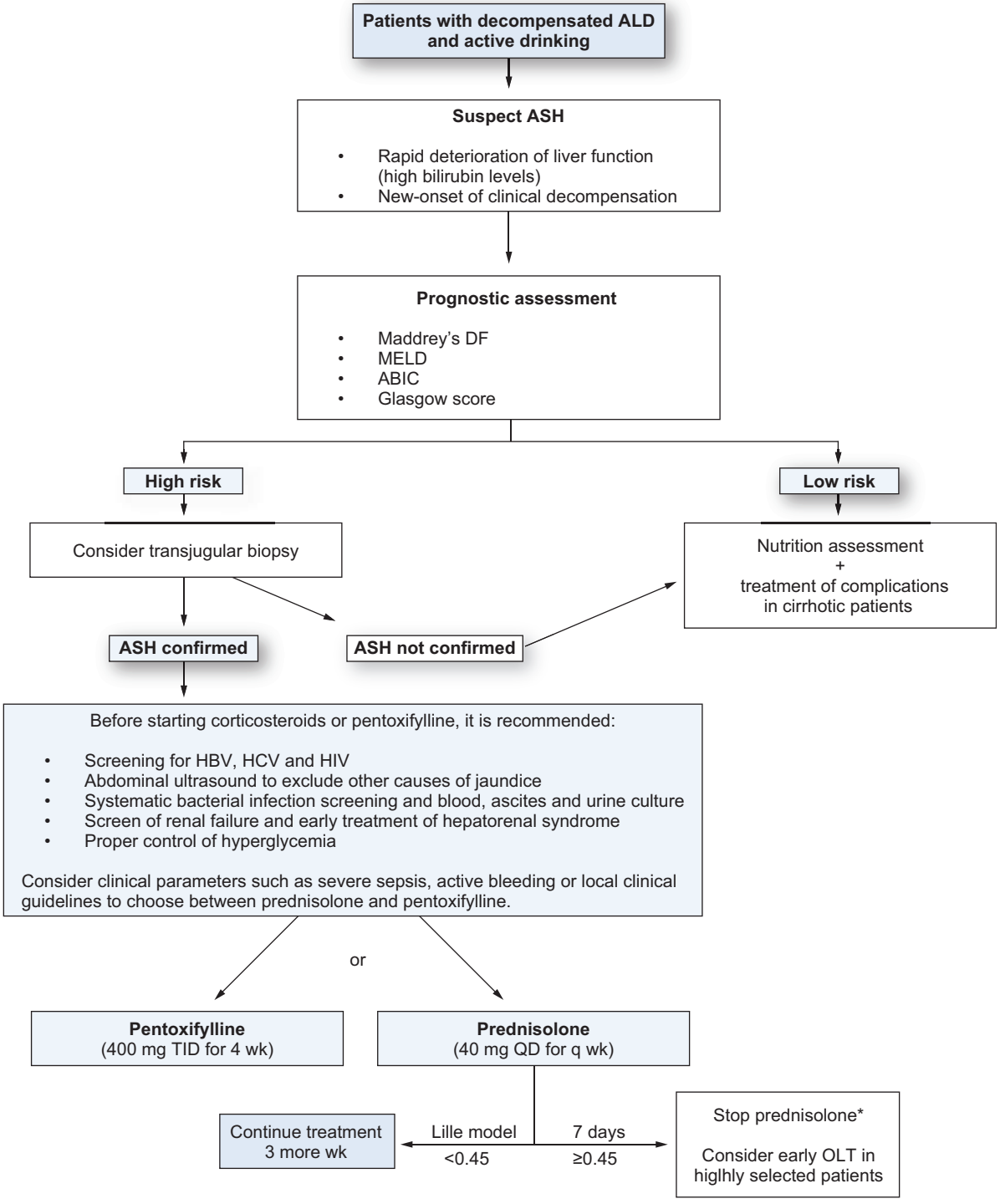

Fig. 2. Therapeutic algorithm for the treatment of patients with alcoholic steatohepatitis (ASH). *A Lille score ⩾0.45 indicating non-response and increased risks of infection and death. In non responders, the interruption of corticosteroids is recommended particularly in those classified as null responders (Lille score >0.56).

circulatory disturbances, liver, and renal parameters. None of these studies have a sufficient sample size to draw any conclusions regarding the use of these systems as a therapeutic option in patients with severe forms of ASH [204].

Three randomized controlled trials did not observe significant effects of propylthiouracil on short-term survival in patients with ASH [205–207]. Two studies did not observe any effect of colchicine on short-term survival [208,209]. Thus, evaluation of

propylthiouracil or colchicine is no longer recommended in future studies evaluating short-term survival.

Need for future studies

The treatment of ASH remains controversial and is one of the main challenges in ALD [170]. Short-term survival has been the primary outcome of studies evaluating therapy in severe forms of ASH. However, assuming a one or two-sided type I error $\leqslant 0.05$ and a power $\geqslant 80\%$, this approach requires huge, unrealistic sample sizes. To overcome this limitation, it may be relevant to consider alternative end points, including early markers of poor outcome and/or combinations of criteria.

Little therapeutic information has been collected in patients with intermediate risk of death who are currently exempt from most clinical trials. Therefore, studies with appropriate designs and end points should focus on this patient population.

Recommendations

- Onset of decompensation in ALD should prompt clinicians to suspect superimposed ASH (**Recommendation B1**)
- Although the presence of ASH can be suspected on clinical and biochemical grounds, a definite diagnosis of ASH requires a liver biopsy (**Recommendation A1**)
- Available scoring systems should be used to identify patients with severe ASH at risk of early death, i.e. within 1-3 months (**Recommendation A1**)
- Renal function and incidence of infection should be closely monitored in patients with severe ASH (**Recommendation A1**)
- First-line therapy in patients with severe ASH includes corticosteroids or, in case of ongoing sepsis, pentoxifylline (**Recommendation B1**) (Fig. 2)
- Early non-response to steroids should be identified and rules for the cessation of therapy should be considered (**Recommendation B1**) (Fig. 2)
- N-acetylcysteine may be useful in patients with severe ASH receiving corticosteroids (**Recommendation B2**)

Suggestions for future studies

(1) Development of non-invasive tools for the diagnosis of ASH is of major interest.
(2) Use of primary end points other than short-term mortality should be encouraged to facilitate testing of new therapies in patients with ASH.
(3) Future studies should also focus on patients with ASH of intermediate severity since they have substantial mortality at 6-months.
(4) Translational studies should identify the molecular patterns, including liver inflammation and regeneration signaling, associated with differences in outcomes.

Alcoholic cirrhosis

Clinical course

Progressive ALD can lead to alcoholic cirrhosis, which is defined by the occurrence of extensive fibrosis and regenerative nodules. In some patients, alcohol abuse coexists with other known causes of liver disease, such as hepatitis C and B virus infection, as an etiological agent of liver cirrhosis. As with other etiologies, patients with alcoholic cirrhosis are prone to develop clinical decompensations due to portal hypertension and liver failure and are at risk for developing HCC [210]. The clinical course of alcoholic cirrhosis is influenced by the pattern of alcohol intake. Thus, periods of excessive alcohol intake can lead to superimposed ASH and the subsequent clinical exacerbations, while prolonged abstinence can compensate previously complicated cirrhosis.

Population-based studies indicate that only about one third of patients with alcoholic cirrhosis are hospitalized before decompensation [210,211], and in the first year thereafter these patients have an approximate 20% risk of developing ascites, a 6% risk of variceal bleeding, and a 4% risk of hepatic encephalopathy [211, 212]. Ascites is typically the first complication [211,212], but other complications such as jaundice, variceal bleeding, and hepatic encephalopathy are also prevalent [70,211,212]. Importantly, patients with alcoholic cirrhosis are particularly prone to bacterial infections [213]. The incidence of HCC among patients with alcoholic cirrhosis ranges range from 7% to 16% [214] after 5 years to as much as 29% after 10 years. Therefore, screening for HCC should be performed as recommended for any patient with liver cirrhosis. Importantly, patients with alcoholic cirrhosis should be screened for alcohol-induced damage in other organs including the heart (alcoholic myocardiopathy), kidney (IgA-induced nephropathy), nervous system (central and peripheral involvement), and the pancreas (chronic pancreatitis). Importantly, in patients with impaired cognitive function, the existence of alcoholic dementia, withdrawal syndrome, and Wernike's encephalopathy should be ruled out. Patients with alcoholic cirrhosis are often malnourished. A careful clinical and analytical evaluation of the nutritional status is advised and proper nutrition should be ensured. In severe cases, the help of a dietitian is recommended.

Population-based studies following patients from hospital diagnosis of alcoholic cirrhosis have shown 1- and 5-year mortality risks around 30% and 60%, respectively [211]. Among the complications defining decompensated cirrhosis, hepatic encephalopathy is associated with the highest mortality [211]. In most centers, the MELD is used to established prognosis and to list patients for OLT. In the intensive care unit setting, the mortality of patients with alcoholic cirrhosis is better predicted with scoring systems developed for intensive care than with systems developed for liver disease [215].

The persistence of alcohol abuse after diagnosis is the most important factor increasing the risk of complications and death [216]. In these patients, the development of superimposed episodes of ASH carries a bad prognosis. Finally, cigarette smoking has been identified as a predictor of mortality [217], and co-morbid diseases increase the risk of both cirrhosis-related and not cirrhosis-related death [218].

Treatment

Current clinical management of alcoholic cirrhosis focuses on alcohol abstinence, aggressive nutritional therapy rich in calories and proteins [219], and primary and secondary prophylaxis of cirrhosis complications. The management of clinical decompensations is hampered by poor patient compliance, especially in those who are actively drinking. Alcohol abuse should be treated by addiction specialists and include motivational therapy and anti-craving drugs. In these patients, the use of disulfiram is not recommended due to potential hepatotoxicity. Recent studies suggest that baclofen is useful and safe in patients with advanced liver disease [61].

Several specific therapies have been tested in patients with alcoholic cirrhosis including S-adenosyl-L-methinonine (SAMe), propylthiouracil, colchicine, anabolic–androgenic steroids, and silymarin. These therapies have revealed no consistent beneficial effects on patient outcome.

Recommendations

- Abstinence from alcohol reduces the risks of complications and mortality in patients with alcoholic cirrhosis and represents a major therapeutic goal (**Recommendation A1**)
- Identification and management of cofactors, including obesity and insulin resistance, malnutrition, cigarette smoking, iron overload and viral hepatitis are recommended (**Recommendation B1**)
- General recommendations for screening and management of complications of cirrhosis should be applied to patients with alcoholic cirrhosis (**Recommendation A1**)
- No specific pharmacological therapy for alcoholic cirrhosis has demonstrated unequivocal efficacy (**Recommendation A1**)

Suggestions for future studies

(1) Further evaluation of the role of s-adenosyl methionine in alcoholic cirrhosis is needed.

Liver transplantation

Trends in liver transplantation of alcoholic liver disease

Alcoholic liver disease is one of the most common causes of cirrhosis and indications for OLT in Europe and the USA [220–222]. The reluctance to transplant livers in alcoholics stems partly from the view that alcoholics are responsible for their illness and that a relapse can damage the allograft. An opinion poll in Great Britain showed that family physicians believed that, given the scarcity of donor organs, alcoholic patients should take lower priority than other candidates, even when the latter had less chance of a successful outcome from transplantation [223]. The conviction that alcoholism is self-inflicted must be reconciled with the strong evidence supporting genetic and environmental influences on alcohol dependence diagnosed by the DSM-IV diagnostic system [224].

However, graft and patient survival rates among alcoholics after LT are similar to those seen after transplantation for other aetiologies of liver disease [225–227]. A significant increase (8.3%) in the proportion of patients transplanted for alcoholic liver disease was observed between the periods 1988–1995 and 1996–2005 [228].

Indications and contraindications

Alcoholic cirrhosis

Most programs require a 6-month period of abstinence prior to evaluation of alcoholic patients. The 6-month period of abstinence is presumed: (a) to permit some patients to recover from their liver disease and obviate the need for LT; and (b) to identify subsets of patients likely to maintain abstinence after LT. Nevertheless, data concerning the utility of the 6-month rule as a predictor of long-term sobriety are controversial. The survival benefit related to LT appears restricted to patients with advanced decompensation (i.e. 11–15 points on the Child–Pugh score) [229]. Conversely, a randomized controlled study demonstrated that immediate listing for liver transplantation did not show a survival benefit compared with standard care for Child-Pugh stage B (i.e. Child–Pugh $\leqslant$9) alcoholic cirrhosis. In addition, immediate listing for transplantation increased the risk for extrahepatic cancer [230].

Alcoholic hepatitis

A substantial number of patients with severe alcoholic hepatitis, fail to recover despite abstinence and medical therapy [231]. Nevertheless, if there is no substantial improvement by 3 months of medical management, including abstaining from alcohol, the chances of spontaneous recovery by patients with ASH and cirrhosis are poor [232]. The classical opinion of European and North American experts considering ASH as a contraindication for transplantation has been recently challenged by a case controlled study showing an unequivocal improvement of survival in patients who received early transplantation [192]. The investigators concluded that despite the fact that early LT for severe AH patients who fail medical therapy improves survival is contravenes the 6-month abstinence rule [192]. These results support future evaluation of LT in carefully-selected patients with severe AH who do not respond to medical therapy. However, early LT is relevant only in a very small minority of patients [192].

Assessing the severity of liver disease and timing for liver transplantation

In Child–Pugh stage B alcoholic cirrhosis, immediate listing for LT did not show a survival benefit compared with standard care [230].

In most centers, the MELD score is mainly used to prioritize patients awaiting LT [233]. MELD can also be used to estimate the survival benefit following LT [233]. ALD does not influence liver transplant survival benefit [234].

Previous studies have failed to demonstrate that other clinical manifestations of liver decompensation, such as variceal hemorrhage, hepatic encephalopathy, new onset ascites or spontaneous bacterial peritonitis, were independent predictors of survival over and above the MELD score [235]. Nonetheless,

the onset of any of these features in an abstinent alcoholic should prompt the managing physician to consider referral to a transplant center.

Evaluation of the alcoholic patient for LT

The 6-month rule

A psycho-social assessment to establish the likelihood of long-term abstinence after liver transplantation should be performed in patients with alcoholic liver disease. It is common practice to evaluate alcohol abuse and dependence according to the well-established diagnostic criteria such as the DSM-IV diagnostic system [224]. Since alcohol abuse and dependence may be associated with personality disorders, depression, anxiety, poly-substance abuse, and other psychiatric disorders, a psychiatric evaluation may be necessary [236]. The role of the length of pre-transplantation abstinence, the so called "6-month rule", as predictor of post-transplantation abstinence is still questionable [237–241]. There is however a subset of patients with end-stage liver disease and alcohol dependence who might be identified before LT as likely to remain abstinent after LT. A multidisciplinary approach that evaluates not only medical but also psychological suitability for liver transplantation is then mandatory.

Medical assessment of the alcoholic candidate

The pre-transplant investigation should assess pancreatic function, renal function, nutritional status as well as detecting central and peripheral neuropathy, myopathy and cardiomyopathy [242–245]. The high prevalence of double exposition to alcohol and tobacco justify additional screening for atherosclerosis and ischemic heart disease. It is also crucial to rule out any neoplastic disease or pre-neoplastic conditions, since such patients appear to have a higher incidence of certain malignancies after LT, especially of the upper airways and upper gastrointestinal tract [242].

Post-LT follow-up and management

Relapse

In studies of alcohol use after LT, "relapse" is defined as any alcohol intake. This is in contrast to studies from the literature on addiction medicine in which success is defined in terms of relative reduction of drinking and relapses as a resumption of heavy alcohol intake. Studies which have evaluated relapse into alcohol consumption after LT for alcoholic cirrhosis have reported a wide range of frequencies (10–50%) in up to 5 years follow-up [227,241]. There are many flaws in these data. First, as mentioned, is the reliance on "any use" to define relapse. Another caveat with these estimates relates to the difficulty of getting accurate data on drinking behavior. Most studies document alcohol consumption after transplantation by retrospective analysis of routine screening tests, questionnaires or interviews with patients and/or family during follow-up. There is a substantial risk that these methods may underestimate the patient's real drinking habits, partly due to retrospection, but also due to the pressures on patients to deny drinking. It is thought that between 33% and 50% of alcoholic transplant recipients start drinking again after transplantation and that about 10% resume heavy drinking mostly within the first year after transplantation [246].

Few studies have attempted to treat alcoholism within the context of LT and alcoholic LT recipients usually refuse standard treatments for alcoholism [247]. A case controlled study observed that alcoholic patients awaiting LT have less craving for alcohol and less motivation for treatment than alcoholics in the non-transplant setting, despite similar lifetime drinking histories [248].

Extrahepatic complications

The incidence of cardiovascular events is higher in patients transplanted for alcoholic liver disease compared to patients transplanted for other causes of liver disease (8% versus 5.3%) [228]. It is also likely that the incidence of chronic kidney disease, diabetes mellitus, hypertension, and other components of the metabolic syndrome may be higher after transplantation for alcoholic liver disease than other indications. Increased vigilance and proactive management are required to further improve long-term outcomes [249].

The risk of *de novo* malignancies rises from 6% before LT to 55% 15 years post LT. These malignancies also account for a significant risk of late death [242,250,251]. The incidence of *de novo* tumors as cause of death was at least twofold higher in patients transplanted for alcoholic liver disease compared to other indications [228]. After LT there were no differences between patients, with or without alcohol relapse, in terms of drug compliance, incidence of rejection or adherence to check-ups [252]. Patients transplanted for alcoholic liver disease return to society and lead active and productive lives, despite the fact they seem less likely to be involved in structured social activities than patients transplanted for non-alcoholic liver disease [253].

Survival

From a recent analysis based on ELTR data, it has been demonstrated that patient survival at 1, 3, 5, and 10 years from first transplantation was 84%, 78%, 73%, and 58%, respectively in alcoholic liver disease patients. This survival rate was significantly higher than in HCV and HBV-related liver disease recipients and cryptogenic cirrhosis patients [228]. The incidence of deaths due to all social causes, including suicide, was twice as high in patients transplanted for alcoholic liver disease compared with other indications [228].

Recommendations

- Liver transplantation confers a survival benefit in patients with ALD classified as Child-Pugh C and/or MELD ≥15 (**Recommendation A1**)
- A 6-month period of abstinence before listing patients obviates unnecessary LT in patients who will spontaneously improve (**Recommendation A1**)
- Regular screening for cardiovascular disease and neoplasms is of particular importance before and after LT (**Recommendation A1**)
- Risk factors for cardiovascular disease and neoplasms, particularly cigarette smoking, should be controlled (**Recommendation B1**)

Suggestions for future studies

(1) Studies evaluating the effects of new immunosuppressive regimens on the risk of cardiovascular disease and *de novo* neoplasms are warranted.
(2) In patients with severe ASH not responding to medical therapy, early LT need to be further evaluated in carefully-selected patients.

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