Clinical Practice Guidelines

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EASL Clinical Practice Guidelines: Management of alcohol-related liver disease☆

European Association for the Study of the Liver*

Summary

The harmful use of alcohol has been estimated to cause approximately 3.3 million deaths every year, corresponding to nearly 6% of all deaths globally. Therefore, the effective management and treatment of alcoholic liver disease is a pertinent public health issue. In the following Clinical Practice Guidelines, the latest data on the treatment and management of alcohol-related liver disease will be reviewed and up to date recommendations for clinical management will be provided.

Guideline development process

A panel of clinicians with an interest in liver disease and alcoholic liver disease (ALD), approved by the European Association for the Study of the Liver (EASL) Governing Board, wrote and discussed this Clinical Practice Guidelines (CPG) document between November 2016 and March 2017. The guidelines were independently peer reviewed, and all contributors to the CPG disclosed their conflicts of interest by means of a disclosure form provided by the EASL Office prior to work commencing. The EASL Ethics Committee reviewed the composition of the panel to eliminate the potential for real or perceived bias. The CPG panel conflict of interests are declared in this submission.

Methods

These guidelines have been produced using evidence published before 1 October, 2017. Where possible, the level of evidence and recommendation are cited (Table 1). The evidence and recommendations in these guidelines have been graded using methods adapted from the grading of recommendations assessment development and evaluation (GRADE system). The strength of recommendations thus reflects the quality of underlying evidence. The GRADE system offers two grades of recommendation: strong or weak (Table 1). The CPG thus consider the quality of evidence: the higher, 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. Where no clear evidence exists, guidance is based on the consensus of expert opinion in the literature and the writing committee. Recommendations must also be interpreted in a context specific manner.

Terminology

The term alcoholic is stigmatising and undermines patient dignity and self-esteem. For this reason, these guidelines will use the following terms (Box 1):

Previous term	Current term	Abbreviation
Alcoholic	Alcohol use disorder	AUD
Alcoholic liver disease	Alcohol-related liver disease	ALD
Alcoholic cirrhosis	Cirrhosis due to alcohol-related liver disease	ALD cirrhosis
Alcoholic steatohepatitis (histologically-defined lesion)	Steatohepatitis due to ALD	ASH
Alcoholic fibrosis	Fibrosis due to ALD	ALD fibrosis
Alcoholic hepatitis	Alcoholic hepatitis*	AH

*However, at this point the term alcoholic hepatitis has become too standardised to change but may be reviewed in future guidelines.

Public health aspects

Alcohol-related morbidity and mortality

According to the World Health Organization's (WHO) 2014 report on noncommunicable diseases, harmful use of alcohol causes approximately 3.3 million deaths every year, corresponding to 5.9% of all deaths. Furthermore, 139 million disability-adjusted life years, or 5.1% of the global burden of disease and injury, were attributable to alcohol consumption. The proportion of global deaths attributable to alcohol differs based on gender, with 7.6% of deaths among males and 4.0% of deaths among females attributable to alcohol.[1]

Alcohol-related morbidity and mortality has a wide geographical variation, with the highest alcohol-attributable fractions reported in the WHO European Region.[1] Within each country there is an excellent correlation between the level of alcohol consumption and the prevalence of alcohol-related harm. In fact, although mean alcohol consumption in the World is 6.2 litres of pure alcohol per person per year, the consumption in Europe is 10.9 litres/year.[1] According to data from the OECD report 2017, alcohol consumption in the OECD countries, averaged nine litres of pure alcohol per person per year. This

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Table 1. Level of Evidence and Grade of Recommendations (adapted from GRADE system).

Level of evidence*		Confidence in the evidence
Level 1	Data derived from meta-analyses or systematic reviews or from (multiple) randomized trials with high quality.	Further research is unlikely to change our confidence in the estimate of benefit and risk.
Level 2	Data derived from a single RCT or multiple non-randomized studies	Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate.
Level 3	Small studies, retrospective observational studies, registries.	Any estimate of effect is uncertain.
Recommendations		
Grade		**Wording associated with the grade of recommendation**
A (strong)	Strong recommendation: factors influencing the strength of the recommendation include the quality of the evidence, presumed patients-important outcomes and cost	"must", "should", or "EASL recommends"
B (weak)	Weaker recommendation: variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption	"can", "may", or "EASL suggests"

* Level was graded down if there is a poor quality, strong bias or inconsistency between studies. Level was graded up if there is a large effect size.

number results from a significant percentage of heavy drinkers: 30% of men and 12% of women binge-drink at least once per month.[2]

Despite divergent trends at the national level, the WHO European Region is still the region with the highest adult per capita alcohol consumption. Between 1990 and 2014, there was a slight decrease in the overall level of consumption due to decreases in the richest countries in the central western European Union (EU) and Mediterranean parts of the Region, while drinking levels in central-eastern EU remained stable over the past 25 years, and increased in the eastern and the south-eastern parts of the WHO European Region.[3] Alcohol consumption over the last 20 years in the UK and Finland has increased significantly, while other countries such as France, Spain and Portugal were able to reduce the number of liver-related deaths.[4]

Alcohol has an impact on over 200 diseases and types of injuries. In most cases the impact is detrimental. The largest number of deaths attributable to alcohol consumption are from cardiovascular diseases, followed by injuries, gastrointestinal diseases (mainly liver cirrhosis) and cancers.[5] However, the alcohol-attributable fraction is highest for liver diseases, especially cirrhosis, and foetal alcohol syndrome.[1]

In the EU, based on the WHO mortality database, 41% of the liver deaths are attributed to alcohol, and 46% are of unknown aetiology. It is probable that a significant percentage of those classified as unknown are actually due to alcohol.[4] In fact, reliability of death certificate codification varies among countries, and 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.[6]

Although alcohol consumption is higher in rich countries, in those with lower economic wealth, the morbidity and mortality risks are higher per litre of pure alcohol consumed than in the higher income countries.[1]

The economic contribution of the alcohol industry, in terms of employment and taxation, are often cited as reasons for not attempting to restrict alcohol consumption using pricing strategies or marketing restrictions. In the EU in 2003, it was calculated that harmful alcohol consumption resulted in estimated costs of €125 billion, equivalent to 1.3% of gross domestic product (GDP).[7] This exceeds by an order of magnitude the reported contribution (about €9 billion) of the alcohol industry to the EU economy.[8]

Consensus on the definition of a "drink" and of "heavy episodic drinking"

The quantification of alcohol consumption is not easy in clinical practice. Although the quantification in grams of alcohol per/day or week is more precise, it is time-consuming and frequently difficult to obtain, since patients are not able to recall the different types of drinks and their amount. Consequently, it may be advantageous to quantify by number of drinks. However, there has been large discrepancy in the definition of a "drink", regarding the grams of alcohol, varying from 8 to 16 g. According to the Dietary guidelines for Americans, one standard drink of "pure" alcohol is defined as 14 g.[9] We suggest standardising the measure to 10 g, to facilitate comparisons among studies, as has been used by the WHO.[10]

According to ICD-10, harmful drinking is considered when alcohol use is causing damage to health that may be either physical or mental: IC10-2016 online (http://apps.who.int/classifications/icd10/browse/2016/en#/F10.1)

Heavy episodic drinking has been defined as consumption of more than 60 g of pure alcohol on one occasion.[11] Binge drinking is the consumption within about two hours of four or more drinks for women and five or more drinks for men.[9]

Levels of alcohol consumption and disease risk

An important aspect of public health policy concerning alcohol has been the attempt to establish a safe threshold for consumption. This pertains mostly to what extent moderate alcohol consumption is cardio-protective, illustrated by the so called 'J' shaped curve in the relationship between alcohol consumption and overall mortality.[12] Although there is strong evidence that heavy alcohol intake associates with increased risk of cardiomyopathy, hypertension, atrial arrhythmias and haemorrhagic stroke, light–moderate drinkers seem to have a lower risk of coronary artery disease.[13] This positive effect of alcohol may offset some of the large array of negative health consequences of even moderate alcohol consumption. However, alcohol is a recognised carcinogen, and no threshold level of consumption exists for the risk of cancer. Alcohol consumption has been associated with an increased risk of several cancers, and in at least four of them, including breast cancer, the risk begins at doses as low as 10 g/1 unit/day.[14]

While alcohol is undoubtedly a risk factor for cirrhosis it is still unclear whether there is a continuous dose-response

relationship or a threshold of consumption at which the risk emerges. In a meta-analysis from 2010 the close dose-response relationships between the average amount of alcohol consumed and the risk of liver cirrhosis were confirmed. The authors' found evidence for threshold effects, with increased risks of mortality from liver cirrhosis among men and women drinking 12–24 g of ethanol per day.[15] Indeed, among women, a significant increase was also seen for those drinking up to 12 g/day. The evidence 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. However, for practical issues, it can be recommended that if alcohol is consumed, limit intake to no more than two drinks for females and three drinks for males (each containing 10 g of alcohol) per day, since this amount was not associated with a significant increase in risk of liver cirrhosis morbidity.[10,15]

One important issue is the impact of alcohol drinking patterns, with controversy regarding the risks of binge drinking. In that respect, Askgaard found that daily drinking was associated with the highest risk of liver cirrhosis,[16] whereas Aberg *et al.* found that binge drinking was associated with an increased risk of liver disease independently of average alcohol intake and confounders.[17] Further clinical and experimental studies are required to define the role of ALD and the underlying mechanisms.

Importantly, there is good 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.[18]

Public health policies to reduce population risk for ALD

Several alcohol-related policies have been shown to be effective and cost-effective. Reducing morbidity and mortality associated with ALD, depends on policies that reduce alcohol consumption in general. Effective interventions include:

- Price based policies
  - o Taxation
  - o Minimum unit pricing
- Limitation of alcohol availability
- Restriction of marketing and advertising

Reducing the affordability of alcohol has been shown to have a significant effect on reducing ALD-related liver deaths.[19,20] Minimum unit pricing, setting a floor price for a unit of alcohol, has been shown to be very effective. In British Columbia, it reduced alcohol-related mortality by 32% one year after implementation.[21] This measure also has the advantage of being more effective for heavy consumers and for low-income groups.

Other effective alcohol policies have been suggested by WHO, that are based on age-related vulnerability, including partial or total advertising bans, restrictions on access to alcohol through minimum ages at which it is legal to purchase alcohol, and laws aimed to prevent any alcohol consumption by young people when driving vehicles.[1]

Children and young adults are particularly sensitive to alcohol marketing. A series of longitudinal experimental studies have proven that marketing impacts on the drinking behaviour of children.[22,23] In fact, reducing advertising in media, mostly publicity targeting young people is important, since they have been shown to be particularly susceptible.[23]

Screening to reduce ALD-related morbidity and mortality

A high proportion of patients admitted with decompensated ALD cirrhosis report having recent consultations in primary care or emergency units.[24] Since the risk of developing liver disease in harmful drinkers decreases with abstinence or decreased consumption, early recognition and interventions with that goal should be implemented.

Screening for harmful alcohol consumption should be done systematically in patients, by their general practitioner (GP), and in patients admitted to emergency facilities. In fact, the feasibility of screening followed by an intervention in an emergency department was recently demonstrated in the UK.[25] In addition, screening for ALD should be undertaken in patients with clinical signs suggestive of harmful alcohol consumption or liver cirrhosis, *i.e.* patients presenting with bilateral parotid gland hypertrophy, muscle wasting, malnutrition, Dupuytren's contracture, gynecomastia or extensive spider naevi.

Screening for ALD should be performed in high-risk populations, such as those in alcohol rehabilitations clinics, or harmful drinkers identified by their GP. Screening in the workplace would be extremely helpful, although difficult to implement.[26] The best way to do such screening is still debatable. The Southampton traffic-light test is an algorithm, based on hyaluronic acid (HA), procollagen-3 N-terminal peptide (PIIINP), and platelet count, that expresses the results as red, amber or green, corresponding respectively to high, intermediate or low risk, and was suggested as a simple screening test.[27] Another possibility is the use of transient elastography (TE) techniques that could be used in portable devices to increase availability for large groups. In fact, it was recently shown that TE has excellent diagnostic value for liver fibrosis in ALD.[28] Whatever form of screening is used, it must be followed by an intervention with a multidisciplinary team. In fact, there is a need to create alcohol care teams to take care of these patients.[29]

Suggestions for future studies

- Priority to be given to further studies on screening in different populations, to diagnose patients prior to the development of end-stage liver disease

Recommendations

- Excess alcohol consumption should be addressed using pricing-based policies and regulation of availability. (**Grade A1**)
- Advertising and marketing of alcohol either directly or indirectly should be banned. (**Grade A2)**
- Primary care facilities for managing AUD need to be made widely available. (**Grade A2**)
- Screening for harmful alcohol consumption should be done by GPs and in Emergency Departments. (**Grade A2**)
- Screening for ALD should be done in high-risk populations, such as those in alcohol rehabilitations clinics, or the harmful drinkers identified by their GP. (**Grade A2**)
- Patients identified through screening should undergo brief intervention and referral to a multidisciplinary team. (**Grade A1**)

Alcohol use disorders

Terminology and definitions

The publication of the DSM-V has been an important step forward to overcome the arbitrary differentiation between alcohol abuse and dependence, through the creation of the overarching concept of alcohol use disorder (AUD).[30] This new concept is not only useful because it unifies the disorder, but also because it introduces a partially dimensional perspective into what has been traditionally called alcoholism. The categorical distinction between who is and who is not an alcoholic is not clinically useful and may be damaging because of stigmatisation.[31]

Instead, the DSM-V defines AUD as a problematic pattern of alcohol use leading to clinically significant impairment or distress, with graded levels of severity depending on the number of diagnostic criteria met. As shown there are 11 diagnostic criteria and anyone meeting at least two of them during the last year qualifies for a diagnosis of AUD (Table 2). Severity is established based on the number of criteria met, ranging from mild (2–3 criteria), to moderate (4–5 criteria) and severe (6 or more criteria).

It is still unclear what option will be taken in ICD-11, but for the moment, the WHO continues to use the terms hazardous and harmful alcohol use and alcohol dependence [5]. Even though it is not officially accepted, the term 'risky drinker' is commonly used to define people who drink excessively and can benefit from brief interventions provided by health practitioners in medical settings.

The drinking habits of patients with liver diseases need to be routinely assessed, using tools with proven reliability.[32]

Screening tools to identify alcohol use disorders

Quantity frequency questionnaires and diaries (Timeline Followback) can be used to calculate patients' drinking habits. The former tools are usually preferred for their simplicity, but in the last few years a relevant number of Apps (*e.g.* Drinkaware) have been developed for this monitoring purpose,[33] making prospective measurement of drinking much easier for motivated patients. A good alternative to quantity frequency questionnaires is the use of screening instruments. 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' (Table 3). 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 3). 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] In fact, it is a standardised way to quickly apply a quantity frequency questionnaire that includes 'binge drinking' occasions. 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 on one occasion?) as a single screening question, which should be followed by the whole AUDIT in case the answer is rated positive.[32]

Screening of patients with psychiatric disorders

Patients with AUD have a high prevalence of psychiatric comorbidity. In general, population surveys of patients with AUD show a high prevalence of anxiety disorders, affective disorders, and schizophrenia.[37–39] Anxiety and affective disorders may be independent or concurrent with alcohol dependence. Independent disorders will need referral for specialised treatment, while concurrent disorders may disappear once the patient is weaned off alcohol.

Patients with AUD have a higher risk of developing other addictions, including nicotine. Because cigarette smoking and alcohol abuse are synergistic in causing cardiovascular diseases and cancer, including hepatocellular carcinoma (HCC), hepatologists are encouraged to promote and assist smoking cessation in patients with ALD.[40] Since patients with AUD tend to be heavier smokers, the treatment of their nicotine dependence may require more intensive support or referral to specialised professionals.[41] Also, patients with AUD who are polydrug users are difficult to manage and should be systematically referred to specialised treatment units. Data suggest that AUD appears

Table 2. DSM-V criteria for alcohol use disorder.

Definition: A problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:
1. Alcohol is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control alcohol use.
3. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.
4. Craving, or a strong desire or urge to use alcohol.
5. Recurrent alcohol use resulting in a failure to fulfil major role obligations at work, school, or home.
6. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.
7. Important social, occupational, or recreational activities are given up or reduced because of alcohol use.
8. Recurrent alcohol use in situations in which it is physically hazardous.
9. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.
10. Tolerance, as defined by either of the following: a. A need for markedly increased amounts of alcohol to achieve intoxication or desired effect. b. A markedly diminished effect with continued use of the same amount of alcohol.
11. Withdrawal, as manifested by either of the following: a. The characteristic withdrawal syndrome for alcohol b. Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms.
The presence of at least 2 of these criteria indicates an AUD. The severity of the AUD is defined as: Mild: The presence of 2 to 3 criteria Moderate: The presence of 4 to 5 criteria Severe: The presence of 6 or more criteria

AUD, alcohol use disorder.

Table 3. AUDIT questionnaire.

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 healthcare worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, during the last year

more than 10 years before the patient is referred for 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 AUD appearing and referral.[42]

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. Symptoms may include increased blood pressure and pulse rate, tremors, hyperreflexia, irritability, anxiety, headache, nausea, and vomiting. These symptoms may progress to more severe forms of AWS, characterised by delirium tremens, seizures, coma, cardiac arrest, and death.[43] Severity scores for AWS are potentially useful in the management of patients. While these scores are insufficiently validated in patients. with ALD, the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) is useful in clinical practice.[44] A CIWA-Ar score >8 indicates a moderate AWS and a score ≥15 indicates severe AWS. Pharmacological treatment is recommended for both moderate and severe AWS using a symptom-triggered regimen rather than fixed dose schedule in order to prevent the accumulation of the drug.[45]

Benzodiazepines are considered the 'gold standard' treatment for AWS, given their efficacy for reducing both withdrawal symptoms and the risk of seizures and/or delirium tremens.[46,47] 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.[48] In Europe, clomethiazole is also used to treat AWS.[49] It should be noted that both benzodiazepines and clomethiazole carry a potential risk of abuse, and it has been documented that patients with AUD are at higher risk. Hence clinicians should avoid the use of those drugs beyond the 10–14 initial days of treatment. Other drugs, such as baclofen and sodium oxybate, have been tested in the treatment of AWS. The additional value of these drugs is that they are also indicated for relapse prevention.[50] Their strengths and limitations are discussed below.

Medical management of alcohol use disorder in patients with ALD

Alcohol abstinence represents a critical goal in patients with ALD since abstinence improves clinical outcomes at all stages of ALD. In the past, disulfiram was the only drug available for AUD. Disulfiram represents an effective alcohol pharmacotherapy;[51] however, disulfiram should be avoided in patients with severe ALD because of possible hepatotoxicity.[52] More recently, the growing understanding of the neurobiology of AUD has led to the development of effective pharmacologic agents that can complement psychosocial treatments, in particular naltrexone,[53] nalmefene[54] and acamprosate.[55] All those drugs are approved to treat AUD, however, disulfiram, naltrexone and acamprosate are approved for abstinence, while nalmefene is approved for the reduction of heavy drinking. It should be noted that these drugs have not been tested in patients with ALD cirrhosis. The opioid antagonist naltrexone has been intensively evaluated, especially the oral formulation.[56] A large trial also showed the efficacy of an intramuscular formulation of naltrexone in alcoholism,[57] but has not been replicated. Given the potential for hepatotoxicity, naltrexone has not been tested in patients with ALD, and its use in this population is not currently recommended. Nalmefene, a different opioid modulator has been approved in Europe for the treatment of AUD with an aim of reducing the amounts drunk. While patients with ALD should not primarily have a reduction goal, nalmefene could be considered in those patients with early stages of liver disease where abstinence proves not to be feasible. Acamprosate is a modulator of the glutamatergic receptor system and a meta-analysis of 24 randomised controlled trials confirmed its efficacy as an alcohol pharmacotherapy.[58] Sodium Oxibate (gamma-hydroxybutyric acid) is approved in some European countries (Italy and Austria) to treat AUD,[59] and at the moment we write this guideline the EMA is about to take a final decision on the approval of this controversial drug at a European level. Among other compounds, topiramate, and baclofen seem the

most promising pharmacotherapies for alcoholism.[60] Topiramate is an anticonvulsant medication, which has demonstrated safety and efficacy in reducing heavy drinking.[61] There was also a decrease in liver enzyme levels in patients treated with topiramate;[62] however, topiramate has not been tested in patients with ALD. Some studies suggest that baclofen, a GABA-B receptor agonist, increases abstinence rate and prevents relapse in alcohol-dependent patients.[63] Moreover, to date, baclofen represents the only alcohol pharmacotherapy tested in patients with AUD, with significant liver disease. A clinical trial demonstrated the safety and efficacy of baclofen in promoting alcohol abstinence in patients with ALD and cirrhosis,[64] but confirmatory studies in cirrhotic patients are warranted, since a recent trial in patients with hepatitis C virus (HCV) did not show any superiority of 30 mg of baclofen over placebo.[65] Studies with high doses of baclofen have provided controversial results[66,67] and the largest study to date[68] did not show any superiority of baclofen against placebo. The French ANSM (Agence nationale de sécurité du medicament) has issued a temporary recommendation for the use of baclofen (not exceeding 80 mg/day) for the treatment of AUD.[69]

Even though many other compounds have been tested for relapse prevention (*i.e.*, gabapentin, ondansetron, *etc.*), no consistent results in large samples have been reported. In summary, all pharmacological treatments for AUD show modest results, and they cannot replace the non-pharmacological management of the addictive process, which is recognised by health authorities as the most relevant element of treatment.[70,71] In fact, this simply implies to add brief intervention techniques to the usual clinical management of patients with ALD.

The effect of brief interventions

There is a large body of evidence on the efficacy[72] and effectiveness[73] of brief interventions to reduce alcohol consumption in primary health care settings. A Cochrane review showed that brief interventions can reduce drinking by an average of 57 g per week in men.[74] Evidence is less conclusive in women and populations under 16 years of age. Its success depends largely on the presentation of objective feedback based on information provided by the physician and customised to the patients' readiness to change (awareness of the risks linked to the existing drinking pattern and willingness to change that pattern). The technique attempts to increase a patient's awareness of the problems caused, consequences experienced, and risks faced as a result of patterns of alcohol consumption. A brief intervention should at least have the components defined in the five As' model:[75]

- Ask about use,
- Advice to quit or reduce,
- Assess willingness,
- Assist to quit or reduce,
- Arrange follow-up.

When a motivational component is added to brief interventions its efficacy improves.[76] Motivational interviewing is a technique which aims to be both non-judgmental and non-confrontational.[77] Essential components of a motivational approach are an empathic attitude and a collaborative approach that respects the patients' autonomy and encourages them to find ways to reach the goals agreed. An example of brief intervention can be found at https://www.youtube.com/watch?v=KRu5uMwSkQg.

Suggestions for future research

- Further trials of pharmacotherapy in patients with advanced ALD are urgently required
- Studies to demonstrate the efficacy of a multidisciplinary team intervention

Recommendations

- The term alcohol use disorder (defined by DSM-V criteria) should be used in preference to alcoholic, alcohol abuse, alcohol dependence or risky drinker (**Grade A**)
- AUDIT or AUDIT-C should be used to screen patients for AUD and dependence (**Grade A1**)
- Patients with AUD should be screened for concurrent psychiatric disorders and other addictions. (**Grade A1**)
- Benzodiazepines should be used to treat AWS but should not be prescribed beyond 10–14 days because of the potential for abuse and/or encephalopathy (**Grade A1**)
- Gastroenterology/Hepatology centres should have access to services to provide effective psychosocial therapies (**Grade A**)
- Pharmacotherapy should be considered in patients with AUD and ALD (**Grade A1**)

Diagnostic tests in the management of ALD

Screening and clinical diagnosis of ALD

Diagnosis of ALD is usually suspected upon documentation of regular alcohol consumption of >20 g/d in females and >30 g/d in males together with the presence of clinical and/or biological abnormalities suggestive of liver injury. As a high proportion of patients with histological features of ALD do not express any clinical symptoms or laboratory abnormalities, asymptomatic patients consuming a critical amount of alcohol should undergo appropriate screening investigations.[78] As previously mentioned, screening should be done in high-risk populations, such as those in alcohol rehabilitations clinics, or the harmful drinkers identified by their GP. Furthermore, ALD should be considered in patients presenting with extrahepatic manifestations of AUD, such as symmetric peripheral neuropathy, pancreatitis, cardiomyopathy and others.[79] A non-invasive model, the ALD/non-alcoholic fatty liver disease (NAFLD) index based on four parameters, mean corpuscular volume (MCV), aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio, body mass index, and gender was proposed for the differential diagnosis of ALD with NAFLD.[80]

Screening investigations should not only include liver function tests (LFTs), *i.e.* gamma glutamyl transpeptidase (GGT), serum ALT and serum AST, but also performance of a test to detect liver fibrosis (*e.g.* TE) since advanced liver fibrosis may present with normal LFTs. In case of any abnormalities an ultrasound should follow. To exclude alternative or additional causes of liver injury further laboratory work-up, including hepatitis B virus (HBV) and HCV serology, autoimmune markers, transferrin and transferrin saturation, α1-antitrypsin and in some cases also caeruloplasmin may be considered[81] In case of suspected advanced fibrosis or cirrhosis, serum albumin, prothrombin

time or international normalized ratio (INR), serum bilirubin levels, as well as platelet and white blood cell counts should be determined in order to evaluate liver function and evidence of portal hypertension. Whenever there is evidence of cirrhosis, upper gastrointestinal endoscopy should be performed to screen for oesophageal varices, unless there is a low risk of having varices requiring treatment based on Baveno criteria (platelets >150,000) and Fibroscan <20.[82] During follow-up clinical, laboratory and ultrasound surveillance is indicated for all patients with cirrhosis.

Liver biopsy

Indication and performance of a liver biopsy

A liver biopsy may be used to establish the definite diagnosis of ALD, to assess the exact stage and prognosis of liver disease and to exclude alternative or additional causes of liver injury.[83,84] Approximately 20% of patients with a history of AUD and abnormal LFTs were found to have a co-existing aetiology of their liver disease.[85,28,86] For this reason, performance of a liver biopsy is recommended within phase II clinical trials, and should be considered in larger scale phase III clinical trials, in case of inconclusive non-invasive test results or in case of any suspicion of a competing liver disease.

Usually the liver biopsy is done percutaneously under ultrasound guidance. Alternatively, it can be performed laparascopically or via a transjugular approach. The latter is specifically recommended in patients with a low platelet count and/or a prolonged prothrombin time. However, a liver biopsy is an invasive procedure with significant morbidity. Severe complications, such as intrahepatic bleeding, pneumothorax and others occur in approximately 2% of patients.[87] Therefore, a biopsy is not generally recommended for all patients with suspected ALD, but the risks should be carefully weighed against the clinical benefits and therapeutic consequences.

Histological features and diagnosis of ALD types

The morphological spectrum of ALD encompasses four groups of elementary lesions which in the pre-cirrhotic stage predominate in the central regions of the hepatic lobuli: (a) macrovesicular steatosis, eventually a variable blend of macro and micro-vesicles (mixed type steatosis); (b) hepatocellular injury with ballooning, potentially necrosis; (c) lobular inflammation; (d) fibrosis or cirrhosis.[88] In a given individual, a single lesion or any combination thereof may be found.[89] The main histological diagnoses in ALD include steatosis, alcoholic steatohepatitis (ASH), fibrosis/cirrhosis, and HCC.[90] The prevalence of histological lesions among drinkers is not well known.[91]

The types of ALD differ with respect to prognosis. About 90% of heavy drinkers have hepatocellular steatosis.[92] Whether alcoholic steatosis is a benign condition or can progress is a matter of debate. Some studies suggest cirrhosis may occur after a median of 10.5 years in 10% of patients with histological steatosis without ASH or fibrosis. The mixed steatosis pattern has also been found associated with higher risk of progression.[93]

Alcoholic steatohepatitis is considered a progressive lesion, which increases the risk of cirrhosis and HCC. The principal morphological features of ASH include steatosis, hepatocellular ballooning, necrosis, and lobular inflammation often predominated by neutrophil polymorphs. However, steatosis may be present in less than 5% of the parenchyma, or even absent in cases with severe ASH, after periods of abstinence, or in cirrhosis despite ongoing alcohol abuse.[90,94–96] Ballooning is an ill-defined morphological term designating swelling, rounding and pale staining of the cytoplasm. Ballooned hepatocytes are characterised by a loss of cytoplasmic staining of keratin 8 and 18 (K8/18, constituents of the intermediate filament cytoskeleton)[97] and expression of sonic hedgehog[98] on immunohistochemistry. Ballooned cells often contain large Mallory-Denk bodies (MDBs) composed mainly of K8/18 and few other proteins.[99] Cholestasis can be observed in severe ASH in pre-cirrhotic or cirrhotic stage.[90]

In most patients, fibrosis is a central-based parenchymal feature. However, a portal-based fibrosis pattern has also been reported.[100] Inflammatory and fibrotic changes can involve hepatic veins (phlebosclerosis), and terminal hepatic venules and adjacent parenchyma (perivenular fibrosis), a severe form of which is referred to as sclerosing hyaline necrosis.[101] With disease progression pericellular fibrosis extends, often in a septal fashion and paves the way for cirrhosis[102–106] which is typically micrododular, but is occasionally mixed micro- and macronodular. Particularly in cases of ongoing drinking, the parenchyma is dissected by severe pericellular fibrosis and nodules may be poorly defined.[94]

Can ASH be distinguished histologically from non-alcoholic steatohepatitis?

The morphological lesions of ALD and metabolic syndrome-associated NAFLD show broad overlap. Hepatocellular injury and fibrosis are often more severe in ALD. In an individual patient it may be impossible to decide on morphological grounds alone if liver disease is alcohol-related or not.[89,107,108] However, some of the lesions of ALD, *e.g.*, sclerosing hyaline necrosis, alcoholic foamy degeneration (*i.e*, large portions of the parenchyma affected by microvesicular steatosis), fibro-obliterative changes in hepatic veins, portal acute inflammation, and cholestasis are very rare or have not been described in patients with pure NAFLD.[80,107,109]

Histology in alcoholic hepatitis

The concordance of clinical alcoholic hepatitis (AH) and ASH is not optimal. In 10–20% of patients liver biopsy does not confirm the clinically suspected diagnosis of AH.[110,111] Furthermore, liver disease not related to alcohol, but requiring appropriate therapy, can be present in 10–20% of cases.[85,112] Histological evaluation also aids in the diagnosis and assessment of liver injury in comorbid conditions.[113–117]

Prognostic utility of histology

Ballooning, MDBs, lobular polymorphs, canalicular and/or ductular cholestasis, fibrosis and megamitochondria have been described as independent predictors of short-term outcome in patients with AH. In addition, visible bile in canaliculi and/or ductular reaction also predicted bacterial infection and sepsis.[84,118–120] Lobular neutrophils,[121] low grade steatosis[122] and ductular reaction[123] may be useful to predict treatment response to corticosteroids. ASH, MDBs and cirrhosis[124,125] have been identified as predictors of long-term survival. Recently, advanced fibrosis, but not clinical or biochemical factors, was found as the only independent predictor of long-term outcome in patients with compensated ALD.[126]

Table 4. Diagnostic performance of some non-invasive serum fibrosis tests for diagnosis of cirrhosis in patients with ALD in studies.

Test	Cut-off	Prevalence of F4 (%)	AUROC (95% CI)	PPV (%)	NPV (%)	Reference
Hyaluronic acid	250 μg/L		0.78	35	98	143
PGAA index*	10	27	0.87 (0.79–0.92)	72	92	144
FibroTest	≥0.70	31	0.94 (0.90–0.96)	73.4	93.5	28,91
	≥0.75	15	0.88 (0.79–0.93)	43.9	92.8	
Enhanced liver fibrosis (ELF) test**	≥10.5	23	0.92 (0.89–0.96)	71	94	142
Fibrometer	≥0.5	31	0.94 (0.90–0.97)	53.7	98.9	91
FIB-4	<1.45	31	0.80 (0.72–0.86)	n.a.	n.a.	28,91
	<1.45	15	0.80 (0.71–0.87)	n.a.	n.a.	

ALD, alcoholic liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUROC, area under the receiver operating characteristic curve; CDT, carbohydrate deficient transferrin; EtG, ethyl glucuronide EtOH, ethanol; GGT, γ-glutamyl transpeptidase; n.a., not available; NPV, negative predictive value; PPV, positive predictive value; UTI, urinary tract infection.
*PGAA index: combines α2alpha-2-macroglobulin, prothrombin time, serum GGT, serum apolipoprotein A1.
**ELF combines hyaluronic acid (HA), the N-terminal pro-peptide of collagen type III (PIIINP) and tissue inhibitor of metalloproteinase-1 (TIMP-1). The test is validated for diagnosis of >F3 fibrosis.

Grading and staging of ALD

Formal grading and staging systems for ALD are few.[94] Based on the wide morphological overlap, some authors proposed that NAFLD grading systems may also be used for ALD,[89,127] but this concept can be challenged by the fact that several prognostic factors, like histological cholestasis, MDBs and megamitochondria are not considered in NAFLD grading. Recently the Alcoholic Hepatitis Histologic Score based on prognostic histological features of ASH was developed for prediction of 90-day mortality for patients with AH and ASH.[84]

Non-invasive test in ALD

Non-invasive markers of AH

The risk of obtaining a liver biopsy in patients with clinically suspected AH is well recognised and has fostered efforts to develop non-invasive tests. Recently serum levels of caspase-cleaved keratin 18 (K18) epitopes M30 and M65 assessed by ELISA in a large cohort of patients with ALD were found to predict the histological diagnosis of AH with modest diagnostic accuracy (AUROCs 0.776 and 0.784, respectively). Furthermore high serum levels of these markers were also predictive of non-HCC liver-related mortality in patients with alcoholic cirrhosis.[128] A comparable result was reported by an independent group [2].[112] In this study, with the definition of two cut-offs, classification of approximately two-thirds of patients with clinically suspected AH was achieved. However, the interpretation of K18 fragment serum levels has to consider the clinical setting, since M30 and M65 levels may also increase during phases of abstinence.[128] At present K18 fragments cannot be recommended in clinical practice.

Non-invasive tests to estimate liver fibrosis

Serum markers that have been evaluated for non-invasive assessment of stage in ALD may be classified as indirect or direct fibrosis tests.[129] In contrast to direct tests, indirect fibrosis tests are routine clinical and biochemical parameters not regarded as surrogate markers of extracellular matrix turn over. Both types of tests, either singly or in combination, have been shown to exhibit good accuracy for distinguishing mild from severe fibrosis, but are less well suited to classify intermediate fibrosis stages and are not helpful in the early diagnosis of ALD.[130] (Table 4).

Liver stiffness measurement (LSM) by TE has been demonstrated to be a useful tool for assessing hepatic fibrosis in patients with ALD.[131–136] In patients with ALD, liver stiffness correlates with the degree of fibrosis. In the studies that did not consider the presence of AH as a potential confounding factor, the cut-off values for F3 and F4 fibrosis were considerably higher than in patients with viral hepatitis. Several studies have shown that patients with alcoholic cirrhosis had significantly higher values of liver stiffness than patients with viral cirrhosis, presumably because of the higher degree of fibrosis in ALD.[137] A recent study indicated that AH markedly increases LSM in patients with ALD independent of fibrosis stage.[131,138] Therefore, elevated liver stiffness values in patients with ALD and AST serum levels >100 U/L should be interpreted with caution, because of the possibility of falsely elevated liver stiffness as a result of superimposed AH.[28,131] Furthermore, inflammation, cholestasis or liver congestion may interfere with LSM, independently of fibrosis.[139] In addition, alcohol consumption may also be a modifying factor as shown by the decrease of liver stiffness in abstainers and the increase in relapsers.[28,131,140] In a recent prospective, cross sectional, biopsy-controlled, single centre study featuring 199 patients with ALD, LSM by TE and 2-dimensional shear wave elastography were shown to be equally suited to rule out rather than rule in advanced fibrosis and cirrhosis. At the defined cut-offs, negative predictive values were above 90% for both techniques.[141] In another prospective multicentre study, the diagnostic utility of serum markers, FibroTest, PGAA index, APRI (AST to platelet ratio index), FIB-4 (Fibrosis-4) and FORNS index or combinations thereof (*i.e.*, TE-FibroTest and TE-PGAA) were compared with TE for the prediction of advanced fibrosis and cirrhosis. The AUROC for the prediction of cirrhosis by TE was slightly better than for prediction of advanced fibrosis, 0.93 and 0.90, respectively, and did not differ significantly from the diagnostic accuracy of any of the serum markers alone or the combinations of serum markers with TE. Based on TE values, an algorithm for management of patients with ALD was proposed that may help to reduce the need for biopsy.[28] In a recent large prospective study performed in Danish primary and secondary healthcare centres the enhanced liver fibrosis test (ELF) determining the three direct markers HA, PIIINP and tissue inhibitor of metalloproteinase-1 (TIMP-1) was found to have the same high diagnostic accuracy (Table 4) for detecting advance fibrosis ≥F3 as the FibroTest. For patients in primary care, ELF values below 10.5 and FibroTest values below 0.58 had negative predictive values for advanced liver fibrosis of 98% and 94%, respectively.[142–144]

Another test based on radiological techniques is transient MR elastography (MRE). In NAFLD, MRE may have higher accuracy in the detection of advanced fibrosis than TE.[145] Although the utility of this method has not been extensively evaluated

Table 5. Direct and indirect markers of alcohol consumption.

Biomarker	Biological material	Detection window	EtOH amount	Sensitivity	Specificity	Confounding factors	Ref.
Indirect alcohol markers							
GGT	Serum		Chronic excessive	42–86%	40–84%	Liver disease, BMI, sex, drugs	79,151,153,154,170
AST	Serum		Chronic excessive	43–68%	56–95%	Liver and muscle diseases, BMI, drugs	
ALT	Serum		Chronic excessive	30–50%	51–92%	Liver disease, BMI, drugs	
MCV	Serum		Chronic excessive	24–75%	56–96%	Vitamin B12, folic acid deficiency, haematological diseases	
%CDT	Serum	1–2 weeks	50–80 g/d for >1–2 weeks	25%–84%	70%–98%	Liver cirrhosis/disease, nicotin, transferrin level, weight, sex, pregnancy, rare genetic variations	
Direct alcohol markers							
Breath alcohol	Exhaled air	4–12 h		97%	93%	Alcohol-containing mouth wash	171
EtOH	Serum	4–12 h					
EtG	Urine	Up to 80 h	>5 g	89%	99%	*Increases results:* - Accidental contamination of food, mouth wash, alcohol free beer, etc. with alcohol - UTI *Incresed results:* - Urine dilution deliberately or by diuretics - UTI	154,163
EtG	Hair	≤6 mo	>20–40 g/d for >3 months	85–92%	87–97%	*Increases results:* - Seriously impaired renal function - EtG containing hair treatment *Decreases results:* - Hair treatment: dying, perming, bleaching	168,172–175

in patients with ALD, it may also emerge as a useful tool for the non-invasive assessment of fibrosis in this setting, as these diseases share many parallels.[146]

Hepatic imaging techniques

Imaging techniques such as ultrasonography, MRI, and CT may allow quantification of steatosis, help exclude other causes of chronic liver disease such as primary sclerosing cholangitis, and contribute to the assessment of advanced liver disease and its complications independently of the aetiology. However, imaging studies do not have a role in establishing alcohol as the specific aetiology of liver disease.

Steatosis can be screened using ultrasonography, CT, and MRI.[147] 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 and can detect 5–10% of steatosis.[148] However, the standardisation of sequence characteristics isare not well established yet and most importantly their cost and availability are limiting. Controlled attenuation parameter (CAP), a novel, inexpensive ultrasound based elastography method was recently shown to represent a useful measure of hepatic steatosis. However, prevalence, aetiology of liver disease, diabetes, and BMI have to be considered in the correct interpretation of CAP results.[149]

Tests for alcohol consumption

Indirect marker for alcohol consumption

As the measurement of GGT, ALT, AST and MCV is easy and inexpensive, they remain the most frequently used markers for early detection of ALD.[150] However, all these laboratory values are only indirect markers for ALD, with low sensitivity and specificity (Table 5).[151–154] No single marker or combination of markers can differentiate between different causes of liver disease. GGT is usually higher in patients with ALD compared to 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.[155] Likewise, elevation of AST may be observed in all forms of ALD with a sensitivity of 50% and a specificity of around 80% (Table 5). AST levels are rarely above 300 U/ml, while serum ALT levels are commonly lower. Also the AST/ALT ratio which is typically greater than 1, is neither specific, nor sensitive, particularly in the cirrhotic stage of disease.[152,156]

In addition, the indirect alcohol marker carbohydrate deficient transferrin (CDT) may be measured to confirm critical alcohol consumption in patients who are suspected to deny or underreport intake. However, CDT can only indicate heavy alcohol consumption, since a daily intake of 50–80 g of ethanol over a period of at least one to two weeks is required for a positive CDT test result. After alcohol cessation, CDT normalises after two to three weeks.[157] There are many confounding factors for the measurement of CDT (Table 5) among which the stage of liver disease is probably most critical.[158,159] So, patients with cirrhosis more commonly have a false negative result. To increase reliability CDT should be expressed as percent of total transferrin, thereby accounting for individual variations in transferrin levels. Furthermore, only one of the isoforms, the disialotransferrin glycoform of CDT, should be measured by high-performance liquid chromatography. So, depending on the assay used and the patient population tested, the sensitivity and specificity of CDT testing varies considerably (Table 5).[157,160,161]

Direct markers for alcohol consumption

In comparison to all these indirect alcohol markers, the direct alcohol markers, *i.e.* ethyl glucuronide (EtG), ethyl sulfate (EtS), phosphatidylethanol (PEth) and fatty acid ethyl esters (FAEEs) have a much higher specificity, since they are all direct

products of the non-oxidative metabolism of ethanol. Furthermore, in comparison to direct determination of ethanol in blood or exhaled air, they have a much longer detection window, which is often critical in order to uncover alcohol intake.[162] To date, determination of the ethanol conjugate EtG in urine (uEtG) is widely applied in many European countries for proving recent alcohol abstinence in forensic settings or for regular monitoring of patients in alcohol addiction programmes and prior to listing for liver transplantation. Depending on the level of alcohol intake, EtG remains in the urine for up to 80 hours. For screening purposes an inexpensive immunoassay is recommended with the possibility of confirmation of positive results via the more expensive liquid chromatography tandem spectrometry.[163] If a cut-off of 0.1 mg/L is used, consumption of very small amounts of alcohol (<5 g) can be detected, so that accidental alcohol intake via, for example, sweets, sauces, alcohol-containing mouth solution *etc.*, may cause a positive test result. Therefore, a higher cut-off is often used resulting in a slightly lower, but still very high sensitivity.[154] Notably, uEtG is not influenced by the presence of compensated or decompensated cirrhosis. So, in a cohort of 141 liver transplant candidates and recipients the sensitivity and specificity of uEtG of 89% and 99%, respectively, outperformed all other indirect alcohol markers, including GGT, AST, ALT, MCV and CDT, in predicting alcohol consumption.

In contrast to urinary EtG, determination of EtG in the scalp hair (hEtG) of patients is a powerful tool for monitoring not only short-term, but long-term abstinence from alcohol over a period of up to six months. Thereby each hair segment of 1 cm length reflects alcohol consumption over approximately one month. However, if samples less than 3 cm or greater than 6 cm are used, the results should be interpreted with caution (www.soht.org). In individuals with short hair, incorporation of EtG from sweat into hair after recent alcohol consumption is a concern.[164] In individuals with long-hair, treatments, such as dying, perming or bleaching, may play an increasing role in reducing EtG concentration in the hair. Also, slower hair growth in sick, cirrhotic patients should be considered when assessing results. Nevertheless, several studies show a high correlation between daily alcohol intake and hEtG concentrations in 3–6 cm long hair segments[165,166] and internationally accepted cut-off values for abstinence (<7 pg/mg), "social drinking" (hEtG 7–30 pg/mg) and chronic excessive alcohol consumption with more than 60 g ethanol intake per day (hEtG >30 pg/mg) have been defined (www.soht.org). Due to its high specificity and sensitivity (Table 5), interest in hEtG testing has grown over the past few years, especially for evaluating alcohol abuse in forensic settings,[167] for example child custody cases, or in confirmation of six-month alcohol abstinence in liver transplant recipients.[168]

To get a comprehensive picture of the true alcohol consumption of a patient, it is best to combine different available methods, *i.e.* questionnaires with uETG and hETG testing. In addition to these already well established direct alcohol markers with high reliability, determination of other direct markers, such as EtS in urine, FAEES in hair and PEth in serum or in dried blood spots may gain increasing recognition in the future, as additional methods for confirming suspected alcohol intake.[28,169–175]

Suggestions for future studies

- Investigations focussed on the mechanisms and prognostic significance of histological cholestasis
- Investigation of the clinical utility of monitoring tests for alcohol consumption
- Investigations to determine the optimal screening tool for liver fibrosis

Recommendations

- Liver biopsy is required where there is diagnostic uncertainty, where precise staging is required or in clinical trials (**Grade A1**)
- Screening of patients with AUD should include determination of LFTs and a measure of liver fibrosis. (**Grade A1**)
- Abstinence can be accurately monitored by measurement of EtG in urine or hair (**Grade A2**)

Management of alcoholic hepatitis

Definition and diagnosis

Alcoholic hepatitis is a distinct clinical syndrome characterised by the recent onset of jaundice with or without other signs of liver decompensation (*i.e.* ascites and/or encephalopathy) in patients with ongoing alcohol abuse.[176] It is not uncommon for patients to have ceased alcohol consumption days or weeks before the onset of symptoms. Underlying this clinical syndrome is steatohepatitis, a disease defined histologically by steatosis, hepatocyte ballooning, and an inflammatory infiltrate with polymorphonuclear neutrophils.[88] However, the clinical features of this syndrome can also result from sepsis, drug-induced liver injury, gallstone migration, *etc.*

The cardinal sign of AH is a progressive jaundice, that is often associated with fever (even in the absence of infection), malaise, weight loss and malnutrition. The laboratory profile of AH reveals neutrophilia, hyperbilirubinemia (>50 μMol/L), serum levels of AST greater than twice the upper limit of normal range, AST >50 IU/ml, although rarely above 300 IU/ml, with an AST/ALT ratio typically greater than 1.5–2.0. In severe forms, prolonged prothrombin time, hypoalbuminemia, and decreased platelet count are frequently observed.

Diagnosis of AH is based on clinical (*i.e.* recent onset of jaundice) and typical laboratory findings mentioned earlier in a patient with a history of heavy alcohol use. Liver biopsy (performed by transjugular route to reduce the risk of bleeding) can be useful to confirm the diagnosis, rule out other diagnoses found in 10–20% of cases,[72,99] and for prognostication.[84,110,111] The main restrictions on the use of liver biopsy in routine clinical practice are access to transjugular liver biopsy, risks and the costs of the procedure. Therefore, the decision to perform biopsy has to take into account the availability of the procedure and experience of the team. Biopsy must only be performed in cases where there is diagnostic uncertainty. In the absence of a liver biopsy more stringent clinical and laboratory criteria should be applied to avoid the misdiagnosis of alcoholic hepatitis, particularly amongst patients with cirrhosis.[83]

The incidence of AH remains largely unknown. A retrospective Danish study based on diagnosis codes revealed an increasing incidence, from 37 cases/million in 1999 to 46 cases/million in 2008 in men and 24 cases/million rising to 34 cases/million in women.[177] Although female sex is an independent risk factor for AH, it is more frequent in men. Excess weight is another risk factor for AH.[178] Although no clear threshold for the amount of

Table 6. Variables incorporated in the five prognostic scores most commonly used in alcoholic hepatitis.

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

Maddrey, Maddrey discriminant function; MELD, model for end-stage liver disease; GAHS, Glasgow alcoholic hepatitis score; ABIC, age, serum bilirubin, INR, and serum creatinine score.

alcohol consumption has been identified, AH generally occurs after decades of heavy alcohol use (>80 g/day).

Evaluation of severity

Different prognostic models have been developed which aim to identify patients at high risk of early death using baseline and dynamic variables (Table 6). The Maddrey discriminant function (DF) was the first score that reliably defined individuals at the highest risk of death in the short-term, and remains the most widely used in clinical practice and clinical trials. DF was originally developed in 1978,[179] and then modified (mDF) in 1989.[180] In its modified version, a cut-off value of 32 identifies patients with severe AH and is usually the threshold used for initiating specific therapy. In the absence of treatment, the one-month survival of patients with mDF ≥32 has improved from 50% in early publication to 85% in recent trials.[181,182] Patients with a non-severe AH (*i.e.* mDF <32) had a less than 10% risk of one-month mortality.[183] However, the long-term prognosis of those patients remains largely unknown.

More recently, several prognostic scores such as the model for end-stage liver disease (MELD), the Glasgow alcoholic hepatitis score (GAHS), and the ABIC (age, serum bilirubin, INR, and serum creatinine) score have been developed in the setting of AH. The MELD score is already a well-validated prognostic score in cirrhosis (www.mayoclinic.org/meld/mayomodel7.html). Its usefulness in assessing the short-term prognosis of AH has been studied in retrospective studies, which suggest that patients with an MELD score above 20 are at a high risk of 90-day mortality.[184] GAHS was derived from five variables independently associated with outcome (age, serum bilirubin, blood urea, prothrombin time, and peripheral blood white blood cell count) and identifies patients at greatest risk of death in the absence of treatment.[185] The GAHS ranges from 5 to 12 and patients with an mDF ≥32 and a GAHS ≥9 have a poor prognosis and an 84-day survival benefit when treated with corticosteroid.[186] The ABIC score classified patients with AH according to low, intermediate and high risk of death at 90 days.[187] These different scoring systems often incorporate the same variables and appear to have similar efficacy in predicting short-term survival.[188,189]

Early improvements in liver function have a major impact on short-term mortality. An early change in bilirubin levels, evaluated at day seven of therapy, was initially proposed to easily identify corticosteroid-treated patients at high risk of six-month mortality.[190] Similarly, an early change in the MELD score in the first week has been shown to predict in-hospital mortality.[191] Subsequently, the Lille model, which is based on pretreatment data plus the response of serum levels of bilirubin to a seven-day course of corticosteroid therapy was developed.[192] This score ranges from 0 to 1; a score ≥0.45 indicates non-response to corticosteroids. A subsequent analysis that re-evaluated the Lille score identified three patterns of response to corticosteroid therapy: complete responders (Lille score ≤0.16), partial responders (Lille score 0.16–0.56) and null responders (Lille score ≥0.56), and strongly suggested that corticosteroids should be discontinued in null responders at day seven of therapy.[193] Recently, the combination of MELD and the Lille model was suggested as an effective predictive algorithm of short-term mortality.[194]

Treatment of alcoholic hepatitis

General measures

Regardless of the severity, alcohol abstinence is the cornerstone of therapy and early management of AUD is recommended in all patients with AH (Fig. 1). In severe AH, a recent paper demonstrated that severity of liver injury determines short-term survival while alcohol abstinence is the main determinant of long-term prognosis.[195] Considering the potential risk of Wernicke's encephalopathy, supplementation with B-complex vitamins is recommended. Other general approaches include treatment of hepatic encephalopathy (lactulose, rifaximin) and treatment of ascites (salt restriction). Patients with severe AH are at risk of developing acute kidney injury (AKI) which negatively impacts survival.[196] Measures aimed at preventing the development of renal failure are therefore recommended. They include avoidance of diuretics and nephrotoxic drugs and volume expansion if needed. Considering prevention of variceal bleeding, it was suggested that the use of beta-blockers increases the risk of AKI.[197]

Nutrition

Malnutrition is commonly associated with cirrhosis and its severity.[198] Several studies have highlighted that protein energy malnutrition is present in almost every patient with severe AH, and is associated with poor prognosis.[199] The European Society for Clinical Nutrition and Metabolism (ESPEN) recommend a daily energy intake of 35–40 kcal/kg of body weight (BW) and a daily protein intake of 1.2–1.5 g/kg of BW in patients with AH.[198] However, these objectives are often difficult to achieve in clinical practice. Therefore, the use of tube feeding is strongly recommended if patients are not able to maintain adequate oral intake. A randomised controlled trial comparing 28 days of total enteral nutrition to corticosteroid treatment in 71 patients with severe AH suggested that these approaches resulted in comparable one- and six-month survival rates.[200] More recently, a multicentre randomised controlled trial compared the combination of 14 days of intensive enteral nutrition using a feeding tube plus corticosteroids for 28 days to corticosteroid therapy alone, and showed that combination therapy did not improve survival.[201] Tolerance of the feeding tube was an important issue, since nearly half of the patients prematurely withdrew the feeding tube. Interestingly, a *post hoc* analysis of this study demonstrated that, regardless of the allocated therapy, patients with a daily calorie intake below 21.5 kcal/kg of BW had a significantly higher risk of one- and six-month mortality and infections. Thus, it appears reasonable to recommend a careful evaluation of nutritional status and energy intake, to target 35–40 kcal/kg of BW and a daily protein intake of 1.2–1.5 g/kg

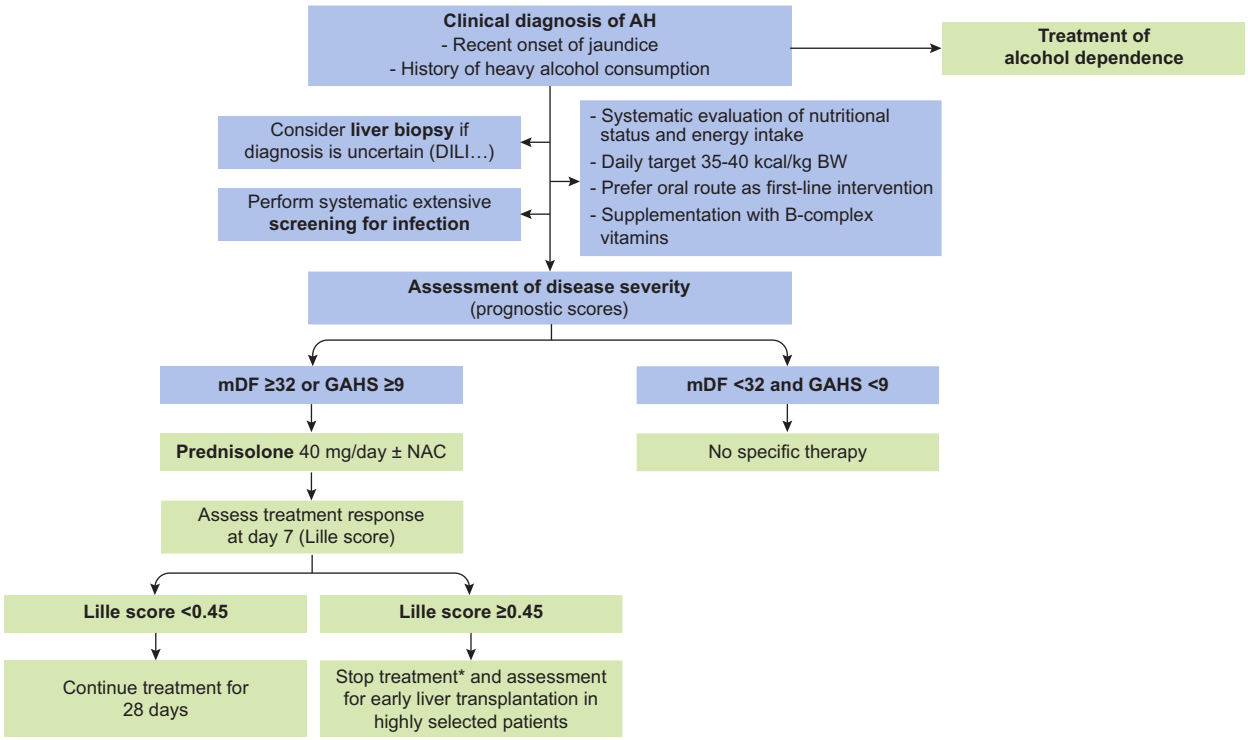

Fig. 1. Treatment algorithm in patients with suspected alcoholic hepatitis. *Particularly in null responders (Lille score ≥0.56). AH, alcoholic hepatitis; BW, bodyweight; DILI, drug-induced liver injury; GAHS, Glasgow alcoholic hepatitis score; mDF, maddrey discriminant function.

of BW and to adopt the oral route as first-line intervention in patients with severe AH.

While parenteral nutrition might circumvent the complications of naso-gastric feeding there is not currently sufficient evidence to support a recommendation, particularly given that parenteral feeding is associated with a high risk of line sepsis.

Corticosteroids

The use of corticosteroids to treat AH has been controversial, owing to the divergent findings of individual studies and meta-analyses.[202–204] A large multicentre randomised trial (STOPAH) was conducted in the United Kingdom between 2011 and 2014, in patients with a clinical diagnosis of severe AH, in order to resolve the controversy over the use of corticosteroids or pentoxifylline (PTX).[181] This study reported a borderline reduction in mortality at 28 days for patients treated with prednisolone 40 mg/day compared with control patients. Importantly, prednisolone therapy provided no benefit to patients after one month, which was subsequently confirmed in a network meta-analysis.[205]

The applicability of corticosteroid therapy is limited by concerns about heightened risks of sepsis and gastrointestinal bleeding. Therefore, early identification of non-responders to corticosteroids is important to define stopping rules and limit unnecessary exposure. The Lille score allows clinicians to predict poor response to corticosteroids at seven days of therapy[192] (see section "evaluation of severity"). In case of poor response, it is recommended that corticosteroids be interrupted, particularly in "null responders" (defined by Lille score ≥0.56).[193]

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. At the end of the course 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.

N-acetylcysteine

Antioxidant therapy is of theoretical interest in the treatment of AH because of increasing evidence that oxidative stress is a key mechanism in alcohol-mediated hepatotoxicity.[206] Ethanol consumption results in depletion of endogenous antioxidant capacities, and patients with AH show evidence of antioxidant deficiencies.[207] Because N-acetylcysteine (NAC) restores the glutathione store and consequently limits oxidative stress, it has been studied, either alone or in combination with other antioxidants, in several trials of severe AH. In those different trials, NAC did not increase survival compared to standard medical therapy.[182,208,209]

A multicentre French trial compared the effects of the combination of NAC and prednisolone to prednisolone and placebo.[210] In this study, NAC was administered intravenously for five days. Mortality at one month was significantly lower in the NAC plus prednisolone group compared to the prednisolone plus placebo arm. Importantly, NAC combined with prednisolone, also significantly reduced the incidence of hepatorenal syndrome and infections. Therefore, the combination of NAC and prednisolone appear to improve prognosis of patients with severe AH, and this combination should be tested in a future large clinical trial to confirm its efficacy.

Granulocyte colony stimulating factor

Granulocyte colony stimulating factor (GCSF) is a glycoprotein that stimulates the bone marrow to produce and release neutrophils and stem cells (CD34+) into the bloodstream. Ineffective liver regeneration has been postulated as one of the key factor leading to progressive liver failure and non-recovery in patients with AH.[123] In animal models, the administration of GCSF was able to mobilise the hematopoietic stem cells, induce liver regeneration, and improve survival.[211] Spahr *et al.* demonstrated that GCSF administered subcutaneously for five days in patients with

AH, mobilised CD34+ stem cells, increased circulating hepatocyte growth factor and induced proliferation of hepatic progenitor cells.[212] A randomised placebo-controlled trial from India using GCSF for one month in patients with ACLF (>50% had AH) showed significantly improved short-term survival, and decreased risk of infection and kidney injury in the GCSF group.[213] Another randomised controlled trial from India assessed the effects of PTX *vs.* a combination of PTX and GCSF.[214] A significantly larger proportion of patients who received PTX plus GCSF survived for 90 days than those who received only PTX. Although the sample size was limited, these findings indicate that GCSF might improve the prognosis of patients with severe AH. Moreover, GCSF is easy to administer and is well tolerated. However, a European study of GCSF in decompensated cirrhosis (mostly caused by AH) reported negative results so further trials are required before it can be recommended as a treatment in severe AH.[215]

Pentoxifylline

Pentoxifylline, a phosphodiesterase inhibitor, has been evaluated in patients with AH for its ability to inhibit production of tumour necrosis factor (TNF). In the initial randomised study comparing PTX to placebo in patients with severe AH, patients treated with PTX had an improved six-month survival.[216] This survival benefit was not accompanied by significant changes in liver function, but it was related to a marked reduction in the incidence of hepatorenal syndrome. A large French multicentre trial, which evaluated PTX *vs.* placebo in 335 Child-Pugh C cirrhotic patients (mainly ALD origin, 133 with AH) reported no significant difference in short-term mortality between both arms, in the overall study and in subjects with AH.[217] The combination of corticosteroids with PTX was also evaluated in different trials. In the Corpentox study,[218] 28-day treatment with PTX (1,200 mg/day) plus prednisolone, compared with prednisolone plus placebo in patients with severe AH, did not result in improved short-term survival. Although not significant, incidence of hepatorenal syndrome was lower in patients receiving the combination of PTX and prednisolone. In the STOPAH trial[181] survival (at one month, three months, and one year) was not better in patients receiving PTX compared to those not receiving PTX. Finally, an early switch to PTX in non-responders to corticosteroids did not improve two-month survival compared to matched non-responders treated with corticosteroids only.[219]

In summary, evidence for a survival benefit of PTX therapy in patients with severe AH is very weak, and the drug can no longer be recommended.

Anti-TNF agents

Based on animal models suggesting a key role of TNF-α in the pathogenesis of ALD,[220] and increased liver and serum levels of TNF-α in human ALD,[221] both infliximab and etanercept were evaluated in AH in randomised controlled trials.[222,223] Those studies showed a higher risk of death and of severe infections in AH patients treated with anti-TNF agents. Therefore, those agents are not considered as a treatment option in AH.

Extracorporeal liver support

Extracorporeal liver support procedures can remove some potentially damaging circulating molecules, and are therefore, of potential interest in patients with severe AH. Some encouraging preliminary data with albumin dialysis were reported in patients with severe AH.[224,225] However, to date, no clear benefit has been demonstrated using these extracorporeal liver support devices.[226]

Infection in alcoholic hepatitis

Infection is a frequent and severe complication in patients with severe AH, and is one of the major causes of death. A recent meta-analysis found a 28-day cumulative incidence of infection of approximately 20%.[227] Other trials reported higher incidence of infection in up to 65% during a three-month follow-up.[201,228] Louvet *et al.* reported that patients with severe AH being infected suffer from a further increase in mortality of 30% at two months.[229] In the STOPAH trial, infections accounted for 24% of all deaths.[181] High incidence of infections may be partly explained by underlying cirrhosis, frequently present in biopsy-proven severe AH and cirrhosis-related defects in the immune system. Cirrhosis-induced immunodeficiency is a complex, multifactorial process, resulting from bacterial overgrowth, dysbiosis and increased translocation on one side, and impaired innate and adaptive immunity on the other.[230]

One of the major controversies of the past few years is whether corticosteroids, used for the treatment of severe AH, increase the risk of infection. A recent meta-analysis has shown that patients treated with corticosteroids had no increased risk of infection or higher mortality from infection than those treated with placebo.[227] Furthermore, it has been implied that development of infection depends more on the response to corticosteroid treatment rather than the treatment *per se*.[229] However, corticosteroids might enhance infection because they are known to induce infectious events in other fields, mainly by inducing a defect in lymphocyte signalling. In the STOPAH trial, serious infections were more frequent in patients treated with prednisolone. In addition, a higher proportion of patients receiving prednisolone developed an infection after treatment than patients not given prednisolone (10% *vs.* 6%). Importantly, development of infection was associated with increased 90-day mortality only in patients treated with prednisolone, independent of baseline disease severity.[189]

Bacterial infections represent the vast majority (approximately 90%) of infectious episodes in the setting of severe AH. Louvet *et al.* distinguished infections at admission from those during treatment and follow-up. At baseline, spontaneous bacterial peritonitis (SBP) or spontaneous bacteremia (SB) occurred more frequently (44%), followed by urinary tract infections (UTI) (32%), while a shift towards respiratory infections was noted (40% of all episodes) during or after corticosteroid treatment.[229] Therefore, a careful screening for infection is recommended before initiating therapy, repeatedly during corticosteroid treatment, and during the follow-up period.

Interestingly, the presence of an infection at baseline does not appear to contraindicate steroid therapy if the infectious episode is well treated and 'controlled'.[229] In a subsequent analysis of the STOPAH trial,[189] in patients with baseline infection who received prednisolone, there was a significant reduction in 90-day mortality associated with continued antibiotic therapy when compared with those patients in whom antibiotic therapy was stopped before initiating prednisolone (13% *vs.* 52%). Of interest, high circulating bacterial DNA predicted infection that developed within seven days of prednisolone therapy. This could help to better define corticosteroid-treated patients who will benefit from preventive antibiotic therapy in the future. Trials evaluating antibiotic prophylaxis in high-risk patients with severe AH, treated with corticosteroids, are ongoing (NCT02281929).

Invasive aspergillosis (IA) has been reported to complicate severe AH. In a prospective cohort of 94 patients with severe AH, undergoing systemic intensive screening for IA, IA incidence was 16% during a three-month follow-up.[228] In this experience, risk factors for the acquisition of IA were ICU admission and a baseline MELD score ≥24. The diagnosis of IA and the distinction with colonisation in these patients are challenging. Serum galactomannan may be a good screening test for IA (cut-off ≥0.5, sensitivity of 89% and specificity of 84%). Despite adequate antifungal treatment, IA was associated with a dramatically poor outcome.

Sporadic cases of pneumocystis pneumonia (PCP) were described in patients with severe AH and concomitant corticosteroid treatment, with a very high mortality rate. In a prospective cohort, PCP was suspected in 8% of patients.[228]

In view of the non-negligible incidence and the dramatic prognosis of IA and PCP despite adequate therapies in patients with severe AH treated with corticosteroids, aggressive screening strategies should be recommended, and prospective studies should be conducted to evaluate prophylactic strategies.

Suggestions for future studies

- Further studies are required to validate the use of the Lille score at day four.
- New strategies need to be developed to reduce the risk of infection

Recommendations

- A recent onset of jaundice in patients with excessive alcohol consumption should prompt clinicians to suspect AH (**Grade A1**)
- Available prognostic scores should be used to identify severe forms of AH, at risk of early mortality (**Grade A1**)
- In the absence of active infection, corticosteroids (prednisolone 40 mg/day or methylprednisolone 32 mg/day) should be considered in patients with severe AH to reduce short term mortality (**Grade A1**). However, corticosteroids do not influence medium to long term survival.
- N-acetylcysteine (for five days, intravenously) may be combined with corticosteroids in patients with severe AH (**Grade B2**)
- A careful evaluation of nutritional status should be performed and patients should aim 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 (**Grade A2**)
- Systematic screening for infection should be performed before initiating therapy, during corticosteroid treatment, and during the follow-up period (**Grade A1**)
- Early non-response (at day seven) to corticosteroids should be identified and strict rules for the cessation of therapy should be applied (**Grade A1**)
- In case of non-response to corticosteroids, highly selected patients should be considered for early liver transplantation (**Grade A1**)

Alcohol-related fibrosis and cirrhosis

Alcohol-related fibrosis

Excessive alcohol consumption may induce a wide spectrum of lesions that include pure alcoholic steatosis, steatohepatitis, progressive liver fibrosis, cirrhosis and HCC.[231] Above a daily consumption of 30 g/day, or a weekly consumption above seven units in women and 14 units in men,[232] the risk of developing ALD is increased.[233] At a daily intake of 100 g/day the relative risk reaches 26.[234] Pure hepatic steatosis, often asymptomatic and overlooked, is almost constant in individuals consuming alcohol in excess (>100 g/day) and may fully reverse following several weeks of abstinence. However, in approximately 10–35% of chronic excessive drinkers, progressive liver injury including AH and liver fibrosis develop and reach the stage of cirrhosis.[231] In excessive drinkers in whom liver biopsy was repeated after four years of follow-up, both steatosis and lesions of AH were independently associated with progression of fibrosis.[106] The presence of mixed macro- and microvesicular steatosis increases the risk of ALD progression.[93] A Danish nationwide registry cohort confirmed an increased risk of cirrhosis at five years in patients with steatohepatitis (16%, 95% CI 7.8–26.8%), with a non-negligible risk of progression in patients with pure steatosis (6.9%; 95% CI 3.4–12.2%).[235] This unexpectedly high rate of progression in a situation accepted as benign should reinforce the need for abstinence in the early phase of ALD. The stage of liver disease in patients with ALD is also a strong predictor of outcome. The liver-related mortality rate at five years is 13% in patients with early alcoholic liver fibrosis but 43% in those with advanced disease.[126]

The progression to advanced ALD (extensive liver fibrosis and cirrhosis) may be influenced by environmental and host factors. Exogenous factors include the amount, type and pattern of alcohol consumption, but also cigarette smoking and coffee drinking. In a population-based study with 20 years of follow-up, smoking ≥1 pack daily tripled the risk of ALD compared to non-smokers, irrespective of alcohol consumption.[236] Conversely, coffee drinking seems to have beneficial effects on the risk of cirrhosis. In a recent meta-analysis, drinking up to two cups of coffee per day decreased by nearly half the risk of alcoholic cirrhosis (relative risk 0.62; 95% CI 0.51–0.73), after adjusting for confounding factors including alcohol consumption.[237] Potential modifiers of natural history of ALD include genetic and non-genetic factors.[231,238] Thus, gender,[239] ethnicity,[240] comorbid conditions such as diabetes and obesity,[241,242] microbial dysbiosis,[243] chronic infection with HBV and HCV[244] and/or human immunodeficiency virus (HIV),[245] α-antitrypsin deficiency, iron overload, and genetic risk factors may influence disease progression.

In addition to the total amount of ingested alcohol, both the type and pattern of drinking seem to influence the development of ALD. A lower risk of alcoholic cirrhosis has been reported in red wine drinkers (relative risk of 0.3) compared to individuals consuming other types of alcoholic beverages.[246,78] Whether this difference relates to some particular composition of wine or if it relates to some confounding factors such as diet is still debated.[246–248] Data from the Dionysos study in northern Italy identified that drinking alcohol outside meals, and consuming more than one type of alcoholic beverage increased the risk of cirrhosis.[233] Drinking frequency influences the risk of cirrhosis. The risk of alcoholic cirrhosis was increased in regular, daily drinkers (HR 3.65; 95% CI 2.39–5.55) compared to those

drinking 2–4 days a week in a prospective cohort study from Denmark. The pattern of *binge drinking*, as defined by a heavy episodic alcohol intake, is becoming highly prevalent in young individuals. Whether binge drinking compared to continuous alcohol abuse accelerates the progression to advanced ALD has been partially resolved by a recent publication from Finland.[249,16] Among 6,000 individuals without baseline liver disease, 25% of alcohol users reported weekly or monthly binge drinking. The risk of liver decompensation and binge drinking episodes was almost linear over time, after adjusting for age and total alcohol consumption.[250] The hazard ratio for weekly and monthly binge drinking was 3.45 and 2.26, respectively, affecting preferentially individuals with the features of the metabolic syndrome (HR for weekly binge drinking 4.29).

Among host related factors, female gender is associated with a greater risk of developing ALD at a given alcohol consumption. This increased susceptibility may result from several factors, including a lower gastric enzymatic capacity for alcohol metabolism resulting in a higher ethanol blood concentration, a higher proportion of body fat accelerating fibrosis formation,[251] and the impact of oestrogens on intestinal barrier function[239] facilitating the development of liver inflammation.

The prevalence of ALD seems to differ according to ethnicity. A higher risk of alcoholic cirrhosis has been reported in Hispanics, both men and women, compared with African Americans and Caucasians,[240] with clinical symptoms appearing 4–10 years earlier, after adjustment for age and alcohol use. However, it is unclear if the apparent susceptibility in this ethnic subgroup is genetically related or influenced by confounding factors such as diabetes and obesity, drinking habits, or differences in socioeconomic status potentially limiting access to medical care.

Excessive BW and obesity are important risk factors for liver fibrosis progression in individuals consuming alcohol. In a French cohort of approximately 1,400 patients with chronic AUD without cirrhosis, being of excess weight in the last 10 years (BMI ≥27 kg/m^2 in men and ≥25 kg/m^2 in women) was an independent factor associated with ALD progression, together with the total amount of alcohol consumption and female sex.[252] The negative effect of obesity in excess drinkers appears synergistic and not only additive. In a Scottish study,[253] obese individuals consuming 15 or more drinks per week had an adjusted relative rate of liver-related death of 18.9 (95% CI 6.84–52.4) compared to 3.16 (95% CI 1.28–7.8) in their lean counterparts. In part, obesity promotes hepatotoxicity through generation of proinflammatory cytokines such as TNF-α, pointing to the role of visceral fat as a modulator of systemic and liver inflammation. Other elements of the metabolic syndrome are frequent in patients with ALD[242] and may contribute to disease progression and severity.[254,255]

Alcohol and infection with hepatitis virus have synergistic effects in the progression of liver fibrosis. Due to some common risk factors, chronic infection with HBV, HCV, or HIV is not uncommon in patients consuming excessive alcohol. The prevalence of HCV infection is 3- to 30-fold higher in patients with AUD compared to the general population,[256] and HCV infection is associated with an increased progression of liver fibrosis and end-stage liver disease. In patients infected with HCV, ingestion of 50 g of alcohol per day carries a 30% increased risk of fibrosis progression compared to non-drinkers.[244] Pathogenic mechanisms include increased oxidative stress, impaired immune response and viral load. Data supporting a major role of alcohol in the development of advanced liver disease in patients with chronic HBV infection are scarce. However, both excessive alcohol and HIV coinfection are associated with increased mortality earlier in life in these patients.[257] In a large cohort of HIV-infected with HIV from Baltimore, a high risk of liver-related mortality was reported in individuals reporting recent heavy alcohol consumption in the past six months (HR 7.28; 95% CI 2.43–21.78).[245] Thus, given the risk of accelerated liver fibrosis in individuals chronically infected with HCV, HBV and HIV, promotion of abstinence should be strongly encouraged.

The risk of liver fibrosis in association with drug-induced liver injury can be influenced by alcohol consumption. Methotrexate-induced fibrosis is frequently influenced by cofactors of fibrogenesis, including obesity, diabetes and alcohol abuse. Consequently, alcohol abstinence is usually advised together with monitoring of liver injury. In recent studies examining risk factors of methotrexate hepatotoxicity, the role of alcohol consumption was not considered as major in patients with psoriasis[258] or rheumatoid arthritis[259] compared to obesity and diabetes. In the latter study,[259] a marginal risk of hepatotoxicity was detected at a weekly alcohol consumption of 15 to 21 units, becoming evident above 21 units per week (adjusted HR 1.85; 95% CI 1.17–2.93). However, in clinical practice investigation of possible liver fibrosis is advised in the presence of chronic alcohol consumption or metabolic cofactors prior to initiation of methotrexate.

The relationship between iron overload and ALD is frequently reported. Chronic excessive alcohol and excess iron participate to oxidative stress and activate fibrogenesis. Patients with hereditary haemochromatosis who consume more than 60 g of alcohol per day have an increased risk of developing advanced ALD.[260] However, although heterozygosity for *HFE* mutations is reported higher in patients with AUD[261,262] and associated with mild iron overload,[263] it has no major influence on the progression of ALD. Therefore, iron depletion is not indicated in patients with AUD with non-*HFE* mutations. It is of note that iron metabolism markers, such as ferritin and transferrin saturation, are frequently elevated in patients with ALD, although to a lesser extent than in patients with homozygous haemochromatosis.[264]

Heterozygosity for the Z allele of α1-antitrypsin deficiency may expose an individual to an increased risk of developing chronic liver disease in the presence of alcohol use. In patients with alcoholic cirrhosis referred for liver transplantation, presence of one Z allele was four times more frequent than other aetiologies.[265] However, no solid data supports a clear association between heterozygous variants of α1-antitrypsin and accelerated liver fibrosis in the presence of alcohol abuse.

Host genetic factors may influence the course of ALD. In twin concordance studies, a greater concordance was found in monozygotic compared to dizygotic twins, with a prevalence of chronic ALD per 1,000 individuals of 14.6 and 5.4, respectively.[266] Candidate gene association studies as well as genome-wide association studies have identified polymorphisms in the *PNPLA3* gene, associated with an increased risk of alcoholic liver injury lesions in Caucasian individuals.[267–270] According to a recent meta-analysis including 10 studies, the odds ratio for alcoholic liver injury and alcoholic cirrhosis in carriers of rs738409 CG is 1.45 (95% CI 1.24–1.69) and 2.09 (95% CI 1.79–2.44), respectively.[270] Additional genetic variants on *TM6SF2* and *MBOAT7* genes also confer an increased risk for

ALD, possibly by influencing hepatocyte lipid trafficking.[271] In NAFLD, a condition that shares similar pathogenic mechanisms with ALD, the association of *PNPLA3*, *TMF6SF2*, *MBOAT7* polymorphisms and histological lesions has been reported.[272] Epigenetic polymorphism on the *NFE2L2* gene could also affect the response to acetaldehyde induced oxidative stress,[273] but this is not well supported by human data.

Management of alcohol-related fibrosis

The management of alcohol-related fibrosis is challenging, as most patients are asymptomatic in the early phase of the disease, seeking medical attention only at the stage of advanced ALD with the development of clinical complications. Complete and sustained alcohol abstinence remains the cornerstone of the management of ALD.[130] Identification of individuals early in the course of ALD when liver fibrosis is incomplete and potentially reversible is meaningful. Accordingly, general screening strategies to detect harmful alcohol consumption in a general hospital admission setting proved feasible and could help to target patients in whom therapeutic intervention for alcohol misuse would be particularly indicated.[25] Treating comorbid conditions such as obesity and other components of the metabolic syndrome must be encouraged together with interventions targeting alcohol misuse. Promotion of physical exercise in obese patients who continue to drink alcohol improves several nutritional parameters but has no effect on hepatic triglycerides, suggesting that persistent alcohol may blunt the effects of physical activity on liver steatosis.[274] Whether moderate alcohol consumption in overweight or obese individuals is associated with an increased risk of developing chronic ALD is still unclear, and a definition of safe alcohol cannot be given in this particular situation.[275] In patients from the non-alcoholic steatohepatitis clinical research network, a daily consumption of up to 20 g/day of alcohol was associated with less improvement in aminotransferases and steatosis on liver biopsy after more than two years of follow-up, compared to abstinent patients.[276] Future developments in the understanding of synergic mechanisms between alcohol and components of the metabolic syndrome may help to formulate clear recommendations in this population.

The concept of extracellular matrix remodelling and possible regression of liver fibrosis comes from experimental studies and clinical observations in chronic liver diseases mostly of viral aetiology.[277] In the setting of ALD, data are few, but the conversion from micronodular to macronodular cirrhosis following several years of alcohol abstinence tend to support this dynamic aspect of liver fibrosis.[94] Will antifibrotic agents help to reverse fibrosis in addition to alcohol abstinence? Antagonising angiotensin II, involved in hepatic stellate cell activation, proved beneficial and safe in humans.[278] This controlled study of 85 abstinent alcoholic cirrhotics demonstrated reduced fibrosis, α-smooth muscle actin positivity and hydroxyproline tissue levels on repeat liver biopsy after six months on the angiotensin-blocking agent candesartan. Conversely, other agents such as S-adenosyl-L-methionine conveyed no change on liver fibrosis as assessed by histology.[279] Thus, future development of molecules targeting extracellular matrix and liver fibrosis may open novel therapeutic perspectives in chronic liver diseases including ALD.[280] Monitoring changes in liver fibrosis may be achieved by TE using Fibroscan as the most reliable non-invasive method in ALD.[281]

Suggestions for future studies

- Large genome-wide analysis should confirm *PNPLA3* rs738409 as an important susceptibility gene in ALD and possibly identify other genetic polymorphisms for better screening
- The interaction between environmental and genetic factors should be investigated
- The mechanisms underlying the additive effects of components of the metabolic syndrome and alcohol on ALD progression should be explored
- Additional studies are required to identify the factors influencing fibrosis regression after drinking cessation and long-term outcome in abstinent patients.

Alcoholic cirrhosis

Liver fibrosis can progress to alcoholic cirrhosis, as defined by a marked distortion of hepatic architecture by extensive fibrosis, typically in a chicken-wire pattern,[94] formation of regenerating nodules and abnormal sinusoidal blood flow. Compared to alcoholic cirrhotics who continue to drink alcohol, patients who reach durable abstinence have no or mild steatosis, and minor parenchymal lymphomonocytic infiltrate, if any. Persistence of steatosis may suggest non-alcoholic fatty liver as a comorbid condition, or result from ongoing alcohol intake. MDBs can be observed up to several months following cessation of alcohol, or when significant cholestasis coexists. Disturbed iron metabolism sometimes observed in patients with alcoholic cirrhosis manifests either by mild stainable iron on liver biopsy (relative risk 2.27; 95% CI 1.2–4.19)[282] or by low serum hepcidin levels (HR 1.63; 95% CI 1.07–2.44),[283] and is an independent predictor of mortality.

Patients with alcoholic cirrhosis may be asymptomatic in a compensated form, or present with jaundice, ascites, variceal bleeding, infections, hepatorenal syndrome, hepatic encephalopathy and cachexia in a decompensated form. The prognosis of these patients is evaluated using commonly used scores such as the MELD or the Child-Pugh scores. A retrospective study identified the development of ascites as the predominant pattern of decompensation in alcoholic cirrhosis, compared to HCC in non-alcoholic cirrhosis.[284] The rates of progression from compensated to decompensated cirrhosis are summarised in a systematic review by D'Amico *et al.*[285] The development of a clinical complication has an impact on outcome. In a Danish population-based cohort of 466 patients with a median age of 53 years who were followed-up during a five-year period, 76% presented with liver-related complications at time of diagnosis. The one-year mortality was 49% following ascites and variceal bleeding, and 64% after clinical episodes of hepatic encephalopathy.[286] However, the factor with the strongest influence on mortality and liver-related outcome is alcohol consumption. In a Norwegian cohort of 100 patients followed-up for 15 years,[287] the mortality rate at 5, 10 and 15 years was 71%, 84% and 90%, respectively. Independent predictors of mortality were age and persistent alcohol consumption (excess alcohol use *vs.* <10 g/day: relative risk 2.9; 95% CI 1.4–5.0). How alcohol triggers decompensation is not fully understood. However, an increase in liver inflammation due to translocation of gut-derived bacterial products following alcohol abuse increases intrahepatic resistance[288] and contributes to multiorgan failure and high mortality in patients with ALD, presenting as acute-

on-chronic liver failure.[289] Portal hypertension and associated circulatory changes are particularly prominent in cirrhosis of alcoholic aetiology,[290] with additional changes when exposed to acute alcohol. Thus, azygos blood flow and hepatic venous pressure gradient deteriorates 15 minutes after oral administration of 0.5 g/kg of alcohol to patients with alcoholic cirrhosis.[291] Thus, even moderate alcohol consumption may worsen portal hypertension and precipitate clinical decompensation.

Patients with alcoholic cirrhosis are at an increased risk of developing HCC. According to data from a surveillance programme of 450 Child-Pugh A and B patients over five years, the annual incidence is 2.6%.[292] According to a meta-analysis, the risk decreased by 6% to 7% a year in patients who become durably abstinent.[293] However, surveillance for HCC is still recommended according to guidelines.[294] Excessive alcohol use is carcinogenic and also associated with an increased risk of malignancies in other organs, as highlighted in recent publications.[295,296] In a registry-based nationwide Danish cohort, patients with ALD cirrhosis had a high risk of developing cancer (HR 2.94; 95% CI 2.70–3.19), with both HCC and oropharyngeal cancer being much more likely to develop in such patients.[297] An increased cancer risk is also reported for the stomach (standardised incidence ratio 2.76), pancreas (standardised incidence ratio 3.71) and the kidney (standardised incidence ratio 2.69) in addition to the pharynx (standardised incidence ratio 9.25) and larynx (standardised incidence ratio 5.2), according to data from Finland.[298] However, in the absence of recommendations, cancer surveillance is not routinely proposed for patients with alcoholic cirrhosis.

Bacterial infection and sepsis are major complications of cirrhosis and an important cause of death, leading to an approximately fourfold increase in mortality, regardless of aetiology. Advanced liver failure, acute variceal bleeding and low protein concentration in ascites are well known risk factors. Whether patients with alcoholic cirrhosis and active alcoholism are at particularly high risk of infections (intestinal permeability, dysbiosis) has been a matter of debate and was recently reviewed.[299] In a population-based cohort of 633 patients followed-up for 10 years,[300] the incidence and severity of bacterial infections increased over time and were apparently more frequent in alcoholic cirrhosis compared to non-alcoholic aetiologies. However, an independent relationship between bacterial infections and alcoholic aetiology could not be demonstrated after adjusting for confounders such as age and MELD score (HR 1.36; 95% CI 0.99–1.87). In a group of 215 patients with cirrhosis, half of whom were of alcoholic aetiology, the infection risk following acute variceal bleeding was higher in actively drinking patients with preserved or moderately affected liver function (Child-Pugh A and B) than non-active drinkers (22.5% *vs.* 6%, p <0.003) in spite of antibiotic prophylaxis.[301] However, the confounding role of malnutrition as a facilitating factor for infection is not systematically examined in the literature. Poor nutritional status and sarcopenia may affect up to 50% of patients with ALD,[302] resulting from increased catabolism, insufficient intake of calories, micronutrients (including zinc[303]) and vitamins. Malnutrition is clinically evident in a majority of patients admitted to hospital with decompensated ALD. However, the use of nutritional markers such as BMI and anthropometric measurements may be helpful for diagnosis and monitoring. Implementation of nutritional support in malnourished patients can provide clinical benefits,[304] although the impact on clinically relevant endpoints is variable.[305,306] Nevertheless, considering the heterogeneity in study designs and patients characteristics, screening and correction of malnutrition is still indicated and should be part of the multidisciplinary management of these patients.

Patients with ALD cirrhosis may also suffer from alcohol-related organ damage external to the liver, including the heart (alcoholic cardiomyopathy), the pancreas (acute and chronic pancreatitis), the kidney (IgA-induced nephropathy) and the nervous system (central and peripheral nerve involvement). Alterations in consciousness and cognitive impairment may be related to hepatic encephalopathy, but Wernicke's encephalopathy, withdrawal syndrome, or other symptoms related to alcohol-related brain damage[307] should also be considered as alternative diagnoses in a patient with ALD cirrhosis and neurological impairment.

Paracetamol at therapeutic doses in chronic alcohol users, whether or not associated with cirrhosis and malnutrition, may produce liver injury. However, because of the complex relationship between alcohol and acetaminophen metabolism the risk of such a therapeutic misadventure may vary. A recent case-control study failed to demonstrate increased episodes of clinical decompensation in actively drinking ALD cirrhotics consuming up to 3 g of paracetamol daily in the previous 30 days.[308] Nevertheless, caution is advised when administering therapeutic doses of this drug to patients with ALD cirrhosis, in particular when malnourished. Administration of N-acetylcysteine should be considered in suspected paracetamol induced liver injury in addition to stopping the drug.

Management of ALD cirrhosis

Current clinical management of patients with ALD cirrhosis focusses on alcohol abstinence, nutritional support including calories, vitamins and micronutrients, as well as primary and secondary prophylaxis of cirrhotic complications. Alcohol-induced damage to extrahepatic organs including cancer of the aerodigestive tract should also be investigated. From a clinical standpoint, ALD should be considered as a dual pathology including both a liver and an addiction disease. Thus, management of alcohol misuse is crucial and should include the competences of an addiction specialist in addition to psychosocial support and optionally prescription of anti-craving drugs.

Several liver specific therapies have been tested in alcoholic cirrhosis including S-adenosyl-L-methionine, propylthiouracil, colchicine, anabolic-androgenic steroids and sylimarin. These treatments did not demonstrate consistent benefits on clinical endpoints.[130] Pro-regenerative strategies aiming to improve decompensated ALD with stem-cell based therapies are overall well tolerated,[309] with similar efficacy as standard of care.[215] Administration of GCSF and erythropoietin was shown to decrease one-year mortality compared to standard of care in patients with decompensated cirrhosis dominated by alcohol-related aetiology.[310]

Suggestions for future studies

- Further evaluation of endpoints (clinical, anthropometrical) and re-nutritional strategies are needed in advanced alcoholic cirrhosis
- Further randomised controlled studies are needed on pro-regenerative strategies in advanced alcoholic cirrhosis using clinically relevant endpoints

- Further work is needed to select alcoholic cirrhotics at high risk of extrahepatic malignancy to implement cancer surveillance
- Additional work may determine if *PNPLA3* variants can be a marker for the development of HCC in alcoholic cirrhosis

Recommendations

- Patients with alcohol-related cirrhosis should be advised and encouraged to achieve complete abstinence from alcohol to reduce the risk of liver-related complications and mortality (**Grade A1**)
- Identification and management of cofactors, including obesity and insulin resistance, malnutrition, cigarette smoking, iron overload and viral hepatitis, are recommended (**Grade A1**)
- General recommendations for screening and management of complications of cirrhosis should be applied to alcoholic cirrhosis (**Grade A1**)

Liver transplantation

Trends in liver transplantation of ALD

Liver transplantation (LT) is the most effective therapeutic option for patients with end-stage liver disease, with post-transplant patient and graft survival of around 80–85% at one year. Liver outcomes after LT in patients with AUD have improved, with graft and patient survival similar to those seen after transplantation for other aetiologies.[311,312] Although only a minority of patients with AUD meet the rigorous criteria required of LT candidates, the number of transplantations done for patients with ALD has increased over the past two decades. Between 2004 and 2013, the number of new liver transplant registrations for ALD in the US increased by +45%.[313] However, MELD score at time of registration was higher in patients with ALD than in those with non-alcoholic steatohepatitis or HCV.[313] In Europe, the proportion of patients transplanted for ALD increased by 8.3% between the periods 1988–1995 and 1996–2000 (Fig. 2).[314] Although the number of patients on waiting lists continues to increase, donor availability is predicted to decrease over the next decade, further exacerbating organ shortages.[315,316] Modification of legislation, expanded criteria of donor suitability, investments in health care, infrastructure and education are important issues to increase the number of deceased organ donors.[317]

Although ALD is classified among the top three indications for LT in Europe and the USA,[313,314] it continues to be the most controversial in terms of public reaction 317,318. The general public and medical professionals continue to question the degree of priority that programmes should give to patients with ALD. Transplantation of alcoholic patients remains a rare example where personal moral judgment may affect the ethical exercise of medicine. Indeed, ALD is considered a self-inflected disease with negative consequences for society as a whole.[319] Opinion polls using anonymous questionnaires showed that the general public and family physicians negatively prioritise LT for patients with AUD and are more likely to allocate organs to patients with inherited or acquired illnesses less directly related to behaviour. Respondents who believe that patients with ALD bear the responsibility for their illness were less likely to allocate organs to patients with ALD than respondents who did not believe personal responsibility played a role in the risk of disease. Personal responsibility for illness was an important consideration in respondents' rationing allocation decisions.[320,321] The conviction that alcoholism is self-inflicted must be reconciled with the strong evidence supporting genetic and environmental influences on AUD.[322]

Selection of the alcoholic patient for LT

Risk factors for alcohol relapse and the six-month rule

A psychosocial assessment to establish the likelihood of long-term abstinence after LT should be performed in patients with ALD. 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.[323] A multidisciplinary approach that evaluates not only medical but also psychological suitability for LT is then mandatory.

A systematic review of the available literature observed that duration of sobriety before LT, poorer social support, and a family history of alcoholism were the three significant risk factors for relapse, but none of these factors were powerfully correlated with alcohol relapse.[324] In order to ration organs, most programmes require a six-month period of abstinence prior to evaluation of alcoholic patients. The six-month period of abstinence is presumed to enable some patients to recover from their liver disease and obviate the need for LT, while also identifying subsets of patients likely to maintain abstinence after LT.[325] Although most liver transplant centres worldwide frequently request a six-month period of abstinence as minimal listing criteria, there is limited evidence to document the validity of this criterion alone in predicting alcoholic relapse. Indeed, numerous studies lent support to the validity of the six-month abstinence criterion, but also observed that its use alone forced a significant number of candidates with low relapse risk to wait for transplant listing. Despite the frequent use of the six-month rule, the United Network for Organ Sharing (UNOS),[326] International LT Society,[323] the EASL clinical practical guidelines on ALD[318] and on transplantation[317] did not endorse this measure as a formal recommendation.

Laboratory tests for abstinence may be used in patients on the transplant waiting list (see section on tests for alcohol consumption above).

Medical assessment of patients with ALD prior to liver transplantation

The pre-transplant investigation should assess pancreatic function, renal function and nutritional status, as well as detecting central and peripheral neuropathy, myopathy and cardiomyopathy.[323,327,328] Special attention is required for ALD and chronic encephalopathy in order to rule out alcohol-related dementia.[323] The high prevalence of concomitant alcohol and tobacco use justify additional screening for atherosclerosis and ischaemic heart disease. It is also crucial to rule out any neoplastic or pre-neoplastic disease, since such patients appear to have a higher incidence of certain malignancies after LT. Cancer in the upper airways and upper gastrointestinal tract are particularly common.[327]

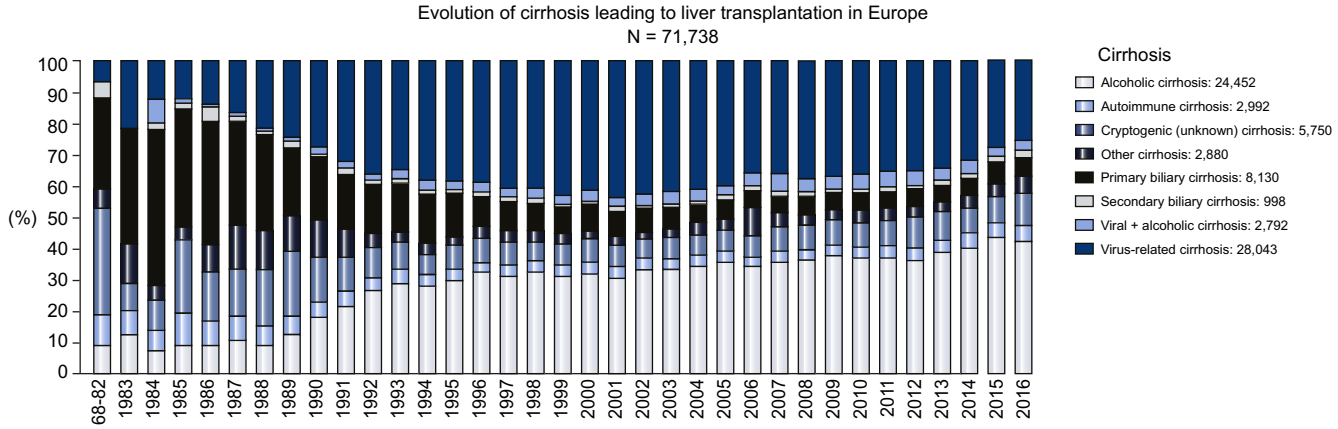

Fig. 2. The trend in aetiologies of cirrhosis leading to liver transplantation in Europe.

Assessing the severity of liver disease and timing for liver transplantation

The survival benefit related to LT is restricted to patients with advanced decompensation[329] whereas no survival benefit is observed in patients with cirrhosis of intermediate severity.[330] Previous studies have failed to demonstrate that other clinical manifestations of liver decompensation, such as variceal haemorrhage, hepatic encephalopathy, new onset ascites or SBP, were independent predictors of survival over and above the MELD score.[331] Nonetheless, the onset of any of these features in an abstinent alcoholic should prompt the managing physician to consider referral to a transplant centre. MELD accurately estimates the survival benefit following LT[332] and is now recommended to prioritise organ allocation.[323] Its prognostic value has been validated in patients with a broad spectrum of ALD including AH.[194,333] However, as for the other aetiologies, a substantial proportion of patients with ALD requiring LT are not identified by MELD alone. More sophisticated patient assessments are required to allow suitable patients to access LT.[317]

Early liver transplantation in patients with alcoholic hepatitis not responding to medical therapy

A prospective pilot case controlled study evaluating early LT in patients with severe AH undergoing their first episode of liver disease and failing to respond to medical therapy showed an unequivocal improvement of survival in patients who received early transplantation.[334] These patients were selected using the following criteria: absolute consensus of paramedical and medical staff, no comorbidities, social integration and supportive family members. Failure of medical therapy was identified using Lille score ≥0.45[335] or worsening of liver function by day seven. As the new allocation system using MELD gives priority to those patients with high MELD scores at listing, in a context of organ shortage, team members requested stringent selection and felt that patients unaware of their underlying liver disease constituted the most urgent problem.[334] This study on early LT challenges previous expert opinion, which considered AH as a contraindication for LT.[336] These favourable results have been recently confirmed in two American studies.[337,338] The rate of alcohol relapse was similar in patients undergoing early LT to those patients transplanted after a period of abstinence.[334,337,338] Post-transplantation graft and patient survival are similar among patients with a listing diagnosis of alcoholic cirrhosis and those with a listing diagnosis of AH.[339]

Despite the excellent outcomes of LT for AH, heterogeneity persists between transplant centres with regard to the adoption of early LT in patients with severe AH. Early LT remains a relative contraindication for LT in most American centres as only 27% of them reported listing patients with AH for LT[340] and no Canadian centres perform early LT for severe AH.[341] In Europe, German regulations strictly require six months of alcohol abstinence in patients with ALD that must be confirmed by repeated urine EtG tests while patients are on the transplant waiting list.[342] Taking into account the recent studies on early LT, the German authorities (Bundesärztekammer) updated their legal regulation and now allow transplant centres to ask to list highly selected patients with ALD who have been abstinent for less than six months.[342] In contrast, Italian experts recently recommended that early LT is a valuable option for patients with severe AH not responding to medical therapy, even without achieving abstinence.[343] The mounting weight of evidence for the efficacy of early LT for patients with severe AH that is not responding to medical therapy support future evaluation of early LT in a carefully-selected subgroup of patients. Selection criteria to identify patients with the highest risk of short-term mortality need to be more clearly defined to limit the number of unnecessary early LT procedures.[194]

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% to 50%) over up to five years follow-up.[323,344] There are many flaws in these data. Firstly, 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 behaviour. 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 because of retrospection, but also because of the pressures on patients to deny drinking. It is thought that between 33% and 50% of ALD

transplant recipients start drinking again after transplantation and that about 10% resume heavy drinking mostly within the first year after transplantation.[345]

A systematic review evaluated patterns of alcohol use among LT recipients with ALD and non-ALD. In patients reporting early alcohol use post-LT, there was no difference in the proportion of transplant recipients with ALD compared with those with non-ALD: 4% *vs.* 5% at six months and 17% *vs.* 16% at 12 months[346] but recipients with ALD were more likely to drink excessively.[346] Occasional or moderate drinking did not impact graft function or patient survival.[347] Short-term survival was not significantly affected by relapse in heavy drinking.[347] whereas recipients who resumed abusive drinking had significantly lower long-term survival than abstinent recipients or those with minor relapses.[348,349] Recurrence of alcoholic cirrhosis was responsible for approximately 90% of deaths in recipients who resumed abusive drinking. A study showed that the integration of an addiction unit in a liver transplant centre was associated with a reduction in the risk of alcohol recidivism after transplantation.[42]

Extrahepatic complications

The incidence of cardiovascular events is higher in patients transplanted for ALD compared to patients transplanted for other causes of liver disease (8% *vs.* 5.3%).[314] 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 ALD than other indications. Increased vigilance and proactive management are required to further improve long-term outcomes.[350]

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.[327,351,352] The incidence of *de novo* tumours as cause of death was at least twofold higher in patients transplanted for ALD compared to other indications.[314] Smoking withdrawal after LT may have a protective effect against the development of *de novo* cancers.[353] Further studies are required to determine whether a strict screening of cancers in LT recipients would increase early-stage detection of cancer and improve patient survival.[354] However, the optimal surveillance protocol after LT needs further exploration. Beside the host factors, immunosuppression is an important contributing factor for developing malignancies. The influence of the type of immunosuppressive regimen and the strategy of calcineurin inhibitor dose reduction on the risk of *de novo* cancers deserves further investigation. Indeed, the additional risk of calcineurin inhibitors is supported by experimental studies, randomised controlled trial in kidney transplantation showing a higher incidence in cancers in the recipients allocated to the regimen with elevated cyclosporine target levels[355] and in cohort studies suggesting a dose-response relationship between early exposure levels to tacrolimus and *de novo* solid cancers post-LT.[356]

Survival and quality of life

Alcoholic liver disease aetiology does not adversely influence LT survival benefit.[357] From an 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 patients with ALD.[314] This survival rate was significantly higher than in HCV- and HBV-related liver disease recipients and cryptogenic cirrhosis patients.[314] The incidence of deaths due to all psych-social causes, including suicide, was twice as high in patients transplanted for ALD compared with other indications.[314] 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.[358] Patients transplanted for ALD 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-ALD.[359] Quality of life is better after LT, but the magnitude of improvement is lower than expected and decreases with time.[360] Patients transplanted for ALD disclose similar ability for work and physical activity as non-alcohol-related liver transplant recipients.[360]

Suggestions for future studies

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

Recommendations

- LT confers a survival benefit Liver transplantation should be considered in patients with ALD (classified as Child-Pugh C and/or MELD ≥15) as it confers a survival benefit (**Grade A1**)
- The selection of patients with AUD should not be based on the six-month criterion alone (**Grade A2**)
- The duration of abstinence before listing should depend on the degree of liver insufficiency in selected patients with a favourable addiction and psychological profile and supportive relatives (**Grade A1**)
- 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 (**Grade A1**)
- A multidisciplinary approach evaluating not only medical but also psychological suitability for transplantation is mandatory before and after LT (**Grade A1**)
- The integration of an addiction specialist may decrease the risk of relapse in heavy drinking individuals (**Grade B2**)
- Early LT should be proposed to a minority of patients with severe AH not responding to medical therapy after a careful selection process (**Grade A1**)
- Patients should be screened regularly for cardiovascular and neurological disease, psychiatric disorders and neoplasms before and after LT (**Grade A1**)
- Risk factors for cardiovascular disease and neoplasms, particularly cigarette smoking, should be controlled (**Grade A1**)
- Early reduction in calcineurin inhibitor therapy may be considered to decrease the risk of *de novo* cancer after LT (**Grade B2**)

Conflict of interest

Mark Thursz reports grant support from Vital therapies; consultant/advisory roles for Gilead, AbbVie, CN-Bio and MSD; sponsored lectures for Gilead, BMS and AbbVie. Antoni Gual reports grant support from Lundbeck, consultant/advisory roles for D&A Pharma and Lundbeck; sponsored lectures for D&A Pharma and Lundbeck. Christophe Moreno reports grant support from Gilead; consultant/advisory roles for Gilead and Promethera; performance of Gilead sponsored clinical trial in alcoholic hepatitis. Carolin Lackner reports consultant/advisory roles associated with Galmed Research and Development Ltd. All other authors report no conflict of interest. Please refer to the accompanying ICMJE disclosure forms for further details.

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