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REVIEW

Management of alcohol-related liver disease: the French Association for the Study of the Liver and the French Alcohol Society clinical guidelines

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Abstract

Excessive alcohol consumption is the leading cause of liver diseases in Western countries, especially in France. Alcohol-related liver disease (ARLD) is an extremely broad context and there remains much to accomplish in terms of identifying patients, improving prognosis and treatment, and standardising practices. The French Association for the Study of the Liver wished to organise guidelines together with the French Alcohol Society in order to summarise the best evidence available about several key clinical points in ARLD. These guidelines have been elaborated based on the level of evidence available in the literature and each recommendation has been analysed, discussed and voted by the panel of experts. They describe how patients with ARLD should be managed nowadays and discuss the main unsettled issues in the field.

KEYWORDS
alcohol, alcohol-related liver disease, guidelines

1 | INTRODUCTION

The harmful effects of excessive alcohol consumption on the liver are the leading cause of liver-related mortality in France. The management of these patients is a daily matter for hepato-gastroenterologists in both hospitals and private practices, in close collaboration with general practitioners, addictologists and health-care providers.

Although these guidelines do not cover the field of epidemiology, the following statistics can be evoked: in 2015 in France, mortality from alcohol-related cirrhosis per 100000 individuals was estimated at 14.9 in males and 5.2 in females according to the French Observatory for Drugs and Drug Addiction.[1] The CépiDC (The French Epidemiological Centre for Mortality by Medical Causes) documented a total of 3614 deaths due to alcohol-related cirrhosis in 2016 (2715 in males and 899 in females). Specific work on this area is in progress and the expected prevalence of decompensated alcohol-related cirrhosis is currently approximately 6000–7000 patients. Alcohol-related liver disease (ARLD) is an extremely broad context and there remains much to accomplish in terms of identifying patients, improving prognosis and treatment and standardising practices.

In order to put forward French guidelines on the management of ARLD, the AFEF wished to organise a day of expert panel discussions before establishing the recommendations on the following aims:

- Help clinicians detect alcohol use disorders (AUD) and refer patients to specialist consultation.
- Supervise withdrawal and support patients in a process of permanent drinking cessation.
- Identify and treat severe complications.
- Distinguish areas for reflection in terms of public health.

Key points

- The French Association for the study of the liver and the French Alcohol Society clinical guidelines elaborated clinical guidelines for the management of alcohol-related liver disease.
- Screening, diagnosis of alcohol consumption and management of patients are discussed according to the GRADE method.
- For each recommendation, the body of evidence and degree of agreement is provided.

Screening for alcohol, identifying complications and promoting areas for improvement in public health is crucial because the most efficient strategies in the field of alcohol misuse are based on prevention. At the population level, several public health measures have proven to decrease alcohol consumption, such as the minimum unit pricing policy, taxation, restriction of advertising and limitation of alcohol availability.[2–5]

Since alcohol units differ between countries, we have decided to quantify the amount of alcohol by referring to 'standard drink' which corresponds to 10 g of pure alcohol.[6,7]

2 | GENERAL ORGANISATION AND METHODOLOGY OF THE GUIDELINES

See Appendix for more details. For each chapter, supplemental information, including references and argumentation, are provided in the Appendix.

2.1 | Chapter 1: How to detect excessive alcohol consumption in general practice and specialist consultations

RECOMMENDATION NO. 1

Alcohol consumption assessment must be systematic in both general practice and specialist consultations.

G1+/STRONG AGREEMENT

Excessive alcohol consumption is a definite and avoidable risk factor for many somatic and psychiatric disorders and the timing of detection is important. The French Alcohol Society (SFA) recommends alcohol misuse screening in all adult patients regardless of age during a routine examination, when prescribing a drug known to interact with alcohol or during an emergency department visit.[8]

RECOMMENDATION NO. 2

The AUDIT-C questionnaire (first 3 questions of AUDIT) must be used in general practice and specialist consultation for the detection of excessive alcohol consumption.

G1+/STRONG AGREEMENT

The majority of the studies indicate that the AUDIT is a valid and effective tool for detecting alcohol misuse[9–12] in people over 18 years of age. A meta-analysis on the effectiveness of AUDIT for the screening of high-risk drinkers showed significant heterogeneity among the studies in terms of sensitivity. However, it concluded that it is reliable in primary care, in emergency departments and the elderly.[13] The following thresholds have been retained for their diagnostic performance in terms of screening being: >6 for any alcohol misuse and >12 for dependence.[10] A positive AUDIT score is also associated with an increased risk of mortality according to a meta-analysis of cohort studies.[13]

RECOMMENDATION NO. 3

Biomarkers are not required in the *systematic* detection of alcohol misuse.

G2−/STRONG AGREEMENT

Alcohol misuse (or unhealthy alcohol use) is defined by the presence of either alcohol use disorder or hazardous use of alcohol in a subject.[14]

Given the difficulties conveyed by physicians in questioning patients and in order to overcome issues of patient denial, many studies have focused on searching for reliable biomarkers for alcohol consumption. In addition to blood alcohol levels, the most frequently used biochemical tests in 2020 are gamma-glutamyltransferase, mean corpuscular volume and carbohydrate-deficient transferrin. Studies to date have consistently shown that these are less effective than questionnaires, such as the AUDIT, for detection.[15–18] These biomarkers have minimal sensitivity and many patients with alcohol misuse present normal biochemical test results. Two studies in the literature have reported on direct metabolites of ethanol (ethylglucuronide in urine and hair and phosphatidylethanol). Both these studies conclude that there is insufficient data to decipher the value of systematic screening in the general population.[19,20] Current dosing techniques do not appear to be suitable for widespread use.

IMPORTANT ISSUE: The jury and experts wish to recall here that the clinical utility of these markers on a case-by-case basis is not undermined as they can be used to refer a patient to a specialist in the management of patients with alcohol misuse (hepato-gastroenterologist, alcohol abuse specialists, etc.). It is their systematic dosage for the detection of alcohol consumption that is not recommended, not their value in the assessment of the effects of alcohol consumption, particularly on the liver. They should not be used as a substitute for a medical interview.

RECOMMENDATION NO. 4

Brief intervention must be offered to patients identified as alcohol misusers. All practitioners must be able to be carried out this brief intervention.

G1+/STRONG AGREEMENT

Brief intervention is for people who misuse alcohol and show minimal or no signs of dependence.

Significant efforts have been made over recent decades to develop and assess brief interventions aimed at reducing excessive alcohol consumption in primary care medicine. Models and contents vary, as do intervention durations. Brief interventions last for approximately 15 min and typically include the following elements:

- A personalised interview on the patient's alcohol use and the associated consequences.
- Clarification of what constitutes low-risk alcohol consumption.
- Information on the risks associated with alcohol consumption.
- Identification of high-risk situations and strategies for dealing with them.
- The benefits expected from a reduction in consumption.
- Advice on how to reduce consumption.
- Motivational interviewing to promote change.
- The development of a personalised consumption reduction plan.[21,22]

In general, the scientific literature indicates that brief interventions in primary care medicine are as effective as more intensive treatments in reducing alcohol use among adults drinking excessively.[21,23,24] In particular, a recent study has shown that brief interventions in primary care medicine are associated with a reduction in the frequency of binge drinking episodes (consuming more than 60 g of pure alcohol on a single occasion)[25,26] and the number of days drinking per week.[21]

2.2 | Chapter 2. Consumption profile (definitions, threshold issues, consumption patterns, age, sex), binge drinking and the liver

RECOMMENDATIONS

It is recommended to screen for binge drinking as a high-risk consumption pattern, particularly in adolescent and young adult

populations. It is always recommended to investigate other alcohol consumption patterns.

G1+/STRONG AGREEMENT

It is recommended to disseminate information to the general population on the risks associated with binge drinking, particularly in terms of cardiovascular morbidity and mortality and physical and psychological injuries.

G1+/STRONG AGREEMENT

The experts recommend the performance of prospective studies for the investigation of the precise effects of binge drinking on the liver.

EXPERT OPINION/STRONG AGREEMENT

The definition of binge drinking varies considerably in the literature depending on the authors.

Both the NIAAA and the EASL have defined binge drinking as the consumption of 4–5 standard drinks, depending on sex and generally in under 2 h.[7]

Beyond the effects on the liver, it is above all the acute effects in terms of risk-taking behaviour associated with binge drinking that was primarily documented.[27]

In the general population, binge drinking is associated with a risk of developing the chronic liver disease with liver decompensation.[28] This risk increases with binge drinking episode frequency over the previous year after adjustment for the quantity consumed in a given month and patient age.[28] However, in contrast to the study by Wood et al.,[29] no adjustment was made for the overall consumption level, making it impossible to firmly state that this increased risk does indeed exist in drinkers with a total consumption of <200 g per week.[30]

Nonetheless, it is important to note that episodic drinking is associated with a lower risk than daily alcohol consumption only in males (RR = 0.56 [95% CI: 0.37–0.85]). This has not been demonstrated in females.[31] Daily drinkers have a greater risk of cirrhosis compared with less frequent drinkers: RR of 1.34 (95% CI: 0.67–2.67) for those who drink less than 1 day a week, 1.30 (95% CI: 0.59–2.87) for drinking 1 day a week, 1.43 (95% CI: 0.84–2.43) for drinking 5–6 days a week and 3.65 (95% CI: 2.39–5.55) for daily consumption.[32]

Data on alcohol-consumption trajectories have emerged. In particular, a relative risk of 2.3 (95% CI: 1.8–3.0) in males and 3.4 (95% CI: 2.4–4.8) in females has been demonstrated for continued binge drinking into young adulthood in the event of binge drinking during adolescence.[33] It is important to note that among 55–65 year olds, former moderate drinkers who initiate heavy episodic drinking have an increased mortality risk 20 years later of more than 2 compared to those who do not engage this consumption pattern.[34]

However, whether the negative effects of binge drinking on survival and liver impairment are linked to a specific risk or are the result of increased consumption, it appears that early detection and treatment of binge drinking are recommended.

2.3 | Chapter 3. Harm-reduction management: objectives according to the presence or absence of cirrhosis

RECOMMENDATION NO. 1

Daily alcohol consumption is associated with health risks that are proportional to the amount ingested. Although this toxicity does not affect all organs uniformly, the overall health risks present from 1 to 2 standard drinks per day.

G1+/STRONG AGREEMENT

RECOMMENDATION NO. 2

As a guideline, weekly alcohol consumption of no more than 10 standard drinks can be suggested in the general population to avoid overall health risks.

G2+/STRONG AGREEMENT

There is no clear threshold below which it can be determined that alcohol consumption does not present a health hazard. The French Public Health Agency and a group of independent experts proposed consumption 'benchmarks' for the general population: not to exceed two standard drinks (i.e. 20 g of alcohol) per day with at least 2 days a week without drinking.[35] It must be emphasised that these thresholds are not based on official statistics and have been put forward only as a benchmark. The French Public Health Agency wanted to issue recommendations that are both valid regardless of sex and easy to apply. Bear in mind that the benchmark suggests consumption of no more than two standard drinks per day, with 2 days per week without drinking, giving a maximum of 10 standard drinks per week. This threshold is debatable given it has not been formally established in studies. It is nevertheless useful for delivering a simple message to the general population.

In addition to its negative impact on the liver, alcohol use is associated with multiple cancers with different toxicity thresholds.[6,36] The most frequent alcohol-related cancers are breast, colon, liver, oesophageal cancer, oral cavity and pharyngeal cancers.[36]

2.3.1 | Risks of alcohol-related liver disease and primary liver cancer

RECOMMENDATION NO. 3

It is recommended not to exceed the consumption of 14 standard drinks per week for females and 21 standard drinks per week for males with respect to the specific risk of alcohol-related cirrhosis.

G2+/STRONG AGREEMENT

RECOMMENDATION NO. 4

Despite the lack of precise data on liver-related risks, it can be proposed to maintain at least one alcohol-free day per week.

EXPERT OPINION/STRONG AGREEMENT

2.3.2 | Link between the amount of alcohol consumed and the risk of cirrhosis

Thresholds for high-risk consumption are difficult to accurately define as they vary widely in the literature and are not consensual, presenting apparently from one standard glass/day[37] with the definition of the standard glass itself varying from one country (and, therefore, from one publication) to another.[38] The median threshold of two standard drinks (corresponding to 20 g) per day appears to be associated with the risk of cirrhosis. Regarding this, two meta-analyses have shown a relative risk of 2.9[39] and 4.9[40] for cirrhosis with daily consumption of approximately 25 and 24 g of pure alcohol, respectively, i.e. slightly more than two standard French glasses. The risk of alcohol-related liver disease increases proportionally with the quantity of alcohol consumed (dose effect).[41] For subjects consuming between 24 and 60 g/day, the relative risk for cirrhosis increases very significantly to 12.5 (95% CI 8.8–17.7).[40]

2.3.3 | Risk of primary liver cancer

A meta-analysis,[42] the EPIC cohort study[43] and two case-control studies[44,45] have suggested an association between alcohol consumption and HCC with an odds ratio above 2 for daily consumption of more than 50[35,42] to 60 g.[44] On the contrary, low consumption (10 g/day) does not appear to influence the risk of HCC.[43] The consumption level associated with a risk of developing HCC is lower in females (odds ratio 1.77 for more than two standard drinks in females and more than four standard drinks in males).[43] Alcohol is thought to cause approximately 10[43] to 30%[41] of HCC and acts synergistically with the hepatitis C virus and diabetes.[45]

Finally, the risk of developing HCC has been considered to decrease following a reduction of 6–7%/year in alcohol consumption, a period of 23 years of abstinence thus being required to return to the same risk level of unexposed subjects.[46]

Alcohol consumption should, therefore, be limited as much as possible in the general population.

In specific subjects with chronic hepatitis C, daily alcohol consumption of more than two standard drinks would aggravate liver fibrosis,[47] but these results remain debated.[48]

It is generally considered that patients with alcohol-related liver disease will not develop HCC in the absence of cirrhosis. However, the information on the presence of underlying cirrhosis is not available in the majority of large epidemiological studies which have assessed the risk of alcohol in the general population.

2.3.4 | Morbi-mortality in patients with cirrhosis, alcoholic hepatitis or HCC

RECOMMENDATION NO. 5

It is likely recommended to completely and permanently stop all alcohol consumption in patients with cirrhosis and/or HCC in order to limit the risk of excess mortality.

G2+/STRONG AGREEMENT

RECOMMENDATION NO. 6

Further studies will be needed to assess the effects of low consumption on the overall prognosis of these patients.

EXPERT OPINION/STRONG AGREEMENT

The harmful role of continued alcohol consumption in cases with cirrhosis is presumed but the level of scientific evidence remains low. One of the two studies available on this subject includes a French cohort of 122 consecutive patients with cirrhosis with a history of excessive alcohol consumption (>80 g/day for at least 10 years). These patients were prospectively followed.[49] Median survival at 5 years was 43%. At the end of follow-up, 30% of patients were abstinent, 27% drank less than two standard drinks/day, 28% drank more than two standard drinks/day and classification was not possible for the remaining patients. According to multivariate analysis, persistent consumption of more than two standard drinks/day was a factor independently associated with mortality.[49] The second prospective study, which followed 490 000 subjects for 9 years, also suggested that the excess mortality of cirrhotic patients is only significant after a daily consumption of more than two standard drinks/day in both males (RR 2.6; 95% CI: 1.6–4.0) and females (RR 2.1; 95% CI: 1.3–3.4).[50]

For patients with severe alcoholic hepatitis, mortality is also correlated with the level of alcohol consumption, with a significantly increased risk for even low levels of consumption.[51] In cases with HCC, prolonged alcohol abstinence is associated with a better overall prognosis than continued drinking,[52] but the effects of very low levels of alcohol consumption are still poorly understood in this setting too.

In the absence of quantitative data in the literature, further studies are needed for the evaluation of the thresholds of harmful consumption and the effects of low alcohol consumption levels on the overall prognosis of these patients.

2.4 | Chapter 4. Medical management of alcohol use disorder: The influence of advanced liver disease

RECOMMENDATION NO. 1

Symptomatic alcohol withdrawal is based on treatment with benzodiazepines (the reference drug class) until symptoms disappear.

G1+/STRONG AGREEMENT

RECOMMENDATION NO. 2

The presence of a decompensated liver disease must encourage prioritisation of a personalised prescription that is symptom adapted and favours short-acting drugs.

G2+/STRONG AGREEMENT

The study by Addolorato et al.[53] on cirrhotic patients found that more than 70% of them did not require pharmacological treatment of withdrawal (no benzodiazepines). This treatment should, therefore, only be given if necessary, especially for cirrhotic patients. Alcohol withdrawal requires regular monitoring and even in the absence of symptoms. The purpose of monitoring is to guide dosage adjustment and to ensure that there is no seizure. Regular monitoring can be stopped after 24 h if no specific signs appear.

It is typically recommended to use short half-life benzodiazepines in cirrhotic patients (oxazepam or lorazepam).[7,54–60] This precaution aims to avoid drug accumulation in patients who are otherwise at risk of developing encephalopathy. Lorazepam appears to be minimally used in France. However, the value of using benzodiazepines with a short—rather than long—half-life in cases with hepatic insufficiency has not been validated by a controlled trial. Contrary to widespread belief, it appears that the metabolism of all benzodiazepines is affected by hepatic insufficiency.[61] In case of overdose, the intravenous administration of flumazenil as an antidote is gradual due to the related risk of convulsions. This is carried out in an adapted structure or intensive care.[8,59]

Finally, it is recommended to prescribe thiamine as part of the withdrawal process in order to prevent the onset of Wernicke's encephalopathy. Thiamine (vitamin B1) deficiency is common in alcohol-dependent people with 30%–80% showing clinical or biological signs of deficiency. Excessive alcohol consumption associated with malnutrition aggravates the limited absorption of thiamine.[62–65] The level of evidence for the prophylactic prescription of thiamine is low but the benefit-risk balance is considered favourable.

RECOMMENDATION NO. 3

Pharmacological treatment must be considered for promoting the maintenance of alcohol consumption targets (abstinence or reduced consumption) in dependent patients.

G1+/STRONG AGREEMENT

There are pharmacological aids to help maintain long-term low or zero consumption targets. These goals are fundamental for preventing liver disease progression and for improving quality of life. The general principles of management and the value of pharmacological treatments were the subject of the SFA recommendations in 2015.[8]

In 2019, five drugs received MA for the long-term treatment of alcohol dependence: disulfiram, acamprosate, naltrexone, nalmefen and baclofen. The first three received MA in helping to maintain abstinence and the last two in controlling consumption. Topiramate and gabapentin, which are available without MA, have shown some effectiveness in the treatment of alcohol use disorder. However, their tolerance profile is not considered harmless. A careful assessment of the benefit-risk ratio is necessary in prescription type.[66]

RECOMMENDATION NO. 4

Naltrexone, nalmefen and disulfiram are contraindicated in cases with hepatic insufficiency according to their Summary of Product Characteristics (SmPC). The absolute nature of these contraindications is not supported by solid data in the literature. The use of these drugs in cases with severe liver disease must, therefore, be assessed on a case-by-case basis according to the risks, expected benefits and other treatment options.

EXPERT OPINION/STRONG AGREEMENT

RECOMMENDATION NO. 5

The presence of liver disease does not change the indications or conditions of acamprosate use.

G2+/WEAK AGREEMENT

RECOMMENDATIONS NO. 6

The presence of liver disease does not generally affect the prescribing of baclofen at the doses recommended by the MA (i.e. up to 80 mg/d).

G2+/STRONG AGREEMENT

A more gradual increase in dose is however recommended in cases with severe liver disease.

EXPERT OPINION/STRONG AGREEMENT

RECOMMENDATION NO. 7

The experts recommend the conduction of specific pharmacological studies on abstinence maintenance drugs in patients with hepatic insufficiency and/or decompensated cirrhosis.

EXPERT OPINION/STRONG AGREEMENT

2.5 | Chapter 5. Invasive and non-invasive diagnosis of fibrosis and steatosis in alcohol-related liver disease

RECOMMENDATIONS

Non-invasive assessment of liver fibrosis is recommended in all patients with alcohol-related liver disease.

G1+/STRONG AGREEMENT

The best-validated methods for the assessment of liver fibrosis in alcohol-related liver disease are elastography and specialised blood tests (FibroTest® or FibroMeter Alcohol®). In the first line, it is recommended to perform the non-invasive assessment of liver fibrosis in alcohol-related liver disease with the FibroScan® or a specialised blood test (FibroTest® or FibroMeter Alcohol®).

G1+/STRONG AGREEMENT

It is recommended to interpret elastography measurement results by applying specific thresholds of AST and bilirubin levels observed at the time of measurement.

G1+/STRONG AGREEMENT

The AST to Platelet Ratio Index (APRI) score is not recommended for the assessment of fibrosis in alcohol-related liver disease.

G1−/STRONG AGREEMENT

Blood tests and CAP (Controlled Attenuation Parameter) are insufficient for the assessment of steatosis in the course of alcohol-related liver disease.

G1+/STRONG AGREEMENT

Liver biopsy in alcohol-related liver disease remains indicated mainly in the case of doubt concerning the presence of associated chronic liver disease, or in the case of a discordant non-invasive examination casting doubt on the presence of cirrhosis.

EXPERT OPINION/STRONG AGREEMENT

In alcohol-related liver disease (ARLD), the degree of liver fibrosis is the main determinant of long-term liver-related outcomes, with an increased risk of death in the advanced fibrosis stage.[67] Non-invasive assessment (blood tests, elastography, imaging methods) represents a very attractive alternative in this context.

FIBROSIS

Simple blood tests, such as the FIB-4 or APRI scores, have the advantage of combining commonly used parameters (age,

transaminases, platelets) and they are easy to calculate. The diagnostic performance of the FIB-4 score for detecting advanced fibrosis (AUROC between 0.63 and 0.85) and cirrhosis (AUROC between 0.65 and 0.80) is moderate in ARLD.[68–71] The diagnostic performance of the APRI score is poor with AUROCs of approximately 0.60 for detecting advanced fibrosis and 0.65 in cirrhosis.[68–70,72] Specialised blood tests include direct markers of fibrosis (hyaluronic acid, α2-macroglobulin, TIMP1, P3NP…) that have derived from a better understanding of the physiopathological mechanisms of fibrogenesis. The specialised blood tests most frequently evaluated in ARLD are the FibroTest® and the FibroMeter Alcohol®.[68–70,72–74] Their diagnostic performance in the non-invasive diagnosis of advanced fibrosis (AUROC: 0.80–0.90) and cirrhosis (AUROC: 0.85–0.95) in ARLD is better than that of simple blood tests.[68–70,72] The proposed diagnostic thresholds for FibroTest® and FibroMeter Alcohol® are summarised in Table 1; their performance in ARLD remains insufficiently validated.[69,70] Data on other specialised blood tests (Hepascore®, ELF) remain limited in ARLD.[68,69,72]

The FibroScan® is the most highly evaluated elastography device in ARLD and there are two meta-analysis studies available on this subject in the literature.[75,76] A study performed on individual participant data confirmed higher diagnostic liver elasticity thresholds than those described in chronic hepatitis C with excellent diagnostic performance ($F \geq 1$: 7 kPa (AUROC 0.83), $F \geq 2$: 9 kPa (AUROC 0.86), $F \geq 3$: 12.1 kPa (AUROC 0.90), $F = 4$: 18.6 kPa (AUROC 0.91)).[75] Sensitivities and specificities were 79% and 71%, 78% and 77%, 81% and 83% and 84% and 85% according to the aforementioned stages of fibrosis, respectively. These high thresholds can be explained by liver inflammation related to the presence of histological signs of alcoholic hepatitis, which are in turn themselves reflected by the transaminase (AST) and bilirubin levels. This suggests that FibroScan® results must be interpreted by taking into account specific diagnostic thresholds based on AST and bilirubin levels.[75] For the diagnosis of cirrhosis, the threshold is 12.1 kPa (AUROC 0.92, sensitivity 85%, specificity 84%) with levels of AST < 38.7 IU/L and bilirubin <9 μmol/L, compared to 25.9 kPa (AUROC 0.90, sensitivity 81%, specificity 80%) with levels of AST > 75 IU/L and bilirubin > 16 μmol/L. For advanced fibrosis, the thresholds are 8.8 kPa (AUROC 0.92, sensitivity 80%, specificity 75%) and 16.1 kPa (AUROC 0.92, sensitivity 83%, specificity 80%) at the same aforementioned AST and bilirubin levels respectively.[74,75]

Stopping alcohol consumption has an effect on liver elasticity level, with one study showing a decrease in median liver elasticity from 7.2 to 6.1 kPa on day 7.[77] This decrease could be linked to a decrease in liver inflammation.[75] This implies that a delay must be complied before measuring liver elasticity after alcohol withdrawal.[77,78] Some studies have directly compared FibroScan®, specialised blood tests and simple blood tests.[69,70,72] The results showed that the FibroScan® was comparable to specialised blood tests, but was better than the simple blood tests. Different elastography techniques (Supersonic Shear Imaging®, Virtual Touch Quantification®) have been evaluated in ARLD with seemingly equivalent performances to that of the FibroScan®.[69,71] However, these results still lack validation. Magnetic Resonance Elastography is a very efficient technology for the evaluation of liver fibrosis[79] but it has not yet been evaluated in ARLD.

2.6 | Chapter 6. Alcohol-related liver disease and comorbidities

RECOMMENDATIONS

Smoking increases the risk of fibrosis and hepatocellular carcinoma in the course of alcohol-related liver disease.

G1+/STRONG AGREEMENT

Helping smokers to stop is, therefore, included in the management of the alcohol-related liver disease.

G1+/STRONG AGREEMENT

The experts recommend screening for the presence of cognitive impairments because of their high prevalence.

EXPERT OPINION/STRONG AGREEMENT

Studies comparing patients to matched controls and observational studies have reported that AUD is frequently accompanied by cognitive impairments.[80] Please see Appendix for a more detailed description of cognitive impairment in ARLD patients.

TABLE 1 Diagnostic thresholds of the Fibrotest®, FibroMeter Alcohol® and FibroScan® in alcohol-related liver disease

	Diagnostic target		
	Septal fibrosis (METAVIR *F* ≥ 2)	Severe fibrosis (METAVIR *F* ≥ 3)	Cirrhosis (METAVIR *F4*)
FibroTest®	≥0.49	≥0.59	≥0.75
FibroMeter Alcohol®	≥0.593		≥0.947
FibroScan® (kPa)[75]			
AST < 38.7 IU/L and bilirubin < 9 μmol/L	≥6.9	≥8.8	≥12.1
AST 38.7–75 IU/L and bilirubin 9–16 μmol/L **OR** AST < 38.7 IU/L and bilirubin 9–16 μmol/L	≥8.1	≥11.2	≥15.4
AST 38.7–75 IU/L and bilirubin 9–16 μmol/L	≥8.8	≥12.3	≥19.9
AST > 75 IU/L and bilirubin > 16 μmol/L	≥11.6	≥16.1	≥25.9

The experts recommend the conduction of studies on the assessment of the potentially deleterious effects of cannabis use on the liver in the course of alcohol-related liver disease.

EXPERT OPINION/STRONG AGREEMENT

The experts recommend involving addiction liaison teams in the care pathway of patients with alcohol-related liver disease.

EXPERT OPINION/STRONG AGREEMENT

Obesity and metabolic syndrome accelerate the progression of alcohol-related liver disease. Therefore, the experts recommend considering specific management of overweight and obesity.

EXPERT OPINION/STRONG AGREEMENT

The experts recommend promoting clinical and translational research in the field of metabolic syndrome and cardiovascular risk factors in alcohol-related liver disease.

EXPERT OPINION/STRONG AGREEMENT

METABOLIC SYNDROME AND ARLD

There are very few studies having evaluated the specific effect of managing one or more components of metabolic syndrome in the course of ARLD. A randomised trial evaluated the effect of a 12-week physical activity programme in overweight or obese subjects with a consumption of 144–336 g of pure alcohol per week for males and 88–224 g per week for females. A decrease in body fat, an increase in lean body mass and a decrease in the caspase-cleaved fragment of cytokeratin-18 (marker of apoptosis) showed no effect on liver steatosis.[81] By analogy with what is recommended in the course of metabolic liver steatosis, investigation and management of the different elements of metabolic syndrome are likely to be useful.[7,82] In overweight or obese patients, weight loss must be considered. A lasting change in lifestyle habits combined with a process of stopping or reducing alcohol consumption must be recommended.[7,82] Weight gain after withdrawal from alcohol or other addictive substances has been reported.[83] An addiction transfer hypothesis has been put forward, but it seems that the propensity for behavioural addiction, which could concern multiple substances, behaviours or even sweet products, is perhaps a better explanation.[84] The implementation of hygiene and dietary measures is, therefore, particularly important.[85]

2.7 | Chapter 7. Screening for alcohol-related liver disease in the general population

RECOMMENDATION NO. 1

In order to identify people with advanced alcohol-related liver disease in the general population, it is likely recommended to define a target group meeting the following criteria: aged ≥ 40–45 years with an AUDIT score predictive of hazardous consumption and/or consumption of ≥14 standard drinks/week.

G2+/STRONG AGREEMENT

For the majority of the reports in the literature, ARLD screening is offered to patients with excessive alcohol consumption. The question that then arises concerns the procedure used: declared alcohol consumption and/or AUDIT or AUDIT-C. The literature generally approaches this subject regarding advanced disease and/or cirrhosis. One study suggests using AST/ALT ratio ≥ 0.8 for the selection of patients to undergo non-invasive evaluation among patients with AUD. A FibroScan® would be performed in this case.[86] This study must be interpreted with caution since ALT levels were normal in 10 patients among the 11 patients in the study with cirrhosis diagnosed by FibroScan®.

The issue of screening for early-onset ARLD, i.e. steatosis, is not discussed in the literature. It is not clear whether the presence of steatosis alters the medical management of patients consuming alcohol. On the contrary, screening for advanced ARLD (fibrosis F3–F4 according to METAVIR classification) is justified by the possibility of recourse to specialist consultation in hepato-gastroenterology and screening for HCC.

RECOMMENDATION NO. 2

It is not recommended to use transaminases for the detection of advanced alcohol-related liver disease in the general population exposed to high-risk consumption.

G1−/STRONG AGREEMENT

RECOMMENDATION NO. 3

It is recommended to use non-invasive assessment in a targeted manner for the detection of advanced fibrosis/alcoholic cirrhosis.

G2+/WEAK AGREEMENT

We assume that all studies evaluating the natural history of histologically proven alcohol-related steatosis, although they provide important information regarding the cumulative risk of cirrhosis, cannot be extrapolated to screening in the general population.[87,88]

Given that liver biopsy is ruled out in a population-wide screening strategy due to its invasive nature, there remain the classic biochemical examinations (liver enzymes), imaging and non-invasive fibrosis assessments. Numerous studies underline normal ALT levels in more than 50% of advanced fibrosis cases, thus making ALT levels obsolete for effective screening.[89] There are no studies on the value of ultrasound. One study focused on the use of the FibroTest®[90] and the other studies used the FibroScan®.[91–93] The literature only evokes advanced ARLD and/or cirrhosis. The challenge is that the majority of studies mix NAFLD and ARLD. This is relevant because in general practice risk factors are often intertwined. In addition, the aim is to detect asymptomatic liver disease rather than an isolated cause.[86,92,93] ALT level in isolation is a poor screening tool according to the vast majority of studies. Indeed, in the study by Harris et al the percentage of patients with fibrosis and normal ALT levels ranged from 40% to 74%.[89]

The studies aforementioned used FibroScan®[86,92–94] or FibroTest®[90] which are easy to interpret, or complex algorithms[95,96] which are unsuitable for screening in the general population.

It must be pointed out that patients at risk of developing NAFLD and those with high-risk alcohol consumption are mixed in many studies. This leads to the consideration of extending screening to a broader liver disease context in the general population.

RECOMMENDATION NO. 4

The experts recommend the implementation of studies based on the care pathway of patients with excessive consumption and

the integration of screening for alcohol-related liver disease in more general liver disease screening, including NAFLD and hepatitis B and C viruses.

EXPERT OPINION/STRONG AGREEMENT

2.8 | Chapter 8. Alcoholic hepatitis

A liver biopsy is recommended to confirm the clinical suspicion of alcoholic hepatitis in patients who are potential candidates for specific treatment.

G2+/STRONG AGREEMENT

In the absence of liver biopsy, the NIAAA classification (National Institute on Alcohol Abuse and Alcoholism) must be used to offer treatment only to patients with probable alcoholic hepatitis.

EXPERT OPINION/STRONG AGREEMENT

In cases of clinical and biochemical suspicion of severe alcoholic hepatitis, the probability that this is actually presented at the liver biopsy level varies from 60% to 90% of cases depending on the patient series.[97,98] For this reason, the experts recommend histological confirmation in order to target patients who actually have alcoholic hepatitis which then justifies specific management.[7,99] However, access to liver biopsy is reserved for centres carrying out liver biopsy via the transjugular route; a technique justified by the frequent presence of coagulation disorders or ascites.

This transjugular liver biopsy technique must also be developed and made available in non-university hospital centres. In order to achieve greater rigour in the identification of patients with symptomatic alcoholic hepatitis, the NIAAA consortium has proposed a diagnostic classification of alcoholic hepatitis with three degrees of certainty.[100] In this classification, definite AH is clinically diagnosed and biopsy proven. Probable AH is clinically diagnosed in patients with heavy alcohol use and typical liver tests without confounding factors. In these patients, a diagnosis other than AH will be made in <10% of patients by liver biopsy. Lastly, possible AH is clinically diagnosed but with potential confounding factors, uncertain alcohol use assessment and atypical laboratory tests (e.g., AST < 50 IU/ml or >400 IU/ml, AST/ALT ratio < 1.5). In patients with possible AH, NIAAA recommends that liver biopsy is performed for histological confirmation. The risk of misdiagnosis is likely limited in the case of probable alcoholic hepatitis, whereas it is high in the case of possible alcoholic hepatitis. In the latter case, a liver biopsy is essential to confirm or invalidate the diagnosis. It must be noted that the diagnostic classification proposed by the NIAAA is based on expert opinions and still requires validation.

The development of non-invasive assessments for the diagnosis of alcoholic hepatitis is strongly recommended. Such assessments could improve the identification and management of patients with severe or non-severe alcoholic hepatitis.

EXPERT OPINION/STRONG AGREEMENT

The development of non-invasive diagnostic scores is strongly recommended for the improvement in patient management. The approach involving new markers is attractive, such as cytokeratin-18 (CK 18) fragment levels.[101] These results need to be confirmed and the prognostic value of these markers also needs to be assessed.

The Maddrey Discriminant Function and the MELD score are the recommended scores for identifying severe forms of alcoholic hepatitis.

G1+/STRONG AGREEMENT

The Maddrey score has been the most widely used score in both randomised trials and current practice. When this score is ≥32, alcoholic hepatitis is considered severe and corticosteroid treatment must be offered.[7,102,103] The precise MELD score threshold for defining a severe form is still poorly defined and is expected to fall between 17 and 20.[104] The MELD score is more commonly used in English-speaking countries. The use of other scores has been proposed, such as the ABIC and the Glasgow Alcoholic Hepatitis scores. However, the prognostic value of these two scores in relation to the Maddrey and MELD scores remains limited.[105,106] It is important to note that all of these scores have been developed as prognostic scores and not as diagnostic scores.

The experts recommend stopping using the expression 'non-severe alcoholic hepatitis' in the event of a Maddrey score below 32 in symptomatic patients given it has an approximate 20% 1-year mortality rate.

EXPERT OPINION/STRONG AGREEMENT

Terminology classifying alcoholic hepatitis as non-severe based uniquely on a Maddrey score < 32 is no longer suitable. Indeed, recent studies conducted in patients with symptomatic alcoholic hepatitis with a Maddrey score < 32 have observed a 10% risk of death at 6 months and 20% at 1 year.[107] Such a risk, therefore, no longer sanctions these forms to be called 'non-severe'. A change in terminology is strongly recommended. In the absence of jaundice, alcoholic hepatitis must be called asymptomatic. Severity could be defined on the basis of a risk of death exceeding 5% at 6 months, with forms formerly classified as severe with a Maddrey ≥32 score being now considered as a therapeutic emergency.

Taking these elements into account, the experts suggest using the term 'symptomatic alcoholic hepatitis' for patients presenting with alcoholic hepatitis with jaundice and associating the adjective 'severe' with a Maddrey score above 32 and 'moderate' with a score below 32.

EXPERT OPINION/STRONG AGREEMENT

The Lille score must be calculated on the seventh day of treatment in order to identify patients not responding to treatment.

G1+/STRONG AGREEMENT

Early improvement in liver function observed within the first week of treatment is a predictor of short-term survival.[108] The Lille score integrates patient characteristics at the initiation of corticosteroid treatment, such as age, albuminemia, serum creatinine, prothrombin time and the change in bilirubin levels in the 1st week of corticosteroid therapy. This score is calculated on the 7th day of treatment and is recommended for the assessment of therapeutic response to corticosteroid therapy.[109] Patients with a Lille score ≥ 0.45 have very low 6-month survival, in the order of 20%–30%, whereas

patients classified as responders (Lille score < 0.45) have a 6-month survival in the order of 70%–80%. The Lille score enables the identification of patients requiring new therapeutic alternatives. A study has suggested that the Lille score could be calculated at day 4 with similar prognostic performance as the calculation at day 7.[110] This requires further validation. In clinical practice in France, most patients are not discharged before day 7.

Patients with a Lille score ≥ 0.45 are considered treatment non-responders and corticosteroid therapy must be stopped in those with a Lille score ≥0.56.

G1+/STRONG AGREEMENT

Patients with a Lille score ≥ 0.45 are classified as non-responders to corticosteroid therapy.[109] Stopping corticosteroid therapy is recommended for those with a score ≥ 0.56 (a Lille score ≥ 0.56 defines patients who are 'null responders' to corticosteroid therapy). In this subgroup, corticosteroid therapy is as effective as the placebo.[111] The decision to continue corticosteroid therapy must be considered on a case-by-case basis in cases with a Lille score between 0.45 and 0.56.

The investigation for infection must be systematically carried out in severe forms of alcoholic hepatitis.

G1+/STRONG AGREEMENT

Infection is observed in 20%–30% of patients on admission and also develops in 25% of cases in the first month of treatment with corticosteroids.[112] In the case of infection on admission, corticosteroid therapy can be offered after effective treatment of infection. The risk of developing an infection is increased in the event of non-response to corticosteroid therapy. Only infection developed under corticosteroids is associated with an increased short-term risk of death. The early identification of patients at risk of developing an infection is a major issue. Approaches using bacterial DNA or LPS assays are attractive but require confirmation by further studies.[113] In practice, an extensive bacteriological examination (microbiological examination of urine, ascites fluid culture and count, blood cultures) must be carried out systematically before initiating corticosteroid therapy.[7] Under treatment, an extensive bacteriological examination and investigation for fungal infection[114] must be carried out in the event of symptoms or clinical signs suggestive of infection.

Combining the Lille and MELD scores is the optimal approach for evaluating short- and medium-term risk of death.

G1+/STRONG AGREEMENT

Predicting the risk of early death is a primary aim in the management of patients with a severe form of alcoholic hepatitis. It enables the adaptation of patient management, particularly for those with a higher risk of death. A recent study combined the MELD and Lille scores in order to obtain the continuous mortality risk prediction that integrates the severity of liver impairment on admission and its early improvement.[115] The use of this combined score is of obvious value for the selection of candidates for fast-track liver transplantation.

Survival in the first 3 months is related to the severity of alcoholic hepatitis and early liver function improvement.

G1+/STRONG AGREEMENT

The experts recommend this criterion for the evaluation of new medication.

EXPERT OPINION/STRONG AGREEMENT

Survival in the first 3 months is mainly related to the severity of liver impairment and the improvement of liver function in this period.[51] Alcohol resumption has little or no influence on the 3-month mortality risk. Consequently, the prescription of 'anti-craving' medication seems of minimal use during this period. The experts recommend using 3-month survival as the primary endpoint for the evaluation of new medication.[100] This recommendation is based on the fact that the short-term outcomes are mainly associated with alcoholic hepatitis. In symptomatic forms but with a Maddrey score below 32, the development of new medication must base early improvement in liver function as the primary outcome.

Long-term outcomes depend mainly on achieving abstinence. Addiction treatment must be systematically offered after an episode of alcoholic hepatitis.

G1+/STRONG AGREEMENT

Addiction treatment is strongly recommended after an episode of alcoholic hepatitis. Abstinence is associated with improved 5-year survival.[107,109] For example, medical treatment responders with maintained abstinence have a 5-year survival rate of 80%, whereas it is only 50% in the event of alcohol relapse. In patients with resumed alcohol consumption, even a reduction in consumption must be sought as it can potentially be associated with a 5-year survival benefit.

TREATMENT

Corticosteroid therapy (prednisolone 40 mg/day or methylprednisolone 32 mg/day) is recommended in patients with a severe form of alcoholic hepatitis. It improves short-term survival without any observations of a medium- or long-term survival benefit.

G1+/STRONG AGREEMENT

The effectiveness of corticosteroid therapy (prednisolone 40 mg/day or methylprednisolone 32 mg/day) administered for 1 month was a subject of controversy for over 30 years. Recent randomised studies, a classic meta-analysis and more recently an individual patient data meta-analysis on 2111 patients with a severe form of alcoholic hepatitis have shown that corticosteroid therapy improves 1-month survival in patients with a severe form.[111,116,117] American and European societies recommend corticosteroid therapy for patients with a severe form in the absence of uncontrolled infection, severe digestive haemorrhage and contraindications to corticosteroid use.[7,99]

The survival benefit related to corticosteroid therapy is nonetheless no longer significant at 3 months.[117] For this reason, the development of new therapeutic strategies is urgently needed to reduce the risk of death at 3 months.

The combination of N-acetylcysteine and corticosteroids can be offered to patients with a severe form of alcoholic hepatitis.

G2+/WEAK AGREEMENT

A randomised study comparing the combination of N-acetylcysteine+corticosteroids to corticosteroids alone did not show a 6-month survival benefit (the study's main endpoint), but

it did show a short-term survival benefit at 1 and 3 months.[118] However, this combination was only evaluated in one trial and therefore did not meet its primary endpoint. Confirmatory studies are therefore necessary before recommending this combination in a systematic way.

Pentoxifylline must no longer be offered to patients with severe alcoholic hepatitis because of its ineffectiveness.

G1−/STRONG AGREEMENT

Even though one randomised study demonstrated a survival benefit for pentoxifylline over placebo, several other recent randomised studies and meta-analyses have shown that pentoxifylline alone or in combination with corticosteroids does not improve 1-month survival.[116,117,119,120] It must, therefore, no longer be prescribed for this indication.

Fast-track liver transplantation must be considered for patients at the end of their therapeutic options. The selection process must be rigorous and multidisciplinary in the reference transplant centre.

G1+/STRONG AGREEMENT

In a French-Belgian pilot study,[121] 26 patients with severe alcoholic hepatitis not responding to medical treatment were transplanted according to the following selection criteria: the first decompensation of the liver disease, the absolute consensus among the medical, nursing and surgical teams, absence of significant co-morbidities and strong social and family support. The patients included were at the end of their therapeutic options and presented either a non-response to medical treatment according to the Lille score or a rapid liver function deterioration despite a favourable Lille score. The results of this study showed a significant improvement in 6-month survival (77% in the transplanted group versus 23% in a control group of non-transplanted non-responders) with maintained survival benefit at 2 years. This innovative therapeutic concept paves the way for new perspectives for this patient type. It does, however, require a drastic patient selection by expert centres. The benefit of this strategy has been confirmed by several European and American groups.[122–125] Candidates for such a strategy must be rigorously selected after a clinical, psychological and addiction assessment. The combined MELD+Lille score[115] is recommended for the selection of patients with the highest death risk in order to adapt the length of the selection process to this mortality risk.

3 | CONCLUSION

The AFEF encourages healthcare practitioners to apply these formal expert guidelines while respecting the multidisciplinary that is essential in the management of patients with ARLD, with particular emphasis on the key role of alcohol abuse specialists. In this respect, the AFEF would like to sincerely thank the SFA, co-organiser of these guidelines, for its valuable assistance and the quality of the scientific exchanges on which these guidelines are based.

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