Editorial

The French guidelines for alcohol-related liver disease—what's new, what's not and what's still needed

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Introduction

Louvet *et al.* recently published the French Association for the Study of the Liver (AFEF) and the French Alcohol Society clinical guidelines (1). The AFEF guidelines are the first specific to the screening and care of alcohol-related liver disease (ALD) in France. We compared these to the guidelines of American Association for the Study of Liver Diseases [AASLD, 2020; (2)] and European Association for the Study of Liver [EASL, 2018 (3)]; some noticeable differences and similarities emerge (*Table 1*).

What's new?

Although the rationale for AFEF to publish guidelines that are separate from the European (EASL) guidelines are not stated by the authors, it becomes clear that some efforts were made to build upon the EASL guidelines and incorporate some aspects of the more recent AASLD guidelines. The AFEF guidelines therefore appear as a merger or marriage of these 2 approaches (*Table 1*). Moreover, the authors employ the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) method for rating the quality and strength of the evidence that supports each recommendation (4), an approach shared by the EASL guidelines (3).

The GRADE approach not only weighs each recommendation by supporting evidence, but also highlights where the gaps in our understanding remain. For example, since alcohol consumption is often underreported, continuous efforts to uncover the surreptitious harmful alcohol use in the general population are important aspects of all 3 guidelines (1-3). Recent work has suggested that biomarkers of alcohol consumption may be useful in screening the general population. However, the GRADE approach led the AFEF to conclude that biomarkers are not required in the systematic detection of alcohol misuse [in contrast to alcohol use disorder identification test (AUDIT)-C questionnaire], since there are insufficient data to decipher the value of systematic screening in the general population at this time.

The AFEF guidelines are also unique in that they systematically recognize that the pattern of drinking is also critical to the field's understanding. Specifically, although it is understood that heavy episodic (i.e., 'binge') drinking puts an individual at higher risk for alcohol harm, these did not translate to specific recommendations in the EASL and AASLD guidelines. The AFEF is specific in instructing clinical practitioners to educate and screen the general population on the risks of binge drinking. The AFEF also highlights that our current understanding of the impacts of binge drinking harm to the liver are incompletely understood and calls for more prospective studies to address this gap.

The AFEF guidelines offer no specific comments or

Table 1 Side-by-side comparison of the recommendations discussed in the AFEF, AASLD and EASL guideline for alcohol-related liver disease

Recommendations	AFEF (1)	AASLD (2)	EASL (3)
Detecting excessive alcohol consumption			
AUD screening			
General population (AUDIT-C)	Yes[a]	Yes	Yes
Cognitive impairment?	Yes	–[b]	Yes
Other addictions (e.g., smoking)	Yes	–	Yes
Brief intervention recommended?			
Psychosocial/behavioral?	Yes	Yes	Yes
Pharmacological intervention?	Yes	Yes	Yes
Biomarkers of alcohol consumption?			
General population	No[c]	Yes	–
Specialist referral	Possible[d]	Yes	Possible
Before/after liver transplant?	–	Yes	Yes
Consumption profile			
Screen for binge drinking	Yes	–	–
Educate on risks of binge drinking?	Yes	–	–
Research on binge drinking?	Yes	–	–
Harm reduction			
Definition of standard drink (grams)	10	14	10
Definition of binge drinking			
Within 2 h (drinks)	–	>4/5 (f/m)	>4/5 (f/m)
Within 24 h (grams)	>60 g	–	>60 g
Definition of daily safe drinking (ALD)			
Daily (drinks)	<2	<1/2 (f/m)	<1
Weekly (drinks)	<10	–	–
Weekly alcohol-free day?	Yes	–	–
No drinking in ALD/cirrhosis?	Yes	Yes	Yes
Medical management of AUD: the influence of advanced liver disease			
Treatment of alcohol withdrawal			
Use of benzodiazepines?	Yes	–	Yes
Modify regimen/drug for liver disease?	Yes	–	Yes
Management of abstinence			
Contraindications in liver disease? (e.g., disulfiram, naltrexone)	Yes	Yes	Yes
Safe drugs for liver disease? (e.g., acamprosate and baclofen)	Yes	Yes	Yes
Invasive and non-invasive diagnosis of fibrosis and steatosis in ALD			
Medical semiology	–	Yes	Yes
Fibrosis assessment			
Imaging (e.g., TE or MRI)?	Yes	Yes	Yes
Blood tests	Yes	Yes	Yes

Table 1 (*continued*)

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Recommendations	AFEF (1)	AASLD (2)	EASL (3)
Steatosis assessment			
Imaging (e.g., CAP, MRI)	No	Yes	Yes
Liver biopsy in non-AH ALD	If needed for differential diagnosis and/or grading of disease severity		
Alcohol-related liver disease and comorbidities			
Screen/treat smoking?	Yes	–	Yes
Screen/treat psychiatric disorders?	Yes	–	Yes
Screen/treat obesity/metabolic syndrome?	Yes	Yes	Yes
Other coexistent liver disease?	–	Yes	–
Screening for ALD in the general population			
Targeted screening?	Yes	–	Yes
Utility of imaging?	Yes	–	Yes
Utility of LFTs?	No	–	Yes
Utility of other blood tests?	Yes	–	Yes
AH			
Biopsy to confirm AH?	If needed for differential diagnosis		
NIAAA criteria in absence of biopsy?	Yes	Yes	Yes
Non-invasive tests for AH (e.g., CK 18)	Yes, but need more to improve diagnosis/prognosis		
Utility of laboratory scores			
Severity assessment	MDF and MELD preferred		
Prognosis assessment	MELD and Lille preferred		
Initiating corticosteroids	MDF (and GAHS) preferred		
Cessation of corticosteroids	Lille preferred		
Tissue-based scores (e.g., AHHS)?	–	Limited use	Limited use
Importance of infection screening	Yes	–	Yes
Treatment of AH			
Abstinence	Yes	Yes	Yes
Nutrition	–	Yes	Yes
Corticosteroids	Yes	Yes	Yes
N-acetylcysteine	Possible	Possible	Possible
GC-SF	–	Possible	Possible
Pentoxifylline	No	No	No
Fast track liver transplant benefit?	Yes	Yes	Yes

The order of comparison was based on the order of discussion and guidelines in the AFEF document (1). Some areas that were discussed in AASLD and/or EASL guidelines (e.g., management of alcohol-related cirrhosis) were not covered in the AFEF guidelines and therefore no comparison was made. [a], "Yes" indicates that a specific guideline recommendation was made in favor; [b], "–" indicates that no specific guideline recommendation was made, even if the topic was discussed; [c], "No" indicates that a specific guideline recommendation was made against; [d], "Possible" indicates that guidelines suggest recommendation, but with limited data to support. AFEF, French Association for the Study of the Liver; AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of Liver; AUD, alcohol use disorder; AUDIT, alcohol use disorder identification test; f/m, female/male; ALD, alcohol-related liver disease; TE, transient elastography; MRI, magnetic resonance imaging; CAP, controlled attenuation parameter; AH, alcohol-related hepatitis; LFTs, liver function tests; NIAAA, National Institute on Alcohol Abuse and Alcoholism; CK 18, cytokeratin 18; MDF, Maddrey's discriminant function; MELD, model of end-stage liver disease; GAHS, Glasgow Alcoholic Hepatitis Score; AHHS, Alcoholic Hepatitis Histological Score; GC-SF, Granulocyte Colony Stimulating Factor.

clinical practice guidance for alcohol-associated cirrhosis, which differs from both the AASLD and EASL guidelines (2,3). It is assumed that the authors viewed inclusion in this document overlapping with their separate guidelines for cirrhosis (5). Nevertheless, the omission appears strange, especially when the care of alcohol-related cirrhosis patients can be more involved than cirrhosis by other etiologies, as they acknowledge.

What's not new, but it is important?

The dimensional perspective provided by the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) was crucial for categorizing the differentiation between alcohol use disorders (AUD) and alcohol misuse/dependance (6). Moreover, DSM-V was a key step forward to overcome the alcohol-related stigmatization. All three guidelines adopt these changes to remove stigmatizing statements in our terminology. Similar to the AASLD and EASL guidelines (2,3), the AFEF guideline emphasize the need to systematically screen the general population for an AUD. Although the French guidelines more explicitly suggest that using the AUDIT-C questionnaire (which consists of the first 3 questions of AUDIT) is often sufficient to detect of excessive alcohol consumption in both general practice and specialist consultations, the guidance for practice remains largely the same between the 3 documents.

The AFEF also emphasizes the need to screen those suspected of an AUD for other psychological disorders and addictions; these recommendations are built on the understanding that alcohol misuse is often part of a spectrum of disorders that are afflicting the patient and may represent, at least initially, efforts at self-medication. All three guidelines emphasize the need and potential benefit of brief psychosocial/behavioral and pharmacological intervention in those identified with an AUD in the general population.

Another notable lack of difference between these 3 documents is in the management and care of alcohol-related hepatitis (AH). The mortality of AH, the most lethal condition of the ALD spectrum, has not decreased significantly in the last decades and it is still up to 20–40% at 3 months. AH treatment has not experienced major advances during the last four decades and corticosteroids, the only approved therapy for patients with severe AH, are of limited efficacy (7,8). Furthermore, all guidelines highlight that the development of novel pathogenesis-based targeted therapies represents an urgent need in clinical hepatology. Thus, these differences are not a criticism of the guidelines, *per se*, but rather a call for more studies.

What's needed in the field?

Children and young adults are particularly sensitive to alcohol marketing, and they should be screened for binge drinking as a high-risk consumption pattern as highlighted in AFEF guidelines. Indeed, AH is contributing to increasing ALD-related burden in the US among individuals aged ≤35-year-old, affecting mostly young people in their most productive years of life (9). However, screening tools, including AUDIT, have been developed and validated in populations over 18 years old (10). The validity of these tools in young/adolescent populations still needs to be validated.

Another significant challenge, especially with the increasing prevalence of obesity, metabolic syndrome, and type 2 diabetes mellitus, is the role of NAFLD (nonalcoholic liver disease) in ALD as a dual etiology entity. Since its first description in 1980, NAFLD has been conceived as a different entity from ALD, despite that both diseases have an overlap in the pathophysiology, share genetic-epigenetic factors, and frequently coexist. The impact of moderate alcohol use on the severity of NAFLD remains controversial. Studies have suggested protective effects in moderate doses; however, most recent evidence shows that there is no safe threshold for alcohol consumption for NAFLD. In fact, given the synergistic effect between alcohol consumption, obesity, and metabolic dysfunction, it is likely that alcohol use serves as a significant risk factor for the progression of liver disease, and even the development of hepatocellular carcinoma, in NAFLD and metabolic syndrome (11). Additionally, a recent study showed that up to 28% of patients classified as NAFLD have positive biomarkers of heavy alcohol use (12). Critical research in this area needs to be increased.

Another critical area for improvement is spanning the gap between those identified with risky alcohol consumption and those truly at risk for ALD. Specifically, although a positive AUDIT-C score has strong specificity and sensitivity for detecting an AUD, not all individuals will progress onto ALD (or other alcohol-related end-organ diseases). Although there are approaches that detect those who are progressing to severe liver disease, including blood (e.g., FIB-4) and imaging (e.g., transient elastography), the accuracy of these approaches are best at later stages of disease progression (e.g., >F2 fibrosis score). Moreover,

given that it is estimated that 1:10 adults have an AUD, the economic burden of applying these more advanced screening approaches to all those testing positive for an AUD would be staggering. What is needed is a relatively inexpensive test/score that better stratifies the risk for ALD much earlier in disease progression, where interventive strategies to reduce alcohol consumption and (potentially) halt disease progression would be more effective. The screening and risk stratification blueprint proposed by Asrani *et al.* (13) could efficiently help to appropriately identify patients with AUD or/and ALD at all levels of clinical practice.

Noninvasive prognostication in patients with severe AH is also an unmet need. This is especially true given that liver transplantation for AH is increasingly seen as a possible therapeutic option (14). Noninvasive approaches are not only more convenient, but also needed because of the significant regional differences in willingness/ability to perform trans-jugular liver biopsy in patients with severe AH. Several recent efforts have been made to discover and validate new biomarkers. One promising biomarker is cytokeratin-19 (CK19) (15), that has shown to be associated with the presence of alcohol-associated steatohepatitis on biopsy and independently predict 90-day survival. Although several ongoing trials for patients with severe AH are in development, results that alter practice are not yet available.

In summary, ALD-related burden is increasing worldwide, and multi-societal efforts are needed to improve the early diagnosis, prognostication, and the development of effective treatments at all levels of care. The AFEF guidelines offer some new advances in the guidance of the clinical management of ALD. However, the fact that different societies cannot find consensus on simple aspects (e.g., definition of a standard drink) highlights a need for a true consensus on several aspects of ALD. An international unifying guideline covering the unmet needs of consensus is therefore needed.

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