



Guidelines

Management of end-stage alcohol-related liver disease and severe acute alcohol-related hepatitis: position paper of the Italian Society on Alcohol (SIA)



Gianni Testino^a, Teo Vignoli^b, Valentino Patussi^c, Emanuele Scafato^d,
Fabio Caputo^{e,f,*}, on behalf of the SIA board (Appendix A) and the external expert
supervisors (Appendix B)

^a Unit of Addiction and Hepatology ASL3 Liguria, San Martino Hospital, Genova, Italy

^b Unit of Addiction Treatment, Lugo, Ravenna, Italy

^c Regional Centre on Alcohol, Careggi Hospital, Firenze, Italy

^d National Observatory on Alcohol, National Institute of Health, Roma, Italy

^e Department of Internal Medicine, SS Annunziata Hospital, Cento, Ferrara, Italy

^f "G. Fontana" Centre for the Study and Multidisciplinary Treatment of Alcohol Addiction, Department of Medical and Surgical Sciences, University of Bologna, Italy

ARTICLE INFO

Article history:

Received 3 May 2019

Accepted 23 September 2019

Available online 19 November 2019

Keywords:

Alcohol use disorder

End stage alcohol-related liver disease

Liver transplantation

Severe acute alcohol-related hepatitis

ABSTRACT

Worldwide, the prevalence of alcohol use disorder (AUD) is 20–30% in men and 10–15% in women, and cirrhosis due to alcohol-related liver disease (ALD) is responsible for 0.9% of global deaths and 47.9% of cirrhosis-related deaths. End-stage ALD (ESALD) is the final condition of alcohol-related cirrhosis, and severe acute alcohol-related hepatitis (SAAH) is a distinct clinical syndrome associated with the consumption of large amounts of alcohol. In some cases, ESALD, and SAAH may need liver transplantation (LT). Thus, the management of ESALD and SAAH in patients affected by AUD may be an essential part of the clinical skills for hepatologists. For these reasons, the national board of the Italian Society on Alcohol have reviewed the most recent data on the management of ESALD, SAAH and LT for ALD in patients with AUD, formulating a position paper with related recommendations regarding four issues of specific clinical interest in this field: (a) the management of hepatic encephalopathy in patients with AUD, and LT in patients with ESALD; (b) the management of SAAH; (c) the management of AUD in patients with ESALD and SAAH; (d) special populations: polydrug addicts.

© 2019 Editrice Gastroenterologica Italiana S.r.l. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Alcohol consumption worldwide is responsible for approximately 5.9% of all deaths (3.3 million deaths) and accounts for 5.1% of the global disease burden [1,2]. In addition, alcohol consumption can lead to approximately 200 different diseases, including fourteen different types of cancer, and it can also have an addictive property [1,2]. Moreover, the worldwide prevalence of alcohol use disorder (AUD) is 20–30% in men and 10–15% in women [3–6].

Cirrhosis due to alcohol-related liver disease (ALD) is responsible for 0.9% of global deaths and 47.9% of cirrhosis-related deaths [7–9]. End-stage ALD (ESALD) with its complications (i.e. ascites) is the final condition of alcohol-related cirrhosis, and severe acute

alcohol-related hepatitis (SAAH) is a distinct clinical syndrome associated with the consumption of large amounts of alcohol. In addition, these two severe clinical conditions may need liver transplantation (LT). So far, the most common causes of LT are the association between alcohol and hepatitis C virus (HCV), and alcohol alone; however, with the introduction into clinical practice of direct antiviral agents, cirrhosis due to alcohol will become the primary cause of LT [10–12].

Thus, a deeper awareness in the management of ESALD and SAAH in patients affected by AUD may be an essential part of the clinical skills of gastroenterologists and hepatologists who frequently encounter patients with this complex disease in their daily clinical practice [8].

* Corresponding author at: Unit of Internal Medicine, SS Annunziata Hospital, Via Vicini 2, 4404, Cento, Ferrara, Italy.

E-mail address: f.caputo@ausl.fe.it (F. Caputo).

<https://doi.org/10.1016/j.dld.2019.09.017>

1590-8658/© 2019 Editrice Gastroenterologica Italiana S.r.l. Published by Elsevier Ltd. All rights reserved.

Table 1
Level of evidence and grade of recommendations (adapted from the Italian Program of Guidelines of the Istituto Superiore di Sanità in accordance with International Programs).

Level of evidence	
Level 1	Data derived from meta-analyses or systematic reviews or from (multiple) randomized controlled trials with high quality
Level 2	Data derived from a single randomized controlled trial
Level 3	Data derived from multiple non-randomized studies
Level 4	Data derived from retrospective observational studies or case–control studies
Level 5	Data derived from case series studies without control groups
Level 6	Data derived from expert opinions or consensus conference
Grade	
A (strong)	Strong recommendation: factors influencing the strength of the recommendation include the quality of the evidence, presumed patient-important outcomes and cost
B (weak)	Weaker recommendation: variability in preferences and values, or more uncertainty
C	The existing evidence is conflicting, and does not allow a recommendation to be made for or against the use of the action; however, other factors may influence decision making
D	There is fair evidence to recommend against the action
E	There is good evidence to recommend against the action

2. Methodology

A panel of clinicians, psychologists, and social-health professionals consisting of specialists in gastroenterology, hepatology, clinical pharmacology, psychiatry, internal medicine, gerontology, toxicology experts in the treatment of AUD, and psychotherapists was identified as appropriate by the board of the Italian Society of Alcoholology (SIA) and met on April 20th 2018 in Genova to draft the SIA's criteria for the management of AUD in patients with ESALD or SAAH. On the grounds of their competence, role, expertise and publications in the field of ESALD and SAAH, and AUD, twenty of them were chosen to collect and finalize the draft and its recommendations. The final paper then underwent revision and approval by the SIA board and, finally, also by three external (not SIA affiliated) expert hepatologists who supervised the final draft of the manuscript and were also invited to join the group. The position paper with its recommendations was produced with the intent of providing specialists in the addiction field, in hepato-gastroenterology and in internal medicine, and transplantation teams with appropriate tools to better manage patients with AUD and complicated ALD and also during evaluation for LT. This discussion lasted until January 31st 2019. The following protocols of internal validity such as the National Programme of Guidelines of the Italian Institute of Health [13], and of external validity [14–16], were used to assign the levels of evidence and grade to the recommendations (Table 1). The recommendations were formulated with the aim of providing grades and levels of evidence not for the entire spectrum of ALD which would have meant performing a more complete analysis (from the pathogenesis of ALD to the intervention strategies in ALD and its complications in patients with AUD), but it was decided to focus attention on four specific issues of more explicit clinical interest in this field: (a) the management of ESALD: hepatic encephalopathy (HE), duration of abstinence before LT, and the role of the multidisciplinary team; (b) the management of SAAH: prognostic scores, acute-on-chronic liver injury, pharmacotherapy, nutritional support, infections, and LT; (c) the management of AUD in patients with ESALD and SAAH: diagnostic tools, detoxification, and maintenance of alcohol abstinence; (d) special populations: polydrug addicts. The data used to prepare the position paper are based on a detailed analysis of the scientific literature published before January 31st 2019. In particular, in the development process of this position paper, we consulted the following guidelines: the European Association for the Study of the Liver (EASL) [17], the American Association for the Study of the Liver (AASL) [18], the American College of Gastroenterology (ACG) [19] guidelines, and the recommendations of an expert panel of transplant hepatologists appointed by the Italian Association for the Study of the Liver (AISF) [20].

3. Management of end-stage alcohol-related liver disease in patients with alcohol use disorder

3.1. End-stage alcohol-related liver disease (ESALD)

ESALD is characterized by severe complications of liver cirrhosis: ascites, hepatic encephalopathy (HE), variceal bleeding, hepato-renal syndrome (HRS), hepato-pulmonary syndrome, infections, spontaneous bacterial peritonitis, and malnutrition. The treatment of ESALD complications do not fit with the aim of our position paper, so for this topic we suggest referring to the EASL guidelines for the treatment of cirrhosis [21]. In order to classify the severity of liver disease, to measure the prognosis and to evaluate patients for LT, a model score (Model for End-Stage Liver Disease–MELD) was implemented and is currently used [17,19]. Indeed, rather than the length of time on the waiting list, the MELD score is now recommended to prioritise organ allocation in those patients with a worse prognosis ($\text{MELD} \geq 15$) [17,19]. The MELD score is based only on laboratory data (creatinine, bilirubin, and international normalized ratio, or INR) in order to be as objective as possible [17,19].

However, particular attention should be paid to HE. HE is defined by the AISF as a brain dysfunction caused by liver failure and/or portal-systemic blood shunting that produces a spectrum of neurological/psychiatric abnormalities ranging from subclinical alterations to coma [22]. Therefore, in patients with ESALD, the symptoms of acute alcohol intoxication (euphoria, nausea, vomiting, confusion, amnesia, seizures, and respiratory depression), alcohol withdrawal syndrome (AWS) (psychomotor agitation, confabulation, hallucinations, seizures, confusion, amnesia, and delirium tremens), and those of HE (asterixis, insomnia, confusion, amnesia, and coma) may overlap. Currently, there are only a few studies in the literature based on limited cases that specifically deal with HE in AUD patients. However, the prompt management of HE in order to avoid hepatic coma is the first step to follow, and treatment aimed at suppressing AWS when present is then mandatory. Therapy with lactulose/lactitol and rifamixin (a drug which modifies the intestinal flora by reducing ammonium production) remains the cornerstone in the treatment of HE [23–25] (Table 2). Moreover, it is certainly advisable to train family caregivers in early identification of this complication in order to limit hospital access and improve the quality of life of the patients and their families [26].

3.2. Liver transplantation in ESALD

To date, the survival rates of patients after LT for ESALD reported at 1, 3, and 5 years are extremely satisfactory; in particular, in Europe survival rates correspond to 84%, 78%, and 73% [27]; in the

Table 2

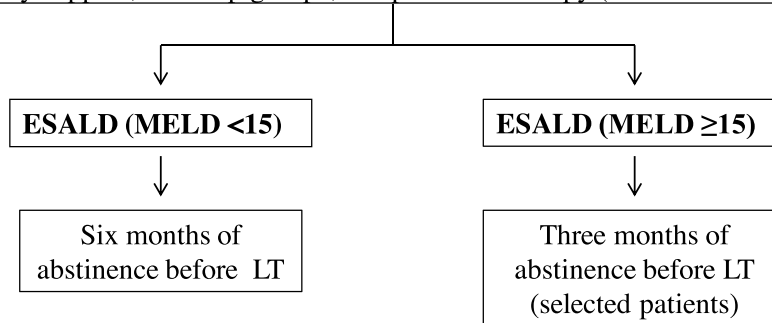
Therapeutic pathway in patients with ESALD and AUD.

-management of ESALD complications (i.e. HE: lactulose / lactitol and rifamixin 400 mg t.i.d. or 550 mg b.i.d. in cases of refractory forms of HE)

-management of AWS with short acting benzodiazepines (lorazepam 1-2 mg q.d or b.i.d orally or i.v. or oxazepam 15 mg q.d or b.i.d orally) following a trigger symptoms regimen

-vitamin supplementation (Vit B1: 200 mg/day for 3-5 days to prevent Wernicke encephalopathy); haloperidol (0.5-5 mg every 30-60 minutes iv or 0.5-5 mg every 4 hours orally) to treat hallucinations; alpha-2 agonists or beta-blockers to reduce autonomic hyperactivity

-maintenance of alcohol abstinence with multi-disciplinary treatment: psychosocial-therapy, family support, self-help groups, and pharmacotherapy (i.e. baclofen 10 mg t.i.d.)*



*Not in the case of hepato-renal syndrome (HRS), hepatic encephalopathy (HE), and neuro-psychiatric contraindications (epilepsy or suicidal ideation).

US to 92%, 86%, and 86%; and in Japan to 81.3%, 78.5%, and 75.7%. Moreover, Kawaguchi et al. [28] reported overlapping survival percentages between ALD and non-alcohol-related liver disease at 1, 3, and 5 years: for ALD survival rates of 100%, 91%, and 91%, and for non-alcohol-related liver disease 90%, 86%, and 83%, respectively.

Although alcohol is the main cause of LT and despite data demonstrating that five-year survival after LT due to alcohol is similar to or in some cases higher than with LT for other causes (i.e. viral, autoimmune), ethical concerns persist in the general population and medical profession [29]: the opinion that ALD is a “self-inflicted” disease is still widespread, even though the donation of an organ, in a period of shortage of donors, should only be carried out with absolute guarantees [30–32].

The so-called “6 months rule” also continues to be debated. Although it is assumed that shorter pre-LT abstinence correlates with higher numbers of post-LT relapses, in reality, a clear and safe period of alcohol abstinence before LT has not yet been defined. Indeed, Braun and Ascher showed that a 6 months abstinence period prior to LT for ALD does not appear to have a significant impact on relapse after LT [30]. Burra et al. [33] found that relapse occurred in a minority of patients (12%); Tandon et al. [34] detected a recurrence of 13%; Miguët et al. [35] stated that only 2 out of 12 studies identified pre-LT abstinence <6 months as a factor associated with post-LT relapse. It is evident that a prolonged period of abstinence before LT does not allow liver transplant access to those patients who, due to the severity of their clinical status, need to undergo LT earlier (3 months), the result being that many patients die before LT. Veldt et al. [36] showed that in patients with ESALD (of whom only 18% have acute alcohol-related hepatitis) the improvement of liver function is possible within the first 3 months of abstinence, and this improvement remains stable in the subsequent months. Therefore, it is suggested that a waiting period of 3 months may be sufficient, and those patients who

significantly improve their liver function may be excluded from the list for LT. To reinforce this issue, Kotlyar et al. [37] stated that selected patients with good social support and no psychiatric problems can undergo LT after 3 months (Table 2). In addition, the recent EASL guidelines on ALD suggest that the selection for LT of patients with AUD should not be based on the six-month criterion alone, thus not endorsing this measure as a formal recommendation [17]. Moreover, the EASL Clinical Practice Guidelines on Liver Transplantation reported that several authors consider that the risk of relapse is more related to psychosocial factors than to the duration of abstinence and that these factors can be evaluated prior to transplantation [38]. Several groups have therefore advocated breaking this 6-month abstinence rule [17,38,39]. However, most transplant centers, both European and US ones, require a minimum period of abstinence of approximately 6 months.

Thus, it becomes crucial to identify those patients more at risk for relapse after LT, as post-LT resumption of drinking is associated with graft injury and increased patient mortality [40]. Assessing the relapse risk requires a more complex patient evaluation, considering that occasional or moderate drinking does not affect LT outcome [41]. Several features are associated with relapse in heavy drinking. Although there is no clear relationship with age and gender [40], AUD severity, social factors, psychiatric comorbidity, and treatment compliance and motivation can predict relapse and should be thoroughly evaluated [40].

In our opinion, regardless of episodes of relapse (a daily intake of >4 drinks on one occasion or an overall consumption of ≥14 drinks per week for at least 4 weeks) or lapse/slip (any episode of alcohol consumption not classified as a relapse) [40,42,43], patients should be enrolled in a multi-disciplinary program. Indeed, as shown in a study by Attilia et al. [43], almost 80% of patients who presented a slip and who underwent multidisciplinary support, avoided relapse

Table 3
Recommendations of the Italian Society on Alcohol (SIA).

Recommendations 1

- Patients with ESALD should be encouraged to achieve and maintain complete abstinence from alcohol to reduce the risk of liver-related complications and mortality (Grade A1).
- HE, when present, should be treated first to avoid the onset of coma (Grade A1).
- LT should be considered in patients with ESALD (MELD ≥ 15) since it confers a survival benefit (Grade A1).
- The selection of patients with AUD should not be based on the “six-month rule” alone; the “six-month rule” is no longer a dogma, since it is not based on scientific evidence (Grade A2).
- The duration of abstinence before LT for ESALD should depend on the degree of liver failure; three months may be enough to evaluate the improvement of liver function, and LT evaluation can proceed in selected patients with a favorable psychological profile with great awareness of their addiction disease, and the presence of social support (Grade A1).
- A multidisciplinary approach evaluating not only medical but also psychological suitability for LT is mandatory (Grade A1).
- The integration of an addiction specialist (hepato-alcoholologist) in the multidisciplinary team may decrease the risk of relapse in heavy drinking individuals (Grade B2).
- Independently of episodes of drinking (relapse, lapse/slip), patients must be enrolled in a multi-disciplinary program to avoid heavy drinking (Grade B2).
- Self-help groups may be added to the multidisciplinary team (Grade C6).
- When alcohol units and LT centers are in the same place, the percentage of post-LT relapses is significantly lower, independently of the six months of abstinence (Grade B2).

Recommendations 2

- A recent onset of jaundice in patients with excessive alcohol consumption should prompt clinicians to suspect alcohol-related hepatitis AH (Grade A1).
- Available prognostic scores (i.e. mDF) should be used to identify SAAH at risk of early mortality (Grade A1).
- Systematic screening for infection should be performed before initiating therapy, and during corticosteroid treatment (Grade A1).
- In the absence of active infection, corticosteroids (prednisolone 40 mg/day or methylprednisolone 32 mg/day) should be considered in patients with SAAH to reduce short term mortality (Grade A1).
- After 28 days of corticosteroid treatment, a tapering procedure of discontinuation should be applied (Grade A1).
- N-acetylcysteine (for five days, intravenously) may be combined with corticosteroids in patients with SAAH in order to reduce the risk of infections and HRS (Grade B2).
- In the case of sepsis (pre-treatment infection), the use of corticosteroid may not be considered an absolute contraindication; after a collegial evaluation of risks and benefits, corticosteroids may be initiated in combination with antibiotic therapy (Grade B2).
- Evidence for a survival benefit of pentoxifylline therapy in patients with SAAH is very weak, and the drug can no longer be recommended (Grade D1).
- A careful evaluation of nutritional status should be performed in patients with SAAH; patients should receive a daily energy intake ≥ 35 –40 kcal/kg with at least 1.2–1.5 g/kg of protein, at least not less than 21 kcal/kg/BW, adopting the oral route as first-line intervention (Grade A1).
- In early non-response after seven days of corticosteroid therapy, treatment should be suspended (Grade A1), and carefully selected patients (especially at the first episode of SAAH) should be considered for early LT (Grade A1).
- In the presence ACLF with organ failures <4 , early LT in selected patients should be considered (Grade B2).
- In the presence ACLF with organ failures ≥ 4 (ACLF-4) LT is not indicated, while withdrawal of care is recommended (Grade B2).

Recommendations 3

- DSM-V is the accepted diagnostic method to identify patients with AUD (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).
- AUDIT or AUDIT-C should be used to screen patients for AUD (Grade A1).
- Metadoxine, due to its efficacy in rapidly reducing the half-life of ethanol, should be used to rapidly improve symptoms of AAI (Grade A2).
- Abstinence can be accurately monitored by measurement of EtG in urine (Grade A2).
- Short acting benzodiazepines should be used to treat AWS with a symptoms trigger approach in order to avoid drug accumulation due to reduced hepatic clearance (Grade A1).
- Pharmacotherapy to reduce craving for alcohol should be considered in patients with AUD and ESALD or SAAH (Grade A1) in accordance with the presence or absence of HE, and liver and renal impairment; baclofen seems to be the safest medication to be used as first line therapy in patients with ESALD and SAAH (Grade B2).

Recommendations 4

- The active use of opioids, cocaine, and synthetic drugs is considered an absolute contraindication for LT (Grade A1).
- The use of methadone maintenance treatment in patients abstinent from heroin is not considered an absolute contraindication to LT (Grade B2).

during the subsequent weeks. Moreover, it has been shown that when both an alcohol unit with hepatologists with skills in AUD and an LT centre are in the same place, the percentage of post-LT relapses is significantly lower, independently of the 6 months of abstinence [43–45] (Table 3, recommendation 1).

In addition, taking into account that indications for LT are changing with a decreased burden of HCV-related end stage liver disease, and an increase of HCC which has become the leading indication [46], organ allocation in Italy was widely discussed in 2015 by an Italian group of hepatologists and transplant surgeons who produced a critical proposal statement [47]. Given the inequity of a purely MELD-based system for governing organ allocation, this national consensus conference generated a “blended principle model” in which a weighted, dynamic, and verifiable balance of different organ allocation principles was judged the best solution. Namely, the consensus stated that, while awaiting more robust transplant benefit prognosticators, the organ allocation system should reflect an appropriate combination of three principles:

urgency, benefit, and utility. A “pure urgency” endpoint was identified for patients at high risk of death in the short term (MELD ≥ 30) who should have access to a broad geographical organ allocation area (nationwide or macro area). The other two endpoints, “benefit” and “pure post-transplant utility,” could be better managed with a regional allocation procedure, offering the advantages of easier donor-recipient matching and greater flexibility [47]. This system has just recently been updated, but the application is still under evaluation at national level.

4. Management of severe acute alcohol-related hepatitis in patients with alcohol use disorder

4.1. Severe acute alcohol-related hepatitis (SAAH)

Acute alcohol-related hepatitis is a distinct clinical syndrome associated with the consumption of large amounts of alcohol [48], and characterized by the recent onset of jaundice, malaise, weight

loss and malnutrition with or without other signs of liver decompensation [i.e. ascites or HE], and rarely associated with fever (even in the absence of infection) in patients with ongoing excessive use of alcohol [17,19]. The laboratory profile of AH reveals neutrophilia, hyperbilirubinemia, and serum levels of AST greater than twice the upper limit of normal range, 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. 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, and for prognostication [17]. There are some specific histological features: confluent necrosis, deposition of intrasinusoidal and pericellular collagen, ballooning degeneration, lobular inflammation (in the early stages in perivenular – zone 3), and Mallory bodies [49,50]. The severity of the inflammation (polymorphonuclear cell infiltration) and cholestatic changes are correlated with a worse prognosis and a lesser response to pharmacotherapy. The presence of megamitochondria is associated with less severe forms of acute alcohol-related hepatitis, as well as a lower incidence of cirrhosis and complications. From a prognostic point of view, the accumulation of progenitor cells (ductile cells positive for cytokeratin-7) is significant [49,51].

Several indices are used in making a prognosis [17,19]. Some are static such as Maddrey's Discriminant Function (mDF) (a worse prognosis ≥ 32), MELD (a worse prognosis ≥ 21), and Glasgow scores (a worse prognosis ≥ 9), and other dynamics such as the Lille Model used to evaluate the response to steroid therapy after one week (a score >0.45 indicates a lack of response to corticosteroid therapy); for some authors, a non-response is identified with a Lille Score of 0.56 [17,52,53]. To date, mDF, and the Lille Model are certainly the most commonly used in real practice (Table 4).

Less severe (mild-moderate) forms of acute alcohol-related hepatitis may regress with abstinence and supportive medical therapy, while SAAH forms (mDF ≥ 32) have a severe prognosis with a one-month mortality rate in approximately 35–40% of cases and six months in around 70% [54]. However, from 10 to 17% of patients with an mDF <32 may still die [19] (Table 3, recommendations 2).

4.2. Acute-on-chronic liver failure

Acute-on-chronic liver failure (ACLF) occurs in 10–30% of hospitalized patients [55]. The World Gastroenterology Organization has proposed the following definition: *a syndrome in patients with chronic liver disease with or without previously diagnosed cirrhosis, characterized by acute hepatic decompensation resulting in liver failure (jaundice and prolongation on the international normalized ratio or INR) and one or more extrahepatic organ failures, associated with increased mortality up to three months* [56]. The most frequent cause of acute damage is alcohol (particularly in the form of BD) followed by the hepatitis A, B and E viruses, a flare of autoimmune hepatitis, and anti-tuberculosis drugs [57]. ACLF is characterized by two types of liver injury in combination: one acute and one chronic. The acute injury can be liver-specific or systemic (i.e. infections), while the chronic component can be misunderstood. Similarly to the SAAH framework, the signs and symptoms range from asymptomatic jaundice to more severe forms characterized by a combination of HE, fever, asthenia, coagulopathy, and leukocytosis, as well as any other complications related to portal hypertension [58]. In this condition, the significant increase of endotoxins in the gut-liver axis induces a significant increase in pro-inflammatory cytokines so that a “systemic inflammation response syndrome” may be observed. ACLF is characterized by organ failure (reduction of albumin synthesis and coagulation factors, hyperbilirubinemia), ascites, HRS, HE, and bleeding from the esophagogastric varices. According to Bajaj et al. [54], the duration of the ACLF event is 12 weeks. Shal-

imar et al. [57] found that ACLF related to alcohol consumption at its onset presents a more severe phenotypic presentation, a greater incidence of organ failure, and a higher mortality. Death is often characterized by an overlap of infections due to elevated endotoxemia, cytokine increase, and decreased immune response [59]. A sophisticated score, the Chronic Liver Failure-Sequential Organ Failure Assessment score (CLIF-SOFAs) [60] which includes six types of organ failure (liver, renal, cerebral, respiratory, circulatory, and alterations of the coagulation process) was introduced to evaluate the grades of ACLF. A score range from 0 to 24 provides information on overall severity, and according to this score the grade of severity of ACLF is divided into three stages: ACLF-1 = patients with single kidney failure, patients with single failure of the liver, coagulation, circulation, or respiration who had a serum creatinine level ranging from 1.5 to 1.9 mg/dL and/or mild to moderate HE, and patients with single cerebral failure who had a serum creatinine level ranging from 1.5 and 1.9 mg/dL (the 28-day and 90-day mortality rates were 22.1% and 40.7%, respectively); ACLF-2 = two organ failures (the 28-day and 90-day mortality rates were 32.0% and 52.3%, respectively); and ACLF-3 = three to six organ failures (the 28-day and 90-day mortality rates were 76.7% and 79.1%, respectively) [60]. In the presence of organ failures ≥ 4 , some authors indicate withdrawal of care [61–63] (Table 3, recommendations 2; Table 4).

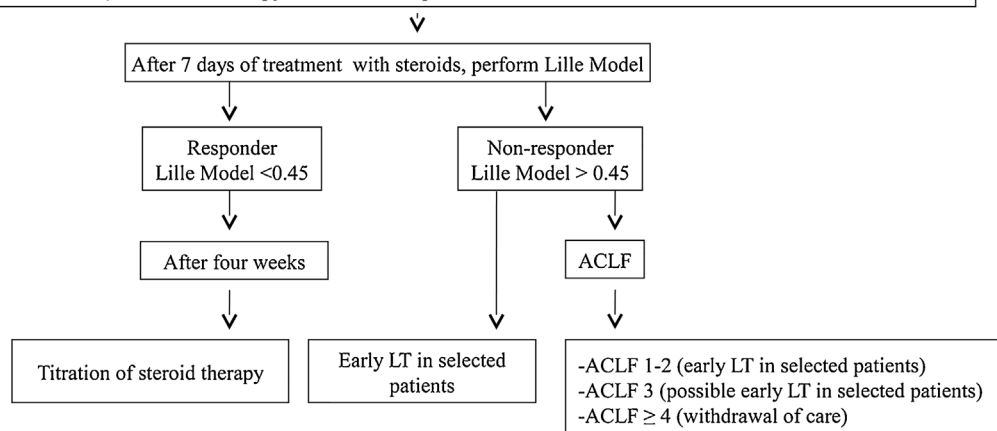
4.3. Nutritional and pharmacological therapy in SAAH

One part of the treatment for patients with SAAH/ACLF is certainly nutrition and reintegration with micronutrients and vitamins [64,65]. The European Society for Clinical Nutrition and Metabolism suggests a daily energy intake of 35–40 kcal of body weight and a daily protein intake of 1.2–1.5 kg of body weight [66] per day. For the EASL [17], the use of tube feeding is strongly recommended if the patient is unable to maintain an adequate caloric intake orally. However, tolerance to tube feeding is not high and the presence of an expert caregiver is mandatory. The oral route is therefore suggested as first-line intervention in patients with SAAH. Indeed, a recent randomized trial [67] in patients with SAAH treated with corticosteroids plus intensive enteral nutrition showed that enteral nutrition was difficult to implement and did not increase the 6-month survival in comparison to those patients treated with corticosteroids and conventional nutrition (44.4% vs 52.1%; $p=0.4$). On the other hand, independently of the route of nutrition, this study also showed that low daily energy intake (<21.5 kcal/kg/BW) was associated with a greater 6-month mortality than with a daily calorie intake of ≥ 21.5 kcal/kg/day (65.8% vs 33.3%; $p<0.0001$). Adequate nutritional intake should thus be the main goal for treatment rather than a specific feeding route [67]. It is therefore advisable never to fall below 21.5 Kcal/kg/day since in these cases there is an increase in mortality at 1 and 6 months [17] (Table 4). Finally, some authors [68,69] have argued that the best nutritional assessment is based on the measurement of sarcopenia (reduction of muscle mass). Among micronutrients and vitamins, supplementation of zinc and thiamine (to prevent Wernicke's syndrome) together with vitamin B6, vitamin B12, vitamin D, and folate is suggested.

In cases of SAAH (mDF ≥ 32 and/or HE), steroid therapy with prednisolone 40 mg/day or methylprednisolone 32 mg/day for 28 days followed by a tapering program should be implemented if no contraindications (bleeding, renal failure, and infections) are present (Table 4). In the event of a response, a survival rate of 28 days higher than 80% has been shown. The evaluation of steroid response is based on the performance of the Lille Model after 7 days of steroid treatment; in the case of a score >0.45 (non-responder), therapy can be discontinued [17]. In any case, therapy is not indicated for mDF >54 [29,49,64,65,70,71]. A recent multicenter clinical

Table 4
Therapeutic pathway in patients with SAAH or ACLF and AUD.

-management of ESALD complications (i.e. HE: lactulose / lactitol and rifamixin 400 mg t.i.d. or 550 mg b.i.d. in cases of refractory forms of HE)
 -nutritional status (>35-40 kcal/kg BW, 1.2-1.5 g/kg proteins; at least not less than 21.5 kcal/kg/BW)
 -management of AWS with short acting benzodiazepines (lorazepam 1-2 mg q.d or b.i.d orally or i.v. or oxazepam 15 mg q.d or b.i.d orally) following a trigger symptoms regimen
 -vitamin supplementation (Vit B1: 200 mg/day for 3-5 days to prevent Wernicke encephalopathy); haloperidol (0.5-5 mg every 30-60 minutes iv or 0.5-5 mg every 4 hours orally) to treat hallucinations; alpha-2 agonists or beta-blockers to reduce autonomic hyperactivity
 -maintenance of alcohol abstinence with multi-disciplinary treatment: psychosocial-therapy, family support, self-help groups, and pharmacotherapy (i.e. baclofen 10 mg t.i.d.)*
 -identification and management of infections
 -in cases of mDF $\geq$ 32: prednisolone 40 mg/day or methylprednisolone 32 mg/day** for 28 days plus N-acetyl-cysteine for 5 days (day 1: 150 mg/kg in 250 ml of 5% glucose solution over a period of 30 minutes, then 50 mg/kg in 500 ml of glucose solution over a period of 4 hours, and 100 mg/kg in 1000 ml of glucose solution over a period of 16 hours; days 2-5, 100 mg/kg/day in 1000 ml of glucose solution) $\pm$ antibiotic therapy in the case of sepsis^o



*Not in the case of hepato-renal syndrome (HRS), hepatic encephalopathy (HE), and neuro-psychiatric contraindications; **not in the case of bleeding, infections, renal failure;
^oin the case of sepsis, the corticosteroid needs to be collegially discussed evaluating risks and benefits.

study (the STOPAH trial) [72] showed 14% and 19% mortality rates in the short-term period (after 28 days) respectively in the prednisolone group and the pentoxifylline group for the treatment of SAAH, without reaching a statistically significant difference for either drug, or in comparison with placebo; this unsatisfactory data was confirmed when compared to placebo both in the medium (after 90 days of treatment) and long-term (12 months of treatment) period [72]. This is due to the lack of monitoring of alcohol consumption after discharging the patients and to a rebound effect of the hepatic inflammation induced by the sudden suspension of corticosteroids without a tapering procedure after the 28 days of treatment. Moreover, pentoxifylline did not show any improvements in the survival rates [72]. Only by performing a secondary analysis including adjustments for baseline determinants of prognosis was a significant advantage with respect to 28-day mortality seen in the prednisolone treated group [72]. In addition, a recent meta-analysis showed that corticosteroid treatment significantly decreased risk of death within 28 days compared with controls or to pentoxifylline; however, no difference in 28-day mortality was seen when patients were given a combination of corticosteroids and pentoxifylline vs corticosteroids alone or between patients given pentoxifylline vs control, and, no significant difference was shown in 6-month mortality when any treatments or controls were compared [73]. In the light of these data, corticosteroids remain the only treatment option for SAAH in the recent EASL guidelines, while pentoxifylline is not suggested as an optional drug [17]. Finally, the lack of efficacy over time indicates a need for new therapeutic strategies to improve medium-term outcomes.

The certainty that TNF plays an important role in the development of acute alcohol-related hepatitis has induced several authors to use the anti-TNF infliximab antibody. However, due to

their increased risk for infections in clinical trials, infliximab and etanercept are currently not recommended [58]. In addition, N-acetylcysteine (NAC), an antioxidant which restores glutathione store and consequently limits oxidative stress, has been studied in SAAH; it does not increase survival when compared to standard medical therapy [74–76]. However, in a French multicenter trial, the administration of NAC intravenously for 5 days in combination with prednisolone reduced the incidence of HRS and infections [77] (Table 4).

Inflammation is considered as a critical factor for causing liver damage in alcohol-related hepatitis; many drugs that target inflammation (including LPS blockers, and probiotics modulating the microbiota) are currently being investigated in clinical trials for the treatment of alcohol-related hepatitis [78–80]. A potential role of fecal microbiota transplantation has been evaluated [48]. IL-22 therapy and granulocyte colony-stimulating factor are currently being tested in clinical trials for the treatment of patients with SAAH [81–84]. Novel manoeuvres aimed at promoting hepatocellular growth, such as bone marrow cell transplantation, may improve the outcome of patients [85]. In addition, clinical trials of extra-corporeal cell therapy for SAAH are also currently ongoing [86] (Table 3, recommendation 2).

4.4. Management of infections

A recent meta-analysis has shown that corticosteroid treatment does not increase the risk of infections compared to untreated cases [87]. Although steroids can promote infections due to their well-known action on lymphocyte signaling, the onset of infections is more related to the response to steroid treatment than to the treatment itself [88,89]. In the STOPAH trial, a greater incidence

of infections occurred in patients treated with prednisolone with respect to placebo (10% vs 6%) [72], and 90% of these were bacterial. Louvet et al. [88] distinguished between infections that developed at the beginning of steroid therapy and those that occurred during the treatment and follow-up and showed that 2 month survival rates are higher in patients with infections already present at their admission than in patients who contracted infections during the steroid treatment ($77.5 \pm 3.2\%$ vs $46.4 \pm 6.9\%$; $p < .00001$) [88]. Screening for bacterial infection before beginning steroid therapy is mandatory. Therefore, any pre-treatment infection is not an absolute contraindication, but must be treated and controlled [90] (Table 4). Indeed, the STOPAH trial [72] demonstrated that antibiotic therapy in association with steroid treatment reduces 90 day mortality rates with respect to placebo (13% vs 52%) (Table 3, recommendation 2).

4.5. Liver transplantation

Due to active alcohol consumption, SAAH has traditionally never been considered a clinical indication for LT. However, the relatively younger age of many patients and the 6-month mortality rate of approximately 70% of cases led some groups to review the criteria for inclusion on the list for LT [72,91–94]. A prospective pilot case controlled study evaluating early LT in patients with SAAH 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 [95]. Recently, several groups have shown that an early LT in patients who were non-responders to corticosteroid therapy for SAAH can achieve excellent results [96–100]. Marot et al. [101] conducted a meta-analysis of trials which evaluated LT in patients with SAAH (325 patients; 240 with clinically-determined SAAH and 85 patients in whom a diagnosis of alcohol-related hepatitis was made on the explant). Only 14% of patients with SAAH relapsed in the post-LT period, and the percentage of relapse was comparable to that found in patients who underwent an elective LT. A recent study by Weeks et al. [102] reported that 1 year after LT, the outcome for SAAH was excellent (both for the patient and for the graft) overlapping with that observed in patients with ALD cirrhosis who were transplanted after 6 months of abstinence; the relapse rate also overlapped between the two groups after a median follow-up of 532 days post-LT. More interestingly, the percentage of patients resuming drinking was similar between ALD cirrhosis (24%) and those transplanted for SAAH (28%), and there was also a comparable percentage of harmful consumption in ALD cirrhosis (6 months of abstinence before LT) (17%) and those transplanted for SAAH (12%). In addition, in cases of ACLF, Artru et al. [103] showed that survival rates of patients with a higher grade of ACLF (ACLF-3) were higher than non-transplanted controls (83.9% vs 7.9% ; $p < 0.0001$), and overlapped with patients with no ACLF (90%), ACLF-1 (82.3%) or ACLF-2 (86.2%). The occurrence of ACLF in patients with ALD who present with acute deterioration changes their prognosis and identifies a distinct subset of patients with an extremely high risk of short-term mortality. LT saves the lives of patients with ACLF due to alcohol, but future studies are needed to better define selection criteria [104].

Moreover, SAAH is still considered a contraindication for LT in most Italian transplant centers, though early LT in selected patients with a first episode of SAAH unresponsive to steroid therapy has been shown to improve survival. In the light of this fact, a document which contains the recommendations of an expert panel of transplant hepatologists, appointed by the Italian Association for the Study of the Liver (AISF), on how to manage this aspect has been published. Some strict criteria (total consensus of the paramedical and medical staff, social integration of the patient with support of the family members, and a clear psychiatric assessment and addic-

tion profile) which need to be explored and met before taking into consideration LT in patients with SAAH [20].

In accordance with the AISF [20] and Anglo-Saxon [65,99,105] indications, SIA advocated early LT in patients with SAAH/ACLF who have good insight into their AUD and good social support (Table 4). In addition, Stroh et al. [106] showed that early LT for SAAH patients does not lead to a decline in donations. To reinforce the ethics of donations, it is advisable to inform the public that AUD are a disease which can be managed. On the other hand, other pathologies deriving from voluntary risk factors such as obesity or metabolic alterations are routinely treated without any kind of social alarm. Prospective studies are needed to optimize selection criteria, management of patients after LT, and long-term outcomes [100] (Table 3, recommendation 2).

5. Management of alcohol use disorder (AUD)

5.1. Alcohol use disorder (AUD): a brief overview of diagnostic tools

Abstinence from alcohol is the cornerstone in managing patients with ESALD and SAAH. Thus, the detection and quantification of alcohol consumption are crucial. AUD is diagnosed based on the criteria set by the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) [3] (Table 5). Compared with the previous editions, the terms *alcohol abuse* and *alcohol dependence* have been substituted with AUD. This version not only allows the stigma to be eliminated, but also favors early treatment [3]. Moreover, DSM-5 criteria do not quantify alcohol consumption. Therefore, drinking habits should be appraised by the time-line follow back (a semistructured interview used mostly in research settings, providing a retrospective estimate of daily drinking, including days of abstinence, over 1 to 12 months before the interview), and risky drinking by the CAGE questionnaire (acronym of: Cutting down, Annoyance by criticism, Guilty feeling, Eye-openers) [8], and the Alcohol Use Disorders Inventory Test (AUDIT) [107] also in its abbreviated form (AUDIT-C). The Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar) evaluates AWS, thus identifying subjects needing pharmacological treatment [108]. Unfortunately, none of these questionnaires was specifically tested in patients with ESALD and SAAH, in whom poor clinical conditions and, especially, frequent HE can weaken their reliability. Therefore, full clinical assessment [8,17] is recommended to assess AWS in patients with ESALD and SAAH. Although the reliability of liver tests or macrocytosis is clearly hampered in ESALD, laboratory tests [(random assessment of ethanol levels in blood, urine or breath, and serum carbohydrate-deficient transferrin (CDT)) should be associated with questionnaires [17–19]. Since a high rate of false-positive results in this setting also makes CDT unreliable for evaluating chronic alcohol abuse [17], blood alcohol level represents the most specific and reliable tool to assess alcohol consumption, and to select abstinent candidates for LT [17]. A narrow detection window, ranging from 12 to 14 h, makes the parameter of blood alcohol level weak in determining alcohol in blood and urine. This shortcoming can be overcome by measuring urinary ethyl glucuronide (uEtG), which reveals the consumption of even small amounts of ethanol (<10 g) for up to 80 h [8,17–19]. The sensitivity of uEtG is improved by its combination with AUDIT-C, which is more accurate than CDT plus AUDIT-C in LT candidates and recipients [109]. Hair EtG (hEtG) determination has further advantages and represents a highly specific tool for monitoring alcohol consumption in patients with ESALD. It detects alcohol consumption up to several months before the test and is far superior to the traditional markers of chronic alcohol abuse [110]. However, its high cost still prevents its widespread use. Moreover, hEtG has not been validated

Table 5
Diagnostic and Statistical Manual of Mental Disorders (DSM) 5th Edition Criteria for Alcohol Use Disorder (adapted from Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), 2013).

- Alcohol is often taken in larger amounts or over a longer period than was intended
- There is a persistent desire or unsuccessful efforts to cut down or control alcohol use
- A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects
- Craving, or a strong desire or urge to use alcohol
- Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home
- Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol
- Important social, occupational, or recreational activities are given up or reduced because of alcohol use
- Recurrent alcohol use in situations in which it is physically hazardous
- 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
- 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
- Withdrawal, as manifested by either of the following:
 - a. The characteristic withdrawal syndrome for alcohol (refer to criteria A and B of the criteria set for alcohol withdrawal)
 - 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 symptoms indicates an alcohol use disorder (AUD). The severity of the AUD is defined as follows: Mild (the presence of 2–3 symptoms), Moderate (the presence of 4–5 symptoms), and Severe (the presence of 6 or more symptoms).

extensively in ALD patients [111,112] (Table 3, recommendation 3).

5.2. Detoxification

In the case of acute alcohol-related intoxication (AAI), no drugs are generally necessary, but vital functions should be monitored, liquids administered in the case of dehydration, and the patient kept under observation for the onset of AWS. In the case of severe AAI with coma, it is important to support ventilation mechanically, identify any additional causes of coma and, if necessary, correct hypoglycemia with 5% glucose solution, hydro-electrolyte imbalance and base acid balance, administer vitamin B and vitamin C supplements, perform gastro-lavage and administer activated charcoal only within 2 h of drinking a considerable amount of alcohol. Due to its antioxidant activity primarily related to its participation in the synthesis of glutathione, metadoxine has been shown to rapidly reduce the half-life of ethanol, and is thus used to treat symptoms of AAI [113]. A double blind controlled study showed that a single intravenous metadoxine administration (900 mg) significantly decreased the half-life of ethanol in the blood in comparison with placebo with faster recovery rates in metadoxine-treated patients than in placebo-treated patients (<1 h vs >2 h) [114]. In Italy, this drug remains the most widespread medication used to treat AAI, and it is mostly used in Emergency Departments. However, its use is not ubiquitous, and it is employed in accordance with each Italian region's health policies [115] (Table 3, recommendation 3).

Moreover, in patients with ESALD and in SAAH it should be stressed that AWS must be distinguished from HE [8,115]. First of all, HE must be detected and treated, then the AWS should be treated. The AWS treatment must be carried out under strict medical supervision and if the CIWA-Ar score is >8 [115]. Benzodiazepines such as lorazepam (1–2 mg q.d or b.i.d orally or i.v.) or oxazepam (15 mg q.d or b.i.d orally) should be preferred to diazepam and chlordiazepoxide due to their short half-life (10–20 h) and the lack of active metabolites [8,115]. Administration at the onset of symptoms (“trigger” approach) is preferable to a fixed dose, to avoid drug accumulation due to reduced hepatic clearance [8] (Tables 2 and 4). In addition, sodium oxybate (gamma-hydroxybutyric acid), a GABA-ergic drug, is approved in some European countries (Italy and Austria) to treat moderate forms of AWS and, as an anti-craving drug, to help patients with AUD in maintaining total alcohol abstinence [115]. Indeed, due to its very short half-life (30–45 min), and the need not to follow a tapering

procedure at its discontinuation, it may be used to treat moderate form of AWS with a higher safety and manageability profile with respect to the short acting benzodiazepines [115]. However, only one case report has been published in ESALD [116] (Table 6); thus, controlled clinical trials to investigate the efficacy and safety of sodium oxybate in patients with ESALD are warranted. The use of parenteral thiamine (200 mg/day for 3–5 days) to prevent Wernicke encephalopathy, haloperidol (0.5–5 mg every 30–60 min iv or 0.5–5 mg every 4 h orally) to treat hallucinations, and, finally, alpha-2 agonists or beta-blockers to reduce autonomic hyperactivity is also warranted [117,118]. Ascites and bleeding do not contraindicate this kind of treatment. There are no data on contraindications to treatment in cases of HRS, although caution is advised (Table 3, recommendation 3).

5.3. Maintenance of alcohol abstinence

In cases of ESALD and SAAH, if the subject resumes drinking alcohol after the period of detoxification, clinical management is complicated, with less than 30% five-year survival probability [17,19]. Verrill et al. [119] found that abstinence for one month after the diagnosis of alcohol-related cirrhosis may be the most important factor in determining seven-year survival (approximately 72%). Thus, achieving abstinence remains the turning point on the therapeutic path. Maintenance of abstinence may be favored by pharmacological and psycho-social treatment. Use of medication is very limited due to the severe deterioration of liver function and/or complications [8] (Table 6). Disulfiram should not be used owing to its potential hepatotoxicity with a 28% mortality rate. Naltrexone is also not recommended due to its hepatotoxicity [117,118,120–123]. Acamprosate is not metabolized in the liver, it does not interact with alcohol, and it has a good safety profile [117,118,123]. However, it antagonizes the glutamate receptors and its long-term use may favor HE [117,118]. Currently, it is indicated for the treatment of AUD in patients with compensated cirrhosis [122]. Among the off-label drugs, topiramate [8] does not undergo extensive liver metabolism, although it has no indication in the course of cirrhosis due to alcohol. The only drug that appears to be safe in cases of ESALD is baclofen (GABA-B receptor agonist) [8]. Baclofen (5 mg t.i.d up to 10 mg t.i.d orally for 30 days) is more effective than a placebo in inducing and maintaining abstinence, leading to an improvement in liver function [124–127]. Baclofen is safe and effective in AUD patients with ESALD and SAAH with or without ascites (Table 6). However, due to its GABA-ergic activity

Table 6

Medications currently approved in the US and in some European Countries for the treatment of alcohol use disorder.

Medication	Dosage	Mechanism of action	Possible use in alcoholic liver disease
Acamprosate ^a	666 mg TID (≥ 60 kg) 333 mg TID (< 60 kg)	Possibly NMDA receptor agonist	Yes (no hepatic metabolism; renal metabolism) Contraindications: -hepatic encephalopathy; -hepato-renal syndrome (creatinine clearance < 30 mL/min) No (hepatic metabolism; cases of liver toxicity have been reported)
Disulfiram ^a	250–500 mg QD	Inhibition of acetaldehyde dehydrogenase	
Naltrexone ^a	PO or IM PO: 50 mg QD IM: 380 mg monthly	μ opiate receptor antagonist	With caution (perceptions of liver toxicity limit use in advanced alcoholic liver disease)
Nalmefene ^b	20 mg “as needed”	μ and δ -opioid receptor antagonist and κ -opioid receptor partial-agonist	Not reported
Baclofen ^c	10 mg TID (80 mg QD max)	GABA _B receptor agonist	Yes (15% hepatic metabolism; 85% renal metabolism). Baclofen has been formally tested in clinical studies with alcohol use disorder and patients with liver cirrhosis Contraindications: -hepatic encephalopathy; -hepato-renal syndrome (creatinine clearance < 30 mL/min) Not reported Only one case report has described safety and efficacy in the treatment of alcohol withdrawal syndrome in a patient with alcoholic liver cirrhosis and ascites ^e
Sodium Oxybate ^d	50–100 mg/kg fractioned into three or six daily dosages	GABA _B receptor agonist	

^a Medications approved by the US Food and Drug Administration (FDA) relapse prevention (abstinence).^b Medication approved by the European Medical Agency (EMA) in some European Countries for the reduction of alcohol consumption.^c Medication approved by the France Agence Nationale du Sécurité du Médicament et des Produits de Santé (ANSM) as a temporary recommendation for use to treat alcohol dependence.^d Medication approved in Italy and Austria for the treatment of alcohol withdrawal syndrome and for the maintenance of alcohol abstinence.^e Caputo F et al. J Clin Psychopharmacol 2011;31(1):140–1.

and its renal metabolism, its use is limited in the presence of HE [17,117,118,126,128] and HRS [117,118], respectively.

Currently, several psychosocial opportunities of treatment are offered to patients affected by AUD [129]. In particular, group therapy, couple or family therapy, and behavioral or cognitive-behavioral treatments have been evaluated and considered satisfactory. Namely, Khan et al. [130] assessed 13 studies including 1945 patients, five of which were randomized controlled trials. The authors showed that cognitive behavioral therapy in association with strengthening motivation produced a significant increase in achieving abstinence (74% versus 48% in the control group; $P=0.02$). Brief interventions [8] can be useful for reinforcing the patient's motivation, and motivational support must be practiced by every team member. Patients with ESALD have difficulty in attending therapeutic sessions since their adherence to interventions is highly variable and ranges from 14% to 90% [131]. Psycho-educational interventions at home [132] could be useful activities, but so far there are no consolidated studies. Attendance of self-help-groups (such as Alcoholic Anonymous) is considered to be good practice and is recommended by the SIA [29,129] (Tables 2 and 4) (Table 3, recommendation 3).

6. Special populations: poly-drug addicts

In patients with AUD, cigarette smoking must be effectively dealt with, not only for oncological and cardiovascular reasons [133]. In fact, it is now known that for those who smoke or who resume smoking, the possibility of alcohol relapse is greater [134,135]. This also applies to the use of cannabinoids [20,136]: there are no absolute contraindications, but adherence to a detoxification program is recommended. In patients undergoing heroin abstinence and being followed up in an addiction unit, the use of methadone is not a contraindication to LT [20,137,138]. Kanachana et al. [137] stated that it is not necessary for patients to be weaned off methadone before LT. It is appropriate to distinguish maintenance therapy from methadone abuse [138]. The active consumption of heroin, cocaine, and synthetic substances is an absolute contraindication for LT [20,136]. In cases of remission and

adherence to a significant care path, the patient is re-evaluated (Table 3, recommendation 4).

7. Conclusions

AUD is the most common cause of ALD. The detoxification treatment may be necessary in some cases with the use of metadoxine to quickly improve symptoms of AAI, while short acting benzodiazepines may be necessary to reduce and suppress AWS. At the end of the detoxification period, abstinence from alcohol is currently the only effective strategy to recover from ethanol-induced liver damage. No medication can improve alcohol-related liver damage without a concomitant reduction in drinking. Combining psychosocial interventions and pharmacotherapy is the most effective way to manage these patients [130], but the risk of liver toxicity or other severe side effects limits the pharmacological options. Overt HE, HRS, and severe jaundice possibly represent the sole conditions in which anti-craving drugs should be avoided. Otherwise, the cautious use of anti-craving drugs can be attempted, with low doses of baclofen appearing to be the safest and most efficient way to treat patients with ascites [17]. Other drugs that can be used in this context include acamprosate and topiramate, although renal impairment may limit their use. Induction and maintenance of abstinence should be pursued through a multidisciplinary approach [17,19,116,123,130]. Indeed, a concerted commitment by physicians, psychologists, psychiatrists, and socio-educational support, along with self-help groups and the patients' families if available is fundamental in order to treat and characterize AUD, to assess and to reinforce motivation to abstain, and to identify patients at risk of relapse. Moreover, clinicians with a dual expertise in both hepatology and alcoholology (the “hepato-alcoholologist”) [29,139] should play a preminent role not only in the management of the liver disease course, but also of the underlying AUD.

Finally, the severity of ESALD can improve after a few months (three months) of abstinence from alcohol, avoiding or delaying the need for LT. Conversely, patients with ESALD with a poor prognosis (MELD ≥ 15) may be candidates for LT after three months of abstinence; in these patients, the 6 months rule needs to be revised. Cases of SAAH with mDF ≥ 32 or ACLF warrant prompt pharma-

cological treatment with corticosteroids with NAC in combination with adequate nutritional support and in association with antibiotic therapy in the case of sepsis. In non-responders to steroid therapy (Lille Model >45), the indication for LT in carefully selected patients is a clinical course to be pursued; in the presence of organ failures ≥ 4 (ACLF-4) where the prognosis after LT is unfavorable, withdrawal of care is recommended.

Thus, the role of a multi-disciplinary team of experts in the management of AUD, ESALD and SAAH working in the same institution [44], the support of the patient's family and self-help groups represent a crucial approach in the reinforcement of motivation to abstain from alcohol, and in helping patients to avoid relapses in heavy drinking when entered in an LT programme.

Conflict of interest

None declared.

Appendix A. the SIA Board

Pierluigi Allosio: Alcohol Unit, Torino, Italy.
 Maria Francesca Amendola: Alcohol Unit, Cosenza, Italy.
 Sarino Aricò: Gastroenterology Unit, Mauriziano Hospital, Torino, Italy.
 Aniello Baselice: Alcohol Unit, Salerno, Italy.
 Patrizia Balbinot: Regional Centre on Alcohol, San Martino Hospital, Genova, Italy.
 Vito Campanile: Alcohol Unit, Bari, Italy.
 Tiziana Fanucchi: Regional Centre on Alcohol, Careggi Hospital, Firenze, Italy.
 Giovanni Greco: Alcohol Unit, Ravenna, Italy.
 Livia Macciò: Alcohol Unit, Savona, Italy.
 Cristina Meneguzzi: Alcohol Unit, Pordenone, Italy.
 Davide Mioni: Nursing Home Parco dei Tigli, Teolo (Padova), Italy.
 Vito Ostelio Palmieri: "Murri" Clinic of Internal Medicine, Department of Biomedical Science and Human Oncology, University of Bari, Italy.
 Michele Parisi: Alcohol Unit, Nicosia (Enna), Italy.
 Doda Renzetti: Department of Internal Medicine, Mater Dei Hospital, Bari, Italy.
 Raffaella Rossin: Alcohol Unit, Milano, Italy.

Appendix B. the external expert supervisors

Prof. Giovanni Addolorato: Alcohol Use Disorder Unit, Department of Internal Medicine, Gastroenterology and Hepatology, Catholic University of Rome, Italy.
 Prof. Patrizia Burra: Multivisceral Transplant Unit, Gastroenterology, Dept. of Surgery, Oncology and Gastroenterology, Padua University Hospital, Padua, Italy.
 Prof. Marco Domenicali: "G. Fontana" Centre for the Study and Multidisciplinary Treatment of Alcohol Addiction, Department of Medical and Surgical Sciences, University of Bologna, Italy.

References

- [1] World Health Organization. Global status report on alcohol and health; 2018.
- [2] GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2018;392:1015–35.
- [3] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. fifth edition Washington DC: American Psychiatric Publishing; 2013.
- [4] Axley PD, Richardson CT, Singal AK. Epidemiology of alcohol consumption and societal burden of alcoholism and alcoholic liver disease. *Clin Liver Dis* 2019;23:39–50.
- [5] Singal AK, Anand BS. Epidemiology of ALD. *Clin Liver Dis* 2013;2:53–6.
- [6] Grant BF, Goldstein RB, Saha TD, Chou SP, Jung J, Zhang H, et al. Epidemiology of DSM-5 alcohol use disorder. *JAMA Psychiatry* 2015;72:757–66.
- [7] Fuster D, Samet JH. Alcohol use in patients with chronic liver disease. *N Engl J Med* 2018;379:1251–61.
- [8] Caputo F, Domenicali M, Bernardi M. Diagnosis and treatment of alcohol use disorder in patients with end-stage alcoholic liver disease. *Hepatology* 2019;70:410–7.
- [9] Fuster D, Sanvisens A, Bolao F, Rivas I, Tor J, Muga R. Alcohol use disorder and its impact on chronic hepatitis C virus and human immunodeficiency virus infection. *World J Hepatol* 2018;8:1295–308.
- [10] Ditah IC, Saeian K, Lalehzari M, Aronsohn A, Gorospe EC, Charlton M. Changes in the prevalence of hepatitis C virus infection, non-alcoholic steatohepatitis and alcoholic liver disease among patients with cirrhosis or liver failure on the waiting list for liver transplantation. *Gastroenterology* 2017;152:1090–9.
- [11] Williams R, Alexander G, Armstrong I, Baker A, Bhala N, Camps-Walsh G, et al. Disease burden and costs from excess alcohol consumption, obesity, and viral hepatitis: fourth report of the Lancet Standing Commission on Liver Disease in the UK. *Lancet* 2018;391:1097–107.
- [12] Godfrey EL, Stribling R, Rana A. Liver transplantation for alcoholic liver disease. An update. *Clin Liver Dis* 2019;23:127–39.
- [13] Istituto Superiore di Sanità. National programme of guidelines; 2002.
- [14] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
- [15] Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, et al. GRADE guidelines: 5. Rating the quality of evidence—publication bias. *J Clin Epidemiol* 2011;64:1277–82.
- [16] Schünemann HJ, Jaeschke R, Cook D, Bria W, El-Solh A, Ernst A, et al. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. *Am J Respir Crit Care Med* 2006;174:605–14.
- [17] European Association for the Study of the Liver. EASL clinical practice guidelines: management of alcohol-related liver disease. *J Hepatol* 2018;69:154–81.
- [18] O'Shea RS, Dasarthy S, McCullough AJ. Practice Guideline Committee of the American Association for the Study of Liver Diseases, Practice Parameters Committee of the American College of Gastroenterology. Alcoholic liver disease. *Hepatology* 2010;51:307–28.
- [19] Singal AK, Bataller R, Ahn J, Kamath PS, Shah VH. ACG clinical guideline: alcoholic liver disease. *Am J Gastroenterol* 2018;113:175–94.
- [20] Burra P, Belli LS, Ginanni Corradini S, Volpes R, Marzoni M, Giannini E, et al. Common issues in the management of patients in the waiting list and after liver transplantation. *Dig Liver Dis* 2017;49:241–53.
- [21] European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol* 2018;69:406–60.
- [22] Montagnese S, Russo FP, Amodio P, Burra P, Gasbarrini A, Loguercio C, et al. Hepatic encephalopathy 2018: a clinical practice guideline by the Italian Association for the Study of the Liver (AISF). *Dig Liver Dis* 2019;51:190–205.
- [23] Suraweera D, Sundaram V, Saab S. Evaluation and management of hepatic encephalopathy: current status and future directions. *Gut Liver* 2016;10:509–19.
- [24] European Association for the Study of the Liver, American Association for the Study of Liver Diseases. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline. *J Hepatol* 2014;61:642–59.
- [25] Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifamixin treatment in hepatic encephalopathy. *N Engl J Med* 2010;362:1071–81.
- [26] Montagnese S, Amato E, Shiff S, Facchini S, Angeli P, Gatta A, et al. A patients and caregivers perspective on hepatic encephalopathy. *Metab Brain Dis* 2012;27:567–72.
- [27] Burra P, Senzolo M, Adam R, Delvart V, Karam V, Germani G, et al. Liver transplantation for alcoholic liver disease in Europe: a study from ELTR (European Liver Transplant Registry). *Am J Gastroenterol* 2010;10:138–48.
- [28] Kawaguchi Y, Sugawara Y, Yamashiki N, Kaneko J, Tamura S, Aoki T, et al. Role of 6-month abstinence rule in living donor liver transplantation for patients with alcoholic liver disease. *Hepatol Res* 2013;43:1169–74.
- [29] Testino G, Burra P, Bonino F, Pian F, Sumbaraz A, Peressutti R, et al. Acute alcoholic hepatitis, end stage alcoholic liver disease and liver transplantation: an Italian position statement. *World J Gastroenterol* 2014;20:14642–51.
- [30] Braun HJ, Ascher NL. Living donor liver transplantation for alcoholic liver disease. *Alcohol Alcohol* 2018;53:178–83.
- [31] Tse J, Chang W, Yeung C. Doctors practicing alternative medicine. The legal considerations. *Hong Kong Med J* 2006;12:164–6.
- [32] Forman LM, Lewis JD, Berlin JA. The association between hepatitis C infection and survival after orthotopic liver transplantation. *Gastroenterology* 2002;122:889–96.
- [33] Burra P, Mioni D, Cillo U, Fagioli S, Senzolo M, Naccarato R, et al. Long term medical and psycho-social evaluation of patients undergoing orthotopic liver transplantation for alcoholic liver disease. *Transpl Int* 2000;13: S174–8.
- [34] Tandon P, Goodman J, Ma MM, Wong WW, Mason AL, Meeberg G, et al. A shorter duration of pre-transplant abstinence predicts problem drinking after liver transplantation. *Am J Gastroenterol* 2009;104:1700–6.
- [35] Miguet M, Mounert F, Vonlennens C, Gache P, Messner M, Hruskowsky S, et al. Predictive factors of alcohol relapse after orthotopic liver transplantation for alcoholic liver disease. *Gastroenterol Clin Biol* 2004;28:845–51.

- [36] Veldt BJ, Laine F, Guillygomarc'h A, Lauvin L, Boudjema K, Messner M, et al. Indication of liver transplantation in severe alcoholic liver cirrhosis: quantitative evaluation and optimal timing. *J Hepatol* 2002;36:93–8.
- [37] Kotlyar DS, Burke A, Campbell MS, Weinrieb RM. A critical review of candidacy for orthotopic liver transplantation in alcoholic liver disease. *Am J Gastroenterol* 2008;103:734–43.
- [38] EASL clinical practice guidelines: liver transplantation. *J Hepatol* 2016;64:433–85.
- [39] Yates WR, Martin M, LaBrecque D, Hillebrand D, Voigt M, Pfab D. A model to examine the validity of the 6-month abstinence criterion for liver transplantation. *Alcohol Clin Exp Res* 1998;22:513–7.
- [40] Dom G, Wojnar M, Crunelle CL, Thon N, Bobes J, Preuss UW, et al. Assessing and treating alcohol relapse risk in liver transplantation candidates. *Alcohol* 2015;50:164–72.
- [41] Lucey MR. Liver transplantation for alcoholic liver disease. *Nat Rev Gastroenterol Hepatol* 2014;11:300–7.
- [42] Dumortier J, Guillaud O, Adham M, Boucaud C, Delafosse B, Bouffard Y, et al. Negative impact of the novo malignancies rather than alcohol relapse on survival after liver transplantation for alcoholic cirrhosis: a retrospective analysis of 305 patients in a single center. *Am J Gastroenterol* 2007;102:1032–41.
- [43] Attilia ML, Lattanzi B, Ledda R, Galli A, Farcomeni A, Rotondo C, et al. The multidisciplinary support in preventing alcohol relapse after liver transplantation: a single centre experience. *Clin Transplant* 2018;32:e13243.
- [44] Addolorato G, Mirijello A, Leggio L, Ferrulli A, D'Angelo C, Vassallo G, et al. Liver transplantation in alcoholic patients: impact of an alcohol addiction unit within a liver transplant center. *Alcohol Clin Exp Res* 2013;37:1601–8.
- [45] Kollmann D, Rasoul-Rockenschau S, Steiner I, Freundorfer E, Gyori GP, Silberhumer G, et al. Good outcome after liver transplantation for ALD without a 6 months abstinence rule prior to transplantation including post-transplant CDT monitoring for alcohol relapse assessment – a retrospective study. *Transpl Int* 2016;29:559–67.
- [46] Burra P, Giannini EG, Caraceni P, Ginanni Corradini S, Rendina M, et al. Specific issues concerning the management of patients on the waiting list and after liver transplantation. *Liver Int* 2018;38:1338–62.
- [47] Cillo U, Burra P, Mazzaferro V, Belli L, Pinna AD, Spada M, et al. A multistep, consensus-based approach to organ allocation in liver transplantation: toward a “Blended Principal Model”. *Am J Transplant* 2015;15:2552–61.
- [48] Sidhu SS, Goyal O, Kishore H, Sidhu S. New paradigms in management of alcoholic hepatitis: a review. *Hepatol Int* 2017;11:255–67.
- [49] Farooq MO, Bataller R. Pathogenesis and management of alcoholic liver disease. *Dig Dis* 2016;34:347–55.
- [50] Altamirano J, Miquel R, Katoonizadeh A, Abalde JG, Duarte-Rojo A, Louvet A, et al. A histologic scoring system for prognosis of patients with alcoholic hepatitis. *Gastroenterology* 2014;146:1231–9.
- [51] Sancho-Bru P, Altamirano J, Rodrigo-Torres D, Coll M, Millán C, José Lozano J, et al. Liver progenitor cell markers correlate with liver damage and predict short-term mortality in patients with alcoholic hepatitis. *Hepatology* 2012;55:1931–41.
- [52] Thurst M, Morgan TR. Treatment of severe alcoholic hepatitis. *Gastroenterology* 2016;15:1823–34.
- [53] Mathurin P, O'Grady, Carithers RL, Phillips M, Louvet A, Mendenhall CL, et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis: meta-analysis of individual patient data. *Gut* 2011;60:255–60.
- [54] Lucey MR, Mathurin P, Morgan TR. Alcoholic hepatitis. *N Engl J Med* 2009;360:2758–69.
- [55] Bajaj JS, Moreau R, Kamath PS, Vargas HE, Arroyo V, Reddy R, et al. Acute on chronic liver failure: getting ready for prime-time. *Hepatology* 2018;68:1621–32.
- [56] Jalan R, Yurdadyin C, Bajaj JS, Acharya SK, Arroyo V, Lin HC, et al. Toward a improved definition of acute on chronic liver failure. *Gastroenterology* 2014;147:4–10.
- [57] Shalimar, Kedia S, Mahapatra SJ, Nayak B, Gunjan D, Thakur B, et al. Severity and outcome of acute on chronic liver failure is dependent on the etiology of acute hepatic insult: analysis of 368 patients. *J Clin Gastroenterol* 2017;51:734–41.
- [58] Testino G, Leone S. Acute alcoholic hepatitis: a literature review and proposal of treatment. *Minerva Med* 2018;109:290–9.
- [59] Jalan R, Pavesi M, Saliba F, Amorós A, Fernandez J, Holland-Fischer P, et al. The CLIF Consortium Acute Decompensation Score (CLIF-C ADs) for prognosis of hospitalised cirrhotic patients without acute-on-chronic liver failure. *J Hepatol* 2015;62:831–40.
- [60] Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013;144:1426–37, 1437.e1–9.
- [61] Potts JR, Howard MR, Verma S. Recurrent severe alcoholic hepatitis: clinical characteristics and outcomes. *Eur J Gastroenterol Hepatol* 2013;38:584–95.
- [62] Gustot T, Fernandez J, Garcia E, Morando F, Caraceni P, Alessandria C, et al. Clinical course of acute on chronic liver failure syndrome and effects on prognosis. *Hepatology* 2015;62:243–52.
- [63] Arroyo V, Moreau R, Jalan R, Gines P, EASL-CLIF Consortium CANONIC Study. Acute-on-chronic liver failure: a new syndrome that will re-classify cirrhosis. *J Hepatol* 2015;62:S131–43.
- [64] Serstè T, Cornillie A, Njimi H, Pavesi M, Arroyo V, Putignano A, et al. The prognostic value of acute-on-chronic liver failure during the course of severe alcoholic hepatitis. *J Hepatol* 2018;69:318–24.
- [65] Mitchell MC, Friedman LS, McClain CJ. Medical management of severe alcoholic hepatitis: expert review from the clinical practice updates committee of the AGA Institute. *Clin Gastroenterol Hepatol* 2017;15:5–12.
- [66] Plauth M, Cabre E, Riggio O, Assis-Camilo M, Pirlich M, Kondrup J, et al. ESPEN guidelines on enteral nutrition: liver disease. *Clin Nutr* 2006;25:285–94.
- [67] Moreno C, Deltenre P, Senterre C, Louvet A, Gustot T, Bastens B, et al. Intensive enteral nutrition is ineffective for patients with severe alcoholic hepatitis treated with corticosteroids. *Gastroenterology* 2016;150:903–10.
- [68] Sinclair M, Gow PJ, Grossmann M, Angus PW. Review article: sarcopenia in cirrhosis-aetiology, implications and potential therapeutic interventions. *Aliment Pharmacol Ther* 2016;43:765–77.
- [69] European Association for the Study of the Liver. EASL Clinical Practice Guidelines on nutrition in chronic liver disease. *J Hepatol* 2019;70:172–93.
- [70] Mandrekarp, Bataller R, Tsukamoto H, Gao B. Alcoholic hepatitis: translational approaches to develop targeted therapies. *Hepatology* 2016;64:1343–55.
- [71] Aday AW, Mitchell MC, Casey LC. Alcoholic hepatitis: current trends in management. *Curr Opin Gastroenterol* 2017;33:1–7.
- [72] Thurst MR, Richardson P, Allison M, Austin A, Bowers M, Day CP, et al. Prednisolone or pentoxifylline for alcoholic hepatitis. STOPAH trial. *N Engl J Med* 2015;372:1619–28.
- [73] Louvet A, Thurst MR, Kim DJ, Labreuche J, Atkinson SR, Sidhu SS, et al. Corticosteroids reduce risk of death within 28 days for patients with severe alcoholic hepatitis, compared with pentoxifylline or Placebo—a meta-analysis of individual data from controlled trials. *Gastroenterology* 2018;155:458–68.e8.
- [74] Phillips M, Curtis H, Portmann B, Donaldson N, Bomford A, O'Grady J. Antioxidants versus corticosteroids in the treatment of severe alcoholic hepatitis—a randomized clinical trial. *J Hepatol* 2006;44:784–90.
- [75] Moreno C, Langlet P, Hittlet A, Lasser I, Degre D, Evrard S, et al. Enteral nutrition with or without N-acetylcysteine in the treatment of severe acute alcoholic hepatitis. *J Hepatol* 2010;53:1117–22.
- [76] Stewart S, Prince M, Bassendine M, Hudson M, James O, Jones D, et al. A randomized trial of antioxidant therapy alone or with corticosteroids in acute alcoholic hepatitis. *J Hepatol* 2007;47:277–83.
- [77] Nguyen-Khac E, Thevenot T, Piquet MA, Benferhat S, Gorla O, Chatelain D, et al. Glucocorticoids plus N-acetylcysteine in severe alcoholic hepatitis. *N Engl J Med* 2011;365:1781–9.
- [78] Singal AK, Shah VH. Current trials and novel therapeutic targets for alcoholic hepatitis. *J Hepatol* 2019;70:305–13.
- [79] Xu M-J, Zhou Z, Parker R, Gao B. Targeting inflammation for the treatment of alcoholic liver disease. *Pharmacol Ther* 2017;180:77–89.
- [80] Sarin SK, Pande A, Schnabl B. Microbiome as a therapeutic target in alcohol-related liver disease. *J Hepatol* 2010;53:260–72.
- [81] Gao B, Shah VH. Combination therapy: new hope for alcoholic hepatitis? *Clin Res Hepatol Gastroenterol* 2015;39:57–11.
- [82] Spahr L, Lambert JF, Rubbia-Brandt L, Chalandon Y, Frossard JL, Giostra E, et al. Granulocyte-colony stimulating factor induces proliferation of hepatic progenitors in alcoholic steatohepatitis: a randomized trial. *Hepatology* 2008;48:221–9.
- [83] Singh V, Sharma AK, Narasimhan RL, Bhalla A, Sharma N, Sharma R. Granulocyte colony-stimulating factor in severe alcoholic hepatitis: a randomized pilot study. *Am J Gastroenterol* 2014;109:1417–23.
- [84] Morgan TR. Is granulocyte colony stimulating factor a new treatment for alcoholic hepatitis? *Clin Gastroenterol Hepatol* 2018;16:1564–5.
- [85] Spahr L, Chalandon Y, Terraz S, Kindler V, Rubbia-Brandt L, Frossard JL, et al. Autologous bone marrow mononuclear cell transplantation in patients with decompensated alcoholic liver disease: a randomized controlled trial. *PLoS One* 2013;8:e53719.
- [86] Thompson J, Jones N, Al-Khafaji A, Malik S, Reich D, Munoz S, et al. Extracorporeal cellular therapy (ELAD) in severe alcoholic hepatitis: a multinational, prospective, controlled, randomized trial. *Liver Transpl* 2018;24:380–93.
- [87] Hmoud BS, Patel K, Bataller R, Singal AK. Corticosteroids and occurrence of and mortality from infections in severe alcoholic hepatitis: a meta-analysis of randomized trials. *Liver Int* 2016;36:721–8.
- [88] Louvet A, Wartel F, Castel H, Dharand S, Hollebecque A, Canva-Delcambre V, et al. Infection in patients with severe alcoholic hepatitis treated with steroids: early response to therapy is the key factor. *Gastroenterology* 2009;137:541–8.
- [89] Vergis N, Atkinson SR, Knapp S, Maurice J, Allison M, Austin A, et al. In patients with severe alcoholic hepatitis, prednisolone increases susceptibility to infection and infection-related mortality, and is associated with high circulating levels of bacterial DNA. *Gastroenterology* 2017;152:1068–77, e1064.
- [90] Jalan R, Fernandez J, Wiest R, Schnabl B, Moreou R, Angeli P, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. *J Hepatol* 2014;60:1310–24.
- [91] Testino G, Leone S, Ansaldi F, Borro P. Alcohol and liver transplantation: the 6-month abstinence rule is not a dogma. *Transpl Int* 2016;29:953–4.
- [92] Fung JYY. Liver transplantation for severe alcoholic hepatitis – the Con view. *Liver Int* 2017;37:340–2.
- [93] Lucey MR. Liver transplantation for severe alcoholic hepatitis – the Pro view. *Liver Int* 2017;37:343–5.
- [94] Artur F, Louvet A, Mathurin P. Liver transplantation for patients with alcoholic hepatitis. *Liver Int* 2017;37:337–9.

- [95] Mathurin P, Moreno C, Samuel D, Dumortier J, Salleron J, Durand F, et al. Early liver transplantation for severe alcoholic hepatitis. *N Engl J Med* 2011;365:1790–800.
- [96] Singal AK, Bashir H, Anand BS, Jampala SC, Singal V, Kuo YF. Outcomes after liver transplantation for alcoholic hepatitis are similar to alcoholic cirrhosis: exploratory analysis from the UNOS database. *Hepatology* 2012;55:1398–405.
- [97] Im GY, Kim-Schluger L, Shenoy A, Schubert E, Goel A, Friedman SL, et al. Early liver transplantation for severe alcoholic hepatitis in the United States — a single-center experience. *Am J Transplant* 2016;16:841–9.
- [98] Lee BP, Chen PH, Haugen C, Hernaez R, Gurakar A, Philpott B, et al. Three-year results of a pilot program in early liver transplantation for severe alcoholic hepatitis. *Ann Surg* 2017;265:20–9.
- [99] Kubilius M, Patel SJ, Hur C, Dienstag JL, Luther J. Early liver transplantation for alcoholic hepatitis: ready for primetime? *J Hepatol* 2018;68:380–2.
- [100] Lee BP, Mehta N, Platt L, Gurakar A, Rice JP, Lucey MR, et al. Outcomes of early liver transplantation for patients with severe alcoholic hepatitis. *Gastroenterology* 2018;155:422–30.e1.
- [101] Marot A, Dubois M, Trepo E, Moreno C, Deltenre P. Liver transplantation for alcoholic hepatitis: a systematic review with meta-analysis. *PLoS One* 2018;13:e0190823.
- [102] Weeks SR, Sun Z, McCaul ME, Zhu H, Anders RA, Philpott B, et al. Liver transplantation for severe alcoholic hepatitis, updated lessons from the World's largest series. *J Am Coll Surg* 2018;226:549–57.
- [103] Artur F, Louvet A, Ruiz I, Levesque E, Labreuche J, Ursic-Bedoya J, et al. Liver transplantation in the most severely ill cirrhotic patients: a multicenter study in acute-on-chronic liver failure grade 3. *J Hepatol* 2017;67:708–15.
- [104] Gustot T, Jalan R. Acute-on-chronic liver failure in patients with alcohol-related liver disease. *J Hepatol* 2019;70:319–27.
- [105] Im GY, Cameron AM, Lucey MR. Liver transplantation for alcoholic hepatitis. *J Hepatol* 2019;70:328–34.
- [106] Stroh G, Rosell T, Dong F, Forster J. Early liver transplantation for patients with acute alcoholic hepatitis: public views and the effects on organ donation. *Am J Transplant* 2015;15:1598–604.
- [107] Saunders JB, Aasland OG, Babor TF, et al. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. *Addiction* 1993;88:791–804.
- [108] Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar). *Br J Addict* 1989;84:1353–7.
- [109] Piano S, Marchioro L, Gola E, Rosi S, Morando F, Cavallini M, et al. Assessment of alcohol consumption in liver transplant candidates and recipients: the best combination of the tools available. *Liver Transpl* 2014;20:815–22.
- [110] Stewart SH, Koch DG, Willner IR, Anton RF, Reuber A. Hair ethyl glucuronide is highly sensitive and specific for detecting moderate-to-heavy drinking in patients with liver disease. *Alcohol Alcohol* 2013;48:83–7.
- [111] Cabezas J, Lucey MR, Bataller R. Biomarkers for monitoring alcohol use. *Clin Liv Dis* 2018;8:59–63.
- [112] Stauffer K, Yegles M. Biomarkers for detection of alcohol consumption in liver. *World J Gastroenterol* 2016;22:3725–34.
- [113] Di Miceli M, Gronier B. Pharmacology, systematic review and recent clinical trials of metadoxine. *Rev Recent Clin Trials* 2018;13:114–25.
- [114] Shpilensky LS, Muzychenko AP, Gasbarrini G, Addolorato G. Metadoxine in acute alcohol intoxication: a double-blind, randomized, placebo-controlled study. *Alcohol Clin Exp Res* 2002;26:340–6.
- [115] Caputo F, Agabio R, Vignoli T, Patussi V, Fanucchi T, Cimarosti P, et al. Diagnosis and treatment of acute alcohol intoxication and alcohol withdrawal syndrome: position paper of the Italian Society on Alcohol. *Intern Emerg Med* 2018;14:143–60.
- [116] Caputo F, Bernardi M, Zoli G. Efficacy and safety of γ -hydroxybutyrate in treating alcohol withdrawal syndrome in an alcohol-dependent inpatient with decompensated liver cirrhosis: a case report. *J Clin Psychopharmacol* 2011;31:140–1.
- [117] Leggio L, Lee MR. Treatment of alcohol use disorder in patients with alcoholic liver disease. *Am J Med* 2017;130:124–34.
- [118] Addolorato G, Mirijello A, Barrio P, Gual A. Treatment of alcohol use disorders in patients with alcoholic liver disease. *J Hepatol* 2016;65:618–30.
- [119] Verrill C, Markham H, Templeton A, Carr NJ, Sheron N. Alcohol-related cirrhosis-early abstinence is a key factor in prognosis, even in the most severe cases. *Addiction* 2009;104:768–74.
- [120] Dugum M, McCullough A. Diagnosis and management of alcoholic liver disease. *J Clin Transl Hepatol* 2015;3:109–16.
- [121] Rosner S, Hackl-Herrwerth A, Leucht S, Vecchi S, Srisurapanont M, Soyka M. Opioid antagonists for alcohol dependence. *Cochrane Database Syst Rev* 2010;8:CD001867.
- [122] Testino G, Leone S, Borro P. Treatment of alcohol dependence: recent progress and reduction of consumption. *Minerva Med* 2014;105:447–66.
- [123] Goh ET, Morgan MY. Review article: pharmacotherapy for alcohol dependence — the why, the what and the wherefore. *Aliment Pharmacol Ther* 2017;45:865–82.
- [124] Addolorato G, Leggio L, Ferrulli A, Cardone S, Bedogni G, Caputo F, et al. Dose-response effect of baclofen in reducing daily alcohol intake in alcohol dependence: secondary analysis of a randomized double-blind, placebo-controlled trial. *Alcohol Alcohol* 2011;46:312–7.
- [125] Addolorato G, Leggio L, Ferrulli A, Cardone S, Vonghia L, Mirijello A, et al. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. *Lancet* 2007;370:1915–22.
- [126] Mosoni C, Dionisi T, Vassallo GA, Mirijello A, Tarli C, Antonelli M, et al. Baclofen for the treatment of alcohol use disorder in patients with liver cirrhosis: 10 years after the first evidence. *Front Psychiatry* 2018;9:474.
- [127] Barrault C, Lison H, Roudot-Thoraval F, Garioud A, Costentin C, Bèhar V, et al. One year of baclofen in 100 patients with or without cirrhosis: a French real-life experience. *Eur J Gastroenterol Hepatol* 2017;29:1155–60.
- [128] Borro P, Leone S, Testino G. Liver disease and hepatocellular carcinoma in alcoholics: the role of anticraving therapy. *Curr Drug Targets* 2016;17:239–51.
- [129] Testino G, Bottaro LC, Patussi V, Scafato E, Addolorato G, Leone S, et al. Addiction disorders: a need for change. Proposal for a new management. Position paper of SIA, Italian Society on Alcohol. *Minerva Med* 2018;109:369–85.
- [130] Khan A, Tansel A, White DL, Kayani WT, Bano S, Lindsay J, et al. Efficacy of psychosocial interventions in inducing and maintaining alcohol abstinence in patients with chronic liver disease: a systematic review. *Clin Gastroenterol Hepatol* 2016;14:191–202.
- [131] American Society of Addiction Medicine (ASAM). Appropriate use of drug testing in clinical addiction medicine, Consensus Statement; 2017. p. 1–56.
- [132] O'Donnell A, Anderson P, Newbury-Birch D, Schulte B, Schmidt C, Reimer J, et al. The impact of brief interventions in primary healthcare: a systematic review of reviews. *Alcohol Alcohol* 2014;49:66–78.
- [133] Mathurin P, Lucey MR. Alcohol, liver disease, and transplantation: shifting attitudes and new understanding leads to changes in practice. *Curr Opin Organ Transplant* 2018;23:175–9.
- [134] Dermody SS. The impact of smoking very low nicotine content cigarettes on alcohol use. *Alcohol Clin Exp Res* 2016;40:606–15.
- [135] Hillmer AT. Nicotine and nicotine abstinence do not interfere with GABA_A receptor neuroadaptations during alcohol abstinence. *Alcohol Clin Exp Res* 2016;40:698–705.
- [136] Dimartini A, Day N, Dew MA, Lane T, Fitzgerald MG, Magill J, et al. Alcohol use following liver transplantation: a comparison of follow-up methods. *Psychosomatics* 2001;42:55–62.
- [137] Kanchana TP, Kaul V, Manzarbeitia C, Reich DJ, Hails KC, Munoz SJ, et al. Liver transplantation for patients on methadone maintenance. *Liver Transpl* 2002;8:778–82.
- [138] Jiao M, Greanya ED, Haque M, Yoshida EM, Soos JG. Methadone maintenance therapy in liver transplantation. *Prog Transplant* 2010;20:209–14.
- [139] Mellinger JL, Scott Winder G, DeJonckheere M, Fontana RJ, Volk ML, Lok ASF, et al. Misconceptions, preferences and barriers to alcohol use disorder treatment in alcohol-related cirrhosis. *J Subst Abuse Treat* 2018;91:20–7.