Alcoholic liver disease: Treatment

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INTRODUCTION

Alcohol is consumed worldwide and has long been identified as a major risk factor for all liver diseases (Figure 1)[1]. Alcoholic liver disease (ALD) is the third most common cause of chronic liver disease, and it has a global burden of mortality[2]. According to a study of the United States, the incidence of chronic liver disease was 72.3 per 100000 among which 24% had chronic liver disease due to alcohol[3]. Globally, alcohol-attributable liver cirrhosis was responsible for 493300 deaths in 2010 (156900 female deaths and 336400 male deaths)[4]. The number of alcohol-related deaths remains high at 2.5 million deaths annually, constituting 4% of all deaths worldwide[5] and death from ALD constitute approximately 25% of deaths due to alcohol consumption[6].

Many factors affect the development of alcoholic liver injury including the dose, duration, and type of alcohol consumption; drinking patterns; sex; ethnicity;
and associated risk factors including obesity, viral disease, and genetic factors. The histological spectrum of ALD varies from simple fatty liver to cirrhosis, including the development of hepatocellular carcinoma.

ALD is preventable and reversible by timely treatment. However, ALD is often asymptomatic in the early stages and can only be identified by laboratory findings. Screening and treatment for alcohol-use disorders is the first approach for treating ALD. ALD treatment varies depending on the stage of the disease. Abstinence is the most important therapeutic intervention for patients with ALD. Various treatments such as abstinence, nutritional therapy, pharmacological therapy, psychotherapy, and surgery are currently available for the spectrums of ALD. In particular, in patients with severe alcoholic hepatitis, steroid or pentoxifylline can be used according to recommendations of the guidelines. In patients with cirrhosis, portal hypertension and complications such as bleeding, encephalopathy, or ascites, should be treated according to the treatment guidelines. However, this medical treatment for ALD has not significantly changed over the past 40 years. The slow therapeutic advance in the field of ALD has resulted from the lack of experimental models of ALD and from difficulties in performing clinical trials in patients with ALD. This review focuses on the current management of ALD and suggests new therapeutic target in the management of ALD.

**ABSTINENCE**

Immediate abstinence is the most important treatment option for patients with ALD. Continued drinking is associated with the eventual development of cirrhosis in approximately 20% of individuals. Abstinence improves the survival and prognosis of patients with ALD and prevents progression to liver cirrhosis through histological improvement and reduction in portal pressure. Alcoholic steatosis can be reversed after abstinence for several weeks and multivariate analysis showed that persistent alcohol intake was an independent poor prognostic marker.

With respect to pharmacological treatment, some medications such as baclofen, acamprosate, and naltrexone have been used to encourage abstinence in patients with alcohol use disorder. However, few data are available regarding the use of pharmacological agents in the treatment of ALD, because agents such as naltrexone or acamprosate undergo extensive liver metabolism; thus drug-related liver damage is possible. More studies that provide evidence of the efficacy and safety of these agents in the treatment of ALD are needed.

Baclofen is a GABAs receptor agonist that is used as an anti-spasticity medication to treat neurological disorders. Some reports have recently suggested that baclofen may be valuable to the treatment of alcohol dependence. Acamprosate reduces withdrawal and cravings for alcohol. In a meta-analysis, acamprosate had a significant beneficial effect on enhancing abstinence in recently detoxified, alcohol-dependent patients. Naltrexone decreases excessive drinking and the recurrence rate and increasing the abstinence duration in patients with alcohol dependence.

With respect to psychotherapy for abstinence, brief intervention is an effective method that includes motivational interviewing and counseling over a limited time span. A meta-analysis found evidence for the positive impact of brief interventions on alcohol consumption and alcohol-related morbidity and mortality. It is necessary for ALD patients to consult with psychologist about psychological and social support for abstinence.

**NUTRITIONAL THERAPY**

Malnutrition is a major complication of ALD and this has been studied, especially in patients with alcoholic hepatitis. Malnutrition worsens clinical outcome in ALD, and nutritional support improves nutritional status and may improve clinical outcome.

The mechanisms for malnutrition are multifactorial. Poor intake, anorexia, vomiting, mal-digestion, iatrogenic causes, metabolic disturbance, or mal-absorption might cause malnutrition in patients with ALD. Mendenhall et al. suggested that most patients with ALD are malnourished. In this study, patients had almost 50% of energy intake from alcohol. Thus, while calorie intake was frequently not inadequate, there was often deficient intake of protein and critical nutrients.

The severity of liver disease generally correlated with the severity of malnutrition. Patients who voluntarily consumed > 3000 kcal/d had virtually no mortality whereas those consuming < 1000 kcal/d had > 80% 6-mo mortality. Moreover, the degree of malnutrition correlated with the development of serious complications such as encephalopathy, ascites, and hepatorenal syndrome.

Early intervention with nutrition therapy may improve treatment response, alleviate symptoms, and improve the quality and quantity of life. In one trial, nutritional supplementation through a feeding tube significantly improved liver function in inpatients with ALD as assessed by serum bilirubin levels and antipyrine clearance, compared to inpatients who ate a hospital diet. In patients with severe hepatitis, the parenteral nutrition group showed an overall mortality rate that was comparable to that of the steroid treatment group.

A symptom-based and supportive approach is necessary to achieve appropriate nutritional therapy in patients with ALD. Nutrition goals include providing adequate calories, protein, and nutrients to support hepatocyte regeneration within the existing metabolic alterations of liver disease. The use of branched chain amino acids (34 g/d) has been shown to decrease the number of hospitalizations due to complications of liver cirrhosis. Depending on the status of ALD, 1.2-1.5 g/kg per day of protein and 35-40 kcal/kg per day should be supplied.
in addition to medical treatment\textsuperscript{[43]}. Vitamin A, thiamine, vitamin B\textsubscript{12}, folic acid, pyridoxine, vitamin D, magnesium, selenium, and zinc may be administered to patients with ALD along with nutritional therapy\textsuperscript{[44,45]}. Enteral nutrition is desired over parenteral nutrition because of cost, risk of sepsis of the parenteral nutrition line, preservation of the integrity of the gut mucosa, and prevention of bacterial translocation and multiple organ failure\textsuperscript{[46]}. Moreover, total parenteral nutrition can, in some instances, cause liver disease as one of its complications.

**ALCOHOL WITHDRAWAL SYNDROME**

Alcohol withdrawal syndrome is characterized by the symptoms and signs that occur 6-24 h following the cessation of alcohol consumption among those who habitually drink excessively. The indications for admission are severe alcohol withdrawal syndrome, high levels of recent drinking, a history of withdrawal seizures or delirium tremens, the co-occurrence of a serious medical or psychiatric illness, or failure to recover in outpatient treatment\textsuperscript{[47]}. Long-acting benzodiazepines (chlordiazepoxide (per...
oral, 25-100 mg every 4-6 h) or diazepam (per oral/intravenous/intramuscular, 5-10 mg every 6-8 h) are recommended for the prevention of seizures, and an intermediate-acting benzodiazepine [lorazepam (per oral/intravenous/intramuscular, 1-4 mg every 4-8 h)] is recommended for patients with severe alcohol withdrawal syndrome, advanced age, recent head trauma, liver failure, respiratory failure, other serious medical comorbidities, or obesity[47-52]. Carbamazepine (per oral, 200 mg every 6-8 h) can be used as an alternative to benzodiazepine and is effective in seizure prevention[47]. Haloperidol (per oral/intramuscular, 0.5-5 mg every 8-12 h) can be used carefully as an adjunctive therapy only in cases of agitation or psychotic symptoms such as hallucinations that are not controlled by benzodiazepine[47-52]. Thiamine should be administered to all patients with alcohol withdrawal syndrome (100-300 mg/d) and maintained for 2-3 mo following the resolution of their withdrawal symptoms[47]. Thiamine should be given before administering fluids containing glucose.

TREATMENT OF ALCOHOLIC HEPATITIS

Corticosteroids

Corticosteroids (prednisolone 40 mg/d for 28 d followed by tapering over 2-4 wk) are the mainstay of treatment for severe alcoholic hepatitis (modified discriminant function ≥ 32 or presence of encephalopathy). The modified discriminant function can be calculated by the equation of \[4.6 \times [\text{prothrombin time}_{\text{patient} - \text{prothrombin time}_{\text{Control}}} (\text{s})] + \text{serum total bilirubin (mg/dL)}\]. Typically, in patients with severe alcoholic hepatitis, mortality rate within 28 d was 30%-50%.

The mechanism is thought to decrease inflammation by reducing the transcription of pro-inflammatory cytokines such as tumor necrosis factor (TNF-α) and interleukin (IL)-8. The efficacy of corticosteroids in alcoholic hepatitis has been evaluated in 13 randomized controlled studies and 4 meta-analyses since 1971[54,55]. However, there have been conflicting results[56,57]. Although there are mixed results from various studies, corticosteroids are overall currently considered to have survival benefit in patients with severe alcoholic hepatitis. Unfortunately, alcoholic hepatitis is unresponsive to corticosteroid treatment in approximately 40% of patients (Table 1).

To predict the prognosis following corticosteroid treatment, early changes in bilirubin levels and the Lille model were introduced[58,59]. Early changes in bilirubin levels are defined as a bilirubin level that is lower at 7 d than on the first day of treatment[59]. Lille’s score (http://www.lillemodel.com), which is a more complicated but comprehensive evaluation method of the treatment response, is measured at 7 d after the start of treatment[59].

A score of ≥ 0.45 suggests that a patient is not responding to corticosteroid therapy and a lower survival rate at 6 mo of 25%, which is lower than that of other reported more lower scores[59]. Recent studies have shown that classification as complete responders (Lille score ≤ 0.16), partial responders (Lille score 0.16-0.56), and null responders (Lille score ≥ 0.56) is associated with the 28-d survival rate[60]. From the finding that non-responders to corticosteroid are associated with the development of infection and a lower survival rate, discontinuing corticosteroid is generally recommended in non-responders (Figure 3)[61].

Pentoxifylline

Pentoxifylline (400 mg 3 times/d for 28 d) is considered as an alternative to corticosteroid treatment in patients with severe alcoholic hepatitis[62]. The exact mechanism is not understood. However, pentoxifylline inhibits phosphodiesterase and increases the intracellular adenosine 3’5’-cyclic monophosphate level inducing inhibition of cytokine expression and macrophage inflammatory protein-1α[63]. Pentoxifylline failed to decrease the serum

| Table 1  Treatment for alcoholic hepatitis |
|---|---|---|
| **Target** | **Method** | **Characteristic** |
| Abstinence | Stop drinking | The role of pharmacologic agents in maintaining abstinence is unclear. |
| Nutritional support | Correct malnutrition | | |
| Corticosteroid | Decrease inflammation | Prednisolone 40 mg/d for 28 d followed by tapering over 2-4 wk | Increase in the serum bilirubin and Lille score > 0.45 after 1 wk of therapy are associated with worse outcome |
| Ablate cytokines | Ablate TNF-α | | Protective effect against hepatorenal syndrome |
| Infliximab | Ablate TNF-α | | |
| Etanercept | Ablate TNF-α | | |
| N-acetylcysteine | Anti-oxidant | | |
| Metadoxine | Anti-oxidant | | |
| Propylthiouracil | Reduce ischemic damage | Not confirmed | Further studies are needed |
| Colchicine | Anti-fibrosis | | |
| PL | Anti-fibrosis | | |
| AIIR blocker | Anti-fibrosis | | |
| Silymarin | Anti-oxidant and anti-fibrosis | | |

PL: Polyunsaturated lecithin; AIIR: Angiotensin II receptor; TNF: Tumor necrosis factor.
Anti-TNF-α therapy

Anti-TNF-α agents have been developed to block TNF-α, a major cytokine involved in alcoholic hepatitis. Two anti-TNF-α agents have been investigated as therapy for alcoholic hepatitis, infliximab and etanercept. In a pilot study, combination therapy with infliximab and steroids was reported to be effective[66,67]. However, the trial was stopped early by the independent data and safety monitoring board because of a significant excess of severe infections and an insignificant increase in the deaths in the infliximab cohort (Table 1)[68].

Etanercept showed an increase in the short-term survival of patients in a pilot study[69]. However, a subsequent randomized, placebo-controlled trial revealed a worse 6-mo survival rate in the group treated with etanercept than in the placebo group[70]. Therefore, anti-TNF-α agents are currently not recommended for treating alcoholic hepatitis.

Anti-oxidants

N-acetylcysteine: The combination of N-acetylcysteine, an antioxidant, with prednisolone has been studied. This study enrolled 174 patients who were randomly assigned to receive either prednisolone 40 mg/d for 28 d along with intravenous N-acetylcysteine for 5 d or prednisolone 40 mg/d for 28 d alone. Combination therapy improved the 1-mo survival in patients with alcoholic hepatitis. However, the 6-mo survival, which was the primary endpoint of the study, did not improve[71,72]. Further research is needed to evaluate the efficacy of N-acetylcysteine.

Metadoxine: Metadoxine, a combination of 2 antioxidants (pyridoxine and pyrrolidone), is potentially a useful drug in the treatment of ALD. In a large randomized controlled trial, there was significant improvement in the liver function tests in both groups. The percentage of patients with persistent hepatic steatosis as assessed by ultrasound, was also significantly lower in the metadoxine group (28% vs 70%)[73]. These positive effects were more noticeable in patients who abstained from alcohol compared to those who continued to drink. However, the clinical implications are still unclear; therefore, metadoxine is not recommended for the treatment of ALD. Further studies are required to better explain the significance of these observations on other clinical endpoints.

Miscellaneous agents

Propylthiouracil: Propylthiouracil has also been evaluated for the treatment of acute hepatitis. In some studies, PTU improved the mortality rate by suppressing hypermetabolic activation[77,78]. However, in a Cochrane meta-analysis of 6 studies with 710 ALD patients that compared propylthiouracil versus placebo, there was no clear improvement in the liver histology or liver-related or overall mortality rate[79,80].

Colchicine: Colchicine affects hepatic fibrogenesis, including the inhibition of collagen production, the enhancement of collagenase activity, and the interference with collagen transcellular trafficking. In addition, colchicine also has favorable effects on cytokine production associated with fibroblast proliferation. In clinical studies involving patients with alcoholic liver cirrhosis, colchicine showed anti-inflammatory and anti-fibrotic effects[81,82] and had a positive effect on survival[83]. However, controlled trials later had conflicting results[84].

Polyunsaturated lecithin: Polyunsaturated lecithin is extracted from soybeans and is a constituent of cell membranes[85]. Polyunsaturated lecithin appears to improve histology and reduce the activation of hepatic stellate cells in baboons with alcoholic liver injury[86]. However, polyenylphosphatidylcholine did not show a clear association with the progression of liver fibrosis in a follow-up randomized controlled study[87].

Angiotensin II receptor blocker: It has been reported...
in one randomized controlled trial that combination therapy with candesartan and ursodeoxycholic acid shows greater histologic improvement compared to monotherapy with ursodeoxycholic acid\[88\].

**Silymarin:** Silymarin, a milk thistle extract with anti-oxidative and anti-fibrotic properties, has been evaluated in many studies as a potential treatment agent for ALD\[92,94\]. Although one study reported that silymarin contributes to improved survival, this result has not been confirmed for ALD patients in meta-analyses such as the Cochrane review\[90\].

**LIVER TRANSPLANTATION**

ALD is one of the most common indications for liver transplantation in North America and Europe\[92,93\]. The survival rate of liver transplantation in ALD is comparable with other causes\[64\]. Indications for transplantation in ALD are identical to those in other end-stage liver diseases. Patients with severe alcoholic hepatitis who do not respond to corticosteroids or pentoxifylline have a mortality rate of 50% to 75% at 6 mo\[98\].

In a review of 22 studies on ALD, relapse ranged from 3% to 49% with graft dysfunction and death ranging from 0% to 27% and 0% to 6.5%, respectively\[99\]. Therefore, it is essential to accurately identify patients before transplantation who are likely to relapse to harmful drinking after receiving the transplant. Six months of abstinence prior to liver transplantation is considered a necessary step\[97,100,104\]. Recidivism following liver transplantation is a common occurrence, which occurs at a rate of approximately 10%-52%. Alcohol consumption following liver transplantation causes histologic damage in the liver, including liver fibrosis\[96,105,106\].

Most European and North American liver transplantation centers do not consider patients with severe alcoholic hepatitis as candidates for liver transplantation because they do not fulfill the criterion of abstinence for 6 mo prior to liver transplantation\[6,100\]. However, a prospective, multi-center study showed an increase in the survival rate with liver transplantation in patients with severe alcoholic hepatitis who are not responsive to medical treatment\[107\]. Therefore, liver transplantation may be considered in the specific group of patients whose severe alcoholic hepatitis has failed medical treatment. However, improvement in long-term survival must be verified in future studies.

Similar to those who have received liver transplantation for other causes, patients who have received liver transplantation due to ALD show a high incidence of de novo cancer in other areas of the body\[82,94,108-111\]. These de novo cancers are associated with an increase in mortality following transplantation. The immunosuppressive drugs that are used post-transplantation may be related to the onset of new cancers. Compared to other causes, liver transplantation due to ALD is associated with a strikingly high rate of cardiovascular complications\[93\].

**STEM CELL THERAPY**

Recent studies have suggested that stem cell therapy may reduce liver inflammation, and subsequently improve fibrosis, which could be a promising strategy for patients with liver cirrhosis\[112\]. Mesenchymal stem cell (MSC) directly inhibit the activation of hepatic stellate cells via MSC-derived cytokines and may also induce hepatic stellate cells apoptosis via the Fas/FasL pathway\[113\]. MSCs have been reported to contribute to the direct production of new hepatocytes as well as to stimulate proliferation of endogenous hepatocytes\[114,115\]. In a pilot study of 12 patients with alcoholic cirrhosis\[116\], bone marrow-derived MSC used as therapy in alcoholic cirrhosis induces a histologic and quantitative improvement for hepatic fibrosis. Further evidence is needed and a 2-phase multicenter trial in humans is now in process. In addition, a significant improvement in Child-Pugh score and albumin was reported in 9 cirrhotic patients given a portal vein infusion of autologous bone-marrow derived stem cells\[117\]. Better liver function after MSC therapy was also documented in patients with cirrhosis\[109\]. However, in others studies, infusion of autologous, expanded, mobilized, adult bone-marrow derived stem cells did benefit patients with ALD\[119,120\]. Therefore, further evidences about the pathogenic and therapeutic roles of bone-derived stem cells are needed.

In the stem cell therapy, unsolved issues in protocols require further investigation, such as the optimal type of transfused MSCs, the optimal therapeutic timing, the most effective number of stem cells, the best route of administration. The long-term clinical benefits and safety of stem cell-based therapies should be confirmed in a large-sized randomized controlled trial.

In the future, with a safe, controllable, and feasible recommendation, the clinical application of stem cells for the treatment of patients with ALD will be further warranted.

**NEW TARGETS**

New treatments or strategies are required to improve the survival of patients with ALD. Recent translational work using human liver tissue has been informative in identifying some potential therapeutic targets for ALD, such as CXC chemokines, IL-22/signal transducer and activator of transcription 3, TNF receptor superfamily, complement, osteopontin, gut microbiota and lipopolysaccharide (LPS), endocannabinoids, and inflammasomes\[121\]. Hepatic expression of CXC chemokines, CXC family of chemokines includes IL-8 and Gro-α; these usually attract neutrophils, is increased and correlates with survival time and the degree of portal hypertension\[122\]. IL-22 might be used to treat patients with ALD because of its antioxidant, antiapoptotic, antisteatotic, proliferative, and antimicrobial effects\[123\]. Complement activation, apoptosis, and osteopontin up-regulation are prominent feature of ALD\[124,125\].

Gut-derived microbial LPS, a component of the
outer wall of gram-negative bacteria, has been known as a central role in the pathogenesis of ALD\cite{126,127}. Alcohol has been known to disrupt the gut barrier function, consequently, promotes the translocation of microbial LPS from the lumen of the intestines to the portal vein, where it travels to the liver. In the Kupffer cell, LPS binds to CD14, which combines with toll-like receptor 4, ultimately activating multiple pro-inflammatory cytokine genes\cite{128}. Therefore, probiotics, prebiotics, antibiotics, or transplantation of gut-microbiota have been proposed as possible treatments for ALD by ablating the increase in LPS or repopulating the gut.

Ethanol consumption causes epigenetic changes that contribute to alcohol-induced liver damage. Exposure to ethanol or its metabolite acetate up-regulates histone acetylation in macrophages, contributing to the up-regulation of several pro-inflammatory cytokines that could promote alcoholic hepatitis\cite{129}. Therefore, epigenetic modifications can be new therapeutic target.

**CONCLUSION**

ALD is a broad term that encompasses a spectrum of phenotypes ranging from simple fatty liver to alcoholic hepatitis, cirrhosis, and hepatocellular carcinoma. The mechanisms underlying the development of these different disease stages are not fully understood. The standard treatment for ALD, which includes abstinence, nutritional therapy, pharmacological therapy, psychotherapy, and surgery, has not changed in the last 40 years. Novel pathophysiology-oriented therapies are needed for patients with ALD in the future.

**REFERENCES**

1. World Health Organization. Global status report on alcohol and health 2011. Available from: URL: http://www.who.int/substance Abuse/publications/global_alcohol_report/en/
2. Rehm J, Samokhvalov AV, Shield KD. Global burden of alcoholic liver diseases. J Hepatol 2013; 59: 160-168 [PMID: 23511777 DOI: 10.1016/j.jhep.2013.03.007]
3. Kim WR, Brown RS, Terrault NA, El-Serag H. Burden of liver disease in the United States: summary of a workshop. Hepatology 2002; 36: 227-242 [PMID: 12085369 DOI: 10.1053/jhep.2002.34734]
4. Room R, Babor T, Rehm J. Alcohol and public health. Lancet 2005; 365: 519-530 [PMID: 15705462 DOI: 10.1016/S0140-6736(05)17870-2]
5. Shaw JJ, Shah SA. Rising incidence and demographics of hepatoellular carcinoma in the USA: what does it mean? Expert Rev Gastroenterol Hepatol 2011; 5: 365-370 [PMID: 21615548 DOI: 10.1586/erg.11.20]
6. O'Shea RS, Dasarathy S, McCullough AJ. Alcoholic liver disease. Hepatology 2010; 51: 307-328 [PMID: 20034030 DOI: 10.1002/hep.23258]
7. MacSweeney RN, Burt AD. Histologic spectrum of alcoholic liver disease. Semin Liver Dis 1986; 6: 221-232 [PMID: 3022386 DOI: 10.1055/s-2008-1040605]
8. European Association for the Study of Liver. EASL clinical practical guidelines: management of alcoholic liver disease. J Hepatol 2012; 57: 399-420 [PMID: 22638386 DOI: 10.1016/j.jhep.2012.04.004]
9. Runyon BA. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology 2013; 57: 1651-1653 [PMID: 2464303 DOI: 10.1002/hep.26539]
10. Suk KT, Baik SK, Yoon JH, Cheong JY, Paik YH, Lee CH, Kim YS, Lee JW, Kim DJ, Cho SW, Hwang SG, Sohn JH, Kim MY, Kim YB, Kim JG, Cho YK, Choi MS, Kim HJ, Lee HW, Kim SU, Kim JK, Choi JY, Jun DW, Tak WY, Lee BS, Jang BK, Chung WJ, Kim HS, Jang JY, Jeong SW, Kim SG, Kwon OS, Jung YK, Choe WH, Lee JS, Kim IH, Shin JF, Cheon C, Bae SH, Seo YS, Choi DH, Jang SJ. Revision and update on clinical practice guideline for liver cirrhosis. Korean J Hepatol 2012; 18: 1-21 [PMID: 22511988 DOI: 10.3330/kjhep.2012.18.1.1]
11. Borovsky S, Strome S, Lott E. Continued heavy drinking and survival in alcoholic cirrhotics. Gastroenterology 1981; 80: 1405-1409 [PMID: 6971772]
12. Pessine F, Ramond MJ, Peters L, Pham BN, Batel P, Rueff B, Valla DC. Five-year survival predictive factors in patients with excessive alcohol intake and cirrhosis. Effect of alcoholic hepatitis, smoking and abstinence. Liver Int 2003; 23: 45-53 [PMID: 12640727]
13. Morgan MY. The prognosis and outcome of alcoholic liver disease. Alcohol Alcohol Suppl 1994; 2: 335-343 [PMID: 8974353]
14. Veldt BJ, Laine F, Guillygomar'ch A, Lauvin L, Boudjema K, Messner M, Briasot P, Deugnier Y, Moirand R. Indication of liver transplantation in severe alcoholic liver cirrhosis: quantitative evaluation and optimal timing. J Hepatol 2002; 36: 93-98 [PMID: 11804670]
15. Luca A, García-Pagán JC, Bosch J, Feu F, Caballería J, Groszmann R, Rodés J. Effects of ethanol consumption on hepatic hemodynamics in patients with alcoholic cirrhosis. Gastroenterology 1997; 112: 1284-1289 [PMID: 9098014]
16. Teli MR, Day CP, Burt AD, Bennett MK, James OF. Determinants of progression to cirrhosis or fibrosis in pure alcoholic fatty liver. Lancet 1995; 346: 987-990 [PMID: 7475991]
17. Mason BJ, Lohert P. Acamprosate for alcohol dependence: a sex-specific meta-analysis based on individual patient data. Alcohol Clin Exp Res 2012; 36: 497-508 [PMID: 21895717 DOI: 10.1111/j.1530-0277.2011.01616.x]
18. Roozen HG, de Waart R, van der Windt DA, van den Brink W, de Jong CA, Kerkhof JA. A systematic review of the effectiveness of naltrexone in the maintenance treatment of opioid and alcohol dependence. Eur Neuropsychopharmacol 2006; 16: 311-323 [PMID: 16361086 DOI: 10.1016/j.euroneuro.2005.11.001]
19. Liu J, Wang L. Baclofen for alcohol withdrawal. Cochrane Database Syst Rev 2011; (1): CD008502 [PMID: 21249712 DOI: 10.1002/14651858.CD008502.pub2]
20. Davidoff RA. Antipsychotics drugs: mechanisms of action. Ann Neurol 1985; 17: 107-116 [PMID: 2858176 DOI: 10.1002/ana.410170202]
21. Agabio R, Marras P, Addolorato G, Carpinelli B, Gessa GL. Baclofen suppresses alcohol intake and craving for alcohol in a schizophrenic alcohol-dependent patient: a case report. J Clin Psychopharmacol 2007; 27: 319-320 [PMID: 17502794 DOI: 10.1097/jcp.0b013e3181785f6e]
22. Addolorato G, Leggio L, Ferrulli A, Cardone S, Vonglia L, Mirjello A, Abenavoli L, D’Angelo C, Caputo F, Zambon A, Haber PS, Gaskin G. 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: 1915-1922 [PMID: 18068515 DOI: 10.1016/S0140-6736(07)61814-5]
23. Stallings W, Schrader S. Baclofen as prophylaxis and treatment for alcohol withdrawal: a retrospective chart review. J Okla State Med Assoc 2007; 100: 354-360 [PMID: 18020041]
24. Mann K, Lohert P, Morgan MY. The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent patients.
individuals: results of a meta-analysis. Alcohol Clin Exp Res 2004; 28: 51-63 [PMID: 14745302 DOI: 10.1097/01.ALC.0000108656.81653.05]

25 Rössner S, Hakki-Herworen A, Leucht S, Vecchi S, Srisurapanont M, Søya M. Opioid antagonists for alcohol dependence. Cochrane Database Syst Rev 2010; (12): CD001867 [PMID: 21154349 DOI: 10.1002/14651858.CD001867.pub2]

26 Søya M, Rössner S. Opioid antagonists for pharmacological treatment of alcohol dependence - a critical review. Curr Drug Abuse Rev 2008; 1: 280-291 [PMID: 19630726]

27 Bien TH, Miller WR, Tonigan JS. Brief interventions for alcohol problems: a review. Addiction 1993; 88: 315-335 [PMID: 8461850]

28 Vasilaki EI, Hosier SG, Cox WM. The efficacy of motivation-alienating as a brief intervention for excessive drinking: a meta-analytic review. Alcohol Alcohol 2006; 41: 328-335 [PMID: 16547122 DOI: 10.1093/alcalc/agl016]

29 Kaner EF, Dickinson HO, Beyer F, Pienaar E, Schlesinger C, de la Maza MP, Gattás V, Barrera G, Petermann M, Icazar G, Gattas V, Ugarte G. Controlled trial on nutrition supplementation in outpatients with symptomatic alcoholic cirrhosis. JPN J Parenteral Enteral Nutr 1993; 17: 119-124 [PMID: 8453122]

30 Plauth M, Cabré E, Campillo B, Kondrup J, Marchesini G, Cabré E, Campillo B, Kondrup J, Marchesini G, Schütz T, Shenkin A, Wendon J. ESPEN Guidelines on Enteral Nutrition: Liver disease. Clin Nutr 2006; 25: 285-294 [PMID: 16701974 DOI: 10.1016/j.clnu.2006.01.018]

31 Mendenhall CL, Anderson S, Weesner RE, Goldberg SJ, Crolica KA. Protein-calorie malnutrition associated with alcoholic hepatitis. Veterans Administration Cooperative Study Group on Alcoholic Hepatitis. Am J Med 1984; 76: 211-222 [PMID: 6421159]

32 Mendenhall CL, Moritz TE, Roselle GA, Morgan TR, Nemchauksy BA, Tamburro CH, Schiff ER, McClain CJ, Marsano LS, Allen JL. A study of oral nutritional support with oxandrolone in malnourished patients with alcoholic hepatitis: results of a Department of Veterans Affairs cooperative study. Hepatology 1993; 17: 364-376 [PMID: 8477961]

33 Mendenhall C, Roselle GA, Gartside P, Moritz T. Relationship of protein calorie malnutrition to alcoholic liver disease: a reexamination of data from two Veterans Administration Cooperative Studies. Alcohol Clin Exp Res 1995; 19: 635-641 [PMID: 7557386]

34 Lee S, Jin Y, Kee C, Chang Y. Nutritional Status in Alcohol-and Virus-Related Liver Cirrhosis. Korean J Hepatol 2000; 6: 59-72.

35 Deichsel F, Hoehn B, Schuppan D, Seitz HK. Review article: Nutritional therapy in alcoholic liver disease. Aliment Pharmacol Ther 2003; 18: 357-373 [PMID: 12940921 DOI: 10.1046/j.1365-3016.2003.01660.x]

36 Henkel AS, Buchman AL. Nutritional support in patients with chronic liver disease. Nat Clin Pract Gastroenterol Hepatol 2006; 3: 202-209 [PMID: 16582962 DOI: ncp-gasthep0443]

37 Kearsn PJ, Young H, Garcia G, Blaschke T, O’Hanlon G, Rinki M, Sucher K, Gregory P. Accelerated improvement of alcoholic liver disease with enteral nutrition. Gastroenterology 1992; 102: 200-205 [PMID: 1727754]

38 Cabrè E, Rodríguez-Iglesias P, Caballera J, Quer JC, Sánchez-Lombrana JL, Pares A, Popo M, Planas R, Gassull MA. Short- and long-term outcome of severe alcohol-induced hepatitis treated with steroids or enteral nutrition: a multicenter randomized trial. Hepatology 2000; 32: 36-42 [PMID: 10896289]

39 Campillo B, Richardet JP, Scherman E, Bories PN. Evaluation of nutritional practice in hospitalized cirrhotic patients: results of a prospective study. Nutrition 2003; 19: 515-521 [PMID: 12781851]

40 Hirsch S, de la Maza MP, Gattás V, Barrera G, Petermann M, Gotteland M, Muñoz C, Lopez M, Bunout D. Nutritional support in alcohol-dependent cirrhotic patients improves host defens-es. J Am Coll Nutr 1999; 18: 434-441 [PMID: 10513125]

41 Marchesini G, Dioguardi FS, Bianchi GP, Zoli M, Bellati G, Roffi L, Martines D, Abbiati R. Long-term oral branched-chain amino acid treatment in chronic hepatic encephalopathy. A randomized double-blind casein-controlled trial. The Italian Multicenter Study Group. J Hepatol 1990; 11: 92-101 [PMID: 2204661]

42 Hirsch S, Bunout D, de la Maza P, Iturriaga H, Petermann M, Icazar G, Gattas V, Ugarte G. Controlled trial on nutrition supplementation in outpatients with symptomatic alcoholic cirrhosis. JPN J Parenteral Enteral Nutr 1993; 17: 119-124 [PMID: 8453122]

43 Plauth M, Cabré E, Riggio O, Assis-Camilo M, Pirích M, Kondrup J, Ferenci P, Holin E, Vom Dahl S, Müllner MJ, Nolte W. ESPEN Guidelines on Enteral Nutrition: Liver disease. Clin Nutr 2006; 25: 285-294 [PMID: 16701974 DOI: 10.1016/j.clnu.2006.01.018]

44 Mayo-Smith MF, Beecher LH, Fischer TL, Gorelick DA, Guillaume JL, Hill A, Jara G, Kasser C, Melbourne J. Management of alcohol withdrawal delirium. An evidence-based practice guideline. Arch Intern Med 2004; 164: 1405-1412 [PMID: 15249459 DOI: 10.1001/archinte.164.13.1405]

45 Lankarani KB, Ghaffarpasand F, Mahmoodi M, Lotfi M, Zamiri N, Heydari ST, Fallahzadeh MK, Maharlooei N, Ba- baienejad M, Mehrvar S, Ceramizadeh B. Non-alcoholic fatty liver disease in southern Iran: a population based study. Hepat Mon 2013; 13: e9248 [PMID: 23922564 DOI: 10.5812/ hepatmon.9248]

46 Saitz R, O’Malley SS. Pharmacotherapies for alcohol abuse. Withdrawal and treatment. Med Clin North Am 1997; 81: 881-907 [PMID: 9222299]

47 Ghamar Chereh ME, Vahedi M, Pourhouseingholi MA, Ashari S, Khedmat H, Amin M, Zali MR, Alavian SM. Estimation of diagnosis and treatment costs of non-alcoholic fatty liver disease: a two-year observation. Hepat Mon 2013; 13: e7382 [PMID: 23914227 DOI: 10.5812/hepatmon.7382]

48 Jung JH, Kim HS. The inhibitory effect of black soybean on hepatic cholesterol accumulation in high cholesterol and high fat diet-induced non-alcoholic fatty liver disease. Food Chem Toxicol 2013; 60: 404-412 [PMID: 23900008 DOI: 10.1016/j.fct.2013.07.048]

49 Day E, Bentham P, Callaghan R, Kuruvilla T, George S, Thiamine for Wernicke-Korsakoff Syndrome in people at risk from alcohol abuse. Cochrane Database Syst Rev 2004; (1): CD004033 [PMID: 14974055 DOI: 10.1002/14651858.CD004033.pub2]

50 Morgan MY. The treatment of alcoholic hepatitis. Alcohol Alcohol 1996; 31: 117-134 [PMID: 8737007]

51 Forrest E, Meller J, Stanton L, Bowers M, Ryder P, Austin A, Day C, Gleeson D, O’Grady J, Masson S, McCune A, Patch D, Richardson P, Roderick P, Ryder S, Wright M, Thursz M. Steroids or pentoxifylline for alcoholic hepatitis (STOPAH): study protocol for a randomised controlled trial. Trials 2013; 14: 262 [PMID: 23985271 DOI: 10.1186/1745-6215-14-262]

52 Rambaldi A, Sacconato HH, Christensen E, Thorlund K, Wet-terslev J, Gluud C. Systematic review: glucocorticosteroids for alcoholic hepatitis--a Cochrane Hepato-Biliary Group
R, Gent M, Rojkind M. Colchicine in the treatment of cirrhosis of the liver. *N Engl J Med* 1988; 318: 1709-1713 [PMID: 32857167 DOI: 10.1056/NEJM198806303182602]

84 Rambaldi A, Glaud C. Colchicine for alcoholic and non-alcoholic liver fibrosis and cirrhosis. *Cochrane Database Syst Rev* 2005; (2): CD002148 [PMID: 15846629 DOI: 10.1002/14651858.CD002148.pub2]

85 Li J, Kim CI, Leo MA, Mak KM, Rojkind M, Lieber CS. Unsatuated lecithin prevents acetadyle-hydrated hepatic collagen accumulation by stimulating collagenase activity in cultured lipocytes. *Hepatology* 1992; 15: 375-381 [PMID: 13719801]

86 Lieber CS, Robins SJ, Li J, DeCarli LM, Mak KM, Fusolo JM, Leo MA. Phosphatidylcholine protects against fibrosis and cirrhosis in the baboon. *Gastroenterology* 1994; 106: 152-159 [PMID: 8276177]

87 Lieber CS, Weiss DG, Grossmann R, Paronetto F, Schenker S. II. Veterans Affairs Cooperative Study of polyenylphosphatidylcholine in alcoholic liver disease. *Alcohol Clin Exp Res* 2003; 27: 1765-1772 [PMID: 14634492 DOI: 10.1097/01.ALC.0000097543.03049.80]

88 Kim MY, Cho MY, Baik SK, Jeong PH, Suk KT, Jang YO, Yea CJ, Kim JW, Kim HS, Kwon SO, Yoo BS, Kim JY, Eom MS, Cha SH, Chang SJ. Beneficial effects of candesartan, an angiotensin-blocking agent, on compensated alcoholic liver fibrosis - a randomized open-label controlled study. *Liver Int* 2012; 32: 977-987 [PMID: 22364262 DOI: 10.1111/j.1478-3231.2012.02774.x]

89 Rambaldi A, Jacobs BP, Iaquinto G, Glaud C, Milk thistle for alcoholic and/or hepatitis B or C virus liver diseases. *Cochrane Database Syst Rev* 2005; (2): CD003360 [PMID: 15846761 DOI: 10.1002/14651858.CD003360.pub2]

90 Ferenci P, Dragonis B, Dittrich H, Frank H, Benda L, Lobs H, Meryn S, Base W, Schneider R. Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. *J Hepatol* 1989; 9: 105-113 [PMID: 2671116]

91 Rambaldi A, Jacobs BP, Iaquinto G, Glaud C. Milk thistle for alcoholic and/or hepatitis B or C liver diseases—a systematic cochrane hepatobiliary group review with meta-analyses of randomized clinical trials. *Am J Gastroenterol* 2005; 100: 2583-2591 [PMID: 16279916 DOI: 10.1111/j.1572-0241.2005.00262.x]

92 Burra P, Senzolo M, Adam R, Delwart V, Karam V, Germann G, Neuberger J. Liver transplantation for alcoholic liver disease in Europe: a study from the ELTR (European Liver Transplant Registry). *Clin Transpl* 2009; 55-64 [PMID: 20524276]

93 Dumortier J, Guillaud O, Majno P, Morel P, Hadengue A, Paliard P, De Gottardi A, Sigaud H, Picot MC, Jacquet E, Puche R, Nüssler NC. Long-term survival and predictors of relapse after orthotopic liver transplantation for alcoholic liver disease. *Liver Transpl* 2007; 13: 197-205 [PMID: 17205563 DOI: 10.1001/lit.2009.2054]

94 Perney P, Bismuth M, Sigaud H, Picot MC, Jacquet E, Puche P, Jaber S, Rigole H, Navarro F, Eledjam JJ, Blanc F, Larrey D, Pageaux GP. Are preoperative patterns of alcohol consumption predictive of relapse after liver transplantation for alcoholic liver disease? *Transplant Int* 2005; 18: 1292-1297 [PMID: 16221161 DOI: 10.1111/j.1398-9975.2005.00208.x]

95 De Gottardi A, Spahr L, Geleiz P, Morard I, Mentha G, Guillaud O, Majno P, Morel P, Hagens VE, Schaapveld M, van den Berg AP, Gent M, Rojkind M, Burra P, Feltracco P, Bonsignore P, Scopelliti M, Cillo U, Neri D, Sršen M, II. Veterans Affairs Cooperative Study of polyenylphosphatidylcholine in alcoholic liver disease. *Alcohol Clin Exp Res* 2003; 27: 417-427 [PMID: 12713874 DOI: 10.1111/j.1572-0241.2003.00267.x]

96 Mathurin P, Moreno C, Samuel D, Dumortier J, Salleron J, Durand F, Castel H, Duhamel A, Pageaux GP, Leroy V, Dharnany S, Lovett A, Boleslawski E, Lucidi V, Gustot T, Francoz C, Letoublon C, Castaing D, Belghiti J, Donckier V, Pruvo FR, Duclos-Vallée JC. Early liver transplantation for severe alcoholic hepatitis. *Arch Intern Med* 2007; 167: 1183-1188 [PMID: 17563328 DOI: 10.1001/archinte.167.11.1183]

97 Pageaux GP, Bismuth M, Perney P, Costes V, Jaber S, Possoz P, Fabre JM, Navarro F, Blanc P, Domergue J, Eledjam JJ, Larrey D. Alcohol relapse after liver transplantation for alcoholic liver disease: does it matter? *J Hepatol* 2003; 38: 629-634 [PMID: 12713874]

98 Tang H, Boulton R, Gunson B, Hubecher S, Neuberger J. Patterns of alcohol consumption after liver transplantation. *Gut* 1998; 43: 140-145 [PMID: 9771419]

99 Vanlennens C, Di Martino V, Milan C, Messner M, Minello A, Duvoux C, Poynard T, Pererau JM, Fiquet MA, Pageaux GP, Dharancy S, Lucey MR, Wiesner RH, Isern A. Immediate listing for liver transplantation versus standard care for Child-Pugh stage B alcoholic cirrhosis: a randomized trial. *Ann Intern Med* 2009; 150: 153-161 [PMID: 19189904]

100 Zanus G, Carraro A, Vitala A, Grigioni E, D’Amico F, Valmasoni M, D’Amico FE, Broelese A, Boccagni P, Neri D, Srsen M, Burra P, Feltracco P, Bonesignore P, Scopelliti M, Cillo U. Alcohol abuse and de novo tumors in liver transplantation. *Transplant Proc* 2009; 41: 1310-1312 [PMID: 19460548 DOI: 10.1016/j.transproceed.2009.03.055]

101 Haagsma EB, Hagens VE, Schapvoeld M, van den Berg AP, de Vries EG, Klompemaker J, Slooff MJ, Jansen PL. Increased cancer risk after liver transplantation: a population-based...
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Suk KT et al.

study. J Hepatol 2001; 34: 84-91 [PMID: 11219192]

Park HW, Hwang S, Ahn CS, Kim KH, Moon DB, Ha TY, Song GW, Jung DH, Park GC, Namgoong JM, Yoon SY, Park CS, Park YH, Lee HJ, Lee SG. De novo malignancies after liver transplantation: incidence comparison with the Korean cancer registry. Transplant Proc 2012; 44: 802-805 [PMID: 22483506 DOI: 10.1016/j.transproceed.2012.01.027]

Zhang Z, Wang FS. Stem cell therapies for liver failure and cirrhosis. J Hepatol 2013; 59: 183-185 [PMID: 23353868 DOI: 10.1016/j.jhep.2013.01.018]

Akiyama K, Chen C, Wang D, Xu Q, Qu C, Yamaza T, Cai T, Chen W, Sun L, Shi S. Mesenchymal-stem-cell-induced immunoregulation involves FAS-ligand-/-FAS-mediated T cell apoptosis. Stem Cell Res 2012; 10: 544-555 [PMID: 22542159 DOI: 10.1016/j.scr.2012.03.007]

Aurich H, Sgoddia M, Kaltwasser P, Vetter M, Weise A, Liehr T, Brulport M, Hengstler JG, Dollinger MM, Fleig WE, Christ B. Hepatocyte differentiation of mesenchymal stem cells from human adipose tissue in vitro promotes hepatic integration in vivo. Gut 2009; 58: 570-581 [PMID: 19022918 DOI: 10.1136/gut.2008.154880]

Kuo TK, Hung SP, Chuang CH, Chen CT, Shih YR, Fang SC, Yang VW, Lee OK. Stem cell therapy for liver disease: parameters governing the success of using bone marrow mesenchymal stem cells. Gastroenterology 2008; 134: 2111-221, 2111-221, [PMID: 18455168 DOI: 10.1053/j.gastro.2008.03.015]

Jang YO, Kim YJ, Baik SK, Kim MY, Eom YW, Cho MY, Park HJ, Park SY, Kim BR, Kim JW, Soo Kim H, Kwon SO, Choi EH, Kim YM. Histological improvement following administration of autologous bone marrow-derived mesenchymal stem cells for alcoholic cirrhosis: a pilot study. Liver Int 2014; 34: 33-41 [PMID: 23782511 DOI: 10.1111/liv.12218]

Terai S, Ishikawa T, Omori K, Aoyama K, Marumoto Y, Urata Y, Yokoyama Y, Uchida K, Yamasaki T, Fujiy O, Okita K, Sakaida I. Improved liver function in patients with liver cirrhosis after autologous bone marrow cell infusion therapy. Stem Cells 2006; 24: 2292-2298 [PMID: 16778155 DOI: 10.1634/stemcells.2005-0542]

Ismail A, Fouad O, Abdelnasser A, Chowdhury A, Selim A. Stem cell therapy improves the outcome of liver resection in cirrhosis. J Gastrointest Cancer 2010; 41: 17-23 [PMID: 20012250 DOI: 10.1007/s12029-009-9092-9]

Pai M, Zacharoulis D, Milicevic MN, Helmy S, Jiao LR, Levicar N, Tai I, Scott M, Marley SB, Jesteke K, Gilbetic M, Bans D, Khan SA, Kyriakou D, Rounts C, Thillainayagam A, Nicholls JP, Jensen S, Apperley JF, Gordon MY, Habib NA. Autologous infusion of expanded mobilized adult bone marrow-derived CD34+ cells into patients with alcoholic liver cirrhosis. Am J Gastroenterol 2008; 103: 1952-1958 [PMID: 18637092 DOI: 10.1111/j.1572-0241.2008.01993.x]

Spahr L, Lambert JF, Rubbia-Brandt L, Chalandon Y, Frossard JL, Giostra E, Hadengue A. Granulocyte-colony stimulating factor induces proliferation of hepatic progenitors in alcoholic steatohepatitis: a randomized trial. Hepatology 2008; 48: 221-229 [PMID: 18537187 DOI: 10.1002/hep.22317]

Orman ES, Odena G, Bataller R. Alcoholic liver disease: pathogenesis, management, and novel targets for therapy. J Gastroenterol Hepatol 2013; 28 Suppl 1: 77-84 [PMID: 23655300 DOI: 10.1111/j.1440-1746.2013.07109.x]

Dominguez M, Miquel R, Colmenero J, Moreno M, Garcia-Pagán JC, Bosch J, Arroyo V, Ginès P, Caballería J, Bataller R. Hepatic expression of CXC chemokines predicts portal hypertension and survival in patients with alcoholic hepatitis. Gastroenterology 2009; 136: 1639-1650 [PMID: 19208360 DOI: 10.1053/j.gastro.2009.01.056]

Ki SH, Park O, Zheng M, Morales-Ibanez O, Kolls JK, Bataller R, Gao B. Interleukin-12 treatment ameliorates alcoholic liver injury in a murine model of chronic-binge ethanol feeding; role of signal transducer and activator of transcription 3. Hepatology 2010; 52: 1291-1300 [PMID: 20842630 DOI: 10.1002/hep.23837]

Pritchard MT, McMullen MR, Stavitsky AB, Cohen JI, Lin F, Medof ME, Nagy LE. Differential contributions of C3, C5, and decay-accelerating factor to ethanol-induced fatty liver in mice. Gastroenterology 2007; 132: 1117-1126 [PMID: 17383432 DOI: 10.1053/j.gastro.2007.01.053]

Seth D, Gorrell MD, Cordoba S, McLaughan GW, Haber PS. Intrahepatic gene expression in human alcoholic hepatitis. J Hepatol 2006; 45: 306-320 [PMID: 16797773 DOI: 10.1016/j.jhep.2006.04.013]

Szabo G, Bala S. Alcoholic liver disease and the gut-liver axis. World J Gastroenterol 2010; 16: 1321-1329 [PMID: 20238398]

Seo YS, Shah VH. The role of gut-liver axis in the pathogenesis of liver cirrhosis and portal hypertension. Clin Mol Hepatol 2012; 18: 337-346 [PMID: 23322248 DOI: 10.3350/cmh.2012.18.4.337]

Lucey MR, Mathurin P, Morgan TR. Alcoholic hepatitis. N Engl J Med 2009; 360: 2758-2769 [PMID: 19553649 DOI: 10.1056/NEJMra0805786]

Kendrick SF, O'Boyle G, Mann J, Zeybel M, Palmer J, Jones DE, Day CP. Acetate, the key modulator of inflammatory responses in acute alcoholic hepatitis. Hepatology 2010; 51: 1988-1997 [PMID: 20232292 DOI: 10.1002/hep.23572]

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