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February 19, 2017

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 31571 review.doc).

Title: Emerging Concepts in Alcoholic Hepatitis

Author: Phoenix Fung, Nikolaos Pyrsopoulos.

Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 31751

The manuscript has been improved according to the suggestions of reviewers:

1. Revisions has been made according to the suggestions of the reviewer.

Reviewer #1.

Reviewer's code: 02940090
Reviewer's country: Germany
Science editor: Fang-Fang Ji

(1) 1. For non-Anglo-American readers it would be useful to give the critical amounts of alcohol intake also in International System units e.g. in milliliters for the size of a standard drink. It would also be helpful to add the alcohol content in grams in figure 1 or in the subsequent paragraph. One standard drink contains approximately 14 grams of alcohol, which is equivalent to 12 ounces (350 mL) of beer (4-5% wt/vol), 6 ounces (177 mL) of wine (8-10%wt/vol), and 2 ounces (59 mL) of hard liquor or whiskey (45% wt/vol).[1] 2. In the section preceding Figure 3 the complex mechanisms how ethanol induced ER stress leads to the mitochondria related hepatocyte apoptosis should be explained a little more in detail. The term "mitochondrial ER stress" is somewhat misleading. Multiple mechanisms, including downstream inflammation and increased oxidative ER stress from hyperhomocysteinemia activates nuclear factor kappa beta (NFKB) and JNK to induce hepatocyte apoptosis via caspase activation.[32,33] Deficiencies of B vitamins or hemocysteine metabolism mutations seen

in chronic ethanol use cause accumulation of homocysteine, which induces the ER stress of the hepatocytes and vascular endothelial cells. In addition, ER stress is associated with fatty acid synthesis via the activation of SREBPs (sterol regulatory element-binding proteins), which enhance cholesterol and triglyceride biosynthesis and fibrosis via stellate cell activation.[34,35] 3. In the section on genetic risk factors for the development of alcoholic hepatitis (after references 51 and 52) Acetaldehyde dehydrogenase gene polymorphisms are meant. Corrected. 4. In the part on new therapeutic options I would prefer if ELAD is listed after the pharmaceutical options. Corrected. 5. On the end of this comprehensive review the conclusion could be more detailed including the key concepts of every part of the review.

Conclusion:

Alcoholic hepatitis is increasingly recognized as a form of acute-on-chronic liver failure in patients with underlying alcohol-related disease.[196,197] Patients with severe alcoholic hepatitis remain a challenging population to treat. New treatment options for AH involving gut microbiota modification, immune modulation, promotion of liver regeneration, apoptosis inhibitors, farnesoid receptors, and ELAD appear promising thus far, however the research is still in the preliminary phases. Currently, early liver transplantation for severe AH failing standard medical therapy is not universally implemented and further investigation is warranted. Solving the complex pathophysiology of alcoholic hepatitis through translational studies with clinical application is challenging. The study of new animal model simulating "true" AH and use of genomic analysis to provide molecular targets are emerging into present day practice. The utilization of clinical trials fuelled by constant evolving concepts discovered via translational research will help determine the endpoints and safety of the new therapeutic options to bridge the gap of a disease with high morbidity and mortality.

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Reviewer #2:
Reviewer's code: 02530787
Reviewer's country: United Kingdom
Science editor: Fang-Fang Ji

(2) 1. More detailed discussion and critical evaluation of the literature is required throughout. Please relate your discussion to the title: "Emerging concepts". Completed 2. The introduction needs improvement. Most of it refers to alcohol related liver disease and alcoholic cirrhosis rather than AH which should be clarified. It should also correctly define AH as a clinical syndrome of recent onset jaundice and coagulopathy in a person who has been a heavy drinker usually for more than a decade (see Lucey, NEJM 2009). It is not only the histological change referred to in the introduction which is alcoholic steatohepatitis. The trigger for AH is unknown and not only related to heavy alcohol consumption as described: "AH is induced by average daily alcohol use > 80 grams for more than five years". Introduction:

Alcoholic hepatitis (AH), is one of the most severe manifestations of alcoholic liver disease. It is a public health issue and worldwide disease associated with high morbidity and mortality. Complications related to alcoholic liver disease result in costly hospitalizations. The one-month survival for severe alcoholic hepatitis is low with mortality rates as high as 30-50%. Current treatment strategies are limited. Abstinence is the first line treatment, however may not improve outcomes in patients with severe AH, defined as discriminant function ≥ 32. The mainstay of therapy is corticosteroids, which have limited efficacy in specific populations. Pursuit of new treatment options for alcoholic hepatitis is the holy grail for patients ineligible or refractory to corticosteroids. The

judicious use of early liver transplantation for severe alcoholic hepatitis has been explored although medical and ethical controversy remains. Exploration of maximal medical management with microbiota modification, immune modulation, liver regenerative factors, farnesoid X receptors, caspase inhibitors, and ELAD (extracorporeal assist device) may be promising for patients with severe alcoholic hepatitis who do not have other options.

Sixty percent of the United States' population reports alcohol consumption.[1] Approximately 8-10% of the US population reports heavy alcohol use, which is defined as ≥ 2 drinks daily in men and ≥ 1 drink daily in women.[2] One standard drink contains approximately 14 grams of alcohol, which is equivalent to 12 ounces (350 mL) of beer (4-5% wt/vol), 6 ounces (177 mL) of wine (8-10%wt/vol), and 2 ounces (59 mL) of hard liquor or whiskey (45% wt/vol).[1] There are progressive and co-existing stages of disease in chronic alcoholism including steatosis, steatohepatitis, fibrosis, and development of compensated to decompensated cirrhosis. In a study examining hospitalized heavy alcohol drinkers with and without alcohol withdrawal, liver biopsies reveal steatosis in 44.9%, alcoholic hepatitis in 34.4%, liver cirrhosis with superimposed alcoholic hepatitis in 10.2%, and cirrhosis only in 10.5%.[3] In other studies, approximately 20% of individuals with chronic alcohol abuse are found to have AH when biopsied.[4]

Alcoholic hepatitis is an acute-on-chronic presentation of liver disease with a wide ranging spectrum of mild to florid, life-threatening injury.[5] It is a clinical syndrome associated with recent onset jaundice and coagulopathy in a person who has been a heavy drinker usually for more than a decade.[6] Although long standing alcohol abuse appears to be associated with the development of AH, the exact trigger for development is unclear. Other factors, such environmental and genetic variables may play a pivotal role. The amount and duration of alcohol abuse needed to produce alcoholic hepatitis is variable depending on the individual patient. Alcohol consumption of approximately 40 grams daily for women and 50-60 grams daily for men for is recognized as a minimal threshold amount for patients at high risk of developing AH. Alcohol consumption is usually within less than 60 days prior to onset of jaundice with heavy alcohol use for more than 6 months for severe alcoholic

hepatitis clinical trial inclusion criterias.[7]

3. Remove figure 1: this does not contribute anything in addition to the text. Completed. 4. In the pathophysiology section on page 5 TH-1 should be defined. T-helper-type 1 (TH1) response. 5. The pathophysiology section should also comment on the immune dysfunction documented in AH including defective monocyte function (Vergis, Gut 2016) and monocyte/T cell signalling (Markwick, Gastroenterol 2015). The innate immunity is impaired in patients with progressive liver dysfunction, contributing to multi-organ failure seen in patients with severe alcoholic hepatitis. Serum analysis of acute alcoholic hepatitis patients compared to patients with alcoholic cirrhosis and healthy controls show a significant reduction in antibacterial innate and adaptive immune responses. An impaired T cell response from AH patients produces fewer interferon gamma when exposed to lipopolysaccharide with impaired neutrophil phagocytosis and defective monocyte oxidative burst when stimulated by bacterial challenge. Defective monocyte oxidative burst reduces the expression of NADPH oxidase, which is responsible for generation of superoxide radicals required for bacterial killing. Higher rates of infection in AH may be explained by this impairment.[46] The T cells of AH patients exhibits increased numbers of PD ligand 1 (PD 1), T-cell immunoglobulin and mucin domain 3 (TIM3), and galectin-9, which are ligands responsible for programmed cell death functioning. The blockade of the PD1 and TIM3 can restored the innate and adaptive immunity by increasing T cell and neutrophil antimicrobial activity.[47]

6. Risk factors for development of AH. This section provides evidence of risks for development of progression of alcoholic liver disease not AH. This should be clarified. It would be preferable to alter this section to only discuss the risk factors for AH which are less well documented and include obesity, gender and ethnicity as well as quantity of alcohol consumption. Studies have identified risk factors towards the development and progression of liver disease. Patterns of drinking, gender, genetic predisposition, and concomitant liver disease may increase the risk of susceptibility. Simultaneous alcohol consumption with food intake has been published to lower risk of alcoholic liver disease compared to those consuming alcohol alone.[9] Variant genes encoding for alcohol

metabolism, such as alcohol dehydrogenase, aldehyde dehydrogenase, and cytochrome CYP2E1 might facilitate hepatotoxicity by increasing alcohol tolerance via delay of acetaldehyde formation or the metabolism of alcohol through other non-oxidative toxic pathways.[49,50]Acetaldehyde dehydrogenase gene polymorphisms may cause varying levels of alcohol sensitivity in Asians and women, who can develop alcoholic liver disease even if they do not consume alcohol as heavily as others. Women are twice as likely to develop hepatotoxicity with lower amounts and shorter duration of alcohol use compared to men, which may be attributable to gastric alcohol differences and higher proportion of body fat in women in addition to differences in dehydrogenase levels.[51-53] CYP2E1 gene polymorphisms can affect the metabolism of alcohol amongst those with different ethnic backgrounds and alcoholics, however the exact pathogenesis is yet to be eludicated.[54]

Variations in patatin-like phospholipase protein 3 (PNPLA3) has a strong association with cirrhosis development in Caucasian and Mexican patients with alcoholism.[55] Patients with G allele of PNPLA3 have a higher risk of steatosis and fibrosis, as well as a significantly higher prevalence of alcoholic cirrhosis compared to those with C allele.[56] Recent data published from a genome wide association study found that severe alcoholic hepatitis risk is associated with PNPLA 3 rs738409 variant, which until recently has been associated with cirrhosis development. Identification of SLC38A4 variant gene is another novel independent risk locus for severe AH.[57]

Caffeine consumption may have a protective effect against development of AH. Recent studies by Chalasani et al. found the risk of AH was 27% with heavy alcohol users with PNPLA3 genotype CC with regular coffee consumption compared to 86% in heavy drinkers with PNPLA3 genotype GG, who did not consume coffee. PNPLA3 CC genotype subjects who were not regular coffee consumers had a 48% risk of AH. The risk of AH with PNPLA3 GC with and without regular coffee drinking was 37% and 62%, respectively. The risk of AH was 57% in patients with PNPLA3 GG gene who were regular coffee drinkers.[58]

Underlying obesity with BMI $\geq$ 30 likely potentiates the severity of alcoholic hepatitis. A common

pathway is postulated for the generation of steatohepatitis through synergetic or additive effects of heavy alcohol use combined with obesity, although the exact mechanism is not well defined.[59] Hart and colleagues published a paper documenting a supra-additive interaction between obesity and heavy alcohol consumption. One unit of alcohol was equivalent to 8 grams. Overweight or obese male subjects who consumed 15 or more alcohol units per week had an increased risk of liver related morbidity and mortality compared to controls. Another UK study examining 107, 742 women found that subjects with high BMI ($\geq$ 25 kg/m^2) who drank $\leq$ 15 units of alcohol have an equivalent risk of chronic liver disease development compared to women with low BMI (<25) who drank $\geq$ 15 units per week. Women with BMI $\geq$ 25 who drank $\geq$ 15 units of alcohol weekly had the poorest outcomes. Even in overweight women who did not drink alcohol, the risk of negative outcomes were present.[60]

7. Diagnosis section (page 10). 25-30% require biopsy – reference needed to support this. It is not consistent with the UK experience of AH. I removed this segment. 8. Abstinence section (page 14). Mention that none of the medications discussed have been trialled in the context of AH and few in patients with advanced chronic liver disease. More detailed discussion of these treatments and the limitations of the published studies would be useful. There are few medication options to prevent recidivism in advanced chronic liver disease. Baclofen is γ aminobutyric acid (GABA) B-receptor antagonist, which is minimally metabolized in the liver. It is one of the few treatments studied in cirrhotic patients. Addolorato et al. performed a randomized double-blinded placebo-controlled in alcoholic-dependent cirrhotics with baclofen 10mg three times daily for 12 weeks in the treatment arm. 71% maintained abstinence compared to 29% in the placebo group. Baclofen may be beneficial to achieving and maintaining abstinence safely in Child-Pugh class A, B, and C cirrhotic patients.[131] Gamma hydroxyl butyrate may be well tolerated in patients with decompensated cirrhosis with alcohol withdrawal symptoms due to the short half life of 4-6 hours. Further studies need to be performed before recommendations on efficacy and safety can be made.[132] None of the medications discussed have been studied in the context of alcoholic hepatitis and remains a challenge to medical practitioners.

9. Nutritional supplementation section (page 15). The recent meta-analysis (Fialla, Liver Int 2015) only included 3 small studies in patients with AH and did not have a separate analysis for this subgroup. The overall data they provide is of low quality. This should be commented upon. I removed this reference because I felt the evidence is low quality and would not add any additional benefit to reader. 10. Corticosteroids (page 16): "Corticosteroids decrease the inflammatory process by suppressing transcription factors nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and activator protein 1 (AP-1)". The mechanism of action of corticosteroids is much more complex than described in this sentence. Corticosteroids have wide ranging immune modulatory functions including suppression of these pro-inflammatory transcription factors. Corticosteroids have a wide range of immune modulatory functions including suppression of pro-inflammatory transcription factors: NFKB and activator protein 1 (AP-1), which lower circulating levels of TNF-α and IL-8.[140,141] 11. Corticosteroids (page 16). The Rambaldi and Mathurin meta-analyses are out of date. Include the updated ones instead: Singh, Gastroenterol 2015 and Thursz, AASLD abstract 2016). The Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH) trial is the largest randomized clinical trial to date, which examined the short and long term mortality of patients with severe alcoholic hepatitis. Results show no reduction in all cause mortality at 28 days for patients treated with prednisolone or pentoxifylline. However, there is a non-significant mortality benefit at 28 days in the prednisolone treated group, which is not seen at 3 and 12 months.[148] Corticosteroids may have some benefit within the first month, but cannot be generalized to a provide long term value.

The meta-analysis of 22 randomized clinical trials performed by Singal et al. show a reduction in short-term mortality in patients with severe alcoholic hepatitis treated with steroids versus placebo. Corticosteroids with N-acetylcysteine (NAC) compared to corticosteroids alone may be effective in improving short-term mortality.[149] More recently, Thurz and colleagues performed a meta-analysis of 9 randomized clinical trials comparing the use of corticosteroids, pentoxifylline, or both for the treatment of severe alcoholic hepatitis. They found that corticosteroid treatment improved 28 day survival compared to pentoxylline and control group. There is no added benefit of treatment with

combination group of corticosteroids and pentoxifylline.[150]

12. Corticosteroids (page 16). Discuss findings of STOPAH trial in this section. Completed. 13. Corticosteroids and pentoxifylline (page 17). Specifically comment on the Mathurin, JAMA 2013 study. Prednisolone use is indicated in patients with DF > 32 or hepatic encephalopathy, but contraindicated in active infection, gastrointestinal bleeding, acute pancreatitis, or renal failure.[142,143] Studies examining the combination of prednisolone and pentoxifylline treatment produced mixed results[144,145] or showed no added benefit of pentoxifylline.[146,147] 14. Immune modulations (page 20). Correct subtitle to read Immune Modulators Completed 15. ELAD (page 23). Comment on specific disadvantages of ELAD (cost, access, patient selection). The most recent ELAD trial, VTL-308 incorporates the new inclusion and exclusion criteria.[192] The preliminary results are eagerly awaited. There are limitations to the use of ELAD, including high cost and stringent inclusion criteria. Patients are usually monitored in the intensive care use with frequent monitoring and blood draws. Currently, there are limited centers performing ELAD research and the patient selection criteria excludes: recent alcohol use > 6 weeks, persons > 50 years old, severe coagulopathy, and advanced renal failure. 16. Conclusions (page 25). This summary paragraph is weak and generic. It should explain what the authors feel is the future of the management of AH and relate it to the title "Emerging concepts in AH". Are we going to be using novel single target.

Future Research

Most of the understanding of alcoholic liver disease pathogenesis stem from animal models of alcoholic liver disease recreated via ad libitum or intragastric ethanol feeding. Recent publications propose a new model of ad libitum feeding with 40% intake of caloric intake from a Western diet high in cholesterol and saturated fat combined with 60% ethanol via intragastric infusion to simulate a "true" model of alcohol hepatitis, where contributing factors such as obesity and alcohol abuse are taken into account. This model recreates findings seen in chronic alcoholic liver disease with superimposed alcoholic hepatitis when a weekly binge dose of ethanol is added. However, the model

could not emulate the acute-on-chronic hepatic decompensation seen in alcoholic hepatitis.[193,194] The search for molecular targets through genomic studies holds the future direction of answering unsolved questions about alcoholic hepatitis pathogenesis. Further study of IL-22's antioxidant, anti-apoptotic, anti-steatosis, antibacterial, proliferative effect, and other hepatoprotective properties in conjunction with the inflammatory and immunomodulatory function of corticosteroids is underway.[12,195] Recent literature highlights the use of biospecimens (i.e. liver tissue, peripheral serum, stool) for in vitro and in vivo studies as a new approach to finding targets for therapy.[194] New findings eludicated under such methods, include impaired bacterial killing from monocyte oxide burst dysfunction and defective T cell function in AH subjects. Although the reversal of defective monocyte oxidative burst is not restored by the IFN-gamma, the negative regulator of Janus Kinase responsible for suppressing cytokine signalling-1 was discovered to have increased expression.[46] Restoration of T- cell interferon gamma production, reduction in production of IL-10 producing T cells, and improvement in neutrophil antibacterial function occurs when antibodies against PD1 and TIM3 are blocked.[47]

Conclusion:

Alcoholic hepatitis is increasingly recognized as a form of acute-on-chronic liver failure in patients with underlying alcohol-related disease.[196,197] Patients with severe alcoholic hepatitis remain a challenging population to treat. New treatment options for AH involving gut microbiota modification, immune modulation, promotion of liver regeneration, apoptosis inhibitors, farnesoid receptors, and ELAD appear promising thus far, however the research is still in the preliminary phases. Currently, early liver transplantation for severe AH failing standard medical therapy is not universally implemented and further investigation is warranted. Solving the complex pathophysiology of alcoholic hepatitis through translational studies with clinical application is challenging. The study of new animal model simulating "true" AH and use of genomic analysis to provide molecular targets are emerging into present day practice. The utilization of clinical trials

fuelled by constant evolving concepts discovered via translational research will help determine the endpoints and safety of the new therapeutic options to bridge the gap of a disease with high morbidity and mortality.

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Reviewer #3:
Reviewer's code: 01713316
Reviewer's country: United States
Science editor: Fang-Fang Ji

(3) 1. Introduction: Should highlight more on AH disease burden data rather than alcoholic liver disease. Completed. Please see above. 2. Pathophysiology section also should also highlight more on AH and also author may consider to shorten this section as seemingly this is too redundant and long. Completed. 3. Risk factors: I think authors again discuss risk factors which predispose to ALD. It should be recognized that the risk factors for development of AH are not well known. There are two recent papers on protection from AH among dinkers with increased coffee consumption and increased risk with PNPLA3 polymorphisms. Completed. Please see above. 4. Diagnosis: Statement that this is a clinical diagnosis seems too strong. Authors may like to give clinical definition of this syndrome and provide data on accuracy of clinical diagnosis. Paper from US on the NIH consortia data earlier this year in Gastroenterology provides the approach to clinical diagnosis of AH and this should be highlighted. Completed. Please see above. 5. One of the most controversial issues in AH management is on liver transplantation and this section seems too short for this review if the focus of the review is AH. Authors are expected to review the literature on this (3 papers in last 12 months in AJT, LT, and Annals of surgery) in addition to two other papers in Hepatology 2012 and NEJM 2011. Liver transplantation:

Liver transplantation may be considered as a last option for patients with alcoholic hepatitis when medical treatment has failed or is contraindicated. Most liver transplant centers require a minimum abstinence of six months prior to donor allocation consideration. Given the donor organ scarcity, the risk of recividism is feared for patients with alcoholic hepatitis undergoing liver transplantation.[156] Data regarding the 6-month rule as a predictor of long-term sobriety remains controversial.[157] Based on a systematic review, there is no difference in early alcohol use in patients transplanted for alcoholic liver disease versus non-alcoholic liver disease at: 6 months (4% versus 5%) and 12 months (17% versus 16%). At 7 years post-OLT, 32% of the patients with alcoholic liver disease reports using

alcohol. Although comparable rates of any alcohol use are reported in patients transplanted for alcoholic liver disease and non-alcoholic liver disease, the risk of heavy drinking appears much higher in alcoholic liver disease patients.[158] There is a wide variation among post-liver transplant alcohol relapse rates reported in the literature, ranging from 20 to 50%. Heavy drinking rates range from 10 to 20%.[159] The duration of pre-transplant abstinence does not appear to correlate with post-transplant survival[160], however studies for long term follow-up of the graft in patients transplanted for alcoholic hepatitis with continued alcohol abuse requires further investigation.

Mathurin reports the results of a multicenter European trial which carefully selected corticosteroid refractory AH patients whom were deemed to have a low risk of recividism after liver transplantation. The episode of AH is deemed as the patient's first liver decompensating event. Other inclusion criteria includes: close and supportive family members, absence of severe coexisting or psychiatric disorders, and a covenant to adhere to life-long alcohol abstinence. The study reports no alcoholic relapse within the initial 6-month follow-up period. Three of 26 patients transplanted for refractory alcoholic hepatitis later resumed drinking alcohol: one at 720 days, one at 740 days, and one at 1140 days after transplantation. Despite counseling by an addiction specialist, 2 patients remained daily consumers (30 g per day and >50 g per day), whereas 1 consumed alcohol occasionally (approximately 10 g per week). None of them had graft dysfunction.[161]

Im and colleagues applied inclusion criteria similar to Mathurin's European trial for early liver transplantation in severe alcoholic hepatitis in the United States. The low candidate acceptance rate (20%) and the high survival rates for transplanted AH patients compared to controls (89% versus 11%) is comparable to the findings in Mathurin's study. Two patients (25%) had alcohol use post OLT. One patient self-reported a "slip" of 60 g and 15 g of alcohol use at day 84 and 260, respectively. Serial urine ethanol testing and self-reporting were negative thereafter. One patient had alcohol relapse, which is defined as: four or more drinks daily or at least one drink for 4 or more days in succession after liver transplantation. When the subject with alcohol relapse was further analyzed, it was deemed that the hepatic decompensation was not the patient's first event and the subject had poor insight to disease

prior to transplant. Limitations to the study include small sample size (n=9) and short follow up period (median=765 days).[162]

A three-year pilot by Lee examined 2 groups of patients selected to receive a liver transplant: severe alcoholic hepatitis as the first episode of liver decompensation versus alcoholic cirrhotics with ≥6 months of abstinence. Early liver transplant provided excellent short-term survival in both groups. There were similar rates of alcohol relapse in both groups: 23.5% versus 29.2%. Although lacking statistical significance, patients transplanted for AH had higher rates of harmful drinking post transplant compared to the control group (23.5% versus 11.5%, P=0.42). The data was particularly concerning given the two out of the four patients with harming drinking patterns died secondary to recurrent alcohol use (alcohol overdose and medication noncompliance with graft failure, respectively).[163]

Although preliminary results may appear promising, ethical issues pertaining to organ shortage, sociocultural concerns about judicious organ allotment, and recividism risk remain.[164] The feasibility of patient selection through strict psychosocial assessment is limited by resources. An addiction psychiatrist experienced in liver transplant may not be readily available in all centers. Liver transplantation for refractory severe acute alcoholic hepatitis should be judiciously employed in highly selected individuals who are at low risk of recidivism.[165]

6. I like to section on biomarkers and predictors of AH (metabolomics data). 7. Section on new targets seems appropriate and well covered (table with existing and potential new therapies will be useful for readers)

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Table 1: New Potential Treatments for Alcoholic Hepatitis

Treatment	Class	Mechanism of Action
Probiotics	Gut microbiota modification	Reduction of bacterial endotoxins and translocation
IL-22 recombinant protein	Immune modulation	Hepatoprotective: antioxidant, apoptotic, proliferative, and antimicrobial properties
G-CSF	Growth factor	Liver regeneration
Obeticholic acid	Farnesoid X receptor	Improvement in cholestasis
Emricasan	Caspase inhibitor	Apoptosis, inflammation, and fibrosis inhibitor
Anakinra (Pentoxifylline + Zinc)	IL-1 receptor	Decreases hepatic inflammation
SAM-e	Glutathione precursor	Decreases oxidative stress
Metadoxine	Antioxidant	Decreases oxidative stress and steatosis
ELAD	Extracorpeal human hepatic cell-based liver treatment	Toxin removal, reduction of inflammation, liver regeneration

Thank You Very Much for reviewing the paper!

Sincerely yours,

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