REVIEW ARTICLE

Alcoholic Hepatitis

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Alcoholic hepatitis (AH) is a clinical manifestation on the spectrum of alcoholic liver diseases related to alcohol consumption. The mildest of these diseases is fatty liver, which can progress to AH and then lead to cirrhosis with continual alcohol use. Alcohol is the leading cause of liver disease in the world and the third most common cause of preventable death in the United States (1, 2). This goes to show that alcohol use is a major problem and the clinical diseases that arise from its use are extremely prevalent among hospitalized patients. Recently, there has been ample research into the pathophysiology, management, and treatment of AH in the hospitalized patient; however, the mainstay of treatment has not changed even though many theoretical options are being investigated.

DEFINING AH

AH is a clinical diagnosis that makes it difficult to come to an agreement on the signs and symptoms that define this condition. However, a common definition is a patient with a history of current, or previous, heavy alcohol use that develops jaundice with elevated serum aspartate aminotransferase (AST) (3). The term 'heavy alcohol use' proves problematic to define, but for the clinical diagnosis patients should have been drinking for >6 months with <60 days of abstinence before the onset of jaundice (3). Other clinical features that are common, but not specific for AH, include: tender hepatomegaly, fever, ascites, and/or encephalopathy (4). With these common signs and symptoms, it is difficult to determine the underlying etiology of liver disease in the absence of alcohol use history. However, laboratory studies may be beneficial to elucidate the underlying etiology. In AH, the AST and alanine aminotransferase (ALT) levels are usually 2-6 times the upper limit of normal with an AST/ALT ratio of greater than 2 (4). Patients may also have associated neutrophilia, hyperbilirubinemia, and coagulopathy due to synthetic liver dysfunction associated with AH (4). Most of these signs and symptoms are common among all liver diseases; however, it is the history of alcohol use that truly points to this diagnosis.

PREVALENCE

Since AH exists on a disease spectrum its exact prevalence is difficult to determine and many patients are completely asymptomatic. Further, it is common for physicians not to seek out this disease when the patient does not give any indication of

alcohol use or abuse. However, a recent study showed that alcohol-related hospitalizations has increased by 25% among 18-25 year-olds in the United States between 1999 and 2008 (5). Another study reported the prevalence of AH in a cohort of 1604 alcoholics to be close to 20% based on liver biopsy data (6). To further illustrate the magnitude of AH, in one study using National Inpatient Sample data, AH accounted for 56,809 hospitalizations in the US in 2007; this was 0.71% of all hospitalizations (6). Thus, as alcohol becomes more available, especially among teenagers and young adults, the incidence of AH is expected to rise in the future.

RISK FACTORS FOR DEVELOPMENT OF AH

The risk of developing AH shares many similarities with development of alcoholic liver disease, and it is based on many environmental and genetic risk factors that have not been fully elucidated to date. However, the strongest predisposing risk factor is alcohol use. In fact, a strong positive correlation between cumulative alcohol intake and degree of liver fibrosis has been widely reported in the literature (7). Interestingly, excessive alcohol use is not sufficient to promote alcoholic liver disease alone. There are other environmental and genetic factors at play because only 1 in 5 heavy drinkers will develop AH and only 1 in 4 will go on to develop liver cirrhosis (8). Since alcohol is a major risk factor for the development of AH, it is important to define how much alcohol is too much. Unfortunately, there is no consensus on the exact amount of alcohol that poses a risk for the development of AH; however, there is more agreement on the amount that can lead to liver cirrhosis. One study found that with an "above a risk 'threshold', of about three standard drinks per day, there is a steep dose-dependent increase in the relative risk of cirrhotic or non-cirrhotic liver disease" (9). Moreover, another study found that the risk of developing cirrhosis increases with ingestion of greater than 60-80 grams per day of alcohol for 10 years or longer in men and greater than 20 grams per day in women (10, 11). These studies demonstrate that there is a dose-dependent relationship between alcohol consumption and the incidence of alcohol related sequelae. Further, it has also been shown that individuals that drink daily are at an increased risk of developing AH as compared to binge drinking (8). Finally, the risk of AH was higher in individuals who drink beer and spirits as compared to drinking wine (6).

Besides the obvious detrimental effects of alcohol, there are many other risk factors for development of AH (table 1). Even though males are more commonly affected by AH, female gender is a widely-accepted risk factor (12). Women are more prone to the effects of alcohol because women have decreased gastric alcohol dehydrogenase levels compared to men, women have a higher proportion of body fat, and women experience changes in gastrointestinal alcohol absorption related to estrogen fluctuations throughout the menstrual cycle (6, 12). Other risk factors are certainly at play in AH and these include: obesity, glucose derangements, and many genetic factors (13). In terms of genetics, the rates of alcoholic liver diseases are higher in African-American and Hispanic males compared to Caucasians and mortality rates are highest in Hispanic males (14). Interestingly, this difference cannot be explained by the amount of alcohol consumption since no significant difference exists among the groups (12). Age is also a commonly reported risk factor since AH is mostly seen in the 40-50-year-old age range (6).

A final risk factor that is currently being heavily studied in terms of management of AH is the extent of malnutrition. The degree of malnutrition plays a direct role in determining outcome and prognosis of patients with AH (15). Mortality increases in direct proportion to the extent of malnutrition and approaches 80% in patients with severe malnutrition (15). There has also been a new focus on micronutrient abnormalities that commonly occur in AH. Alcohol may cause hepatic vitamin A depletion or depressed vitamin E levels which may aggravate and propel liver disease (16). Further, diets rich in polyunsaturated fats have also been shown to increase progression of alcohol-induced liver disease in animals (17). Thus, nutritional support in AH is an active area of research and investigators are trying to determine the best management strategies and discover how nutritional status affects long-term management.

Table 1. Associated risk factors for AH

1. Female Gender
2. Race (African-American and Hispanic)
3. Age (40-50-year-old age range)
4. Malnutrition
5. Obesity
6. Dysglycemia

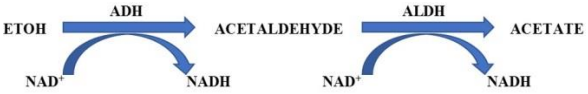
PATHOPHYSIOLOGY OF ALCOHOLIC HEPATITIS

Ethanol is oxidized by three metabolic pathways:
1. Ethanol (EtOH)→Acetaldehyde→Acetate
2. Cytochrome P450 2E1
3. Catalase

1. Ethanol (EtOH) → Acetaldehyde → Acetate Pathway:

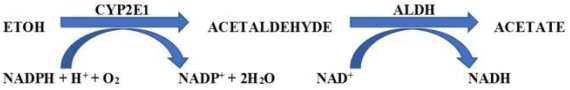
Ethanol → Acetaldehyde → Acetate is the major oxidative pathway of alcohol metabolism in the liver, as 90% of ethanol is metabolized through this pathway. Ethanol is initially oxidized by alcohol dehydrogenase (ADH) to acetaldehyde in the hepatocyte (13). Acetaldehyde is a highly toxic molecule that can build up before it is metabolized to acetate by mitochondrial acetaldehyde dehydrogenase (ALDH) (18-20).

This oxidation process involves an intermediate carrier of electrons, nicotinamide adenine dinucleotide (NAD^+), which is reduced to form NADH. As a result, alcohol oxidation generates a highly reduced cytosolic environment in hepatocytes and hepatocytes become vulnerable to tissue injury by free radicles.



2. Cytochrome P450 2E1 Pathway:

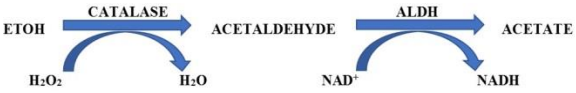
The cytochrome P450 system is also intimately involved in the metabolism of alcohol; more specifically the cytochrome P450 2E1 (CYP2E1) isoenzyme is involved (21). About 10% of ethanol oxidation occurs in the microsomal cytochrome P450 CYP2E1. CYP2E1 is upregulated in response to chronic alcohol intake which leads to an increased production of free radicals through oxidation of nicotinamide adenine dinucleotide phosphate (NADPH) to $NADP^+$ (22).



3. Catalase Pathway:

Catalase has a minor role in oxidation of ethanol. Located in peroxisomes, catalase is capable of oxidizing ethanol in vitro in the

presence of a hydrogen peroxide (H_2O_2) - generating system, such as the enzyme complex NADPH oxidase or the enzyme xanthine oxidase.



Consequences of Alcohol Metabolism:
The damage to hepatocytes is caused by these inter-related pathways.

A. Increase in the NADH/NAD$^+$ ratio:
Both, alcohol dehydrogenase and acetaldehyde dehydrogenase, cause a reduction of NAD^+ to NADH (21). This leads to an increase in the NADH/NAD^+ ratio in the hepatocyte, which promotes lipogenesis and decreases gluconeogenesis and fatty acid oxidation (21). Increased lipogenesis in hepatocytes leads to fat accumulation (steatosis) throughout hepatocytes and liver parenchyma.

B. Acetaldehyde adducts:
Furthermore, the intermediate acetaldehyde can easily form adducts with hepatocyte proteins which can cause conformational changes and dysfunction in those proteins (22). Acetaldehyde also induces inflammation in hepatocytes by causing direct activation of transforming growth factor beta (TGF-β). TGF-β then goes on to induce fibrosis by activating hepatic stellate cells (23).

C. Increased free radicals:
CYP2E1 is upregulated in response to chronic alcohol intake which leads to increased production of free radicals through oxidation of NADPH to $NADP^+$ (22). The increased free radicals cause depletion of glutathione leading to more rapid adverse effects. Injury is induced by these free radicals by lipid peroxidation in cell and organelle membranes. The endoplasmic reticulum and mitochondria are especially affected ultimately leading to hepatocyte death (13).

D. Hypoxia:
NADH is a major byproduct of alcohol metabolism, which is later oxidized in mitochondria and generates metabolic water by binding molecular oxygen and protons. Hepatocytes, in close proximity to this chemical reaction, take up more oxygen, resulting in decreasing arterial oxygen supply to distally located cells. Thus, peri-venular hepatocytes are first to have hypoxic damage due to alcohol consumption (24, 25).

In addition, ethanol directly activates Kuppfer cells resulting in increased consumption of oxygen. Activated Kuppfer cells release many stimulatory cytokines including prostaglandin E2, which increases the metabolic activity of hepatocytes. Many essential molecules are broken down and formed because of activation of chemical reactions requiring oxygen, resulting in worsening of hypoxia induced cell damage to hepatocytes (26).

E. Alcohol induced gut permeability with endotoxemia and inflammatory cascade:
Recent research on the effects of alcohol has elucidated its effect on the gut microbiome and the alteration in the delicate balance among pathogenic and commensal organisms (27). Alcohol disrupts the intestinal mucosal barrier and allows lipopolysaccharide (LPS) from gram-negative bacteria to be absorbed more easily and enter the portal circulation (13). Once at the liver, the LPS can cause activation of Kupffer cells and a signaling cascade through Toll-Like-Receptor-4 (TLR4) (28). TLR4 activation leads to the production and secretion of pro-inflammatory cytokines

such as IL-1, IL-6, and tumor necrosis factor alpha (TNF-α) (13). These cytokines have been shown to act on hepatocytes and surrounding hepatic structural cells to contribute to inflammatory and fibrogenic processes (13).

DIAGNOSIS OF AH

Even though AH is a clinical diagnosis and there is no universally accepted diagnostic criteria, the diagnosis in patients comes down to documentation of excess alcohol use and evidence of liver disease (29).

History:

Even with exam and laboratory findings suggestive of liver sequelae, alcohol abuse should be elucidated and documented to diagnose AH. The simplest way to do this is to talk to patients about previous and current alcohol use practices. Unfortunately, many patients are not forth-coming about their alcohol use, so certain screening practices have been developed to identify these patients. The CAGE questionnaire is a four-question screening test that is widely used among practitioners to identify alcohol use in patients (30). A meta-analysis found the CAGE questionnaire to have a sensitivity and specificity of 0.71 and 0.95, respectively (30). The AUDIT questionnaire is also an acceptable alternative to screen for alcohol use disorders, but is more cumbersome to perform. The initial step in diagnosing AH is to screen patients for alcohol use by means of talking with them or administering screening questionnaires, which can initiate communication between patient and provider.

Physical Finding:

In terms of physical exam findings, patients may range from no exam findings to those seen in advanced liver disease. Further, physical exam features generally have low sensitivity, even for the detection of advanced liver disease or cirrhosis (10). However, some exam findings are more commonly seen in liver disease caused by alcohol, such as parotid enlargement, Dupuytren's contracture, and feminization in males (31). AH has considerable overlap with other liver disease etiologies and they share common nonspecific symptoms, such as: anorexia, weight loss, abdominal pain, abdominal distention, fatigue, nausea, and vomiting (21). More advanced liver disease, or decompensated AH, may present with symptoms, such as jaundice, ascites, spider angiomas, fever, and encephalopathy (21).

Laboratory Findings:

Laboratory findings may give clues to alcohol as the underlying etiology. The serum AST is commonly 2-6 times the upper limit of normal. Further, in 70% of patients the AST/ALT ratio is usually greater than 2; ratios greater than 3 are even more suggestive of AH (10, 32-34).

Imaging & Liver Biopsy:

To further elucidate the diagnosis of AH, imaging studies and liver biopsy can be helpful, but are not usually warranted. Imaging studies can confirm the presence of underlying liver disease, but cannot point to a specific etiology (10). Thus, imaging can be used to rule out other causes of hepatic injury, such as thrombosis or carcinoma. Moreover, liver biopsy is useful in establishing the diagnosis of AH but is not necessary for the management of AH (35). Biopsy results vary among AH patients depending on the extent and stage of hepatic injury determined by alcohol use and duration (10). Common pathological findings include: steatosis, lobular neutrophilic inflammation, periportal fibrosis, Mallory bodies (aggregates of cytokeratin intermediate filaments), nuclear vacuolation, bile duct proliferation, and

fibrosis or cirrhosis (36). Luckily, biopsy findings may indicate some prognostic factors. The severity of inflammation and cholestatic changes correlate with increasingly poor prognosis and may predict response to treatment (37, 38). Further, mega-mitochondria seen on biopsy may be associated with a milder form of AH, lower incidence of cirrhosis, and fewer complications with good long-term survival (39). Even though pathologic findings may provide prognostic value, management and treatment of AH is not affected by these biopsy results.

Current recommendations set forth by the American Association for the Study of Liver Diseases (AASLD) regarding diagnosis of AH state that clinicians should initially screen patients for alcohol use disorders. If an alcohol use disorder is identified, the patient should then have laboratory testing done to exclude other causes of liver injury. Once alcohol has been established as the culprit of the hepatic injury, patients should then be screened for evidence of other end-organ damage. In patients where a clinical diagnosis is uncertain, or for patients with severe AH where medical therapy is being considered, a liver biopsy is recommended to further clarify the etiology, severity, and prognostic factors (10).

PROGNOSTIC ALGORITHMS

Several models are available to predict disease severity, survival, and treatment response in hepatic injury.

Maddrey's discriminant function:

One of the most widely accepted models is the Maddrey's discriminant function (MDF) (40). An MDF greater than 32 has been shown to have a short-term mortality around 20-50% at one month (3).

Maddrey's Discriminant Function: 4.6 * (Prothrombin time of patient – Prothrombin time of control) + serum bilirubin mg/dL

Model for End-Stage Liver Disease:

Another commonly used scoring system is the Model for End-Stage Liver Disease (MELD) (13). A MELD score greater than 21 has a sensitivity of 75% and a specificity of 75% in predicting 90-day mortality (41). MELD incorporates 3 widely available laboratory variables including the international normalized ratio (INR), serum creatinine, and serum bilirubin. The original mathematical formula for MELD is:

MELD = 9.57 × log (creatinine) + 3.78 × Log (total bilirubin) + 11.2 × Log (INR) + 6.43

The score can be calculated on handheld computing devices, and is available at www.mayoclinic.org/gi-rst/mayomodel5.html

Lille model:

If patients are undergoing treatment for AH, the Lille model can be used to guide treatment decisions and effectiveness (13, 42). Based on the Lille score, corticosteroid treatment (the mainstay of treatment for AH) can be stopped in patients with no improvement in Lille score after a week of therapy and alternative treatment options should be sought (13, 43).

Lille Score : 3.19 – 0.101 * (age in years) + 0.147 * (albumin day 0 in g/L) +0.0165 *(evolution in bilirubin level in M) - (0.206 * renal insufficiency) - 0.0065 * (bilirubin day 0 in M) -0.0096 * (PT).

TREATMENT OF AH

Although AH has been a major problem for many decades there have been few advances in the treatment of this disease.

Abstinence from alcohol and supportive care:

It has been shown time and time again that abstinence from alcohol is the most important treatment in patients with AH (44). If a patient is willing to undergo abstinence from alcohol, a multidisciplinary team of hepatologists, psychologists, psychiatrists, social workers, and other health care team members is highly recommended (45).

In addition, there are many medications that can be implemented to help patients abstain from alcohol use. A recent meta-analysis showed that both, acamprosate and oral naltrexone, were equally efficacious in reducing the number of patients who returned to drinking (46). If medications are to be used, the specific medication should be tailored to the patient based on physician comfort level, side effect profile, availability, and cost (46). In patients who abstained from alcohol, one study found that three-year survival approaches 90% and survival was less than 70% in those who did not abstain (21, 47). Once patients have abstained from alcohol, if their disease is still active, the MDF should be calculated to determine whether treatment will be beneficial. If a patient has an MDF score of <32 without hepatic encephalopathy, or a MELD score of <18, then treatment consideration is less urgent (10). These patients will likely improve spontaneously with abstinence from alcohol and supportive care (10). This spontaneous improvement is more likely in patients whose scores improve during hospitalization or who have a decrease in total bilirubin level (10).

Corticosteroids:

For patients on the opposite end of the spectrum with MDF scores that indicate treatment (MDF >32), corticosteroids are the mainstay of treatment. Recommendations set forth by the AASLD are to prescribe patients prednisolone (40 mg/day for 4 weeks then taper over 2-4 weeks) (10, 48). Although, corticosteroids are currently recommended, there is much debate about their efficacy and whether side effects may outweigh the benefits. A recent meta-analysis compared the use of glucocorticoids to placebo and found no benefit in clinical outcomes for patients on prescribed steroids (49). This meta-analysis did have high risk of bias and low quality of evidence but at the very least it demonstrates the controversy surrounding corticosteroid use and the need for higher quality studies regarding AH treatment (49). Moreover, the recent STOPAH Trial showed that prednisolone improved 28-day mortality, but this did not reach statistical significance, and showed no improvement in mortality at 90 days or 1 year (50). Thus, there is conflicting data about whether corticosteroids are the most efficacious treatment for patients with AH, but it is the best option clinicians currently have.

In addition, it is important to keep in mind that patients with AH can have many comorbidities associated with alcohol and the use of corticosteroids has not been fully evaluated in patients with pancreatitis, gastrointestinal bleeding, renal failure, or active infection (10). In patients with these associated comorbidities the risks and benefits should be fully explained and weighed before treatment is initiated. If corticosteroid therapy is initiated, the patients' laboratory markers and Lille Score should be closely followed. After seven days of therapy, if the Lille score is <0.45 then the corticosteroids should be continued for the full course (44). However, if the Lille

score is >0.45, or if the patient's bilirubin is static or increasing after seven days of therapy, the corticosteroids are not beneficial and the risks of infection outweigh the benefits and alternative therapies should be sought (44).

Pentoxifylline:

Newer experimental treatment options are aimed at targeting specific cytokines and inflammatory markers involved in the pathophysiology of AH. Pentoxifylline, a TNF-α inhibitor, has been found to lead to a reduction in the development of hepatorenal syndrome (HRS). A randomized placebo controlled clinical trial investigated pentoxifylline in 101 hospitalized patients with severe AH (51). This study found that in-hospital mortality was 40% lower in the pentoxifylline arm compared to placebo because of a lower likelihood of developing HRS leading to death (10, 51). Currently, the AASLD guidelines recommend pentoxifylline for patients with severe AH (MDF >32) and the recommended dose is 400mg orally 3 times daily for 4 weeks (10). This therapy is especially recommended in patients in whom steroid therapy is not effective or with contraindications to steroid use (10, 52).

Even though pentoxifylline is recommended by the AASLD guidelines, the STOPAH trial showed that pentoxifylline did not improve mortality in patients with AH at 28 days, 90 days, or 1 year. (50). Furthermore, in a select subset of patients who do not respond to corticosteroids, pentoxifylline has traditionally been the alternative treatment. However, a recent study by Louvet et al., demonstrated that switching to pentoxifylline early in the course of treatment in patients who do not respond to corticosteroids showed no difference in mortality outcomes (53). This trial showed that in non-responders there was no difference in mortality outcomes with continuing corticosteroids, discontinuing corticosteroids, or switching to pentoxifylline early on. (53). There are many conflicting studies and recommendations regarding the use of pentoxifylline, and unfortunately there is no clear answer as to its effectiveness. Sadly, patients who do not respond to corticosteroids are particularly disadvantaged because there is no effective treatment.

N-acetylcysteine:

N-acetylcysteine (NAC) has also shown benefit in the treatment of AH. A recent randomized clinical trial examined the use of combination therapy of corticosteroids and NAC compared to corticosteroids alone. The study found that patients in the NAC plus corticosteroid group had improved one-month survival and had lower rates of infection and hepatorenal syndrome; however, there was no difference in survival at six months (54). While these are promising results, larger studies are needed before these treatments become standard of care.

Liver transplantation:

The definitive cure for AH is liver transplantation. This life-saving intervention is reserved for patients when medical treatment has failed or is contraindicated because of organ scarcity and the increased risk of alcohol relapse in this population (55). Most liver transplant centers require a minimum six months of abstinence before a patient can begin the work-up for transplantation. The six-month abstinent period lacks evidence as a predictor of long-term sobriety (56). Interestingly, the duration of abstinence before undergoing transplant does not appear to correlate with post-transplant survival. Studies have shown that there is not a significant difference

between early alcohol use in transplanted patients with AH versus non-alcoholic liver disease. Sadly, at 7 years post-liver transplant, 32% of patients with previous AH reported using alcohol (57). Unfortunately, data for long term follow-up of abstinence in liver transplant patients requires further investigation (52). Thus, the potentially curative liver transplant is reserved for patients in whom medical management has failed because of the high rate of alcohol relapse and the scarcity of donors.

Recently, there has been a flurry of activity surrounding new therapeutic options for the management and treatment of AH.

Probiotics:

Probiotics are an area of interest because patients with AH have been shown to have increased bacterial overgrowth, intestinal mucosal damage, increased gut permeability, and associated endotoxemia because of this increased permeability (52). Certain probiotics have shown decreased ALT, AST, lactate dehydrogenase, and partial restoration of gut flora (52). Furthermore, AH patients have increased levels of inflammatory cytokines and probiotics have been shown to reduce overall inflammatory cytokine burden leading to decreased liver disease severity and hospitalizations (58, 59). With all of this excitement regarding probiotic use, these results were from initial studies and much more research is needed into these therapies before they become mainstream.

Stem cell therapy:

One of the most exciting advancements has been in the realm of stem cell therapy. Laboratory studies have shown that granulocyte colony-stimulating factor (G-CSF) can mobilize bone marrow stem cells to hepatic injury and cause differentiation into hepatocytes (60). A small study of 46 patients with severe AH were randomized to receive G-CSF for 5 days with standard medical therapy (consisting of pentoxifylline with nutrition) vs standard medical therapy. Results from the study showed an improvement in the patients Child Pugh score, MELD, and MDF for up to three months (61). While these results are promising, larger studies are needed to assess the overall efficacy of this treatment in AH patients.

Extracorporeal human hepatic cell-based liver treatment system:

One of the most promising advancements is the Extracorporeal human hepatic cell-based liver treatment system (ELAD). ELAD is currently undergoing Phase 3 clinical trials and has shown promising results thus far (62). Unfortunately, ELAD has only been tested in trials with stringent inclusion criteria so the available results are not generalizable. Moreover, ELAD comes with a high cost and requires specially trained staff, usually in an intensive care unit.

Despite potential therapies and exciting results, treating AH has remained difficult. Even though there is debate over the use of corticosteroids and pentoxifylline, these medications are currently the first-line treatments.

CONCLUSION

Alcoholic hepatitis is an all-to-common disease for the hospitalist. The main risk factor for development of this disease is alcohol use and there is a direct correlation between alcohol intake and the development of AH. The by-products of alcohol metabolism lead directly to hepatocyte damage, apoptosis, and activation of reparative, inflammatory, and fibrogenic processes. Even with the explosion of research, there has been little change in the

management and treatment of AH. Abstinence from alcohol, corticosteroids, and proper nutrition are the mainstay of treatment for this disease. There are many theoretical treatment options on the horizon, but unfortunately none have been proven more effective thus far.

Notes

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References:

1. Zakhari S, Li TK. Determinants of alcohol use and abuse: Impact of quantity and frequency patterns on liver disease. Hepatology. 2007;46(6):2032-9.
2. Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. Lancet. 2009;373(9682):2223-33.
3. Crabb DW, Bataller R, Chalasani NP, Kamath PS, Lucey M, Mathurin P, et al. Standard Definitions and Common Data Elements for Clinical Trials in Patients With Alcoholic Hepatitis: Recommendation From the NIAAA Alcoholic Hepatitis Consortia. Gastroenterology. 2016;150(4):785-90.
4. McPherson S, Lucey MR, Moriarty KJ. Decompensated alcohol related liver disease: acute management. BMJ. 2016;352:i124.
5. White AM, Hingson RW, Pan IJ, Yi HY. Hospitalizations for alcohol and drug overdoses in young adults ages 18-24 in the United States, 1999-2008: results from the Nationwide Inpatient Sample. J Stud Alcohol Drugs. 2011;72(5):774-86.
6. Dugum MF, McCullough AJ. Acute Alcoholic Hepatitis, the Clinical Aspects. Clin Liver Dis. 2016;20(3):499-508.
7. Bataller R, North KE, Brenner DA. Genetic polymorphisms and the progression of liver fibrosis: a critical appraisal. Hepatology. 2003;37(3):493-503.
8. Grant BF, Dufour MC, Harford TC. Epidemiology of alcoholic liver disease. Semin Liver Dis. 1988;8(1):12-25.
9. Day CP. Alcohol and the liver. Medicine.35(1):22-5.
10. O'Shea RS, Dasarathy S, McCullough AJ, Practice Guideline Committee of the American Association for the Study of Liver D, Practice Parameters Committee of the American College of G. Alcoholic liver disease. Hepatology. 2010;51(1):307-28.
11. Mandayam S, Jamal MM, Morgan TR. Epidemiology of alcoholic liver disease. Semin Liver Dis. 2004;24(3):217-32.
12. Kumar V, Abbas AK, Aster JC. Robbins & Cotran Pathologic Basis of Disease E-Book: Elsevier Health Sciences; 2014.
13. Torok NJ. Update on Alcoholic Hepatitis. Biomolecules. 2015;5(4):2978-86.
14. Stinson FS, Grant BF, Dufour MC. The critical dimension of ethnicity in liver cirrhosis mortality statistics. Alcohol Clin Exp Res. 2001;25(8):1181-7.
15. 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(3):635-41.
16. Leevy CM, Moroianu SA. Nutritional aspects of alcoholic liver disease. Clin Liver Dis. 2005;9(1):67-81.
17. Mezey E. Dietary fat and alcoholic liver disease. Hepatology. 1998;28(4):901-5.
18. Tuma DJ, Casey CA. Dangerous byproducts of alcohol breakdown--focus on adducts. Alcohol Res Health. 2003;27(4):285-90.
19. Viitala K, Makkonen K, Israel Y, Lehtimaki T, Jaakkola O, Koivula T, et al. Autoimmune responses against oxidant stress and acetaldehyde-derived epitopes in human alcohol consumers. Alcohol Clin Exp Res. 2000;24(7):1103-9.
20. Thiele GM, Klassen LW, Tuma DJ. Formation and immunological properties of aldehyde-derived protein adducts following alcohol consumption. Methods Mol Biol. 2008;447:235-57.
21. Fairbanks KD. Alcoholic Liver Disease. Cleve Clin J Med. 2012.
22. Stewart S, Jones D, Day CP. Alcoholic liver disease: new insights into mechanisms and preventative strategies. Trends Mol Med. 2001;7(9):408-13.
23. Ceni E, Mello T, Galli A. Pathogenesis of alcoholic liver disease: role of oxidative metabolism. World J Gastroenterol. 2014;20(47):17756-72.
24. Arteel G, Thurman RG, Yates JM, Raleigh JA. Evidence that hypoxia markers detect oxygen gradients in liver: pimonidazole and retrograde perfusion of rat liver. Br J Cancer. 1995;72(4):889-95.

25. Ishak KG, Zimmerman HJ, Ray MB. Alcoholic liver disease: pathologic, pathogenetic and clinical aspects. Alcohol Clin Exp Res. 1991;15(1):45-66.
26. Thurman RG. II. Alcoholic liver injury involves activation of Kupffer cells by endotoxin. Am J Physiol. 1998;275(4 Pt 1):G605-11.
27. Yan AW, Fouts DE, Brandl J, Starkel P, Torralba M, Schott E, et al. Enteric dysbiosis associated with a mouse model of alcoholic liver disease. Hepatology. 2011;53(1):96-105.
28. Chen P, Starkel P, Turner JR, Ho SB, Schnabl B. Dysbiosis-induced intestinal inflammation activates tumor necrosis factor receptor I and mediates alcoholic liver disease in mice. Hepatology. 2015;61(3):883-94.
29. Levitsky J, Mailliard ME. Diagnosis and therapy of alcoholic liver disease. Semin Liver Dis. 2004;24(3):233-47.
30. Aertgeerts B, Buntinx F, Kester A. The value of the CAGE in screening for alcohol abuse and alcohol dependence in general clinical populations: a diagnostic meta-analysis. J Clin Epidemiol. 2004;57(1):30-9.
31. Cozzolino G, Francica G, Lonardo A, Cerini R, Cacciatore L. [Variability of the clinical and laboratory aspects in the presentation of chronic liver diseases in relation to their etiology. Analysis of a case study and review of the literature]. Minerva Med. 1985;76(16):753-60.
32. Nanji AA, French SW, Mendenhall CL. Serum aspartate aminotransferase to alanine aminotransferase ratio in human and experimental alcoholic liver disease: relationship to histologic changes. Enzyme. 1989;41(2):112-5.
33. Niemela O. Biomarkers in alcoholism. Clin Chim Acta. 2007;377(1-2):39-49.
34. Nyblom H, Berggren U, Balldin J, Olsson R. High AST/ALT ratio may indicate advanced alcoholic liver disease rather than heavy drinking. Alcohol Alcohol. 2004;39(4):336-9.
35. Bird GL. Investigation of alcoholic liver disease. Baillieres Clin Gastroenterol. 1993;7(3):663-82.
36. Lefkowitch JH. Morphology of alcoholic liver disease. Clin Liver Dis. 2005;9(1):37-53.
37. Mathurin P, Duchatelle V, Ramond MJ, Degott C, Bedossa P, Erlinger S, et al. Survival and prognostic factors in patients with severe alcoholic hepatitis treated with prednisolone. Gastroenterology. 1996;110(6):1847-53.
38. Nissenbaum M, Chedid A, Mendenhall C, Gartside P. Prognostic significance of cholestatic alcoholic hepatitis. VA Cooperative Study Group #119. Dig Dis Sci. 1990;35(7):891-6.
39. Chedid A, Mendenhall CL, Tosch T, Chen T, Rabin L, Garcia-Pont P, et al. Significance of megamitochondria in alcoholic liver disease. Gastroenterology. 1986;90(6):1858-64.
40. Carithers RL, Jr., Herlong HF, Diehl AM, Shaw EW, Combes B, Fallon HJ, et al. Methylprednisolone therapy in patients with severe alcoholic hepatitis. A randomized multicenter trial. Ann Intern Med. 1989;110(9):685-90.
41. Dunn W, Jamil LH, Brown LS, Wiesner RH, Kim WR, Menon KV, et al. MELD accurately predicts mortality in patients with alcoholic hepatitis. Hepatology. 2005;41(2):353-8.
42. Louvet A, Naveau S, Abdelnour M, Ramond MJ, Diaz E, Fartoux L, et al. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. Hepatology. 2007;45(6):1348-54.
43. Mathurin P, Lucey MR. Management of alcoholic hepatitis. J Hepatol. 2012;56 Suppl 1:S39-45.
44. Farooq MO, Bataller R. Pathogenesis and Management of Alcoholic Liver Disease. Dig Dis. 2016;34(4):347-55.
45. Sandahl TD, Jepsen P, Thomsen KL, Vilstrup H. Incidence and mortality of alcoholic hepatitis in Denmark 1999-2008: a nationwide population based cohort study. J Hepatol. 2011;54(4):760-4.
46. Jonas DE, Amick HR, Feltner C, Bobashev G, Thomas K, Wines R, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA. 2014;311(18):1889-900.
47. Alexander JF, Lischner MW, Galambos JT. Natural history of alcoholic hepatitis. II. The long-term prognosis. Am J Gastroenterol. 1971;56(6):515-25.
48. Uribe M, Schalm SW, Summerskill WH, Go VL. Oral prednisone for chronic active liver disease: dose responses and bioavailability studies. Gut. 1978;19(12):1131-5.
49. Pavlov CS VD, Casazza G, Tsochatzis E, Nikolova D, Gluud C. . Glucocorticoids for people with alcoholic hepatitis. Cochrane Database of Systematic Reviews. 2017;2017(11).
50. Thursz MR, Richardson P, Allison M, Austin A, Bowers M, Day CP, et al. Prednisolone or pentoxifylline for alcoholic hepatitis. N Engl J Med. 2015;372(17):1619-28.
51. Akriviadis E, Botla R, Briggs W, Han S, Reynolds T, Shakil O. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. Gastroenterology. 2000;119(6):1637-48.
52. Fung P, Pyrsopoulos N. Emerging concepts in alcoholic hepatitis. World J Hepatol. 2017;9(12):567-85.
53. Louvet A, Diaz E, Dharancy S, Coevoet H, Texier F, Thevenot T, et al. Early switch to

pentoxifylline in patients with severe alcoholic hepatitis is inefficient in non-responders to corticosteroids. J Hepatol. 2008;48(3):465-70.
54. Nguyen-Khac E, Thevenot T, Piquet MA, Benferhat S, Goria O, Chatelain D, et al. Glucocorticoids plus N-acetylcysteine in severe alcoholic hepatitis. N Engl J Med. 2011;365(19):1781-9.
55. Mackie J, Groves K, Hoyle A, Garcia C, Garcia R, Gunson B, et al. Orthotopic liver transplantation for alcoholic liver disease: a retrospective analysis of survival, recidivism, and risk factors predisposing to recidivism. Liver Transpl. 2001;7(5):418-27.
56. Beresford TP, Everson GT. Liver transplantation for alcoholic liver disease: bias, beliefs, 6-month rule, and relapse--but where are the data? Liver Transpl. 2000;6(6):777-8.
57. Bravata DM, Olkin I, Barnato AE, Keeffe EB, Owens DK. Employment and alcohol use after liver transplantation for alcoholic and nonalcoholic liver disease: a systematic review. Liver Transpl. 2001;7(3):191-203.
58. Loguercio C, Federico A, Tuccillo C, Terracciano F, D'Auria MV, De Simone C, et al. Beneficial effects of a probiotic VSL#3 on parameters of liver dysfunction in chronic liver diseases. J Clin Gastroenterol. 2005;39(6):540-3.
59. Dhiman RK, Rana B, Agrawal S, Garg A, Chopra M, Thumburu KK, et al. Probiotic VSL#3 reduces liver disease severity and hospitalization in patients with cirrhosis: a randomized, controlled trial. Gastroenterology. 2014;147(6):1327-37 e3.
60. Theocharis SE, Papadimitriou LJ, Retsou ZP, Margeli AP, Ninos SS, Papadimitriou JD. Granulocyte-colony stimulating factor administration ameliorates liver regeneration in animal model of fulminant hepatic failure and encephalopathy. Dig Dis Sci. 2003;48(9):1797-803.
61. 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(9):1417-23.
62. Randomized, Open-Label, Multicenter, Controlled, Pivotal Study to Assess Safety and Efficacy of ELAD in Subjects w/ AILD.