ALCOHOLIC LIVER DISEASE: A COMPREHENSIVE REVIEW

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ABSTRACT

Alcoholic liver disease, a leading cause of morbidity, mortality, and cirrhosis, can range from simple steatosis to hepatocellular carcinoma. Multiple mechanisms such as oxidative stress, mitochondrial dysfunction, and alteration in gut-liver axis have been proposed for the pathogenesis of alcoholic liver disease. Based on different prognostic models, alcoholic hepatitis patients can be stratified into sub-groups and specific pharmacological therapy can be started. Alcohol abstinence has a clear cut mortality benefit and nutritional support is very important as most of the patients are malnourished and in a hypercatabolic state. Other than conventional glucocorticoids and pentoxifylline, newer agents and combination therapy can be used in severe alcoholic hepatitis in patients not responsive to conventional glucocorticoid therapy. Liver transplantation improves survival in advanced alcoholic cirrhosis and it can be an option in severe alcoholic hepatitis patients who are not responding to other medical therapies. Whether early transplantation can improve the survival compared with the conventional waiting period of 6 months is an active area of investigation. This is due to the fact that most of the disease-related mortality occurs in the first 2 months.

Keywords: Alcoholic hepatitis, alcoholic liver disease, cirrhosis, steatohepatitis, hepatocellular carcinoma (HCC), liver transplantation.

INTRODUCTION

Alcohol related toxicity is the third most common cause of morbidity[1] and the fifth most common cause of disease burden worldwide.[2] Alcohol abuse is the leading cause of mortality in people aged 15–49 years, and the total expenditure amounts to billions of dollars.[2] In developed countries, alcohol is the most common aetiology of cirrhosis.[3] The National Institute on Alcohol Abuse and Alcoholism recommends that both males and females should not drink more than 28 g and 14 g per day, respectively.[4]

NATURAL HISTORY OF ALCOHOLIC LIVER DISEASE

Histological abnormalities occurring in alcoholic liver disease can range from steatosis to hepatocellular carcinoma (HCC) (Figure 1):[5]

- Hepatic steatosis: 90–95% of heavy alcohol drinkers develop macrovesicular steatosis in the centrilobular area (Zone 3).[5] Patients are usually asymptomatic. Although reversible, cirrhosis may develop in 10% of heavy drinkers[6]
- Steatohepatitis: 10–35% of heavy drinkers develop necroinflammation along with steatosis, known as steatohepatitis or alcoholic hepatitis.[6] An estimated 40% of patients with alcoholic hepatitis develop alcoholic cirrhosis; this entity has high short-term mortality and can cause portal hypertension in the absence of cirrhosis[6-8]
- Cirrhosis: 8–20% of chronic alcoholics develop micronodular or Laennec's cirrhosis.[8] Secondary factors that accelerate the progression to cirrhosis are: patterns of alcohol drinking (chronic daily heavy drinkers more than binge drinkers),[9] female gender (due to low levels of gastric alcohol dehydrogenase, and higher body fat proportion and oestrogen levels),

obesity,[10] genetic polymorphisms,[11] and comorbid conditions such as infection with hepatitis B or C virus and/or human immunodeficiency virus and haemochromatosis[5,12]
- HCC: 1.5% of patients with cirrhosis of any aetiology develop HCC[13] and 3–10% of alcoholic cirrhosis patients ultimately develop HCC

PATHOGENESIS OF ALCOHOLIC LIVER DISEASE

Ethanol Metabolism

Alcohol is metabolised to acetaldehyde by both alcohol dehydrogenase (at low alcohol concentrations) and CYP2E1 (at higher concentrations, >10 mM), which is further metabolised by aldehyde dehydrogenase to acetate. Acetaldehyde forms protein adducts which causes hepatocyte injury directly or by autoimmune reaction.[14]

Oxidative Stress

Excess pro-oxidants (i.e. NAD phosphate oxidase and inducible nitric oxide synthase) in Kupffer cells, and a decrease in antioxidants (selenium, glutathione, vitamin E),[14,15] causes protein, lipid, and DNA oxidation, and causes direct cell injury by DNA damage, lipid peroxidation, and tumour necrosis factor (TNF) production signalling via nuclear factor kappa B.[14,15]

Mitochondrial Dysfunction

Hepatocyte mitochondria are devoid of catalase and are protected from oxidative stress by the transport of glutathione from cytosol, which is impaired in alcoholic liver disease.[16]

Hypoxia

In alcoholic liver disease, liver specific hypoxia inducible factors (HIF) are upregulated which leads to steatosis, and intestinal HIF is down regulated, which leads to increased intestinal permeability and endotoxaemia (this underscores the role of probiotics containing *Lactobacillus GG*, which preserve intestinal HIF).[17]

Impaired Proteasome Function

Impaired proteasome function leads to an accumulation of damaged protein in the cells known as Mallory–Denk bodies. Interleukin (IL)-8 and IL-18 from dead hepatocytes propagate hepatocyte injury.[18]

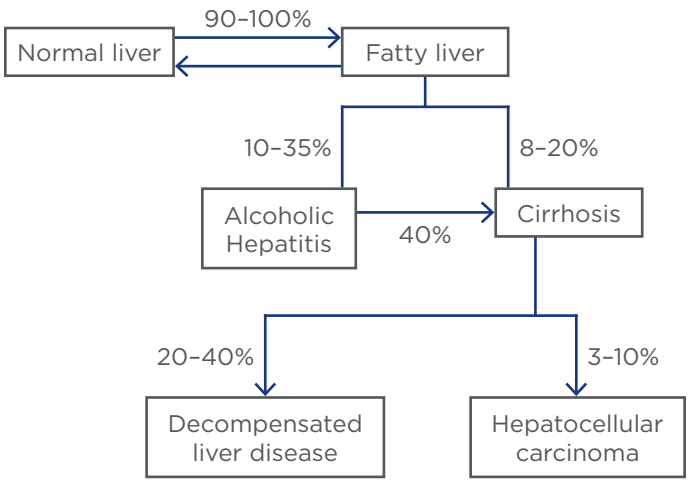

Figure 1: The spectrum of alcoholic liver disease. Percentages represent the proportion of patients who progress from one stage to the next.

Abnormal Metabolism of Methionine, S-Adenosylmethionine, and Folate

S-adenosylmethionine (SAMe) is produced from methionine catalysed by methionine adenosyltransferase (MAT), and is further converted into S-adenosylhomocysteine (SAH) and homocysteine, which are toxic to the liver. Methionine can be regenerated by betaine and folic acid via 5-methyltetrahydrofolate (5-MTHF). Reduced functional activity of MAT leads to deficiency of SAMe, which maintains levels of mitochondrial glutathione (an antioxidant).[19]

Gut-Liver Axis

Chronic alcoholism causes increased growth of gram negative bacteria and diminished levels of *Bifidobacterium spp*. and *Lactobacillus spp*.[20] in the gut, and also increases intestinal permeability by depletion of the zonula adherens protein, ZO-1, at the tight junctions. The lipopolysaccharides of gram negative bacteria cause activation of Toll-like receptors and increase production of cytokines like TNF in the liver; this results in hepatocyte injury.[14,20]

Fibrosis

Quiescent stellate cells are transformed into myofibroblasts (by tumour growth factor β via Toll-like receptor 4 signalling), which produces collagen. Impaired fibrinolysis and accumulation of extracellular fibrin in the sinusoids cause hepatocyte hypoxia and progressive fibrosis.[21]

Table 1: Alcohol content in different beverages.

Beverage	Volume (mL)	Alcohol content (g)
Whisky	30	10
Wine	100	10
Beer	250	10

DIAGNOSIS OF ALCOHOL ABUSE

Screening strategies are important as most patients are identified in the cirrhotic stage, and women of childbearing age, teenagers, and the elderly are often undiagnosed. Screening tools include the 3-item AUDIT-C (Alcohol Use Disorders Identification Test consumption questions); and the 4-item CAGE (need to Cut down, Annoyed by criticism, Guilty after drinking, need for an Eye-opener in the morning) questionnaire;[22,23] 10-item AUDIT; single question to identify risk drinking: 'How many times in the past year have you had x or more drinks a day?' (x=5 for men, 4 for women); and specific tools for pregnant women.[22,23]

There are several types of objective evidence used to diagnose alcohol abuse. These include blood and breath alcohol measurements, with the highest sensitivity and specificity being for recent drinking, but not for remote drinking due to the short half-life of ethanol. Another example is carbohydrate-deficient transferring, which has increased sensitivity when combined with mean corpuscular volume and gamma-glutamyl transpeptidase.[24] Phosphatidylethanol and ethyl glucuronide can also be used as a promising biomarker for recent alcohol abuse, and urinary ethyl glucuronide[25] is useful for monitoring in patients before and after liver transplant. Modern transdermal sensors are also used.[26]

DIAGNOSIS OF ALCOHOLIC LIVER DISEASE

History and Clinical Picture

The consumption of 40–80 g/day of alcohol in men and 20–40 g/day of alcohol in women for 10–12 years is required for significant risk of liver disease (Table 1).[4] Patients with fatty liver are asymptomatic at presentation, whereas most patients with alcoholic hepatitis present with jaundice and other constitutional symptoms.[27,28]

Clinically tender hepatomegaly, hepatic bruit (likely due to increased blood flow in hepatic artery), jaundice and ascites (in 60% of patients), and hepatic encephalopathy (in severe disease) can be seen in patients with alcoholic hepatitis. The liver becomes hard and smaller in size with progression of liver disease. Approximately 30% of cirrhotic patients have ascites.

In alcoholic cirrhosis, ascites is the initial pattern of decompensation compared with HCC in non-alcoholics, although ascites does not predict higher mortality, as in non-alcoholics.[27-29] The presence of stigmata of chronic liver disease in these patients (spider angioma, palmar erythema, gynecomastia, parotid and lacrimal gland enlargement, muscle wasting, and Dupuytren's contractures) usually suggests underlying alcoholic cirrhosis.[27,29]

Investigations

In alcoholic hepatitis, aspartate aminotransferase (AST) levels are <300 U/L, alanine aminotransferase (ALT) is only mildly elevated and the AST/ALT ratio is typically >2 (ALT synthesis in the liver requires pyridoxal phosphate, more so than AST synthesis). Alcoholic hepatitis is typically associated with elevations in serum hepatic alkaline phosphatase and gamma-glutamyl transpeptidase, and with hyperbilirubinaemia.[14,27,28]

Liver biopsy in alcoholic hepatitis shows swollen hepatocytes containing amorphous eosinophilic Mallory bodies surrounded by neutrophils,[7] and intra-sinusoidal fibrosis is characteristic, which can lead to sclerosing hyaline necrosis (i.e. obliteration of the terminal hepatic venules). Alcoholic cirrhosis is typically micronodular and may gradually transform to macronodular cirrhosis (indistinguishable from other forms of cirrhosis).[7]

Differential diagnosis

Differential diagnosis includes non-alcoholic fatty liver disease (patients who present with metabolic syndrome and a weekly alcohol intake of <21 drinks for men and <14 for women),[7,14] hereditary haemochromatosis (presence of *C282Y* and *H63D HFE* gene mutations and a hepatic iron index value >1.9 µMol/g per year, although it can occur in alcoholic cirrhosis and iron overload) and Budd–Chiari syndrome (for which Doppler ultrasound may be useful).[30] Amiodarone hepatotoxicity may also histologically resemble alcoholic liver disease.[14]

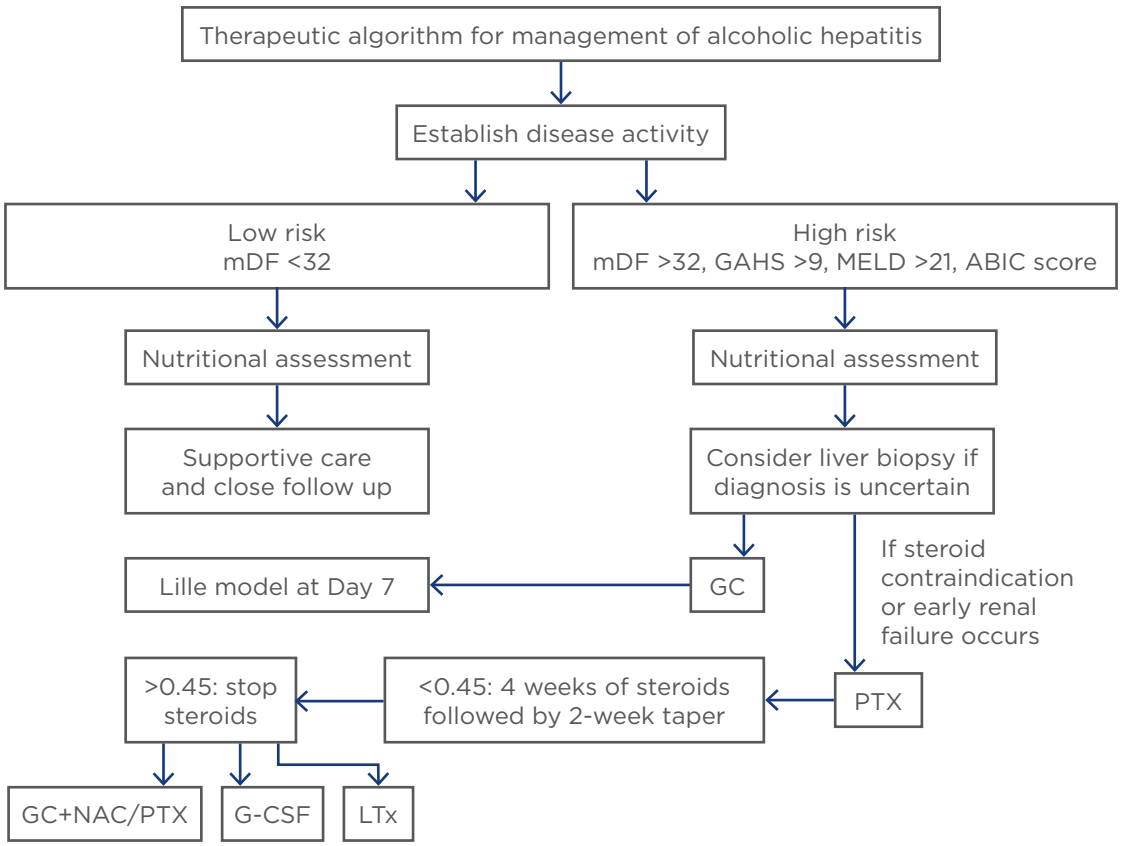

Figure 2: Therapeutic algorithm for management of alcoholic hepatitis.
mDF: Maddrey's discriminant function; GAHS: Glasgow Alcoholic Hepatitis Score; MELD: Model For End-Stage Liver Disease; ABIC: Age, serum Bilirubin, International normalised ratio, and serum Creatinine level; GC: glucocorticoids; NAC: N-acetyl cysteine; G-CSF: granulocyte colony stimulating factor; LTx: liver transplantation; PTX: pentoxifylline.

ASSESSING THE SEVERITY OF ALCOHOLIC HEPATITIS

A Maddrey's modified discriminant function (mDF = 4.6 × prothrombin time [PT] − control value [seconds]) + serum bilirubin [mg/dL]) value of >32 (which indicates severe alcoholic hepatitis and warrants corticosteroid treatment) and/or hepatic encephalopathy in patients without treatment has a 28-day survival rate of 65%.[31] Non-standardisation of PT is a limitation, depending upon the type of thromboplastin used.

A GAHS (Glasgow alcoholic hepatitis score) of ≥9 at Day 1 and 7 was more accurate than mDF in predicting survival at 28 days and 84 days but is not widely validated.[32] A MELD (model for end-stage liver disease) score (based on serum levels of bilirubin, creatinine, and international normalized ratio [INR]) of ≥21 (associated with a 90-day mortality rate of 20%) is the threshold for initiating corticosteroids and is helpful in patients with alcoholic hepatitis who are candidates for liver transplantation.[33,34] Based on ABIC (Age, serum Bilirubin, INR, and serum Creatinine level) score, patients can be stratified into low, intermediate, and high-risk, with 3-month survival rates of 90%, 70%, and 25%, respectively.[35]

The stopping rule for corticosteroids is based on bilirubin levels and can be determined by the Lille score. If it is >0.45 after 7 days of corticosteroids, then it should be stopped as they have higher 6-month mortality than in patients with a score of <0.45. However, the score cannot be calculated at onset.[36] So, physicians may utilise mDF and the Lille score for initiating corticosteroid treatment and for assessing treatment response to steroids in patients with alcoholic hepatitis, respectively (Figure 2).

ALCOHOLIC CIRRHOSIS

Five-year survival in alcoholic cirrhosis can be best predicted by Child–Pugh (CP) score

(based on serum bilirubin, albumin, PT, hepatic encephalopathy, and ascites; patients with cirrhosis can be stratified into groups A: 5–6; B: 7–8; or C: ≥9). One-year mortality in CP score A, B, and C are 15%, 25–30%, and 70–80% respectively.[33] One-year mortality is 30% in patients with alcoholic cirrhosis with ascites, 50% in those with ascites and variceal bleeding, and 65% in patients with hepatic encephalopathy.[14] Other prognostic models include the Beclere model (based on serum bilirubin, albumin, age, and hepatic encephalopathy) and MELD score (which predicts short-term survival and is used for allocation of donor livers).[14]

Acute-on-chronic liver failure can occur in stable compensated alcoholic cirrhosis, most commonly due to an increase in alcohol intake, acute viral infections (Hepatitis A, E, and B, and influenza A), and hepatotoxic drugs (paracetamol toxicity, idiosyncratic drug reactions, and herbal medicines).[37] The SOFA (sequential organ failure assessment) score can predict prognosis of hospitalised intensive care unit (ICU) patients; the 90-day mortality rate of patients who require ICU management for ≥3 failing organ systems due to infection, hepatic encephalopathy, sepsis, acute kidney injury, or multi-organ failure exceeds 90%.[38] In alcoholic liver disease, the chance of HCC is 2 to 3-times higher and co-existent hepatitis C virus (HCV) infection doubles the risk. The risk of HCC is higher in males and the elderly.[39]

TREATMENT

Abstinence from Alcohol

Alcohol abstinence improves liver histology and reduces the risk of a portal hypertensive bleed. Abstinence for 3 months leads to clinical improvement in 66% of patients and after 2 years, improvement is seen in laboratory parameters, such as muscle mass, and medications and diuretics can be stopped in some patients. Three years of abstinence increases survival rate to 70–80% (compared to 20–30% in those who drink heavily), but only 10% of patients maintain safe drinking after 1 year and 75% of patients relapse within a year.[40,41] Among the different medications available to treat alcohol dependence, disulfirum is the oldest, but has poor tolerability and there is little evidence that it increases abstinence. Short-term treatment with opioid antagonists such as naltrexone (available in injectable extended release form) is useful in lowering the risk of relapse. The $GABA_B$ receptor agonist, baclofen, is shown to improve abstinence and decrease relapse. Among these agents, baclofen is a relatively safe and effective agent (devoid of hepatotoxicity) in advanced cirrhosis, and is the most preferred mode of treatment.

N-methyl-D-aspartate receptor blockers are currently being investigated as a new pharmacological treatment. Alcohol abstinence support groups may also be helpful for alcohol cessation.[40-43] At the same time, the majority of patients classed as alcoholics also smoke. Smoking cessation decreases progression of hepatic fibrosis, risk of sepsis related deaths, risk of HCC, and post-transplant complications (such as hepatic artery thrombosis, cardiovascular complications, sepsis, and extrahepatic malignancies such as laryngeal, pharyngeal, and lung malignancy).[40,41,44]

Nutritional Support

Causes of malnutrition in alcoholic liver disease include the following:

- Poor oral intake
- Nausea and vomiting
- Diarrhoea and malabsorption
- Fasting for procedures, poor palatability of foods due to low salt (in ascites), and protein-restricted diet (in hepatic encephalopathy)
- Hypercatabolism
- Effects of cytokines
- Deficiencies of vitamins (B, A, D, and E) and micronutrients (magnesium, zinc, and selenium)
- Complications of liver disease, such as ascites and hepatic encephalopathy

Depletion of hepatic glycogen stores in cirrhotic patients leads to early starvation at 12 hours (which leads to peripheral muscle proteolysis after brief starvation), compared with 48 hours in normal individuals. Therefore, protein restriction should be limited to an initial 24–48 hours in hepatic encephalopathy. Branched-chain amino acids may be substituted for standard enteral formula if the latter causes hepatic encephalopathy.[45-47]

Bedside tests for malnutrition include handgrip strength, mid-arm muscle mass, SGA (subjective global assessment) based on wasting of muscles, oedema, subcutaneous fat loss, glossitis, and cheilosis. Pre-albumin and albumin better reflect the extent of liver disease than nutrition. Altered renal function and fluid retention make body mass index and the creatinine height index unreliable markers of malnutrition.[45-47] Both malnourishment

and obesity are poor outcome predictors in liver transplantation. Psoas muscle cross-sectional area determination by computed tomography scan is an objective method to predict poor outcomes in liver transplant patients with malnourishment.[45]

The risk of severe malnutrition in CP Class A and CP Class C cirrhosis is 45% and 95%, respectively. Even in patients with stable, compensated cirrhosis, malnutrition is associated with higher 1-year mortality (20% versus 0%) and complication rates (65% versus 13%).[44]

Nutritional Therapy in Alcoholic Hepatitis

In two large Veterans Administration studies, the 6-month mortality rate in severe alcoholic hepatitis correlated in a dose-response fashion with voluntary dietary intake. Despite this, two-thirds of the patients failed to consume the recommended caloric intake of 2,500 kcal/day. Therefore, there should be hesitation in placing a nasogastric feeding tube if the patient cannot voluntarily ingest at least 2,500 kcal/day, even when oesophageal varices are present. Glucocorticoid therapy can increase voluntary dietary intake, but providing adequate calories through enteral feeding provides the same 1-month survival benefit with significantly lower mortality at 1 year.[16,45-47]

TREATMENT OF ALCOHOLIC HEPATITIS

Glucocorticoids

In severe alcoholic hepatitis with mDF >32 or spontaneous hepatic encephalopathy (with no contraindications to steroids, no active gastrointestinal bleeding, serum creatinine ≤175 µmol/L, no active infectious process, or underlying chronic renal insufficiency), 28 days of methylprednisolone followed by a 2-week taper (Figure 2) reduced short-term mortality from 35% to 6%, and from 47% to 7% in patients who had hepatic encephalopathy at onset.[48,49] The interruption of treatment with corticosteroids can be based on Lille score. If the Lille score is >0.45 after 7 days of corticosteroid treatment, treatment should be stopped as 6-month survival is estimated at 25% contrary to patients with a Lille score below this cut-off (85%). The 2-month mortality of patients on glucocorticoid in most of the trials is 20–30%. In an active infection, glucocorticoid can be used if there is rapid clinical improvement (as shown in a prospective study), otherwise 25% of patients will not be considered for therapy.[50] Twenty-five percent of patients are steroid resistant, and have a 6-month survival rate of 25%.[50]

Pentoxifylline

In patients with severe alcoholic hepatitis, in whom glucocorticoids cannot be used, pentoxifylline is an effective alternative that has been shown to have short-term mortality (30-days) benefit, and to reduce incidence of hepatorenal syndrome.[51] Renal failure as a cause of death in patients with cirrhosis is remarkably low in the patients treated with pentoxifylline (10% compared with 70%).[51] In steroid non-responders (according to the Lille model), switching to pentoxifylline (Figure 2) rather than continuing glucocorticoid treatment does not increase short-term mortality.[52] In another head-to-head trial, pentoxifylline had lower short-term (2 months) mortality (15% compared with 35%) and incidence of hepatorenal syndrome, compared with glucocorticoids in patients with severe alcoholic hepatitis.[53] In a large (n=1103) multicentre, double-blind, randomised trial investigating whether prednisolone and/or pentoxifylline are effective in alcoholic hepatitis, pentoxifylline did not improve survival. Prednisolone was associated with a reduction in short-term mortality without any effect on intermediate and long-term mortality.[54]

Combination Therapy and Comparative Efficacy

Glucocorticoids plus N-acetyl cysteine therapy for 5 days have lower short-term (30 days) mortality compared with glucocorticoids alone, but had increased incidence of hepatorenal syndrome with no difference in medium-term mortality (90–180 days).[55] Glucocorticoids and pentoxifylline combination therapy have similar mortality but a lower incidence of hepatorenal syndrome as cause of death compared to glucocorticoids alone.[56] Comparative efficacy of pharmacological agents and network analysis has shown that in severe alcoholic hepatitis, glucocorticoid monotherapy or combination therapies and pentoxifylline reduce short-term mortality without any decrease in medium-term mortality.[57]

Newer Agents

In a new randomised, pilot study, granulocyte colony stimulating factor has emerged as a new promising therapy in severe alcoholic hepatitis, as it has been shown to improve liver function and 3-month survival (Figure 2).[57]

THERAPY FOR ALCOHOLIC CIRRHOSIS

None of the existing therapies (silymarin, SAMe, vitamin E, and pentoxifylline) improved survival in alcoholic cirrhosis other than abstinence.[14,40,41]

Liver Transplantation

Concurrent HCV infection, smoking, and destructive drinking after liver transplant reduce survival in post-transplant patients with alcoholic cirrhosis. However, advanced alcoholic cirrhosis patients not showing significant recovery after 3 months of alcohol abstinence are unlikely to survive without transplant and should be placed on the transplant waiting list (traditional 6-month waiting period in most transplant centres). A CP score >11 in spite of at least 6 months of abstinence have improved survival with liver transplantation,[14,59] and in CP Class B cirrhosis mortality increases with transplant due to the development of different malignancies in the postoperative period.[14]

In a study, early transplantation has been shown to improve survival in patients with their first episode of alcoholic hepatitis not responding to medical therapy (6-month survival rate of 30%, with most dying within 2 months), more than transplantation following the traditional 6-month waiting period (because of the fear of relapse of drinking and that they may respond to medical therapy or abstinence).[60]

CONCLUSION

In alcoholic liver disease, alcohol abstinence and nutritional support is of paramount importance as none of the pharmacological agents increase intermediate and long-term mortality. Alcoholic liver disease with sepsis and multi-organ dysfunction has dismal prognosis, so alcohol abuse should be diagnosed early. HCC surveillance should be done as in other causes of cirrhosis. Glucocorticoids and pentoxifylline either alone or in combination, along with other newer agents, can reduce short-term mortality but the long-term benefit is uncertain. Liver transplantation can substantially improve the survival in selected patients with alcoholic cirrhosis and severe alcoholic hepatitis that are resistant to all forms of therapy.

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