GI CLINICAL UPDATES

Issue - 2

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Editor
Gourdas Choudhuri

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ALCOHOLIC LIVER DISEASE

ISBN: 978-93-83988-28-0

Published by: Kontentworx, a division of KWX Communications Pvt. Ltd.

Medical Director: Dr Shveta Dhamija Khera

Director: Suketu Kothari

Registered Office: 12/402, GF, Sunder Vihar, Outer Ring Road, Paschim Vihar, New Delhi -110087, INDIA

Sold in India by: Vora Book Agency, Mumbai

Printed in India

Preface

Alcoholic Liver Disease constitutes a major clinical problem and management challenge for most hepatologists and physicians. While its frequency may vary from place to place across countries, regions and religious-ethnic groups it remains the most important cause of liver damage in several populations, as also the major health issue of most alcohol consumers.

This disease is a complex one for several reasons and raises questions that defy simple answers. Why do only some who consume alcohol go on to develop the serious forms of the disease while others do not? Is there a single measure of a toxic dose or duration that applies to all individuals? How does a family, friend or doctor recognize the beginning of a serious disease? How is it linked with the bio-psycho-social behavior of drinking? What is currently best available treatment for this disease?

Another reason why alcohol is and will remain a common health problem is due to its long history of usage by man across countries and its intertwining with cultures, having thereby acquired a degree of social acceptance and sanction. Any discussion on alcohol related liver injury therefore cannot evade addressing some aspects of habit and behavior, and their consequences on health.

This book has been compiled by contributions from acclaimed hepatologists of the country, who have extensive knowledge, experience and understanding of the disease. In this short easy reckoner handy volume for gastro-hepatologists and physicians, we have kept the discussion focused primarily on the toxic injury of alcohol on the liver, and tried to provide all the relevant information that doctors, fellows and medical student need to be versed with.

I commend Kontentworx, particularly Shveta Dhamija, for their efficiency and effort in putting together this volume of GI Clinical Update, and hope you will find it an useful comprehensive aid in understanding, recognizing and managing alcohol related Liver problems in your practice.

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Global and Indian Epidemiology of AUD: Alcohol Consumption and Addiction

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INTRODUCTION

Alcohol consumption has existed all over the world since ancient times and at present is ubiquitous, but patterns of alcohol use and its socioeconomic and health consequences have markedly changed in last few decades.[1] About 2.3 billion people in the world drink alcohol. And more than 50% people in Europe, North America, South America and western Pacific regions actively drink.

According to WHO global status report, harmful use of alcohol caused approximately 3 million deaths in 2016, about 5.3% of overall deaths in the world that year. Most of deaths were seen in males. Alcohol is supposed to be the fourth leading cause of preventable death in developed nations after smoking, Hypertension (HTN) and obesity. Harmful alcohol intake results in more deaths as compared to diabetes melitus (DM), HIV/AIDS, HTN and tuberculosis.[2]

Estimated economic cost of excessive alcohol intake was about $249 billion in year 2010, about $2.05 per drink.[3] Alcohol consumption is expected to increase further in future as well as associated harms like injuries, violence and other associated disease.[4]

In developed nations like united states alcohol level consumption seems to have stabilized while emerging trends shows that in developing countries alcohol consumption is increasing. Which serves as a warning to the developing world as consumption tends to rise with prosperity as in countries like Brazil, China, and India.[5]

ALCOHOL CONSUMPTION – PATTERN AND PREVALENCE

According to WHO global status report published in 2018 total alcohol per capita consumption is about 6.4 liters per year, about 13.9 grams of pure alcohol per day. However, there is wide variation in total alcohol consumption across the world. With few exceptions' highest per capita consumption of alcohol (10 liters or more) is seen in Europe. While relatively high (7.5–9.9 liter) intake are found in Americas and Western Pacific Region. Peoples in Eastern Mediterranean Region or other Muslim-majority countries have least (<2.5 liters) alcohol consumption.[2]

Alcohol is consumed by more than half of the population in three WHO regions – Europe (59.9% of current drinkers), Americas (54.1%) and the Western Pacific Region (53.8%). It is consumption is rapidly rising among adolescent and young adults with about 27% of all 15- to 19-year-olds consuming alcohol globally. Total alcohol per capita consumption has increased globally from 5.5 liters in 2005 to 6.4 liters in 2016. And this rise is mainly driven by increased consumption in India and China.

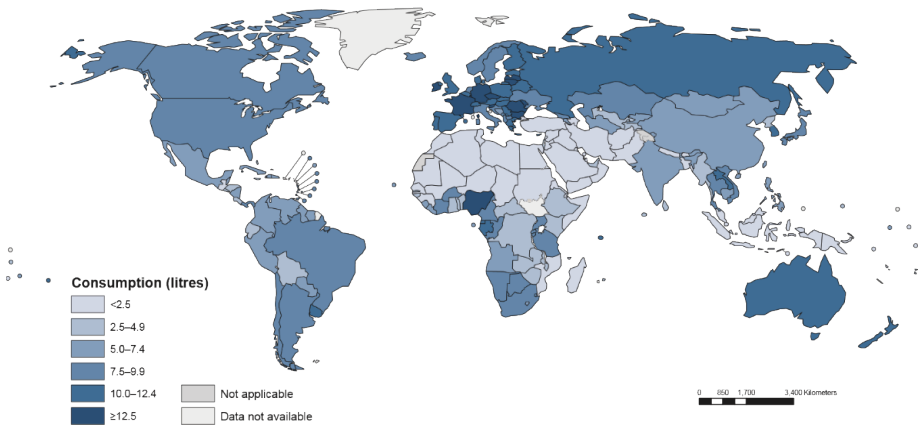

Figure 1. Total alcohol per capita consumption (>15 year; in liters of pure alcohol)

Source: WHO Global status report on alcohol and health

ALCOHOL CONSUMPTION IN INDIA

India is one of the fastest growing alcohol markets in the world. Rapid increase in urban population, sizeable middle-class population with rising spending power, and a sound economy are important reasons behind increase in consumption of alcohol in India.

Alcohol market in India is growing by 8.8% of annual growth rate and projected to reach 16.8 billion liter of alcohol consumption in 2022. Although India is one of the

largest consumers of alcohol in the world owing to its huge population, the per capita alcohol consumption of India is very low as compared to the Western countries.[6]

In year 2005 reported alcohol users in India was about 62.5 million while 17% of them were alcohol dependent.[7] In national household survey on drug use in India alcohol consumption was 21% among the adult male and 5% in females in year 2004.[8]

Alcohol per capita consumption (APC) in adult population has increased from 2.4 liters in 2005 to 5.7 liters in 2016. Males accounted for much higher consumption about 9.4 Lt as compared to 1.7 liters in female in year 2016. While per capita consumption among drinkers-only was 18.3 liters and 6.6 liters in male and female respectively for the same year. About 53.5% adults in India are life time abstainers (39.1% of males and 68.8% of females).[2]

Compared to western countries India has low alcohol consumption but this is mitigated by hazardous drinking pattern in India like heavy and binge drinking.[9] Further in last few decades alcohol consumption has increased markedly in India. Southeast Asia and India has recorded 50% and 106% increase in per person alcohol consumption respectively in last 3 decades.[8] Alcohol consumption is estimated to reach about 6.5 billion liters in 2020.[10]

Pattern of alcohol use and AUD varies across geographical regions in India. Ironically, significantly higher use has been recorded among tribal and lower socioeconomic urban areas.[11] Alcohol consumption is prohibited in states of Bihar, Gujarat, Nagaland and union territory of Lakshadweep. However, states of Andhra Pradesh, Telangana, Kerala, Karnataka, Sikkim, Haryana, Arunachal Pradesh and Himachal Pradesh are amongst the largest consumers of alcohol in India.

Alcohol consumption rates have been found lowest in western Gujarat (<7%), while highest consumption rate up to 75% seen in Arunachal Pradesh.[12] Reported prevalence of alcohol consumption from south India varies from 33%-50%.[8] Alcohol consumption has been reported to be as high as 66% in few areas like Kolkata slum areas.[13] In north India alcohol consumption is prevalent in 25-40% adult population.[14,15] A study reported prevalence of alcohol consumption among male and female in rural Tamil Nadu as 16.8% and 1.3%, respectively. Among drinkers, 56% patients have experienced harmful effects because of drinking.[16] Studies from central rural India have shown alcohol consumption to be up to 23.8% and 0.6% in males and females respectively. In Sikkim, among young population of more than 21 years alcohol consumption is present in about 35% which is much higher than the national average.[15]

Other socioeconomic factors also affect the alcohol consumption in India. Low use prevalence seen (<15%) among Gujarati, Hindi and Urdu-speaking persons, compared with higher consumption (>40%) among Kannada, Malayalam, Tamil and Telugu speaking persons. Highest consumption is reported among Christians (61.2%) and Buddhists (58.6%) while lowest among Muslims (9.4%). Education

also influences the consumption with illiterates and those with primary education having higher consumption.[15]

Alcohol consumption prevalence among adults (%) reported from different regions of India

Region	Alcohol consumption prevalence among adults	Reference
North India	25-40%	(14,15)
Central India	24 %	(15)
South India	33-50%	(8)
Western India	7-19%	(15,17)
North East and East India	35-75%	(12,13,15)

PATTERNS OF DRINKING

It is not only the amount of alcohol consumed but also the drinking patterns like episodic heavy drinking or binge drinking determine the adverse health outcome.

Type of Beverage

Globally, 44.8% of total alcohol is consumed in the form of spirits, which is also the most consumed beverage type in South-East Asia (87.9%), Eastern Mediterranean Region (48.3%) and Western Pacific Region (58.8%). Beer is the second most common type and accounts for 34.3% of all alcohol consumption in world. Beer is also the most consumed type of beverage in America (53.8%) and Europe (40.0%) followed by wine. Only 11.7% of total recorded alcohol is consumed in the form of wine.[2]

India is the largest consumer of whiskey in the world. While wine and vodka consumption also increasing significantly. A large population (especially the lower socio-economic strata) in India also consumes locally brewed liquor. This illicitly brewed liquor not only has high risk of ALD but also other health hazards.[19] Many people die every year due to poisoning related to contaminated/adulterated country liquor consumption.

High Risk Drinking Pattern

Heavy episodic drinking (HED) among drinkers is very common (≥ 60% of current drinkers) in Russia, European countries, and in some sub-Saharan African countries. Australia and brazil also show high percentages (45-60%) of heavy episodic drinking. In India, on an average about 55 episodes of heavy drinking occur among drinkers in a year.[2]

ALCOHOL AND GENDER

Excessive Alcohol intake was thought be a male only problem until recently and most of the research has been focused on males not females.[1] In the past, males

exhibited much higher rates of substance use, abuse as well as dependence. In recent times women's role in society is rapidly changing in term of education, life style and economic independence. Alcohol consumption in females is still lower as compared to males but both consumption and AUD has been rapidly increasing in females. Male: female ratio of AUD has changed from 5:1 in 1990 to 3:1 in more recent studies globally.[20,21]

In all over world, females are less often current drinkers than males. More than half of the world's adult females are lifetime abstainers (54.6% or 1.489 billion) compared to 34.5% or 941 million males. Females drink less amount of alcohol and engage less often in heavy episodic drinking (HED) (M/F ratio 2.1-4.2). Total alcohol per capita consumption (APC) among drinkers (M/F ratio), varies between 2.7-2.8.

Alcohol consumption has increased among females in India also, but still much less as compared to males. Per capita alcohol consumption is 7 times more in males than Females. HED also about 2.5 times more prevalent among male drinkers. Alcohol consumption is more prevalent among women of rural areas then urban areas, especially in 41–50 year age group. However, in some areas like Sikkim consumption is high among women compared to national average.[15]

ALCOHOL: BURDEN OF MORBIDITY AND MORTALITY

In a 2018 study, threshold for lowest all-cause mortality was found to be less than 100 gm per week of alcohol. And decreasing alcohol intake from 196 gm to less than 100 gm at age of 40 was associated with increasing life expectancy of 1-2 year. Beers and spirits drinking as well as binge drinking is associated with highest all-cause mortality.[22]

Alcohol consumption is maximum in high income countries but morbidity and mortality seen more in low GDP countries. Europe has the highest levels of alcohol consumption while Africa bears the heaviest burden of disease and injury attributed to alcohol. Harms from a given amount and pattern of drinking are higher for poorer drinkers and their families than for richer drinkers in any given society.[23]

More than 60 medical conditions have been causally related to alcohol.[24] A systemic analysis of 67 risk factors and risk factor clusters for death and disability globally concluded that alcohol alone was the 3rd. leading risk factor for death and disability responsible for 5.5% of disability adjusted life (DALY) lost globally.[25] In the same study alcohol was among the first 10 risk factors and responsible for about 3% of DALY loss in India. Alcohol consumption related disease and injuries resulted in 132.6 million DALYs in 2016 about 5.1% of all DALYs in that year, about 1758 DALYs per lac people globally.

Alcohol was responsible for 5.3% of all deaths in world in 2016. Highest 10.8% was for European region, lowest 0.7% for east Mediterranean and 4.1% and 4.6% for Africa and south east Asia respectively. WHO has estimated alcohol attributable death (AAD) about 38.8 per 1 lac world population in 2016. AAD were highest in

African region (70.6), lowest for east Mediterranean region,[7] while it was about 36.8 in southeast Asia.[2]

Cause	AAD per 100,000 Globally
All cause	38.8
Communicable, maternal, perinatal and nutritional conditions	5.0
Noncommunicable diseases	22.4
Malignant tumor	4.8
Diabetes mellitus	(0.3)
Alcohol use disorder	0.2
Epilepsy	7.4
Cardiovascular diseases	8.3
Digestive diseases	
Digestive diseases	
Injuries	11.4
Unintentional	8.3
Intentional	3.1

Age-standardized alcohol-attributable deaths per 100,000 people in world, 2016. The numbers in brackets indicate beneficial health effects.

Source- WHO Global status report on alcohol and health

ALCOHOL USE DISORDER AND DEPENDENCE

Alcohol use disorder as defined in DSM-5 criteria is a problematic pattern of alcohol use leading to clinically significant impairment or distress as manifested by multiple psychosocial, behavioral or physiologic features.[26] According to DSM-5 diagnostic criteria, unhealthy alcohol use involves the use that put patients at risk of health consequences and causing behavioral problems. Globally, an estimated 237 million men and 46 million women have alcohol-use disorders, with the highest prevalence in Europe, USA and Latin Americas.[2] Estimated worldwide prevalence of AUD and alcohol dependence is 4.1% and 3% respectively.[27]

Prevalence of AUD among adults in India is 4.9%, much higher in males (9.1%) as compared to females (0.5%). While alcohol dependence seen in 3.8 % of adults, 7% and 0.4% among male and female, respectively.[2]

ALCOHOL RELATED LIVER DISEASE

Alcohol related liver disease is a significant cause of morbidity and mortality around

the world. Alcohol is the most common cause of liver cirrhosis in developed countries and also has become one of the leading causes of cirrhosis in countries like India.

Daily intake of 40-80 gm alcohol in males and 20-40 gm in females for at least 10 years can lead to significant liver damage.[28]

Long term intake of alcohol in significant amount can lead to liver injury resulting in a spectrum of disease. Fatty liver is the most common and earliest change that may progress to cirrhosis and HCC with continued alcohol consumption.

Digestive diseases especially liver cirrhosis are important cause of mortality and morbidity globally. Liver cirrhosis not only results in mortality but also causes heavy economic burden and poor quality of life.

Liver cirrhosis related mortality has increased about 46% in last 3 decades, becoming 11th most common cause of death globally.[29] Every year about 2 million lives are lost because of liver diseases, half of them due to cirrhosis. Mortality being more common in developing nations. And about 18% of these cirrhosis related deaths occur only in India because of its huge population.[27]

About half of the cirrhosis related death globally are due to alcohol. Alcohol consumption resulted in 637000 digestive disease related deaths (mainly cirrhosis and pancreatitis) and 23.3. millions digestive disease DALYs globally in 2016. Alcohol related cirrhosis alone resulted in 607,000 deaths and 22.2 million DALYs worldwide in 2016. Burden of alcohol related digestive disease death is highest in Africa followed by Western Pacific.[2]

About 45.8 males and 14.7 females per 100,000 population die in India yearly because of cirrhosis, while alcohol attributed to 60% and 33.3% of them, respectively. ALD results in about 140632 death in India yearly.[2]

In developed nations alcohol is the common cause of liver cirrhosis. NASH also is fast becoming another important cause. In the CANONIC study, involving ACLF patients from 8 European counties alcohol was the cause of cirrhosis in more than 60% cases.[30] Alcohol is an important cause of cirrhosis in united states, NASH and hepatitis C being the other common cause. An epidemiological study reported ALD and Hepatitis C as the leading cause of cirrhosis among white male and African Americans respectively, NASH was the most common cause in entire cohort.[31] Alcohol also is the most common cause of cirrhosis (>40%) in many Latin American nations.[32,33] Hepatitis B is the leading cause of cirrhosis in china and other Asian countries like magnolia.[27,34]

ALD is one of the most common indication for liver transplantation worldwide.[35] Alcoholic cirrhosis account for about 20% of all liver transplants in Europe and its proportion is growing only.[36] In united states analysis of transplant registries and databases shows declining numbers of HCV related cirrhosis on transplant waiting list. Proportion of alcohol and NASH related cirrhosis is increasing among the patients who underwent transplant as well as on waiting list.[37,38] ALD accounted for

36.7% of liver transplants in 2016 as compared to 24.2% in 2002. While proportion of HCV with ALD increased from 15.3% to 30.6% during same period, showing about 100 % increase in transplants for ALD.[39]

Studies from various part of world have shown that post-transplant survival in alcohol related cirrhosis is comparable to other causes of cirrhosis at 1, 3 and 5 year post transplant.[40] However post liver transplant survival beyond 5 year is reduced in alcoholic cirrhosis due increased risk of cardiovascular disease, cerebrovascular disease and malignancies especially oropharyngeal and lung cancer.[41] Patients who resume drinking after transplant have markedly reduced survival.[42]

India

In a review of Indian studies of liver cirrhosis cases between 1933 to 1975, alcohol was the cause only in 16% cases. But scenario has changed in recent decades. A multi-center study conducted in 10 centers across India reported alcohol as the most common (57%) cause of cirrhosis.[43]

A recently published study from New Delhi showed alcohol as the most common (49%) etiology of cirrhosis, while second most common cause was NASH.[44] Other studies from Delhi also reported alcohol as the most common cause of cirrhosis.[45,46]

Studies in other north Indian states like Himachal Pradesh reported even higher (62%) prevalence of alcohol related cirrhosis.[47]

In central and western parts of India also alcohol is most common cause of cirrhosis accounting for more than 45% of liver cirrhosis cases.[48,49] In northeast and eastern part of India proportion of alcohol related chronic liver disease is even higher. Studies have reported alcohol as the cause of cirrhosis in 70% and 65% cases in north east and Odisha respectively.[18,50] Alcohol has also been reported as the most common cause (60%) of cirrhosis in southern part of India.[51,52]

ACLF is an important entity with in the spectrum of CLD. Studies in India has reported alcohol as the leading cause of not only the underlying cirrhosis but also acute insult in ACLF patients.[43]

FUTURE TRENDS

Global alcohol consumption is expected to rise further. Per capita consumption of alcohol projected to reach 7 liters from 6.4 liters in 2025. This rise will be mainly driven by increased consumption in south east Asia and Western Pacific region. In India alone consumption is expected to rise by 2.2 liters in 2025. With increasing consumption alcohol related morbidity and mortality will further rise as will the associated economic losses. Effective strategies and action plans are needed at global and national level to prevent and manage alcohol related health issues.

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Alcohol Metabolism and Mechanisms of Liver Injury

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INTRODUCTION

Chronic and excessive intake of alcohol can cause serious health problems affecting almost all organs of human body. As per WHO, in 2016 around 3 million deaths (5.3% of total deaths) all over the world were attributed to detrimental health effects of alcohol. Alcohol related mortality was greater than that due to tuberculosis (2.3%), HIV/AIDS (1.8%), diabetes (2.8%), hypertension (1.6%), digestive diseases (4.5%), road injuries (2.5%) and violence (0.8%). Digestive diseases accounted for 21.3% of alcohol-related deaths and nearly half of those deaths are due to liver disease.[1] WHO data further shows that about 1,40,632 deaths in cirrhosis of liver were attributable to alcohol in India during 2016.[2] Since liver is the primary organ which metabolizes alcohol, it takes a heavy toll from the toxic effects of ethanol. As a result, alcohol related liver disease (ALD) is one of commonest health ailments in patients with alcohol use disorders (AUD). ALD is a spectrum of conditions ranging from alcoholic fatty liver to steatohepatitis, cirrhosis and finally hepatocellular carcinoma (HCC). Till date, there are no definitive or approved pharmacological treatment for alcoholic steatohepatitis and cirrhosis related to alcohol. The present standard of care includes abstinence, good nutrition and supportive care measures such as control of ascites, malnutrition, infection and the treatment of esophageal varices. Liver transplantation is the only potential curative option. It is indicated for a selected subgroup of patients with end-stage liver disease, severe alcoholic hepatitis (AH) and HCC. In many

transplant centers, the patients listed for transplantation are required to abstain from alcohol abuse for a period of 6 months prior to the surgery. A clear insight of the pathophysiology in ALD is essential for future studies to bridge the gap in knowledge and to develop effective therapies. This chapter outlines the metabolism of alcohol and molecular mechanism of liver injury at cellular level.

METABOLISM OF ALCOHOL

The commonly used term alcohol is chemically ethyl alcohol [International Union of Pure and Applied Chemistry (IUPAC) name: ethanol]. It is a short chain (two carbon chain) aliphatic hydrocarbon with a hydroxyl group at one end. Its ambiguous polarity renders it more soluble in water than organic solvents and enables prompt diffusion across biological membranes.[3] All the alcoholic beverages used are derived from natural plant derived products by the process of fermentation in which glucose is converted to ethanol. After consumption, it is absorbed by passive diffusion through upper gastro-intestinal tract.[4] Most of the absorption occurs in duodenum and proximal jejunum (80%) followed by stomach (20%). The factors affecting the rate of absorption are[5]:

1. Concentration of alcohol in the lumen of gastrointestinal tract: As the diffusion of alcohol occurs along the concentration gradient, higher the concentration of alcohol in the beverage consumed, faster the rate of absorption.
2. Irritant properties of alcohol: Being a direct toxin, mucosal injuries induced by alcohol on the mucosa hinders absorption.
3. Rate of ingestion: Higher rate of consumption leads to greater concentration of ethanol in the lumen resulting more rapid absorption.
4. Gastric emptying: Quick gastric emptying increases the blood alcohol level rapidly by delivering more concentrated alcohol in duodenum.
5. Food: Presence of food usually delays the gastric emptying and eventually reduces the pace of absorption. In contrast, the maximum blood alcohol levels are higher if alcohol is consumed with an empty stomach.

A small amount of the alcohol ingested orally is oxidized in the stomach by gastric alcohol dehydrogenase enzyme and it does not enter the systemic circulation.[5] This first pass metabolism modulates bioavailability of alcohol and ultimately determines alcohol toxicity. It may also explain the higher susceptibility of women to ALD with a lower dose of alcohol intake due to a smaller first-pass metabolism associated with a lower gastric ADH activity, which boosts the bioavailability of ethanol along with a decreased volume of ethanol distribution (due to higher body fat proportion) leading to a higher blood alcohol level.[6] After absorption, most of the alcohol consumed (more than 90%) is metabolized in liver by oxidation into its metabolites such as acetaldehyde and acetate. Rest of the amount is excreted in breath, sweat and urine. In the liver ethanol is oxidised to acetaldehyde by 3 different enzymes such as alcohol dehydrogenase (ADH), the microsomal ethanol-oxidizing system (MEOS) consisting of cytochrome enzymes (mostly CYP2E1), and catalase (Fig. 1). In the hepatocyte, ADH is present in the cytosol (cytoplasm), MEOS in the microsomes and catalase in

the peroxisomes. ADH is usually saturated at low concentrations of alcohol due to its low Km value (1mM). Km value is the Michaelis-Menten constant which refers to the concentration of the substrate when the reaction velocity is equal to half the maximal velocity for the reaction.[7] On the contrary MEOS plays major role in alcohol oxidation in excessive ethanol intake because of its high Km value (7-11 mM). Besides, MEOS activity is induced by alcohol leading to increased enzyme synthesis with chronic alcohol intake. Acetaldehyde generated from ADH and MEOS in hepatocytes, is further oxidized in the mitochondria by the enzyme acetaldehyde dehydrogenase (ALDH) to acetate. Acetate is released into the systemic circulation and taken up by various metabolic pathways (such as Kerbs cycle, fatty acid synthesis and cholesterol synthesis) and ultimately oxidized to CO_2 in various extrahepatic tissues.

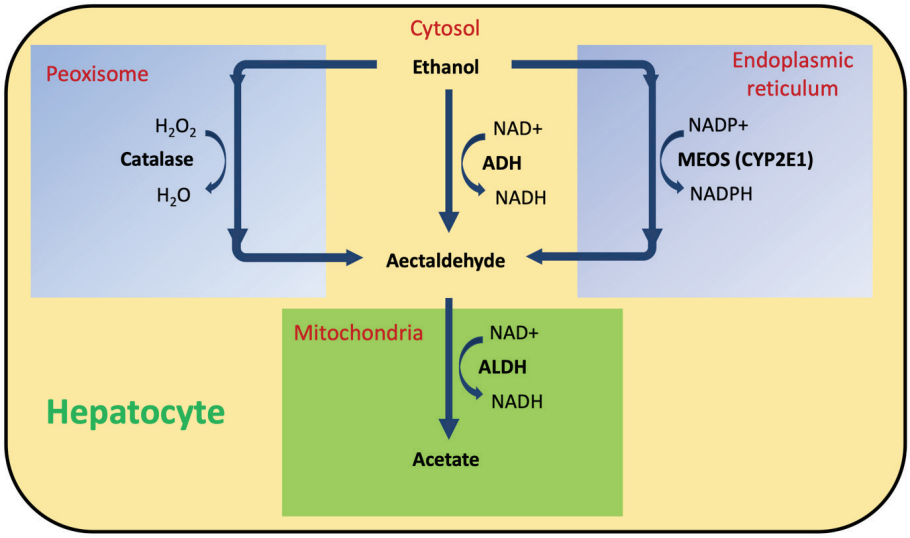

Figure 1. Oxidizing pathways of Ethanol in the liver

There is a close interrelation between ALDH, ADH, and MEOS at the level of reducing equivalents. The cytosolic ADH and mitochondrial ALDH require NAD+ (nicotinamide adenine dinucleotide) and generate NADH+ H+ for the oxidation of alcohol and acetaldehyde respectively. Thus ALDH competes with cytosolic ADH for NAD+. Higher NADH/NAD+ ratio in hepatocytes leads to accumulation of acetaldehyde, which is toxic unlike acetate. On the other hand MEOS requires reducing equivalents in the form of NADP+ (Nicotinamide adenine dinucleotide phosphate) Mitochondrial impairment due to acetaldehyde results decrease activity of ALDH and eventually initiates a vicious circle leading to accumulation of toxic acetaldehyde.

MECHANISMS OF LIVER INJURY

Molecular Mechanisms

Oxidative stress

Chronic alcohol intake leads to induction of hepatic MEOS and CYP2E1 levels, which enhance production of reactive oxygen species (ROS).[8] ROS along with accumulated acetaldehyde cause direct injury to hepatocytes. The non-parenchymal liver cells such as Kupffer cells (KCs) also play their part in generation of ROS after activation by intestinal bacterial translocation (discussed later). Moreover along with hepatic stellate cells (HSCs), KCs produce pro-inflammatory cytokines leading to inflammation and neutrophilic infiltration, which contributes as another source of ROS.[9] These ROS and other reactive molecules are usually scavenged by natural antioxidants (glutathione, vitamin A, vitamin C and vitamin E) and antioxidant enzymes (superoxide dismutase, glutathione reductase and catalase). However, excess generation of free radicals exhausts the protective mechanisms and worsens the oxidant burden. ROS along with proinflammatory cytokines (IL-1β and TNFα) from Kupffer cells, promote apoptosis and necrosis of hepatocytes which incites local inflammation and eventually liver injury.

Aldehyde adduct formation

As discussed in the metabolism, increased NADH/NAD+ ratio and mitochondrial impairment causes excess accumulation of acetaldehyde. Being a toxic and highly reactive molecule, it covalently combines with various cellular macromolecules such as proteins, lipids and nucleic acids giving rise to aldehyde adducts. These transformations leads to disruption of normal structure and function of these macromolecules. Furthermore, these bulkier adducts have capability of inducing immune response, which adds to the ongoing process of liver injury.

Role of altered lipid metabolism

Alteration in normal lipid metabolism in liver leads to alcoholic fatty liver steatosis, which is the earliest stage in the spectrum of ALD. It develops among 90% people with heavy alcohol intake.[10] It does not present significant clinical symptoms, and is usually reversible. However, it may serve as a precursor for AH, fibrosis and finally cirrhosis. The evidences accumulated by recent research studies favours that alcohol induced steatosis is multifactorial (Fig. 2).

1. Enhanced lipogenesis: As discussed earlier, oxidation of ethanol to acetaldehyde increases the ratio of NADH/NAD+. The resultant alteration in the cellular redox potential favours lipid synthesis. Ethanol downregulates activity of the enzyme adenosine monophosphate-activated kinase (AMPK). Reduced AMPK activity stimulates mammalian target of rapamycin complex 1 (mTORC1) resulting activation of sterol regulatory element-binding protein-1c (SREBP-1c). SREBP-1c is a transcription factor which enhances lipid synthesis from a higher expression of lipogenic enzymes (such as fatty acid synthase, acyl CoA carboxylase etc).

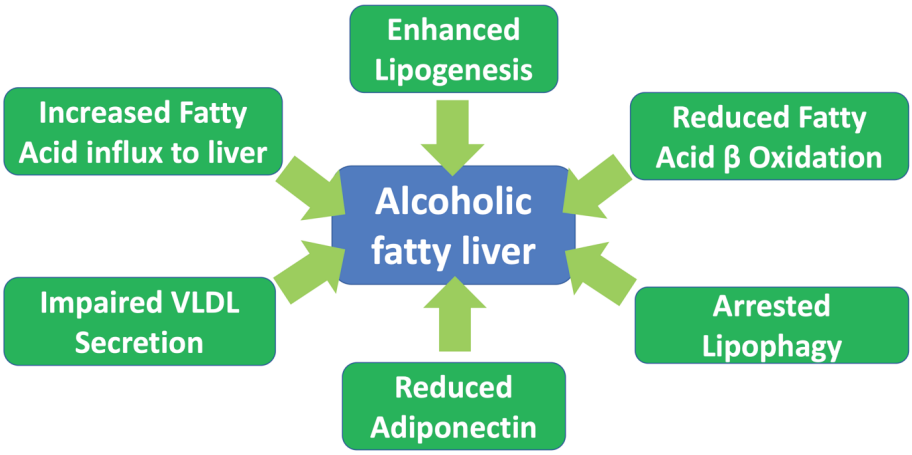

Figure 2. Pathophysiological mechanisms contributing to alcoholic fatty liver.

2. Decreased β-oxidation of fatty acid: Heavy alcohol ingestion reduce the rates of β-oxidation of fatty acids. There are several factors responsible for the same. The altered hepatocyte redox state due to high NADH/NAD+ ratio directly inhibits mitochondrial β-oxidation. Secondly, acetaldehyde impedes the peroxisome proliferator activated receptor alpha (PPAR-α) pathway. PPAR-α is a transcription factor which plays a pivotal role in fat metabolism. Inactivation PPAR-α in ALD leads to downregulation gene expression for mitochondrial and peroxisomal β-oxidation of fatty acids and upregulation of genes involved in fatty acid synthesis. Consequently ethanol transforms liver from a lipid metabolizing organ to a lipid storing organ.
3. Arrested Lipophagy: Lipids are present in form of droplets in hepatocytes, which are broken down by a unique intracellular process known as lipophagy. The droplets are taken up by membrane–bound vacuoles and consequently, get delivered to lysosomes. In the lysosomes, the lipid droplets are disintegrated by lipases into free fatty acids, which subsequently undergo β-oxidation in mitochondria. Chronic ethanol exposure inhibits the process if autophagy by decreasing the activity of AMPK and activating mTORC1. Furthermore, alcohol also reduces the activity of proteins, (such as Rab7 and Dyn2) which are critical for fusion of autophagosomes and lysosomes leading to faulty lysosomes. Reduced autophagy enhances lipid accumulation.
4. Reduced adiponectin: Adipose tissue is the storage house of energy, which provide free fatty acids from breakdown of triglycerides during demand of energy. Its importance in liver diseases has been reflected by higher prevalence, rapid progression as well increased severity of cirrhosis due to various etiologies (especially ALD, chronic hepatitis C) in patients with obesity.[11] The adipocytes present in adipose

tissue secrete a set of polypeptide factors known as adipokines such as leptin and adipokinin, which play key role in lipid metabolism, inflammation and tissue repair. Chronic alcohol abuse usually increases serum levels of pro-inflammatory and pro-fibrogenic leptin,[12] whereas reduced expression and secretion of adiponectin are found to be associated with ALD.[13] The reasons for decreased adiponectin production are ethanol-induced oxidative stress due to activity of MEOS[14] and altered methionine metabolism leading to increased homocysteine levels.[15] Leptin promotes hepatic steatosis (by suppression of fatty acid biosynthesis), fibrogenesis (because of up-regulation of TGF-β1) and inflammation (through stimulation of secretion of proinflammatory chemokines). On the contrary, adiponectin inhibits steatosis (by supressing fatty acid synthesis and stimulating fatty acid oxidation), TGF-β1 induced fibrogenesis and inflammation (though inhibition of proinflammatory cytokines and chemokines). The resultant altered levels of adipokines lead to alcoholic fatty liver and hepatitis.[16]

5. Impaired very low density lipoprotein (VLDL) secretion and increased fatty acid influx to liver: Liver exports triglycerides and cholesterol to peripheral tissues as constituents of VLDL particles. Excessive ethanol intake reduces the activity of phosphatidylethanolamine methyl-transferase leading to impaired phosphatidylcholine synthesis. As phosphatidylcholine is utilized for assembly and secretion of VLDL, alcohol intake leads to impaired VLDL secretion.[17] Besides hepatic microsomal triglyceride transfer protein is found to decrease in ethanol-fed experimental animals, which helps in assembling VLDL.[18] Besides, alcohol consumption favours lipolysis in by the enzyme adipose triglyceride lipase and inhibits the uptake of circulating free fatty acids for storage in the adipose tissue.[19] As a result, there is increase in circulating non-esterified free fatty acids leading to a huge fatty acid flux to the liver. The exact molecular mechanism by which ethanol stimulates lipolysis is not clear. It is hypothesized that ethanol mediated resistance to the lipogenic activity of insulin[20] might be a factor as the catecholamine-induced lipolysis remains unchanged in ALD.[21] Further, the circulating fatty acids can also activate toll like receptor-4 (TLR4), promoting hepatic necro-inflammation.[22]

Gut liver axis

Excessive alcohol consumption causes bacterial overgrowth (due to reduced gastro-intestinal motility) and alters the normal composition of the intestinal microbiome which involves diminished beneficial bacteria such as Bacteroidetes, Lactobacillus and increased harmful bacteria like Proteobacteria and bacilli (Fig. 3).[23] Moreover alcohol induced inhibition of prostaglandin synthesis injures normal mucosa causing intestinal barrier dysfunction. The resultant increased gut permeability leads to intestinal bacterial translocation.[24] These microbes are delivered to the liver by portal venous system and stimulate KCs and HSCs by lipopolysacharide (LPS) mediated toll like receptor 4 (TLR4) activation.[25] Subsequently KCs and HSCs produce pro-inflammatory cytokines and mediators (IL-1, IL-6, TNFα and ROS) which promotes hepatic necro-inflammation and fibrogenesis.

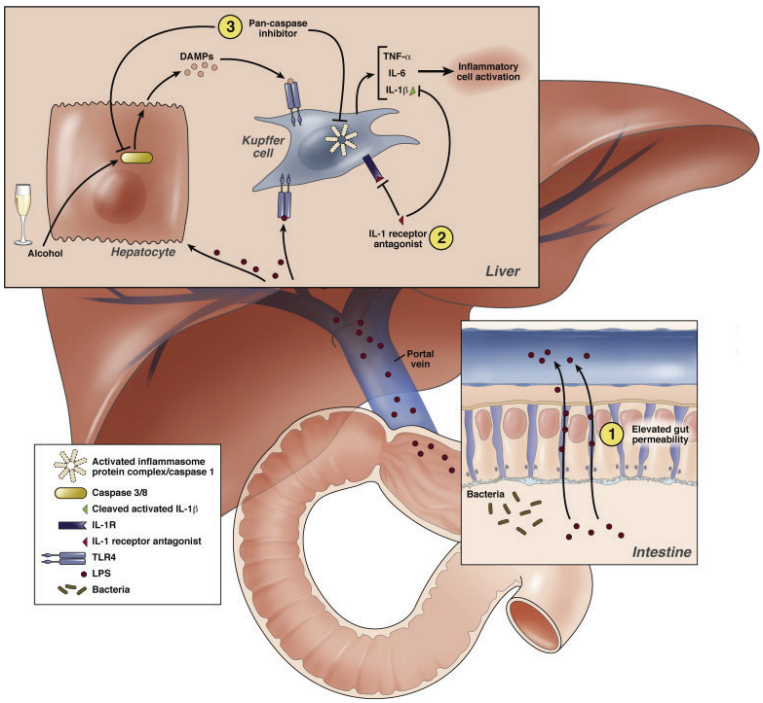

Figure 3. Gut liver axis in ALD. The text in red indicates various options of treatment that are being tried according to their proposed mechanism of action. *(Adapted from: Singhal AK. Clinical Gastroenterology and Hepatology 2014;12:555–564)*

Impact on the immune system

The activation of gut liver axis initiates and perpetuates both innate and adaptive immunity contributing to the damage and inflammation in liver.

1. Innate immunity: Innate immunity is comprised of physico-chemical barriers such as mucous membranes, pH protective layer of mucus and cellular defences including both non-parenchymal immune cells in liver with the proteins secreted from them (cytokines and chemokines). They act as a natural policemen against any invading microbial agent, which is perceived as harmful by the immune system.[26] In normal scenario, the innate immunity is well balanced in such a way that senses and responds to only harmful agents while avoiding unnecessary immune activation to commensal gut microbiota. Ethanol disrupts this balance, and there by inducing excessive detrimental immune activation due to unopposed transmigration of gut bacteria that result in inflammation.[27] LPS mediated TLR4 activation, to external antigens (pathogen associated molecular patterns: PAMPs) stimulates the nuclear factor κB (NF-κB), triggering the transcription of genes for several pro-inflammatory cytokines such as TNFα and IL-17. In addition,

ROS and acetaldehyde mediated liver damage also activates innate immune cells, triggering an inflammatory response even in the absence of invading pathogens.[28] This sterile inflammation results from activation of nucleotide-binding oligomerization domain-like receptors, or NOD-like receptors (NLRs) in KCs by the molecules released by breakdown hepatocyte necrosis, which are also known as or alarmins. [damage-associated molecular patterns or DAMPs].[29] Moreover, secretion of chemokines such as monocyte chemoattractant protein-1 (MCP-1) are upregulated in ALD.[30] MCP-1 along with IL8 recruit circulating neutrophils to liver. The resultant neutrophilic infiltration and activation further perpetuates the inflammation. These immune pathways are usually necessary for clearing the tissues from damaged cells and cellular debris, but can also cause liver damage. Their persistent activation by ethanol, a vicious circle ensues leading to unrestricted liver damage.

2. Adaptive immunity: Chronic alcohol exposure affects almost all components of the adaptive immune system. Both experimental animal studies and studies on human have revealed that chronic alcohol use reduces the peripheral T cells pool.[31] The mechanism is excessive T cell apoptosis due to increased expression of pro-apoptotic molecules like BCL2 Associated X, Apoptosis Regulator (bax) and reduced expression of anti-apoptotic ones such as B-cell lymphoma 2 (bcl-2) protein.[32] Besides, ethanol use causes chronic activation of the T-cells leading to impaired T-cell functioning with reduced migration and diminished ability to respond to pathogens. This state of anergy contributes to an increased susceptibility to infections. Furthermore, continuous activation results in activation induced cell death of T cells.[33]

   Chronic alcohol exposure is associated with depletion of peripheral B cells population especially the conventional B-2 subtype of B cells, which produce high-affinity antibodies and can develop into long-lived memory to pathogens critical for protection against subsequent infection.[34] On the other hand, there is rise in B-1 cells which secrete increased immunoglobulins including antibodies directed against liver autoantigens liberated during hepatocyte death.[35] The presence of these auto-antibodies can result in increased production of inflammatory cytokines, which in turn may exacerbate liver damage.

Ubiquitin proteasome pathway

Liver cells' function is regulated by a specialized mechanism of protein degradation known as ubiquitin proteasome pathway.[36] It is a defence mechanism for regulation of quality control of intracellular proteins, where damaged and irregular proteins generated by genomic mutations, errors in translational and oxidative stress are removed. Chronic ethanol ingestion results in impairment of in proteolytic activity of the proteasome.[37] This leads to accumulation of abnormal proteins in the form of Mallory-Denk bodies.[38] Hepatocytes dying due to inhibition of proteasome pathway release inflammatory cytokines which leads to neutrophilic infiltration and hepatic necro-inflammation.

Fibrogenesis

In ALD, KCs and HSCs are stimulated by both gut microbiota translocation mediated TLR4 activation as well as damaged hepatocytes mediated NOD like receptors activation. Besides, KCs secrete prostaglandin D2 which further stimulates the HSCs. HSCs transform into myofibroblast leading to TGF induced deposition of extracellular matrix especially collagen type 1 in an irregular fashion.[39] Moreover, activated HSCs also contribute to the inflammatory response by recruitment and stimulation of circulating leucocytes to liver. Hence, perpetuation of ongoing inflammation sustains the process of fibrosis.

CONCLUSION

The pathophysiology of ALD is complex and multifactorial. Each pathway plays its role in the pathogenesis and is a potential target for therapy. Most of our current understanding of the molecular mechanism involved in ALD are limited to animal models especially rats and mice. Moreover, we are yet to get an effective treatment for each spectrum of ALD. Therefore, improved animal models are imperative for the development of successful and safe therapeutic strategies.

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3

Genetic Predisposition, Immunology and Histology of Alcoholic Liver Disease

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INTRODUCTION

In 2016, 5.6% of all-cause mortality worldwide was related to alcohol use.[1] Of all deaths attributable to alcohol consumption, digestive disorders was the second most common cause of mortality (21%) second only to injuries (28%). Alcohol contributes to 40% of liver cirrhosis globally.[1]

Chronic alcohol consumption leads to steatosis in >90%. This is reversible on abstinence. Upto 20% of those with steatosis, develop acute alcoholic hepatitis (AH), which, if severe, can lead to death. Cirrhosis develops in 8-20% of patients with steatohepatitis on liver biopsy. Cirrhosis progresses to decompensation and hepatocellular carcinoma (HCC) (3-10% of cirrhotics develop HCC).[2] There are environmental, genetic and other cofactors which modify the risk of developing liver disease in a person consuming alcohol. This review shall focus on genetic and immunological factors which play role in pathogenesis of alcoholic liver disease (ALD).

GENETIC MUTATIONS ASSOCIATED WITH ALCOHOLIC LIVER DISEASE

Genetic factors may affect either susceptibility to alcohol abuse or the progression of alcohol induced liver injury.

Susceptibility to Alcohol Abuse

Alcoholism is considered as a familial disorder. Twin, family and adoption studies have proven hereditary pattern of alcohol abuse. Meta-analysis of these studies have shown the hereditability of alcohol abuse ranges from 34-50%. The hereditability of alcohol related liver cirrhosis was three times higher in monozygotic twins as compared with dizygotic twins.[3,4]

Progression of Alcohol related Liver Injury

With advent of whole genome sequencing, considerable progress has been made in identifying candidate genes involved in the progression of ALD. Three genes have been noted to have association with ALD:

PNPLA-3

Genome wide association studies (GWAS) has identified the genetic risk loci associated with progression of ALD in patatin like phospholipase domain containing 3 (PNPLA-3) gene. This gene is located on chromosome 22 and encodes a protein-adiponutrin. Adiponutrin is an intracellular membrane lipase located in endoplasmic reticulum and at surface of lipid droplets, which is involved in lipid remodeling in hepatocytes and adipocytes. It is also strongly expressed in hepatic stellate cells. rs738409 variant of PNPLA-3 is associated with progression of alcohol related liver disease. This variant decreases the enzyme activity and inhibits other lipases. This variant also impairs the amount of VLDL secretion, leading to reduced triglyceride turnover and increased fat deposition in hepatocytes.[4]

MBOAT7/TMC4

The rs641738 variant in the Membrane bound O-acyltransferase domain containing 7-Transmembrane channel-like 4 (MBOAT7/TMC4) locus has been related to a higher risk of cirrhosis in alcohol abusers and with liver disease progression in NAFLD. MBOAT7 catalyzes the transfers of polyunsaturated fatty acids, such as arachidonoyl-CoA to lysophospholipids, thus maintaining the fluidity of membranes. The variant rs641738 in MBOAT7/TMC4 reduces membrane fluidity and enhances the amount of free arachidonic acid, triggering hepatic inflammation.[4]

TM6SF2

A variant causing an amino acid change (E167K) in the Transmembrane 6 superfamily member2 (TM6SF2) gene, has been associated with the development and severity of NAFLD. TM6SF gene product is involved in VLDL secretion. The variant causes decreased VLDL synthesis and release from hepatocytes which causes increased hepatic steatosis. This variant has been associated with increased risk of progression to alcohol related cirrhosis in alcohol abusers of European descent and development of HCC.[4]

EPIGENETIC MODIFICATIONS ASSOCIATED WITH ALCOHOLIC LIVER DISEASE

Epigenetic modification refers to the modification of gene expression, without altering nucleotide sequence in DNA. This can be achieved by DNA methylation and RNA silencing by micro RNAs (miRNAs).

DNA Methylation

Methylation of cytosine in CpG motifs results in gene silencing. Methylation of cytosine is achieved by transfer of methyl residue from S-Adenosyl Methionine (SAM). Homocysteine is converted to methionine by transfer of methyl residue

from methyl-tetrahydro folate, a reaction catalysed by methionine synthetase (Fig 1). Alcohol decreases folate level and decreases activity of methionine synthetase. This leads to decreased formation of SAM and resultant decreased methylation of CpG motifs in DNA. Absence of methylation leads to gene activation and in some murine models, this has been associated with development of HCC.[4]

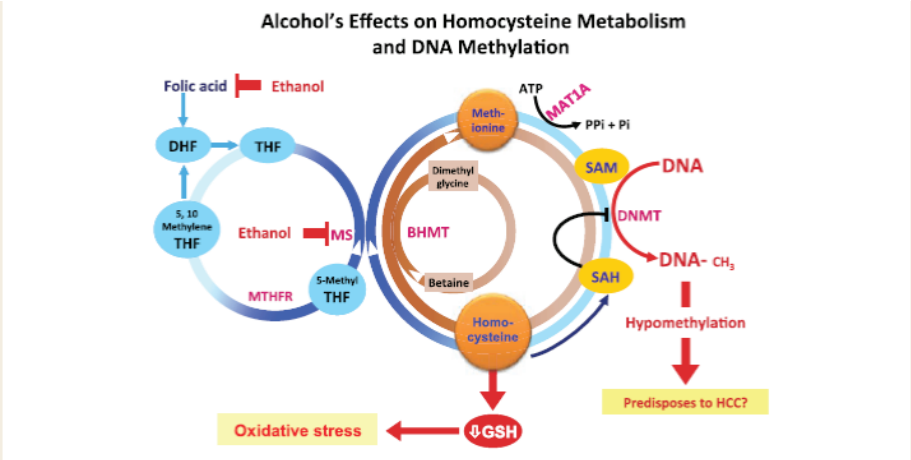

Figure 1. Effect of alcohol on DNA methylation

(Adapted from: Zakhari S. Alcohol metabolism and epigenetic changes. Alcohol Res. 2013;35(1):6-16.

Micro RNA

Micro RNAs (miRNA) are short single stranded RNA (19-22 nucleotides long) which do not code for any aminoacid. They bind to complementary sequence on messenger RNA (mRNA) via base pairing and inhibit protein translation. miRNAs mainly related to alcohol related liver disease include miR-122, miR-212, miR-155, miR-34a, and miR-21.[4]

Micro RNA expression in enterocytes, hepatocytes and Kupffer cells is modified by alcohol consumption leading to increased intestinal permeability, resulting in endotoxemia leading to increased hepatic inflammation and fibrosis. miR-122 and miR-212 expression has been shown to be increased in patients with ALD. It caused increased intestinal permeability by loosening zona occludens leading to increased concentration of Lipopolysaccharide (LPS) in portal circulation. LPS triggers TLR 4 mediated Kupffer cell and macrophage activation in liver leading to hepatic inflammation. Increased miR-34a, mi-R155 and mi-R21 expression in hepatocytes leads to increased IL-6/STAT 3 signalling and enhanced oxidative stress mediated through TNF. This leads to further worsening of hepatic inflammation.[4]

IMMUNE DYSFUNCTION IN ALCOHOLIC LIVER DISEASE

Immune dysregulation has been implicated in the pathogenesis of ALD. ALD includes a spectrum of disorder ranging from steatosis to hepatitis and cirrhosis.

Pathogenesis of Hepatic Steatosis in ALD

Fatty liver can occur with either binge drinking or prolonged, heavy alcohol intake. The pathogenesis of alcoholic fatty liver is multifactorial (Fig 2).

1. Insulin resistance and efflux of free fatty acids from adipocytes: Increased alcohol consumption leads to insulin resistance, enhancing the flux of free fatty acids from adipose tissue and de novo lipogenesis in hepatocytes.
2. Increased hepatic lipogenesis: Sterol regulatory element-binding protein (SREBP-1c) regulates genes involved in hepatic lipogenesis. Chronic alcohol intake increases expression of SREBP-1, leading to steatosis.
3. Decreased VLDL synthesis: Prolonged exposure to alcohol decreases VLDL synthesis, which is the main mode of transferring triglycerides out of hepatocytes, leading to steatosis.[5]
4. Impaired lipid breakdown: Lipid breakdown (Lipophagy) is affected by

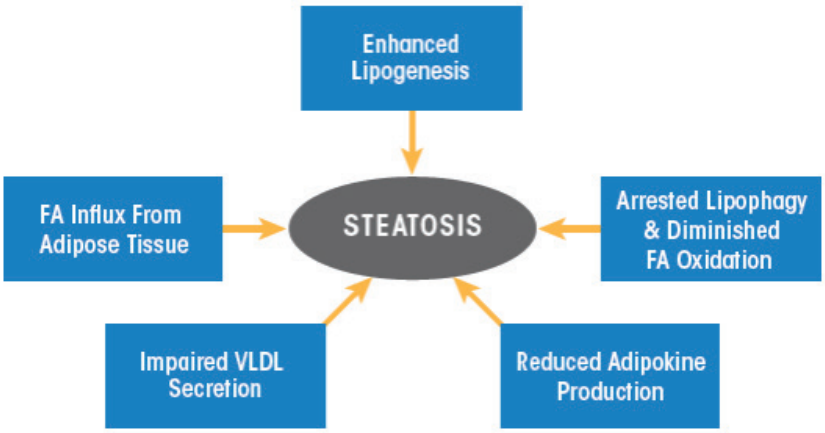

Figure 2. Mechanism of development of hepatic steatosis.

(Adapted from: Osna NA, Donohue TM, Kharbanda KK. Alcoholic liver disease: Pathogenesis and current management. Alcohol Res. 2017;38(2):147-161.[5]

alcohol consumption. Normally, lipids in hepatocytes are in the form of lipid droplets, which are engulfed within double membrane bound vacuoles called autophagosomes which transport it to lysosomes. Lipases in lysosomes breakdown lipids and release fatty acids which undergo beta-oxidation in mitochondria. This mechanism is affected by chronic alcohol consumption which leads to defective lysosome production and function, resulting in decreased breakdown of lipids and

thus results in increased hepatic steatosis.[5]

5. Impaired fatty oxidation in mitochondria: Alcohol consumption reduces rate of beta oxidation of fatty acids in mitochondria. This is due to change in redox potential in mitochondria (low NAD+/NADH ration), inhibition of PPAR-α and reduced adiponectin release from adipocytes. Impaired fatty acid oxidation leads to accumulation of fatty acids in hepatocytes.[5]

Pathogenesis of Alcoholic Hepatitis and Progression to Fibrosis: Role of Immune Dysregulation

With continued alcohol intake, upto 20% of patients with hepatic steatosis progress to develop alcoholic steatohepatitis characterized by inflammatory changes in hepatocytes and/or associated fibrosis.[2]

Both innate and adaptive immunity are involved in the pathogenesis and progression of ALD. Chronic alcohol consumption alters gut permeability and results in endotoxemia in portal circulation. Endotoxins trigger innate immune response in liver resulting in hepatic inflammation. Alcohol and its metabolic intermediates in liver, acetaldehyde, malondialdehyde result in protein adducts which triggers adaptive immunity and results in hepatitis.

Gut permeability

Gut permeability is altered by alcohol resulting in increased lipopolysaccharide (LPS), a cell wall component of Gram negative bacteria in gut, reaching portal circulation. LPS activates innate immune cells (Kupffer cells) through Toll like receptors (TLR-4) resulting in inflammatory response. Chemokines like monocyte chemoattractant protein-1 (MCP-1) results in recruitment and activation of macrophages from periphery. The cytokines released by activated macrophages results in hepatic inflammation, necrosis.[5]

Role of alcohol metabolism intermediates

Alcohol is oxidized in cytosol of hepatocytes by alcohol dehydrogenase to acetaldehyde (Fig 3). This is a toxic product which can covalently bind to proteins, fat and nucleic acids which can disrupt the structure and function of these molecules. Hepatocytes decrease the toxicity of acetaldehyde by oxidising it to acetate in mitochondria. This reaction is catalysed by enzyme, aldehyde dehydrogenase. Acetate can diffuse out of hepatocytes into circulation.[6] NADH is produced as byproducts of these two oxidation reactions. NAD+/NADH ratio, known as cellular redox potential, is altered. This alters cellular metabolism from oxidative metabolism to reductive synthesis of fatty acids, thus, exacerbating the lipid accumulation in hepatocytes.

Apart from alcohol dehydrogensase, alcohol can be metabolised to acetaldehyde by catalase in peroxisomes and cytochrome CYP2E1 in endoplasmic reticulum. CYP2E1 is the inducible enzyme whose activity increases with increasing alcohol consumption. This is the reason for "metabolic tolerance" in chronic alcoholics, whereby, they require more alcohol to achieve the same level of intoxication as they achieved earlier with

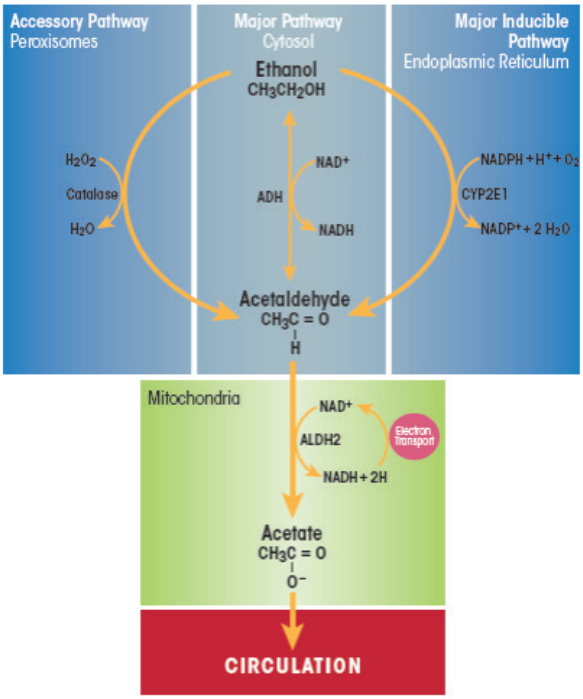

Figure 3. Metabolism of alcohol in hepatocytes.

(Adapted from: Osna NA, Donohue TM, Kharbanda KK. Alcoholic liver disease: Pathogenesis and current management. Alcohol Res. 2017;38(2):147-161.[5]

lesser amount of alcohol. The byproduct of CYP2E1 metabolism is the formation of reactive oxygen species (ROS) like superoxide, hydroxyl and hydroxy ethyl radical. Rate of production of ROS by inducible cytochrome exceeds the capacity of liver to deactivate them with antioxidants like glutathione, vitamin E, C and other enzymes like superoxide dismutase, glutathione reductase etc., ROS reacts with lipids resulting in formation of lipid peroxides, which react with acetaldehyde to form bulkier adducts like malondialdehyde adducts, which trigger immune response.[6]

Role of Kupffer cells in progression of ALD

Kupffer cells are resident macrophages in liver which constitute 15% of liver cell mass. They reside in liver sinusoids and constitute the first line of defence- part of innate immune system. Kupffer cells can exist into two different functional state- M1(pro-inflammatory) or M2 (anti-inflammatory) depending on the presence of cofactors like cytokines, pathogen associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs). Kupffer cells are usually exposed to numerous antigens, toxins and pathogens from portal circulation and hence maintained in the state of tolerance (M2 functional state).[5] With chronic alcohol intake, increased endotoxemia (gut bacteria derived lipopolysaccharide) in portal circulation and protein adducts

(aldehyde adducts), trigger the change to M1 functional state. This causes increased secretion of TNF-α, interleukins (IL-1, IL-2, IL-17, IFN-γ) and chemokines which attract multiple proinflammatory cells to liver. These perpetuate injury resulting in hepatocyte necrosis. TNF-α leads to hepatocyte apoptosis through activation of TRAIL (TNF related apoptosis inducing ligand) and Fas ligand. The release of small vesicles (exosomes) from hepatocytes further activates Kupffer cells.[5]

Role of hepatic stellate cells in progression of ALD

Hepatic stellate cells (HSCs), earlier referred as Ito cells, reside in the space of Disse (between hepatic sinusoids and endothelium). In quiescent state, they store lipids (retinyl esters). When hepatocytes are injured, stellate cells are activated. Activated stellate cells secrete various cytokines and adhesion molecules. MCP (Monocyte chemoattractant protein) results in chemotaxis of leucocytes. Transforming growth factor (TGF-β) and platelet derived growth factor (PDGF) are involved in increased and irregular deposition of like Type 1 collagen and impaired degradation of extracellular matrix. This results in fibrosis.[5] Fibrosis is a transient and reversible wound healing response, which may resolve if alcohol ingestion is stopped early. In the setting of persistent alcohol intake, recurrent episodes of injury and scar formation, ultimately results in progression to cirrhosis.

Miscellaneous alterations in innate and adaptive immunity

Prolonged alcohol consumption is associated with altered immune response involving both innate and adaptive immunity (Fig. 4). Neutrophil infiltration is characteristic feature of ALD. However, neutrophil phagocytic activity is reduced. Natural killer

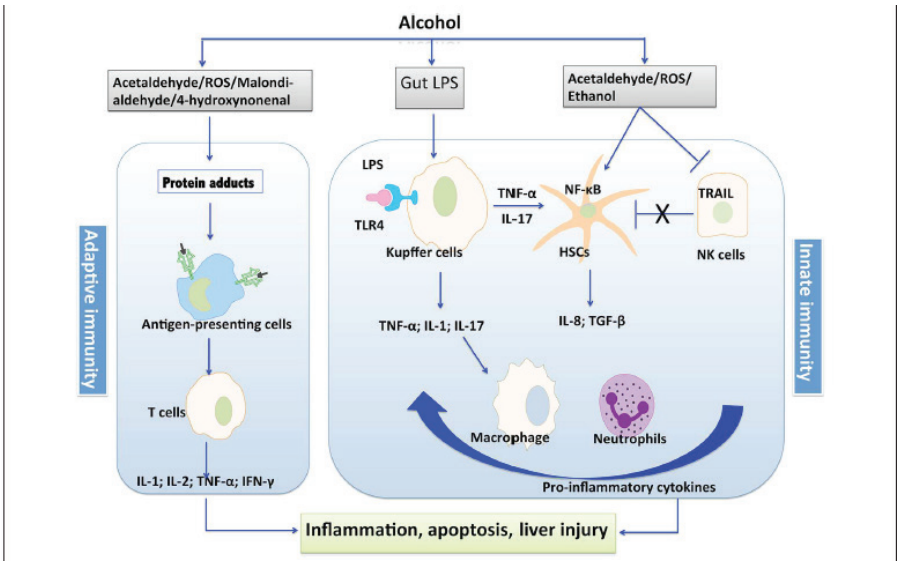

Figure 4. Pathogenesis of alcohol related inflammation.

(Adapted from: Li S, Tan HY, Wang N et al. Recent Insights Into the Role of Immune Cells in Alcoholic liver disease Frontiers in Immunology 2019 doi: 10.3389/fimmu.2019.01328.7

cells (NK cells) have decreased cytolytic activity. There is impaired cytotoxic T cells, decreased T regulatory cells and increased Th 17 cells.[7]

Hepatoprotective cytokines, such as IL-6, and anti-inflammatory cytokines, such as IL-10, also play an important role in ALD. IL- 6 activates signal transducer and activator of transcription 3 (STAT3) and the subsequent induction of a variety of hepatoprotective genes in hepatocytes. IL-10 inhibits alcoholic liver inflammation via activation of STAT3 in Kupffer cells and the subsequent inhibition of liver inflammation. The balance between pro inflammatory and anti inflammatory cytokines decide the fate of hepatic injury- either resolution or progression.[7]

HISTOLOGY OF ALCOHOLIC LIVER DISEASE

Alcoholic liver disease has three main categories of histological changes- steatosis, steatohepatitis and fibrosis with considerable overlap

Steatosis

Hepatocellular steatosis starts as small droplet fat accumulation (formerly labeled as microvesicular steatosis) and progresses to large droplet fat accumulation (macrovesicular steatosis). Usually, a mixed picture is seen. The hepatocytes around the central venule (Zone 3) are initially affected most, as they are the site rich in enzymes involved in alcohol metabolism. With increasing severity of disease, these changes spread outward towards the portal tract. Hepatocellular steatosis may occur alone or in co-existence with steatohepatitis/fibrosis. Foamy degeneration is an uncommon form of steatosis, in which all hepatocytes are filled with microvesicular fat droplet. This indicates acute mitochondrial dysfunction and is similar to the findings in Reyes syndrome or acute fatty liver of pregnancy. Megamitochondria may be seen which is due to the defects in mitochondrial membranes caused by alcohol.[8]

Steatohepatitis

Steatohepatitis includes all forms of hepatocyte injury with or without presence of inflammatory infiltrates. The classical finding is hepatocyte ballooning with cell swelling, rarefaction of cytoplasm and disruption of cytoskeleton, often with formation of Mallory-Denk bodies (hyaline inclusions containing disrupted cytoskeleton fragments) (Fig. 5). These changes begin in zone 3 (perivenular) and extend outwards towards periportal area with increasing severity. Inflammation may be variable, ranging from mild mononuclear cell infiltration around portal tracts to characteristic neutrophilic infiltration, which may be focal around ballooned hepatocytes or diffuse coursing through entire lobule.[8]

Fibrosis

Fibrosis begins in perivenular region and extends outwards along the sinusoids. Initial collagen deposition occurs in space of Disse. With increasing severity, the perivenular and pericellular fibrosis extends outwards resulting in classical chicken wire fence fibrosis (Fig 6). Central vein may sometimes be obliterated by scar. This is termed as sclerosing hyaline necrosis. Hepatocyte regeneration occurs within fibrous webs

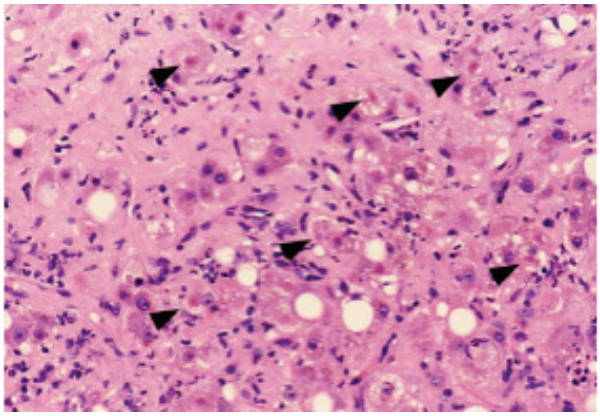

Figure 5. Alcoholic hepatitis. Black arrows highlight Mallory Denk bodies. The image depicts macrovesicular steatosis, ballooning of hepatocytes and neutrophil infiltration (H&E, x20; image courtesy of Wilson Tsui, Hong Kong, 2012).

Adapted from: Theise ND Histopathology of alcoholic liver disease. Clinical liver disease 2013;2(2) doi: 10.1002/cld.172.[8]

resulting in regenerative nodules, which compress and lead to atrophy of adjacent hepatocytes. This leads to condensation of fibrous scars into dense septa. With repeated cycles of scar formation and regeneration within nodules, regenerated parenchyma is subdivided further and results in micronodular cirrhosis.[8]

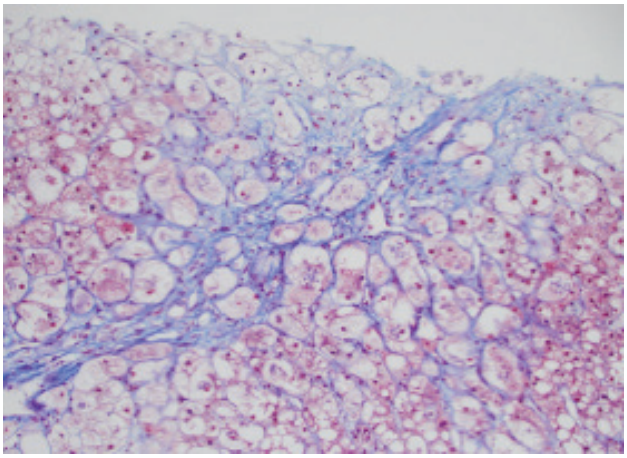

Figure 6. Chicken wire fence pattern of fibrosis in ALD (Modified Trichrome stain) image courtesy of Wilson Tsui, Hong Kong, 2012).

Adapted from: Theise ND Histopathology of alcoholic liver disease. Clinical liver disease 2013;2(2) doi: 10.1002/cld.172.[8]

Differentiation between Alcoholic and Non-alcoholic Liver Disease

There is considerable overlap in histologic features between alcoholic and non ALD. Two features are distinctly seen in ALD- cholestasis (indicative of acute decompensation) and sclerosing hyaline necrosis (in which central vein is obliterated). In alcoholic liver diseae, steatohepatitis may be more prominent with diffuse neutrophilc infiltration, dense Mallory bodies and more megamitochondria.[8]

Changes with Abstinence

With abstinence, steatosis disappears early. Inflammatory infiltrates disappear over few weeks. Mallory bodies may persist longer over few months. Early stage perivenular, pericellular fibrosis may regress. Comparison of explant liver during transplantation of patients who were active drinkers with those who were abstinent for more than 6 months, show that late stage fibrosis and nodules also remodel. With abstinence, fibrous scars regress and nodule become more confluent resulting in macronodular appearance.[8]

Alcoholic cirrhosis continues to be one of the leading cause of liver related mortality worldwide. The risk of developing advanced liver disease is variable and is modified by genetic predisposition and immune response. Knowledge about the genetic factors and immunological mediators will help develop better treatment strategies in the future.

KEY LEARNING POINTS

- Alcohol consumption, either binge or chronic alcohol intake results in steatosis. However, progression to advanced liver disease occurs only in 20%.
- Genetic and epigenetic factors have been identified for progression of liver disease. PNPLA 3, MBOAT7 and TM6SF2 genes have been identified as risk factors for progression of ALD.
- Alcohol increases gut permeability by loosening zona occludens in intestinal epithelium and causes endotoxemia in portal circulation. Products of alcohol metabolism like acetaldehyde form large molecules like adducts in association with proteins and lipids, which trigger immunological response.
- Kupffer cells are activated by endotoxins and secrete interleukins, chemokines which attract inflammatory cells and inducing hepatocyte apoptosis.
- Activated hepatic stellate cells secrete cytokines like PDGF and TGF—β which result in irregular deposition of collagen and impaired degradation of extracellular matrices, resulting in fibrosis.
- Micro/macrovesicular steatosis, hepatocyte ballooning degeneration, neutrophilic infiltration and perivenular chicken wire fence fibrosis starting around Zone 3 are characteristic histological changes noted in ALD.

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4

Clinical Patterns of Alcohol-associated Liver Disease

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INTRODUCTION

Worldwide, harmful use of alcohol is associated with 3.3 million deaths every year, 139 million disability-adjusted life years, and accounts for 5.1% of the global burden of disease and injury. Chronic hepatitis B is the leading cause of death due to cirrhosis in the Asia-Pacific region, followed by alcohol consumption.[1] The annual per-capita consumption of pure alcohol is 14·6 L (18·3 L in men and 6·6 L in women) and the prevalence of heavy episodic drinking is 44·4% (55·1% in men vs. 21·4% in women) in India.[2]

ALCOHOL USE DISORDER (AUD)

The DSM-V (Diagnostic and Statistical Manual of Mental Disorders) defines AUD as a problematic pattern of alcohol use leading to clinically significant impairment or distress. The definitions of drinking behaviors have been explained in Table 1. AUDIT (Alcohol Use Disorders Inventory Test) remains the 'gold standard' for screening and identifying alcohol abuse. Of the ten questions in the AUDIT scoring, 1 to 3 questions explore consumption, 4th to 6th question predict dependence, and 7th to 10th questions aid in diagnosing alcohol-related problems.[3] The AUDIT-C is the shorter version of the AUDIT, which can be used in day-to-day practice to identify risky drinking.[4] AUDIT-C includes the first three questions of the AUDIT, which are: How often do you have a drink containing alcohol? How many drinks containing alcohol do you have on a typical day when you are drinking? And lastly, How often do you have five or more drinks on one occasion? AUDIT-C questionnaire is more sensitive in identifying alcohol misuse than the CAGE questionnaire.[5]

Table 1. Definition of alcohol abuse terminologies.

Definition	Males	Females
AUD	>3 drinks/day	>2 drinks/day
Binge	>5 drinks/day in 2 hrs	>4 drinks/day in 2 hrs
Heavy Drinker	>14 drinks/week	>7 drinks/week
Low-risk Drinking	<14 drinks/week and no more than 4 drinks on any single day	<7 drinks/week and no more than 3 drinks on any single day
Heavy episodic drinking	60-grams pure alcohol on one occasion	

1 drink=10 g of pure alcohol.

CLINICAL PATTERNS

The stage of diagnosis determines the outcomes, and hence it becomes imperative to diagnose the stage of alcoholic liver disease (ALD). Regular alcohol consumption for ~2 weeks leads to the development of fatty liver in almost 90-100% of individuals. Continued abuse for >6 months leads to alcoholic hepatitis (AH) in 10-35% of individuals, and 8-20% of individuals who abuse for 5-10 years develop alcoholic cirrhosis.

Alcoholic steatosis: This is the first stage and is usually asymptomatic. Some patients might have abdominal pain and hepatomegaly on examination. Ultrasonography reveals fatty liver and liver function tests are most often normal. Annually, 3% (2-4%) of alcoholic steatosis progress to cirrhosis and 6% succumb if hazardous drinking is continued.[6] Abstinence of alcohol is the only treatment for alcoholic steatosis.

Alcoholic hepatitis: The usual age of presentation is 40 to 60 years. Female sex is an independent risk factor for AH. However, more men drink to excess, and there are more men than women with ALD.[7] Jaundice in a patient with an alcoholintake of 40 g/day for females and 60 g/day for males for >6 months (with last intake <2 months prior to presentation) with biochemical evidence of hepatic injury is referred as AH. Hepatic injury for AH includes serum bilirubin >3 mg/dL with aspartate aminotransferase (AST>50 IU/mL) and AST to alanine aminotransferase (ALT) ratio of >1.5 with an AST and ALT <400 IU/mL. It is vital to identify AH because severe alcohol hepatitis is associated with 50% mortality at 30 days, progression to cirrhosis is nine times greater than in those with steatosis alone, and is treatable (steroid responder has good outcome).

Clinical presentation: Rapid onset jaundice is the cardinal sign of AH. Other common symptoms include fever, malaise, right upper quadrant abdominal pain, and proximal muscle loss. A variable number of patients may present with decompensation. Almost 70% have ascites, and 15-20% may present with encephalopathy or variceal bleeding.[8]

Typically, the liver is enlarged and tender.

Diagnosis is through clinical history, which is supported by laboratory tests. Liver biopsy is indicated only when the diagnostic dilemmas exist and to establish consistency regarding AH in patients recruited to clinical trials. The prebiopsy clinical diagnosis of ALD is significantly associated with a histological diagnosis of ALD with a sensitivity of 80% and specificity of 98%.[9] Several severity scores aid in predicting the prognosis of severe AH. The components of each score are shown in Table 2. Maddrey's discriminant function, the Glasgow score, and MELD score aid in initiating corticosteroids therapy, whereas the Lille score helps the clinician decide whether to continue/stop corticosteroids after one week.The most commonly used score is the modified Maddreys Discriminant function score. mDF>32 implies sAH and is the cut-off for initiating steroids. mDF is calculated by [4.6 × (patient's prothrombin time – control prothrombin time, in seconds)] + serum bilirubin level, in milligrams per deciliter. Steroids are indicated if the MELD score ≥21 which predicts mortality of 20% at 90 days.[10]

TREATMENT

Strict alcohol abstinence is a crucial aspect of managing alcoholic use disorder. Baclofen, a GABA-B (γ aminobutyric acid-B) receptor agonist, is the onlyproven therapy to be effective in advanced liver disease patients to maintain alcohol abstinence and prevent relapse.[11] Baclofen is started at a dose of 5 mg three times a day for the initial three days, and subsequently, the dose is increased to 10 mg thrice daily for 12 weeks. Naltrexone and Acamprosate are FDA approved drugs for AUD treatment. But there is a lack of safety and efficacy data in liver disease patients for Naltrexone and Acamprosate. Short-acting benzodiazepines (Lorazepam) are safe and effective in treating alcohol withdrawal symptoms but should not be prescribed beyond 10–14 days because of the potential for abuse and to precipitate encephalopathy. Regular motivational interviewing and brief interventions are also an essential component of AUD.

Hepatoprotective properties of ursodeoxycholic acid (UDCA) in alcoholic liver injury have been described.[12,13] The protective effect of UDCA on liver alcoholic steatohepatitis has been explained by its beneficial influence on mitochondrial oxidation,[14] improvement of plasma membrane physical properties[12] and recovery of liver prostaglandin level.[13]

UDCA mechanisms of action

- Anti-inflammatory
- Immune modulation
- Alterations of bile pool acid
- Cell signaling
- Mitochondrial integrity

Table 2. Components of scoring systems for AH and its clinical relevance.

Score	Bilirubin	PT/ INR	Creatinine Urea	Leucocytes	Age	Albumin	Change in bilirubin (Day 0 to 7)	Clinical use
Maddrey DF	+	+	–	–	–	–	–	≥32 start steroids
Lille	+	+	+	–	+	+	+	<0.45 discontinue steroids
MELD	+	+	+	–	–	–	–	≥21 start steroids. Prognostication
GAHS	+	+	+	+	+	–	–	Poor prognosis ≥9. Start steroids if GAHS≥9 and mDF≥32
ABIC	+	+	+	+	–	+	–	High mortality risk >9; Intermediate: 6.71-9; Low risk: <6.71

DF-Discriminant function score; MELD-Model for end-stage liver disease; GAHS- Glasgow alcoholic hepatitis score; ABIC- Age, Bilirubin, INR, Creatinine score.

- Choleretic
- Anti apoptotic

Nutrition is the most crucial aspect of treating AH. Patients should aim to achieve a daily calorie intake of 35 to 40 Kcal/kg body weight and protein intake of 1.2-1.5 g/kg body weight. The preferred route is oral. Alcoholics are deficient in zinc and micronutrients; hence micronutrient supplementation is a part of AH management. Steroids are indicated if mDF>32 or MELD>21 and are contraindicated in active sepsis, gastrointestinal bleed, renal failure, and if the jaundice is for more than three months duration. Nearly 40-50% respond to steroids.Management of AH is depicted in Fig. 1. Liver transplant is indicated in case of AH if the patient is a non-responder to medical therapy (Lille ≥0.45), and severe AH is the first liver-related decompensating event. Also, there should bea strong presence of close, supportive family members, the absence of severe coexisting/psychiatric disorders, and agreement by the patient to adhere to lifelong total alcohol abstinence.[15] Previously most transplant programmes required six months of abstinence before liver transplant. The six months of sobriety was presumed to enable some patients to recover from their liver disease and obviate the need for liver transplant, while also identifying subsets of patients likely to maintain abstinence after liver transplant. In a recent multicenter retrospective trial of 147 patients with severe AH (Median MELD-35; Males-73%) who underwent liver

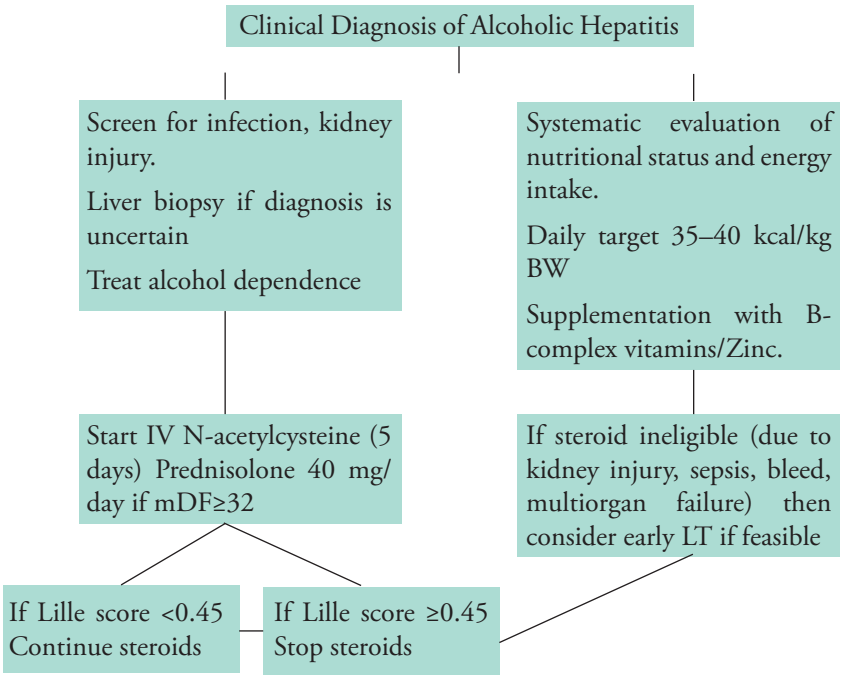

Figure 1. Management approach to alcoholic hepatitis.

transplant within a two months after last drink demonstrated a significant survival benefit of 94% at 1-year and 84% at 3-years with liver transplant. More than 50% of these patients were steroid non-responders. Of these 147 patients, 10% at 1-year and 20% at 3-years had sustained alcohol use after transplant.[16] Hence the six month rule may be unjust in denying a life saving treatment.

ALCOHOLIC CIRRHOSIS

The risk of cirrhosis increases proportionally with consumption of more than 30 g of alcohol per day; the highest risk is associated with consumptionof more than 120 g per day.[17] Globally, alcohol-attributable liver cirrhosis is responsible for 493,300 deaths and 14,544,000 DALYs.[18] The burden of alcohol-attributable liver cirrhosis and liver cancer is high and entirely preventable.

Some of the factors which may increase the risk of cirrhosis in patients with alcohol abuse are:

- Female gender - low gastric alcohol dehydrogenase
- Cigarette smoking increases the risk of hepatocellular carcinoma
- Daily drinking and binge drinking
- Drinking at non-meal times (i.e., empty stomach drinking)
- PNPLA3 -main genetic determinant[19]
- Concomitant HBC/HCV infection[20]

Natural history

The clinical presentation of alcoholic cirrhosis also predicts the outcome.[21] Nearly 25% have no complications, 55% present with ascites alone, 6% with variceal bleed, 4% with both ascites and variceal bleeding, and 11% as hepatic encephalopathy. One-year mortality is 17% among patients with no initial complications, 20% following variceal bleeding alone, 30% following ascites alone, 50% following ascites and variceal bleeding, and 64% following hepatic encephalopathy. The risk of complications is about 25% at one year and 50% at five years for all patients without hepatic encephalopathy. Although patients initially without complications usually developed ascites first (12% within one year), many developed either variceal bleeding first (6% within one year) or hepatic encephalopathy first (4% within one year).[21] Annually 0.7-2% of alcoholic cirrhosis develop hepatocellular carcinoma and HCC accounts for 6% mortality.[22,23]

Management of alcoholic cirrhosis: Strict alcohol abstinence is of utmost importance in a patient with alcohol-associated liver disease. Even after adjustment for baseline prognostic scoring systems (MELD and its components, age), complete abstinence is independently associated with better survival.[24] The management of alcoholic cirrhosis is similar to cirrhosis of other etiologies. Variceal screening in patients with platelet count ≤1,50,000/mm^3 and liver transplant is indicated in patients with high MELD and decompensations.

In conclusion, alcohol is one of the leading causes of liver disease. Diagnosis is mainly on the history of alcohol abuse and the classical history of AH, as described before. Treatment is aimed at maintaining abstinence and providing adequate nutrition irrespective of the stage of liver disease.

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5

Public Health Strategies in Management of Alcoholism and Alcoholic Liver Disease

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INTRODUCTION

Can you imagine an audit on my contribution as a clinician to society? The spotlight is on managing alcohol related cirrhotic patients. There has been no scarcity of blood, toil, sweat or tears over the years. These lull me into feeling self-important, and believing that I did a lot. The auditor chooses to plot a graph, and compare my contribution to community, with that of a village general practitioner who vaccinates children and gives advice on nutrition. Sadly, my curve does not emerge from the baseline, while his, is way up. Prevention doubtless is far better than cure; inexpensive too.

If as health care providers, we wish to make a difference in the care of alcohol related disease, or such lifestyle diseases as the Non-Alcoholic Fatty Liver Disease, we need to intervene long before the symptoms set in, long before the patients feel impelled to see us. We are almost always 15-20 years too late. Hence we very often offer only palliation. How can we change this?

Alcohol has been with man since prehistory. It has been a social and religious icon, a companion during trying and pleasurable times. It relaxes the mind and elevates the mood. It has been a commodity for sale too. It has also been a psychotropic agent that enslaves him, destroying his mind, maiming his body, family and society. It accounts for about 4% of all deaths, at par with Tuberculosis and more lethal than tobacco. It contributes to one of every ten deaths along with other diseases. It kills youth through accidents, crime and underachievement. It harms the society with violence, killings and burdens the systems of law and health care. It accounts for more than 7% of the total Disability Associated Life Years (DALYs) lost, through intoxication, hangover and worsening physical illnesses. It is a social pathogen with a huge footprint.

PUBLIC HEALTH AND CURATIVE MEDICINE

Curative medicine deals with ailments of individuals. Public Health concerns itself with prevention of diseases and injuries in human populations and maintenance/enhancement of their wellbeing. Public health involves governmental action in society as a whole to achieve physical, mental and social wellbeing of all. This needs collective action of the community. Individual endeavor alone is not enough.

Prohibition is not a practical solution to alcohol induced harm. We need to make persons accept a safer type of alcohol use where harm to the individual, family and community are kept to the minimum. We should delay or reduce alcohol intake of adolescents. We have to pick out those who indulge in high risk drinking early and correct at least some of them. How can this be achieved? Education and controlling the environment wherein persons are encouraged not to indulge in risky abuse may work. This is made attractive by use of both carrot and stick (Fig. 1).

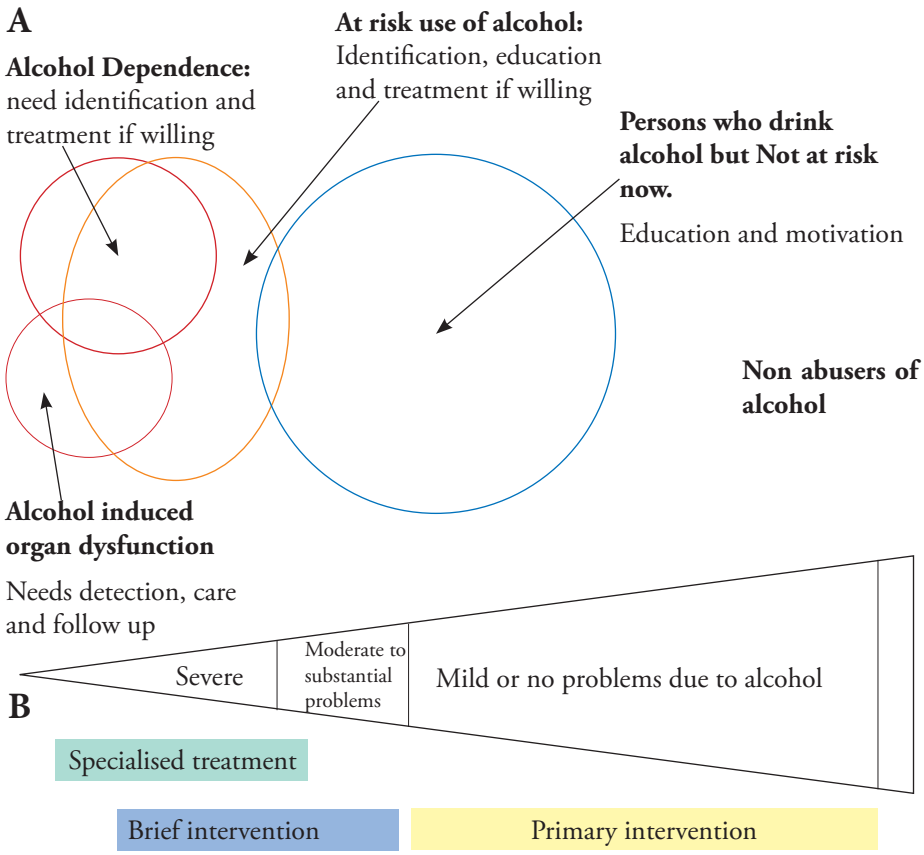


Figure 1. (A) A significant minority indulge in at risk use of alcohol, some of whom may have alcohol dependence while a group have organ dysfunction. A large number abuse alcohol but not by definition at risk. However even a rare drink can increase risk of death by an accident. **(B)** Represents the spectrum of disease and possible interventions as treatment.

THE DYNAMICS OF PREVENTION, PUBLIC HEALTH

Let us look at prevention or control of two maladies: one of the body and the other of our society; Malaria and corruption. Malaria is caused by the parasite plasmodium transmitted by a vector, the mosquito. Poverty and unhygienic environment worsen its impact. Multipronged measures against the pathogen, the vector, environment and improving health and immunity of the host are the logical options (Fig. 2).

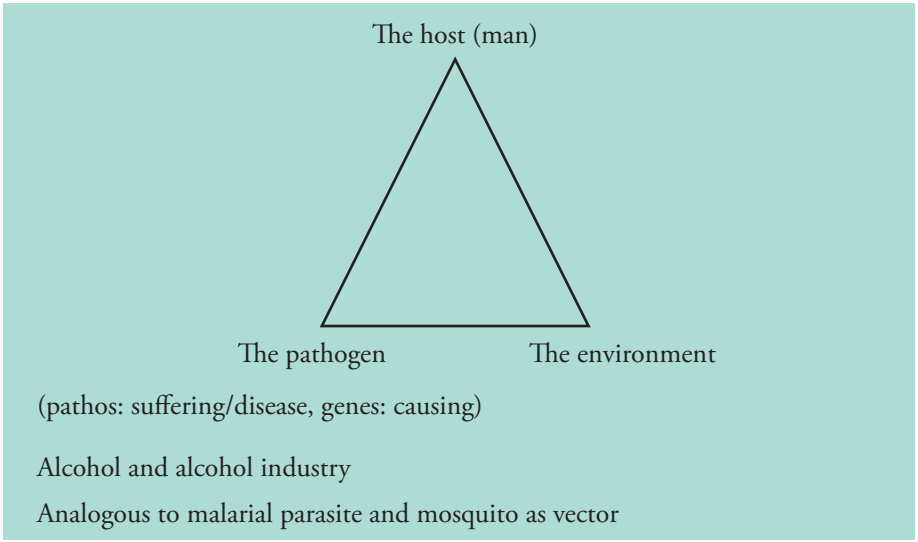


Figure 2. Epidemiological triad.

Harmful use of alcohol (at risk use): A pattern of alcohol use that is causing physical or mental damage (ICD -10)

Alcohol dependence (ADS): A cluster of behavioral, cognitive and physiologic phenomena that develop after repeated use. (ICD-10)

Corruption is rampant in society and is more difficult to control than physical illnesses. Man does not gain from malaria, but a lot of people thrive on corruption. There are laws for prevention of corruption, measures to detect, gather evidence and speedy dispensation of justice. However, most measures do not or are not allowed to work. These laws are not backed by either commitment or conviction and are undermined by those who are in positions of power, many of who gain from it.

I choose the above examples rather deliberately as "controlling alcohol abuse" has similarities to both. It is a human disease affecting the person who abuses ethanol, and needs to be fought in many fronts. It is a social disease as well, affecting the abuser's family, society and even persons not abusing it. Its pathogen is a commodity for commerce. The manufacturing Indian and multinational giants profit from its sale. Many powerful and influential persons in all walks of life gain from the industry's

largesse. Like the battle against corruption, preventing harm due to alcohol or similar intoxicants shall never be over and done with.

NON-TARGETED PUBLIC HEALTH MEASURES

Kettil Bruun[1] in his book *Alcohol Control Policies in Public Health Perspective* notes that the higher the average amount of alcohol consumed by a society, the greater the amount of harm experienced by it. A corollary is that, if we succeed in lowering the average consumption by the population, the harm due to alcohol will come down. In the West, alcohol consumption has been declining in the last decade whereas it doubled in India. Kerala has a per capita consumption that is four times India's average. In those under twenty, alcohol consumption has increased by more than three-fold. We are in the cusp of an evolving catastrophe if we fail to act. Studies abroad reveal many effective interventions (Fig. 3).

Measures affecting supply of alcohol	**Measures that shape safer drinking practices**	**Manipulating the environment to reduce hazards**
Make alcohol costlier (tax/price)	Discourage public drinking	Safer roads, cars, work places
Reduce availability (time/space/number)	Discourage drunk driving	Random checks
Enfore minimum age	Graduated licensing of youth	
	Train servers at bars	

Figure 3. Various options that would reduce ethanol use in community.[2]

TAXATION AND RAISING THE COST OF ALCOHOL

In the hypothetical situation of absence of formal controls over production, distribution and sale of alcohol, the price of alcoholic beverages would be set by market conditions of supply and demand. Law of Demand states that quantity demanded of a product is inversely related to its price. Therefore, if price (money or effort spent) goes up, the demand comes down.

In Denmark in 1917, World War I led to increase of spirits prices by a factor of 12 and beer prices doubled. Alcohol consumption fell by three quarters over 2 years.

More recently, decreased import duties in Switzerland reduced price of spirits by 30-50%. Spirits consumption increased by 30% in three months. Philip J Cook had studied effect of tax changes in 30 states of the United States in a fifteen year period spanning 1960-'74. Consistently, he shows in various studies that increase in price reduces consumption and harm due to alcohol and *vice versa*. Mortality due to liver

disease drops with higher taxes.[3]

Raising taxes will tempt the most recalcitrant of Governments as it increases revenue. It also has been proved to reduce harm to person and community. The major flipside can be the growth of illicit liquor, drugs and criminality.

REDUCING DENSITY OF SHOPS, HOURS OF SALE, MINIMUM PURCHASE AGE

Reducing density of shops in a geographic area, reducing hours of sale and having holidays on paydays, banning price reduction and 'happy hours' have been useful. State run monopolies could help.

Minimum age for purchasing alcohol needs clarification and proper enforcement in India. Trials show that it should be not less than 21 years, as alcohol abuse even in the late teens cause great harm to intellectual and social development. It nearly doubles the chance of the youth being alcohol dependent in his forties.

By licensing and training salespersons in on and off-premises outlets (bars, restaurants and shops), they could be made to not sell alcohol to underage and intoxicated persons. Any new law in our country often degenerates to being another opportunity for corruption. That has to be avoided.

DRUNK-DRIVING PREVENTION

Nearly 1.25 million people die in road crashes each year, on average 3,287 deaths a day worldwide. An additional 20-50 million are injured or disabled. More than half of all road traffic deaths occur among young adults aged 15-44. There is one death every four minutes due to a road accident in India. Drunken driving is one of the leading causes of road fatalities.

Whereas high income countries in the WHO European region have road traffic fatality of about 11 per 100,000, those for the African region is over 28 per 100,000 and in Asia it is 17 per 100,000. Increased cost of alcohol, reduced availability near highways, random breath tests and enforcing minimum age for purchase have all been shown to reduce accidents and deaths.[4]

Blood Alcohol Concentration (BAC) and Driving

BAC is defined as mass of alcohol per volume of blood. For example a BAC of 0.02% means 0.02 grams of alcohol in 100 ml of the person's blood. Lowering BAC levels from 0.1 g/dL to 0.08 g/dL has been noted to reduce fatal crashes by 14.8% in USA. Reduction to 0.05 g/dL has been effective in Europe. However greater effectiveness is noted only when this lowering was accompanied by frequent sobriety check points and administrative license revocation (ALR) laws.

Punishment/Penalties

Deterrence theory states that punishment for a behavior must be sufficiently severe, if it is to reduce the likelihood of recurrence of that behavior. However all these can become ineffective if there is poor enforcement and if the legal system gets burdened

and tardy. Suspending license with one to three offences would help if enforced effectively. After issuing a license, the youth needs to have at least one adult with him always when he drives for a year in graduated licensing.[5] This has been found to be effective in reducing accidents and fatalities which are highest in the first year after learning to drive. Safer roads, better cars and interlock devices could improve safety in future. Many other measures would improve safety of the environment where alcohol is partaken.

EDUCATION, CHANGE OF ATTITUDE

Studies around the world showed that the cost-effectiveness of such programmes is low. Hence literature promoted by alcohol lobby stress on such measures where alcohol sales do not drop. However, it is possible that longer follow-ups are needed. In the case of adolescent abuse, group education of family as a unit with correction and avoiding of inciting situations may help.

Educational institutions may be encouraged to have participatory groups where students, faculty and parents should brainstorm to evolve non-overbearing interventions such as help groups, play-acting and the like. Conditional amnesty if they turn over a new leaf, have been found to be effective for heavily abusing university students abroad. In India, we need to look at alcohol and other substance abuse with greater urgency and sensitivity.

We have a large population of youth who do not attend educational institutions. Tax income from alcohol may be given to voluntary organizations with good track record in youth welfare or such vital issues to fill this vacuum.

Table 1. Policy approach with underlying theoretical assumption.

Policy Approach	Theoretical Assumption	Cost-effectiveness
Alcohol tax/price controls	Increase economic cost	Among the most effective
Regulate physical avaiability	Limited supply, outlets, hours	Very effective
Drunk driving countermeasures	Deterrance, punishment	Very effective
Education, persuasion	Health information	Not effective
Regulate advertisement	Reduce exposure	Effective in youth to an extent
Screening and brief intervention	Reduce risk of heavy drinking, medications	Moderate effectiveness

TARGETED INTERVENTIONS

When the likelihood of harm to the individual's (or family's) health increases, more targeted interventions will be necessary. However to target an intervention, the person or group needing treatment or an intervention, need to be identified.

HOW TO IDENTIFY THOSE NEEDING HELP? (SCREENING)

Patients with unhealthy alcohol use, often present either asymptomatically with early stage problems, or with problems that are not recognized as being alcohol-related. All adults should ideally be screened with a validated survey instrument such as the Alcohol Use Disorders Identification Test (AUDIT -C). The questionnaire shall need validation and modification in our setting.

AUDIT-C (Alcohol Use Disorder Identification Test)

Q 1. How often did you have a drink containing alcohol in the preceding year?

	(Points)
• Never	0
• Once a month or less	1
• Two to three times monthly	2
• Two to three times weekly	3
• Four or more times weekly	4

Q 2. How MANY drinks you had on a typical day of drinking in the preceding year?

	(Points)
• 1 or 2	0
• 3 or 4	1
• 5 or 6	2
• 7 to 9	3
• 10 or more	4

Q 3. How OFTEN did you have six or more drinks on one occasion in the preceding year?

	(Points)
• Never	0
• Less than once a month	1
• Monthly	2
• Weekly	3
• Daily or almost daily	4

This is scored in a scale of 0 to 12. Score of 0 indicate no alcohol use. In a man, a score of 4 is considered positive and in a woman, a score of 3 is considered positive.

WHEN TO SCREEN?

As part of reducing harm caused by alcohol in the community, ideally, screening

should be done by all clinicians when examining a patient. This definitely needs to be done in the emergency department, when a person is brought in with injury or after an accident. This may need to be enquired by the treating physician when evaluating a patient with cardiac rhythm disturbances, liver disease, insomnia, depression, anxiety, trauma, chronic pain, diabetes and hypertension. Screening may be done by the clinician, nurse, or clinical assistant. With experience, it can be completed in 5 to 10 minutes.

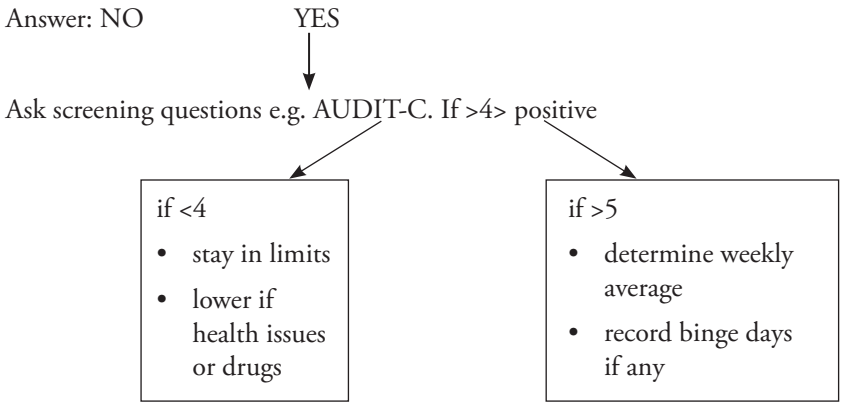
CAGE questions — The CAGE is not recommended as a screening tool, but it can be useful for quickly finding out if someone who screens positive on AUDIT-C, has or has had a more severe problem. The CAGE questions are:

- Have you ever felt you should **Cut** down on your drinking?
- Have people **Annoyed** you by criticizing your drinking?
- Have you ever felt bad or **Guilty** about your drinking?
- Have you ever taken a drink first thing in the morning **(Eye-opener)** to steady your nerves or get rid of a hangover?

Two affirmative responses are 77% sensitive and 79% specific for alcohol abuse and dependence, but only 53% and 70%, respectively, for unhealthy alcohol use.

SCREENING

Step 1: Do you drink alcohol containing drinks anytime?



Go to Step 2

Step 2: Assessment for alcohol use disorders (AUD) (Does his drinking pattern predispose to distress or impairment.

Ask if in the preceding year he

- Drank while driving, operating machinery or swam
- Has relationship impairment with family or friend
- Failed in carrying out roles at home, work and society
- Faced problems with law, arrests or other issues.

If Yes to one or more, he has Alcohol Use Disorder (AUD)

Ask if the patient in the preceding year had

- Been unable to stick to drinking limits (excessive)
- Been unable to stop or reduce
- Been drinking more to get the same effect (tolerance)
- Withdrawal on not drinking (tremours, sweating, sleeplessness)
- Kept drinking despite physical and psychological problems
- Spent lot of time drinking or recovering from being drunk
- Spent less time in other activities that used to give him pleasure or valued

If YES to three or more the person has alcohol dependence (ADS)

If NO, Patient is still at risk, go to step 3 and 4

If YES, he has alcohol dependence, go to steps 3a and 4a

Step 3: Advise and assist (brief intervention)

State your conclusions and concerns clearly, without being judgemental. ("Your alcohol intake is more than what is considered medically safe. I strongly advise that you quit/cut down. I shall help.")

Assess willingness to change.

if not willing

- Don't be discouraged or be angry. You may restate your concerns, request him to reflect and promise to help if changes his mind.

if willing to change

Help set goal and suggest possible actions such as

- Avoid bars
- Drink less with more water
- Keep track of intake
- How to deal with high-risk situations
- Who may help him? Family, friends
- Provide educative materials

Step 4: At follow-up - continue support, document alcohol use and review goals at each visit.

Was the patient able to meet goals?

No

- Agree that change is difficult
- Support any positive changes and help with problems
- Renegotiate goals
- Consider help if acceptable. e.g. Psychiatrist, AA, counselors
- Reassess diagnosis, Depression?

Yes

- Reinforce. Support continued adherence
- Renegotiate drinking goals if needed
- Encourage patients even if there are ocassional lapses
- Review after 6 months or an year

Step 3A: State your conclusions and advise without being judgemental ("I believe you have alcohol use disorder which can cause health and social problems. I strongly advice that you stop taking alcohol. I shall help.") Discuss his concerns and results of the tests.

Inform the patient that abstaining is the better option for him. Consider further evaluation by a psychiatrist, or addiction specialist especially if medically assisted withdrawal is required. Give medications yourself, if indicated. Consider mutual help groups such as AA.

Step 4A: At follow-up continue giving support. Document alcohol intake and review goals. Was the patient able to meet and sustain his drinking goals?

No

Agree abstinence can be difficult. Support his effort, but stress the need to abstain. If not acceptable to him then:

- Referral to psychiatrist to rule out any psychiatric disorder
- Suggest mutual help groups such as AA
- Prescribe medicines
- Treat coexistent medical and psychiatric problems

Yes

- Reinforce & Support continued adherence
- Coordinate care with a specialist if patient agrees
- Maintain medications for alcohol dependence for 3 months or longer, if indicated
- Address medical and psychiatric issues

Brief Intervention

Brief Intervention refers to a 10-15 minute long non-judgmental interaction (listening, advice, feedback, goal-setting etc.) by a doctor, nurse or trained person. It also involves two or more telephonic communications if needed. Doctor should not be paternalistic. He should be concerned, patient, but firm and communicate clearly.[6] (I am failing repeatedly to meet the above specifications).

Randomized trials on Brief Intervention (10 minutes with a primary care person followed by two telephone calls) in diverse setting, (Doctor's consultation, emergency, colleges and police stations) showed reduction of risky drinking at 6 months, or even later by about 10.5%. Intake of alcohol came down by 3-9 drinks per week in the intervention group.

At three to four years, the intervention group was less likely to be engaged in risky drinking; prevalence 23% versus 35% in controls (who were given a booklet to read) and needed less hospitalizations, and had fewer legal issues. The biggest problem with this promising intervention has been the cool reception by health care personnel.

WHY PUBLIC HEALTH MEASURES AGAINST ALCOHOL FAIL?

Anthony Downs[7] observes that our most intractable public problems have two noteworthy characteristics. First, they occur to a relative minority (in our country, it can be a rather powerless, probably illiterate majority as well) of the population. This group may number even many millions. Second, they result in a significant part from arrangements that are providing substantial benefits or advantages to a majority, or a powerful minority of citizens.

Thus solving or even ameliorating these problems, would require painful losses, restructuring of society, or acceptance of new burdens by the more powerful, numerous, to benefit the least powerful, or less numerous (in our country this group can be the majority, but powerless).

Downs observes that this bleak truth has plagued finding solutions to many a problem. The examples include poverty, racial or caste discrimination, poor housing, unemployment, or abandonment of the aged or handicapped, as well as control of alcohol related harm.

Hence though health ministry may be interested in reducing alcohol consumption, ministries such as finance, tourism, labor and excise may not be really sympathetic. Alcohol industry in India has been taken over by international giants, who are adept at misinformation[8] and controlling media, politicians and executive. The illicit liquor lobby still has a lot of clout in India. So in a very unequal battle in the policy arena, really effective policies to reduce alcohol related harm have brief, endangered lives.

We, the medical profession too have been guilty of allowing preventive aspects of our science to languish (hiding behind the argument that prevention is primarily the responsibility of the Government). In the last half century, doctors' center of activity has moved away from the community to imposing hospitals which often are ivory

towers. If we seriously want to help the community effectively, we need to be sensitive to their fears and aspirations, and fight for the marginalized patients and people.

Even successful programmes like preventing drunk driving with random breath tests flourish only sporadically. Police, media or governmental interest in alcohol harm reduction is too brief. Alcohol lobby has a powerful presence in government, opposition and various pillars of our democracy, and any spotlight on alcohol issues is soon extinguished.

WHAT MAY HELP IN MAKING THE POLICIES WORK?

Even in the West, with more evolved and participatory democracies and responsive governments, alcohol harm reduction has been difficult. They have had great success with control of many preventable diseases. A proactive electorate could make the government, media and others more responsive to the needs of the people. The very powerful presence of the shadowy alcohol industry, has to be neutralised by an organized coalition of alcohol harm control organizations. They have to build a visible and audible presence, which cannot be ignored by policy makers. Medical fraternity have to play a great role in educating people and policy makers. Effective policies need to be brought to the attention of government and people. A research group should assess objectively the benefits, rectify pitfalls of effective programmes. The ineffective programmes should be jettisoned. Misinformation by alcohol sponsored groups need to be countered.

A National Institute for Alcohol Studies?

A certain percentage of the tax from alcohol should be earmarked to establish an autonomous body (analogous to National Institute of Alcohol Abuse and Alcoholism, NIAAA in US or Institute of Alcohol Studies, IAS) headed by public health person(s) of impeccable credentials. Politicians and superannuated administrators should be avoided, as it can be the kiss of death to the venture. Medical colleges all over the state/country can be made to join in. Preventive and Social Medicine departments with help from medical, psychiatry and nursing departments and social workers could do survey of carefully selected representative populations near each institution. Medical and nursing students could be the foot soldiers. This data could be fed to a master computer. The data could help fine-tuning programmes and assessing their cost effectiveness. It will give national programmes, feedback in real time. Studies around the world on controlling harm due to alcohol stress the need for local data as cultural variation is far too wide.

While it is important to offer the best available treatment for persons with alcoholism and alcohol related liver disease, we clinicians need to take up preventive approaches with greater commitment as it shall definitely be more rewarding to the community and for us too as professionals.

KEY LEARNING POINTS

- Alcohol is a killer at par with Tuberculosis. It accounts for >7% of the total DALYs (Disability associated life years) lost.
- Clinicians often get to see only after organ damage had progressed considerably. Preventive public health measures could help to preempt, if enforced effectively.
- Alcohol abuse particularly in the youth is rising rapidly in India. It is an evolving industrial epidemic, if unchecked, can and will destroy the nation's future.
- Raising the cost of alcohol and drunk driving prevention are among the most effective interventions, and need no additional personnel for enforcement. However sustained, effective, enforcement can be a problem.
- Many powerful forces including alcohol industry, impede effective policies and programmes to control alcohol related harm.
- Screening and Brief Intervention should be taken up by clinicians and nurses in hospitals, so that many with alcohol use disorders could be identified, cautioned and offered timely assistance.
- A national institute on alcohol studies may help in gathering and studying our population, and cost-effectiveness of programmes. Money could be obtained from raised tax on alcohol.

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6

Alcohol Liver Disease and Cirrhosis

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INTRODUCTION

Alcohol-associated cirrhosis contributes up to 50% of overall cirrhosis burden in the world. It is a typically co-morbid condition that is associated with alcohol use disorder. Alcoholic cirrhosis is often co-existent with other conditions. Several non-invasive methods are available to diagnose the presence of alcoholic cirrhosis. The natural history of alcoholic cirrhosis is determined by the continued drinking or abstinence by patients. All treatment starts with abstinence. The moment decompensation occurs in alcohol associated cirrhosis, it heralds the progression to chronic liver failure and death. When patients have deteriorated and ineligible for liver transplant, palliative care should be considered.

EPIDEMIOLOGY OF ALCOHOL-ASSOCIATED CIRRHOSIS

Alcoholic associated cirrhosis is thought to contribute 50% of the overall cirrhosis burden worldwide. Recent studies support three broad conclusions with regards to alcohol cirrhosis.

1. The annual increase of deaths from cirrhosis has increased by 65% and annual deaths from hepatocellular carcinoma (HCC) doubled. It is also seen that persons in the age group of 25-34 years age bracket experienced highest average annual increase in cirrhosis – related mortality due to alcohol related liver disease.
2. It is seen that alcohol-associated cirrhosis causes disproportionate medical injury and expense compare with other forms of cirrhosis. These patients were sicker at presentation, readmitted more often and had more than double the health costs compared to non-alcohol related cirrhosis.
3. The proportionate burden of alcohol related cirrhosis is likely to increase in the

next 10 years. It is because other causes of cirrhosis are likely to be eclipsed by vaccination (Hepatitis B virus) or early effective treatment (Hepatitis C virus), the contribution of alcohol related cirrhosis to the overall burden of liver disease is likely to increase.

INFLUENCE OF COMORBIDITY ON ALCOHOL ASSOCIATED CIRRHOSIS

Excessive consumption of alcohol has unwanted synergistic effects on various forms of chronic liver disease particularly chronic viral hepatitis and metabolic disease as shown in Table 1.

Table 1. Effects of alcohol consumption on various forms of liver disease.

Disease	Comment	Reference
Chronic HCV	Promotes cirrhosis at lower doses of alcohol	Corrao & Aricò, 1998
Chronic HBV	In addition to progression, promotes HCC	Ohnishi et al, 1982
NAFLD	Earlier data regarding benefit in NAFLD of moderate drinking have been refuted	Westin et al, 2002; Naveau et al, 1997
	Alcohol increases the rate of HCC in NASH	Ascha et al, 2010
Hemochromatosis	Excess alcohol increases the expression of cirrhosis	Fletcher et al, 2002
PBC	Moderate drinking linked to fibrosis in 1 study	Sorrentino et al, 2010

The consequence of these interactions leads to faster progression of fibrosis, increased decompensation rates, enhanced risk of HCC and increased rate of death. In recent times, the co-infection of HCV has gained the greatest attention because of its prevalence at risk communities. In a study from US in 2013, 60,533 patients had cirrhosis. About 59% had alcohol related cirrhosis and 29% had alcohol related cirrhosis and HCV infection. However, there are no data to suggest that excessive intake of alcohol reduces the efficacy of direct acting antiviral agents against HCV. Patients with alcohol related cirrhosis are at risk for many illnesses and injuries that initially might not seen to be linked to it. They are commonly accompanied by other addictive behaviors most common being addiction to tobacco. It is important that in treatment of alcohol related cirrhosis cessation of smoking remains a key part of treatment. It is shown that patients with alcohol liver disease (ALD) to undergo liver transplant and who were smokers at the time of transplant have a high rate of relapse in tobacco smoking. The association of smoking in alcohol related cirrhosis also has an impact on the rates of aerodigestive cancers and cardiovascular disease. A recent data from Denmark and UK suggests that hip fractures occur more than 5 times

more frequently in persons with alcohol-associated cirrhosis than the people without the disease. In addition, it is shown that 11% of patients with alcoholic cirrhosis die within 30 days after their hip fracture.

DIAGNOSIS OF ALCOHOL ASSOCIATED CIRRHOSIS AND NATURAL HISTORY

There are many ways to confirm the presence of cirrhosis in an at-risk patient. This question is particularly important in patients with alcohol use disorder (AUD) who has not experienced a decompensating event such as jaundice, variceal hemorrhage, encephalopathy or ascites. Percutaneous liver biopsy is the gold standard for diagnosis of cirrhosis, but it is invasive and carries some risk. Presently, there are battery of non-invasive methods starting with simple blood test. The circulating platelet count is an inexpensive surrogate marker for portal hypertension. The current available non-invasive methods are

1. Simple in-direct markers that are not directly involved in fibrogenesis or lysis – platelet count, aspartate platelet ratio index and the Fibrosis-4 index.
2. Complex markers that are more directly linked to fibrogenesis and lysis, and measures of liver stiffness in form of elastography – shear wave elastography and magnetic resonance elastography. In clinical practice, generally a combination of clinical history and examination, allied with tests: platelet count, elastography, and appearance on trans-sectional imaging is used.
3. If patient is found to have significant fibrosis or cirrhosis, upper GI endoscopy is done to screen for varices.
4. Co-existing viral infections and metabolic co-morbidity are generally screened for.

Greater than 50% of patients presenting with clinical syndrome of alcoholic hepatitis (AH) have established cirrhosis. Many patients with alcohol related cirrhosis and who are yet to present with a decompensating event such as variceal hemorrhage, hepatic encephalopathy, jaundice or ascites have subtle features of cirrhosis like thrombocytopenia or amenorrhea. There is not much data on the duration of the pre-clinical phase of alcohol related cirrhosis. The onset of decompensation is an important clinical event in the natural history of the patient with alcoholic cirrhosis. In a Danish cohort of 466 patients, 24% were well compensated cirrhosis, 55% had ascites alone, 6% had variceal bleeding, 4% had bleeding plus ascites and 11% had hepatic encephalopathy. Fig. 1 illustrates the clinical course of alcohol related cirrhosis according to the initial presentation.

This study provides following insights:

1. Most patients at the time of hospital diagnosis have at least 1 decompensating feature.
2. There was no particular pattern of progression after presentation and diagnosis.
3. The mortality was high across the groups once they had decompensated.
4. The decompensating events can occur together and in concert. The presence of continued drinking contributed to the outcome of the patients.

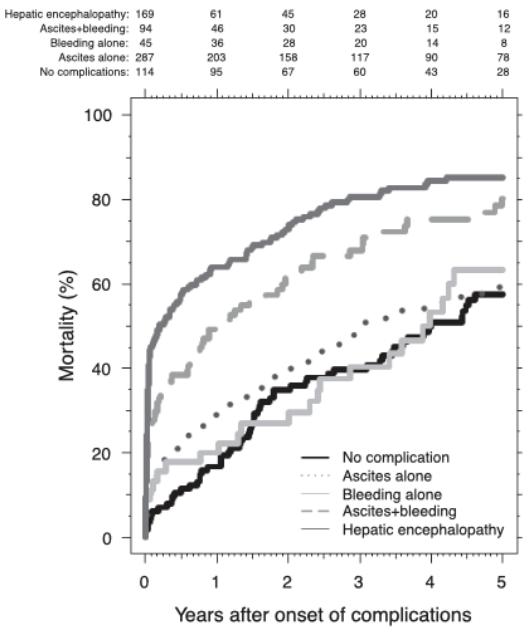

Figure 1. Clinical course of AC in a Danish population cohort. *(From Jepsen P, Ott P, Andersen PK, et al. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. Hepatology 2010;51(5):1675–82; with permission)*

LINK BETWEEN DRINKING AND DECOMPENSATION

The presentation of and outcome from decompensation are closely linked with drinking. This is most commonly seen in AH which is onset of jaundice in close temporal relationship to drinking. Since 50% of patients with AH have cirrhosis, AH can be seen as decompensating event in cirrhotic patients directly linked to drinking. Variceal hemorrhage is another event often occurring after a drinking binge probably due to the effect of alcohol on stellate cells in the space of Disse leading to increase resistance to the blood flow in sinusoids. It is found that patients who have AUD and cirrhosis continue to drink even after a variceal hemorrhage event. This is because the complex psychological foundation of addiction is such that the urge to drink still overcomes the fear of death. Return to drinking was more common in patients with AUD with 25% reporting drinking in the course of follow up. In a classic study by Powell and Klatskin, patients who continue to drink after the onset of decompensation had higher mortality than patients who were abstinent. In another French and Spanish study, long term survival of patients who recovered from an episode of AH was determined by abstinence (Fig. 2).

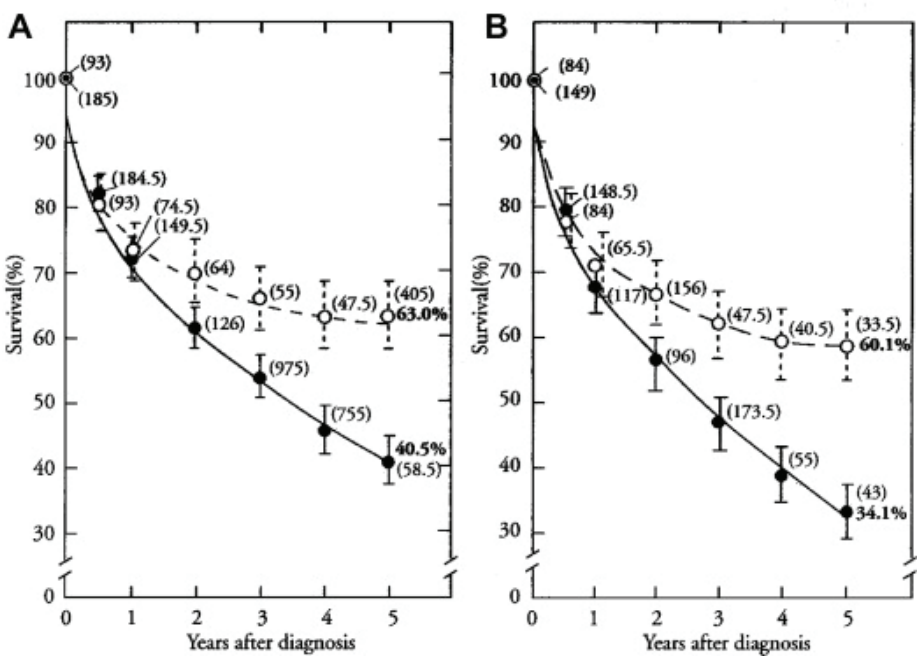

Figure 2. Survival stratified according to drinking or abstinence from diagnosis of AC (Panel A), or first decompensation (Panel B). *(From Powell WJ Jr, Klatskin G. Duration of survival in patients with Laennec's cirrhosis. Influence of alcohol withdrawal, and possible effects of recent changes in general management of the disease. Am J Med 1968;44:406–20; with permission)*

CAUSE OF DEATH IN ALCOHOL RELATED CIRRHOSIS

The outcome of decompensation is stabilization of hepatic function if patient is abstinent or further deterioration and death. In cohort of 1951 Danish patients, with the first-time episode of ALD collected between 1999 and 2008, 401 persons died within 84 days of admission and 600 died later. Death in the former group resulted in liver failure (40%), infections (20%) and hepatorenal syndrome (11%). Beyond 84 days, patients with cirrhosis died of liver failure (34%), infections (16%) or variceal bleeding (11%). It is also noted that patients developed acute-on-chronic liver failure (ACLF) defined as a clinical status of the patients with cirrhosis who have been admitted to the hospital with organ failure is associated with high mortality.

Hepatocellular carcinoma is an additional and serious complication of alcohol related cirrhosis that can lead to death. Patients with alcohol related cirrhosis have an estimated risk of developing HCC of 1-2% annually. Other factors including older age, male sex, obesity, diabetes mellitus and environmental exposure to aflatoxin represent additional factors in development of HCC in cirrhosis.

MANAGEMENT OF PATIENTS WITH ALCOHOL-ASSOCIATED CIRRHOSIS

All management of alcohol related cirrhosis begins with encouragement to maintain abstinence from alcohol. The management of abstinence involves

1. Helping patients achieve and maintain abstinence.
2. The need for multi-disciplinary care for patients with alcohol use disorder and alcoholic cirrhosis.
3. Alcohol cessation - what a medical provider can do in a clinic.
4. Psychological and behavioral approaches for alcohol use treatment for patients with alcohol liver disease.
5. Relapse prevention medication.

The hepatology and primary care providers are often challenged in caring for patients with alcohol liver disease. The first step in management of ALD should be directed to an early recognition of excessive alcohol intake by both the patient and the physician. Patients often under report alcohol intake and a motivational and empathetic relationship with provider is highly advised. It is recommended that the physicians taking care of these patients also get some training in motivational and addiction medicine. In fact, a proportion of alcohol abusers many times also consume other drugs and have significant tobacco addiction. The current long-term management of alcohol related cirrhosis should focus on alcohol abstinence, aggressive nutritional therapy, rich in calories and proteins, prevention/early therapy of cirrhosis complications, i.e., variceal bleeding and HCC.

Fig. 3 summarizes an algorithm for diagnosis and management of ALD and AUD.

Alcohol Abstinence

Achieving prolonged alcohol abstinence is the main therapeutic goal in all patients with alcohol liver disease regardless of the stage. Abstinence decreases morbidity and mortality in both early and advanced alcohol cirrhosis of liver. A significant aspect of heavy alcohol consumption is the tendency of relapse after both long and short period of abstinence. Of the patients that survive an episode of AH, more than 60% patients' relapse. In many cases, alcohol relapse occurs years after the index episode of AH. The intermediate and long-term prognosis is governed by abstinence or relapse. Alcohol abstinence in cirrhosis is shown to decrease the decompensating events like variceal hemorrhage, ascites and encephalopathy.

Psychosocial Therapy and Behavioral Treatment

Brief motivational intervention lasting not more than 5-10 mins are useful and recommended for patients with active drinking. The main goals of these interventions are to educate the patient about the impact of alcohol and to simulate their desire to discontinue alcohol intake. Although these interventions alone are not sufficient to impact alcohol depends in heavy drinkers, they might reinforce compliance to medications. Specific psychological and behavioral therapies should be kept in mind as important tools to identify triggers resulting in relapse and modifying maladaptive

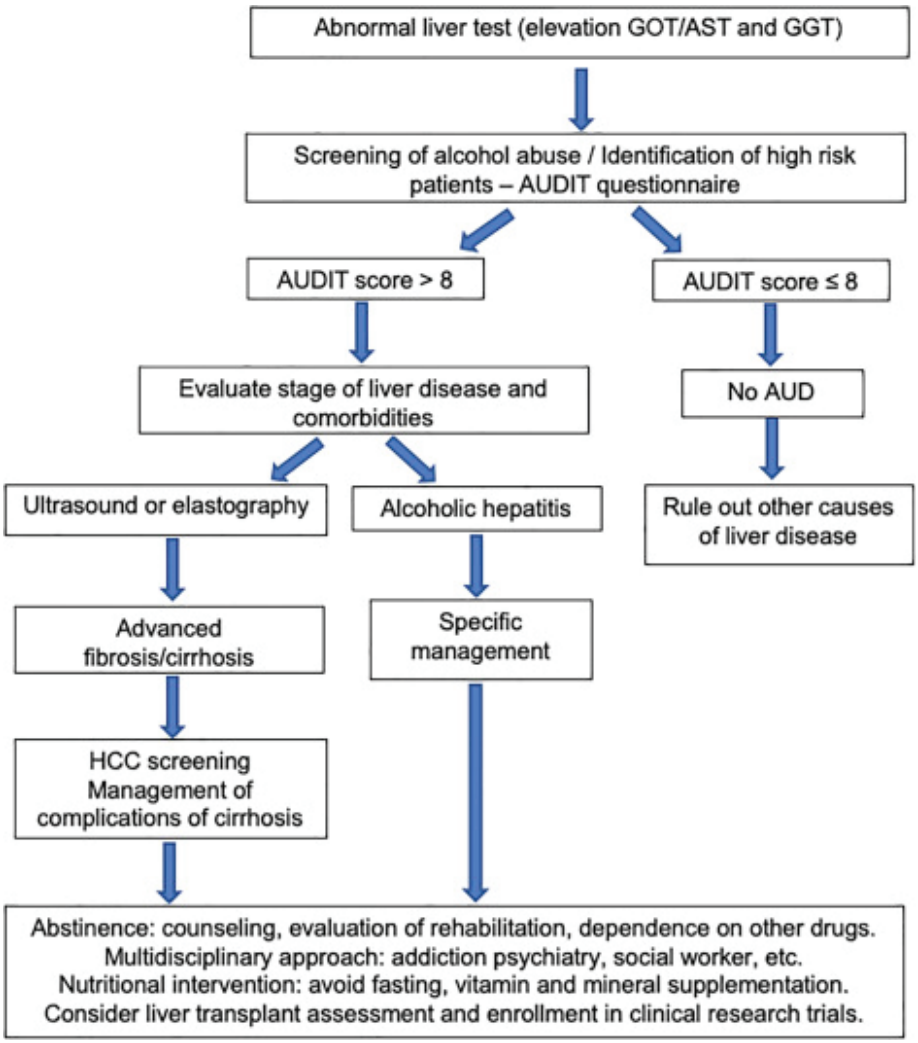

Figure 3. Algorithm for diagnosis and management of ALD and AUD.

behaviors. This includes facilitating 12 steps such as cognitive behavioral therapy (CBT) and motivational enhancement therapy (MAT). The 12-step facilitation intervention is abstinence based that involves participation of patients in alcoholic anonymous (AA) meetings. MET is intent to modify alcohol intake and help these patients developing resistance and to change alcoholic habits. CBT focuses on identifying triggers that compulsively lead to relapse. Since none of the psychosocial intervention alone have proved to be efficient in maintaining abstinence. The combination of two approaches – CBT and MET are useful to increase abstinence rates.

Pharmacological Therapy

Pharmacological treatment is useful to prevent relapse in patients with ALD. However, few studies have assessed the efficacy and safety of anti-craving drugs in patients with alcohol liver disease. In particular, naltrexone and acamprosate, two FDA approved drugs for alcohol use disorders (AUD) have not specifically been tested in ALD patients. Moreover, drugs such as disulfiram causes severe hepatotoxicity and are contraindicated in patients with ALD. Baclofen, a GABA receptor agonist is the only anti craving drug tested in controlled trials in patients with severe ALD. In placebo-controlled trial, baclofen was useful and safe to prevent relapse in alcohol related cirrhosis.

Table 2. Proposed medications to treat alcohol use disorders in cirrhotic patients.

Proven to be safe and efficient in ALD
Baclofen (10 mg TID; 80 mg QD max)
Probably safe but not proven in ALD patients
Acamprosate (666 mg TID)
Naltrexone (PO: 50 mg QD IM: 380 mg monthly)
Nalmefene (Max daily dose: 1 tablet 18 mg)
Topiramate (300 mg QD)
Gabapentin (900–1800 mg QD)
Varenicline (2 mg QD)
Ondansetron (1–16 mcg/kg BID)
Contraindicated medications in cirrhosis
Disulfiram

Nutritional Support

Malnutrition and with/without sarcopenia is common among patients with ALD. Although alcohol is high a calorie power beverage, it provides empty calories. More than 50% of patients with alcohol related cirrhosis have some degree of protein calorie malnutrition. Complications of portal hypertension (variceal bleeding, encephalopathy and ascites) are also commonly observed in malnourished cirrhotic patients. Increased catabolism decreased food intake due to alcoholic gastritis and esophagitis, diarrhea induced by malabsorption, pancreatic insufficiency and complications of cirrhosis contribute to malnutrition in ALD. Most studies have shown disappointing results with parental nutrition. However, enteral nutrition increases survival. Most of the current guidelines recommend a protein intake of 1.2-1.5 gm per kg of body weight and a calorie intake of 30-40 Kcal per kg of body weights including late evening snack. It is important that vitamins and micronutrient deficiencies are corrected.

Prophylaxis of variceal bleeding

Screening for varices should be implemented in patients with alcohol related cirrhosis. If elastography is available, a liver stiffness < 20 kPa together with a platelet count of more than 150 in a compensated patient indicates a very low risk of varices and endoscopy can be avoided. In compensated patients with no varices at screening endoscopy and with ongoing liver injury (i.e., active drinking) surveillance endoscopy should be repeated at two-year intervals. In compensated patients with small varices and with ongoing liver injury, surveillance endoscopy should be repeated at one-year interval. In compensated patients with no varices at screening endoscopy and in whom etiological has been removed (i.e., long standing abstinence) and who don't have co-factors like obesity, surveillance endoscopy should be repeated at two-year intervals. Primary prophylaxis of varices should be performed in all patients with alcohol related cirrhosis with either beta-blocker or variceal ligation. Secondary prophylaxis should be performed similarly to that in other etiology of cirrhosis.

Pharmaceutical Treatment for Fibrosis/Cirrhosis

The most effective therapy to treat liver fibrosis associated with ALD is permanent alcohol abstinence. None of the antifibrotic drugs investigated in patients with ALD, including S -adenosyl- l -methionine, propylthiouracil, colchicine, and sylimarin have been validated enough to be recommended for clinical use. Current clinical trials to treat liver fibrosis include drugs aimed at:

1. Eliminating or attenuating the underlying liver disease,
2. Antagonizing receptor-ligand interactions and intracellular signaling,
3. Inhibiting fibrogenesis, and
4. Promoting fibrosis resolution.

ALD also has many cholestatic features and a beneficial effect for UDCA is therefore hypothesized. One of the important issues in the development of drugs to treat alcohol liver-related cirrhosis is the "dogma" that abstinence is a sine qua non for treating patients. It is probably time to accept that patients have to be treated, even if active drinking is kept, as with other diseases where treatments are accepted, although patients do not comply with a change of lifestyle or losing weight, as in NAFLD.

KEY LEARNING POINTS

- Complete abstinence is the most important therapeutic tool that decreases mortality and liver related complications in patients with severe alcoholic cirrhosis.
- Baclofen has been proven to be effective and safe in preventing relapse and maintaining abstinence.
- Malnutrition is common in patients with alcoholic cirrhosis. Adequate food intake with proper protein and caloric content should be included in the treatment protocol.

- Medical treatment of alcohol associated cirrhosis should be performed by multidisciplinary teams including alcohol addiction specialist.
- Psychosocial therapy and behavioral treatment is recommended to maintain abstinence and prevent relapse in patients with alcohol liver cirrhosis.
- General recommendations for screening and management of cirrhosis for complications should be applied to patients with alcohol related cirrhosis.
- No pharmacological drug has proven to be beneficial to reverse fibrosis/cirrhosis in alcohol liver disease and investigational drugs should be used in clinical trials.

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Liver Transplantation in ALD: Controversies, Outcomes and Recidivism

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INTRODUCTION

Alcoholic-related liver disease (ALD) is one of the most common indications for liver transplantation (LT) worldwide, including India.[1-3] Several studies have also shown that alcoholic related acute-on chronic liver failure (ACLF) contributes to significant proportion of patients with ACLF, both as chronic and acute components.[4-6] The review will discuss several issues related to LT for ALD; controversy of using cadaveric organs for patients with ALD, outcomes after LT and predictors of recidivism.

Controversies in LT for ALD: The main controversies are; prerequisite of a certain period of abstinence, patients being sick with high MELD score and the issue of living donor liver transplantation (LDLT) versus deceased donor liver transplantation (DDLT).

The main fear in LT for ALD is the risk of relapse as the LT cures the liver disease, but it doesn't cure alcoholism. Alcohol relapse (if defined as any amount of alcohol intake after LT) has been shown in 16% to 33.8% of LT recipients and harmful drinking is shown to be present in 10% to 18% of LT recipients in various studies. As different studies have taken different definitions of relapse (some studies have studied only harmful alcohol intake) and have studied different profiles of patients with variable follow-up and risk factors for relapse, the figures of relapse vary widely across studies.[7] Harmful (and not occasional) alcohol relapse is associated with poor survival.[8] DDLT for patients with ALD raises several ethical issues. There is a shortage of organs in all

countries with a significant wait list mortality. The livers from deceased donors are considered a public resource and allocation of organs to patients with ALD would amount to giving limited resources to patients with self-inflicted (due to alcoholism) disease, which may recur after LT and even lead to graft failure. Thus, 6-month abstinence rule was proposed and patients with ALD were considered for listing only in presence of >6 months of sobriety. This 6-month rule serves 2 purposes; a certain period of sobriety is supposed to be associated with low risk of relapse after LT (although many studies contradicted this theory later) and patient might recover on medical management. The 6-month abstinence rule was rather empirical than based on many studies.[7,9] While some studies have found a shorter duration of pre transplant sobriety as a risk factor for relapse, other studies have not found such an association.[10-13] There are 2 major issues with 6-month abstinence rule; a smaller abstinence period does not predict post-transplant relapse/recidivism with good accuracy, and sick patients like those with severe alcoholic hepatitis (AH) not responding to medical treatment or patients with ACLF are unlikely to survive for a period of 6 months. Louvet et al showed only 25% survival in non-responder to steroids at 6 months.[14] Mathurin et al showed a survival of 23±8% at 6 month in patients with severe AH who could not undergo LT, while the survival was remarkably better in LT cohort (77±8%, $p<0.001$).[15] Im et al analyzed 94 patients with severe AH not responding to medical therapy The 6-month survival rate was 89% in liver transplant recipients (n=9) as compared to only 11% in controls ($p<0.001$).[16] In a study from our center, the 1-year survival was 84.5% in patients with severe AH undergoing LT and not responding to medical management.[17] In addition to patients with severe AH, ALD related ACLF is another entity, which is associated with poor survival.[18] As opposed to poor survival with medical management, LT is associated with good survival even in grade 3 ACLF patients.[5] Thus, majority of patients with these 2 conditions (severe AH and ACLF) will not survive to fulfill the requirement of a 6-month abstinence rule and should be considered for early LT in DDLT setting.

In contrast to the west, DDLT programs are not well developed in the East. LDLT is the predominant form of LT in east. As a living family member donates graft to a prospective LT recipient, the organs in LDLT are not a form of public resource. The LDLT avoids risk of wait list mortality in sick patients with ALD like severe AH, ACLF and hepatocellular carcinoma. Also, LDLT can be timed early or at optimization of organ failures in patients with ALD related ACLF. Generally, LDLT reflects the presence of a strong social support and relapse rates may be different as the donor may be living with recipient in same household.[3,5]

OUTCOMES AFTER LIVER TRANSPLANTATION

LT for ALD is associated with good outcomes that are comparable to transplantation for other etiologies. The data from European liver transplant registry (1988-2005) showed a 73% 5-year and a 59% 10-year survival rate for ALD in a cohort of 9880 patients, this survival was better as compared to patients with hepatitis C and cryptogenic cirrhosis. The following were causes of death/graft failure more commonly

in ALD patients: de novo malignancies, cardiovascular and social causes.[2]

A recent analysis of United Network for Organ Sharing database database (USA) from 2001 to 2016 compared 9438 ALD with 23475 non-ALD patients. The proportions of LT for ALD increased from 15.3% in 2002 to 18.6% in 2010 and 30.6% in 2016 when patients with hepatitis C were also included. The cumulative unadjusted 5-year survival was 79% versus 80% for ALD and non-ALD respectively. The cumulative unadjusted 10-year post LT survival was 63% for ALD vs 68% for non-ALD ($p = .006$).[1] As discussed earlier, while DDLT is the common form of LT in western world, LDLT is the predominant form of LT in Asia. Most of data of outcomes of liver transplantation and relapse after transplantation is from DDLT centers, and there is limited literature LDL. Table 1 shows 2 important registry analyses from USA and Europe, and 2 LDLT studies from Asia.

Table 1. Outcomes of LT for ALD.

Author (year)	n	Patient survival	Comments
Lee, 2019[1]	9438	79% at 5-years, 63% at 10-years	Worse survival in long-term
Burra, 2009[2]	9880	73% at 5-years, 58% at 10-years	Lower survival if hepatitis C also present
Egawa, 20141[3]	140	10-year survival 73.8% (no relapse), 21.9% (relapse)	22.9% relapse
Saigal S, 2016[3]	408	88.5 % at 3 years	9.5% relapse, 23% of relapses were harmful relapse

It should be noted that the long-term outcomes of LT for ALD are affected by relapse of alcohol intake (causes graft dysfunction) and smoking (increases risk of de novo malignancy), both of these factors are modifiable.[8,19] There is a higher risk of de novo malignancies in recipients of ALD as compared to other etiologies.[19-21] It is important to instruct these patients to avoid smoking and alcohol intake. Avoidance of these factors and smokeless tobacco becomes even more important in our setting where oropharyngeal malignancies are the most common form of de novo malignancies.[22]

RISK FACTORS FOR RELAPSE/RECIDIVISM

Following risk factors have been shown to be important for post transplant relapse or recidivism: a pre LT abstinence < 6 months, younger age, lack of social support, psychiatric illness prior to transplantation, history of substance abuse or alcohol treatment, non-compliance with clinic visits, smoking and complication post LT as shown in Table 2 (references 10,11,13,23-34). All these factors are not universal findings across all studies. Several risk scores have been proposed, 2 of these scores are shown in Table 3 (references 35,36), but validations is done by few studies only.[11,30]

It is important to identify relapse versus recidivism. Occasional alcohol intake is not associated with worse outcomes, while recidivism is associated with worse otcomes.8 Rice et al analyzed data of 300 LT recipients for ALD, 48 (16.0%) had relapse. The patterns of relapse were a single event (n=10) intermittent relapses (n=22) and continuous heavy drinking (n=16). The continuous heavy drinking was associated with allograft loss in multivariate analysis; hazard ratio 2 .57, p = 0.006.[26]

Table 2. Risk factors for relapse.

Risk factor	References	Comment
Abstinence < 6 months	10,11,23-25	Not important in some studies12,13
Age	10, 11, 26,27	Not important in some studies28,29
Lack of social support	13, 23,30-32	Not a universal finding
Psychiatric issues	11,25, 30,33	Not a universal finding
Pre-LT substance abuse or alcohol treatment	30	Not a universal finding
Non-compliance with clinic visits	13	LDLT study
Smoking	13,31,32	Also associated with increased risk of malignancies
Complication post LT	34	Single study

Table 3. Risk scores to predict relapse of alcohol after liver transplantation

Risk score, author (year)	Score calculation	Comments
Alcohol Relapse Risk Assessment (ARRA), Rodrigue[35] (2013)	One point to each of following 9 parameters; absence of HCC, tobacco dependence, continued alcohol use after liver disease diagnosis, low motivation for alcohol treatment, poor stress management skills, lack of rehabilitation, limited social support, lack of nonmedical behavioral consequences, engagement in social activities with alcohol	Score range 0-9, relapse rates were 0% for the ARRA I (score 0), 8% for the ARRA II (score 1-3), 57% for the ARRA III (score 4-6), and 75% for the ARRA IV (score 7-9), ARRA classification was also associated with intensity of relapse

High-Risk Alcoholism Relapse (HAR) model, Yates,[36] 1993	Duration of heavy drinking in years, (< 11 years = 0, 11-25 years = 1, > 25 years = 2), usual daily number of standard drinks, (< 9 = 0, 9-17 = 1, > 17 = 2) number of previous alcoholism inpatient treatments (0 = 0, 1 = 1, >1 = 2)	Score 4-6 (HAR group) 61% were re-admitted within 6 Months compared to 28% of the low-risk alcoholism relapse (score 1-3)

CONCLUSION

LT for ALD is associated with good short and long-term outcomes. Long-term survival is affected by recidivism and de novo malignancies; several of risk factors like alcohol relapse and smoking are modifiable. Occasional alcohol relapse is not associated with poor outcomes; recidivism is associated with worse graft and patient survival. Pretransplant abstinence of 6 months is difficult to apply for patients with poor short-term prognosis, like AH and ACLF.

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8

Assessment and Management of Alcoholic Hepatitis

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INTRODUCTION

Alcoholic hepatitis (AH) is a serious acute liver condition which may be superimposed on underlying cirrhosis and thereby can present as acute on chronic liver failure. However, it is not uncommon to have severe AH with no underlying cirrhosis. Severe AH has high short term (28 day) mortality and thereby needs early diagnosis and appropriate management.[1,2]

Population based studies in Denmark report 34 to 46 cases of AH per million in women and men respectively.[3] A survey in USA found that AH accounted for nearly 1% of all hospital admissions.[4]

DEFINITION AND TERMINOLOGY

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) Alcoholic Hepatitis Consortia defines AH as "a clinical entity with rapid onset of jaundice and elevated serum AST (aspartate transferase) in the background of heavy alcohol use".[5] In this definition, jaundice refers to serum bilirubin >3 mg/dL, raised AST >50 IU/ml and AST/ALT ratio >1.5. The thresh hold of heavy alcohol use is >40 gm/day for women and >60 gm/day for men. The duration of heavy alcohol use is typically >6 months and the period of abstinence is <60 days prior to the onset of jaundice.

The degree of certainty of making a diagnosis of AH has been based on histological confirmation and ruling out additional etiology of hepatitis. Thus, the diagnosis of AH can be classified as definite (with clinical, laboratory and biopsy features of steatohepatitis), probable (clinical and laboratory features, liver biopsy not done) and possible (if there is confounding etiology or unclear history of amount of alcohol consumption).[6]

SEVERITY OF ALCOHOLIC HEPATITIS

This is classified based on discriminant function (DF) score and model for end stage liver disease (MELD) score (Table 1).[1] Categorizing patients as per disease severity is useful in making clinical management decisions. For example, patients with mild disease do not need admission, while those with severe disease need to be hospitalized. Disease severity classification is also important to identify homogenous patient populations for research for example: to study a new treatment.

Table 1. Classification of severity of AH.[1]

Severity of AH	
Mild	DF <32 and MELD ≤10
Moderate	DF <32 and MELD 11-20
Severe	DF ≥ 32 or MELD > 20
Very severe	DF > 60 or MELD > 30

Is severe AH the same as alcohol related acute on chronic liver failure (ACLF)?

Both severe AH and ACLF are characterised by acute hepatic decompensation, multi-organ failure and high short-term mortality. The two terms describe different disease entities which overlap. While all ACLF patients have underlying cirrhosis, some patients with severe AH do not have cirrhosis.[7]

The two commonly used definitions of ACLF by APASL[8] and by EASL (EASL-CLIF score)[9] do not identify the same group of patients. For example, serum bilirubin level to diagnose ACLF is ≥5 mg% by APASL definition and ≥12 mg% by EASL-CLIF definition. Extra-hepatic organ failure is not needed to diagnose ACLF by APASL definition, in contrast, this is needed by EASL-CLIF definition.

In 165 patients with biopsy proven severe AH (DF ≥32), 79 patients (48%) had ACLF, when AH was diagnosed. Over 168 day follow up period, 29 patients (18%) developed incidental ACLF. These findings were confirmed in a validation cohort of 97 patients. The authors noted that ACLF was frequent during the course of severe AH and was associated with high mortality. Infection was a strong predictor of the development of incidental ACLF.[10]

PATHOPHYSIOLOGY

Raised serum immunoglobulin A levels seen in patients with ALD indicate gut damage by alcohol. The leaky gut allows gut-derived pathogen-associated molecular patterns (PAMPs) to travel via the portal venous system to enter the liver. In addition, alcohol damages hepatocytes leading to release of danger-associated molecular patterns (DAMPs). Alterations in the gut microbiota and DAMPs activate innate immune system, in turn triggering pro-inflammatory cytokine production. Spill-over of the pro-inflammatory cytokines into systemic circulation may contribute to development of multi-organ failure.[11]

Uncontrolled activation of the innate immune system in the liver causes further liver injury. Macrophages, monocytes and neutrophils are innate immune cells. Macrophages are the primary source of ferritin and raised serum ferritin levels indicate macrophage activation. The APASL ACLF Research Consortium studied MAS / HLH in ACLF (mostly alcohol related) patients from 52 centres across Asia Pacific. Of 615 patients with serum ferritin >500 µg/l, the five diagnostic criteria of HLH were met in 90 patients. The presence of HLH was a poor prognostic marker in these patients.[12]

The levels of soluble mannose receptor, a marker of macrophage activation, are elevated in patients with ALD, especially in AH patients and predict long-term mortality in alcohol related cirrhosis.[13]

von Willebrand factor (VWF) is released by activated endothelium. VWF protein acts as a carrier of coagulation factor VIII and is also a platelet adhesive protein. In severe AH, raised VWF levels may impede microcirculatory perfusion in the liver and other vital organs and cause liver/multi-organ failure. In 50 ACLF patients, mostly alcohol related, baseline plasma VWF levels were 5-7 fold raised, correlated with ACLF grade and predicted in-hospital death.[14]

The activation of macrophages and of endothelium seen in patients with AH are interlinked. VWF is cleared by tissue resident macrophages in the liver (Kupffer cells).[15]

HISTOPATHOLOGY OF ALCOHOLIC HEPATITIS (FIG. 1)

Alcoholic hepatitis is the clinical correlate of the histological condition of alcoholic steatohepatitis. The classical findings of AH on histology include hepatocyte ballooning, lobular neutrophilic infiltration, peri-venular steatosis and Mallory - Denk bodies. Neutrophils are innate immune cells and the predominant neutrophilic infiltration of the liver reflect disproportionate innate immune response, localized to the liver, in these patients.

Based on liver biopsy alone it may not be possible to differentiate NASH (non-alcoholic steatohepatitis) from ASH (alcoholic steatohepatitis).

Severe AH maybe superimposed on underlying alcohol related cirrhosis. Liver biopsy done in 30 patients with severe AH showed that 10 patients (33%) had cirrhosis (33%).[16]

Clinical Assessment

Clinical presentation of a patient with AH is distinct from that of a patient with alcohol related cirrhosis. However, a significant proportion of patients with AH have cirrhosis as well on liver biopsy. In contrast to patients with decompensated cirrhosis, the distinctive feature of AH is the presence of systemic inflammatory response syndrome (SIRS) – the latter reflects pro-inflammatory cytokinemia. Thus, the patient with AH may have fever, tachycardia, icterus, multiple spider nevi and

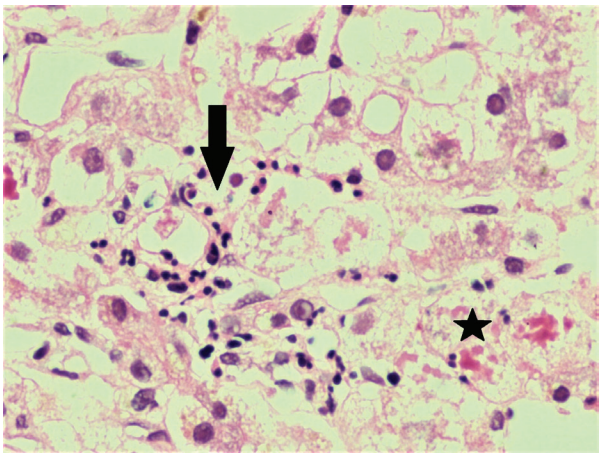

Figure 1. Photomicrograph displaying ballooning degeneration (arrow) of hepatocytes with neutrophil satellitosis (arrow) and Mallory Denk body (star) (H&E, 400x magnification).

enlarged mildly tender liver, sometimes with a bruit over it.

Investigations

The ratio of serum AST/ALT ratio was analysed by De Ritis in different etiologies of hepatitis. The half-life of AST (18 hours) is shorter than that of ALT (36 hours), hence the time course and aggressiveness of different etiologies of hepatitis maybe reflected in this ratio. ALT is only present in the hepatocyte cytoplasm, in contrast AST is present in both cytoplasm and mitochondria of hepatocytes. While AST/ALT ratio ≥ 1.5 helps identify patients with AH, this can also be seen in non alcoholic fatty liver disease and other causes of hepatitis.[17]

Prognostic Scores

Of the multiple prognostic scores described in patients with AH, the most widely used scores are discriminant function (DF), MELD score and Lille score. While DF score best predicts short term (28 day) mortality, MELD score predicts short and medium term (30-90 day) mortality. Lille score helps assess response to steroid.

Maddrey et al in 1978 described DF score [4.6 x prothrombin time (PT) in seconds x serum bilirubin (mg/dL)]. Patients with DF >93 who were treated with placebo had a 28-day survival of 25%, while those with DF ≤ 93 had 100% survival (4). In 1989 the score was modified (mDF) by using prolongation of prothrombin time (instead of the absolute value of prothrombin time). mDF score ≥ 32 and/or hepatic encephalopathy predicted 65% survival at 28 days (14).[18] At present, mDF score ≥32 is considered a trigger to initiate steroids.[1,2]

In patients with AH, MELD scores have sensitivity and specificity of 86% and 81%, respectively, for predicting 30 day mortality.[19]

Other prognostic scores for AH include Glasgow AH severity score and ABIC score (Age, Bilirubin, INR, Creatinine) score.

Lille score is used to measure and predict response to steroid treatment in severe AH. This score requires age, creatinine, albumin, prothrombin time and bilirubin at baseline and bilirubin after 7 days of steroid treatment to be computed. Lille score >0.45 on day 7 identifies steroid non-responders and predicts poor 6 months survival (25%).[20] This score is useful to decide on early liver transplantation for steroid non-responders.

VWF levels were higher in severe AH compared to mild AH or cirrhosis. Patients who died had much higher VWF levels compared to survivors.[21] In a study of 50 ACLF patients (predominantly alcohol related), the ability of baseline VWF levels to predict in-hospital survival was comparable with MELD, ACLF grade and SOFA scores. Normal plasma VWF antigen and activity levels are 50-150%. The hazard ratio for VWF activity level >1000% to predict poor outcome over the next 7 days was ∞ (infinity).[14]

Microvesicles are membrane bound extracellular vesicles released from cells that undergo apoptosis. CD 34+ (hematopoietic) and ASGPR+ (hepatocyte) microvesicles in peripheral blood were higher at baseline in patients with severe AH, correlated with histological disease severity, poor response to steroid and poor outcome. After treatment, non-responders had higher CD 34+ and ASGPR+ microvesicles compared to responders.[22]

Apart from the prognostic scores discussed above, the presence of underlying cirrhosis is an important determinant of prognosis. Sepsis is the most common non-liver related cause of death in AH patients irrespective of their response to steroids.[23]

TREATMENT

Patient with mild AH (also termed "walking" AH) can be managed as outpatient. Severe AH patients require admission and may need intensive care. Alternative causes of acute hepatitis like hepatitis viral infections, idiosyncratic drug induced liver injury (due to allopathic and complementary alternate medications) need to be looked for.

Alcohol abstinence is important. Psychological and social support needs to be provided to the patient.

Nutrition is of paramount importance, as most patients are malnourished. (Please see the chapter on "Role of nutrition in alcoholic liver diseases" for more details).

Supportive treatment includes watching for/treating alcohol withdrawal, to screen for sepsis.

Therapeutic Interventions for Severe AH

In 2015, a systematic review and network meta-analysis compared the efficacy of corticosteroids, pentoxiphylline and N-acetylcysteine in reducing short-term mortality (at 4 weeks) and medium-term mortality (at 6 months). This analysis of 22

RCTs concluded that pentoxiphylline and steroids (alone and in combination with pentoxiphylline or N-acetylcysteine) can reduce short-term mortality. However, no treatment decreased medium-term mortality.[24]

Treatment of severe AH is witnessing a paradigm shift from anti-inflammatory therapy such as steroids to newer treatments like liver regenerative treatment (ex: granulocyte colony stimulating factor) and fecal microbiota transplantation.[25] For SAH pts who are nonresponsive to medical treatment, liver transplantation may be considered. Preliminary data suggest that these newer therapies improve medium term survival (Table 2).

1. Corticosteroids: The most extensively studied intervention to date to treat severe AH is corticosteroids. However, despite multiple (>20) randomized controlled trials, the results are inconsistent, probably due to methodological issues like bias due to heterogeneity and lack of power. Different investigators have conducted meta-analysis to interpret the results of these randomized controlled trials. Most meta-analyses indicate short term survival benefit with steroids. However, superadded bacterial infection is a concern in treating severe AH patients with steroid. Prednisolone tablets 40 mg once daily for 4 weeks is advocated in patients with severe AH.[1,2] Contraindications for the use of Prednisolone are GI bleed, acute kidney injury and infection. About 25% of patients do not respond to steroid therapy.
2. Pentoxyphylline: Has been tried for its anti-TNF effects, to counter the hypercytokinemic milieu in severe AH. Pentoxyphylline use improved in renal insufficiency in severe AH patients in two studies. While the network meta-analysis reported reduction in short term mortality with Pentoxyphylline,[24] this was not borne out in subsequent studies like the STOPAH trial.[26]

The STOPAH trial[26] - the largest randomized controlled trial to date - compared corticosteroid and pentoxyphylline in severe AH in four treatment arms: placebo-placebo, placebo-pentoxyphylline, prednisolone-placebo and pentoxy-phylline-prednisolone. While the 28 day survival was not significantly different between the patient groups, prednisolone-placebo arm suggested potential survival benefit. Infection rate was 13% in patients who received steroid compared to 7% in those not on steroid (p=0.002). Multivariable analysis done post hoc showed corticosteroids were associated with improved survival at 28 days but not at 90 days or at 1 year. The results of STOPAH trial and of previous meta-analyses offer modest support for use of prednisolone but not for pentoxiphylline to treat severe AH.[1]

EMERGING TREATMENT MODALITIES

As current literature suggests steroids as the mainstay of treatment, most newer therapies are being studied in either patients who do not respond to steroids ("steroid non-responders") or in patients who have relative contra-indications to steroid use ("steroid ineligible" patients). Non-response to steroid is assessed based on Lille score (a dynamic score). As newer and more effective treatments emerge, it is possible that

Table 2. Newer treatments for severe alcoholic hepatitis (SAH)

Newer treatment	Study subjects	Survival				
Early liver transplantation	SAH patients: steroid non-responders	**6 month survival**				
		Cases		Controls	p value	
		77 ± 8%		23 ± 8%	<0.001	Mathurin et al. N Engl J Med. 2011[27]
GCSF		**90 day survival**				
		Cases		Controls	p value	
	SAH patients: steroid non-responders	64%		29%	0.04	Shasthry et al. Hepatology. 2019[29]
	SAH patients	78.3%		30.4%	0.001	Singh et al. Am J Gastro. 2014[31]
GCSF + NAC	SAH patients	GCSF	GCSF +NAC	Controls		
		89%	68%	30%	0.0001	Singh et al. Clin Gastro Hepat. 2018[30]
		1 year survival				
		Cases		Controls	p value	
Fecal microbiota transplantation	SAH patients: steroid ineligible	87.5%		33.3%	0.018	Philips et al. Clin Gastro Hepat. 2017[32]

steroids may no longer be the primary treatment modality to treat severe AH.

Early liver transplantation: The high short term mortality in severe AH meant that many patients do not survive the "6 months of abstinence" rule, prior to liver transplantation. Mathurin et al demonstrated survival benefit by early liver transplantation for patients who did not respond to steroid (using Lille score).[27] The ethical aspects of early liver transplantation in severe AH , especially in a cadaveric liver transplantation programme, have been debated.[28]

Granulocyte colony stimulating factor (GCSF): Hematopoietic stem cells mobilized by GCSF therapy may promote hepatic regeneration in patients with severe AH.[29-31]

Fecal microbiota transplant: Altered gut microbiota may contribute to pathogenesis and progression of AH. Healthy donor fecal microbiota transplantation aims to correct gut dysbiosis and thus treat severe AH.[32]

Other promising newer therapies being explored in severe AH include low volume plasma exchange with low dose steroid[33] (aims to ameliorate the disproportionate innate immune response, endothelial and macrophage activation and secondary HLH) and bovine colostrum[34] (immunomodulatory effects, reduces portal and systemic endotoxemia).

Public Perception of the Disease Process

A major challenge in treatment of AH is social stigma attached to what is perceived as a self-inflicted disease. A caring and compassionate approach is needed by the care givers in the family, the treating health care workers as well as health policy decision makers in this regard. Successful rehabilitation to a productive life is beneficial to the individual concerned, his family and society at large.

CONCLUSIONS

Severe AH is a devastating illness with high short term mortality rates. Better understanding of the pathophysiology of this disease has brought in exciting newer treatments, which seem to improve medium term survival. With multiple clinical trials of newer treatments in progress, the prognosis of severe AH is starting to improve.

Acknowledgements: We gratefully acknowledge Dr. Thomas Alex, Pathology department, Christian Medical College, Vellore for providing the photomicrograph of histology of severe AH.

KEY LEARNING POINTS

- Clinical features of systemic inflammatory response syndrome help differentiate patients with AH from those with cirrhosis.
- Severe AH carries high short term mortality.
- While many patients have contraindications for or did not respond to corticosteroids, the most widely advocated treatment to date; promising new treatments are now emerging to treat severe AH.

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9

Alcohol - How Much is too Much?

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INTRODUCTION

Alcohol occupies a unique place in human society. It is a widely used (often abused) substance, finding a place in celebrations, social interactions among individuals, some religious ceremonies, rituals and in everyday transactions. But it is also contributes extensively to illness, violence, social disorder and morbidity & mortality. Alcohol and tobacco are important products of the global addictive demand and have experienced a rapid increase in per capita consumption. Alcohol is causally related to more than 60 medical conditions.[1] Overall, 3.5% of the global burden of disease is attributable to alcohol, which accounts for as much death and disability as tobacco and hypertension.[2,3] Excess consumption of alcohol is associated with both short-term and long-term liver damage, several types of cancers, unintentional injuries both in the workplace and on the road, domestic and social violence, broken marriages, and damaged social and family relationships.[4]

Chronic alcohol use may cause several types of liver injury. Regular alcohol use, even for just a few days, can result in a fatty liver (also called steatosis), a disorder in which hepatocytes contain macrovesicular droplets of triglycerides. Although alcoholic fatty liver resolves with abstinence, steatosis predisposes people who continue to drink to hepatic fibrosis and cirrhosis.[5]

ALCOHOL AND GLOBAL BURDEN

Taking into account both recorded and unrecorded consumption , the highest amount of alcohol consumed per adult resident is in Europe, especially in Russia and its surrounding countries, and in North America. The least amount of alcohol

consumed per resident is in the mostly Islamic regions of the Eastern Mediterranean and in the lesser developed region of Southeast Asia, dominated by India.[6]

Table 1. Global burden of alcohol.

WHO regions	Grouping within regions*
Developing countries	
Islamic Middle East and Indian subcontinent	Very high or high mortality; lowest consumption
Poorest countries in Africa and America	Very high or high mortality; low consumption
Better-off developing countries in America, Asia, Pacific	Low mortality; emerging economies
Developed countries	
North America, Western Europe, Japan, Australasia	Very low mortality
Former Socialist, Eastern Europe and central Asia	Low mortality

*Defined by WHO based on mortality

Table 2. Major disease and injury conditions (%) attributable to alcohol worldwide.

Condition	Men	Women	Both
Malignant neoplasms			
Mouth and oropharynx	22	9	19
Esophageal	37	15	29
Liver	30	13	25
Breast	NA	7	7
Neuropsychiatric disorders			
Unipolar depressive	3	1	2
Epilepsy	23	12	18
Alcohol use: Dependence and harmful use	100	100	100
Cardiovascular disorders			
Ischemic heart disease	4	-1	2
Hemorrhagic stroke	18	1	10
Ischemic stroke	3	-6	-1
Cirrhosis of the liver	39	18	32

Unintentional injury			
Motor vehicle accidents	25	8	20
Drowning	12	6	10
Fall	9	3	7
Poisoning	23	9	18
Intentional injury			
Self inflicted	15	5	11
Homicide	26	16	24

INDIAN SCENARIO

Although the recorded alcohol consumption per capita has fallen since 1980 in most developed countries, it has risen steadily in developing countries, alarmingly so in India. The per capita consumption of alcohol by adults ≥15 years in India increased by more than 100% between 1970–72 and 1994–96.[7] The pattern of drinking in India has changed from occasional and ritualistic use to social use. Today, the common purpose of consuming alcohol is to get drunk.[8] These developments have raised concerns about the health and the social consequences of excessive drinking. [9] The spirits industry in India is divided into three segments: 'India-made foreign liquor' (IMFL: whisky, gin, rum, brandy, liqueurs, vodka); 'India-made country liquor' (licensed distilled spirits, made locally); and the illicit liquor sectors.[10,11] The common varieties of 'country liquor' are arrack, desi sharab and tari.

In India there are regional differences in alcohol consumption, maximum consumption reported from Sikkim, Kerala & Punjab, closely followed by most metros.

ALCOHOL AND PUBLIC HEALTH

To understand excessive drinking, it is important to define one standard drink.

A standard drink - A standard drink is equal to 14.0 grams (0.6 ounces) of pure alcohol.[12] Generally, this amount of pure alcohol is found in

- 12 ounces (360 ml) of beer (5% alcohol content).
- 8 ounces (240) of malt liquor (7% alcohol content).
- 5 ounces (150 ml) of wine (12% alcohol content).
- 1.5 ounces (45 ml) or a "shot" of 80-proof (40% alcohol content) distilled spirits or liquor (e.g., gin, rum, vodka, whiskey).

Note - One 12-ounce beer has about the same amount of alcohol as one 5-ounce glass of wine or 1.5-ounce shot of liquor. It is the amount of alcohol consumed that affects a person most, not the type of alcoholic drink.

Moderate Drinking or Drinking in Moderation (i.e less than risky)

According to the Dietary Guidelines for Americans[12] moderate alcohol consumption is defined as having up to 1 drink per day for women and up to 2 drinks per day for men. This definition refers to the amount consumed on any single day and is not intended as an average over several days. However, the Dietary Guidelines do not recommend that people who do not drink alcohol start drinking for any reason.

Moderate (i.e., less than risky) use of alcohol may be beneficial, but what constitutes "moderate" depends on age, sex, genetic characteristics, coexisting illnesses, and other factors. Observational studies indicate that for men under the age of 34 years and women under the age of 45 years, those who report no alcohol intake have the lowest mortality. Above these age cutoffs, weekly intakes of no more than five drinks for men or two drinks for women are associated with the lowest mortality.[13] The balance of harm (an increased risk of liver disease, motor vehicle crashes, hypertension, hemorrhagic stroke, and some cancers) and benefit (a reduced risk of ischemic heart disease and ischemic stroke) determines these amounts.

Excessive Drinking (Too much or risky drinking)

The definitions of Excessive alcohol (defined below) apply only to those individuals with a normal/healthy state (no pre-existing liver or pancreatic disorder or other conditions)

- Binge drinking: For women, binge drinking is 4 or more drinks consumed on one occasion (one occasion = within 2-3 hours). For men, binge drinking is 5 or more drinks consumed on one occasion*.
- Heavy drinking: For women, heavy drinking is 8 drinks or more per week. For men, heavy drinking is 15 drinks or more per week.
- Underage drinking: Any alcohol use by those under age 21.
- Pregnant drinking: Any alcohol use by pregnant women

*One occasion = within 2 to 3 hours

Binge drinking - Binge drinking is defined as a pattern of alcohol consumption that brings the blood alcohol concentration (BAC) level to 0.08% or more. This pattern of drinking usually corresponds to 5 or more drinks on a single occasion for men or 4 or more drinks on a single occasion for women, generally within about 2 hours.[12]

Health Problems associated with Excessive Alcohol Use

Excessive drinking both in the form of heavy drinking or binge drinking, is associated with numerous health problems, including but not exclusive of following:

- Chronic diseases such as liver cirrhosis (damage to liver cells); pancreatitis (inflammation of the pancreas); various cancers, including liver, mouth, throat, larynx (the voice box), and esophagus; high blood pressure; and psychological disorders.

- Unintentional injuries, such as motor-vehicle traffic crashes, falls, drowning, burns, and firearm injuries.
- Violence, such as child maltreatment, homicide, and suicide.
- Harm to a developing fetus if a woman drinks while pregnant, such as fetal alcohol spectrum disorders.
- Sudden infant death syndrome (SIDS).
- Alcohol use disorders.

ALCOHOL USE DISORDER

Problem drinking that becomes severe is given the medical diagnosis of "alcohol use disorder" or AUD. AUD is a chronic relapsing brain disease characterised by compulsive alcohol use, loss of control over alcohol intake, and a negative emotional state when not using.

To be diagnosed with AUD, individuals must meet certain criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM). Under DSM–5, the current version of the DSM, anyone meeting any two of the 11 criteria during the same 12-month period receives a diagnosis of AUD.

The severity of AUD—

- mild (i.e. presence of 2 to 3 symptoms),
- moderate (i.e. presence of 4 to 5 symptoms), or
- severe (i.e. presence of 6 or more symptoms)

To assess whether you or loved one may have AUD, here are some questions to ask. In the past year, have you:

- Had times when you ended up drinking more, or longer than you intended?
- More than once wanted to cut down or stop drinking, or tried to, but couldn't?
- Spent a lot of time drinking? Or being sick or getting over the aftereffects?
- Experienced craving — a strong need, or urge, to drink?
- Found that drinking — or being sick from drinking — often interfered with taking care of your home or family? Or caused job troubles? Or school problems?
- Continued to drink even though it was causing trouble with your family or friends?
- Given up or cut back on activities that were important or interesting to you, or gave you pleasure, in order to drink?
- More than once gotten into situations while or after drinking that increased your chances of getting hurt (such as driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)?
- Continued to drink even though it was making you feel depressed or anxious or

adding to another health problem? Or after having had a memory blackout?

- Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?
- Found that when the effects of alcohol were wearing off, you had withdrawal symptoms, such as trouble sleeping, shakiness, irritability, anxiety, depression, restlessness, nausea, or sweating? Or sensed things that were not there?

If you have any of these symptoms, your drinking may already be a cause for concern. The more symptoms you have, the more urgent the need for change. A health professional can conduct a formal assessment of your symptoms to see if AUD is present.

However severe the problem may seem, most people with AUD can benefit from treatment. Unfortunately, less than 10 percent of them receive any treatment.

Excessive drinking and AUD- About 90% of people who drink excessively would not be expected to meet the clinical diagnostic criteria for having a severe AUD.[14] A severe AUD, previously known as alcohol dependence or alcoholism, is a chronic disease.

ALCOHOL AND LIVER DISEASE

The association between alcohol intake and alcoholic liver disease (ALD) has been well documented, although cirrhosis of the liver develops in only a small proportion of heavy drinkers. The risk of cirrhosis increases proportionally with consumption of more than 30 g of alcohol per day; the highest risk is associated with consumption of more than 120 g per day.[15] The point prevalence of cirrhosis is 1% in persons drinking 30 to 60 g of alcohol a day and up to 5.7% in those consuming 120 g daily. Hence it is presumed that other factors, such as sex,[15,16] genetic characteristics,[17] and environmental influences (including chronic viral infection),[18] also play a role in the genesis of ALD.

Association with Dose, Threshold and Sex

There is no doubt that excessive alcohol consumption leads to liver disease—from simple fatty liver to cirrhosis—in certain individuals. Although alcohol per se is the most important risk factor for alcoholic cirrhosis, only about 35% of heavy drinkers develop the disease.[19] Moreover, even light drinkers, who consume one to two drinks a day, are at increased risk of alcoholic cirrhosis compared to abstainers.[20] Therefore, other risk factors besides the amount of alcohol must be important for alcoholic cirrhosis. For example, sex, smoking, obesity and chronic viral hepatitis C have been found to be associated with an increased risk.[21-23] Women have a higher risk of alcoholic cirrhosis compared to men for a given level of alcohol intake.[20,24]

There is general agreement that excessive alcohol consumption is associated with an increased risk of cirrhosis. However, there is no consensus on the exact dose or a specific dose–response relationship for cirrhosis.[26] Evidence suggests that there is an increased risk with ingestion >60–80 g/day of alcohol in men and >20 g/day in women.

However, 6%–41% of those drinking these amounts will develop cirrhosis.[25-27]

Most of the relevant data have, until very recently, come from retrospective studies assessing alcohol intake in hospitalised patients at the time of diagnosis. Clearly, these studies on highly selected patients are subject to many confounding influences,[28] and are also unable to provide any information on the risk of liver disease in the population stratified into drinking categories.

A prospective longitudinal study conducted by Becker et al[29] established an association between self-reported alcohol intake and the risk of future liver disease in a large population (prospective cohort of 13285 subjects enrolled into the Copenhagen City Heart Study). Twelve years after enrolment the incidence of liver disease was determined from death certificates and hospital discharge records. They observed a steep dose dependent increase in relative risk of alcohol induced liver disease above a "threshold" of 7–13 drinks per week in women and 14–27 drinks per week in men. Women had a significantly higher relative risk than men for any given level of intake. Importantly, of those individuals consuming more than 70 drinks per week, only 7% were cirrhotic and only 19% had any evidence of alcohol induced liver disease at all.

Bellentani et al[30] have used a different approach as part of the impressive Dionysos Study, a cross-sectional study that determined the prevalence of chronic liver disease in the entire adult population of two towns in northern Italy. They reported a risk threshold for both non-cirrhotic and cirrhotic liver disease of 21 drinks per week in men and women with a step-wise increase in risk with increasing intake. The lifetime intake threshold for disease was 100 kg. The risk of disease was twice as high in women than men, but only in the dose range 3–8 drinks/day. Only 4% of individuals consuming more than 6 drinks daily had cirrhosis and only 10% had any evidence of liver disease at all. Also Bellentani et al.[25] showed that even in patients with an extremely high daily alcohol intake (>120 g/day), only 13.5% developed alcohol-induced liver damage. It is believed that other factors such as genetic susceptibility and dietary intolerance may be co-factors in alcohol-induced liver damage.

Alcohol drinking pattern and risk of alcoholic liver cirrhosis

Few studies have investigated the influence of alcohol drinking patterns (Fig.1) on the risk of alcoholic cirrhosis in the general population. Patterns of drinking includes

- drinking frequency
- binge drinking (drinking at least four or five drinks per occasion)[31,32]
- lifetime alcohol consumption, and
- beverage type

Most studies on drinking frequency and risk of alcoholic cirrhosis have found that daily drinking compared to episodic or binge drinking is associated with an increased risk.[24,35–37] Moreover, death from cirrhosis might have explained the increased risk of overall mortality found in frequent drinkers (5–7 days per week) compared to

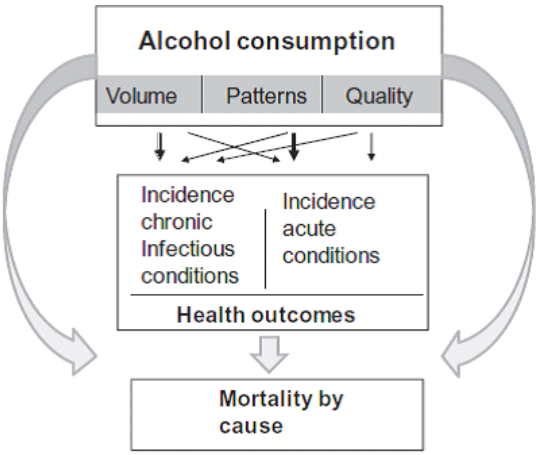

Figure 1. Alcohol consumption and outcomes

infrequent drinkers (1–4 days per week) in a Japanese study, although a Danish study reached the opposite conclusion.[33,34]

Alcohol Amount, Drinking Frequency and Beverage Type

Various past and recent studies have confirmed the dose-response relationship between alcohol amount and alcoholic cirrhosis but its relationship with pattern of drinking has not been established beyond doubt. In a landmark Danish prospective cohort study including 55,917 participants by Askgaard and colleagues,[38] a significant correlation of daily drinking with an increased risk of alcoholic cirrhosis as compared to less frequent drinkers when alcohol amount was taken into account has been shown (Table 3). Recent alcohol consumption and not lifetime alcohol consumption, is the strongest predictor of alcoholic cirrhosis.

They also showed no risk of cirrhosis among life time abstainers. As compared to subjects drinking fewer than 14 drinks per week(Moderate drinking) risk of cirrhosis was 7 times higher in recent abstainers and then with subsequent increase in weekly amount hazard increased steeply following a J- shaped curve (Fig. 2).

Beverage Type - Upto a moderate level of weekly alcohol amount, compared to beer and liquor, wine seems to be associated with a lower risk of alcoholic cirrhosis. In analyses controlled for consumption of other beverage types, the HR for alcoholic cirrhosis was lower for weekly amount of wine than for other beverage types, in both men and women drinking more than 14 drinks weekly (Fig. 3).

Table 3. HR for alcoholic cirrhosis according to drinking frequency.

Hazard ratio	Not drinking alcohol at baseline		Drinking alcohol at baseline				
	Lifetime abstainers	Current abstainers	<1	1	2-4	5-6	7
Adjusted for age	NA	7.7 (3.35; 17.7)	1.67 (0.88; 3.19)	1.13 (0.52; 2.50)	1.0	2.26 (1.35; 3.81)	8.29 (5.52; 12.4)
Adjusted for age and alcohol amount	NA	10.4 (4.50; 24.8)	0.89 (0.40; 1.98)	1.32 (0.60; 2.90)	1.0	1.69 (1.00; 2.85)	4.83 (3.20; 7.29)
Adjusted for age, alcohol amount, and confounders*	NA	10.0 (4.32; 23.0	1.34 (0.67; 2.67)	1.30 (0.59; 2.87)	1.0	1.43 (0.84; 2.43)	3.65 (2.39; 5.55)

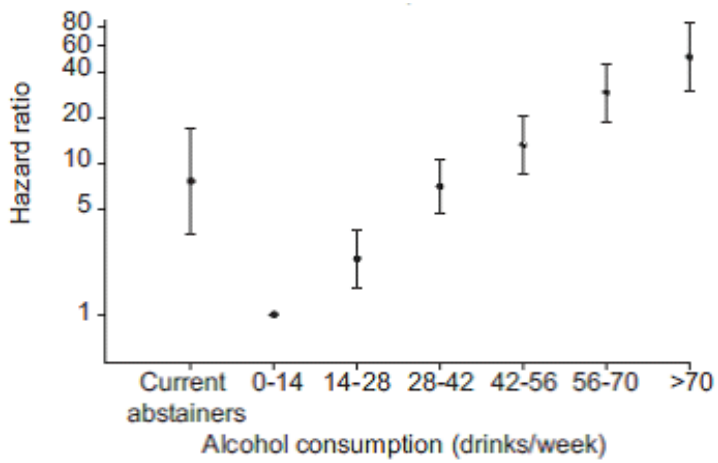

Figure 2. Risk of alcoholic cirrhosis according to weekly alcohol amount.

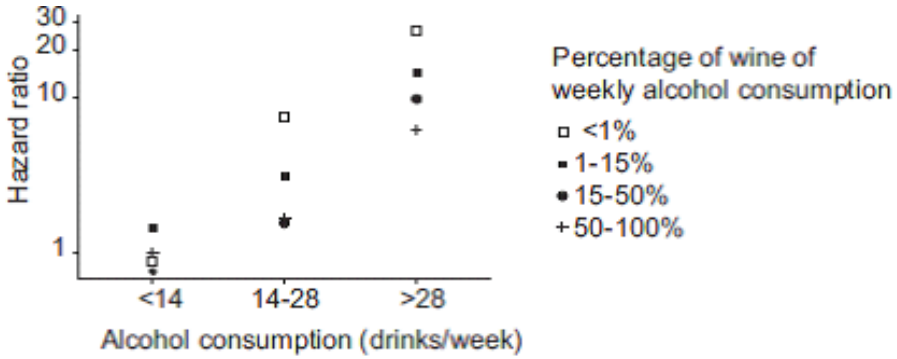

Figure 3. Risk of alcoholic cirrhosis in relation to percentage of wine of weekly alcohol amount.

INDIAN SCENARIO

India is a diverse nation with cultural variations among ethnic, religious and linguistic groups, and there are major differences between the urban and rural areas. However, in recent years, the prevalence of alcohol-related cirrhosis is increasing. In a recent study in Kerala, in 60% of patients with cirrhosis in a large tertiary hospital, alcohol consumption was the cause. Nearly 80% of the alcoholics were also smokers. Almost all alcoholics develop fatty liver, which is reversible following abstinence from alcohol. Many alcoholics develop alcoholic hepatitis, which may be subclinical, and may be diagnosed only on biopsy. Only one-third of alcoholics develop liver cirrhosis; the vulnerability is probably decided by genetic and dietary factors. Hepatocellular carcinoma develops in about 5% of cases of alcoholic cirrhosis.

Drinking Pattern in India

Prevalence - Studies in northern India found the 1-year prevalence of alcohol use to be between 25% and 40%.[40,41] In southern India, the prevalence of current alcohol use varies between 33% and 50%, with a higher prevalence among the lesser educated and the poor.[42] In western India, a study conducted among 50,220 middle-aged people in a community Gupta et al[39] found current alcohol use was reported by 18.8% and past use by 4.9%. More than 76% of the individuals had 'never used' alcohol.

Age - Sethi and Trivedi[43] found alcohol misuse to be 11.3% among the 55–64 years' age group and 16.8% among the 65–74 years' age group in a rural population in north India. Varma et al[41] found 18.3% of those >50 years of age to be current users of alcohol and 23.3% to be 'ever' users of alcohol. Sikkim, tops among the states in terms of alcohol consumption with nearly 35% of the population >21 years of age being chronic alcoholics, the figure being very high compared to the national average. Relapse rates after deaddiction for alcohol abuse are also very high.[44]

Sex - Among various epidemiological studies conducted in various regions of India, The most consistent finding in all the studies was that men are the primary consumers of alcoholic beverages. However, the percentage of men who had consumed an alcoholic beverage varied widely among different regions, ranging from 16.7% in Chennai city in southern India to 49.6% in a village in Punjab in northwest India. Conversely, the alcohol consumption rates among women were consistently low (<5%).[45] In another study, Mohan et al[46] reported a prevalence of alcohol use of 20%–38% in men and 10% among women in three districts of central, north and northeast India.

Amount - Gupta et al[39] reported that the number of people consuming alcohol was lower than, for example, in developed countries; but the amount of alcohol consumed by drinkers was high, which suggests the risk of serious public health problems. The volume of consumption as well as the patterns of drinking, especially irregular heavy drinking, have been shown to determine the burden of disease.[47-49]

Type of alcoholic beverage - A study by Bennett et al[50] in Bangalore showed that the following three types of alcoholic beverages were consumed most often:

1. Arrack, a traditional drink produced (both legally and illegally) by distilling fermented molasses, raw brown sugar, palm wine, rice or palm sugar; it has an alcohol content ranging from 20% to 40%.
2. Palm wine, another traditional beverage produced from either the coconut tree or other palm trees, has an alcohol content ranging from 20% to 40%.
3. Imported liquors such as whisky, brandy and rum.

Studies among the Rajputs of northwestern India identified three preferred types of alcoholic beverages:[51]

1. Daru, a drink distilled from the flowers of the mahwa tree, has an alcohol content ranging from 20% to 40%.
2. Spirit produced from solvents, which varies greatly in alcohol content and, at the time of the study, was drunk only by 'untouchables' and members of other lower castes.
3. 'English alcohol,' a distilled liquor—usually whisky or gin— associated with the British rule.

Table 4. Drinking practices among Indians.

Drinking practices	Indian context
Women	Predominantly abstinent (about 95%)
Men	Highly variable across regions
Young persons	Increasing concern
Most commonly consumed beverage	Arrack, palm wine, beer, imported liquor
Context of drinking occasions	No regular context established; not part of daily life or rituals
Extent of major concerns about alcohol-related problems	Increasingly seen in health, social and economic areas

ALCOHOL USE IN PATIENTS WITH NAFLD

NAFLD comprises a continuum of disease severities, from steatosis to inflammation and steatohepatitis, and can potentially progress to fibrosis and cirrhosis.[52,53] However, cardiovascular disease (CVD) remains the most common cause of mortality and morbidity in patients with NAFLD.[54-56] There is observational evidence that modest alcohol consumption, as compared to no or heavy alcohol intake, decreases the risk of adverse cardiovascular outcomes.[57-61] There is also evidence for beneficial effects of modest alcohol consumption on risk of metabolic syndrome and insulin resistance which are important components of the NAFLD disease process.[62-64] However, the effect of alcohol consumption on survival and how much is safe limit in patients with NAFLD is not well-described. A large prospective cohort, with data collected over 23 years (1988 to 2010) from USA,[65] has shown that among patients with NAFLD and compared to non-drinkers, modest alcohol consumption (here defined as drinking an average of half to one and a half drinks of alcohol per day i.e <10 drinks/week) was associated with a significant 41% lower risk of death (HR=0.59, 95% CI 0.40-0.85, p value=0.005) after adjusting for age, gender, and smoking status, while drinking more than or equal to one and a half drinks per day showed a significant harmful effect in these patients (HR=1.45, 95% CI 1.01-2.10, p value=0.047).[65] So the conventional wisdom of 14 drinks per week does not apply to NAFLD patients. The safe amount in this subgroup is less than 10 drinks a week.

KEY LEARNING POINTS

- Excessive alcohol consumption leads to liver disease (from simple fatty liver to cirrhosis) in certain individuals with influences of sex, genetic characteristics and environmental factors.
- There is no risk of alcoholic cirrhosis among lifetime abstainers.
- If you choose to drink , do so in moderation. No one should begin drinking or drink more frequently based on potential health benefits.
- Upto 1 drink /day (or 7 drinks/wk) for women and upto 2 drinks /day (or 14 drinks/wk) for men have been found to be safe and classifies as moderate drinking.
- Excessive drinking (too much drinking) i.e binge drinking, Heavy drinking [≥ 8 drinks/wk in female & ≥ 15 drinks/wk in males), underage drinking, Pregnant drinking is harmful and should be avoided.
- In patients with pre-existing NAFLD (without advanced fibrosis), Moderate (i.e safe) alcohol consumption limit is lower than the healthy population (drinking an average of half to one and a half drinks of alcohol per day i.e <10 drinks/week).
- Any amount of alcohol is excessive in those with advanced liver fibrosis.
- Avoid drinking at all if one is underage (<21), pregnant or may be pregnant, OR have health problems that could be made worse by drinking.
- Daily drinking and recent alcohol consumption rather than earlier in life are the most significant risk factor of alcoholic cirrhosis.

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10

Management of Alcohol Use Disorder

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DEFINITION

Alcohol use disorder (AUD) has been defined in the West as consumption of >3 drinks per day in males and >2 drinks per day in females, or binge drinking.[1] The latter is defined by the US National Institute of Alcoholism and Alcohol Abuse (NIAAA) as >5 drinks in males and >4 drinks in females, consumed over a 2-hour period; one drink is defined as a beverage containing about 14 g of alcohol. Binge drinking is also defined in the US as a pattern of alcohol consumption that brings the blood alcohol concentration level to 0.08 g/dL or above within two hours.[2] An earlier report from Australia[3] defined binge drinking as six or more standard drinks on a single occasion. Many binge drinkers may not be alcohol dependent, but binge drinking makes them susceptible to health problems.

Considering the wide variation and the interplay of individual (genetic, metabolic) and environmental (nutrition, beverage types, contaminants, ethnicity) factors, it is impossible to fix universal cut-off levels for defining alcohol abuse. Genes influencing the susceptibility for alcoholism include modifiers of neurotransmission such as γ-amino butyric acid and modifiers of alcohol metabolism such as alcoholic dehydrogenase and acetaldehyde dehydrogenase enzymes.[4] The polymorphisms in these genes may be involved in an individual's susceptibility to alcoholism, with wide allelic variation between different ethnic groups.

More than 76 million people worldwide are estimated to have diagnosable AUD (alcohol abuse or dependence).[5] In the US, it is estimated that close to 15 million people aged 12 or older had AUD in 2018, accounting for over 5% of the population[6]; only around 6.5% of adults with AUD actually seek treatment. In the absence of reliable figures, estimating the cost consequences and the need to allot resources is to a large extent empiric.

IDENTIFYING AUD

As patients often under report alcohol intake, questioning the patient or the use of standard questionnaires can be gainfully supplemented by information from family/relatives/social contacts. It is customary in India to obtain such complementary information, often even without the patient's consent, considering our social fabric. Objective measures (e.g., physical signs of chronic alcohol use, such as the so-called Le Go grid, which includes conjunctival injection, abnormal vascularization of the facial skin, coating of the tongue, and hepatomegaly) are add-ons. Individually, tests suggestive of alcohol abuse (i.e., elevated blood alcohol level, or elevation of γ-glutamyl transpeptidase or urinary ethyl glucuronide) or liver biopsy showing signs of alcohol-induced liver damage, are not easily available or are not all highly specific for alcohol use.

AUDIT is a 10-item questionnaire, with a score of 0–40, that has been validated as an accurate clinical tool for the detection of alcohol consumption.[7] It was developed from a six-country (Australia, Bulgaria, Kenya, Mexico, Norway, USA) WHO collaborative project, and covers the domains of alcohol consumption (3 questions), drinking behavior (3 questions), and alcohol-related problems (4 questions). An AUDIT score of >8 constitutes "hazardous or harmful alcohol consumption", and a score of >20 qualifies for diagnosis of alcohol dependence. Among its many advantages are the fact that it is cross-cultural, uses language that can be easily translated, has a graded response (not just yes/no), and is not meant to detect only alcoholism but also milder problem cases. A shorter version, or AUDIT-C,[8] has been found to be as accurate as an initial screening test.

The earlier 24-item Michigan Alcoholism Screening Test (MAST) was sensitive for detecting the more serious alcoholism or dependence (alcoholic), at 5 or more points, although those who scored 4 points were identified as early or middle problem drinkers. The revised MAST has 22 items and is available free online for self-use.

The CAGE questionnaire has four simple questions (Have you ever felt you should **cut** down on your drinking? Have people **annoyed** you by criticising your drinking? Have you ever felt bad or **guilty** about your drinking? Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover **[eye-opener]**?).

MANAGEMENT OF AUD

Initiating and maintaining abstinence from alcohol are the two primary long-term goals of managing AUD. Addressing associated social or psychological precipitants, and taking care of concomitant nutritional deficiencies and liver disease, are the other steps (management of the social aspects as well as nutrition and liver disease is covered in other chapters).

Emergency Management

DSM-V defines alcohol withdrawal as two or more of the following symptoms that develop within hours to days following a significant decrease in alcohol consumption

after a prolonged period of heavy drinking: nausea or vomiting, autonomic hyperactivity, insomnia, increased anxiety and agitation, tremor, perceptual disturbances and seizures. This can happen even when the blood alcohol levels are still high.

A majority of individuals experience only minor withdrawal symptoms such as increased anxiety, headache, nausea, vomiting, insomnia, and mild tremors, sometimes with tachycardia, hypertension, and hyperthermia. These symptoms begin by 6 hours after an acute reduction in alcohol use, typically last a day or two, and disappear within a week.[9]

Nearly a third of patients presenting for AUD will experience moderate to severe withdrawal symptoms. A small group will experience a more complicated syndrome that includes hallucinations, seizures, delirium and/or more severe autonomic hyperactivity. Seizures set in 12-24 h after the last drink and can last up to two days; in <5%, status epilepticus can result. Delirium tremens also occurs in approximately 3-5% of hospitalized patients, and are characterized by confusion, altered consciousness, severe autonomic changes and hallucinations. They typically begin after 1-3 days of abstinence, and mortality rates can be as high as 20%.[9]

The immediate management includes ABCD (airway, breathing, circulation, disability) assessment and prompt intervention. Administration of dextrose (if blood glucose level is low), fluid resuscitation with monitoring particularly of sodium levels, and naloxone can be life-saving. Thiamine (vitamin B1) should be administered, usually as 100 mg in intravenous fluid infusion, for prevention of Wernicke's encephalopathy and Korsakoff's psychosis. If the latter are suspected, higher doses up to 200-500 mg every 8 h for a minimum of 72 h should be given.

Benzodiazepines such as intravenous diazepam 5-10 mg or lorazepam 2-4 mg can be repeated in 5-10 minutes. Midazolam can be given intramuscularly at 2-4 mg if IV access is not available. Oral chlordiazepoxide is an alternative. Gabapentin has also been used for withdrawal symptoms, and is a safer alternative for unmonitored management of milder cases. Patients in status epilepticus will require phenytoin or phenobarbital, valproic acid, propofol and ketamine, depending on response.

Long-term Management

A typical protocol for the long-term management of AUD includes:

- Physical, psychological and social evaluation to determine the full spectrum of interventions needed
- Enrolment in a detoxification programme
- Treatment of any concurrent mental health disorders
- Enrolment in support groups, with plans for lifelong commitment
- Monitoring of abstinence by random screening for alcohol

The role of a professional set-up with committed social workers, counsellors, psychologists and psychiatrists cannot be overemphasized. Return to normal family and social life, including job rehabilitation, should feature among the goals.

Detoxification Settings

Taking the first step in seeking help for AUD can be overwhelmingly stressful for the individual, especially if any associated social or psychological reason for the abuse is not addressed. This step often follows family or contact pressure, and including their support in the management is important. However, patients frequently implicate family or social contacts as the reason for their addiction, so prudence is advised in involving them in the care plan.

The type of detoxification programme depends on personal and social circumstances, and can be broadly classified in order of severity as below. Choice of programme is individualized, but can be done in sequence depending on need and response; a step-down approach (from inpatient programmes to outpatient programmes with recovery) is the usual sequence for most affected individuals.

Outpatient Programmes

- Standard programme: This is reserved as a first step for the exceptional individual with short history, self-realization, and a strong desire to overcome the addiction. Patients continue to live at home while on treatment, allowing them to fulfil family or work obligations. An important requirement is that the home environment be stable, supportive, and alcohol- and drug-free; unfortunately, in many homes, the spouse or other members are also alcohol consumers, although may be not to the same intensity. Visits to the counsellor / physician / hospital may be limited to a few times a week, preferably off work hours.
- Intensive programme: These programmes are for individuals who have the commitment but are unable to de-addict on their own or do not have conducive environs. They do not require 24-hour supervision or detoxification; they can continue with their off-site lives, but are committed to developing coping strategies and have the support systems in place to help with relapse management.

Inpatient Programmes

- Day programme: Such programmes require the patient to report to the facilitation centre on weekdays, after work hours, to participate in an intense treatment schedule or group therapy. They require stable living environments and support networks, to prevent going down a slippery path when unsupervised.
- Residential programme: Supervised inpatient programmes are for the severely addicted and may indeed be the first step for many patients, to be followed by a gradually easing intensity of supervision and treatment culminating in standard outpatient programmes. At these centres, patients are provided 24-hour care and rehabilitation, with physicians and psychiatrists available for medication

whenever required. As the situation improves, a road to recovery is charted out, with individual and group counselling sessions, training in coping skills, and guidance on relapse prevention. It is generally recommended that individuals needing residential inpatient programmes be kept at the centre for at least 90 days to optimize outcomes.

Medications

Currently, there are three medications approved by the US FDA to treat alcohol dependence: disulfiram, oral and extended-release injectable naltrexone, and acamprosate.

Disulfiram, the oldest of the three (discovered in 1920 and approved by the US FDA in 1951), inhibits mitochondrial aldehyde dehydrogenase. In the presence of alcohol, even in small amounts, the drug produces flushing, headache, respiratory difficulty, nausea, vomiting, sweating and thirst. Other symptoms, some of them severe side effects, include respiratory, cardiovascular and neurologic catastrophes, and death. A meta-analysis of 22 studies showed that disulfiram was superior to control in open-label controlled but not in blinded trials.[10]

Naltrexone (approved by the US FDA in 1994; extended release injectable formulation approved in 2006) binds to the μ-(MOR), κ-(KOR) and, to a lesser extent, δ-(DOR) opioid receptors; it attenuates the pleasant sensations associated with alcohol drinking and is also reported to reduce alcohol craving. Methylnaltrexone and nalmefene are closely related medications used for the same purpose. The overall benefits of naltrexone have been described as modest.[11]

Acamprosate (approved by the US FDA in 2006) is thought to stabilize the balance of neurotransmitters in the brain that would otherwise be disrupted by alcohol withdrawal. Like naltrexone, it acts by reducing craving or the urge to drink and reduced heavy drinking. It works best in combination with psychosocial support.[12] At concentrations well above those that occur clinically, it has been reported to inhibit glutamate receptor-activated responses, enhance N-methyl-D-aspartate (NMDA) receptor function, and exhibit weak antagonism of the NMDA receptor with partial agonism of the polyamine site of the NMDA receptor.[13] Thus, the drug provides modest but potentially valuable improvements in alcohol-consumption outcomes.[14]

Other drugs that have shown promising results in reducing alcohol dependence, relapse and craving, and can be repurposed for AUD include the anticonvulsants gabapentin, pregabalin, and topiramate, and the antipsychotics quetiapine and aripiprazole; the latter are of particular interest in those who have associated psychiatric problems. Ondansetron, a selective 5-HT3 antagonist, and nalmefene, an opioid-receptor antagonist, have also shown promise in trials to reduce alcohol intake and dependence.[13]

Antidepressant drugs such as duloxetine and other SSRIs have been evaluated for this purpose. Except in those who need these medications for depression, they are generally

not recommended; there is a potential for drug-induced liver injury. Guanfacine, a drug used to treat ADHD, has also been reported to attenuate stress-induced relapse of craving.[13]

The P2X receptor (P2XR) is a family of cation-permeable ligand gated ion channels activated by synaptically released extracellular ATP.[15] Preclinical studies have shown that alcohol acts as a negative allosteric modulator for P2XR, and alters the function of P2X4R. Ivermectin is an FDA-approved broad-spectrum antiparasitic avermectin that is also a selective positive allosteric modulator of P2X4R; it acts on P2X4R sites that are thought to be modulated by alcohol. The drug is under recent favorable evaluation for the treatment of AUD.[15]

In patients of ALD, alcohol-induced compression of intrahepatic biliary radicles and increased permeability of the bile ductules appears to predispose patients to develop cholestasis.[16] Hepatoprotectives such as UDCA are showing promising effects in ALD induced IHC in chronic cholestatic liver disease patients.[17] There was improvement in clinical presentation of the patients and reduction in biochemical markers over 12 weeks of treatment.

Psychological and Social Support Measures

Preventive governmental steps for AUD include regulating and limiting alcohol sale and consumption, banning or restricting advertisement (including surrogate advertisements – quite common on Indian TV), aggressive media education about the ill effects of alcoholism, and appropriate taxation of alcoholic drinks. The latter is a two-edged measure: too high taxes may drive alcoholics to cheaper illicit and toxic alternatives. In 'progressive' India, social norms have eased in recent years, and a prestige is attached to drinking among the youth, including girls; we may grow out of this social immaturity some day. Identification and monitoring of those likely to turn alcoholic (family history, childhood trauma, early start, poor family and social support), and removal of triggers for drinking, will help.

Supportive therapy includes self-help and mutual-help groups and developing coping mechanisms. Alcoholics Anonymous is easily the best known among such groups; the twelve-step programme they originally propagated has been adapted successfully to treat other substance abuse.[18] Aftercare should be built into such programmes. Social support ideally should follow a zero-tolerance approach, although some have advocated a harm-reduction approach; most follow-up studies have shown poor results with the latter.[19]

CONCLUSIONS

Alcohol use disorder is a worldwide phenomenon. In countries with suboptimal health registries, such as India, the true extent and cost of this disorder and its management is not known but is likely to be substantial. Social prevention programmes and early identification are underestimated steps but more cost-effective in the long term. Management of AUD should be multi-pronged, with involvement of the affected individual, the family and social contacts (especially in the Indian context),

professionals, and support groups. Lifelong monitoring is required in all cases because this is a dreaded disease with a high propensity to relapse, and not just a personal aberration as is commonly perceived.

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11

Role of Nutrition in Alcoholic Liver Disease

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INTRODUCTION

Alcohol related liver disease (ALD) has now become the commonest cause of chronic liver disease in developing and developed nations. The term "ALD" is a spectrum of liver injury which includes steatosis (fatty liver) with or without fibrosis, alcoholic hepatitis (AH), alcohol related cirrhosis and hepatocellular carcinoma. It is also the commonest indication for liver transplantation worldwide. Patient may be asymptomatic and diagnosed with fatty liver on routine ultrasound or may present with jaundice or complications of cirrhosis like variceal bleed, ascites or hepatic encephalopathy. Sometimes alcohol abuse or alcohol dependence is considered same as chronic liver disease but it is not synonymous with clinically important ALD. Majority of patients with alcohol abuse do not develop clinical significant liver disease, only about 10–20% of chronic heavy drinkers develop severe forms such as AH or cirrhosis.[1]

NUTRITION IN PATIENT WITH ALCOHOL ASSOCIATED CIRRHOSIS

The prevalence of malnutrition in patients with ALD varies from 20% to 60% and depends upon the method used for analysis. It is more in patients with decompensated cirrhosis and almost universally seen in patients with cirrhosis and AH. ALD represents a strong independent predictor of malnutrition which may in turn promote complications of cirrhosis like encephalopathy and/or bacterial infections. These complication further increases malnutrition in these patients.[2,3]

Common mechanism of malnutrition in patients with ALD include poor dietary

intake (due to anorexia, dysgeusia, altered smell, nausea and vomiting), maldigestion and malabsorption secondary to associated chronic pancreatitis, bile salt deficiency or bacterial overgrowth, portal enteropathy, hypermetabolic state, insulin resistance, inflammatory cascade leading to less protein synthesis (Table 1). Malnutrition has also been associated with a prolonged hospital stay after liver transplantation due to longer stays in intensive care units, difficult extubation and increased chances of bacterial infections.[4,5] Nutrition plays an important role in the management of ALD along with abstinence. Nutrition assessment and therapy for protein–calorie deficiency and any specific micronutrient deficiencies (i.e. vitamin and mineral deficiency) has been endorsed by the American Association for the Study of Liver Disease.[1,6]

Table 1. Basis of nutritional deficiency in patients with alcoholic liver disease (ALD).

Decreased calorie intake • Poor intake of non alcohol calories • Loss of appetite • Social myths about diet • Decompensated liver disease: ascites	**Results** • Poor calories and deficiency of vitamins and minerals
Poor absorption and digestion of food • Altered intestinal mobility and function • Less bile salts • Small intestinal bacterial overgrowth • Pancreatic insufficiency	**Results** • Poor amino acid and vitamin absorption • Fat soluble vitamin deficiency and lipid maldigestion • Poor digestion of protein and fat
Poor reserve of nutrients • Advanced liver disease	**Results** • Decreased energy stores and utilization of muscle and protein for energy utilization leading to sarcopenia

NUTRITIONAL ASSESSMENT IN ALCOHOLIC LIVER DISEASE

It is recommended that all patients with advanced chronic liver disease, AH and decompensated cirrhosis should undergo detailed nutritional assessment. Malnutrition affects complications related to cirrhosis, overall hospital stay and increase mortality in patient on waitlist for liver transplantation.

Patients should be assessed for fat and water-soluble vitamins also also various minerals deficiencies in ALD. However, routine measurement of these vitamins and minerals are not available in majority of countries and are expensive so routine measurement is not required. History taking and physical examination to look for each deficiency

which produces specific symptoms, signs, and complications is the best way of assessment (Table 2). Of the several clinical markers of malnutrition, the body mass index (BMI, kg/m^2)and the degree of weight loss are the most relevant ones, though they have potential unreliability in presence of fluid retention.[1,6]

Subjective Global Assessment (SGA) which is based on a standardized questionnaire and aim at assessing any changes in dietary intake, changes in body weight over a period of time, gastrointestinal symptoms which affects nutrition, functional capacity, and physical signs of malnutrition which is measured by loss of subcutaneous fat or muscle mass, edema, and ascites is the most common tool used for assessment of nutrition status. In the study by Detsky et al, SGA was 82% sensitive and 72% specific compared with laboratory or anthropometric measurements.[7] Other parameter of nutrition assessment like albumin, prealbumin, and transferrin lack accuracy as they are synthesized by the liver and albumin is replaced commonly in admitted patients.

Sarcopenia which is defined as loss of muscle mass and function can be assessed by measuring psoas muscle thickness by computed tomography (CT) scanning. Various other tools to assess nutrition in patient with cirrhosis and AH are enumerated in Table 3 with their limitation and ease of use.[8]

Table 2. Common symptoms of vitamin deficiency.

Vitamin and Minerals	Symptoms and Signs
Folate, s-adenosylmethionine	Anemia, altered methylation, epigenetic effects
Vitamin B1/thiamine	Wernicke-Korsakoff syndrome, neurologic symptoms, beriberi with high output heart failure
Vitamin B2/riboflavin	Glossitis, cheilitis, lingual papillae atrophy
Vitamin B6 (pyridoxine)	Neuropathy, sideroblastic anemia, increased AST/ALT ratio
Vitamin A/retinol	Abnormal dark adaptation, rough skin,increased fibrosis
Vitamin C	Scurvy with purpura and petechiae
Vitamin D	Altered bone metabolism, altered gut barrier/immune function, Osteopenia and osteoporosis
Vitamin E	Oxidative stress,skin changes
Niacin (Vitamin B3)	Skin photosensitivity, confusion, Pellagra, dementia, diarrhea
Selenium	Myopathy, cardiomyopathy
Magnesium	Insulin resistance, muscle cramps
Zinc	Dysgeusia and taste problems and repeated G I infections
Vitamin K	Petechiae and purpura

Vitamin B12	Megaloblasticanemia, SACD, neuropathy
Phosphorus	Cardiac arrhythmias, delirium tremens
Iron	Anemia
Calcium	Osteopenia and osteoporosis

The guidelines for assessing micronutrient deficiency in ALD patients are scanty and evidence supporting their supplementation is still inconclusive. Moreover in view of high prevalence of malnutrition both in terms of calories and micronutrients and vitamins prophylactic supplementation with multivitamin is frequently advised by experts.[8]

Table 3. Screening and diagnosis tools for sarcopenia in cirrhosis.[2,8]

	Anthro-pometry	DEXA	CT/MRI	BIA	Handgrip
Measures	Overall body size (BMI, MAC), predicted muscle (MAMC), predicted visceral ad-ipose tissue (WC, W:H, TSF)	Whole-body and regional fat, lean, bone mineral content and BMD	L3-SMI,	Calculate lean and fat mass	Muscle strength
Simplicity	+++	++	+	+	+++
Cost	+	++	++++	++	+
Validity	+	++	++++	++	+
Clinical use	++	+	++	+	++

Abbreviations: BIA, bioelectrical impedance analysis; BMD, bone mass density; BMI, body mass index; CT, computed tomographic; DEXA, dual-energy x-ray absorptiometry; MAC, mid-arm circumference; MAMC, mid-arm muscle circumference; MRI, magnetic resonance

MANAGEMENT OF NUTRITION IN PATIENTS WITH ALCOHOL RELATED LIVER DISEASE

Nutrition supplementation is an essential component in the management of patients with ALD.It not only improves patient nutrition, but also helps in improved outcome of hospitalization, surgery, and transplantation if required. Goals of nutritional supplementation are to meet basic needs as in a normal person of his/her

age and provide additional sources for hypermetabolic state. Patients in whom daily requirements are not met through diet should receive supplementation with either enteral route or parental route. Estimations of the caloric needs of patients with ALD are as per guidelines (Table 4,5).

Unnecessary dietary restrictions should be avoided to prevent malnutrition or micronutrient deficiency and a low-sodium diet should be only recommended in decompensated cirrhosis with ascites and edema. Due to the limited reserves and inability of the liver to handle prolonged starvation, these patients should be taken on priority for any in hospital procedure like endoscopy/colonoscopy/ultrasound abdomen or computed tomography if admitted. Additionally, cirrhotic patients fasting for more than 12 hours should receive intravenous glucose at the rate of endogenous hepatic glucose production (2–3 mg/kg/d). Patients with advanced cirrhosis and AH should avoid any dieting or religious fasting due to reduced gluconeogenesis, rather patients with cirrhosis are recommended to assume frequent meals, including night time snacks.[8]

Table 4. Summary of general nutrition guidelines for patients with cirrhosis, released by the European Society for Clinical Nutrition and Metabolism.[9]

Intervention
• Overall provision 30–35 kcal/kg dry body weight Calories distribution (%): » Carbohydrates 50–60 » Proteins 25–30 (1–1.5 g/kg body weight) » Fats 15–20
• Avoidance of unnecessary dietary restriction
• A low-sodium diet (<2 g/day) should be recommended only if ascites or edema is present
• Frequent (4–6) small meals including night-time snacks: to be encouraged
• Screen for deficiency of serum zinc, calcium and vitamins A, D, E and K and supplement as needed
• Protein restriction for acute hepatic encephalopathy only
• In case of protein intolerance: vegetable or dairy and branched chain aminoacids to be supplemented

Table 5. Daily requirement of Multivitamin and Minerals in patients with ALD.[2,6,9]

- Thiamine 100 mg/d
- Folic acid 1 mg/d
- Multivitamin Daily
- Vitamin D 50,000 U 3 times/wk
- Vitamin A 10,000 U/d or 25,000 U 3 times/wk
- Vitamin E 400 IU/d
- Sodium 90 mEq/d with fluid retention if ascites present
- Iron Use only if iron deficiency
- Calcium 1200–1500 mg/d
- Zinc 220 mg 2 times/d

ROLE OF NUTRITION THERAPY IN ALCOHOLIC HEPATITIS

Patients with advanced liver disease and AH are often malnourished and these patients also have superimposed infection with added stress metabolism, which increases nutritional demands. Nutritional therapy has no contraindication compared to steroids which can be given in a subset of patients with severe AH. In a metanalysis of thirteen randomized controlled trials with 329 allocated to enteral (nine trials) or intravenous (four trials) nutrition and 334 controls, random-effects meta-analysis showed that nutritional therapy reduced mortality 0.80 (95% CI, 0.64 to 0.99). However these results were not confirmed in sequential analysis. Fixed-effect analysis suggested that nutrition prevented overt hepatic encephalopathy and infection, but the results were not confirmed in random-effects analyses. All trials were classed as having a high risk of bias.[10]

In a study by Cabreet al[11] comparing corticosteroids, which is currently the standard of treatment for severe AH, and enteral supplementation it was seen that death due to infections was less frequent among patients receiving enteral nutrition. In this study survival was also better at 1 year with enteral nutritional supplementation compared with corticosteroids treated patients. Nutritional supplementation should be provided early and for sufficient period of time for better results. Patients with AH are very sick with high short term mortality therefore need adjuvant treatment with specific drugs like steroids if no contraindication. A combination of enteral nutritional support and corticosteroids showed benefit in a study of 13 patients with severe AH. Decrease in serum bilirubin by greater than 50% at day 15 allowed tapering of steroids, and marked improvement in 3 weeks allowed discontinuation of nutritional support.[12] Table 6 and 7 represents some important studies showing results of nutritional therapy in patients with severe AH.

Five RCTs have shown an improvement both in nutritional status and liver function with enteral nutrition in patients with AH but data on the long-term survival are often inconclusive as limited toa small samples or derived from a short-term follow-up.[11,13,16]

Table 6. Studies on AH using enteral nutrition.

Author	Year	T=treatment, C=control, N=number	Duration	Response
Cabre et al[11]	2000	T (n=36): BCAA-enriched EN 2000 kcal (72 g protein/d) C (n=35): Prednisolone (40 mg/d)	28 days	31% 25%
Calvey et al[13]	1985	T (n=42): standard diet 65 g protein (20 g BCAA/145 g AA or 65 g protein) C (n=22): standard diet (1800–2400 kcal/ 70–100g protein/d)	21 days	37% 32%
Mendenhall et al[14]	1985	T (n=18): diet/ protein supplement/ hepatic acid C (n=34): 2500 kcal/d	30 days	17% 21%
Mendenhall et al[15]	1993	T (n=137): oxandrolone (1200 kcal and 45 g protein/d) C (n=136): placebo (198–264 kcal and 5–7 g protein/d, supplement)	180 days	35% 39%
Moreno et al[16]	2010	T (n=28): 27 kcal/kg/d / NAC IV 300 mg/kg/d C (n=24): EN 27 kcal/kg/d / 5% dextrose IV	14 days	30% 16%

Table 7. Studies on parental nutrition in AH.

Author	Year	T=treatment, C=control, N=number	Duration	Response
Bonkovsky et al[17]	1991	T (n=27): standard diet (70 g AA supplement G oxandrolone 20 mg qid C(n=12): standard diet (30 kcal/kg IBW/ 1 g protein/kg IBW/d)	21 days	31% 25%
Achord et al[18]	1987	T (n=14): Standard diet/ IV AA (42.5 g protein/ 830kcal/d) C (n=14): standard diet (2674 kcal (100 g protein/d)	21 days	7% 20%

In patients with severe AH or advanced liver disease who are unable to meet their

caloric requirements through normal feeding, supplementary feeding ensures the adequate energy and protein intake without the risk of complications.

Enteral nutrition is preferred over parenteral nutrition due to the lower cost and complications. Enteral nutrients also act as trophic factor for intestinal mucosa, hence prevent bacterial translocation and maintain gastrointestinal functions. Home made foods which contain whole protein are generally recommended as there is no problem with gut enzymes and more concentrated high-energy formulae are preferable in patients with ascites to avoid fluid unbalance. Branched chain amino acids (BCAA) may be administered to patients who are intolerant to whole protein diet or in patient with encephalopathy. The oral route is always preferable. Tube feeding is recommended in limited patients who fulfil criteria as per Table 8.

Table 8. Criteria for tube feeding.

1.Intolerance to enteral nutrition
a. Nausea and vomiting
2 Enteral route unsafe or not possible
a. Encephalopathy and altered sensorium
b. Compromised swallow and cough reflexes with risk of aspiration
c. Acute pancreatitis with alcohol associated liver disease where jejunal feeding can be done

Enteral nutrition is preferable over parenteral nutrition whenever feasible and is associated with improvement in nutritional status and liver function in ALD patients, even if data on long-term survival are often inconclusive. EN has been reported to be as effective as PN, therefore the current indication for PN support is restricted to a small group of ALD patients for whom enteral feeding has failed or is contraindicated, or when patients need to stay fasting for 72 h or more.

Presence of esophageal varices or endoscopic band ligation is not a contraindication for oral feeding. Patients who have large esophageal varices, nasogastric tube feeding can be done without much added risk of bleeding. Patients who underwent endoscopic band ligation can be given food orally within 24 hours of their stabilization

Role of branched chain amino acids- Patients who are not able to tolerate high protein diet supplementing with branched-chain amino acids (BCAAs) have shown nutritional and/ormetabolic effects on the liver, muscles, and brain.Their levels in patients with cirrhosis are reduced. There is evidence that long-term oralBCAA supplementation (about 0.25 g/kg) exerts nutritionalbenefits and decreases recurrence of encephalopathy.Two RCTs focused on the long-term use of BCAAs (1–2 years) amongpatients with alcoholic cirrhosis reported a decreasedmorbidity and mortality and an improved quality of life. BCAA supplementation should be recommended in ALD patients withhepatic encephalopathy, intolerant to whole protein formula and in prevention of recurrence of covert and overt encephalopathy.[19,20]

CONCLUSION

Majority of patients with advanced liver disease related to alcohol and AH are malnourished with respect to protein and calories and deficient in vitamins and minerals. Malnutrition and sarcopenia in this population increases risk of developing complications,prolonged hospital stay, increase wait list mortality for liver transplantation and post liver transplantation complications. Thus, hepatologist should take a proper history, do a good physical examination to diagnose signs and symptoms of vitamin deficiency to treat nutritional deficiencies earlyin this subset of patients. The baseline evaluation of a patient's nutritional status by SGA, anthropometric measurements and handgrip strength is recommended. Nutritional support for malnourished ALD patients is aimed at improving their calories intake and various vitamins deficiencies. Studies have shown that nutritional therapy along with steroid has better outcome in the management of AH patients. Enteral route should be preferred over parental route, however short term parental route is used if enteral feeding is not possible. Routine use of BCAA in all patients with cirrhosis still needs more data but their use in patients with recurrent hepatic encephalopathy or in patient intolerant to whole protein diet is recommended.

KEY LEARNING POINTS

- Alcohol related liver disease (ALD) and alcoholic hepatitis (AH) patients are at high risk for malnutrition.
- Malnutrition and sarcopenia negatively affects both theclinical outcome both before and after liver transplantation.
- Bedside nutritional assessment using Subjective Global Assessment (SGA) andanthropometric measurements should be done in all patients with ALD.
- Routine supplementation with vitamins and minerals should be done in all patients with cirrhosis and AH.
- Unnecessary dietary restrictions should be avoided and appropriate dietary intake should be given according to guidelines
- Both enteral (first choice), and parenteral nutrition seem to improve the nutritional parameters and liver function.
- Frequent meals with one late evening snack, no dieting or fasting, shorter waiting time for procedures for indoor patients should be practised.

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IND2144358 26 Jun 2020

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KWX Communications Pvt. Ltd.
12/402, Ground Floor, Sunder Vihar
Outer Ring Road, Paschim Vihar,
New Delhi 110087, INDIA
kwxpublishing@gmail.com

ISBN 978-93-83988-28-0
9 789383 988280