‘Alcoholic Hepatitis – To Transplant or Not To Transplant, That is the Question’

Arjmand Mufti, MD, MRCP (UK)

Division of Digestive and Liver Diseases

University of Texas Southwestern Medical Center

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This is to acknowledge that Arjmand Mufti, M.D. has disclosed that he does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Mufti will not be discussing off-label uses in his presentation.

Dr. Arjmand Mufti is an Assistant Professor of Medicine in the Division of Digestive and Liver Diseases at UTSW.

Biography:

Dr. Mufti received his medical degree from the United Medical and Dental Schools of Guy's and St. Thomas' in the UK. He graduated with honors and received his initial medical training at Kings College Hospital in London and is a Member of the Royal College of Physicians (UK). After completing a Research Fellowship at the University of Michigan, he moved to the University of Chicago, where he subsequently completed his Internal Medicine Residency and Gastroenterology and Transplant Hepatology fellowships. During his residency, he was elected to membership of the AOA Honor Medical Society. He is currently a transplant hepatologist at UT Southwestern and his main research interest is acute on chronic liver failure.

Purpose & Overview:

The purpose of this presentation is to briefly outline the burden of alcoholic liver disease and to specifically discuss the entity of alcoholic hepatitis as distinct from alcoholic cirrhosis. I will outline treatment modalities for alcoholic hepatitis and the debate surrounding liver transplantation for alcoholic hepatitis. I will also outline some of the ethical issues which arise when patients with severe alcoholic hepatitis are considered for liver transplantation.

Educational Objectives

After this lecture, the reader should be able to:

1. Describe the burden of alcoholic liver disease worldwide and in the USA
2. Recognize and screen for alcohol use disorders
3. Describe the clinical presentation of alcoholic hepatitis
4. Be familiar with the controversies around liver transplantation for alcoholic liver disease including alcoholic hepatitis
5. Understand the ethical considerations of transplantation for patients with alcoholic liver disease

Introduction

Liver transplantation is the optimal therapy for patients with end stage liver disease. Liver disease which develops in patients with alcohol use disorder (AUD) is a major cause of morbidity and mortality all over the world. Consequently, alcoholic liver disease (ALD) is now the second most common diagnosis among liver transplant recipients in the USA in 2015 and the most common diagnosis among patients who underwent liver transplantation in Europe during the same period[1]. However, the ability of patients with a history of AUD to undergo liver transplantation has historically been very controversial both within the medical profession and the public at large. In fact, the National Institute of Health consensus development conference on liver transplantation in 1984 predicted that not many patients with ALD would be selected for liver transplantation[2]. In particular, patients with a diagnosis of severe alcoholic hepatitis (AH) whose illness portends a very poor outcome have been entirely excluded from the pool of patients for whom liver transplantation was an option[3]. I will discuss the treatment options for patients with alcoholic hepatitis and review the changing landscape of liver transplantation for alcoholic hepatitis.

Nomenclature

The nomenclature of alcohol related disease has changed recently. In 2013, the Diagnostic and Statistics Manual (DSM-V) adopted the term 'alcohol use disorder' and this is defined as the 'harmful consequences of compulsive alcohol use'. The DSM-V definition of AUD does not distinguish between alcohol abuse and alcohol dependency which had previously been described as two distinct disorders in DSM-IV with specific criteria for each. A diagnosis of AUD is based on 11 criteria in four areas (biological, medical harm, behavioral and social harm) and can be mild (2 to 3 symptoms), moderate (4 to 5 symptoms) or severe ($\geq$6 symptoms). The terminology around alcohol use is also very loaded. Historically, the term 'recidivism' has denoted a return to harmful alcohol use. 'Recidivism' literally means a 'return to criminal activity' and therefore the very label used when discussing patients who 'relapse' (the preferred term) perpetuates the stigma surrounding AUD. The terms that should be used are 'slip' which denotes a temporary return to drinking, which is recognized by the patient as potentially harmful and results in renewed efforts to remain abstinent and 'relapse' which represents a more sustained resumption of alcohol use which can be characterized as harmful or abusive drinking.

Alcoholic Liver Disease is a Global Problem

Alcoholic liver disease is a worldwide problem. In 2012, 3.3 million net deaths, or 5.9% of all global deaths, were attributable to alcohol consumption. In the 2010 Global Burden of Disease (GDB) study, alcoholic cirrhosis resulted in 493,300 deaths worldwide (0.9% of all deaths) and accounted for 48% of all deaths due to cirrhosis[4]. The young are disproportionately affected by alcohol use disorders. According to the World

Health Organization (WHO), in the 20 – 39-year-old age group, approximately 25 % of the total deaths are attributable to alcohol. There is a causal relationship between harmful use of alcohol and a range of mental and behavioral disorders, other non-communicable conditions as well as injuries.

A quarter of worldwide consumption (24.8%) is unrecorded (usually homemade or illegally produced alcohol) and spirits make up 50.1% of total alcohol consumed. Approximately 16.0% of drinkers aged 15 years or older engage in heavy episodic drinking worldwide and alcohol use correlates with Gross Domestic Product (GDP) and high-income countries have the highest alcohol per capita consumption (APC) and the highest prevalence of heavy episodic drinking among drinkers. Higher consumption of alcohol increases the risk of serious forms of alcoholic liver disease and cirrhosis and multiple studies have indicated that women have a lower threshold to develop alcoholic liver disease than men[5]. Alcohol is associated with a substantial proportion of human violence, and perpetrators are often under the influence of alcohol. It is a key factor in 68% of manslaughters, 62% of assaults, 54% of murders and attempted murders and 48% of robberies in the USA[6].

Approximately 136 million adults drink alcohol in the USA with 17 million meeting the criteria for alcohol use disorder (Table 1). Excessive alcohol use is the third leading preventable cause of death in the USA. Between 2006-1010, approximately 88,000 deaths and 2.5 million years of potential life lost (YPLL) each year in the United States were due to excessive alcohol use. The lives of those who died were reduced by an average of 30 years. Excessive drinking was also responsible for 10% of deaths among working-age adults aged 20-64 years. The economic costs of excessive alcohol consumption in 2010 were approximately $249 billion[7].

Alcohol Limit	Men	Women
On any single DAY	No more than **4 drinks**	No more than **3 drinks**
	AND	AND
Per WEEK	No more than **14 drinks**	No more than **7 drinks**
Only 2% of the population who drink within both the single-day and weekly limits will develop an AUD		

Table 1: National Institute on Alcohol Abuse and Alcoholism (NIAAA) definition of low risk drinking limits

Alcohol use is impacted by genetic factors, environmental factors including alcohol availability as well as social mores. In the right setting, this can result in a harmful total dose of alcohol with the resultant development of an alcohol use disorder. Subsequently, the interaction of genetics, gender or other co-morbid conditions can lead to alcoholic liver disease (Figure 1).

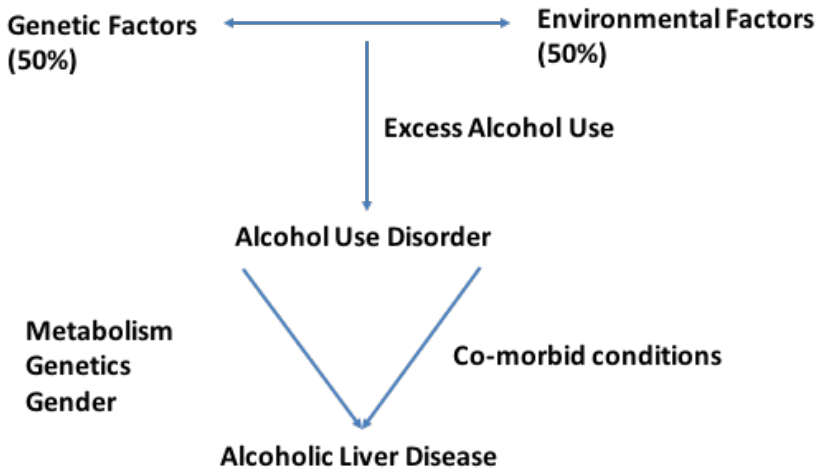

Figure 1: The two-step process resulting in the development of alcoholic liver disease

Assessment of Alcohol Use

The United States Preventive Services Task Force (USPSTF) has recommended that all adults in primary care should be screened to identify unhealthy alcohol use. One of the most commonly used set of questions are the CAGE questions (Table 2)

'Have you ever...	• Score of 2 or greater is clinically significant • 77% sensitive and 79% specific for alcohol abuse
felt you should cut down on your drinking?	
felt annoyed by criticism of your drinking?	
felt bad or guilty about your drinking?	
had a drink first thing in the morning (eye opener)?	

Table 2: CAGE questions

Additional tools include the Alcohol Use Disorders Identification Test (AUDIT) which is the most widely validated test. It is a 10-question tool, each with five possible answers, developed by the WHO and is a simple method to screen for excessive drinking. The AUDIT score ranges from 0 to 40 and a score of 8 or greater is considered a positive test for unhealthy alcohol use. The AUDIT-C is a screening test comprised of the first three questions of full AUDIT test and it is scored between 0 to 12. A positive test for unhealthy drinking is ≥3 in women and ≥4 in men and should trigger completion of the full AUDIT test[8].

Natural History of Alcoholic Liver Disease

Alcoholic liver disease encompasses histological abnormalities that include simple steatosis, steatohepatitis, acute alcoholic steatohepatitis (ASH), progressive fibrosis and cirrhosis and hepatocellular carcinoma (HCC). The majority of individuals who consume greater than 60 g of alcohol per day (e.g. half a bottle of wine or more than 1 liter of beer) develop steatosis but only a small proportion of patients with steatosis progress to ASH and 10–20% eventually develop cirrhosis (Figure 2).

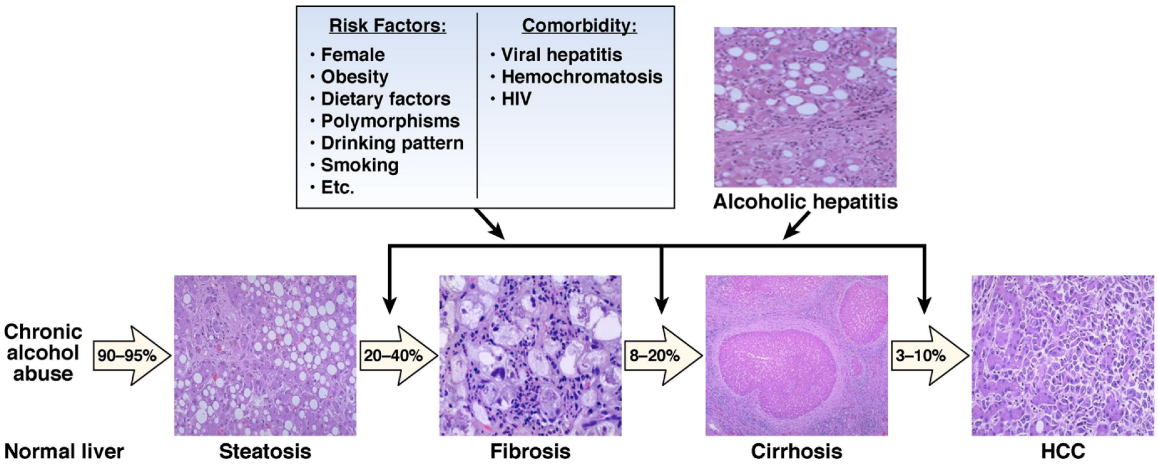

Figure 2: Natural History of Alcoholic Liver Disease

It should be noted that hepatic steatosis was historically thought to be a benign and reversible histological abnormality. However, some patients with steatosis and continued alcohol use can develop fibrosis and, occasionally cirrhosis, without first developing clinical steatohepatitis (Figure 2)[9]. Only 30-40% of heavy drinkers develop advanced ALD (fibrosis, steatohepatitis, acute alcoholic hepatitis, cirrhosis) highlighting the role of additional risk factors that are necessary for the development of the disease. These include sex (women are more susceptible than men), obesity (presence of concurrent non-alcoholic steatohepatitis with accelerated progression of fibrosis), drinking patterns (more common with binge drinking), non–sex-linked genetic factors, viral hepatitis (hepatitis B or C, HIV) and hemochromatosis (both of which result in more rapid progression of liver fibrosis, cirrhosis, and HCC) (Table 3). However, the mechanisms underpinning the development of ALD are not completely understood and

better mouse models and translational studies are needed to develop novel targeted therapies for these patients[10].

Dose of alcohol	Higher intake more likely to result in liver disease (poor dose response curve)
Gender	Women at higher risk than men
Co-morbid diseases	Chronic Hepatitis B
	Chronic Hepatitis C
	Hemochromatosis
	Alpha-1-Antitrypsin (A1AT) deficiency
	Non alcoholic steatohepatitis (NASH)
Genetic propensity	Patatin-like phospholipase domain-containing 3 (PNPLA3) – Increased hepatic triglyceride content and risk factor for disease progression
	TM6SF2
	MBOAT7
Protective Factors	Abstinence
	Coffee

Table 3: Factors associated with the development of alcoholic liver disease

Role of the Liver Biopsy in the Diagnosis of Alcoholic Hepatitis

Histologically, findings that are seen in severe alcoholic hepatitis include centrilobular steatosis, hepatocyte necrosis and ballooning in zone 3 of the lobule, the presence of Mallory-Denk Bodies and an inflammatory infiltrate (see Table 4 for details). However, these histological features are not specific for ASH but are also found in liver biopsies of patients with non-alcoholic steatohepatitis. In patients presenting with severe alcoholic hepatitis, the role of the liver biopsy remains controversial. On the one hand, historic data suggests that without histological confirmation, the diagnosis of AH will be inaccurate in 10-20% of patients[11]. More recently, Mookerjee and colleagues attempted to address the role of liver biopsy in the diagnosis and prognosis of patients presenting with acute deterioration of alcoholic cirrhosis using histological criteria. They demonstrated that the presence of Systemic Inflammatory Response Syndrome (SIRS) and clinical features suggestive of ASH, predicted severe ASH histologically in only 50% of cases and 41% of SIRS-negative patients who were thought to have a different diagnosis were found to have ASH on liver biopsy. Conversely, liver biopsy in the diagnosis of alcoholic hepatitis is costly (transjugular approach usually needed), requires expertise that may not be available at all medical centers, it can be inconvenient to obtain and patients are coagulopathic and at risk of bleeding. There remains healthy disagreement and the American Association for the Study of Liver Diseases (AASLD) does not require a liver biopsy whilst the European Association for the Study of the Liver (EASL) recommends that 'histology is required for the conformation of the diagnosis and evaluation of the severity of ALD and that liver biopsy should be considered in patients

with aggressive forms of ALD requiring specific interventions.'

Histological Finding	Etiology
Steatosis	Accumulation of lipid droplets in the cytoplasm of hepatocytes
Hepatocyte ballooning (or oncosis)	Single or scattered foci of cells undergo swelling due to accumulation of fat, water and proteins
Mallory-Denk Bodies	Accumulated cytokeratin intermediate filaments
Inflammation	Neutrophil predominant infiltrate in the hepatic lobule, esp. around degenerating hepatocytes. Lymphocytes and macrophages also seen
Hepatocyte necrosis and apoptosis	Ballooned hepatocytes undergo oncotic necrosis and swollen hepatocytes rupture. Apoptosis is also seen
Regeneration	May see evidence of liver regeneration and repair
Fibrosis	Prominent activation of sinusoidal stellate cells and portal tract fibroblasts
Cirrhosis	Culmination of long standing disease. Usually develops slowly but can develop within 1-2 years in the presence of aggressive alcoholic hepatitis

Table 4: Histological features of alcoholic liver disease

Syndrome of Alcoholic hepatitis

Alcoholic hepatitis is a syndrome characterized by infiltration of the liver by inflammatory cells and hepatocellular injury. AH develops in patients with steatosis and is usually associated with progressive fibrosis. The prevalence of AH has not been accurately determined; it is believed to occur in 10% to 35% of heavy drinkers and includes encompasses a spectrum of diseases that range from mild injury to severe, life threatening injury. At least 80% of patients who present with severe alcoholic hepatitis have cirrhosis. Patients with alcoholic cirrhosis may have histologically active alcoholic hepatitis for 12-18 months after stopping all alcohol. Clinically, patients present with jaundice, abdominal pain, and liver failure that generally occurs after decades of heavy alcohol use (mean intake, approximately 100 g per day). The serum bilirubin is typically > 3.0 mg/dL, the AST > 50 IU/L but < 400 IU/L and the serum AST/ALT ratio > 1.5. Patients will often stop alcohol a few weeks prior to admission and the typical age at presentation is 40 to 60 years. It is more common in men than women and the type of alcohol consumed does not affect risk of developing the syndrome[12].

Pathogenesis of Alcoholic hepatitis

A large body of evidence indicates that many factors contribute to alcohol-induced inflammation. In health, immune surveillance in the gastrointestinal tract, the normal composition of the microbiome and maintained integrity of the gut epithelial barrier minimize the entry of bacterial products via the portal circulation. In addition, hepatocytes and Kupffer cells scavenge lipopolysaccharide (LPS) in the liver and this helps to prevent inflammation and maintain hepatic immunotolerance. Alcohol use (binge drinking and long-term use) disrupts gut epithelial tight junctions, results in bacterial overgrowth and impairs immune surveillance in the gut. The net result is increased bacterial translocation (and microbial components such as LPS) to the liver via the portal system. This promotes activation of hepatic Kupffer cells and production of pro-inflammatory cytokines such as TNF-alpha, IL-1β and IL-6. A feedback loop develops whereby these cytokines further increase intestinal permeability and this fosters the cycle of inflammation characteristic of alcoholic hepatitis (Figure 3)[13].

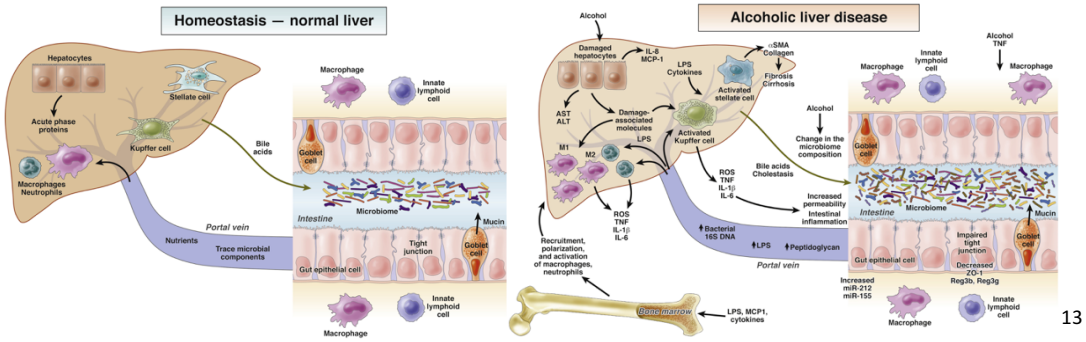

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Figure 3: Pathogenesis of alcoholic hepatitis[13]

Assessment of Severity of Alcoholic Hepatitis

A number of scoring systems have been used to assess the severity of alcoholic hepatitis. These are summarized in table 4 below[14].

	Bilirubin	PT/INR	Creatinine/ urea	Leucocytes	Age	Albumin	Change in bilirubin from day 0 to day 7
Maddrey score	+	+	-	-	-	-	-
MELD score	+	+	+	-	-	-	-
GAHS score	+	+	+	+	+	-	-
ABIC score	+	+	+	-	+	+	-
Lille score	+	+	+	-	+	+	+

Maddrey score, Maddrey discriminant function; GAHS, Glasgow Alcoholic Hepatitis Score; ABIC score, age, serum Bilirubin, INR, and serum Creatinine (ABIC) score; MELD score, Model-for-End-Stage-Liver-Disease score.

Table 4: Scoring systems for alcoholic hepatitis[14]

The best-known scoring system remains Maddrey's discriminant function. It was originally described in 1977 when Maddrey and colleagues carried out a placebo-controlled study to assess the benefit of steroids in patients with alcoholic hepatitis[15]. In

the original study, the formula, 4.6 x prothrombin time (PT)(seconds) + serum bilirubin (mg/dL) was used to risk stratify patients who would most benefit from steroids. Patients with a discriminant function of > 93 and treated with placebo had a 28-day survival of 25%, whereas those with a score of ≤ 93 had 100% survival. In 1989, the modified discriminant function (MDF) (4.6 x [PT – control PT]) + (serum bilirubin), using prolongation of PT in seconds (over control) was used. It was noted that patients without treatment and with an MDF score of ≥32 and/or the presence of encephalopathy had a 28-day survival of about 65% compared to a 94% survival in the steroid group[16].

The Model for End-Stage Liver Disease (MELD) score (based on serum bilirubin and creatinine levels and international normalized ratio (INR)) is used to select and prioritize patients for liver transplantation. It was originally developed to predict 90-day mortality in cirrhotic patients with portal hypertension after placement of transjugular intrahepatic portosystemic shunt (TIPS)[17]. A modification of this score was successfully shown to estimate 3-month mortality in patients with compensated and decompensated cirrhosis and is an important predictor of wait-list mortality. The MELD score has been successfully used as the method of allocating organs in the USA for patients awaiting liver transplantation since 2002[18]. A MELD score >20 predicts high mortality rate within 90 days and serial monitoring of MELD score with a change in score of 2 or more points in the first week of hospitalization has independently predicted in-hospital mortality. The Lille system is a prognostic scoring system for patients who have been treated with steroids[18]. A Lille Score of >0.45 after 1 week of steroid non-response is predictive of a high risk of death at 6 months.

Management of Alcoholic Hepatitis

Nonpharmacologic Therapy

Abstinence

Abstinence is the most important step in the management of alcoholic hepatitis. It has been shown to improve prognosis in early and advanced stages of the disease. Alcohol cessation can result in a complete recovery from alcoholic steatosis, and is essential for the treatment of alcoholic hepatitis and compensated and decompensated alcoholic cirrhosis[19,20].

Nutrition

Malnutrition is very common in patients with alcoholic hepatitis and nutritional support is recommended in patients with AH. Improvements in nutritional status are associated with improved liver function and may prolong survival. The recent AGA expert review recommended a diet with 1–1.5 g protein and 30–40 kcal/kg body weight for adequate recovery. If anorexia or altered mental status are present, a feeding tube should be considered as parenteral nutrition alone is inadequate[12].

Pharmacologic Therapy

Corticosteroids

The jury remains out on the efficacy of steroids in the treatment of patients with alcoholic hepatitis. In 2011, Mathurin and colleagues carried out a meta-analysis of individual patient data from 5 RCTs which used steroids in AH. In multivariate analysis, corticosteroids use was independently predictive of 28-day survival[21]. More recently, the Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH) trial, a multicenter, 2x2 factorial, double blinded trial was recently completed[22].

	Placebo	Prednisolone
Placebo	n=272	N=274
Pentoxifylline	N=273	n= 273

1103 adult subjects were randomized over 3 years at 65 British Hospitals. In this trial, prednisolone was associated with a reduction in 28-day mortality that did not reach significance and there was no improvement in outcomes at 90 days.

28 day mortality	Placebo	Prednisolone
Placebo	16.7%	14.3%
Pentoxifylline	19.4%	13.5%

However, one of the limitations of the trial was the low mortality rate in the placebo group of 17%. The AASLD guidelines and the AGA expert review recommend giving steroids when the MDF is >32 although the duration of therapy is a source of controversy.

Pentoxifylline

This is a weak nonspecific phosphodiesterase (PDE) inhibitor resulting in increased cAMP. It inhibits TNF-alpha and IL-8 and attenuates liver injury and fibrosis in animal models of liver disease. An early study showed that it improved survival by decreasing the incidence of hepatorenal syndrome (HRS) but interestingly, serial TNF levels were unchanged between the two groups[23]. No benefit was seen with Pentoxifylline in the STOPAH trial.

IV N-Acetylcysteine (NAC) and Prednisolone

Nguyen-Khac and colleagues compared the use of prednisolone and IV NAC (for 5 days) with prednisolone alone[24]. The primary outcome was survival at 6 months. There was significantly higher survival in the combination therapy group at 1 month but no survival benefit was seen at 6 months. A network meta-analysis conducted by Singh and colleagues used data from all published randomized trials in severe alcoholic hepatitis including STOPAH[25]. The results confirmed that steroids have only a modest impact on

short term mortality with no benefit at 3 or 12 months whilst Pentoxifylline has little impact on survival. However, the combination of steroids with IV NAC was ranked as the optimal therapeutic intervention and the addition of IV NAC was associated with a significant reduction in infections and in acute kidney injury.

Liver Transplantation for Alcoholic Liver Disease

Liver transplantation is routinely used in selected patients with end-stage liver disease secondary to alcoholic cirrhosis. Outcomes are excellent and are equal to or better than those for other causes of end-stage liver disease. Historically, there has been a 6-month abstinence period for patients with AUD before liver transplantation is available as a destination therapy. Indeed, the 6 month wait remains the current pre-transplant requirement at most transplant centers in the USA. In addition, patients with AUD have to demonstrate regular attendance at licensed counseling or Alcoholics Anonymous and there are no exceptions for patients with high MELD scores. The 6-month rule dates to the 'Reports of a joint conference between American Society of Transplant Physicians and American Association for the Study of Liver Diseases'[3] in 1998. The idea was to formulate minimal criteria by which patients with severe liver disease can be placed on the waiting list for liver transplantation. For patients with AUD, it was deemed that there should be 'favorable assessment by a substance abuse professional and reported abstinence of at least 6 months at time of listing…'. However, this is not the entire story. What is often forgotten is that the same report stipulated that 'exceptional patients with alcoholic liver disease who have not been abstinent for 6 months and yet whom the transplant program believes are good candidates for liver transplantation can be referred to the regional review boards for consideration.' However, this has not been the practice in Europe and the US where most centers still require a period of abstinence. The advantages of the 6-month rule are that it is easy to apply across transplant centers and has been adopted by many insurers. In addition, it allows time for the liver to stabilize and recover, prevents unnecessary liver transplants, challenges patients' commitment to sobriety and theoretically decreases the likelihood of relapse after transplant.

However, it is a weak indicator of 'any use' of alcohol after transplant. In 2006, DiMartini and colleagues carried out a prospective study of post liver transplant alcohol use in ALD recipients and who had fulfilled the 6-month abstinence rule. 22% of patients had used any alcohol by the first year and 42% had a drink by 5 years. By 5 years, 26% exhibited heavy alcohol use and 20% drank in a frequent pattern[26]. Even if patients drink alcohol, numerous studies have shown that post-transplant survival is unchanged irrespective of alcohol use and there is no excess graft loss because of recurrent disease (2% at 10 years). In studies that show increased graft loss, it is due to death from cancer and atherosclerotic disease[27].

Recently, there has been a thawing of attitudes regarding liver transplantation for patients with severe alcoholic hepatitis due to data suggesting that transplant has a role in the management of a subset of these patients. A retrospective review of the

UNOS database from 2004 to 2010 found 130 patients who had been listed for transplantation with a diagnosis of alcoholic hepatitis. 59 patients ended up with a liver transplant and despite confounding elements such as HCV infection in 14 patients (25%), and the fact that only 11 patients had histological evidence of alcoholic hepatitis on explant pathology, graft and patient survival were similar in the patients with alcoholic hepatitis and in a control cohort of recipients without a history of chronic excessive alcohol use[28].

In 2011, a prospective study from 7 transplant centers in France and Belgium evaluated liver transplantation as therapy for patients with severe alcoholic hepatitis that did not respond to steroid treatment for 7 days[29]. There was strict patient selection requiring agreement among all members of the multidisciplinary team. The median MELD score of the 26 transplanted patients was 34. Patients received a transplant on average 9 days after placement on the waiting list, and 13 days after stopping corticosteroids. The 6‐month survival of patients who received a transplant was 77.8%, compared with 23.8% in historical controls with similar severe alcoholic hepatitis, unresponsive to medical therapy. Fewer than 2% of patients admitted for an episode of severe alcoholic hepatitis were selected for transplant. Only three subjects returned to drinking at 720, 740 and 1,140 days after transplantation, respectively. In the USA, Im and colleagues reported their single center experience when transplanting for alcoholic hepatitis[30]. A total of 111 patients were reviewed between 2012 and 2015 at Mount Sinai in New York and ultimately, 94 patients with severe AH were evaluated for liver transplantation. The primary end point was mortality at 6 months or early liver transplantation. A total of 9 patients were transplanted and demonstrated excellent 6-month survival of 89%. Eight recipients were alive at a median of 735 days and there had been a single alcohol relapse.

Barriers to transplantation

Given the excellent outcomes in patients with alcoholic hepatitis who undergo liver transplantation, what are the barriers that remain before patients can be considered for liver transplantation across the country?

Transplant Evaluation Committee

The final decision about which patients are placed on the transplant waiting list is taken by a transplant selection committee. Typically, in the USA, this is comprised of transplant hepatologists, transplant surgeons, a social worker, transplant psychologist or psychiatrist, addiction specialist and nursing staff who are involved in the liver transplant evaluation process. Volk and colleagues carried out a prospective evaluation of 4 transplant selection committees and found that there was a need for more written program rules. In addition, there were inconsistent judgements within committees and there was often a lack of consensus between committee members. Unsurprisingly, there was often an expression of opinions outside committee members' areas of

expertise and interestingly, patients with alcoholic liver disease generated the most challenging discussions[31].

Ethical Considerations

Many ethical issues arise as the lack of organ availability creates a need to prioritize organ allocation. Historically, the reluctance to perform liver transplantation in severe alcoholic hepatitis was because alcohol use disorders were considered to be self-inflicted as well as due to the concern for relapse post-transplant[32]. The debate surrounding liver transplantation in alcoholic cirrhosis and alcoholic hepatitis illustrates the frequent conflict between the ethical principles of justice, equity, utility, beneficence and autonomy[33].

Patients with ALD receive a higher level of scrutiny than other patients with liver disease and have a higher threshold to be waitlisted. Therefore, they experience a different level of justice to other transplant patients on the waiting list. Putatively this notion of justice prioritizes graft survival, purportedly by reducing rates of relapse. However, justice for all other liver patients means prioritizing medical need whilst in ALD and certainly alcoholic hepatitis, medical need is trumped by personal behavior. Using different definitions for justice for the same patient population is certainly questionable[34].

It is also important to understand that AUD is an organic condition, not a moral failing. Nevertheless, transplantation for patients with AUD has generated widespread debate among the general public, health care professionals, patients, living donors, and family members. Patients also carry the stigma and personal responsibility for health. In the West, morality is rooted in Judeo-Christian principles. Individual and societal comportments are frequently judged through a prism of good and bad, and faults are considered to be justification for some form of punishment. We also should be cognizant of sociocultural values and assumptions as negative public perception of the use of transplantation in patients with alcoholic hepatitis could theoretically negatively impact organ donation. Hence, it could be argued that what justifies giving patients with AUD or AH lower priority for a liver transplant is that they are not only causally but also morally responsible for liver failure especially as the advocacy of personal responsibility for health relies on a punitive conception of 'giving people what they deserve'.[34]

However, the principle of equity represents an ethical requirement for access to transplantation. Theoretically, all patients should be treated in the same manner. A commitment to equity demands that 'the only reason to give alcoholic patients lower priority for transplantation is if subgroups of alcoholics can be shown to have unacceptably poor transplant prognoses'. Physicians have a duty to treat regardless of causation. In addition, this is a slippery slope as several liver diseases such as viral hepatitis, deliberate acetaminophen overdose and obesity which result in liver transplantation can also be deemed to be self-inflicted[35]. Nevertheless, the distinction of deserving and non-deserving patients is widely shared by society and the medical

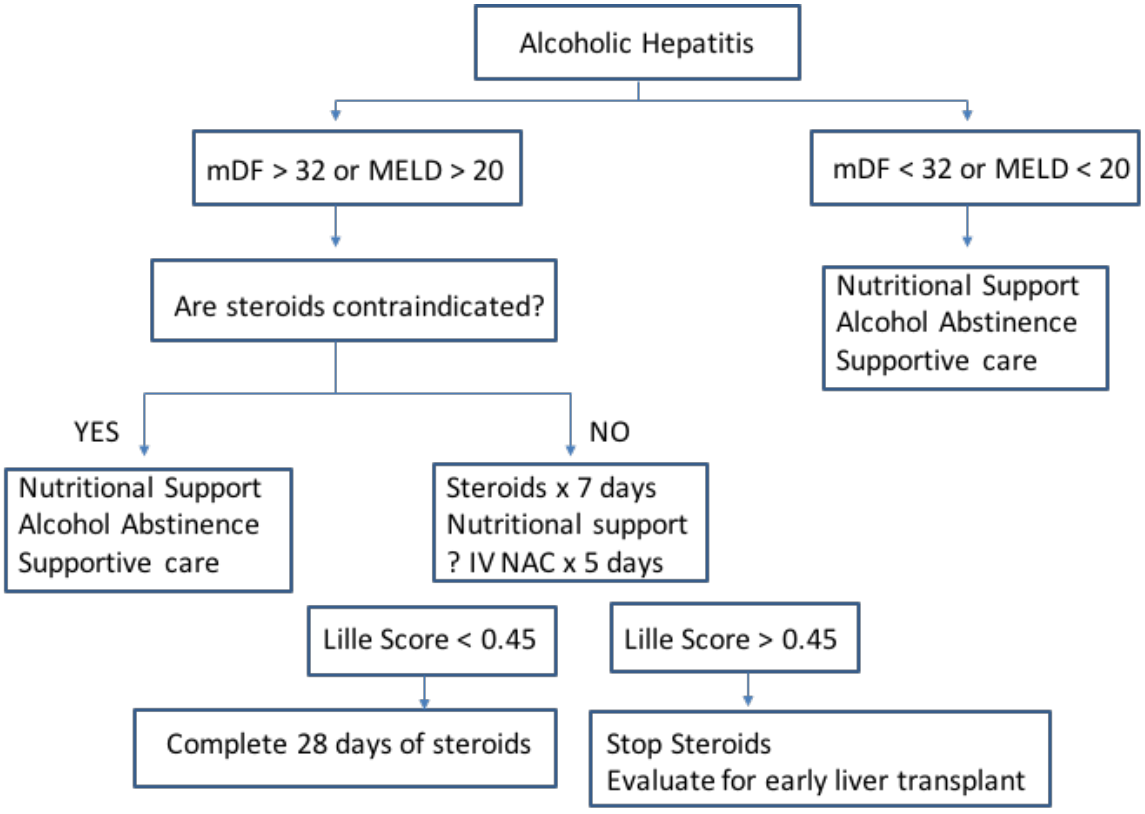
community. Several studies of healthcare providers and the general public have found that patients with ALD are considered to be a very low level of priority for transplantation, regardless of stage of disease and prognosis post-transplant and are only just above people who have been imprisoned for violence.

The focus on disease causality also violates the principle of beneficence as health care providers are supposed to act in the best interests of the patient regardless of disease etiology. In addition, clinician decision making based on predicting patients' behaviors undermines patient autonomy by failing to respect patients' individuality and expressions of free choice. Liver transplantation for severe alcoholic hepatitis can also be justified from a utility standpoint as outcomes in carefully selected patients are markedly better in those who undergo liver transplantation compared to those who follow the natural course of the disease[36].

Medical ethics also compels that therapeutic acts should be performed according to the latest scientific information. For patients with severe alcoholic hepatitis who do not respond to medical therapy, abstention from alcohol alone and by proxy, denial of a liver transplant can result in harm to the patients. We must not discriminate against patients and their access to the best possible therapy must take precedence over moral considerations. As a medical community, we need to continue to better define a role for liver transplantation in patients with alcoholic hepatitis in the future.

UTSW Protocol for Alcoholic Hepatitis

At UTSW, the liver transplant program follows the protocol outlined below. All patients see a social worker, transplant psychologist and are also seen by a dedicated addiction psychiatry team. Patients are then presented at the transplant selection committee and placed on the transplant waiting list if (s)he is considered a good candidate.



Conclusions

Alcohol use disorders are common and can be deadly. In the transplant world, we have many years of experience in managing patients with alcoholic cirrhosis. However, severe alcoholic hepatitis carries a significant mortality risk and prediction models should be used to help determine eligibility for treatment and to assess outcomes. In the event that these models predict a poor outcome with medical therapy, evaluation for liver transplantation should be considered in the appropriate setting.

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