The Ethics of Liver Transplantation in Alcoholic Patients

By
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According to “Alcoholics and Liver Transplantation” one in every ten Americans is a heavy drinker, and one in three families has at least one member with alcohol cirrhosis. Alcohol related liver disease is the most common cause of liver failure in America\(^1\). What is alcoholism? According to the Mayo Clinic alcoholism is defined by a preoccupation with alcohol and impaired control over alcohol intake\(^1\). It is a chronic, and sometimes progressive disease, which can be fatal if it is not controlled\(^1\). Some characteristics portrayed by alcoholics include uncontrollable drinking, preoccupation with alcohol along with impaired thinking, and denial of alcohol leading to negative social and medical problems\(^2\). What is a liver transplant? According to the American Liver Foundation a liver transplant, as the words describe it, is a type of surgery where you replace a diseased liver with a new healthy liver or a portion of a healthy liver from a donor\(^3\).

According to the Mayo Clinic in 2007 there were more than 15,000 patients on the Waiting List for a Liver Transplant, but there are only 4,500 liver donors available each year\(^4\). Of the patients on the waiting list 50% of them have end stage liver disease due to alcohol, however only 10% of them receive a liver transplant\(^9\). Who should get transplants?. During 1988 to 1999 the time spent on the waiting list has risen from one month to more than one year\(^4\). As we progress into the future the shortage of donor organs is expected to rise. This raises the question whether alcoholics should compete equally other patients for a liver?

This has become an ethical issue because according to “Should Alcoholics Compete Equally for Liver Transplantation” “Until recently, liver transplantation for patients with alcohol-
related end stage liver disease was not considered a treatment option.” In the past physicians believed alcoholics who were given a donor liver had a higher rate of relapse and eventually led to liver failure and a higher percentage of mortality. The option of a liver transplant became available to alcoholics in 1988, after Starzl and colleagues reported equivalent survival rates for patients with alcohol induced liver disease and non-alcoholic end stage liver disease.

Should a treatment option be used if it works and saves lives? In the case of alcohol induced liver disease it raises an ethical issue because you are using a limited resource at the hopes of the patient not relapsing. This raises the question of whether alcoholics should be eligible for a liver transplant. To answer this question we must evaluate the prevention and treatment options available to alcoholics, signs and symptoms of liver disease, consequences of relapse post transplant, risk of relapse, and the opinions of pharmacy students as well as registered pharmacists.

Before we answer this question we must first start by determining who qualifies for a liver transplant. Each institution has its own set of “indications for transplant”. I evaluated the California Pacific Medical Centers Liver Transplant program’s “Indications for Transplant”\textsuperscript{6}. The patient being considered should have signs and symptoms of severe fatigue, unacceptable quality of life, recurrent variceal bleeding, and intractable ascites, recurrent or severe hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, and/or development of small hepatocellular carcinoma. Alcoholics compete with patients with end stage chronic liver disease, chronic cholestatic liver disease (eg. primary biliary cirrhosis and primary sclerosing cholangitis), and chronic heptaocellular diseases such as chronic hepatitis with cirrhosis. End stage chronic liver disease patients are automatically qualified to be placed on the waiting list for a liver transplant. If a patient has chronic cholestatic liver disease of primary sclerosing
cholangitis then the patient must also have serum bilirubin above 8-10 mg/dL, intractable pruritus, intractable bone disease, malnutrition or recurrent bacterial cholangitis, and/or severe or intractable encephalopathy to be considered a candidate for liver transplant. Patients with chronic hepatocellular diseases must have either serum albumin below 3.5 g/dL, prothrombin time greater than 3 seconds above control or INR above 1.3, encephalopathy, ascites, or bilirubin above 2 mg/dL. As noted there are specific criterias patients must meet before they are considered for a transplant. The criterias described above are natural in cause and not specifically caused by something a patient might have done. Alcohol induced liver failure on the other hand is due to patients’ negligence to accept treatment.

Before we can truly say alcoholism induced liver failure is due to negligence we must look at the cause, prevention, and treatment options available. By looking at these we will be able to determine whether alcohol induced liver failure is preventable by a person or it is due to natural causes such as with hepatocellular carcinoma, chronic cholestatic liver disease, and other forms of end stage chronic liver disease. Alcoholism, also known as alcohol addiction is where a person is physically dependent on alcohol to function. It does not occur suddenly, but instead it is a gradual problem. Alcoholism is a chronic disease. It develops after 10 to 20 years of heavy alcohol consumption. Alcoholics should be held responsible for seeking and obtaining treatment that might have prevented end stage liver disease due to alcohol. There are numerous factors that make a person prone to becoming an alcoholic. They include: hereditary, environmental, physiological, biochemical, and genetic.

Drinking alcohol creates a chemical imbalance in gamma-aminobutryic acid (GABA), which inhibits impulsiveness, and glutamate, associated with excitement in the nervous system.
Drinking raises dopamine levels, a neurotransmitter related to the pleasure of drinking. A person becomes dependent on alcohol because chronic drinking depletes or leads to an excess of chemicals, requiring a person to drink to restore balance. Dependency can also occur due to genetics, which cause a person to be vulnerable to addiction. Emotional state, psychological factors such as low self-esteem or depression could also make a person more likely to abuse alcohol. As we notice there are numerous factors that make a person susceptible to becoming an alcoholic.

However, there are numerous prevention techniques which if employed can sometimes prevent alcoholism from worsening to the point of requiring a liver transplant. The main problem encountered in preventing alcoholism is recognizing there is a problem of abuse. Prevention is more likely to be successful if intervention is done early. Addiction is easier to prevent or reverse if there is less influence from parents, peers, other role models, genetics, and psychological factors. Treatment starts with the patients recognizing they are dependent on alcohol. This the first but the hardest step. Treatment options include an evaluation, brief intervention, counseling, residential inpatient stay, or pairing drinking alcohol with an aversive response. The residential treatment options include detoxification and withdrawal, medical assessment and treatment, psychological support and psychiatric treatment, emphasis on acceptance and abstinence, and/or drug treatments, which includes a disulfiram like drug as an aversive agent. There are also support groups known as Alcoholics Anonymous and Al-Anon and Alateen, to help with alcohol abuse or dependency. As we can see there are many options a person who drinks alcohol has available to prevent alcoholism or treat it if they feel they are becoming dependent or already have become dependent on alcohol.
If we presume that patients with liver disease did not take responsibility for maintaining their health and this lead to the development of their liver disease therefore they should not qualify for a liver transplant. Then the same logic must be applied before treating patients that develop other diseases due to negligence. If we refuse to transplant patients with alcohol related end stage liver disease then we must ask ourselves why we treat patients who smoke and develop lung cancer or other chronic pulmonary disease, obese patients who develop type II diabetes, patients who have HIV, patients who have uncontrolled high blood pressure or cholesterol and develop coronary artery disease, and athletes who have sport related injuries. However, according to the Louis Harris and Associates national survey, which was administered to the general public, physicians, nurses, employers, and politicians the results showed a majority of participants agree with providing treatment to cancer patients and infants a higher priority and a lower priority to alcohol induced liver disease. This implies the public’s stance regarding liver transplant in alcoholics being one of not denying an alcoholic a transplant and putting them at a lower priority on the waiting list.

An explanation as to why public’s views differ regarding alcoholic liver transplant compared to other diseases such as HIV and others mentioned above is the availability of public support groups to treat alcoholism. Programs such as Mothers Against Drunk Driving, Students Against Drunk Driving, and corporate employee assistance programs provide alcoholics enough support to prevent or treat their addiction and reverse its impact, unlike diabetes, blood pressure, and HIV, which once developed, can only be controlled and the damage cannot be reversed.

Alcohol is not the main culprit of liver disease but instead it is the acetylaldehyde, which is formed by the liver’s degradation of alcohol. This buildup can lead to alcohol hepatitis or
alcoholic cirrhosis. In order to prevent or reverse alcoholism it is important to catch it early in its progression. The symptoms of hepatitis include anorexia, vomiting, jaundice, weight loss, fever, hepatomegaly (enlargement of liver), arterial angiomata, ascites, edema, spleenomegaly (enlargement of spleen), and varices. These symptoms help to narrow down the possible disease states, however by looking at the laboratory findings we can more accurately diagnose alcoholic hepatitis. The laboratory findings will include an AST/ALT ratio of greater than 2, increase in bilirubin, decrease in albumin, along with coagulation and hematological abnormalities. Discontinuation of alcohol along with good nutrition and rest with or without correcting electrolyte deficiencies can help reverse mild to moderate alcoholic hepatitis completely.

In cases of severe alcoholic hepatitis there is a 15 to 50% risk of developing complications. An accumulation of acetylaldehyde can also lead to alcoholic cirrhosis. It usually occurs in 8 to 20% of chronic alcoholics, 120-180 grams of alcohol per day for more than 15 years. Alcoholics who develop this have over a 50% rate of mortality because it is an irreversible disease. These are the alcoholics who need a liver transplant. The symptoms experienced by these patients include fatigue, weight loss, nausea and vomiting, worsening jaundice, pruritus (itching), erythema (skin lesions), hypogonadism (male breasts and testicular atrophy), ascites, portal hypertension, spleenomegaly, leucopenia, thrombocytopenia, and anemia. These symptoms help to narrow down the possible disease states, however by looking at the laboratory findings we can more accurately diagnose alcoholic cirrhosis. The laboratory values include arterial ammonia, which is decreased, elevation in bilirubin, increase in Blood Urea Nitrogen (BUN), decrease in albumin, hyperglycemia, hypomagnesemia, hypokalemia, and hyponatremia. Alcoholic cirrhosis is an irreversible disease therefore there is no treatment but only supportive care. It includes bed rest, good caloric diet, and correcting fluid and electrolyte
deficiencies through fluid intake. One of the first signs of hepatic disease include hepatic encephalopathy, which is the result of an accumulation of ammonia levels. Encephalopathy includes an alteration in mental status, which is presented as confusion or coma.

After a liver transplant there are a cocktail of drugs a patient must receive. The duration of treatment varies depending on the condition of the patient at time of evaluation and hospital protocol. When we evaluate the Henry Ford Hospital Liver Transplant Protocol we find that post liver transplant patients receive a unique combination of drugs such as tacrolimus (Prograf®), cyclosporine (Neoral®), mycophenolate mofetil (Cellcept®), methylprednisone (Medrol®), sulfamethoxazole and trimethoprim (Bactrim DS®), clotrimazole (Mycelex®), and ganciclovir (Cytovene®). Patients will receive additional drugs based on side effects they experience from the necessary post transplant drugs or if they were on a drug outpatient pre-transplant.

Alcoholics are at high risk for relapse, therefore we have to evaluate the impact alcohol might have on these drugs. Tacrolimus is highly protein bound, mainly to albumin. The distribution of the drug can be affected in someone that drinks alcohol or someone that is started on the drug without a few months of sobriety because they will have lower albumin levels. Chronic alcoholics and heavy drinkers will have higher rates of malnutrition, which will be correlated with lower albumin levels. Hence, there will be fewer drugs available so the patient will require a higher dose of the medication to achieve therapeutic concentrations. When you give a higher dose to a patient you increase the risk for side effects. Cyclosporine is metabolized by cytochrome P-450 in the liver. When someone drinks alcohol it also needs to be metabolized through the liver leading to reduction in the metabolism of cyclosporine. Also if the liver is injured the metabolism done by cytochrome P-450 is also impaired. This leads to a higher
concentration of the drug, which can increase in the risk for developing side effects, or the risk of reaching toxic levels. Mycophenolate mofetil is 97% bound to albumin. This drug is associated with similar problems as tacrolimus, alcoholics have malnutrition and this leads to a decrease in albumin. Decrease in albumin is associated with a decrease in the concentration of the drug in the body. Hence an alcoholic who relapses to alcoholism post transplant and someone who has not had a minimal amount of alcohol free period is likely to achieve a lower concentration of the drug. This means they must be given a higher concentration of the drug to achieve therapeutic levels and this can increase the risk of side effects or even rejection if the levels are not met.

When we evaluate methylprednisone’s impact on the liver we notice that it has been associated with a slight increase in alanine transaminase (ALT, SGPT), aspartate transaminase (AST, SGOT), and alkaline phosphatase. Alcohol also causes an increase in liver enzymes. An elevation of liver enzymes is associated with liver injury, which can be reversible or irreversible, and in the case of alcohol it is reversible if alcohol is discontinued early enough. If a person drinks alcohol while on methylprednisone they run the risk of liver damage due to a greater risk in the increase in AST, ALT, and alkaline phosphatase.

Besides immunosuppressive drugs patients must also receive antibiotics. The liver is responsible for making Vitamin K, which helps with clotting. A heavy drinker or someone with alcohol cirrhosis has a longer clotting time. When a patient is on sulfamethoxazole and trimethoprim they may have an extended prothrombin time. If a patient is on sulfamethoxazole and trimethoprim and alcohol they have an increased risk of bleeding because they do not have adequate clotting factors. This can lead to an increase risk for the new organ to be rejected because bleeding without clotting leads to other complications such as infection or hospitalization. Patients according to the Henry Ford Hospital’s Liver Transplant protocol also
receive clotrimazole troughs for one month post transplant. The troughs have been known to cause an elevation in AST in 15% of patients. Alcohol plus this can cause an elevation of liver function tests, which can increase the risk of rejection. The only drug that a previous history of alcohol consumption or post transplant alcohol does not impact, is ganciclovir. According to rxlist.com there seems to be no problems with alcohol consumption and the efficacy of the medication because it is not protein bound and does not rely on cytochrome P-450 for metabolism.

According to “Liver Transplant and Alcohol: Who Should Get Transplants?” the rate of relapse is considered the most important parameters to use before transplanting an alcoholic. To reduce the risk of relapse occurring post transplant, an alcoholic patient waiting to be transplanted must be sober for at least six-months, have stable and supportive environment which discourages drinking, and should participate in alcohol counseling program to provide him encouragement. A six-months abstinence period has a significant impact on the percentage of relapse along with determining the survival rate post transplant. It has been shown that a patient who has developed jaundice, ascites, and hematemesis has a 60% 5 year survival rate if they discontinue drinking. The 5 years survival rate of patients who stopped alcohol and received a liver transplant compared to those who only stopped alcohol was 50 to 75% and 60% , respectively. Also when we look at studies conducted by the Mayo Clinic, Byrd, Kumar, and Lucey evaluating 151 patients we discover the rate of relapse to alcohol after six-months of no alcohol to be 43% to 100%. Dafoe’s study used 17 patients and evaluated the results of sobriety of less than three months to have a 60% rate of relapse when compared to 42 patients who have been sober for more than six months who showed only a 24% relapse rate. According to Valliant’s study it was proven that a short duration of alcohol free period does not help predict
future relapse rate. Abstinence and early recognition both play a role in achieving high survival rates and good prognosis. If a patient does not present a minimum abstinence period of six-months they should be excluded from the waiting list because they have a higher risk factor for causing liver failure in the transplanted liver. Also, alcohol interferes with the efficacy of the multi-drug regimen a patient is on post transplant. This can also lead to the new organ being rejected. A study using 387 patients who had alcoholic cirrhosis between 1989 and 2003 was conducted in Switzerland and France. The mean age was 51.3 years of age and they were followed for 61.2 months. At the end of the study the patients showed a relapse rate of 11.9%. The study showed the participants which had an age greater than 50, length of sobriety less than six months before transplant, presence of psychiatric comorbidites, or a life partner which promoted alcohol, and a score of three or higher on the high risk alcoholism relapse scale (HRAR) had a higher rate of relapse. If someone did not have these risk factors the relapse rate was 5%, whereas the relapse rate with one, two, or three factors showed a relapse rate of 18, 64, and 100% respectively.

The following survey was given to third year Pharmacy Students at Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University and Registered Pharmacists in the State of Michigan. The survey was designed to obtain and evaluate the opinions of pharmacy students and Pharmacists in an ethical crossroad regarding the use of a scarce resource; in this case, a donor liver to treat alcohol induced liver disease. The pharmacy students and Pharmacists were asked to answer four multiple choice questions. The survey was voluntarily conducted and the individual responses were kept anonymous. A total of 62 pharmacy students and 15 Registered Pharmacists completed the survey.
Disclaimer: This survey is being conducted for a research project by a Wayne State University Pharmacy Student (P3). This survey is completely voluntary and anonymous with the intention of evaluating and reporting the responses of pharmacy students and Pharmacists. The results will be used for opinion purposes and there will be no attempt to identify participants of the survey. Thank you.

1. Do you believe organ transplant is ethical?
   a. Yes --- 62/62 (100%) pharmacy students; 15/15 (100%) Pharmacists
   b. No --- 0/62 (0%) pharmacy students; 0/15 (0%) Pharmacists

2. Do you know anyone that is an alcoholic?
   a. Yes --- 40/62 (64.5%) pharmacy students; 9/15 (60%) Pharmacists
   b. No --- 22/62 (35.5%) pharmacy students; 6/15 (40%) Pharmacists

3. Do you know anyone that is on the Organ Waiting List?
   a. Yes --- 5/62 (8.1%) pharmacy students; 1/15 (6.7%) Pharmacists
   b. No --- 57/62 (91.9%) pharmacy students; 14/15 (93.3%) Pharmacists

4. Do you believe alcoholics should compete equally for a liver transplant?
   a. Yes --- 12/62 (19.4%) pharmacy students; 4/15 (26.7%) Pharmacists
   b. No --- 38/62 (61.3%) pharmacy students; 9/15 (60%) Pharmacists
   c. Don’t Know --- 12/62 (19.4%) pharmacy students; 2/15 (13.3%) Pharmacists

Evaluating the survey will allow us to draw conclusions on a possible solution to such an ethical issue as seemed reasonable by pharmacy students/tomorrow’s Pharmacists and Registered Pharmacists/current practicing Pharmacists. The questions were designed in order to obtain a general idea regarding transplant, background information of students and pharmacists, bias that might impact the end thought of whether alcoholics should be given an equal chance on the waiting list for a liver transplant.
100% (62/62) pharmacy students and 100% (15/15) registered Pharmacists responded to question #1 with “a” or “yes” as an answer when asked, “Do you believe organ transplant is ethical?” When we evaluate the results we notice that everyone shows beneficence or do good to all because they all agree with the idea of transplantation. Transplantation will only lead to beneficial results for the patient receiving the new organ and cause no harm to patients donating an organ. In the worst case scenario a patient receiving the new organ might have a rejection and will have to be relisted and be in the same scenario as before.

65.5% (40/62) pharmacy students and 60% (9/15) registered Pharmacists responded to question #2 with “a” of “yes” as an answer when asked, “Do you know anyone that is an alcoholic?” This question was designed to obtain an estimate of biases that might exist in answering question # 4. When we evaluate the results it leads us to believe that of the 40 pharmacy students and 9 Pharmacists that answered “yes” to this question might have answered “no” to question #4 solely based on the characteristics or their experiences with an alcoholic. The alcoholic they know might be abusive, deny dependency on alcohol, and ignore others advice or help.

8.1% (5/62) of pharmacy students 1/15 (6.7%) of registered Pharmacists responded to question #3 with “a” or “yes” as an answer when asked “Do you know anyone that is on the Organ Waiting List?” The intent of this question was to find any biases that might exist which could influence the answer to question #4. The 5 pharmacy students and 1 Pharmacist that answered “yes” might have answered “yes” to question #4 leading to a false evaluation of the true number of pharmacy students and Pharmacists which believe alcoholics should compete equally for a liver transplant. If someone knows a close relative or friend that is on the Waiting
List due to alcoholism they might be more inclined to vote for equal opportunity between an alcoholic and someone with non-alcoholic end stage liver disease for a new liver for transplant.

19.4% (12/62) pharmacy students and 4/15 (26.7%) Pharmacist answered “a” or “yes”, 61.3% (38/62) pharmacy students and 9/15 (60%) Pharmacist answered “b” or “no”, and 12/62 (19.4%) pharmacy students and 2/15 (13.3%) Pharmacists answered “c” or “don’t know” when asked “Do you believe alcoholics should compete equally for a liver transplant?” This question provides us with a general idea that 38 out of the 62 pharmacy students and 2/15 Pharmacists who participated in the survey believe in the idea of non-maleficence. Many of the pharmacy students and pharmacists agree with the idea of not inflicting harm intentionally. This is implied with the answer “no” because this means they agree with alcoholic patients not being given an equal opportunity on the Waiting List for Liver Transplant, which therefore means they should be put at a lower priority. This means you are not intentionally harming the patient because the patient already harmed themselves by drinking and causing liver disease. The patient needing a new liver is still being helped by being placed on the waiting list, even if it is lower, instead of completely voiding them of a liver transplant as was done more than two decades ago. However based on the answer to question #3 it seems as if 5 out of the 12 pharmacy students and 1 out of 4 Pharmacists that answered yes might have done so because they know someone that is waiting for a new liver and if the policy of lower priority was adopted then the alcoholics that are waiting might not receive a new liver in time. Even if we ignore the biased answers we are still left with 7 pharmacy students and 3 Pharmacists that answered yes. Also, 40 pharmacy students and 9 pharmacists that answered yes to question #2 were most likely to say “no” to this question and this leads us to believe their reason might be because they might have tried to stop the alcoholic they know from drinking and provided the adequate social support but the alcoholic might not be
willing to quit leading to 38 pharmacy students and 9 pharmacists to answer no to question #4. The decision to transplant alcoholics should be based upon the opinion expressed by the general public. From question #4 we find support based on a sample size consisting of the opinions held by future and current Pharmacist. Based on the responses to this question it seems as if our participants believe alcoholics needing liver failure should not compete equally for a liver transplant, because it is their fault.

A possible solution to this ethical issue might be to list alcohol induced liver disease patients lower on the waiting list than other end stage liver disease patients. We do not violate nonmaleficence, do not cause harm intentionally. The alcoholic patients with end stage liver disease had developed it due to chronic alcoholism and not due to being given a lower priority on the waiting list. We follow the rule of beneficence, do good, because we are giving alcoholics a chance to receive a liver and allowing nonalcoholic end stage liver disease patients a greater opportunity to receive a liver transplant instead of ignoring an alcoholic’s need for a new liver, as was done in the past. Justice is given when we split it up into two parts. The first part or distributive justice states there should be proper distribution of goods between different people\textsuperscript{11}. The second part or retributive justice states that the solution should take the situation or wrongdoing into consideration\textsuperscript{11}. By placing an alcoholic at a lower priority we are actually following the path of retributive justice because we are providing a solution or response that is based on the fact that the patient choose to drink chronically and when the appropriate opportunities were provided to reverse them, the patient showed negligence and eventually developed end stage liver disease requiring a need for a liver transplant.

By placing alcoholics lower on the waiting list we are not violating the ethical rule of nonmaleficence, following the rule of beneficence, and showing justice. Patients who need a
liver transplant due to congenital problems or cirrhosis should be higher on the waiting list than patients with alcoholic liver disease because of the scarcity and livers available for transplantation. Until we determine for certain the success rate of liver transplant in alcoholics compared to nonalcoholic end stage liver disease patients in a larger study, the length of abstinence required to prevent relapse, and the best social support groups to obtain good prevention of relapse we cannot deny alcoholics a liver transplant. However, by ranking them lower on the waiting list we have a way to maintain public respect for the liver transplant program. “If we accept the case of equal access, but if we simply cannot, physically cannot, treat all who are in need, it seems more just to discriminate by virtue of categories of illness, rather than between rich ill and poor ill” according to Outka.
References


