Introduction
Alcohol abuse is the leading cause of liver disease in Western countries, and an estimated 50% of the population above 18 years-old in the United States drinks alcohol. There are three overlapping liver diseases that can result from alcohol use: hepatic steatosis, alcoholic hepatitis, and cirrhosis [1]. Hepatic steatosis may or may not be a precursor to alcoholic hepatitis, but regardless of the presence of steatosis, both extreme exposures to alcohol and/or prolonged, high-dose exposures put individuals at a greater risk for developing alcoholic hepatitis [1]. Patients with severe acute alcoholic hepatitis have a 20-25% chance of dying despite traditional treatment with corticosteroids and/or tumor necrosis factor alpha (TNF-α) antagonists, and have a 40% chance of dying within six-months of diagnosis [2]. Liver transplantation would be a definitive treatment for these patients, however, a shortage of organs, the concern of recidivism without the standard six-month period of alcohol abstinence, and insufficient research data on outcomes of transplantation in these patients, has made alcoholic hepatitis a contraindication of transplantation at most institutions [3].

Although data on early transplantation (done without a defined abstinence period) is currently inadequate, some prospective studies have shown that patients who receive early transplantation have significantly higher rates of survival up to two years post-transplantation compared to patients who do not receive transplantations [2,4].

Despite these promising data, many programs are still reluctant to begin doing this type of transplantation. One concern of doing early transplantation in patients with acute alcoholic hepatitis is a potential negative public reaction to doing transplantations in patients with active alcohol abuse and/or patients whose dedication to caring for their new liver turns out to be less than adequate. For example, if a donated organ is given to a patient who was initially thought to be unlikely to relapse into alcohol abuse, but subsequently dies due to continued alcohol abuse, potential organ donors may be reluctant to donate if they think their organs could be distributed irresponsibly.

The goal of this project is to explore the reaction of both healthcare professionals and the public to early transplantation in patients with acute alcoholic hepatitis, which will aid in future clinical decisions and provide a foundation for additional research on the topic of public response to changes in transplantation indications.

Background
Acute alcoholic hepatitis is a disease caused by prolonged, excessive drinking, and is thought to be a precursor to cirrhosis [5]. Alcohol itself is a hepatotoxin which also has toxic metabolites. These metabolites generate endotoxins, inhibit fatty acid oxidation, and initiate pro-inflammatory cascades which trigger hepatocyte necrosis or apoptosis [5]. Traditionally, the treatment for this condition has been corticosteroids and/or TNF-α antagonists, but as mentioned above, a significant number of patients who develop acute alcoholic hepatitis do not respond to pharmacologic therapy [2]. In 2007, there were approximately 57,000 hospital admissions in the United States for alcoholic hepatitis, for which there was a mortality rate of 6%. Thus, the number of these patients in need of early liver transplantation is a relatively small sub-set of patients within the category of liver disease secondary to alcohol damage [17]. An additional, new therapy that has been introduced in recent years is the Molecular Adsorbent Recirculating System (MARS), which is used to remove protein-bound toxins in the blood using dialysis.
through an albumin-impregnatated membrane [6]. However, data on this treatment are insufficient and more research on this technique must be done. If these initial treatments are ineffective, as is the case in 20-25% of severe cases [2], patients do not have a good prognosis. Cases lie on a spectrum that range from mild to severe, but estimates of mortality in severe cases range from >50% in 30 days to 40% in six months [5,2].

The short time frame in which transplantation is possible has been a primary reason why these patients have not been considered for transplantation in the past because a minimum six-month abstinence from alcohol and counseling is generally required prior to transplantation by most programs [3]. The abstinence period is mandated as a way to make sure the patient can successfully commit to refraining from further alcohol intake and is dedicated to caring for the donated organ. Interestingly, a review of the literature evaluating the six month abstinence rule came to the conclusion that the six month period of abstinence was only one of several important factors in reducing post-transplant recidivism rates, such as family support, economic stability, and counseling [8]. Additionally, a recent prospective study of 167 patients who underwent liver transplantation for alcoholic liver disease of varying lengths of sobriety showed that abstinence length was a significant predictor of recidivism, and that with each month of abstinence there was a lower risk of recidivism [7]. However, almost half of the patients in that study had consumed alcohol post-transplantation and almost one quarter of the patients had engaged in harmful alcohol consumption. Importantly, the researchers noted that long-term studies of alcohol sobriety indicate that stable sobriety is achieved after about 5 years of abstinence [7], and they suggest that counseling and a supportive social network are more important than a few additional months of sobriety. Thus, these results do not suggest that abstinence length prior to transplantation is unimportant, rather, they suggest that a minimum of six months may not be necessary.

Currently, early transplantation in patients with acute alcoholic hepatitis is in its infancy, so the data on outcomes is lacking. However, in a study comparing patients receiving transplants with alcoholic cirrhosis alone and those with acute alcoholic hepatitis did not find significant differences between the two groups regarding survival or recidivism [9]. Importantly, abstinence periods for some patients were less than six-months and pre-transplant abstinence was not found to be a predictor of recidivism nor graft-survival [9]. Even stronger data comes from a study that examined patients who had clinically severe acute alcoholic hepatitis (Maddrey Discriminant Function of >32) [10]. All of the patients in this study had abstinence periods of less than two months, and the three year post-transplant survival rate was 78% and recidivism rates were similar to patients receiving transplantation for alcoholic cirrhosis with a six-months abstinence [10,11]. Additional research has also found similar survival and recidivism rates between patients with acute alcoholic hepatitis and those with alcoholic liver disease without acute hepatitis [14]. One prospective study followed 18 patients who received liver transplants after an average of 9 days after being diagnosed as non-responsive to therapy. These patients were compared to 18 matched patients who did not receive transplant, and 1-year survival rates of transplanted were significantly higher (83% vs 44%), with over half of the non-transplanted patients dying within the first two months of being non-responsive to therapy [15]. Importantly, only one of the transplanted patients returned to drinking after 2.5 years [15].

Although the available data shows that transplantation for patients with acute alcoholic hepatitis is promising in regards to outcome and recidivism rates, implementation of early transplantation
has not been widespread. Although there are multiple reasons for this, one contributing factor is the concern of a negative reaction from potential organ donors. This study hopes to shed light on these concerns and allow transplant teams to make informed decisions regarding this issue.

**Subject Selection Criteria**
Subject selection is divided into two groups. The first group of subjects will be selected based on their affiliation with the Midwest Transplant Network and Gift of Life organizations. Healthcare professionals from the Midwest Transplant Network and members of the Gift of Life will be selected to receive the survey.
The second group of subjects will be selected through the Amazon Mechanical Turk. A request for the survey will be made available to all members of the Amazon Mechanical Turk who are United States citizens.

**Methods and Measurement Tools**
This project will be carried out by distributing online surveys to physicians, nurses, transplant coordinators, and members of the general public. The survey will be created on and distributed through the KUMC Vovici Survey Workbench Enterprise and on the Amazon Mechanical Turk interface (AMT).
The survey will begin with introductory information on the topic of liver transplantation and early liver transplantation in patients with acute alcoholic hepatitis. Respondents will be asked to indicate their specific level of involvement in the healthcare field and/or transplantation. The respondents will then be asked to provide some demographic information including age, gender, race/ethnicity, and the state in which they were raised. They will then be asked if they plan to be an organ donor, and if so, what actions have they taken to do so. The self-reported level of alcohol intake will then be evaluated, and a question regarding their history of DUI’s will be used as an indirect marker for prior alcohol abuse. Respondents will also be asked if they think there are any circumstances in which a person should receive a liver transplant for a liver disease secondary to alcohol.

The respondents will then be presented with a series of case vignettes describing a patient who develops acute alcoholic hepatitis who does not respond to pharmacologic therapy and will die without a liver transplant. The hypothetical patients will vary based on age, gender, level of family/social support, and socioeconomic status (ability to pay). With each vignette, the respondents will be asked to rate how they would feel about that patient getting a liver transplant without undergoing a six-month period of abstinence on a scale from 1-10 (1=very upset, 10=very happy).

At the end of survey, the respondents will be asked if news of transplantation in one of these patients would cause them to not want to donate their organs, and if so, to indicate which case(s). Respondents will also have an opportunity to rate how important they perceive age, family/social support, and socioeconomic status are when considering when to do early liver transplantation. Additionally, there will be a question asking if doing transplantations of this sort would change their perception of transplantation programs, and if so, how. After completion of the survey, there will be a thank you message with a short debriefing message assuring them that their responses are anonymous.

For more details on the survey, please see a copy of the survey accompanying this proposal.
The survey will be delivered to patients electronically either via email or using Amazon’s Mechanical Turk. The respondents contacted via e-mail will obtained through Dr. Forster’s contacts at the aforementioned transplantation centers and organizations.

The AMT is a well-known method of distributing surveys online and is widely used in behavioral research to easily gain access to large, diverse populations of people [16]. The AMT works by providing the survey taker a small payment for completion of the survey. The survey will be launched with a finite amount of money in an account, and once the account runs out of money, the survey will be automatically deactivated. Respondents will be paid only after the survey quality has been verified. In order to verify the quality of the survey, one additional question will be inserted into the survey requiring respondents to read the entire question and mark a specific, pre-determined answer. This is recommended for use with the AMT because there are some people who are only interested in completing as many surveys as they can to make money; they do not read the surveys, but, rather, mark down random answers to complete the surveys as quickly as possible. This additional question will be the only difference between the surveys distributed on Vovici and AMT.

Statistical Analyses
Statistical analyses will be done using Microsoft XLSTAT Pro statistical software. Data will be expressed as mean ± standard error of the mean. The reactions of physicians, other healthcare professionals, and the general public for the different cases will be compared, as well as reactions among cases within each group. Statistical significance will be determined by two-way repeated measures analysis of variance (ANOVA).

Significance
Organ shortages are a constant concern of physicians in transplant medicine, and, therefore, actions that could affect organ donation are of great concern. However, these physicians also want to provide definitive care to patients who will benefit from it and are also able to responsibly care from themselves after transplantation. The results from this study will provide an initial understanding of whether the reaction to an implementation of early transplantation for acute alcoholic hepatitis would result in backlash from potential organ donors. Transplant programs considering the acceptance of acute alcoholic hepatitis as an indication for transplantation (early transplantation), will find this data useful in their decision making process. In addition to contributing to information used for clinical judgments, this research will also provide initial data in a previously unstudied area. Because no other research has been done concerning public reaction to early transplantation for patients with acute alcoholic hepatitis, this study will be a source upon which addition research can be based.

Additional Experiences
In addition to this research component of this project, I plan to shadow Dr. Forster and his colleagues, in both the clinics and operating room to gain a better understanding of the process of liver transplantation from the perspectives of both physicians and patients, and also to better understand the ethical considerations that go into liver transplantations. I believe that these additional experiences will greatly add to my understanding of the ethical issues accompanying this topic, such as physician autonomy, a patient’s right to the highest quality care, and utilitarian concerns of organ distribution and utilization of public funds.

Budget
Living Expenses -- $850
Mechanical Turk Fees (500 respondents at $2 per survey + 10% commission) -- $1100
References


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i Maddrey Discriminant Function is an index of liver damage that measures the patients total serum bilirubin and a comparison of the patient’s prothrombin time (pt) to normal pt time (ptc). The formula used is $(4.6 \times pt - ptc) + \text{serum bilirubin} \left( \frac{\text{mg/dL}}{} \right)$. A Maddre Discriminant Function great than 32 has been used as a marker of severe alcoholic hepatitis [10, 12].

ii The Gift of Life is a non-profit organization based in Overland Park, KS. Their mission is to build awareness of the need for organ and tissue donation, and to provide assistance to transplant patients, their families, and living donors.