

a series of fact sheets written
by experts in the field of liver
disease

HCV Disease Progression: Liver Transplantation

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Over years or decades, chronic hepatitis C virus (HCV) infection can progress to severe liver problems including cirrhosis and hepatocellular carcinoma (HCC). When the liver is no longer able to perform its vital functions—whether due to acute liver failure or advanced end-stage liver disease—a transplant may be the only option.

Liver damage due to hepatitis C is the most common reason for liver transplants in the U.S., accounting for about 30% of cases. In comparison, hepatitis B is responsible for less than 10% of transplants, largely thanks to an effective vaccine. Other reasons include alcoholic liver disease and acute liver toxicity (for example due to acetaminophen overdose or poisonous mushrooms).

Advances in surgical techniques and medical management have led to improvements in liver transplant outcomes in recent decades. Today the overall one-year survival rate is approximately 90%—up from about 30% in the 1970s—and the five-year survival rate is in the range of 70% to 80%. But patients with hepatitis C, on average, do not fare as well as people receiving transplants for other causes.

Liver Transplant Procedures

The most common transplant procedure is orthotopic liver transplantation (OLT), in which the damaged liver is removed and replaced with a new one (known as an allograft), usually from a recently deceased donor, and

the major blood vessels and bile ducts are connected to the new organ.

Unfortunately, the supply of donor livers does not come close to meeting the demand, meaning most people who require a transplant are put on a waiting list. In the U.S., livers are allocated on a regional basis by the United Network for Organ Sharing (UNOS).

In 2002 UNOS adopted a system called MELD (Model for End-Stage Liver Disease) that uses three lab tests—bilirubin, creatinine, and prothrombin time (a measuring of blood clotting)—to predict how likely patients are to die. The system is intended to give priority to people who need new livers most urgently, but are still well enough to benefit, rather than those who have been waiting longest.

According to a study published in 2004, the number of liver transplants increased by 10% and deaths on the waiting list fell by nearly 4% after MELD was adopted. But the system has required some adjustment so it does not favor certain groups, such as people with liver cancer. While the current method has reduced the disparity between white and black patients, a study presented at the 2010 meeting of the European Association for the Study of the Liver (EASL) found that women are more likely than men to die while awaiting a new liver.

However they are allocated, there are not enough good quality deceased donor livers to meet the existing need. In 2008, according to the U.S. Organ Procurement and Transplantation Network (OPTN), approximately 6,000 liver transplants were performed, nearly 1,800 patients died while awaiting a donor liver, and there were about 16,000 people on the liver waiting list at the end of the year.

To address the shortage of deceased donor livers, alternative methods have been developed to increase the liver supply:

- **Split Liver Transplant:** Thanks to the liver's ability to regenerate itself, a deceased donor liver can be split into two pieces and transplanted into two recipients, with each piece growing into a fully functioning organ. Split liver transplants produce the best results when the

larger right lobe is given to an adult and the smaller left lobe to a child. An Italian study presented at the 2008 EASL meeting found that over a ten-year period split-liver transplant outcomes were comparable to those of whole-liver procedures, leading the researchers to conclude that, “all livers meeting suitability criteria should be used as split-liver transplants to increase the availability of grafts for transplantation.”

- **Living Donor Transplant:** A living donor transplant uses a liver segment from a live person, usually a relative (although livers do not require close genetic matching like some other organs). The procedure, which was developed in the late 1980s, accounted for nearly 10% of transplants in 2001, but the proportion decreased to about 4% by 2010. Once hailed as a way to dramatically increase the supply of livers, the procedure has somewhat fallen out of favor due to the risk of complications, including death, for the donor.
- **Lower Quality Livers:** Transplants produce the best outcomes when using infection-free livers from young donors, with a short cold ischemic time (amount of time kept on ice, without a supply of oxygen, after removal from the donor). A study published in 2005, for example, found that the five-year graft survival rate was 72% when the liver came from a donor younger than 60 years, compared with 35% when the donor was age 60 or older. Under some circumstances, however, a poorer quality allograft is preferable to no new liver at all. In particular, a liver from a donor with hepatitis B or C may be given to a recipient who already has the same infection(s). Researchers reported at the 2009 American Association for the Study of Liver Diseases (AASLD) Liver Meeting that hepatitis C patients who received liver grafts infected with HCV or both HBV and HCV had survival rates similar to those of people who received uninfected livers.

Although the number of liver transplants has decreased slightly from its peak in 2006, it is expected to remain high as people infected with HCV decades ago reach the stage of advanced liver disease. Some advocates have called for implementation of a “presumed consent” system, like those in some European countries, that considers everyone a potential organ donor unless they explicitly opt out. Researchers are also studying transplants using animal

livers and human liver cells grown in a laboratory, as well as various artificial liver dialysis methods.

Post-Transplant Complications

Liver transplant recipients may experience a number of complications following surgery, including graft rejection, increased risk for infection, and blood vessel or bile duct leakage. Rejection, infection, and recurrence of the original disease—for example hepatitis C or liver cancer—are the leading causes of post-transplant mortality.

Liver graft rejection may occur either as an acute episode soon after transplantation (usually within the first two weeks) or gradual worsening over a longer period. Signs and symptoms of graft rejection may resemble those of viral hepatitis, including fever, fatigue, weakness, abdominal pain, jaundice, and elevated liver enzymes. Sometimes chronic rejection does not cause symptoms initially but can damage the new liver over time.

Transplant recipients must take immunosuppressive drugs to prevent the immune system from attacking the foreign organ. These agents generally work by altering T-cell activity and cytokine production.

The most commonly used medications include corticosteroids, azathioprine, cyclosporine, mycophenolate, sirolimus (also known as rapamycin), and tacrolimus. These and other drugs are typically used in combination regimens, and the mix may change over time. Acute rejection is usually managed with a high dose of steroids. Studies have shown that many patients can safely reduce and eventually stop steroids after the first few months without significantly increasing their risk of organ rejection.

Because their immune function is suppressed, transplant recipients are at increased risk for infection. During the first weeks or months after surgery, when the strongest immunosuppressive regimens are used, patients are prone to develop bacterial infections, viral, and fungal infections.

Transplant patients are susceptible to some of the same opportunistic illnesses affecting people with AIDS, including cytomegalovirus (a virus in the herpes family), pneumocystis pneumonia, toxoplasmosis, and persistent yeast infections.

Immune suppression also increases the risk of developing certain cancers. Some of these infections can be prevented by using prophylactic drugs, and most can be successfully treated. In addition to using antibiotics and other specific medications, doses of immunosuppressive drugs may need to be reduced.

Transplant recipients who do not experience overt organ rejection or develop opportunistic infections may still experience detrimental effects over the long term.

As described in the December 2009 issue of *Liver Transplantation*, for example, transplant patients are more likely to develop metabolic syndrome—characterized by excess abdominal fat, abnormal blood cholesterol and glucose levels, and high blood pressure—which increases the risk of cardiovascular disease, heart attacks, and stroke. And in the May 2010 issue of *Liver Transplantation*, British researchers reported that transplant recipients showed signs of premature T-cell aging or senescence, losing the ability to proliferate in response to invaders.

Liver transplant patients with hepatitis C face additional challenges. HCV almost always recurs and can cause fibrosis, cirrhosis, and ultimately failure of the liver graft. Fortunately, successful hepatitis C treatment with sustained virological response can control the virus and halt liver disease progression. Novel direct-acting anti-HCV drugs—the first of which are expected to be approved this year—will improve the likelihood of curing hepatitis C and preventing damage to the new liver after transplantation.

HCV Recurrence and Treatment

Hepatitis C is the leading indication for liver transplantation in the U.S. Advances in surgical techniques and medical management have improved transplant outcomes, but people with hepatitis C virus (HCV) still do not fare as well as patients receiving new livers for other reasons.

In most cases HCV infects the donor liver graft, usually soon after surgery. Just as it did in the original liver, the virus—or more precisely, the body's response to the virus—can lead to fibrosis, cirrhosis, and hepatocellular carcinoma.

Research has shown that disease progression is more rapid, on average, among liver transplant recipients. An estimated

25% to 30% of HCV-infected transplant recipients develop cirrhosis within five to ten years, a process that typically takes decades in people with their original livers. Some transplant patients, however, do not experience aggressive disease progression.

A number of virus and host factors are associated with rapid fibrosis progression, including HCV genotypes 1 or 4 (versus 2 or 3), non-white race/ethnicity, older donor and recipient age, and longer ischemia time (how long the graft goes without oxygen between removal from the donor and insertion into the recipient).

In the August 30, 2010, *Journal of Experimental Medicine*, French researchers reported that only the most efficient pre-transplant HCV strains could evade immune defenses and re-infect the new liver. Another team reported in the July 2010 issue of *Virology* that patients with less HCV genetic diversity were more likely to experience poor post-transplant outcomes.

Recent research finds that host genetic factors also play a role. A study presented at the 2010 American Association for the Study of Liver Diseases (AASLD) Liver Meeting showed that variations in the IL28B gene—which has been linked to spontaneous HCV clearance and response to interferon-based therapy—also influences the timing of HCV recurrence after liver transplantation. M. Charlton and colleagues from the Mayo Clinic found that transplant recipients with the protective rs12979860 C/C pattern had later recurrence.

Immunosuppressive medications used to prevent organ rejection can impair immune response to HCV, resulting in higher viral load and faster fibrosis progression. But studies have produced conflicting findings about which immunosuppressive drugs have the most detrimental effects and which are the safest for transplant recipients with hepatitis C.

Liver transplant patients with hepatitis B virus (HBV) can take antiviral drugs, immune globulin (antibodies), and the hepatitis B vaccine to prevent the virus from attacking their new liver graft. Unfortunately, such measures do not work well for people with hepatitis C. There is no effective HCV immune globulin product or vaccine, and anti-HCV therapy

has only limited success. As a consequence, recurrent HCV is a leading cause of graft failure and death among liver transplant recipients.

Pre-Transplant Treatment

The optimal time to start interferon-based therapy for patients undergoing liver transplantation remains unclear. People with advanced liver damage awaiting transplants have lower sustained virological response (SVR) rates and often have difficulty tolerating the side effects of interferon and ribavirin, but this group has the most pressing need for effective treatment.

Antiviral therapy has traditionally been considered contraindicated for individuals with decompensated cirrhosis, but several studies have shown that it can be successful with careful monitoring.

At the 2008 Digestive Disease Week conference, A. Retana and J. Wong reported findings from a systematic review of studies looking at the risks and benefits of pre-transplant interferon-based therapy for hepatitis C patients with decompensated cirrhosis. Among 255 total participants, the overall SVR rate was 23%. Although 30% of patients required dose reductions due to adverse effects and 24% discontinued treatment, those who remained untreated fared worse, with a higher likelihood of adverse outcomes and a two-fold higher mortality rate.

Some studies find that patients who achieve SVR while awaiting liver transplantation may have a reduced risk of post-transplant HCV recurrence. In an August 2005 review article in *Hepatology*, for example, G. Everson from the University of Colorado estimated that successful pre-transplant treatment prevents HCV recurrence in as many as 25% of cases.

But most apparent sustained responders with “undetectable” HCV RNA still experience recurrence after transplantation, indicating that some virus remains in the body waiting for an opportunity to attack the new liver. Several studies have shown that people with unmeasurable post-treatment viral load using standard PCR tests can have residual detectable HCV RNA using more sensitive assays.

Even though low-level HCV remains in the body, however,

pre-transplant treatment responders have less severe recurrence on average, with lower viral loads and less rapid fibrosis progression compared with nonresponders. While tolerability of therapy remains a serious concern, Everson advised that it is often worth pursuing since pre-transplant treatment can improve post-transplant outcomes.

Post-Transplant Therapy

After transplantation patients may either start preemptive antiviral therapy right away in an effort to prevent HCV recurrence and liver damage, or else wait until liver disease progression has started to occur.

As noted, interferon-based therapy does not really act as post-exposure prophylaxis to prevent HCV from infecting the liver graft, as antiviral drugs do in the case of HBV. Nevertheless, interferon-based treatment after transplantation has been shown to improve outcomes in numerous studies. The new direct-acting anti-HCV drugs have not yet been tested in people with decompensated cirrhosis or liver transplant recipients.

Thinking that treatment might work best if started early while HCV RNA levels are still low and damage to the new liver has not yet occurred—researchers have studied preemptive interferon-based therapy within the first few weeks after transplantation. Results have been disappointing, however, since transplant recipients at this stage often have blood cell deficiencies, kidney dysfunction, and increased susceptibility to infection, making it hard to tolerate the side effects of interferon and ribavirin. A 2007 review of randomized trials of preemptive therapy found SVR rates ranging from about 10% to about 30%.

Based on a more recent systematic review of medical literature and conference presentations published in the January 2011 issue of *Alimentary Pharmacology and Therapeutics*, P. Guillouche and C. Feray concluded that while antiviral therapy “must be considered” before liver transplantation, it is “poorly tolerated and has poor results in patients with cirrhosis and end-stage liver disease or hepatocellular carcinoma.”

For this reason, many experts recommend a “watch and wait” strategy, deferring therapy until liver biopsies and other tests indicate disease progression. The advantage of

this approach is that transplant recipients who will never experience serious recurrent liver damage can avoid unnecessary treatment.

Looking at post-transplant interferon-based therapy for patients who do experience disease progression, most studies have observed SVR rates around 30% to 40% for patients with a mix of HCV genotypes—considerably lower than sustained response rates for non-transplant patients. Reduced response is attributable in part to inability to use adequate doses of interferon and ribavirin for a long enough period of time.

For example, the PROTECT study, reported at the 2010 annual meeting of the European Association for the Study of the Liver (EASL), evaluated the safety and efficacy of pegylated interferon plus weight-adjusted ribavirin in 125 U.S. transplant recipients. SVR rates were 24% for patients with HCV genotype 1 and 55% for genotypes 2 or 3. Among participants who completed therapy, however, sustained response rates rose to 51% and 69%, respectively. But more than half the patients required dose reductions and 30% discontinued treatment due to adverse events.

As reported in the August 2008 *Journal of Hepatology*, M. Berenguer and colleagues performed a systematic review of published studies of pegylated interferon plus ribavirin in patients with recurrent liver disease after transplantation. They identified 19 studies published between 2004 and 2007 that included a total of 611 patients (86% with HCV genotype 1). Participants started treatment an average of two years after transplantation, at which point most had mild to moderate liver disease.

The overall average SVR rate was 30%, rising to 60% or higher for patients with non-1 genotypes. But about three-quarters of participants required dose reductions and about 25% discontinued treatment due to side effects. Guillouche and Feray's review likewise found combination therapy response rates of up to 30% in patients with post-transplant HCV recurrence.

In Charlton's study, the protective IL28B C/C pattern was more common in donor livers than in recipients, meaning some patients got a liver graft with a more favorable pattern. The post-transplant SVR rate was 86% if both the recipient

and donor had the C/C pattern, 50% if only the donor liver had the favorable pattern, 42% if only the recipient had the C/C pattern, and just 16% if neither had the favorable pattern. A Spanish study likewise found that favorable patterns at both the rs12979860 and rs8099917 gene locations led to better treatment response. Four patients who did not carry protective IL28B patterns themselves went from being pre-treatment nonresponders to post-treatment responders after receiving donor livers with more favorable patterns. Both research teams suggested that donor livers with favorable IL28B patterns might be preferentially allocated to hepatitis C patients, since this group stood to benefit more than individuals receiving transplants for other reasons.

Clinical Benefits

Sustained response to interferon-based therapy not only suppresses viral load in transplant patients, but also leads to clinical benefits.

Several studies have demonstrated that sustained response slows or halts fibrosis progression. Berenguer's review, for example, found that liver biopsies of treatment responders generally showed lack of progression or even improvement in histological activity.

Similarly, a 30-person study by A. Kornberg and colleagues, published in the August 15, 2008, issue of *Transplantation*, found that none of the one-third of recipients who achieved sustained response to interferon/ribavirin experienced fibrosis progression, while all nonresponders did so.

At the 2007 EASL meeting Spanish researchers reported findings from a study in which transplant recipients with mild (F0-F2) or severe (F3-F4) recurrent liver fibrosis were treated with pegylated interferon/ribavirin. People who achieved SVR had a reduced fibrosis progression rate, and patients with stable or improved fibrosis also experienced stabilized or reduced hepatic vein pressure, an indicator of liver decompensation. These results, the researchers concluded, "support a less restrictive indication" for antiviral therapy in transplant patients with advanced liver disease.

At the 2010 AASLD meeting M. Rendina and colleagues reported that successful post-transplant treatment also reduces mortality. An analysis of medical records from 448 Italian transplant patients with recurrent HCV over 20

years showed that 35% achieved SVR. Sustained response was “highly protective” against liver-related death, the researchers found. In fact, all but one of the patients who died—73% of them due to HCV-related causes—had been unable to achieve SVR.

Taken together, these findings show that liver transplant recipients are considerably less likely to respond to interferon-based therapy, but those who do have reduced fibrosis, fewer negative clinical outcomes, and lower mortality. Further studies are needed to determine whether new direct-acting antiviral drugs will improve response rates in this difficult-to-treat population.

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