LIVER - Data CYE 2005- CYE 2008

LIVER	**AHCCCS Data for Cases Members >21 years**			
	2005	**2006**	**2007**	**2008**
Listed During year	102	101	80	65
# listed Dual or TPL	unknown	0	0	0
Total Wait listed	Estimated at 149, 1 removed due to incarceration, 23 members expired while wait listed	231, several members expired waiting or were removed	291, 2 expired waiting	293, 8 expired waiting, 2 were denied by center and 6 removed
Transplanted	8	18	14	15
Mortality	3 post transplant	Not reported	1	0
Approved Costs for Components during contract year	**$2,059,090.00**	**$9,680,541.81**	**$ 5,329,652.00**	**$ 4,149,890.00**

Note- 2005 a transplant log of all members was not maintained as accurately as other logs

SUMMARY OF FINDINGS:

Liver transplantation has evolved rapidly from an experimental procedure to standard therapy for patients with end-stage liver disease. One- and five-year patient survival for deceased donor liver transplants is reported to be between 77.4 - 83 and 67- 70 percent respectively, due to advances in surgical techniques, immunosuppression, and organ preservation. While the number of liver transplants performed in the US has reached approximately 6000 per year, the demand for donor organs far exceeds the supply. There are approximately 17,000 patients listed for liver transplantation in the United States. Thus, many patients succumb to the complications of end-stage liver disease while awaiting organ transplant. As a result, there are more than 2000 deaths per year on the liver transplant waiting list. The relative shortage of donor organs provides the basis for many of the ethical issues associated with liver transplantation.

Specific ethical issues are raised in the clinical setting specific to the following diagnosis:

Alcohol-related liver disease

Convicted criminals

Suicidal overdoses/ attempts

HIV infected patients

The one and five-year survival rate for retransplantation, is reported as between 48 and 53.7% in comparison to the initial transplant rates reported above.

The scarcity of donor organs is the limiting factor in liver transplantation. While over 6000 transplants are performed annually in the United States, more than 2000 candidates die each year on the liver transplant waiting list. Living donor liver transplantation (LDLT) provides one means to expand organ availability. Living-donation of the lateral segment of the left lobe of the liver has become highly successful in pediatric transplantation. Some transplant centers perform adult-to-adult right lobe LDLT. Advantages of LDLT

include thorough donor screening, optimization of timing for transplantation, minimal cold ischemia time, and potentially decreased cost. LDLT has also been associated with lower recipient mortality compared with waiting for a deceased donor.

However, LDLT poses a risk to the donor. The number of LDLT procedures performed in the United States peaked at 519 in 2001 and then decreased to approximately 320 per year starting in 2003 as enthusiasm for the procedure was tempered by concerns about the long term effects on the donor, including reports deaths and need for subsequent need for a transplant. In 2008 Mayo Clinic- Scottsdale had to perform an emergent liver transplantation for a donor. Living donors are usually close family members or spouses, although some transplant programs do accept unrelated "good Samaritan" living donors (now termed "anonymous nondirected" donors). ABO blood type compatibility is preferable and donors are usually less than 60 years of age to attempt to minimize complications to the donor. It has not been the policy of AHCCCS to approve living donors for anyone but children. The above statistics are not applicable to living donor for children, and the Children's Hospital Los Angeles, with whom AHCCCS is contracted for children, has a 1 year survival of 97% and a 5 year rate of 80%. The reason for the difference is that in the case of a child, very little liver tissues are removed from the parent, thereby reducing the risk to the donor...

Criteria for listing:

Shortage of donor livers has necessitated the development of an allocation schema, whereby priority for donor organs are given to the most seriously ill patients. An ideal system should select candidates based upon the potential for improving survival post transplant. Thus, being able to predict survival is crucial. A great challenge has been the creation of an organ allocation system that optimizes potential outcomes and that is also fair to all potential recipients.

The most commonly used prognostic model for estimating disease severity and survival is the Model for End-stage Liver Disease (MELD). MELD has been prospectively validated in several patient populations and is currently used by the United Network for Organ Sharing (UNOS) to prioritize candidates with chronic liver failure for organ allocation. MELD has also been adopted widely in transplant programs in other countries In the United States, allocation of deceased donor livers for both adults and children is based on the "model for end-stage liver disease" known as the MELD score. This employs a statistical model for predicted survival in patients with end stage liver disease. When this criterion is strictly adhered to, the five year survival rate is reported at 75%. For children the score is referred to as the "pediatric model for end-stage liver disease" and is referred to as the PELD score. This allows additional points to be added to the score for a child and should move the child higher on the priority list for receipt of an organ. The MELD score is based on the patients' serum bilirubin, serum creatinine, and international normalized ratio (INR) in a log transformed equation to estimate likelihood of three-month survival. The higher the score the worse the short term prognosis. Three-month survival is less than 20 percent in patients with a MELD score of 40. Implementation of MELD for organ allocation has decreased pretransplant mortality without having a negative impact on post-transplant mortality. Implementation of MELD for organ allocation has decreased pretransplant mortality without having a negative impact on post-transplant mortality.

The MELD score at which a patient will realistically receive a liver varies by region and organ demand as defined by the number of candidates on the waiting list and their blood type. Providers need to be aware of the average MELD at time of transplant for each blood group in their region, information that is important for determining the appropriate timing for referral.

In addition, time on the waiting list and disease severity at transplant are associated with the volume of transplants at individual centers. Transplant centers with high volume (≥100 transplants per year) tend to transplant patients with lower MELD scores and have shorter waiting times than transplant centers with lower volumes. The reasons for these differences are unclear. Based on UNOS data effective 12/12/08 the three centers reported transplants for 2008 at: Banner Good Samaritan Hospital reported 31 transplants; Mayo Clinic- Scottsdale reported 52 transplants and University Medical Center Tucson reported 19 for a total of 102 with adults comprising 92 of those transplants. UNOS reports adults as individuals who are 18 or older.

In the case of patients with Hepatocellular Carcinoma (HCC), the MELD criteria is of limited usefulness as many of these patients do not have liver failure until much later in the disease. Additionally, the fact that the wait time for an organ can be up to 24 months in some parts of the country, in which time the HCC would probably progress and then preclude the patient from transplant has resulted in UNOS developing a supplemental system for priorization of organ allocation. Under the UNOS allocation criteria a patient with a diagnosis of HCC are given priority based on tumor size and number. The assignment of a relatively high MELD score reflects an estimated three month mortality rate of 15% and the risk of the tumor progressing beyond the Milan criteria (single tumor $\leq$ 5 cm in size, or $\leq$ 3 tumors each $\leq$ 3 cm in size, no macrovascular invasion) with an estimated increase in mortality for each 3 month period of waiting for an organ.

Transplant infrequently cures the underlying disease; recurrent liver disease after transplantation occurs in anywhere from 0 to 100 percent of patients depending upon the disease for which the transplant was performed. In a patient with fulminant hepatic failure secondary to drug related injury, recurrence does not occur provided that the offending agent is avoided. However, in a patient with chronic Hepatitis C Virus (HCV), recurrent disease is expected. In a limited study published in February of 2006, the viral load of the virus was monitored post transplant and the finding were reported that although post transplant viral load were decreased immediately after transplant, the viral load increased after an average of 23 hours rebounding to amounts greater than in the original viral load in all but one of the six patient. Generally the viral can be expected to return to levels found pre-transplant in 24-27 months.

Thus, the selection of a transplant candidate requires a risk-benefit analysis, in which the inherent risks of surgery, recurrent disease, and long-term immunosuppression must be weighed against the potential benefits of transplantation. These benefits differ for each patient but may include improvements in survival, prevention of long-term complications, and better health-related quality of life with the exception of cholestatic HCV.

Indications for liver transplant: The Clinical Practice Committee of the American Society of Transplantation has attempted to identify and define criteria for the non-transplant physician on indications for and timing of solid organ transplantation.

The first premise states that an early referral to a transplant center should be the standard of care. This allows patients, families, referring physicians, and transplant centers ample time to become acquainted and identify any potential problems of undergoing a transplant. Transplant care is provided by a team including medical specialist (e.g. cardiologist, hepatologist), surgeons, transplant coordinators (often nurses or nurse practitioners), psychiatrist, and social workers. The exact composition of providers varies at different centers.

Multiple disease processes can result in liver failure and/or cirrhosis. Any patient with documented fulminant hepatic failure (FHF), decompensated cirrhosis, or hepatocellular carcinoma within defined criteria (no single lesion greater than 5 cm or no more than three lesions, the largest $\leq$3 cm) is a potential candidate for liver transplantation. Although the end-result (e.g., requiring a liver transplantation) is the same, differences in the underlying causes have implications for the transplant evaluation process and the expectations after transplant.

Hepatitis C virus (HCV): HCV infection causes about 40 percent of all chronic liver disease in the United States and HCV-associated cirrhosis is the most common indication for orthotopic liver transplantation (OLT) among adults. HCV infection remains a problem after transplantation and recurrent hepatic infection is the leading cause of graft failure. The influence of HCV genotype (particularly genotype 1b) on the severity of disease recurrence following OLT is controversial and there are no established standards on the use of this genotype for transplant evaluation. The range of findings that have been reported can be illustrated by the following examples:

- In a series of 652 patients from 15 European centers, genotype 1b was an independent risk factor for recurrent hepatitis but not for patient or graft survival.

- In a prospective study of 60 patients from France and Japan who were followed for three years after OLT, patients infected with genotype 1b were more likely than those infected with other genotypes to develop both acute hepatitis (77 versus 40 percent) and chronic active hepatitis (59 versus 22 percent).

- In a series of 42 patients from the Mayo Clinic, histologic evidence of hepatitis occurred with similar frequency (90 percent) with all genotypes. However, development of cirrhosis was more common in those with the 1b genotype: 6 of 17 (35 percent) compared to 2 of 25 (8 percent) infected with other genotypes.

In contrast to these findings, other larger series (124, 166, and 155 patients) found no difference in the rate or degree of hepatitis, or in graft or patient survival between 1b and non–1b patients.

The degree of divergence of HCV quasispecies may also be enhanced in patients with severe recurrent HCV, suggesting that the selection for or emergence of many new HCV variants may influence disease progression.

Recurrence of HCV following OLT occurs in over 95 percent of patients. Nucleotide sequence studies of HCV demonstrate that the disease following OLT results from the same viral strain present before OLT. Virologic reinfection at the time of transplantation is not surprising, since almost all patients are viremic at the time of transplantation. Reinfection occurs during reperfusion of the allograft in the operating room, and viral titers reach pretransplant levels within 72 hours. Furthermore, peripheral monocytes may also harbor virus and act as a source for reinfection of the donor liver. De novo infection in previously HCV-negative patients can result from transfusion of blood products during OLT but has become rare since 1992 due to blood product screening.

Variables that influence the progression of recurrent HCV following OLT are incompletely understood, but donor characteristics (donor type, age), viral characteristics (genotype, viral load), and the patient's immune status may be important. Serum HCV RNA levels increase from 4- to 100-fold following liver transplantation. However, the relationships between pretransplant viral load, and viral load after transplant on graft and patient survival are not well understood. In a recent study the recurrence of the viral load was reported to begin within 72 hours post transplant.

Studies examining the effect of pretransplant HCV viral load on the likelihood of HCV recurrence have produced discordant results. Several reports found that pretransplant viral load did not correlate with either the likelihood or timing of HCV recurrence following OLT and did not predict the severity of liver disease when it occurred. In contrast, in one series of 166 HCV-infected liver transplant recipients, those with HCV RNA titers greater than 1 million viral equivalents/mL had a significantly shortened cumulative five-year survival compared to patients with lower pretransplant titers (57 versus 84 percent). High titers of HCV RNA in the explanted liver may also be a risk factor.

The influence of viral load following OLT is also uncertain. Some studies have suggested that viral titers in patients after transplant do not correlate well with the severity of histologic disease, which is similar to the lack of correlation observed outside the transplant setting. In contrast, other studies have found that an increase in viral titers was associated with worse histologic activity and increased risk of fibrosis.

Fulminant hepatic failure: Fulminant hepatic failure is defined as the acute onset of severe liver failure/ injury with impaired synthetic function and the development of encephalopathy in a short period of time in a person who previously had a normal liver or had well-compensated liver disease. The etiology varies but the progression is similar in all cases. In the absence of liver transplantation, patients with FHF will either have a complete recovery of liver function or will die within days. It is not always possible to predict accurately which the most likely outcome in this situation is. Patients with FHF are given the highest priority on the transplant list (United Network of Organ Sharing (UNOS) - Status 1). Fulminant hepatic failure can result from a wide variety of causes, of which viral or toxin-induced (particularly acetaminophen (Tylenol)) hepatitis are the most common.

The only therapy proven to improve patient outcome in FHF is orthotopic liver transplantation. Thus, patients with liver failure should be transferred as early as possible to a transplant center, since transportation may be hazardous if complications, such as severe coagulopathy or increased intracranial pressure, develop. As a result, early referral to a transplant center is critical to offer the best chance for a favorable outcome.

The decision to transplant depends upon the probability of spontaneous hepatic recovery, which cannot be predicted by any single factor alone. The most important variables for predicting the outcome in FHF are the degree of encephalopathy, prothrombin time, the patient's age, and the cause of FHF.

Cirrhosis: The presence of cirrhosis alone is not sufficient to warrant transplantation. Transplantation is generally considered when a patient has suffered from either a complication of portal hypertension or a manifestation of compromised hepatic synthetic function. Variceal hemorrhage, ascites, and encephalopathy are the primary manifestations of end-stage liver disease and as a group are designated as markers of decompensation. The onset of decompensation is associated with significantly impaired survival. The development of hepatorenal syndrome is an ominous marker that signals the need for immediate transplant evaluation.

All of these indications are non-specific, reflecting overall hepatic deterioration regardless of the underlying disease etiology. There are also certain conditions that have specific indications for transplantation, such as recurrent cholangitis in patients with primary sclerosing cholangitis (PSC) or intractable pruritus in patients with primary biliary cirrhosis (PBC). Although these are not manifestations of liver failure, they are disease-specific problems that affect survival or quality of life.

***Hepatitis B Virus (HBV)*:** Despite advances in treatment of chronic hepatitis B virus (HBV) infection, liver transplantation remains the only hope for many patients with end-stage liver disease due to HBV. In a study of the natural history of HBV-related cirrhosis, the five-year survival was 71 percent for the entire group of patients, but only 14 percent for those with decompensated disease.

The initial results with liver transplantation for chronic hepatitis B in the 1980s were disappointing, with graft reinfection rates approaching 80 to 100 percent. In many patients, reinfection was associated with severe and rapidly progressive liver disease, resulting in two-year graft and patient survival of 50 percent compared to 80 percent in those transplanted for other types of chronic liver disease. With these poor results and limited supply of donor organs, many centers and third party payers abandoned liver transplantation for patients with chronic hepatitis B.

Since the late 1980s, the introduction of effective measures to prevent and treat reinfection using strategies involving hepatitis B immune globulin (HBIG) and subsequently nucleoside(tide) analogues have significantly improved the outcome of liver transplantation. The overall survival of patients transplanted for HBV-related cirrhosis now exceeds 85 percent at one year and 75 percent at five years. Furthermore, rates of transplantation for HBV-related end-stage liver disease have dropped substantially.

HBV Reinfection after liver transplant: The high rate of HBV reinfection after liver transplantation is probably due to enhanced virus replication resulting from immunosuppression and direct stimulatory effects of steroid therapy on the glucocorticoid-responsive enhancer region of the HBV genome Extra-hepatic reservoirs of HBV, such as peripheral blood mononuclear cells, spleen, and other organs, may also contribute to graft reinfection. The average time for conversion to a positive HBV status is reported as approximately 1.7 months.

Treatment of Hepatocellular Carcinoma (HCC): For patients with localized HCC who are not candidates for resection, deceased donor orthotopic liver transplantation (OLT) is an appropriate strategy for patients with a single lesion ≤5 cm, up to three separate lesions, none larger than 3 cm, no evidence of gross vascular invasion, and no regional nodal or extrahepatic distant metastases. When these criteria are strictly applied, five-year survival rates 75 percent or higher can be achieved. Overall survival in carefully selected patients undergoing OLT for HCC is similar to or only slightly worse than the survival of patients undergoing OLT for nonmalignant causes. Although randomized trials have not been carried out,

uncontrolled series suggest that survival following OLT is as good as or better than it is after alternative treatments for HCC in carefully selected patients.

Treatment of End-Stage Alcoholic Liver Disease:

Successful transplantation in patients with end-stage alcoholic liver disease depends upon careful patient selection. Transplantation is generally performed in patients with advanced disease as determined by the MELD model. A randomized controlled trial comparing listing of patients for transplant with Child-Pugh stage B alcoholic cirrhosis to usual care (in which transplantation is generally performed in patients with Child-Pugh stage C cirrhosis), found no survival benefit from early listing.

Consensus has not been achieved on optimal selection criteria, particularly in areas the minimal duration of alcohol abstinence and predicting the likelihood of recidivism. Transplant centers have developed their own criteria but several common themes have emerged relative to the above stated ethical issues in liver transplantation. **Alcohol abstinence and psychosocial factors** — Sobriety and adequate social support are essential. No absolute interval of sobriety is required because some patients who are otherwise suitable candidates will not survive a six-month period.

However, a period of six months of sobriety is used widely for predicting recidivism. Three small studies are frequently cited to support the six-month rule's ability to predict post-transplant drinking. Recidivism ranged from 8 to 20% dependant upon the study reviewed.

Primary Biliary Cirrhosis (PBC): Liver transplantation is successful in treating patients with primary biliary cirrhosis (PBC). However, transplantation has an associated morbidity and is quite costly. As a result it is important to determine which patients will benefit the most and when is the optimal time to perform the procedure. The development of living donor related liver transplantation has allowed transplantation to be performed electively in some patients, before the development of serious complications that adversely affect the outcome of liver transplantation.

In the United States, the average age of patients undergoing transplantation for PBC is in the range of 53 to 55 years. The total number of transplants performed for PBC in recent years has declined slightly, possibly reflecting benefits of early treatment.

Liver Transplant Contraindications: Although organ allocation is centralized, many criteria and contraindications to listing for transplantation are center-specific. The following are contraindications accepted by most centers:

- Cardiopulmonary disease that cannot be corrected and is a prohibitive risk for surgery
- Malignancy outside of the liver within five years of evaluation (not including superficial skin cancers) or not meeting oncologic criteria for cure
- Active alcohol and drug use. Most programs require a minimum period of abstinence of at least six months with participation in a structured rehabilitation and abstinence program and adequate social support to help maintain sobriety.
- Advanced age and HIV disease are examples of relative contraindications that are site-specific and are often decided on a case-by-case basis. Liver transplantation can be performed in those older than 65 provided that there has been a comprehensive search made for comorbidities.
- Smoking, more will be addressed on this under mortality and morbidity

Timing of Referral: Timing of transplant referral is always a critical question. Organ allocation was initially based upon waiting time on the transplant list. As a result, early referral and listing worked to the benefit of the patient. A major problem with the system was that it did not necessarily allocate organs to patients who were at the greatest risk of dying without transplantation. The system was revised in 2002 to its present form where the driving force is disease severity (based mostly upon the MELD score described

below) and **there is no inherent benefit to early referral**. In fact, referral **too early may waste time and resources for testing that will have to be repeated when the patient has a more realistic chance of obtaining an organ.** On the other hand, while early referral may not change the timing of transplantation, there continues to be a strong benefit in having the patient meet the transplant team prior to the last stages of liver disease. Often at the final stages of liver disease, there is not adequate time for education, and the patient may have an impaired mental status from underlying encephalopathy. Most Centers view the prior minimum listing criteria of a MELD score of 10 or any complication of portal hypertension as markers for the need for transplant evaluation and listing.

The first step in deciding the timing of referral is to determine if there has been a complication of end-stage liver disease. This is followed by a determination of severity of illness using the MELD system. Several on-line calculators are now readily available for calculating the MELD score:www.unos.org/resources/MeldPeldCalculator.asp?index=98. Following these steps the provider can determine when transplantation referral is necessary. As a general rule, any patient with one of the defined complications of end-stage liver disease (e.g., ascites, variceal bleeding, encephalopathy, hepatorenal syndrome, or hepatocellular carcinoma) and/or a MELD score of 10 should be referred for transplant evaluation.

Post Transplant Mortality and Morbidity:

The application of this treatment must therefore be addressed in terms of the outcomes based on the underlying diagnosis or reason for the transplant.

Efficacy of Liver Transplantation:

End-stage alcoholic liver disease was responsible for 18 percent of all orthotopic liver transplants between 1992 and 2001 in the United States. The first large experience with liver transplantation for alcoholic cirrhosis was reported from Pittsburgh, where survival among 42 patients was equal to that for other forms of liver disease. Similar data has now been accumulated from several other centers. In one report, for example, actuarial one-, five-, and seven-year patient and graft survival rates among 123 patients were 84 and 81 percent (one year), 72 and 66 percent (five years), and 63 and 50 percent (seven years). Without transplant, five-year survival is as low as 23 percent. Full integration into society is likely following liver transplantation in appropriately screened and managed alcoholic patients.

Early referral for liver transplantation is not always accomplished in part because of active alcoholism. In an illustrative report of 199 potential liver transplantation candidates with end-stage alcoholic liver disease, only 41 (21 percent) were recommended for referral while only 15 (8 percent) actually underwent transplant evaluation. The main reason for not referring patients was active alcohol use. The likelihood of transplantation for patients with End Stage Alcoholic Liver Disease was significantly lower than for patients with other forms of end-stage liver disease.

Few studies have addressed the success of post-OLT alcoholism treatment programs to prevent relapse. One uncontrolled study of alcoholism treatment in the post-OLT population revealed a 22 percent relapse rate of any drinking over a four-year period after requiring that all patients be followed by an addiction treatment psychiatrist. Historical controls revealed a relapse rate of 48 percent in their post-OLT patients before the alcoholism treatment program started. In the United Kingdom, all patients who underwent transplantation for alcoholic liver disease are followed by an addiction treatment psychiatrist. Such a program is recommended but not mandatory in the United States.

Hepatocellular Carcinoma: Overall survival and disease recurrence rates after OLT in carefully selected patients are similar or only slightly worse than survival for patients undergoing OLT for non-malignant causes. In approximately 20% of cases, recurrent HCC is the limiting factor for long term survival. Five year survival in patients with recurrent disease is 25% as compared with the group without recurrence who demonstrated a survival rate of 61%. In a separate study conducted at the University of Pittsburg, the recurrence rate of 40% was reported. For patients who experienced a recurrence of disease, 35% had recurrence within the first year and 90% within 2 years, although recurrence after 6 years has been reported.

Hepatitis C virus (HCV): The clinical course following OLT for HCV infection is variable. Five-year survival after transplantation is approximately 60 to 80 percent in most series, which is comparable to transplants performed for alcoholic liver disease, and better than historic rates for hepatitis B, hemochromatosis, or cancer. In one series, for example, the cumulative survival for 149 patients receiving OLT for HCV following transplantation was 79, 79, and 70 percent at one, three, and five years, respectively; these results were not significantly different from 623 patients undergoing OLT for non-HCV disease]. Another report found that the similar outcomes persisted at 10-year follow-up. Multivariate analysis on a large series of HCV patients transplanted at 15 European centers demonstrated that hepatocellular carcinoma was the only predictive factor for five-year patient or graft survival.

Transplantation of HCV infected grafts: Because of the shortage of organs, transplantation of livers from HCV-infected donors to HCV-infected recipients has been attempted. A study evaluating the outcome of 23 such patients found that five-year survival was similar to a control group of HCV-infected recipients who had received grafts from HCV-negative donors (89 versus 88 percent) [57]. Furthermore, an interesting observation was that patients in whom the donor strain became predominant after transplantation had significantly longer disease-free survival compared to patients who retained their original HCV strain (90 versus 15 percent). This observation was hypothesized to be related to impaired ability of CD8 and CD4 cells to recognize viral antigens presented in the context of liver transplantation with poorly matched class I and class II HLA antigens.

HCV Morbidity: HCV-associated cirrhosis is the most common indication for liver transplant in the United States. Recurrent HCV infection following OLT remains a major cause of morbidity and mortality in the post-transplant setting. The clinical course following OLT for HCV infection is variable. As a general rule, the course of HCV infection appears to be accelerated compared to the pretransplant setting. Several patterns of recurrence have been described.).

Many predictors of outcome following transplant have been described, but their accuracy in predicting the course in individual patients or to guide interventions is uncertain. The use of older donors is likely associated with adverse outcomes.

Despite the overall reported patient survival after transplantation for HCV, several medical problems in addition to rejection are routinely encountered by physicians caring for patients after liver transplantation. These can be divided into the following categories:

- Complications of immunosuppression including hypertension, renal insufficiency, infection, malignancy, a variety of dermatologic conditions, and metabolic diseases such as diabetes mellitus, obesity, hyperlipidemia, and bone disease

- Technical factors involved in the transplant operation such as biliary complications

- Recurrent liver disease, particularly viral hepatitis, is another important problem for many patients. This issue is discussed separately on the appropriate topic reviews for the individual diseases.

HCV Viral load: The diagnosis of recurrent HCV infection is based upon the detection of HCV RNA, and compatible histologic characteristics. No effective measure to prevent recurrence has been established. Optimal treatment of recurrence is unclear. A suggested a course of combination therapy with pegylated interferon plus ribavirin in patients with significant histologic recurrence (e.g., Grade 3 or 4 inflammation or stage 2 through 4 fibrosis (Grade 2B). Such therapy should be attempted only at centers with considerable experience in managing post-transplant patients. There is no evidence to support a survival benefit for therapy; thus, preemptive therapy is not currently supported by available data. Serum HCV RNA levels increase from 4- to 100-fold following liver transplantation. However, the relationships between pretransplant viral load, and viral load after transplant on graft and patient survival are not well understood.

Studies examining the effect of pretransplant HCV viral load on the likelihood of HCV recurrence have produced discordant results. Several reports found that pretransplant viral load did not correlate with either

the likelihood or timing of HCV recurrence following OLT and did not predict the severity of liver disease when it occurred. In contrast, in one series of 166 HCV-infected liver transplant recipients, those with HCV RNA titers greater than 1 million viral equivalents/mL had a significantly shortened cumulative five-year survival compared to patients with lower pretransplant titers (57 versus 84 percent). High titers of HCV RNA in the explanted liver may also be a risk factor.

The influence of viral load following OLT is also uncertain. Some studies have suggested that viral titers in patients after transplant do not correlate well with the severity of histologic disease, which is similar to the lack of correlation observed outside the transplant setting. In contrast, other studies have found that an increase in viral titers was associated with worse histologic activity and increased risk of fibrosis. However, the course of HCV infection after OLT appears to be accelerated compared to the pretransplant setting. The favorable estimates of outcomes described above may reflect publication bias, since centers with worse outcomes may be less likely to report their findings. Survival statistics can be found in the UNOS database.

Effects of Immunosuppression relative to HCV: The level and type of immunosuppression following transplantation likely influence the severity of disease recurrence. The impact of immunosuppression is most pronounced when high-intensity regimens are used to treat acute rejection, particularly with high dose bolus steroids and anti-lymphocyte antibody preparations. There are no convincing data to support the use of any specific induction or maintenance regimen.

HCV and CD4 T-cell response: The specific CD4 T-cell response to HCV appears to be an important determinant of viral clearance during acute HCV infection and of the severity of histologic recurrence following liver transplantation. The latter was illustrated in a series that included 43 patients transplanted for HCV in whom histologic recurrence of HCV was categorized as mild or absent (80 percent) or severe (20 percent). Patients with severe recurrence were far less likely to have a CD4 T-cell response to HCV antigens (0 versus 40 percent with a response to at least one HCV antigen).

PBC Outcomes after Liver Transplantation: Liver transplantation both relieves symptoms and improves survival in patients with advanced PBC. Pruritus and complications of end-stage liver disease, such as encephalopathy, variceal bleeding and hepatorenal syndrome are usually promptly reversed after. Jaundice and ascites resolve somewhat more slowly, over a period of days to a few months. Splenomegaly usually persists although the enlarged spleen may decrease slightly in size. Skin xanthomas also resolve within a few weeks.

In contrast, it may take 12 to 18 months before improvement is seen in hepatic osteodystrophy, despite vitamin D and calcium supplementation. As a result, bone disease is a possible source of long-term morbidity (due to vertebral compression fractures, pain, opiate dependence, and immobility) despite successful liver transplantation. In one report that included 400 consecutive patients, one-, five- and 10-year survival was 83, 78, and 67 percent, respectively. One year survival rates of 90 to 95 percent are now common at many medical centers.

These results **are significantly better than the predicted survival in nontransplanted patients.** A survival benefit can be demonstrated by three months after transplantation. As an example, one study monitored 161 patients with PBC after liver transplantation and compared (in a nonrandomized fashion) the results to patients with the same diagnosis who were managed without transplantation. The three-month survival in this group was significantly higher than the predicted values in nontransplanted patients. The two-year survival was also higher with transplantation (74 versus 31 percent), a benefit that was seen in patients from all pretransplant risk groups.

Although all patients with PBC benefit from liver transplantation, those who are chronically ill and malnourished prior to surgery do not do as well as those with less severe disease. The prognostic index discussed below can help to identify high-risk patients. Unfortunately, the shortage of donor organs often limits transplantation to patients with advanced disease, except for those with a suitable living donor.

As with transplantation for other liver diseases, a very small number of patients with PBC require a second transplant, less than 2 percent in our experience. Most such cases occur within the first month due to

problems such as primary liver nonfunction, hepatic artery thrombosis, chronic rejection, acute rejection, and portal vein thrombosis. This is an important issue because of the shortage in donor organs.

Recurrence of PBC in the transplant: It is now generally accepted that PBC can recur following liver transplantation, although there was much initial debate.

Rate of recurrence of PBC: A precise estimate of the recurrence rate is uncertain since not all studies have used uniform criteria for defining recurrent PBC, and studies have had variable follow-up. Two of the largest series with the longest follow-up (in which the diagnosis of recurrent PBC was based upon histologic features) probably represent the best available estimates. In a report of 421 patients from Pittsburgh, recurrent PBC was observed in 8 percent of patients after five years, and 22 percent after 10 years. Higher rates were described in a series of 400 patients from Birmingham, England where recurrence was observed in 18 percent at five years and 30 percent at 10 years. A later report from the same group involving 485 patients found a recurrence rate of 23 percent during a median of 79 months. These studies have not been replicated in the United States.

Universal Morbidities in Liver Transplantation:

Hypertension: Approximately 65 to 70 percent of liver transplant recipients develop hypertension within the first year posttransplant. In addition, some patients lose the normal circadian blood pressure patterns and develop nocturnal hypertension.

Acute and chronic renal disease: Reversible renal injury develops frequently in the early posttransplant period due to acute tubular necrosis and cyclosporine (or tacrolimus) toxicity. Calcineurin inhibitor-related acute renal failure is due to renal vasoconstriction and improves with dose reduction. Chronic liver disease can also be induced by these drugs, warranting continued monitoring of the plasma creatinine concentration.).

The best data on the incidence of chronic liver disease come from a cohort study of almost 37,000 liver transplant recipients who were followed for a median of 36 months. The incidence of chronic liver disease (defined as an estimated GFR ≤29 mL/min per 1.73 m2) was 14 percent at three years and 18 percent at five years. Risk factors for chronic renal failure included calcineurin inhibitor therapy (given in at least 89 percent), older age, lower pretransplant glomerular filtration rate, female sex, postoperative acute renal failure, baseline diabetes and hypertension, hepatitis C virus infection, and transplantation before 1998.

Another study evaluated changes in liver function in 432 patients maintained on tacrolimus who were followed for a mean of 3.7 ± 2.0 years. Estimated GFR declined ≥30 percent after the transplant admission in 36 percent of patients. Following an initial decline during the first six months posttransplant, mean GFR remained stable for the duration of follow-up.

There are conflicting data as to whether chronic nephrotoxicity in liver transplant recipients is more common with cyclosporine or tacrolimus. Some patients progress to end-stage renal disease requiring dialysis or renal transplantation.

Diabetes mellitus: Prednisone, cyclosporine, tacrolimus and weight gain predispose to the development of diabetes following liver transplantation. For unclear reasons, the risk also appears to be increased in patients transplanted for hepatitis C. Patients who are diabetic prior to transplantation typically require insulin posttransplant, and 13 to 30 percent of recipients develop de novo diabetes. The incidence of de novo diabetes is somewhat higher with tacrolimus than cyclosporine (e.g., 15 versus 8 percent in the comparative European trial mentioned above).

The development of diabetes does not adversely affect survival in the first year following transplantation. This was illustrated in one series in which 26 of 497 (5 percent) liver transplant recipients who developed diabetes mellitus posttransplant were compared to matched nondiabetic posttransplant controls. The total number of days in the hospital, graft survival, renal function, and type and number of infections were similar between the groups during the subsequent 12 months. However, increased 10-year mortality related to infection was reported in a cohort of OLT recipients with sustained, new onset diabetes compared to

patients with established diabetes pretransplant, patients with transient posttransplant diabetes, and those without diabetes combined.

The lack of deleterious effect of diabetes in the first year is important clinically because diet, weight loss, and tapering of immunosuppressant medications results in amelioration or resolution of de novo diabetes in many patients. In one series of 88 patients who were not diabetic prior to liver transplantation, the prevalence of diabetes fell from 27 percent at one year to 7 percent at three years in association with a reduction in the daily prednisone dose from 13 to 2 mg [17]. Furthermore, some patients who remain diabetic on low doses of corticosteroids become euglycemic after prednisone withdrawal.

Nicotinic acid can decrease glucose tolerance and raise uric acid levels, leading to symptomatic gout in some patients.

Obesity: Patients with end-stage liver disease frequently have compromised nutritional status. Following transplantation, improved health and treatment with prednisone predispose to weight gain. Body weight tends to increase during the two years after transplantation before stabilizing. In one series of 774 patients, for example, mean body mass index increased from 24.8 kg/m2 at baseline to 27.0 kg/m2 at year one to 28.1 kg/m2 at year two; there was very little change with subsequent observations. Excessive weight gain is frequent, and 20 to 40 percent of patients become obese (defined as a body mass index above 30 kg/m2). The dose of prednisone has been identified as an independent predictor of the development of obesity. However, once obesity is established, tapering of prednisone may not lead to weight loss.

Hyperlipidemia: Hyperlipidemia is common after liver transplantation. Hypercholesterolemia develops in 16 to 43 percent of patients and hypertriglyceridemia in 40 to 47 percent; reduced serum HDL-cholesterol is also common. Hypertriglyceridemia usually develops within the first month posttransplant and then remains stable throughout the first year; in comparison, serum cholesterol increases gradually and plateaus at six months. Patients with elevated pretransplant cholesterol levels are most likely to develop hypercholesterolemia following transplantation.

The hyperlipidemia observed in liver transplant recipients is mostly related to the side effects of the cortocosteroids, cyclosporine and tacrilimus. Immunosuppression consisting of tacrolimus monotherapy with early corticosteroid withdrawal, which is common at many centers, was associated with lower rates of hypercholesterolemia and hypertriglyceridemia at six months posttransplant compared with dual therapy with tacrolimus and corticosteroids. Furthermore, tacrolimus appears to have a less prominent effect than cyclosporine, and there is some evidence that conversion from cyclosporine to tacrolimus can improve lipid profiles in liver transplant patients.

Cardiovascular risk: As described above, risk factors for coronary artery disease are frequent in liver transplant recipients including hypertension, diabetes mellitus, obesity, and hyperlipidemia. It is likely that cardiovascular complications will become more common with longer follow-up, and with the acceptance of older transplant candidates who have preexisting risk factors. In a report that described the cause of death in 299 adult liver transplant recipients who lived for more than three years, 8 out of 38 deaths (21 percent) were due to cardiovascular complications. Similarly, in a study of 542 patients who survived at least one year after OLT, **cardiovascular events accounted for 18 of 43 (42 percent) of nongraft related deaths.**

Metabolic bone disease: Bone loss is an important source of morbidity in liver transplant recipients Osteopenia following transplant mostly results from use of the corticosteroids, although animal studies have suggested that cyclosporine and tacrilimus also increase bone resorption. Other contributing factors may include immobility, hypogonadism, and certain chronic liver diseases (such as primary biliary cirrhosis and autoimmune hepatitis treated with corticosteroids and some patients with alcohol-related liver disease). This topic is discussed in detail elsewhere. Another steroid-related complication that can occur in transplant recipients is osteonecrosis (also known as aseptic necrosis, avascular necrosis, or ischemic necrosis).

Malignancy: As in other solid organ transplants, the incidence of malignancy is increased in liver transplant recipients. The Israel Penn International Transplant Tumor Registry collects information on

patients who developed malignancy following transplantation (www.ipittr.uc.edu/Home.cfm). Lymphomas, primarily non-Hodgkin lymphomas, accounted for 57 percent, more than one-half of which were associated with antilymphocyte globulin (ALG) or OKT3 administration. The median time to presentation was six months. Lymphoma was identified in the allograft in 44 percent of cases. Other common sites of involvement included lymph nodes, bowel, and tonsils.

The overall incidence of posttransplant lymphoproliferative disease (which includes benign forms of lymphoproliferation) is approximately 1 percent, 30 to 50 times higher than in the general population. The risk is greatest in patients with more marked degrees of immunosuppression. Other possible risk factors include infection with hepatitis C, age older than 50, and alcoholic cirrhosis..

Epstein Barr virus infection is thought to be responsible for most posttransplant lymphomas. A study of liver transplant recipients who developed lymphoproliferative disease demonstrated EBV mRNA in hepatic tissue in most patients before overt lymphoproliferative disease was documented; this finding was generally absent in controls who did not go on to develop lymphoproliferative disease.

Skin cancers (mainly basal cell and squamous cell carcinoma) were also commonly reported through the Transplant Registry. Ten cases of Kaposi's sarcoma were documented, arising primarily in patients of Eastern Mediterranean origin. Disease was limited to the skin in five patients and involved visceral organs in the others. Lung, breast, and cervical cancers were also reported in the Registry. However, a later study suggested that the incidence of de novo breast cancer was not increased compared with the general population. The underlying liver disease also may be a determinant of cancer risk in liver transplant recipients. An association with the following diseases and an increased risk of cancer has been noted:

- Primary sclerosing cholangitis and ulcerative colitis with colon cancer
- Recurrent viral hepatitis with hepatocellular carcinoma
- Alcoholic cirrhosis with oropharyngeal squamous cell carcinoma

A single center study provides a further perspective on the development of malignancy after liver transplantation. Fifty-three de novo malignancies were identified in 1043 liver transplant recipients (5.3 percent) over 12 years. Skin cancer was most common (32 percent of malignancies), followed by gastrointestinal malignancies (21 percent, consisting of six colorectal cancers and five small bowel malignancies), and hematological malignancies (17 percent). Patients with skin cancer had similar survival to matched control liver transplant recipients without malignancy, whereas survival was significantly reduced in patient with non-skin cancers compared to controls.

Neurologic events: Neurologic complications, such as vascular damage, infections, immunosuppressive-associated leukoencephalopathy, and metabolic abnormalities, occur in 20 to 80 percent of liver transplant recipients. Clinical symptoms are usually mild, but major neurologic sequelae are observed in some patients.

The development of serious neurologic events in the first month posttransplant was evaluated retrospectively in a series of 168 liver transplant recipients. The most common events consisted of encephalopathy including somnolence, mental status changes, and confabulation (19 percent) and seizures (5 percent). Less common complications included ischemia and seizures (related to heparin-induced thrombocytopenia) central pontine myelinolysis, stroke, and posterior leukencephalopathy syndrome.

Another series evaluated 60 patients in whom CNS lesions were evident by imaging tests, the most common etiologies were:

- Vascular events — 52 percent
- Infections — 18 percent
- Immunosuppressive associated leukoencephalopathy — 12 percent

- Central pontine myelinolysis — 8 percent
- Malignancy — 3 percent
- Miscellaneous — 7 percent

CNS lesions occurred a median of 49 days after transplantation; 75 percent occurred within 90 days of transplantation. Clinical, radiologic, and laboratory features permitted the correct diagnosis without abscess aspiration or brain biopsy in the majority of patients.

Hearing impairment: At least one report suggested that hearing impairment may be common following transplant. The most common hearing complaints in a survey of 521 transplant recipients was hearing loss (52 percent), tinnitus (38 percent), and otalgia (30 percent). An association with tacrolimus-based immunosuppression was suggested in multivariate analysis.

Infectious complications: The leading cause of mortality following liver transplantation is infection. In one autopsy series, for example, infections accounted for 64 percent of 321 deaths. Serious infections occur most frequently within the first three months posttransplant, the time of greatest immunosuppression. However, patients with poor graft function who require increased levels of immunosuppression to treat recurrent cellular rejection or chronic rejection continue to be at risk for opportunistic infection.

A variety of pathogens can cause infection posttransplantation. In the autopsy series noted above, bacteria, fungi, and viruses accounted for 48, 22, and 12 percent of infections, respectively. The representation of these different classes of agents did not vary significantly over the 15 years in which these data were

Fatigue: Fatigue is a major problem after liver transplantation. One of the most detailed studies included 96 transplant recipients who were followed for up to 15 years. Sixty-six percent of patients reported fatigue while 44 percent reported severe fatigue based upon validated quality of life instruments. A decrease in health-related quality of life correlated with the severity of fatigue. Fatigue did not appear to improve with time. Effective treatments for fatigue in the posttransplant setting have not been established.

Sexual Dysfunction: Sexual dysfunction is common before liver transplantation and often continues afterward in men and women.

Late Biliary Complications: The most common biliary complications following liver transplantations are leaks and strictures, both of which appear to be more common in those undergoing living compared with deceased donor transplantation.

Smoking: — Independent of relapse, smoking remains a significant risk factor for post-transplant morbidity and mortality. Long-term follow-up of patients who have undergone OLT for alcoholic liver disease has shown an increased rate of lung, liver, and oropharyngeal cancer compared to patients transplanted for other indications. It is likely that this association is due to the relatively high prevalence of smoking in this population combined with the impact of immunosuppression on tumor surveillance. One report found that up to 40 percent of patients who had undergone transplantation for alcoholic liver disease resumed smoking early in the posttransplant course, underscoring the need for continued counseling and monitoring.

Increasing emphasis or insistence on enrollment of patients into smoking cessation programs has been advocated to reduce morbidity post-transplantation. Some authorities have advocated removing patients from the transplant waiting list who continue to smoke despite these interventions. Roughly 20 percent of transplant centers report that they will refuse to list patients due to smoking.

Quality Of Life after Transplantation:

Social Scientists have developed a tool for evaluation of Quality of Life indicators. Most studies have found that liver transplant show that the patients rate their quality of life is marked improved in the

following areas: physical health, psychological health, social functioning, sexual functioning, ability to perform daily living activities and sense of well-being. The most significant improvement was in general health with only a slight improvement in psychological health.

Only one-third of patients are employed at the time of transplant, most of whom quit work greater than 1 year prior to the transplant. About one-half of the patients will return to work after transplant. If a patient is under 50 years old and were employed prior to the transplant are the most likely.

Liver Patient Care Cost Analysis:

According to Milliman, the average total cost of a liver only transplant in 2007 was $519,600 and $523,400 in 2008. This figure includes the cost of obtaining donor organs and does not specify the difference in cost of a cadaveric or living donor. The average cost of procurement is $59,100 in 2007 and $67,500 in 2008; hospitalization was $248,100 in 2007 and $286,100 in 2008, additional costs are listed as: $25,900 for the transplant evaluation in 2007 while in 2008 the costs are reported as 30 days pre-transplant which is listed at $21,200, in 2007 physician's fees were $66,900 and in 2008 they are listed as $44,100; 2007 lists the cost of post-operative care as $88,500 and in 2008 the costs are listed as $77,800 for the 180 days post the transplant admission date; and for immunosuppressive prescription medications in 2007 the cost was $31,100, while in 2008 the costs for immunosuppressants and other prescriptions is listed as $20,600.

The UNOS site projects costs at $314,600 for the first year charges and an annual follow up costs of $21,900. Additionally stating that anti-rejection drugs will "easily exceed" $10,000 annually.

The evaluation and post-operative care of living donors can add to the cost of liver transplantation. One analysis compared the cost of care from 90 days before transplantation through one year post-transplant between adult LDLT and deceased donor liver recipients. All living donor costs including evaluation of rejected and accepted donors and donor follow-up care for one year were considered, as was the cadaveric organ acquisition fee. The cost of LDLT exceeded that of cadaveric transplantation by 21 percent (approximately $25,000 to $30,000), although this difference did not reach statistical significance. AHCCCS does not cover LDLT.

AHCCCS Experience with Liver-Cadaveric Transplants (based on Data Warehouse numbers eff. 5/09)

43 members	Average Encounter Based Allowed Costs for time frame of 2 years pre-transplant	Average Encounter Based Allowed Costs for time frame for 1 year pre-transplant	Average Cost of member during transplant year	Average Cost per member for 1st year post transplant	Average Cost per member for 2nd year post transplant
Billed Amount	$59,008.76	$143 ,031.03	$712,393.32	$137,420.34	$219,259.21
Allowed Amount	$12,045.28	$127.439.03	$112,494.10	$43,482.48	$39,998.92
Paid Amount	$10,127.71	$84,459.46	$82,891.22	$26,000.12	$35,567.05
Health Plan Paid Amount	$11,444.20	$48,525.48	$148,086.94	$26,225.69	$33,859.56

AHCCCS Experience with Liver-Living Transplants (based on Data Warehouse numbers eff. 5/09)

1member	Average Encounter Based Allowed Costs for time frame of 2 years pre-transplant	Average Encounter Based Allowed Costs for time frame for 1 year pre-transplant	Average Cost of member during transplant year	Average Cost per member for 1st year post transplant	Average Cost per member for 2nd year post transplant
Billed Amount	$19,797.97	$611,425.74	$488,330.46	$26,932.64	No Data
Allowed Amount	$4,490.55	$100,002.49	$110,393.46	$5,668.88	No Data
Paid Amount	$649.99	$6,593.97	$3,995.94	$1,140.39	No Data
Health Plan Paid Amount	$660.40	$10,098.91	$2,796.87	$742.46	No Data

AHCCCS Experience with Liver-Fulminate Transplants (based on Data Warehouse numbers eff. 5/09)

1member	Average Encounter Based Allowed Costs for time frame of 2 years pre-transplant	Average Encounter Based Allowed Costs for time frame for 1 year pre-transplant	Average Cost of member during transplant year	Average Cost per member for 1st year post transplant	Average Cost per member for 2nd year post transplant
Billed Amount	No Data	$475.22	$983,129.91	No Data	No Data
Allowed Amount	No Data	$429.20	$81,569.28	No Data	No Data
Paid Amount	No Data	$399.05	$77,412.34	No Data	No Data
Health Plan Paid Amount	No Data	$399.05	$217,416.24	No Data	No Data

AHCCCS Wait listed member outcomes (based on Data Warehouse numbers eff. 5/09)

29members	Year listed-Averages	1 year post listing Averages	2 year post listing Averages	3 year post listing Averages	4 year post listing Averages	AVG costs of the MM costs excluding evaluation year
Billed Amount	$156,162.49	$44,474.37	$33,179.27	$33,977.67	$12,273.24	$30,976.14
Allowed Amount	$29,134.31	$10,715.85	$8,139.50	$4,199.55	$3,592.06	$6,661.74
Paid Amount	$14,971.05	$7,603.82	$6,614.07	$5,051.50	$3,130.10	$5,599.87
Health Plan Paid Amount	$17,111.13	$8,065.36	$6,622.50	$4,070.57	$3,053.23	$5,452.92

Insurance Coverage Summary: Medicare covers liver transplants when medically reasonable and necessary for specified conditions. (http://www.cms.hhs.gov/CertificationandCompliance/20_Transplant.asp#TopofPage)

Aetna coverage of liver transplantation for adults and requires a MELD score of greater than 10 and members must be approved by the regional UNOS Regional Review Board before authorization is given.

Blue Cross / Blue Shield of Florida covers liver transplantation when it is considered a last resort for their end stage liver disease. BC/BS of Florida considers a liver transplant experimental or investigational for patients with extrahepatic malignancy, including cholangiocarcinoma, any hepatocarcinoma that has extended beyond the liver, ongoing alcohol or substance abuse, active infection and limits the procedure to certain diagnosis. http://mcgs.bcbsfl.com/index.cfm?fuseaction=main.main&doc=Liver%20Transplant

Medicaid: Kansas covers liver transplants; **Oregon** covers up to one transplant and has criteria that the member must have irreversible, progressive liver disease which has advance to the point where conventional treatment offers no prospect for prolonged survival and there is not reasonable alternative either through medical or surgical therapy. The member's 5 year survival rate is at least 20% as supported by medical literature ; **Florida** does cover liver transplants for recipients $\geq$ 21 years ; **Hawaii** covers liver transplants; **Oklahoma** simply states they cover all medically necessary transplants with prior authorization.

Recommendations:

Early referral to a transplant center should be the standard of care if the patient is free of all contraindications for the following patient conditions:

Any patient with documented fulminant hepatic failure, decompensated cirrhosis, or hepatocellular carcinoma within defined criteria (no single lesion greater than 5 cm or no more than three lesions, the largest $\leq$3 cm and Extrahepatic lesions) is a potential candidate for liver transplantation. Any patient with one of the defined complications of end-stage liver disease (e.g. ascites, variceal bleeding, and

encephalopathy or hepatocellular carcinoma) and/or a MELD score of 10 should be considered for referral to a transplant center.

Contraindications to transplant include cardiopulmonary disease that cannot be corrected and is a prohibitive risk for surgery, malignancy outside of the liver within five years of evaluation (not including superficial skin cancers) or not meeting oncologic criteria for cure, and active alcohol and drug use.

The first step in deciding the timing of referral is to determine if there has been a complication of end-stage liver disease. This is followed by a determination of severity of illness using the MELD system. Several on-line calculators are now readily available for calculating the MELD score: www.unos.org/resources/MeldPeldCalculator.asp?index=98.

As the current models are further developed and refined, physicians caring for patients with advanced PBC will be able to select the optimal time for liver transplantation. They are, however, only estimates of probability and application to individual patients cannot be extremely precise. As noted above, prioritization for liver transplantation is currently based upon the MELD score).

We suggest that patients with PBC be referred for transplant evaluation if one or more of the following findings is present:

- The plasma bilirubin concentration is greater than 5 mg/dL and increasing
- The serum albumin concentration is below 2.8 g/dL (28 g/L) and is decreasing
- Signs of decompensation or portal hypertension develop, such as ascites, variceal bleeding, coagulopathy malnutrition, or encephalopathy
- The patient has intractable pruritus
- The patient has recurrent, debilitating nontraumatic bone fractures

Criteria will be modified based on the published research on morbidity and where there is an expectation of a curative process. This would eliminate transplant as an option for Hepatitis C Virus as this virus recurs 100% of the time. This is the primary diagnosis for transplant. Criteria will be further evaluated for members with end-stage alcoholic disease, where a mandatory 1 year rehabilitation program will be required for one year post transplant based on the recidivism rate of alcoholism. Smokers or members with a history of smoking will be required to meet the same criteria as all substance abuse members, including 3 negative blood tests for nicotine. A MELD score must be submitted by requesting provider utilizing the MELD tool provided by UNOS, comprehensive evaluation and clearance of all co-morbid conditions and documentation on the social support system in place for the member. Further evaluation of the AHCCCS specialty contracts with the transplant centers on payment of the evaluation at a FFS rate vs. the component cost since re-evaluation of a member to remain on the transplant list is required every 3 months and consists of simple labs. It may be more cost effective to eliminate the initial evaluation component from the contract. AHCCCS should consider requiring that the facility requesting the transplant provide the UNOS approval for listing the member prior to authorization.

All current members on the transplant waiting list should be re-evaluated.

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92. Up to Date, Model for End-stage Liver Disease (MELD), Last literature review version 17.1: January 2009, **This topic last updated:** December 17, 2008

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