Liver Transplantation

Number: 0596

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Aetna considers liver transplantation medically necessary for the indications listed below for adolescents and adults with either (i) a Model of End-stage Liver Disease (MELD) score (see Appendix) greater than 10; or (ii) who are approved for transplant by the United Network for Organ Sharing (UNOS) Regional Review Board, and for children less than 12 years of age who meet the transplanting institution's selection criteria. Requests for liver transplantation for adolescents and adults with a MELD score of 10 or less who have not been approved by the UNOS Regional Review Board are subject to medical necessity review. In the absence of an institution's selection criteria, Aetna considers liver transplantation medically necessary for adolescents and adults with a MELD score greater than 10 or who are approved by the UNOS Regional Review Board and for children who meet the medical necessity criteria specified below.

I. Medically Necessary Indications (not an all-inclusive list)

Aetna considers orthotopic (normal anatomical position) liver transplantation (with cadaveric organ, reduced-size
organ, living related organ, and split liver) medically necessary for members with end-stage liver disease (ESLD) due to any of the following conditions.

A. Cholestatic diseases:

1. Biliary atresia
2. Familial cholestatic syndromes
3. Primary biliary cirrhosis
4. Primary sclerosing cholangitis with development of secondary biliary cirrhosis

B. Hepatocellular diseases:

1. Alcoholic cirrhosis
2. Chronic active hepatitis with cirrhosis (hepatitis B or C)
3. Cryptogenic cirrhosis
4. Idiopathic autoimmune hepatitis
5. Post-necrotic cirrhosis due to hepatitis B surface antigen negative state

C. Malignancies:

1. Primary hepatocellular carcinoma confined to the liver when all of the following criteria are met:
   
a. Any lung metastases that have been shown to be responsive to chemotherapy; and
b. Member is not a candidate for subtotal liver resection; and
   c. Member meets UNOS criteria for tumor size and number; and
   d. There is no identifiable extra-hepatic spread of tumor to surrounding lymph nodes, abdominal organs, bone or other sites; and
   e. There is no macrovascular involvement.

Note: These criteria are intended to be consistent with UNOS guidelines for selection of liver transplant
candidates for hepato-cellular carcinoma (HCC).

2. Hepatoblastomas in children when all of the following criteria are met:

   a. Member is not a candidate for subtotal liver resection; and
   b. Member meets UNOS criteria for tumor size and number; and
   c. There is no identifiable extra-hepatic spread of tumor to surrounding lungs, abdominal organs, bone or other sites. (Note: Spread of hepatoblastoma to veins and lymph nodes does not disqualify a member for coverage of a liver transplant.)

3. Epithelioid hemangioendotheliomas;
4. Intra-hepatic cholangiocarcinomas (i.e., cholangiocarcinomas confined to the liver);
5. Large, unresectable fibrolamellar HCCs;
6. Metastatic neuroendocrine tumors (carcinoid tumors, apudomas, gastrinomas, glucagonomas) in persons with severe symptoms and with metastases restricted to the liver, who are unresponsive to adjuvant therapy after aggressive surgical resection including excision of the primary lesion and reduction of hepatic metastases.

D. Vascular diseases:

   1. Budd-Chiari syndrome
   2. Veno-occlusive disease.

E. Metabolic disorders and metabolic liver diseases with cirrhosis (not an all-inclusive list):

   1. Alpha 1-antitrypsin deficiency
   2. Hemochromatosis
3. Inborn errors of metabolism
4. Protoporphyria

F. Miscellaneous:

1. Familial amyloid polyneuropathy
2. Polycystic disease of the liver
3. Porto-pulmonary hypertension (pulmonary hypertension associated with liver disease or portal hypertension) in persons with a mean pulmonary artery pressure by catheterization of less than 35 mm Hg
4. Toxic reactions (fulminant hepatic failure due to mushroom poisoning, acetaminophen (Tylenol) overdose, etc.)
5. Trauma
6. Hepato-pulmonary syndrome when the following selection criteria are met:

   - Arterial hypoxemia (PaO2 less than 60 mm Hg or AaO2 gradient greater than 20 mm Hg in supine or standing position); and
   - Chronic liver disease with non-cirrhotic portal hypertension; and
   - Intrapulmonary vascular dilatation (as indicated by contrast-enhanced echocardiography, technetium-99 macroaggregated albumin perfusion scan, or pulmonary angiography).

II. Retransplantation

Aetna considers retransplantation following a failed liver transplant medically necessary if the initial transplant was performed for a covered indication.

III. Contraindications
Aetna considers liver transplantation not medically necessary for members with any of the following absolute contraindications to liver transplantation:

A. Active alcoholism or active substance abuse  
B. Active sepsis outside the biliary tract  
C. Other effective medical treatments or surgical options are available  
D. Presence of significant organ system failure other than kidney, liver or small bowel.

IV. Experimental and Investigational Procedures

Aetna considers the following indications/procedures regarding liver transplantation experimental and investigational because their safety and effectiveness has not been established:

A. Bioartificial liver transplantation  
B. Ectopic or auxiliary liver transplantation  
C. Hepatocellular (hepatocyte) transplantation  
D. Malignancies other than those listed as covered above  
E. Peri-operative use of vasopressin in liver transplantation, and (iii) the use of everolimus to prevent organ rejection after liver transplantation  
F. Peri-operative use of sorafenib in liver transplantation  
G. Peri-operative use of vasopressin in liver transplantation  
H. Use of everolimus to prevent organ rejection after liver transplantation  
I. Use of ursodeoxycholic acid (UDCA) as an adjuvant treatment to prevent acute cellular rejection after liver transplantation  
J. Xenotransplantation.

Note: For policy on hepatitis B immune globulin for prophylaxis of recurrent hepatitis B infection in HbsAg positive liver transplant recipients, see CPB 0544 - Immune Globulins for Post-exposure Prophylaxis (0544.html).
Background

Progressive liver diseases that result in death either in short-term or long-term is known as end-stage liver disease (ESLD), which is evidenced by irreversible, progressive liver dysfunction, variceal bleeding, encephalopathy, synthetic dysfunction, poor growth, or poor nutritional status. The most common causes of ESLD include infection (e.g., acute or chronic hepatitis), toxic effects (e.g., alcohol, medications), disorders of metabolism (e.g., hemochromatosis, Wilson’s disease), tumors (primary or metastatic), and malformations (e.g., primary biliary atresia). Liver transplantation is an effective treatment for fulminant (acute) hepatic failure and for many chronic liver diseases.

A liver transplant is usually positioned in the normal anatomical position (orthotopic) following a total hepatectomy of the recipient. In auxiliary liver transplantation, a second liver is implanted ectopically and the recipient's own liver remains in-situ. A major concern of ectopic transplantation is the recipient's diseased liver may harbor bacterial, fungal or viral infection or cancer. Advances in surgical techniques and immunosuppressive drugs have resulted in increased survival rates (with 1-year survival rates in the 85 to 90 % range, and 5-year survival rates exceeding 70 %). Currently, 10 to 20 % of liver transplanted patients are retransplanted with a success rate of greater than 50 %.

Hepatitis C cirrhosis is the most common indication for liver transplantation. Alcoholic liver disease remains a controversial indication for liver transplantation but carefully selected patients do well. Some of the common indications for liver transplantation are as follows:

1. Alcoholic liver disease (after a period of abstinence)
2. Chronic active hepatitis (usually secondary to hepatitis B and C)
3. Cryptogenic cirrhosis
4. Primary biliary cirrhosis
5. Primary sclerosing cholangitis
Hepato-cellular carcinoma (HCC) complicates many chronic liver diseases. However, a small tumor is not a contraindication to transplantation since tumor rarely recurs in these patients. In contrast, most patients with large (greater than 5 cm in diameter) or multiple hepatomas or most other types of cancer are not considered for transplantation since tumors recur rapidly. At present, there is insufficient evidence that liver transplantation is an effective treatment for other malignancies that affect the liver such as metastatic disease, bile duct carcinoma, and epitheloid hemangioendothelioma, among others. An assessment by the Agency for Healthcare Research and Quality (Beavers et al, 2001) on liver transplantation for malignancies other than HCC concluded that “[t]he available evidence does not provide a clear profile of patients who might be optimal candidates for such therapy.” Contraindications to liver transplantation include extra-hepatic malignancy, severe cardiopulmonary disease, systemic sepsis, and an inability to comply with regular pharmacotherapy.

Liver transplantation is an effective treatment for a variety of acute and chronic diseases of the liver in the pediatric (less than 18 years of age) population. Approximately 15% of the liver transplantsations performed yearly in the United States are in pediatric patients. Most children who need liver transplantation are young (age less than 3 years) and small (body weight less than 45 pounds). Size-matched organs are given preference in organ allocation. However, because of the severe scarcity of pediatric donor livers, techniques such as reduced size (“cut down”) and split (a liver is split between 2 recipients) liver transplantsations are used to reduce the size of adult donor livers to fit pediatric recipients. Donation of the left lobe of the liver by a living adult relative (“living related donor”) is also an option. Liver transplantation in children is indicated for ESLD from any etiology in the absence of contraindications. The most common indication for pediatric liver transplantation is biliary atresia, often after failure to respond to a porto-enterostomy. In addition, unresectable tumors and liver-based metabolic deficiencies may be indications for liver transplantation.
The Model for End-Stage Liver Disease (MELD) is a numerical scale, ranging from 6 (less ill) to 40 (gravely ill), that is used for adult liver transplant candidates. It gives each individual a 'score' (number) based on how urgently he or she needs a liver transplant within the next 3 months. The number is calculated by a formula using bilirubin, prothrombin time, and creatinine. Candidates under the age of 12 are placed in categories according to the Pediatric End-stage Liver Disease (PELD) scoring system. PELD is similar to MELD but uses some different criteria to recognize the specific growth and development needs of children. PELD scores may also range higher or lower than the range of MELD scores. The PELD scoring system takes into account the patient's bilirubin, prothrombin time, albumin, growth failure, and whether the child is less than 1 year old. A liver transplantation is rarely necessary for persons with a MELD score of less than 10. According to data from the United Network for Organ Sharing (UNOS), of almost 5,000 liver transplants that were performed in 2002, only 181 transplants were performed on patients with a MELD score of less than 10.

The MELD/PELD score is a well-validated measure of short-term mortality from liver disease; however, referring physicians who believe a patient faces a greater mortality risk than predicted by the MELD/PELD score can request accelerated listing. UNOS Regional Review Boards can approve or deny these requests, and a study by Voight et al (2004) concluded that these boards fairly and accurately distinguish between high- and low-risk patients. The study found that the denials of physicians' requests for accelerated listings did not increase mortality for those patients. To determine the effect of UNOS Regional Review Board decisions on the mortality of physician-referred patients, investigators analyzed 1,965 nationwide referrals to UNOS Regional Review Boards. They noted which cases were approved and which were denied, and gathered information about patient deaths while awaiting transplantation. The investigators found that there was no significant difference in survival to transplantation whether accelerated listing was approved or denied for adult or pediatric cases. In addition, the
researchers examined whether or not referring physicians predicted death better than the MELD/PELD score. The investigators found that the physicians had poor predictive capacity and added no additional information to the risk assessment by the MELD/PELD score. The investigators concluded that the MELD-PELD score is a better predictor of mortality than the judgement of the referring physician, but the UNOS Regional Review Board process adds additional information (e.g., Voight et al, 2004).

Dimmock et al (2008) noted that deoxyguanosine kinase (DGUOK) deficiency is the commonest type of mitochondrial DNA depletion associated with a hepato-cerebral phenotype. These researchers assessed predictors of survival and therapeutic options in patients with DGUOK deficiency. A systematic search of MEDLINE, LILAC, and SCIELO was performed to identify peer-reviewed clinical trials, randomized controlled trials, meta-analyses, and other studies with clinical pertinence. Deoxyguanosine kinase deficiency was searched with the terms dGK, DGUOK, mitochondrial DNA depletion, mtDNA, and hepatocerebral. Bibliographies of identified articles were reviewed for additional references. A total of 13 identified studies met the inclusion criteria and were used in this study. The analysis revealed that DGUOK deficiency is associated with a variable clinical phenotype. Long-term survival is best predicted by the absence of profound hypotonia, significant psychomotor retardation, or nystagmus. In the presence of these features, there is increased mortality, and liver transplantation does not confer increased survival. The authors concluded that liver transplantation appears to be futile in the presence of specific neurological signs or symptoms in patients affected with DGUOK deficiency. Conversely, in the absence of these neurological features, liver transplantation may be considered a potential treatment.

**Bioartificial Liver Transplantation:**

Artificial and bioartificial livers have been developed for use as a bridge to transplant in patients with liver failure or to allow
recovery in persons with acute liver failure. Liu et al (2004) reported on the results of a meta-analysis of 12 trials of artificial or bioartificial support systems versus standard medical therapy, involving 483 patients, and 2 trials comparing different artificial support systems, involving 105 patients. Most trials had unclear methodological quality. Compared to standard medical therapy, support systems had no significant effect on mortality (relative risk [RR] 0.86; 95% confidence interval [CI]: 0.65 to 1.12) or bridging to liver transplantation (RR 0.87; 95% CI: 0.73 to 1.05), but a significant beneficial effect on hepatic encephalopathy (RR 0.67; 95% CI: 0.52 to 0.86). Subgroup analysis indicated that artificial and bioartificial livers may reduce mortality by 1/3 in acute- on-chronic liver failure (RR 0.67; 95% CI: 0.51 to 0.90), but not in acute liver failure (RR 0.95; 95% CI: 0.71 to 1.29). The authors noted that the incidence of adverse events was inconsistently reported. They concluded that, although artificial support systems may reduce mortality in acute- on-chronic liver failure, “considering the strength of the evidence additional randomised clinical trials are needed before any support system can be recommended for routine use.”

More recently, Demetriou et al (2004) reported on the first prospective, randomized controlled trial of bioartificial liver, the HepatAssist Liver Support System in 171 patients with severe acute liver failure, including both fulminant/subfulminant hepatic failure and primary non-function following liver transplantation. For the entire patient population, survival at 30 days was 71% for patients assigned to the bioartificial liver versus 62% for patients in the control group (p = 0.26). After exclusion of primary non-function patients, survival was 73% for persons assigned to the bioartificial liver versus 59% for persons in the control group (p = 0.12). When survival was analyzed accounting for confounding factors, in the entire patient population, there was no difference between the 2 groups (risk ratio = 0.67; p = 0.13). However, differences in survival between bioartificial liver and control patients with fulminant/subfulminant hepatic failure reached marginal statistical significance (risk ratio = 0.56; p = 0.048). The authors
concluded that this study demonstrated improved survival in patients with fulminant/subfulminant hepatic failure. These results would need to be confirmed in additional prospective randomized studies before conclusions can be drawn about the effectiveness of the bioartificial liver.

_Peri-Operative Use of Sorafenib:_

Qi and colleagues (2015) examined if the application of sorafenib during the peri-operative period of LT improves prognosis in liver cancer patients. These investigators searched PubMed, EMBASE and MEDLINE for eligible articles. A total of 4 studies were found that fulfilled the previously agreed-upon standards. They then performed a systematic review and meta-analysis on the enrolled trials that met the inclusion criteria. Out of the 104 studies identified in the database, 82 were not clinical experiments, and 18 did not fit the inclusion standards. Among the remaining 4 articles, only 1 was related to the pre-operative use of sorafenib, whereas the other 3 were related to its post-operative use. As the heterogeneity among the 4 studies was high, with an I(2) of 86 %, a randomized effect model was applied to pool the data. The application of sorafenib before LT had a hazard ratio (HR) of 3.29 (95 % CI: 0.33 to 32.56). The use of sorafenib after LT had an HR of 1.44 (95 %CI: 0.27 to 7.71). The overall pooled HR was 1.68 (95 %CI: 0.41 to 6.91). The authors concluded that the results showed that the use of sorafenib during the peri-operative period of LT did not improve patient survival significantly. In fact, sorafenib could even lead to a worse prognosis, as its use may increase the hazard of poor survival.

Mancuso et al (2015) stated that data on survival and safety of sorafenib for hepatocellular carcinoma recurrence after LT are still equivocal. These researchers performed a meta-analysis of published studies, with the aim of estimating the 1-year rates of survival, analyzing the variability in survival rates and, finally, identifying the factors associated with a longer survival. Data from 8 of the 17 selected studies were pooled, while the other 9 were excluded because survival rates were missing. All
included studies were retrospective. Overall, the 1-year survival ranged from 18% to 90%. Tumor progression was the main cause of death. The second cause was bleeding, reported only in patients undergoing m-Tor inhibitor therapy. The pooled estimate of 1-year survival was 63%. There was a significant heterogeneity among studies (\( p < 0.0001 \)). Among the 34 variables assessed by univariate meta-regression, 5 were associated with an increase in the 1-year survival rate: (i) male gender (\( p = 0.001 \)); (ii) time to progression (\( p = 0.038 \)); and adverse drug events, divided in (iii) gastrointestinal (\( p = 0.038 \)), (iv) cardiovascular (\( p = 0.029 \)), and (v) dermatological (\( p = 0.014 \)). The authors concluded that additional data from multi-center prospective studies are needed to clearly determine if sorafenib is a safe and acceptable treatment in hepatocellular carcinoma recurrence after LT. Nevertheless, its association with m-Tor inhibitors should be discouraged.

An UpToDate review on “Long-term management of adult liver transplant recipients” (Gaglio and Cotler, 2015) does not mention the use of sorafenib as a management agent.

**Split Liver Transplantation versus Whole Liver Transplantation:**

Wan and colleagues (2015) noted that split liver transplantation (SLT) has proven to be an effective technique to reduce the mortality of children on the waiting list, but whether creating 2 split grafts from 1 standard-criteria whole liver would compromise outcomes of adult recipients remains uncertain. These investigators conducted this meta-analysis to compare outcomes of right lobe SLT and whole liver transplantation (WLT) in adult patients. PubMed, Embase, and the Cochrane Library were searched for relevant articles published before December 2014. Outcomes assessed were patient survival, graft survival and major surgical complications after transplantation. Pooled odds ratios (OR) with 95% CI were calculated to synthesize the results. A total of 17 studies with a total of 4,8457 patients met the full inclusion criteria. Patient survival and graft survival rates were all found to be equivalent between SLT and WLT recipients. However, SLT was associated
with higher rates of overall biliary complications (OR = 1.66, 95 % CI: 1.29 to 2.15, p < 0.001), bile leaks (OR = 4.30, 95 % CI: 2.97 to 6.23, p < 0.001), overall vascular complications (OR = 1.81, 95 % CI: 1.29 to 2.53, p < 0.001), hepatic artery thromboses (OR = 1.71, 95 % CI: 1.17 to 2.50, p = 0.005) and outflow tract obstructions (OR = 4.17, 95 % CI: 1.75 to 9.94, p = 0.001). No significant difference was observed in incidences of biliary stricture, portal vein complications, post-operative bleeding requiring surgical treatments, primary non-function and re-transplantations. In subgroup analyses, biliary and vascular complications only increased after ex-vivo SLT rather than in-situ SLT, and SLT recipients had more re-transplantations if they matched with WLT recipients in terms of urgent status. The authors concluded that adult right lobe SLT was associated with increased biliary and vascular complications compared with WLT, but it did not show significant inferiority in patient and graft survivals.

_Ursodeoxycholic Acid for Prevention of Acute Cellular Rejection after Liver Transplantation:_

Deng et al (2014) noted that acute cellular rejection (ACR) after LT is one of the most common problems faced by transplant recipients in spite of advances in immunosuppressive therapy. Recently, clinical trials reported that ursodeoxycholic acid (UDCA) reduced the incidence of ACR significantly. However, others have shown contradictory conclusion. Therefore, these investigators performed a meta-analysis of rigorous randomized controlled trials (RCTs) to determine the effectiveness of UDCA in reducing ACR after LT. All RCTs that evaluated effectiveness of UDCA as an adjuvant treatment to prevent ACR after LT were searched from PubMed/MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, ScienceDirect databases and Web of Science (from January 1981 to March 2012). There was no language limitation in these searches. Relevant abstracts of international meetings were also searched. References of each included study were searched manually. A total of 234 patients from 4 high-quality RCTs (Jadad score 4 to 5) were included in this meta-analysis. Prophylactic use of UDCA did not decrease
the incidence of ACR (RR: 0.94, 95 % CI: 0.77 to 1.16, p > 0.05), steroid-resistant rejection (RR: 0.77, 95 % CI: 0.47 to 1.27, p > 0.05) and the number of patients with the multiple episodes of ACR (RR: 0.60, 95 % CI: 0.28 to 1.30, p > 0.05). Different intervention programs (high-dose versus low-dose UDCA; early versus delayed UDCA treatment) also did not alter the outcomes. The authors concluded that UDCA, as an adjuvant treatment, was not able to prevent ACR and steroid-resistant rejection after LT. They stated that further trials should be done to determine whether higher dose of UDCA will be beneficial.

An UpToDate review on “Long-term management of adult liver transplant recipients” (Gaglio and Cotler, 2015) does not mention the use of ursodeoxycholic acid as a management agent.

Xenotransplantation:

The success of transplantation has led to a marked increase in the number of candidates to over 16,000 places on the national waiting list. However, there has been little growth in the supply of available cadaveric organs, resulting in an organ shortage crisis. With waiting times often exceeding 1 to 2 years, the waiting list death rate now exceeds 10 % in most regions. Researchers have investigated novel approaches such as xenotransplantation, hepato-cellular transplantation and bioartificial liver to address the growing disparity between the limited supply and excessive demand for suitable organs. However, all these approaches are considered investigational in nature at this juncture.

Studies on xenotransplantation are performed using primates (e.g., baboons, and smaller monkeys). Transmission of diseases, which can be transmitted from animals to humans under natural conditions (zoonoses) as well as hyper-acute rejection remains major concerns in xenotransplantation. Hepatocellular transplantation is used either to temporarily or permanently replace the diseased liver. Hepatocytes are seeded onto biodegradable polymer that serves as a temporary
extra-cellular matrix and to induce vascular in-growth. The seeded polymer is then implanted into a vascular rich area, such as the mesentery of the small intestine. Other techniques including direct injection into the spleen or liver. A bioartificial liver is designed to treat liver disease in the manner similar to a dialysis machine treats renal disease. Investigators use porcine hepatocytes or a transformed line of hepatocytes housed in a bioreactor allowing plasma from patients with liver failure to perfuse through it. It can be used either as a bridge to liver transplantation or to allow recovery of the native liver.

*Everolimus for Prevention of Organ Rejection:*

National Institute for Health and Care Excellence (NICE)'s clinical practice guideline on “Everolimus for preventing organ rejection in liver transplantation” (2015) stated that “Everolimus is not recommended within its marketing authorisation for preventing organ rejection in people having a liver transplant”.

An UpToDate review on “Liver transplantation in adults: Long-term management of transplant recipients” (Gaglio and Cotler, 2016) states that “Everolimus may be another alternative, though its role in the management of patients following liver transplantation has yet to be established”. Furthermore, UpToDate reviews on “Treatment of acute cellular rejection in liver transplantation” (Cotler, 2016) and “” () do not mention everolimus as a management option.

*Peri-Operative Immuno-Nutrition:*

Lei and colleagues (2015) stated that no consensus has been reached concerning the effects of peri-operative immuno-nutrition in patients undergoing liver transplantation. These researchers conducted a meta-analysis to evaluate the effects of peri-operative immuno-nutrition on clinical outcomes and liver function in patients undergoing liver transplantation. The PubMed, Embase, Cochrane Central Register of Controlled Trials, Web of Science, and google scholar were searched to
identify all available RCTs that compared peri-operative immuno-nutrition support (arginine, glutamine, ribonucleic acids, and ω-3 polyunsaturated fatty acids) with standard nutrition. The data analysis was performed using Revman 5.2 software. A total of 7 RCTs involving 501 patients were included. Peri-operative immuno-nutrition significantly reduced the risk of infectious complications (RR: 0.51; 95 % CI: 0.27 to 0.98, p = 0.04) and shortened the post-operative hospital stay [weighted mean difference (WMD): -3.89; 95 % CI: -7.42 to -0.36; p = 0.03]. Furthermore, peri-operative immuno-nutrition improved liver function by decreasing the levels of aspartate aminotransferase (AST) in the blood (WMD: -25.4; 95 % CI: -39.9 to -10.9, p = 0.0006). However, these investigators did not find statistically significant differences in serum alanine aminotransferase (ALT), total bilirubin (TB) and direct bilirubin (DB) levels. There were no statistically significant differences in mortality and rejection reaction. The authors concluded that peri-operative nutrition support adding immuno-nutrients like arginine, glutamine, ribonucleic acids, and ω-3 polyunsaturated fatty acids may improve outcomes in patients undergoing liver transplantation. Moreover, they stated that due to the limited sample size of the included trials, further large-scale and rigorously designed RCTs are needed to confirm these preliminary findings.

Peri-Operative Use of Vasopressin:

In a meta-analysis, Won and associates (2015) evaluated the effect of peri-operative terlipressin (an analog of vasopressin) on post-operative renal function in patients who have undergone living donor liver transplantation (LDLT) and analyzed the hemodynamic data during transplantation surgery. These investigators assessed the post-operative peak serum creatinine level and changes in the hemodynamic data (e.g., the mean arterial pressure, heart rate, and systemic vascular resistance). They collected RCTs from PubMed, Embase Drugs and Pharmacology, Cochrane Controlled Trials Register, and Cochrane Database on Systematic Reviews. Analysis was conducted using RevMan 5.2. Data from each trial were pooled
and weighted by their mean differences and corresponding 95 % CI. A heterogeneity assessment was performed. A total of 3 trials (151 patients) were included. The difference in the mean (95 % CI) peak serum creatinine (mg/dL) levels post-operatively was not significant between the intervention and control groups (WMD: -0.27; CI: -0.55 to 0.01; p = 0.06). Terlipressin significantly decreased heart rate during the anhepatic phase (WMD: -6.58; 95 % CI: -8.85 to -4.31; p < 0.00001) with a low heterogeneity (I(2) = 41 %) and significantly decreased heart rate during the neohepatic phase (WMD: -9.82; 95 % CI: -11.96 to -7.68; p < 0.00001), although the heterogeneity was high (I(2) > 50 %). The authors concluded that an iv infusion of terlipressin peri-operatively for LDLT had no effect on the creatinine values post-operatively. Moreover, they stated that larger RCTs on terlipressin infusions during liver transplantation are needed.

Appendix

A tool to calculate MELD score is available at the following website: http://optn.transplant.hrsa.gov/resources/professionalResources.asp?index=8 (http://optn.transplant.hrsa.gov/resources/professionalResources.asp?index=8).

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<th>CPT Codes / HCPCS Codes / ICD-10 Codes</th>
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<td>CPT codes covered if selection criteria are met:</td>
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**Other CPT codes related to the CPB:**

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<th>Description</th>
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<td>47120 - 47130</td>
<td>Hepatectomy, resection of liver; partial lobectomy; trisegmentectomy; total left lobectomy; or total right lobectomy</td>
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**ICD-10 codes covered if selection criteria are met:**

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<td>E85.1</td>
<td>Neuropathic heredofamilial amyloidosis</td>
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<td>I82.0</td>
<td>Budd-Chiari syndrome</td>
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<td>K70.2</td>
<td>Alcoholic fibrosis and sclerosis of liver</td>
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<td>Alcoholic cirrhosis of liver</td>
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<td>K70.31</td>
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<tr>
<td>K73.1 -</td>
<td>Chronic hepatitis, not elsewhere classified</td>
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<tr>
<td>K74.3</td>
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<td>K74.4</td>
<td>Secondary biliary cirrhosis</td>
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<td>K74.69</td>
<td>Other cirrhosis of liver [cryptogenic cirrhosis (of liver)] [post-necrotic cirrhosis (of liver)]</td>
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<tr>
<td>K75.4</td>
<td>Autoimmune hepatitis</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
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<tr>
<td>K75.81</td>
<td>Other and unspecified inflammatory liver diseases</td>
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<td>K76.5</td>
<td>Hepatic veno-occlusive disease</td>
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<td>Hepatopulmonary syndrome</td>
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<td>Cholangitis [primary sclerosing cholangitis with development of secondary biliary cirrhosis]</td>
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<td>Obstruction of bile duct</td>
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<td>Cystic disease of liver</td>
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<td><strong>ICD-10 codes not covered for indications listed in the CPB:</strong></td>
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<td>Sepsis, unspecified organism</td>
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<td>F10.10</td>
<td>Alcohol dependence syndrome, drug dependence, and nondependent abuse of drugs</td>
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<td>F14.99</td>
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**The above policy is based on the following references:**


42. Dousset B, Saint-Marc O, Pitre J, et al. Metastatic endocrine tumors: Medical treatment, surgical resection,


53. Benhamou G, Marmuse JP, Le Goff JY, et al. [Pancreatic gastrinoma with hepatic metastasis treated by supra-
mesocolic exenteration and hepatic transplantation.]
therapeutic approaches in the treatment of children with
2002;24(9):751-755.
transplantation for unresectable hepatoblastoma.
hepatoblastoma management: Transplant versus
liver transplantation and vena cava reconstruction after
total hepatectomy including the vena cava for
transplantation for hepatoblastoma in the pediatric
60. Reyes JD, Carr B, Dvorchik I, et al. Liver transplantation
and chemotherapy for hepatoblastoma and
hepatocellular cancer in childhood and adolescence. J
liver transplantation for unresectable hepatoblastoma: A
hepatic tumors in childhood and the role of liver
63. Superina R, Bilik R. Results of liver transplantation in
transplantation in the treatment of unresectable liver


76. Swedish Council on Technology Assessment in Health Care (SBU). Dialysis for acute hepatic failure - early


86. Canadian Coordinating Office for Health Technology Assessment (CCOHTA). Living donor liver transplantation. Pre-Assessment No. 24. Ottawa, ON: CCOHTA; October
2003.


106. Segev DL, Sozio SM, Shin EJ, et al. Steroid avoidance in


116. Rice JP, Lucey MR. Should length of sobriety be a major determinant in liver transplant selection? Curr Opin


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Liver Transplantation

There are no amendments for Medicaid.