Clinical Policy Title: Liver transplantation

Clinical Policy Number: CCP.1212

Effective Date: January 1, 2016
Initial Review Date: November 18, 2015
Most Recent Review Date: November 6, 2018
Next Review Date: November, 2019

Related policies:

None.

ABOUT THIS POLICY: AmeriHealth Caritas has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas’ clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas’ clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas’ clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas will update its clinical policies as necessary. AmeriHealth Caritas’ clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas considers the use of liver transplants to be clinically proven and, therefore, medically necessary when the patient has been diagnosed with end-stage liver disease. Indications for liver transplant include, but are not limited to:

Acute liver failure complications of cirrhosis:
- Ascites.
- Chronic gastrointestinal blood loss due to portal hypertensive gastropathy.
- Encephalopathy.
- Liver cancer.
- Refractory variceal hemorrhage.
- Synthetic dysfunction.

Liver-based metabolic conditions with systemic manifestations:
- a1 antitrypsin deficiency.
- Familial amyloidosis.
- Glycogen storage disease.
- Hemochromatosis.
- Primary oxaluria.
- Wilson disease.

Systemic complications of chronic liver disease:
- Hepatopulmonary syndrome.
- Portopulmonary hypertension.

In addition, re-transplantation following one or more failed liver transplant(s) is considered medically necessary if the initial transplant was performed for one of the criteria above (Squires, 2014; Martin, 2013).

**Limitations:**

Liver transplants are contraindicated for any of (but not limited to) the following:
- Model for End-Stage Liver Disease score <15.
- Severe cardiac or pulmonary disease.
- Acquired Immunodeficiency Syndrome. (patients that have active current syndrome defining illness or meet definition for the disorder while still on appropriate active antiretroviral therapy. NOTE: Human Immunodeficiency Virus-positive recipients that are adherent to antiretroviral therapy with either a non detected viral load or adequate sustained viral response would be eligible for transplantation under current federal and American Association for the Study of Lung Disease and United Network for Organ Sharing standards. Per federal regulations, Human Immunodeficiency Virus-positive patients can receive organs from donors with the virus).
- Ongoing alcohol or illicit substance abuse.
- Hepatocellular carcinoma with metastatic spread.
- Uncontrolled sepsis.
- Anatomic abnormality that precludes liver transplantation.
- Intrahepatic cholangiocarcinoma.
- Extrahepatic malignancy.
- Fulminant hepatic failure with sustained intracranial pressure >50 mm/Hg or cerebral perfusion pressure <40 mm/Hg.
- Hemangiosarcoma.
- Persistent noncompliance.
- Lack of adequate social support system.
AmeriHealth Caritas also considers other criteria as medically necessary or contraindicated, according to the recommendations of the American Association for the Study of Liver Disease, for adolescents and adults (Martin, 2013) and children (Squires, 2014).

**Alternative covered services:**

None.

**Background**

Liver transplants are only for patients with End Stage Liver Disease marked by extreme liver dysfunction. Liver transplants were first performed in 1963. Throughout the 1960s and 1970s, the technique was largely experimental, and about 75 percent of patients did not survive one year. After rising to a peak of 6,650 such procedures performed in the United States in 2006, the number slightly declined to 6,256 in 2012 (Organ Procurement and Transplantation Network, 2015) at 144 hospitals throughout the nation (Scientific Registry of Transplant Recipients, 2017). Retransplants are sometimes necessary; for example, between 9-29 percent of pediatric liver transplantations result in retransplant (Dreyzin, 2015).

The efficacy of liver transplants has increased in the past several decades. The survival rate has jumped to 85 – 90 percent after one year, and 75 – 85 percent after five years. About 16,000 patients await a donated liver at any given time, and about 1,500 die waiting for a transplant in the United States each year (United Network for Organ Sharing, 2018b).

The scoring system known as the (model for End Stage Liver Disease) is used to determine whether a liver transplantation is required, and is a reliable predictor of mortality. The model for End Stage Liver Disease scale ranges from 6 to 40 points, with higher scores representing sicker patients. There is also a pediatric End Stage Liver Disease scale that uses the same scoring system. In general, any patient with a score from either scale under 10 is not likely to need liver transplantation.

The federal Organ Procurement and Transplantation Network serves as the basis for the priority for transplant according to mortality risk and severity of illness. Patients are assigned to categories status 1A (1A and 1B for children), calculated or exception model for End Stage Liver Disease or Pediatric End Stage Liver Disease score, and inactive status with status 1A representing most urgent, i.e., the patient has liver failure with life expectancy under seven days. Previously, waiting time was a factor in assigning priority to potential liver recipients, but this factor is no longer considered, as it is a poor predictor of mortality (Organ Procurement and Transplantation Network, 2017; United Network for Organ Sharing, 2018a). Types of liver transplantations include:
- Transplantations performed using a liver from either a living or deceased donor.
- Auxiliary live transplantations, which occur when a second liver is implanted ectopically, while the patient’s original liver remains.
- Split-liver transplantations, which occur when a donor’s liver is broken into smaller parts and implanted into the patient. This technique is often used for pediatric patients.
- Xenotransplantations, which use a liver donated from primates. Transmission of diseases remains a concern for this approach.
- Bioartificial liver transplantations, which use an artificial liver. Results to date show that this method is generally not recommended for use.
- Retransplantations of livers, which can take place when a liver transplant recipient again experiences End Stage Liver Disease.

**Searches**

AmeriHealth Caritas searched PubMed and the databases of:
- UK National Health Services Center for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services.

We conducted searches on September 7, 2018. Search terms were: “liver transplantation,” “survival” and “mortality.”

We included:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

The American Association for the Study of Liver Disease recently published detailed practice guidelines for the evaluation of adult and child patients for liver transplants (Martin, 2013; Squires, 2014). These guidelines include 56 and 94 recommendations for adults and children, respectively, according to the patient’s condition and severity. The Association also addressed contraindications for liver transplantation in these guidelines. The European Association for the Study of Liver added a comparable guideline in 2016 (European Association for the Study of Liver, 2016).
Mortality outcomes for liver transplant recipients have improved markedly. In an early study, the one-year and three-year survival rates were only 26 and 12 percent, respectively (Scharschmidt, 1984). Current survival has risen to 93 and 76 percent for one-year and five-year periods (Stepanova, 2015). In two decades, improvements have been observed in average length of hospital stay (42 to 20 days), percent acute post-transplant rejections (33 to four percent), and discharges from the hospital alive (78 to 91 percent) (Stepanova, 2015).

Mortality after liver transplant using living donors and deceased donors was studied in 672 patients with model for End-Stage Liver Disease scores over 35. The percent of recipients of a liver from a living versus a deceased donor were similar after one year (88.9 versus 94.7 percent), three years (87.0 versus 86.9 percent), and five years (84.8 versus 83.3 percent). Similar rates between the two groups were observed for postoperative complications, hospital mortality, and graft survival (Chok, 2017). Another study found that recipients from live donors had higher perioperative complications, but those from deceased donors tended to have more serious complications (Reichman, 2013). In a systematic review of 19 studies (n=5450), higher complication rates were observed in recipients from live donors, but no difference in mortality existed between living and deceased donors (Wan, 2014).

A systematic review/meta-analysis comparing mortality by age of deceased donors included eight nonrandomized comparative studies (n=4376); 20.1 percent of the grafts were from donors age 70 or greater. Patient survival was similar between the older and younger groups at one year ($P = .54$), but the older group had statistically greater survival three and five years after surgery ($P = .007$ and $P < .0001$, respectively). Similar results were found for graft survival (Dasari, 2017).

In a systematic review of 17 studies (n=48,457) comparing split and whole liver transplants, no difference in mortality was observed. However, recipients of split transplants had significantly higher rates of biliary and overall vascular complications, along with bile leaks, hepatic artery thromboses, and outflow tract obstruction (Wan, 2015).

Partial liver transplants (which use a portion of an adolescent or adult donated liver), introduced for young children requiring a new liver, initially had an mortality rate higher than whole liver donations. More recently, mortality for partial and whole-liver transplants is relatively similar (Cauley, 2013).

In a meta-analysis of 62 studies, mortality for liver resection and liver transplantation for persons with hepatocellular cancer was compared. Overall survival for transplant patients exceeded that of resection patients at one, three, and years five years (13, 29, and 39 percent higher, each $P < .001$). Recurrence was 30 percent less ($P < .001$) among transplant patients (Zheng, 2014).

Age is another mortality factor in liver transplantation. One study of 2,938 patients found that mortality increased with patient age, probably because older patients are more often on dialysis and have more medical comorbidities (Chen, 2016). A comparison of adult and child liver recipients found that after surgery, child survival rates exceeded that of adults after five years (89 versus 73 percent), and after 20
years (77 versus 50 percent) (Petrowsky, 2013). A systematic review/meta-analysis of 22 studies compared transplant recipients over and under age 65 (n=23,660 and 218,827), and calculated that the mortality ratio for the elderly group was insignificantly higher \( (P = .09) \) (Gomez Gavara, 2018).

Infections are not uncommon in liver transplant recipients. One study of 201 patients found no difference in infection rates between those with a model for End-Stage Liver Disease score of 6 – 20, 21 – 30, and 31 – 40, even though survival declines as the score increases (Juntermanns, 2015). A systematic review and meta-analysis demonstrated risk of post-operative invasive fungal infections is reduced by 63 percent if prophylaxis is used; fluconazole and liposomal amphotericin B are equally effective (Evans, 2014).

Factors that affect mortality in lung cancer transplantation include weight. A systematic review of 24 studies (n=132,162) showed that mortality is significantly higher for morbidly obese (body mass index over 40) transplant recipients than those at normal weight (18.5 to 30) at all post-operative time periods, except for three years after surgery (Barone, 2017). In a review of 75,942 liver transplantation recipients, pre-existing diabetes mellitus also significantly raised the risk of death (by 40 percent), along with risk for graft loss (by 28 percent) (Li, 2017a).

Racial and ethnic disparities exist for rates of liver transplantation. A study of 22,933 hospitalizations for hepatocellular cancer found that blacks had a 57 percent lower chance of having a liver transplantation than did whites (Rajbhandari, 2017). Another study of 33,062 cases of hepatocellular cancer concluded that restricted utilization of liver transplantation is an important contributor to poorer survival of African Americans (Li, 2017b).

A study of 33,017 liver transplantation candidates compared utilization among Medicaid patients for the periods 2012-13 and 2014-15, before and after Medicaid expansion from the Affordable Care Act. In states that elected to increase Medicaid insurance coverage, transplant centers experienced a significant 49 percent rise \( (P < .001) \) in the proportion of candidates enrolled in Medicaid. However, total patients listed for liver transplantation did not change in these states, leading authors to conclude the law did not increase access to this procedure (Turnin, 2017).

**Policy updates**

A total of two guidelines/other and two peer-reviewed references were added to, and two guidelines/other and one peer-reviewed reference removed from this policy, in September, 2018.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
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<tbody>
<tr>
<td>Dreyzin (2015)</td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td>Long term outcomes for pediatric liver transplants</td>
<td>- Between 9 percent (%) – 29% of pediatric liver transplant patients required retransplant.</td>
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<tr>
<td></td>
<td>- Since 2002, one- and five-year survival has risen to 98% and 87%.</td>
</tr>
<tr>
<td>Citation</td>
<td>Content, Methods, Recommendations</td>
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</tbody>
</table>
| Wan (2015)    | **Key points:**  
|               | • Systematic review/meta-analysis of 17 studies, 48,457 patients, split- versus whole-liver transplants.  
|               | • Survival rates were similar.  
|               | • Group with split transplants had higher rates of 1) biliary complications, 2) bile leaks, 3) vascular complications, 4) hepatic artery thromboses and 5) outflow tract obstructions. |
| Evans (2014)  | **Key points:**  
|               | • Systematic review/meta-analysis of 14 studies of liver transplant patients.  
|               | • Antifungal prophylaxis patients had fewer invasive fungal infections (actual and suspected), and lower mortality from fungal infections. |
| Wan (2014)    | **Key points:**  
|               | • Systematic review/meta-analysis of 19 studies, 5,450 patients, outcomes of living versus deceased donor liver transplantation.  
|               | • Living donor cases have higher rate of surgical complications after transplant, but they still offer greater access to transplants.  
|               | • Improvement is possible with greater experience. |
| Zheng (2014)  | **Key points:**  
|               | • Meta-analysis of 62 studies.  
|               | • Liver transplant versus resection, patients with hepatocellular carcinoma.  
|               | • Transplant group had higher survival and lower recurrence rate. |
| Petrowsky (2013) | **Key points:**  
|                | • Review of 5- and 20-year survival of liver transplants, n=152.  
|                | • After five years, children had a higher survival (89% versus 73%).  
|                | • After 20 years, children had a higher survival (77% versus 50%).  
|                | • Without transplants, fewer than 5% would survive. |

**References**

**Professional society guidelines/other:**


Scharschmidt BF. Human liver transplantation: analysis of data on 540 patients from four centers. *Hepatology.* 1984; 4(1 suppl.):95S-101S.


**Centers for Medicare & Medicaid National Coverage Determinations:**

Local Coverage Determinations:

No Local Coverage Determinations identified as of the writing of this policy.

Commonly submitted codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill in accordance with those manuals.

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<th>Description</th>
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<td>47135</td>
<td>Liver allotransplantation; orthotopic, partial or whole, from cadaver or living donor, any age</td>
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