Guidance to Liver Transplant Programs and the National Liver Review Board for: Pediatric MELD/PELD Exception Review

Contents

Summary and Goals

The MELD[1] or PELD[2] score and status (1A or 1B) are used to prioritize candidates on the waiting list, and are good discriminators of death without a transplant for many pediatric patients with chronic liver disease. However, for some patients, complications of the liver disease and not the degree of liver dysfunction determine the need for liver transplant. Statuses and MELD or PELD scores do not reflect these complications, which have an increased risk of mortality or waitlist dropout without access to timely transplant.[3] This document summarizes available evidence to assist clinical reviewers in approving candidates for status 1B exceptions and MELD or PELD exceptions. It contains guidance for use by the Review Board or the OPTN Liver & Intestinal Organ Committee (hereafter, "the Committee") to evaluate common exceptional case requests for pediatric candidates with the following diagnoses, not all of which are appropriate for an exception:

- Status 1B exceptions (including neoplasms)
- Neoplasms
  - Metastatic Neuroendocrine Tumor (NET)
  - Hepatocellular Carcinoma (HCC)
  - Hilar Cholangiocarcinoma
- Complications of Liver Disease
  - Growth failure or nutritional insufficiency

[1] Model for End-Stage Liver Disease
[2] Pediatric End-Stage Liver Disease
[3] Waitlist dropout is removal from the waiting list due to the candidate being too sick to transplant.

    - Infections
    - Complications of portal hypertension, including ascites and gastrointestinal bleeding
    - Encephalopathy
    - Hepatopulmonary syndrome
    - Developmental delay
    - Pruritus
    - Metabolic Bone disease
    - Metabolic Liver Disease
    - Cystic Fibrosis
- Congenital Portosystemic Shunts
- Post-transplant complications
    - Chronic Rejection
    - Cholangiopathy
    - Vascular Complications

These guidelines promote consistent review of these diagnoses and summarize the Committee's recommendations to the OPTN Board of Directors. This resource is not OPTN Policy, so it does not carry the monitoring or enforcement implications of policy. It is not an official guideline for clinical practice, nor is it intended to be clinically prescriptive or to define a standard of care. This resource is intended to provide guidance to transplant programs and the Review Board.

Background

For allocation purposes, a liver candidate is either registered in a status or receives a MELD or, if less than 12 years old, a PELD score. Candidates are registered in either status 1A or 1B if the candidate meets certain clinical criteria defined by policy, and transplant programs may request to register a candidate in a status if the candidate does not meet the policy requirements. The Committee retrospectively reviews candidates registered in a status by exception.

The MELD and PELD scores are intended to reflect the candidate's disease severity, based on the risk of 3-month mortality without access to liver transplant. When the calculated score does not reflect the candidate's medical urgency, a liver transplant program may request an exception for a higher score. A candidate that meets the criteria for one of the diagnoses in policy is approved for a standardized MELD or PELD exception.[4] If the candidate does not meet criteria for standardized exception, the Review Board considers the request. Pediatric candidates with approved exceptions who turn 18 while still waiting with an approved exception continue to be eligible to receive pediatric exceptions unless or until the candidate is removed from the waiting list.[5]

The Committee has developed guidance for pediatric status and MELD or PELD exception candidates. To support a recommendation for approving an exceptional status registration or additional MELD or PELD

[4] Policy 9.3.C: Specific MELD/PELD Exceptions, Organ Procurement and Transplantation Network Policies.
[5] Policy 9.1: Status and Score Exceptions, Organ Procurement and Transplantation Network Policies.

exception points, there must have been adequate evidence of increased risk of mortality associated with the complication of liver disease.

This guidance replaces any independent criteria that OPTN regions use to request and approve exceptions, commonly referred to as "regional agreements." Review Board members, transplant programs, and the Committee should consult this resource when considering status or MELD/PELD exception requests for pediatric candidates registered before turning 18 years old. Any guidance contained within this document that differs from the guidance offered for adult MELD exceptions is intentional, and is based on peer-review literature and/or clinical practice.

Recommendation

Status 1B

Status 1B - Chronic liver disease

Generally candidates that do not meet criteria in *Policy 9.1.C: Pediatric Status 1B Requirements* should not receive a status 1B exception. Candidates without renal replacement therapy may be considered for a status 1B exception if they meet all other criteria in policy and require a liver support device (such as Molecular Adsorbent Recirculating System (MARS), albumin dialysis, plasmapheresis).

Status 1B – Neoplasm

Under *Policy 9.1.C.2*, candidates with biopsy-proven hepatoblastoma without evidence of metastatic disease qualify for status 1B. In some instances, it may also be appropriate to consider the following pediatric candidates with hepatoblastoma for a status 1B exception:

- Candidates less than 8 years old with hepatoblastoma[6] but not biopsied with radiographic criteria consistent with unresectable hepatoblastoma, and all of the following:
    - No evidence of metastasis at time of listing
    - AFP greater than 100
- Candidates with a biopsy-confirmed embryonal sarcoma that has not metastasized[7,8,9]
- Candidates with vascular malformation (congenital, infantile, or other) and hospitalized with presence of Kasabach-Merritt syndrome or presence of high output cardiac failure requiring pressor or ventilatory support

There is inadequate evidence to support approving Status 1B exception for pediatric candidates with

[6] Meyers et al, in press, Lancet Oncology, 2016

[7] Ismail H, Dembowska-Baginska B, Broniszczak D, et al. Treatment of undifferentiated embryonal sarcoma of the liver in children--single center experience. J Pediatr Surg 2013;48:2202-6.

[8] Plant AS, Busuttil RW, Rana A, Nelson SD, Auerbach M, Federman NC. A single-institution retrospective cases series of childhood undifferentiated embryonal liver sarcoma (UELS): success of combined therapy and the use of orthotopic liver transplant. J Pediatr Hematol Oncol 2013;35:451-5.

[9] Walther A, Geller J, Coots A, et al. Multimodal therapy including liver transplantation for hepatic undifferentiated embryonal sarcoma. Liver Transpl 2014;20:191-9.

rhabdoid tumors.[10,11,12,13] There is also inadequate evidence to support approving Status 1B exception for pediatric candidates with angiosarcoma.[14]

Neoplasms

Hepatoblastoma

Candidates with non-metastatic hepatoblastoma are eligible for status 1B under *Policy 9.1.C Pediatric Status 1B Requirements*.

Epithelioid Hemangioendothelioma (HEHE)

Candidates with (HEHE) with unresectable lesions unresponsive to therapy may be considered for exceptions.[15]

Metastatic Neuroendocrine Tumor (NET)

A review of the literature supports that candidates with NET are expected to have a low risk of waiting list drop-out, though they benefit from transplantation.[16]

The Review Board should consider the following criteria when reviewing exception applications for candidates with NET:

1. Resection of primary malignancy and extra-hepatic disease without any evidence of recurrence at least six months prior to MELD or PELD exception request.
2. Neuroendocrine Liver Metastasis (NLM) limited to the liver, Bi-lobar, not amenable to resection.
3. Tumors in the liver should meet the following radiographic characteristics on *either* CT or MRI:
    a. If CT Scan: Triple phase contrast
        i. Lesions may be seen on only one of the three phases
        ii. Arterial phase: may demonstrate a strong enhancement
        iii. Large lesions can become necrotic/calcified
    b. If MRI Appearance:
        i. Liver metastasis are hypodense on T1 and hypervascular in T2 wave images
        ii. Diffusion restriction
        iii. Majority of lesions are hypervascular on arterial phase with wash –out during portal venous phase
        iv. Hepatobiliary phase post Gadoxetate Disodium (Eovist): Hypointense lesions are characteristics of NET

[10] Kachanov D, Teleshova M, Kim E, et al. Malignant rhabdoid tumor of the liver presented with initial tumor rupture. Cancer Genet 2014;207:412-4.
[11] Agarwala S. Primary malignant liver tumors in children. Indian J Pediatr 2012;79:793-800.
[12] Sugito K, Uekusa S, Kawashima H, et al. The clinical course in pediatric solid tumor patients with focal nodular hyperplasia of the liver. Int J Clin Oncol 2011;16:482-7.
[13] Marzano E, Lermite E, Nobili C, et al. Malignant rhabdoid tumour of the liver in the young adult: report of first two cases. HPB Surg 2009;2009:628206.
[14] Xue M, Masand P, Thompson P, Finegold M, Leung DH. Angiosarcoma successfully treated with liver transplantation and sirolimus. Pediatr Transplant 2014;18:E114-9.
[15] Rodriguez, J.A., Becker, N.S., O'Mahony, C.A. et al. J Gastrointest Surg (2008) 12: 110. doi:10.1007/s11605-007-0247-3
[16] V. Mazzaferro, C. Sposito, J. Coppa, et. al., The Long-Term Benefit of Liver Transplantation for Hepatic Metastases From Neuroendocrine Tumors, Am. J. Transplantation, 16:(10), DOI 10.1111/ajt.13831

4. Consider for exception only those with a NET of Gastro-entero-pancreatic (GEP) origin tumors with portal system drainage.

   Note: NET with the primary located in the lower rectum, esophagus, lung, adrenal gland and thyroid are not candidates for automatic MELD exception.

5. Lower - intermediate grade following the WHO classification. Only well differentiated (Low grade, G1) and moderately differentiated (intermediate grade G2). Mitotic rate <20 per 10 HPF with less than 20% ki 67 positive markers.
6. Tumor metastatic replacement should not exceed 50% of the total liver volume
7. Negative metastatic workup should include one of the following:
   a. Positron emission tomography (PET scan)
   b. Somatostatin receptor scintigraphy
   c. Gallium-68 (68Ga) labeled somatostatin analogue 1,4,7,10-tetraazacyclododedcane-N, N', N",N'"-tetraacetic acid (DOTA)-D-Phe1-Try3–octreotide (DOTATOC), or other scintigraphy to rule out extra-hepatic disease, especially bone metastasis.

   Note: Exploratory laparotomy and or laparoscopy is not required prior to MELD or PELD exception request.

8. No evidence for extra-hepatic tumor recurrence based on metastatic radiologic workup at least 3 months prior to MELD or PELD exception request (submit date).
9. Recheck metastatic workup every 3 months for MELD or PELD exception increase consideration by the Review Board. Occurrence of extra-hepatic progression – for instance lymph-nodal Ga68 positive locations – should indicate de-listing. Patients may come back to the list if any extra-hepatic disease is zeroed and remained so for at least 6 months.
10. Presence of extra-hepatic solid organ metastases (i.e. lungs, bones) should be a permanent exclusion criteria

Hepatocellular Carcinoma (HCC)[17,18,19,20]

Status 1B exceptions may be considered for pediatric candidates with HCC in the presence of metabolic

[17] Jacfranz J. Guiteau, Ronald T. Cotton, Saul J. Karpen, Christine A. O'Mahony, John A. Goss, Pediatric liver transplantation for primary malignant liver tumors with a focus on hepatic epithelioid hemangioendothelioma: The UNOS experience, Pediatric Transplantation, 2010, 14, 3, 326

[18] Beaunoyer, Mona and Vanatta, Jason M. and Ogihara, Makoto and Strichartz, Debra and Dahl, Gary and Berquist, William E. and Castillo, Ricardo O. and Cox, Kenneth L. and Esquivel, Carlos O. Outcomes of transplantation in children with primary hepatic malignancy Pediatric Transplantation 11(6) url =http://dx.doi.org/10.1111/j.1399-3046.2007.00751.x}, p655—660, 2007

[19] Mazzaferro, V. and Sposito, C. and Coppa, J. and Miceli, R. and Bhoori, S. and Bongini, M. and Camerini, T. and Milione, M. and Regalia, E. and Spreafico, C. and Gangeri, L. and Buzzoni, R. and de Braud, F. G. and De Feo, T. and Mariani, L. The Long-Term Benefit of Liver Transplantation for Hepatic Metastases From Neuroendocrine Tumors}, American Journal of Transplantation},16 (10) doi = {10.1111/ajt.13831},{2892--2902},2016

[20] Pham TA, Gallo AM, Concepcion W, Esquivel CO, Bonham CA. Effect of Liver Transplant on Long-Term Disease-Free Survival in Children with Hepatoblastoma and Hepatocellular Cancer. JAMA Surg 150(12): 1150-8, 2015)

liver disease (such as hereditary tyrosinemia).

Policy 9.5.I: Requirements for Hepatocellular Carcinoma (HCC) MELD or PELD Score Exceptions also permits the Review Board to award exceptions for candidates with HCC in certain circumstances. In the absence of metabolic disease, data from the Pediatric Liver Unresectable Tumor Observatory (PLUTO) registry and other single center experience suggests criteria may be expanded beyond Milan and University of California – San Francisco (UCSF) criteria. Extrahepatic metastasis should be an absolute contraindication but exception points for unresectable HCC limited to liver may be considered on a case by case basis in pediatric candidates.

- Children do not need to be within Milan criteria
- Documentation of metastatic work up (including cross-sectional imaging of the chest and bone scan or PET) and no evidence of tumors outside the liver

Hilar Cholangiocarcinoma

Candidates with hilar cholangiocarcinoma may be considered for a MELD or PELD exception if the candidate meets the requirements in *Policy 9.5.A: Requirements for Cholangiocarcinoma (CCA) MELD or PELD Score Exceptions.*

Chronic Liver Disease[21,22,23,24,25,26,27]

Growth Failure or Nutritional Insufficiency

The PELD-Cr score improves accuracy of capturing growth failure, but still may not entirely capture growth failure as it accounts only for height and weight z-scores, and does not correct the weight for ascites or organomegaly. Exceptions should be considered for candidates who meet any of the following criteria:

- Growth parameters[28]
    - <5th percentile for: height, weight (may adjust to estimated dry weight if ascites)[29,30]
    - Z-score (BMI/weight-for-length) less than 2 standard deviations below the mean for age and sex
- Anthropometrics
    - Triceps skin fold thickness or mid-arm muscle circumference < 5th percentile for age and sex [31]

[21] Tamir M et al pediatric liver Transplantation for Primary Sclerosing Cholangitis Liver Transplantation 17:925-933 2011
[22] Elgendy H et al The outcome of critically ill children afterliving donor liver transplant Exp Clin Transplant Suppl 1 : 100-7 2015
[23] Malatack etal Choosing a pediatric recipient for orthotopic liver transplantation J Pediatr 111: 479-489 1987
[24] Sarin SK etal Young adult cirrhotics: a prospective comparative analysis of the clinical profile, natural course and survival Gut 29: 101-107 1988
[25] Matloff RG The Kidney in Pediatric Liver Disease Curr Gastroenterol Rep 17: 36
[26] Dara N et al Liver function, paraclinical tests, and mortality risk factors in pediatric liver transplant candidates Comparative clinical Pathology 25 (1) : 189-195 2015
[27] Keating et al Clinical course of cirrhosis in young adults and therapeutic potential of liver transplantation Gut 26: 1359-1363 1985
[28] Sokol RJ etal Anthropometric evaluation of children with chronic liver diseases Am J Nutrition 52:203-208 1980
[29] World Health Organization global Database on Child Growth and Malnutrition
[30] Yang etal Living donor liver transplantation with body weight more or less than 10 kilograms world J Gastroenterol 21 (23) 7248-53 2015
[31] UptoDate 2016. Table for skin fold thickness percentiles.

- Failure of nasoenteric tube feedings as evidenced by failure to demonstrate improvement in growth failure in the previous month based on either weight or anthropometrics[32]
- Requirement for TPN nutrition to allow for growth or to maintain euglycemia

Infections

Approval of MELD or PELD exception points for pediatric candidates with recurrent cholangitis or other life-threatening infection may be appropriate in some instances. Documentation submitted for case review should indicate one of the following:

- Two or more episodes of spontaneous bacterial peritonitis (SBP)[33] (specify date of each episode)
- At least one episode of other life-threatening infection with sepsis requiring ICU stay
- Two or more episodes of cholangitis within 6 months requiring IV antibiotics requiring placement of a PICC or central line for > 2 continuous weeks for ongoing administration of antibiotics (specify date of each episode)

Complications of portal hypertension, including ascites and gastrointestinal bleeding

Approval of MELD or PELD exception points for hospitalized pediatric candidates with complications of portal hypertension may be appropriate in some instances. Documentation submitted for case review should indicate:

- Gastrointestinal bleeding with on-going transfusion requirement, specification of interventions and treatments attempted or contraindicated to their use, and the amount and dates of transfusions [34]

There is insufficient evidence to support approval of exception points in the presence of splenomegaly or varices without bleeding. There is also insufficient evidence to support approval of exception points for pediatric candidates with ascites controlled by diuretics in the outpatient setting. Exception points may be considered for candidates with severe or complicated ascites in at least one of the following clinical scenarios:

- Serum sodium less than 130, two times greater than 2 weeks apart (specify dates, values, and treatment required to demonstrate persistence and severity) [35]
- Multiple therapeutic paracenteses (at least 2 in the previous 30 days, not including diagnostic paracentesis)
- Hydrothorax requiring chest tube or therapeutic thoracentesis (at least 2 in the previous 60 days, not including diagnostic thoracentesis)
- Patients requiring a hospitalization of at least 5 days with ascites not adequately controlled

[32] Chin SE the nature of malnutrition in children with end-stage liver disease awaiting orthotopic liver transplantation Am J Clin Nutr 56:164-168 1992
[33] Larcher VF Spontaneous bacterial peritonitis in children with chronic liver disease, clinical features jpediatr 106: 907-912 1985
[34] Iwatsuki S et al: Liver transplantation in the treatment of bleeding esophageal varices Surgery 104 (4) : 697-705 1988
[35] Pugliese R et al Ascites and serum sodium are markers o increased waiting list mortality in children with chronic liver failure Hepatology 59: 1964-7 2014

by oral diuretics and requiring IV diuretic therapy

Encephalopathy

Approval of MELD or PELD exception points for hospitalized pediatric candidates with symptomatic encephalopathy may be appropriate in any of the following instances:

- Clinically refractory to medical management with lactulose or rifaximin
- Infant Glasgow coma score less than 12

Hepatopulmonary Syndrome

Approval of additional MELD or PELD exception points for pediatric candidates who meet the standardized criteria for hepatopulmonary syndrome according to *Policy 9.5: Specific Standardized MELD or PELD Score Exceptions* may be appropriate in some instances, such as if the candidate is hospitalized, or if the candidate is debilitated or exhibits progressive decompensation.

Developmental Delay

There is insufficient evidence to support approval of exception points for pediatric candidates with developmental delay.

Pruritus

Approval of MELD or PELD exception points for pediatric candidates with pruritus may be appropriate in some instances. Documentation submitted for case review should indicate that the candidate has evidence of cutaneous mutilation with bleeding and scratching nonresponsive to medications such as rifampin, ursodiol and naltrexone.

Candidates should not be awarded additional MELD or PELD exceptions points on the basis of xanthomas or an indwelling biliary catheter.

Metabolic Bone Disease

Approval of MELD or PELD exception points for pediatric candidates with metabolic bone disease may be appropriate in some instances. Documentation submitted for case review should indicate:

- Documented pathologic fractures or bone deformity
- Patient is unresponsive to vitamin D, mineral supplementation

Metabolic Liver Disease

In addition to the standard metabolic indications for transplant, there are rare metabolic diseases that present in childhood with liver failure, cirrhosis, or other life-threatening complications that may be successfully ameliorated by liver transplant. An exhaustive list of rare disorders that could be appropriate for a MELD or PELD exception is beyond the scope of this guidance. Approval of MELD or PELD exceptions may be appropriate in cases of rare metabolic disease in which liver transplant can ameliorate the life-threatening risk of the disease.

Transplant programs should submit:

- How liver transplant addresses disease complications and mortality risk
- Reference to other comparable MELD or PELD exception categories as appropriate, to justify points requested
- Experience from other cases in which liver transplant was utilized, from published literature or other.

Cystic Fibrosis

The current criteria for a standard exception for cystic fibrosis (CF) outlined in *OPTN Policy 9.5: Specific Standardized MELD or PELD Score Exceptions* often do not apply to children and adolescents with CF-related liver disease (CFLD) who are listed for liver-only transplant. The major causes of liver-related morbidity and mortality in children with CFLD include cirrhosis with hepatic dysfunction and microscopic portal venopathy, leading to portal hypertension without hepatic dysfunction. CF-related comorbidities, including lung disease, sinusitis, CF-related diabetes, multi-drug resistant organisms and pancreatic insufficiency, may impact survival as well.

Calculated MELD or PELD scores may underestimate the risk of waitlist mortality for pediatric liver candidates with CFLD, particularly in those with complications of portal hypertension or with other CF-related morbidities. **Evidence currently supports that pediatric liver transplant candidates with CFLD should be considered for additional MELD or PELD exception points when any of the following criteria are met:**

- Candidate has portal hypertension with complications and the transplant program demonstrates that the patient has failed or is not a candidate for medical, endoscopic or surgical interventions to prevent or treat these complications.
- Candidate has growth failure as a result of liver disease, defined by age and sex-specific weight, length/height, weight-for-length, and/or BMI percentiles or has moderate to severe malnutrition. Children and adolescents with CF and growth failure have a higher risk of waitlist mortality than children with non-CF related liver disease and therefore calculated MELD or PELD may not fully capture their risk of mortality.[36]
- Candidate has an FEV_1 <70% or evidence of decline in FEV_1 of ≥5% per year, as these children may be expected to move toward advanced lung disease, reducing the opportunity for liver transplant.[37]

Since CFLD is an uncommon indication for liver transplant, there is minimal direct evidence on mortality risk conferred by other CF-related morbidities in CF liver transplant candidates. Other CF-related morbidities should thus be considered as justification for MELD or PELD exceptions on a case-by-case basis.

[36] Katherine Cheng et al., "Liver Transplant in Children and Adults with Cystic Fibrosis: Impact of Growth Failure and Nutritional Status," *American Journal of Transplantation* 22, no. 1 (September 2, 2021): pp. 177-186, https://doi.org/10.1111/ajt.16791.
[37] A. Jay Freeman et al., "A Multidisciplinary Approach to Pretransplant and Posttransplant Management of Cystic Fibrosis–Associated Liver Disease," *Liver Transplantation* 25, no. 4 (2019): pp. 640-657, https://doi.org/10.1002/lt.25421.

Congenital Portosystemic Shunts

Pediatric patients with congenital portosystemic shunts as Abernathy syndrome may be evaluated on the basis of their complications (hyperammonemia and encephalopathy or hepatopulmonary syndrome) rather than as a unique disease category.

Post-Transplant Complications

Chronic rejection

Chronic rejection (CR) may cause long-term graft dysfunction and fibrosis. The Banff group defined the minimal histological features of CR as biliary epithelial changes affecting a majority of bile ducts with or without duct loss, foam cell obliterative arteriopathy, or bile duct loss affecting greater than 50% of portal tracts.[38,39]

In the Studies of Pediatric Liver Transplantation (SPLIT) database, CR remains at a less than 5% incidence; however 38% of reported patients proceeded to retransplanation.[40] When evaluating late graft loss (more than one year after transplant), 37% of all lost grafts in SPLIT were due to CR. Retransplantation is indicated for those patients who do not respond to treatment of rejection.

Chronic rejection alone is not sufficient for an exception. Exceptions for clinical complications or manifestations of chronic rejection may be appropriate if the transplant program submits evidence of a comorbid condition from the Chronic Liver Disease section above, as well as other evidence including:

- Evidence of chronic rejection on liver biopsy
- Recurrent infections – cholangitis, spontaneous bacterial peritonitis (SBP) (similar criteria regarding quantification and severity of infections to cholestatic patients)
- Growth failure/nutritional insufficiency, complication of portal hypertension, hyponatremia – sodium less than 130, intractable ascites, intractable pruritis

Cholangiopathy

The rates for biliary strictures range from 5% to 25% in pediatric liver graft recipients (Duffy, Tanaka).[41,42] The main cause of late biliary strictures is graft ischemia; ischemic biliary strictures are frequently multiple and affect all aspects of the biliary tree. In contrast, solitary anastomotic strictures are usually short and may respond to percutaneous or endoscopic dilatation. Non-anastomotic strictures are harder to manage, and often result from Hepatic Artery Thrombosis (HAT) or ischemia-

[38] Ng VL, Fecteau A,Shepherd R, Magee J,Bucuvalas J, Alonso E, et al.; for Studies of Pediatric Liver Transplantation Research Group. Outcomes of 5-year survivors of pediatric liver transplantation: report on 461 children from a North American multicenter registry. Pediatrics2008;122:e1128-e1135.
[39] Wallot MA, Mathot M,Janssen M, Hölter T, Paul K, Buts JP, et al. Long-term survival and late graft loss in pediatric liver transplant recipients—a 15-year single-center experience.Liver Transpl 2002;8:615-622.
[40] Ng VL, Fecteau A,Shepherd R, Magee J,Bucuvalas J, Alonso E, et al.; for Studies of Pediatric Liver Transplantation Research Group. Outcomes of 5-year survivors of pediatric liver transplantation: report on 461 children from a North American multicenter registry. Pediatrics2008;122:e1128-e1135.
[41]Duffy JP, Kao K, Ko CY,Farmer DG, McDiarmid SV,Hong JC, et al. Long-term patient outcome and quality of life after liver transplantation: analysis of 20-year survivors. Ann Surg 2010;252:652-661.
[42] Tanaka H, Fukuda A,Shigeta T, Kuroda T,Kimura T, Sakamoto S,Kasahara M. Biliary reconstruction in pediatric live donor liver transplantation: duct-to-duct or Roux-en-Y hepaticojejunostomy. J Pediatr Surg2010;45:1668-1675.

reperfusion injury. Some can also be due to primary immune injury. Cholangitis remains the most common manifestation along with progressive fibrosis. Retransplantation may be required for diffuse and multiple biliary strictures and particularly for those associated with late HAT; retransplantation should be considered in patients with diffuse cholangiopathy.[43]

Exceptions for clinical complications or manifestations of chronic graft dysfunction due to biliary cause may be appropriate if the transplant program submits evidence of a comorbid condition from the Chronic Liver Disease section above, as well as other evidence including:

- Radiological evidence (imaging study such as MR; percutaneous or endoscopic findings of cholangiopathy) of cholangiopathy is required specify:
- Recurrent infections/cholangitis, including:
    - development or evolution of bacterial resistance
    - SBP (similar criteria regarding quantification and severity of infections to cholestatic patients)
    - Growth failure/nutritional insufficiency
    - Complication of portal hypertension
    - Hyponatremia – sodium less than 130
    - Intractable ascites
    - Intractable pruritis

[43] Sunku B, Salvalaggio PR,Donaldson JS, Rigsby CK,Neighbors K, Superina RA,Alonso EM. Outcomes and risk factors for failure of radiologic treatment of biliary strictures in pediatric liver transplantation recipients. Liver Transpl2006;12:821-826.

Vascular complications[44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60]

Exceptions for clinical complications/manifestations of late vascular complications may be appropriate if the transplant program submits evidence of a cobmorbid condition from the Chronic Liver Disease section above, as well as other evidence including:

- Recurrent infections, including:
    - cholangitis
    - SBP (similar criteria regarding quantification and severity of infections to cholestatic patients)
    - Growth failure/nutritional insufficiency
    - Complication of portal hypertension
    - Hyponatremia – Sodium less than 130
    - Intractable ascites
    - Intractable pruritis

Specific criteria for arterial, or vascular cause of graft dysfunction requiring transplantation are listed below.

Late HAT

[44] Ng VL, Fecteau A,Shepherd R, Magee J,Bucuvalas J, Alonso E, et al.; for Studies of Pediatric Liver Transplantation Research Group. Outcomes of 5-year survivors of pediatric liver transplantation: report on 461 children from a North American multicenter registry. Pediatrics2008;122:e1128-e1135.
[45] Wallot MA, Mathot M,Janssen M, Hölter T, Paul K, Buts JP, et al. Long-term survival and late graft loss in pediatric liver transplant recipients—a 15-year single-center experience.Liver Transpl 2002;8:615-622.
[46] Duffy JP, Kao K, Ko CY,Farmer DG, McDiarmid SV,Hong JC, et al. Long-term patient outcome and quality of life after liver transplantation: analysis of 20-year survivors. Ann Surg 2010;252:652-661.
[47] Tanaka H, Fukuda A,Shigeta T, Kuroda T,Kimura T, Sakamoto S,Kasahara M. Biliary reconstruction in pediatric live donor liver transplantation: duct-to-duct or Roux-en-Y hepaticojejunostomy. J Pediatr Surg2010;45:1668-1675.
[48] Sunku B, Salvalaggio PR,Donaldson JS, Rigsby CK,Neighbors K, Superina RA,Alonso EM. Outcomes and risk factors for failure of radiologic treatment of biliary strictures in pediatric liver transplantation recipients. Liver Transpl2006;12:821-826.
[49] Yazigi NA.Long term outcomes after pediatric liver transplantation. Pediatr Gastroenterol Hepatol Nutr. 2013 Dec;16(4):207-18
[50] Marshalleck F. Pediatric arterial interventions. Tech Vasc Interv Radiol2010;13:238-243
[51] Kelly DA, Bucuvalas JC, Alonso EM, et al Long-term medical management of the pediatric patient after liver transplantation: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Liver Transpl. 2013 Aug;19(8):798-825.
[52] Buell JF, Funaki B, Cronin DC, Yoshida A, Perlman MK, Lorenz J, et al. Long-term venous complications after full-size and segmental pediatric liver transplantation. Ann Surg2002;236:658-666.
[53] iraglia R, Maruzzelli L,Caruso S, Marrone G,Carollo V, Spada M, et al.Interventional radiology procedures in pediatric patients with complications after liver transplantation.Radiographics2009;29:567-584.
[54] Cheng YF, Chen CL,Huang TL, Chen TY, Chen YS, Wang CC, et al.Angioplasty treatment of hepatic vein stenosis in pediatric liver transplants: long-term results. Transpl Int 2005;18:556-561.
[55] Skaro AI, Jay CL, Baker TB, et al. The impact of ischemic cholangiopathy in liver transplantation using donors after cardiac death: the untold story. Surgery. 2009;146(4):543-553.
[56] Berrocal T, Parrón M,Alvarez-Luque A, Prieto C,Santamaría ML. Pediatric liver transplantation: a pictorial essay of early and late complications.Radiographics2006;26:1187-1209.
[57] Maheshwari A, Maley W, Li Z, Thuluvath PJ. Biliary complications and outcomes of liver transplantation from donors after cardiac death. Liver Transpl. 2007;13(12):1645-1653.
[58] Bellingham JM, Santhanakrishnan C, Neidlinger N, et al. Donation after cardiac death: a 29-year experience. Surgery. 2011;150(4):692-702.
[59] Hong JC, Venick R, Yersiz H, et al. Liver transplantation in children using organ donation after circulatory death: a case-control outcomes analysis of a 20-year experience in a single center.JAMA Surg. 2014 Jan;149(1):77-82
[60] Bartlett A, Vara R, Muiesan P, et al. A single center experience of donation after cardiac death liver transplantation in pediatric recipients. Pediatr Transplant. 2010;14(3):388-392.

Late HAT (greater than 30 days post-transplant) are underrecognized and are usually due to ischemic or immunologic injuries.[61] The liver function is usually fairly preserved due to the presence of extensive collateralization, and bile ducts complications are the defining morbidities. Because the blood supply to transplanted bile ducts is derived solely from the hepatic artery, HAT is frequently associated with biliary pathology – typically non-anastomotic strictures, often in the hilum and complex in nature. Bilomas and biliary sepsis are common.

A definitive diagnosis of late HAT requires more advanced imaging (e.g. CT, MR, or standard angiographies). If treatment is required, thrombolysis and anticoagulation are rarely effective, and surgical reconstruction is contraindicated. Radiological treatment of biliary strictures is indicated if necessary, and drainage of intrahepatic abscesses/bilomas is required. For symptomatic late HAT with cholangitis, hepatic abscesses, or diffuse biliary stricturing, retransplantation is frequently necessary.

Specific information regarding the following is helpful to substantiate the request:

- Radiological or angiographic evidence of HAT complicated by both of the following:
    - Recurrent infections – cholangitis, sepsis
    - Failure or inapplicability of percutaneous or endoscopic biliary interventions: specify

Patients with early HAT just beyond the 7 day status 1A cut off or the 14 day standard exception cut off with evidence of severe graft dysfunction may be considered for MELD exception, depending on the clinical scenario.

Portal Vein Thrombosis (PVT)*[62,63]*

PVT is estimated at 2-10% in all pediatric recipients. Portal hypertensive complications manifest mostly as hypersplenism and gastrointestinal (GI) bleeding. Currently scarce systematic data is available on those patients' outcomes. Surgical shunts (selective distal splenorenal, systemic mesocaval, and meso-Rex) are useful, but retransplantation may be indicated. A REX shunt (meso-rex bypass) is favored when technically feasible.

Endovascular interventions should be attempted in patients with portal vein stenosis.

Data requested to substantiate exception requests include:

- evidence of PVT on imaging study or angiography required with complication requiring retranplantation (i.e. refractory complications of portal hypertension, hepatopulmonary syndrome)

[61] Porrett PM, Hsu J, Shaked A. Late surgical complications following liver transplantation. Liver Transpl 2009: 15(Suppl 2): S12–S18
[62] Jensen MK, Campbell KM, Alonso MH, Nathan JD, Ryckman FC, Tiao GM. Management and long-term consequences of portal vein thrombosis after liver transplantation in children. Liver Transpl. 2013;19:315–321
[63] de Ville de Goyet J, Gibbs P, Clapuyt P, Reding R,Sokal EM, Otte JB. Original extrahilar approach for hepatic portal revascularization and relief of extrahepatic portal hypertension related to later portal vein thrombosis after pediatric liver transplantation. Long term results. Transplantation1996;62:71-75.

- Contraindication to surgical shunt: specify
- Failure of surgical shunt: specify

Conclusion

Liver transplant programs, Review Board members and the Committee should consult this resource when assessing pediatric MELD, PELD and status exception requests. Liver programs should also consider this guidance when submitting exception requests for pediatric candidates with these diagnoses. However, these guidelines are not prescriptive of clinical practice.

This guidance may not be reflective of all available evidence pertinent to a specific case. Additional evidence pertinent to a child's clinical course can also be considered when reviewing exception applications.