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Walter Graham, Executive Director

PUBLIC COMMENT NOTICE

To: OPTN members and other interested persons
From: Douglas A. Heiney, Director
Department of Membership Services and Policy Development
Re: OPTN policy proposals for public comment
Date: November 21, 2005

Attached for your consideration is a policy proposal that is being issued for public comment. This proposal addresses guidelines for the Liver Regional Review Boards (RRBs) to use when evaluating exceptional case requests for candidates with specific diagnoses. The issues presented in this proposal were discussed during recent meetings of the Liver and Intestinal Organ Transplantation Committee.

Following public comment and reconsideration by the appropriate committee(s), this proposal may be offered for consideration by the committee(s) to the Board of Directors in 2006. Please mail, fax, or email your comments on this proposal to UNOS by January 5, 2006.

UNOS appreciates receiving your response to these important issues.

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Background

The United Network for Organ Sharing (UNOS) is a tax-exempt medical, scientific, and educational organization. On October 1, 2000, UNOS received a federal contract to continue operation of the national Organ Procurement and Transplantation Network (OPTN) and development of an equitable, scientific and medically-sound organ allocation system. The OPTN is charged with developing by-laws and policies that maximize utilization of organs donated for transplantation, assuring the quality of care for transplant candidates and recipients, and addressing other complex medical issues related to organ transplantation in the United States. All by-laws and policies receive broad input from numerous constituencies including transplant candidates and recipients and family members, donors and donor families, the OPTN membership, and concerned individuals and organizations throughout the United States.

By-Laws and policies are adopted by the OPTN Board of Directors pursuant to the UNOS contract with the United States Department of Health and Human Services (DHHS) and after circulation and discussion among organ transplant professionals and patient representatives. These by-laws and policies have been submitted to the Secretary of DHHS and are considered voluntary guidance to OPTN members unless recommended by the Board of Directors and approved by the Secretary of DHHS as OPTN rules and requirements enforceable under Section 1138 of the Social Security Act. UNOS is responsible for updating these by-laws and policies and for monitoring compliance by OPTN members. Instances of noncompliance with by-laws and policies may lead to disciplinary action, including, for example, designation as a member-not-in-good-standing by the Board of Directors. In addition, instances of non-compliance are reported to the Secretary of DHHS.

The proposal that follows addresses issues considered during recent meetings of the Liver and Intestinal Organ Transplantation Committee. Following public comment and reconsideration by the appropriate committee(s), the proposal in this document may be offered for consideration by the Board of Directors in 2006.

These policy proposals are also available for review on the OPTN and UNOS Internet Web sites at www.optn.org and www.unos.org. Comments on these proposals may be submitted electronically at these sites.

Circulation of Notice

UNOS maintains a public comment distribution list for policy and by-law proposals. To be included on the distribution list, submit a written request to UNOS at the address below. All policy and by-law proposals issued for public comment are mailed to the distribution list. UNOS typically accepts comments from the public for at least 45 days after publication of the proposals and public hearings on the proposals are arranged if warranted.

Comment Deadline

The proposal in this document is being issued for public comment on November 21, 2005. To be considered, comments must be submitted in writing, or by completing the enclosed Public Comment Response Form, and sent to the UNOS contact person at the following address by **January 5, 2006**:

**United Network for Organ Sharing
700 North 4th Street
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FAX (804) 782-4896**

UNOS Contact Persons

Inquiries regarding the policy proposals in this document should be made to the appropriate UNOS Regional Administrator at (804) 782-4800. The UNOS Regional Administrators are as follows:

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Region 1 - Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Eastern Vermont

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Proposal for Standard Guidelines for MELD/PELD Exceptions (Liver and Intestinal Organ Transplantation Committee)

Summary

This proposal contains specific guidelines to be used by the Liver Regional Review Boards (RRBs) to evaluate exceptional case requests for candidates with: ascites; Budd-Chiari syndrome; cholangiocarcinoma; cystic fibrosis and coexistent chronic liver disease; hepatic encephalopathy; familial amyloidotic polyneuropathy (FAP); hepatopulmonary syndrome (HPS); hereditary hemorrhagic telangiectasia (HHT); primary hyperoxaluria; polycystic liver disease; portopulmonary hypertension (POPH); severe pruritus; recurrent bacterial cholangitis associated with structural biliary disease; portal hypertensive GI bleeding; small for size syndrome after liver transplantation; uncommon hepatic tumors; and uncommon metabolic diseases. The intent of the proposal is to promote consistent review of these exceptional case diagnoses using evidence-based criteria.

Background

The MELD and PELD scores used to prioritize offers for liver transplant candidates¹ are an estimate of a candidate's risk of 3-month waiting list mortality. These scores allow candidates to be ranked based on their relative urgency for a liver transplant. However, in some cases the calculated MELD/PELD score may not reflect a candidate's need for a liver transplant, due to the etiology of the liver disease. This issue is addressed in separate sections of the policy. Under Policies 3.6.4.5.1 (Liver Candidates with Hepatopulmonary Syndrome (HPS)) and 3.6.4.5.2 (Liver Candidates with Familial Amyloidosis or Primary Oxaluria), candidates "may be referred to the RRB for consideration of a MELD score that would allow them to be transplanted within 3 months." While Policy 3.6.4.5 (Liver Candidates with Exceptional Cases) provides for RRB review of exceptional case requests, it does not include specific recommendations for selection criteria or MELD/PELD score assignments or timing for increasing the MELD/PELD scores.

The MELD/PELD allocation system has been in place since February 27, 2002. As the OPTN/UNOS Liver and Intestinal Organ Transplantation Committee gained more experience with the MELD/PELD system and the types of cases being submitted for exceptional case requests, the Committee began to seek a more standardized process for exceptional case reviews. In 2003, a Subcommittee was formed to make recommendations regarding the feasibility of a nationally standardized review process. This culminated in a list of guidelines that were approved by the Board in November 2004. These provided specific criteria for evaluation of HPS, familial amyloidosis, primary oxaluria, metabolic disease, cholangiocarcinoma, and other indications for which research protocols have been developed. These were based primarily on a review of the agreements used in each of the Regions in the U.S. It was stated that the (1) the guidelines were intended to promote consistent review of exceptional cases throughout the country; (2) it was expected that the RRBs will take them into consideration when reviewing exceptional case MELD/PELD requests; and (3) that a more detailed set of Guidelines is being developed by the Liver Committee.

In 2005, the Subcommittee began the development of detailed "white papers" on 17 specific diseases/disease categories for which MELD/PELD exceptions might be requested. One or more outside experts was paired with a Subcommittee member to review existing literature and data and to develop guidelines for listing these candidates as exceptions based on the evidence provided in the literature. Proposed increases in MELD/PELD scores were to be based on the mortality risk posed by each indication if supported by data found in peer-reviewed literature.

Proposal

The guidelines for each individual diagnosis are set forth below as separate proposals for comment. A description of the disease/condition and its implications for liver transplant candidates is provided in each guideline, including a review of the peer reviewed medical literature. The authors made a concerted attempt to minimize the use of

¹ In this document, the word 'candidate' specifically refers to those awaiting liver transplantation, while the word 'patient' may refer to someone with a particular disease/condition regardless of their status as a potential transplant candidate.

abstracts, case reports, case series or testimonials. A synthesis of the available scientific data was used to determine whether a MELD/PELD score assignment based on mortality risk is recommended as well as increases in the assigned MELD/PELD score over time. Where applicable, the guidelines include a list of the information that should be provided upon application to the review board. This data collection will permit future analyses of mortality risk in instances where the data are currently limited.

A consensus conference is planned for March 2006, where these guidelines will be discussed prior to submission to the Board of Directors. Ultimately, the Committee envisions three pathways for exceptional case applications. In some cases, the criteria may be defined strictly, such that cases could receive automatic approval, as is currently the case for candidates with HCC. In some cases, UNetSM data entry screens could be developed for indications that would not receive automatic approval, but for which standardized data collection forms can be developed. This would allow enhanced consistency of review and provide standardized data collection for future analysis. A third category would include rare diagnoses and conditions that would still require a narrative submission to the review board. These narratives should include the key information requested in the white papers presented in this document.

The Committee is asking that comments include the following information:

- For each specific diagnosis, please comment on the selection criteria, medical evidence provided, and proposed MELD/PELD score, where applicable.
- Are there other data elements that should be included as part of the exceptional case request
- In general, should candidates receive increased scores upon extension, regardless of disease progression?

In each case, please provide references to peer review documents to support your contention if possible.

MELD Exception Guidelines for Candidates with Ascites
Steven Colquhoun, M.D., Robert Gish, M.D. and Bruce Runyon, M.D.

Background

Ascites is a common clinical finding among liver transplant candidates. Mild ascites can often be managed with diuretic therapy and dietary sodium restriction. When ascites becomes more severe it may persist despite medical therapy, and is said to be refractory. There is no objective, universally agreed, definition of refractory ascites. Nevertheless, there is a strong common belief that refractory ascites is associated with an unacceptably high mortality, including transplant waiting list mortality(1;2). Additional data have supported ascites as the single most highly predictive factor of mortality that is not included in the MELD score(3). Given the association between ascites and waiting list mortality, a system has been sought to reliably identify the subgroup of candidates with severe ascites that should be compensated with additional MELD points(4). It is critical that such a system is objective and reliable given the failure of the subjective parameters utilized by the previous CTP organ allocation system, to fairly provide extra priority to just those candidates that have a higher near term mortality risk.

Currently there are little objective, quality data to identify that subgroup of candidates with ascites who have a higher near term risk of mortality. Suggestions have included those candidates with ascites “refractory” to the standard treatments of sodium restriction and diuretics. Other suggestions have included the volume and frequency of paracentesis or thoracentesis in those candidates requiring such measures. Candidates with failed or contraindicated transjugular intrahepatic portal systemic shunt (TIPS) have been identified as a group at higher risk. The occurrence of an episode of spontaneous bacterial peritonitis has been long associated with an increased 60 day and six-month mortality(5;6) with recent reports in 2000 of in hospital mortality rates of 30-50%(7-9). The presence of resistant organisms has also been identified to portend a poor outcome. A manuscript by Huo et al identifies candidates with SBP as at higher risk of death for patients with ascites with equal MELD scores(10). Hepatic hydrothorax is an unusual complication of ESLD and ascites(11). Less is known about this condition in terms of additional mortality when added to a candidate’s MELD calculation. While any or all of these parameters could be considered as potential MELD exceptions, all suffer from their subjective nature.

Serum sodium has long been clinically correlated with severe refractory ascites. In anticipation of its usefulness for allocation considerations, serum sodium values have been collected in UNetSM for all newly listed candidates as of November 17th, 2004 (modifications to 3.6.4.1.1 and 3.6.4.1.2). In recent publications by Ruf and Biggins, serum sodium was found to be a strong independent predictor of mortality at 3 and 6 months among patients awaiting transplantation(12;13). An additional study by Heuman also identified an association between hyponatremia and mortality for candidates with MELD less than 21, but did not find an association for candidates with a MELD over 21(14). The Scientific Registry of Transplant Recipients has begun to analyze national data on serum sodium to assess whether hyponatremia is associated with waiting list mortality in the national cohort of candidates awaiting liver transplantation. Analysis of these objective data may support proposals for consideration of ascites in the future. In candidates with multiple complications, the analysis of current data becomes even more complex, i.e. if a patient has ascites and additional predictors of increase mortality, the current MELD system is not able to take such additive or synergistic complications into account (7).

Synthesis of Available Data

There is insufficient objective evidence available at the present time to justify additional priority beyond the calculated MELD/PELD score for candidates with ascites.

Suggested Data for Submission to Regional Review Boards

Applications that are submitted to regional review boards for MELD exceptions should include the following documentation: 1) contraindication to TIPS; or 2) the presence of a failed TIPS; 3) volume of ascites removed per paracentesis; 4) number paracentesis per month; 5) days in hosp per month for ascites management; and 6) number of episodes of SBP.

Proposal for Standardized MELD Exceptions for Candidates with Ascites

At this time, we propose that intractable or complicated ascites should continue to be addressed by the Review Board and additional priority (i.e., a higher MELD/PELD score than the calculated score) assigned on a case by case basis after the above described data have been submitted to the RRB. Additional priority should not be automatically granted at this time.

After sufficient data have accrued, the serum sodium data should be studied in a manner similar to that utilized in by Ruf and Biggins *et al*(12;15). With a much larger sample size and without the inherent bias of a single-center study, the predictive quality of serum sodium can be confirmed or disproved as an indirect tool to determine if candidates with ascites with hyponatremia are at higher risk of dying. If confirmed, then changes to OPTN/UNOS policy incorporating these data should be expedited.

The elements described above should be collected prospectively through UNetSM for future re-evaluation of ascites as justification of additional MELD exception points.

There are no data that permit extrapolation of this recommendation to pediatric candidates.

Reference List

- (1) Christensen E, Schlichting P, Andersen PK, Fauerholdt L, Schou G, Pedersen BV et al. Updating prognosis and therapeutic effect evaluation in cirrhosis with Cox's multiple regression model for time-dependent variables. *Scand J Gastroenterol.* 1986;21:163-74.
- (2) Adler M, Van Laethem J, Glibert A, Gelin M, Bourgeois N, Vereerstraeten P et al. Factors influencing survival at one year in patients with nonbiliary hepatic parenchymal cirrhosis. *Dig Dis Sci.* 1990;35:1-5.
- (3) Salerno F, Borroni G, Moser P, Badalamenti S, Cassara L, Maggi A et al. Survival and prognostic factors of cirrhotic patients with ascites: a study of 134 outpatients. *Am J Gastroenterol.* 1993;88:514-19.
- (4) Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL et al. A model to predict survival in patients with end-stage liver disease. *Hepatology.* 2001;33:464-70.
- (5) Altman C, Grange JD, Amiot X, Pelletier G, Lacaine F, Bodin F et al. Survival after a first episode of spontaneous bacterial peritonitis. Prognosis of potential candidates for orthotopic liver transplantation. *J Gastroenterol Hepatol.* 1995;10:47-50.
- (6) Bac DJ. Spontaneous bacterial peritonitis: an indication for liver transplantation? *Scand J Gastroenterol Suppl.* 1996;218:38-42.
- (7) Fernandez-Esparrach G, Sanchez-Fueyo A, Gines P, Uriz J, Quinto L, Ventura PJ et al. A prognostic model for predicting survival in cirrhosis with ascites. *J Hepatol.* 2001;34:46-52.
- (8) Fernandez J, Bauer TM, Navasa M, Rodes J. Diagnosis, treatment and prevention of spontaneous bacterial peritonitis. *Baillieres Best Pract Res Clin Gastroenterol.* 2000;14:975-90.
- (9) Garcia N, Sanyal AJ. Ascites. *Curr Treat Options Gastroenterol.* 2001;4:527-37.
- (10) Huo, T. L., Hou, M. C., Lin, H. C., Wu, J. C., Lee, F. Y., Lee, P. C., Chang, F. Y., and Lee, S. D. Limitation of the Model for End-stage Liver Disease for Outcome Prediction in Patients with Cirrhosis-related Complications. *Liver Transplantation in press.* 2005.

- (11) Kinasewitz GT, Keddissi JI. Hepatic hydrothorax. *Curr Opin Pulm Med*. 2003;9:261-65.
- (12) Ruf AE, Kremers WK, Chavez LL, Descalzi VI, Podesta LG, Villamil FG. Addition of serum sodium into the MELD score predicts waiting list mortality better than MELD alone. *Liver Transpl*. 2005;11:336-43.
- (13) Biggins SW, Rodriguez HJ, Bacchetti P, Bass NM, Roberts JP, Terrault NA. Serum sodium predicts mortality in patients listed for liver transplantation. *Hepatology*. 2005;41:32-39.
- (14) Heuman DM, Abou-Assi SG, Habib A, Williams LM, Stravitz RT, Sanyal AJ et al. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. *Hepatology*. 2004;40:802-10.
- (15) Biggins SW, Rodriguez HJ, Bacchetti P, Bass NM, Roberts JP, Terrault NA. Serum sodium predicts mortality in patients listed for liver transplantation. *Hepatology*. 2005;41:32-39.

MELD Exception Guidelines for Candidates with Budd-Chiari Syndrome
Ken Washburn, M.D., Robert Gish, M.D., and Patrick Kamath, M.D.

Background

The Budd-Chiari syndrome (BCS) is an unusual clinical scenario characterized by obstruction of the hepatic venous outflow(1). The clinical presentation of this syndrome can vary from indolent slowly progressive liver disease, fulminant liver failure or sudden advanced symptoms of cirrhosis and portal hypertension. Liver transplantation has been shown to be an effective therapy for patients with Budd-Chiari syndrome. However, only a small portion of patients ultimately require transplantation. Patients with advanced symptoms related to liver disease such as ascites, encephalopathy, hyperbilirubinemia, or coagulopathy may be the best candidates for transplantation. A recent publication by Murad et al, defines quite clearly those patients at risk for mortality(2). In that multi-center study of 237 patients, the researchers were able to classify patients into one of three categories after modeling using a Cox regression formula. This multivariate analysis demonstrated four variables with prognostic value in these patients with Budd-Chiari syndrome. The presence of encephalopathy had a risk ratio of 3.58, ascites risk ratio of 3.83, prothrombin time greater than 2.3 a risk ratio of 2.05 and the presence of hyperbilirubinemia is a continuous variable with a risk ratio of 1.004. A linear prognostic formula was developed which is as follows: $1.27 \times \text{encephalopathy} + 1.04 \times \text{ascites} + 0.72 \times \text{PT} + 0.004 \times \text{bilirubin}$. Ascites and encephalopathy were scored as present (1) or absent (0) and prothrombin time as higher (1) or lower (0) then 2.3. Bilirubin was included as a continuous variable. The three classes of patients identified were; Class I representing a total score of 0 to 1.1, Class II from 1.1 to 1.5, and Class III a total score of 1.5 and higher. The five-year survival of patients in these three groups was 89% for Class I, 74% for Class II, and 42% for Class III. This study also demonstrated a trend towards improvement in survival in patients in the Class II category who underwent a porto-systemic shunt. In reference to liver transplantation, the data support that patients who fall into the Class III category with evidence of advanced liver disease in the form of encephalopathy, ascites or advanced coagulopathy would be candidates for liver transplantation. Patients in Class II category have equivalent results with transplantation or non-transplant therapy (surgical treatment, shunts and anticoagulation therapy). In this large group of patients, selected over a 17-year period between several different multi-national centers, approximately 20% of the 237 patients studied fell into the Class III category. These patients would appear to have a risk-benefit ratio which would favor transplantation over conservative therapy. Other smaller studies have provided data that would support the recommendation that only patients with advanced decompensated liver disease would benefit from liver transplantation (3;4). Surgical options provide excellent long term outcomes in most patients, as recently published by Xu, in 1360 patients with BCS(5) as well as anticoagulation(6) and TIPS shunts (7). The inherent weakness with this scoring system is the inclusion of the subjective variables of encephalopathy and ascites.

Synthesis of Available Data:

At present there is no evidence to justify additional priority for candidates with Budd-Chiari Syndrome beyond the calculated MELD/PELD score.

Proposal for Standardized MELD Exceptions for Candidates with Budd-Chiari Syndrome:

1. Candidates that fulfill criteria for fulminant hepatic failure with BCS should be listed as Status 1A.
2. Other candidates should be listed and receive their medical calculated MELD score. These candidates will actually have an additional advantage being on anticoagulation medications such as coumadin or alternate anticoagulation.

The data elements described above should be collected prospectively through UNetSM for future reevaluation of Budd-Chiari as justification of additional priority.

There are no data that permit extrapolation of this recommendation to pediatric candidates.

Reference List

- (1) Menon KV, Shah V, Kamath PS. The Budd-Chiari syndrome. N Engl J Med 2004; 350(6):578-585.

- (2) Murad SD, Valla DC, de Groen PC, Zeitoun G, Hopmans JA, Haagsma EB et al. Determinants of survival and the effect of portosystemic shunting in patients with Budd-Chiari syndrome. *Hepatology* 2004; 39(2):500-508.
- (3) Hemming AW, Langer B, Greig P, Taylor BR, Adams R, Heathcote EJ. Treatment of Budd-Chiari syndrome with portosystemic shunt or liver transplantation. *Am J Surg* 1996; 171(1):176-180.
- (4) Shaked A, Goldstein RM, Klintmalm GB, Drazan K, Husberg B, Busuttil RW. Portosystemic shunt versus orthotopic liver transplantation for the Budd-Chiari syndrome. *Surg Gynecol Obstet* 1992; 174(6):453-459.
- (5) Xu PQ, Ma XX, Ye XX, Feng LS, Dang XW, Zhao YF et al. Surgical treatment of 1360 cases of Budd-Chiari syndrome: 20-year experience. *Hepatobiliary Pancreat Dis Int* 2004; 3(3):391-394.
- (6) Pati HP, Dayal S, Srivastava A, Pande GK, Acharya SK. Spectrum of hemostatic derangements, in Budd-Chiari syndrome. *Indian J Gastroenterol* 2003; 22(2):59-60.
- (7) Rossle M, Olschewski M, Siegerstetter V, Berger E, Kurz K, Grandt D. The Budd-Chiari syndrome: outcome after treatment with the transjugular intrahepatic portosystemic shunt. *Surgery* 2004; 135(4):394-403.

MELD Exception Guidelines for Candidates with Cholangiocarcinoma **Gregory Gores M.D., Robert Gish M.D., and Debra Sudan M.D.**

Background

Cholangiocarcinoma is a devastating disease with limited treatment options. There has been an increasing incidence of cholangiocarcinoma in the US with current estimates at 3,000-4000 per year, with high rates being reported in patients with primary sclerosing cholangitis(1;2). The majority of patients with unresectable cholangiocarcinoma only live 12-16 months(3). The disease has two anatomic presentations: i) intrahepatic cholangiocarcinoma which presents as a mass within the hepatic parenchyma; and ii) periductal cholangiocarcinoma that involves the extrahepatic bile ducts and the perihilar region (the confluence of the right and left hepatic ducts). Liver transplantation with concomitant immunosuppression for intrahepatic cholangiocarcinoma is fraught with rapid disease recurrence and has been abandoned by most transplant centers(4). Liver transplantation without neoadjuvant therapy for perihilar cholangiocarcinoma likewise has a very high recurrence rate. However, excellent survival (78% 5-year survival) has been achieved in highly selected patients with unresectable cholangiocarcinoma receiving neoadjuvant chemo-irradiation followed by liver transplantation has been reported (5;6).

These patients have a 50-75% mortality rate at 12 months (1). Therefore, it is estimated that 50% will have disease progression precluding liver transplantation by 6 months. The impact of pre-operative chemo-irradiation on disease progression is unclear and data from centers employing a protocolized approach are preliminary. Currently there are insufficient data to justify additional priority for candidates that have dysplasia. Insufficient data also exist to provide guidance for pediatric candidates.

Synthesis of Available Data

The excellent results of these protocolized approaches, the lack of alternative therapies, and the universal disease-related mortality, justify additional priority for candidates with cholangiocarcinoma.

Proposal for Standardized MELD Exceptions for Candidates with Cholangiocarcinoma

Candidates that meet the selection criteria described below will be granted a MELD score equivalent to 10% mortality at 3 months. The MELD score should increase by an incremental 10% mortality equivalent at 3 month intervals.

1. Candidates must have a cholangiogram demonstrating a biliary stricture and a biopsy or cytologic study demonstrating neoplasia. Cellular studies demonstrating aneuploidy are considered to be neoplastic.
2. The disease must be unresectable due to technical considerations or underlying liver disease (e.g. primary sclerosing cholangitis).
3. If a mass lesion is identified by cross-sectional imaging studies, (CT or MR) it must be <3 cm.
4. Intra-and-extrahepatic metastases must be excluded by cross-sectional imaging studies of the chest and abdomen. Regional lymph node and peritoneal metastases should be excluded by surgical assessment (laparotomy and/or laparoscopic evaluation).
5. The center must have a written protocol approved by their own institutional IRB providing information regarding inclusion criteria, exclusion criteria, and the administration of the neoadjuvant therapy. The protocol must also be submitted to and approved by the Liver and Intestinal Organ Transplantation Committee. Pre-transplant neoadjuvant therapy must be a component of the protocol.

The data elements described above should be collected prospectively by UNOS for future re-evaluation of cholangiocarcinoma as justification of additional priority.

There are no data that permit extrapolation of this recommendation to pediatric candidates.

Reference List

- (1) Burak K, Angulo P, Pasha TM, Egan K, Petz J, Lindor KD. Incidence and risk factors for cholangiocarcinoma in primary sclerosing cholangitis. *Am J Gastroenterol.* 2004;99:523-26.
- (2) Olnes MJ, Erlich R. A review and update on cholangiocarcinoma. *Oncology.* 2004;66:167-79.
- (3) Farley DR, Weaver AL, Nagorney DM. "Natural history" of unresected cholangiocarcinoma: patient outcome after noncurative intervention. *Mayo Clin Proc.* 1995;70:425-29.
- (4) Meyer CG, Penn I, James L. Liver transplantation for cholangiocarcinoma: results in 207 patients. *Transplantation.* 2000;69:1633-37.
- (5) Sudan D, DeRoover A, Chinnakotla S, Fox I, Shaw B, Jr., McCashland T et al. Radiochemotherapy and transplantation allow long-term survival for nonresectable hilar cholangiocarcinoma. *Am J Transplant.* 2002;2:774-79.
- (6) Heimbach JK, Gores GJ, Haddock MG, Alberts SR, Nyberg SL, Ishitani MB et al. Liver transplantation for unresectable perihilar cholangiocarcinoma. *Semin Liver Dis.* 2004;24:201-7.

MELD Exception Guidelines for Candidates with Cystic Fibrosis and Coexistent Chronic Liver Disease **Simon Horslen, M.D., Stuart Sweet, M.D., Robert Gish M.D., and Ross Shepherd M.D.**

Background

Cystic fibrosis (CF) is a multi-system disease resulting from mutations in a single gene, *CFTR*, and is the most frequent potentially fatal inherited condition in Caucasians (1/2000 births). Progressive pulmonary disease is the major contributor to morbidity and mortality, and CF is the most common indication for lung transplantation in adolescents. Liver disease occurs in many patients with cystic fibrosis but progression to cirrhosis is uncommon, occurring in 3-7% of all patients and 10% of patients over 16 years of age. Of these, still fewer progress to end-stage liver disease necessitating consideration for liver transplantation. In the first 32 months following the introduction of MELD/PELD, 38 patients have undergone liver transplantation with this diagnosis (approximately 14 patients per year). The mean age at transplant was 15.7 years. Of the 38 transplants, 31 were liver only, 4 liver-lung, 2 liver-pancreas, and 1 liver-kidney.

Outcome data from several small series in the literature suggest that 1 year survival (~90%) for CF patients receiving a liver alone is similar to that for other diagnoses(1;2). Five year survival of 75% was achieved in the Pittsburgh series(3). Late mortality is in general related to progression of pulmonary disease. However, most studies found significant improvements in pulmonary function in patients undergoing orthotopic liver transplantation (OLT) alone when compared to pre-transplantation status(4). Those CF patients with advanced liver disease and significantly compromised lung function ($FEV_1 < 40\%$) may be candidates for combined liver and lung transplantation(5). Anecdotally, it appears that as the hepatic insufficiency advances, deterioration in pulmonary function accelerates. Conversely, seriously impaired lung functions may increase the probability of variceal bleeding (PHT being a major component of CF liver disease) and compromises the ability to support a patient during an episode of bleeding. Dual organ failure clearly will increase the mortality risk above that predicted by the calculated MELD score(5). The degree of this mortality risk has not been established and it is probable that the numbers involved will be too small to estimate the increased waitlist mortality risk with any degree of accuracy. Added to this apparent disadvantage is the relative scarcity of suitable donors from whom both liver and lungs can be procured.

Despite the fragile state of these patients prior to transplantation, survival data for combined lung/liver transplantation is very encouraging, with this cohort of patients doing at least as well as other groups of patients receiving lung transplantation(5), and in the experience of the group in St. Louis even better (1 death in 5 patients from 1991- 2003 with none developing bronchiolitis obliterans – unpublished data). The group from Broussais Hospital, Paris, France have published actuarial survivals for CF patients undergoing combined liver/lung transplantation of 85.7% 1 year and 64.2% at 5 years(6;7).

Synthesis of Available Data

The available data do not justify additional priority for candidates with CF and with well-preserved pulmonary function. Additional priority is justified for candidates listed for liver transplantation alone that have significantly compromised lung function, because these patients need to be transplanted before their lung disease necessitates consideration for combined transplantation or they die of complications while on the waitlist. Additional priority is justified for those candidates listed for combined liver and lung transplantation because of their difficulty in gaining access to the few suitable donors of both suitable liver and lung.

Proposal for Standardized MELD exceptions for candidates with Cystic Fibrosis

The data elements described below (FEV1) should be collected prospectively through UNetSM on exceptional case applications with a diagnosis of cystic fibrosis.

Pulmonary function	Transplant listing	MELD/PELD exception
FEV ₁ > 40%	Liver alone	None – calculated score appropriate
FEV ₁ < 40%	Liver alone	MELD/ PELD + 10% mortality equivalent, to be increased by a further 10% every 3 months if there is evidence of progressive lung disease by PFT
FEV ₁ < 40%	Liver & lung	40 MELD points

Reference List

- (1) Noble-Jamieson G, Thiru S, Johnston P, Friend P, Barnes ND. Glomerulonephritis with end-stage liver disease in childhood. *Lancet* 1992; 339:706-707.
- (2) Noble-Jamieson G, Valente J, Barnes ND, Friend PJ, Jamieson NV, Rasmussen A et al. Liver transplantation for hepatic cirrhosis in cystic fibrosis. *Arch Dis Child* 1994; 71(4):349-352.
- (3) Fridell JA, Bond GJ, Mazariegos GV, Orenstein DM, Jain A, Sindhi R et al. Liver transplantation in children with cystic fibrosis: a long-term longitudinal review of a single center's experience. *J Pediatr Surg* 2003; 38(8):1152-1156.
- (4) Milkiewicz P, Skiba G, Kelly D, Weller P, Bonser R, Gur U et al. Transplantation for cystic fibrosis: outcome following early liver transplantation. *J Gastroenterol Hepatol* 2002; 17(2):208-213.
- (5) Genyk YS, Quiros JA, Jabbour N, Selby RR, Thomas DW. Liver transplantation in cystic fibrosis. *Curr Opin Pulm Med* 2001; 7(6):441-447.
- (6) Couetil JP, Houssin DP, Soubrane O, Chevalier PG, Dousset BE, Loulmet D et al. Combined lung and liver transplantation in patients with cystic fibrosis. A 4 1/2-year experience. *J Thorac Cardiovasc Surg* 1995; 110(5):1415-1422.
- (7) Couetil JP, Soubrane O, Houssin DP, Dousset BE, Chevalier PG, Guinvarch A et al. Combined heart-lung-liver, double lung-liver, and isolated liver transplantation for cystic fibrosis in children. *Transpl Int* 1997; 10(1):33-39.

MELD Exceptions Guideline for Candidates with Hepatic Encephalopathy

John Ham, M.D., Robert Gish, M.D., and Kevin Mullen, M.D.

Background

Hepatic encephalopathy (HE) is a common and well-known complication of cirrhosis and end-stage liver disease. It is also a predictor of death in univariate and multivariate analyses of patients with liver failure(1;2). The Model for End-Stage Liver Disease (MELD) does not provide priority for patients with encephalopathy (4). In the original multivariate analysis leading to the institution of the MELD score, the inclusion of an encephalopathy factor did not increase the ability of the score to predict 3 month pre-transplant mortality (5). Recently, data have begun emerging that support encephalopathy as an additional predictive factor for short term mortality, suggesting that the inclusion of encephalopathy would improve the MELD score. An analysis by the Scientific Registry of Transplant Recipients showed a striking improvement in the ability to predict short term death over MELD(6) when HE was included. Said et al(7) also recently identified encephalopathy as an independent predictor of mortality (8). Other publications support the idea that hepatic encephalopathy provides additional useful prognostic information(9;10). Despite this evidence, encephalopathy is a subjective diagnosis and an easily quantifiable and verifiable method for scoring patients is lacking.

Recurrent or poorly responsive hepatic encephalopathy often has an underlying pathophysiology which may be controlled in the setting of otherwise relatively good liver function. Examples include large spontaneous porto-systemic shunts – a proportion of which can be closed, recurrent dehydration which can be managed by rehydration, sepsis which can be treated by identifying the underlying cause, and correctable dietary non-compliance. Cases that are submitted to the Review Boards for additional priority because of “failure to respond to maximal medical therapy” should include clear documentation of compliance with neomycin, lactulose, sodium benzoate or Buphenyl, rifaximin, and or metronidazol.

Other conditions that Review Boards might consider for additional priority include grade IV coma requiring ICU hospitalization and intubation. Cerebral edema associated with encephalopathy in cirrhosis is rapidly lethal and may justify an exception if the ICP is elevated(11;12). Another example might be profound encephalopathy associated with a large portosystemic shunt that cannot be occluded for technical reasons. Chronic intermittent sepsis in a patient with a low MELD score who has, for example, a low grade prostatitis, break-through severe encephalopathy requiring hospitalization, and airway protection, could also potentially justify a MELD exception.

To facilitate the development of an accurate method of fairly prioritizing candidates with encephalopathy, data on encephalopathy should be collected using one or more of the attached scoring systems. These data and information can then be evaluated for their utility in determining if an objective estimate of encephalopathy is possible, and to determine if an additional mortality risk factor based on encephalopathy is justified. Testing could include a combination of quantitative or semi-quantitative tests such as neuropsychological tests and EEG or MRI.

Synthesis of available data

Currently, there is no justification for the automatic and systematic provision of increased priority for candidates with encephalopathy symptoms.

Suggested data for submission to review boards

Encephalopathy should be defined with the following standard nomenclature (13;14): Type A: HE associated with acute liver failure; Type B: HE associated with portosystemic bypass(non-cirrhotic); Type C: HE associated with chronic liver disease/cirrhosis with the following subclassifications: 1. Episodic HE – single or recurrent, 2. Persistent HE – mild or severe, 3. Subclinical HE – alternatively minimal HE.

Data on encephalopathy should be collected prospectively through UNetSM using one or more of the attached scoring systems. Intracranial pressure monitoring data should also be included if available.

Clearly, MELD/PELD exception requests are driven by the perceived need to avoid death. This clinical information should be collected prospectively through UNetSM, including: the number of hospitalizations for hepatic

encephalopathy; days in ICU with the primary diagnosis of hepatic encephalopathy; presence of a TIPS complicated by worsening encephalopathy; number of episodes grade IV encephalopathy requiring intubation; and pulmonary complications of intubation including pneumonias.

Proposal for standardized MELD Exceptions for Candidates with Hepatic Encephalopathy

At this time, due to the lack of a quantifiable, verifiable, and reproducible method of documenting encephalopathy, we propose that intractable or complicated encephalopathy should continue to be addressed by the review board and additional priority assigned after the above described data have been submitted on a case by case basis. Additional priority should not be not automatically granted at this time.

The data elements described above should be collected prospectively through UNetSM for future reevaluation of encephalopathy as justification for additional priority.

There are no data that permits extrapolation of this recommendation to pediatric candidates.

1. Assessment of Hepatic Encephalopathy (HE):

HE will be assessed at baseline, daily (prior to and 6 hours following each HLM-100 Adsorption Column treatment), the day after the last treatment, and at study completion by both the West Haven criteria⁵⁰⁻⁵² (primarily) and calculation of the hepatic encephalopathy index and its individual components (secondarily). Sedation will be stopped a minimum of 2 hours prior to mental status assessment.

Table: West Haven Criteria:

<u>Grade 0</u>	<u>Normal, no clinical signs or symptoms</u>
<u>Grade 1</u>	<u>Trivial lack of awareness</u>
	<u>Euphoria or anxiety</u>
	<u>Shortened attention span</u>
	<u>Impaired performance of addition</u>
<u>Grade 2</u>	<u>Lethargy or apathy</u>
	<u>Minimal disorientation for time or place</u>
	<u>Inappropriate behavior</u>
	<u>Subtle personality change</u>
	<u>Impaired performance of subtraction</u>
<u>Grade 3</u>	<u>Somnolence to semi-stupor, but responsive to verbal stimuli</u>
	<u>Confusion</u>
	<u>Gross disorientation</u>
<u>Grade 4</u>	<u>Coma (unresponsive to verbal or noxious stimuli)</u>

Hepatic Encephalopathy Index (HEI)

The HEI developed by Sanyal et al will be utilized secondarily to assess changes in HE during this study. Mental status, asterixis, serum ammonia and the trail-making test from parts A and B are utilized in the calculation of this index. The original index, as developed by Conn et al, utilized each of these features as well as the changes in EEG. For this study, each parameter is scored utilizing a scale from 0 to 4, as noted above. Each parameter is then multiplied by the following weight/age factors:

Mental status:	3
Asterixis:	1
Serum ammonia:	1
Trail Test grade:	1

The hepatic encephalopathy index (HEI) is then calculated by dividing the sum of the weighted scores by the maximum possible score of 24. According to this index, the four independent parameters of HE are assessed as follows:

Mental Status:

Mental status will be assessed by the Parson-Smiths criteria.⁵⁰⁻⁵² According to this criterion, changes in mental status will be graded as follows:

0	Normal
1+	Lack of awareness or abnormal sleep pattern and shortened attention span
2+	Lethargy and disorientation with or without obvious personality change
3+	Somnolence and response to pain present
4+	Deep coma

Asterixis:

Asterixis will be graded as described by Conn et al.⁵³ Determined by arm and forearm extension with wrist in dorsiflexion for 30 seconds (This may be conducted manually if the subject is unable to assist) and evaluated by the following scale:

0	None
1+	Rare flap
2+	Occasional irregular flaps
3+	Frequent flaps
4+	Continuous flaps

Serum ammonia:

Arterial ammonia correlates somewhat better with mental status changes in subjects with hepatic encephalopathy than venous ammonia. However, there is marked overlap between arterial and venous values and their overall correlation with mental status is similar. The values of serum ammonia will be converted to a 1- 4 scale as follows:

1+	1 - 60 $\mu\text{mol/L}$
2+	61 - 90 $\mu\text{mol/L}$
3+	91 - 120 $\mu\text{mol/L}$
4+	≥ 121 $\mu\text{mol/L}$

Trail-making scores

Standard trail-making test part A and part B will be performed as described in Attachment D. The scores obtained to complete the trail-making test will be compared to those of a normal population as previously published. The following scale will be used:

1+	15 - 30 seconds \geq controls	Control Group Part A	≤ 39 seconds
2+	31 - 60 seconds \geq controls	Control Group Part B	≤ 85 seconds
3+	61 - 120 seconds \geq controls		
4+	121 seconds \geq controls		

Reference List

- (1) Adler M, Verset D, Bouhdid H, Bourgeois N, Gulbis B, Le Moine O et al. Prognostic evaluation of patients with parenchymal cirrhosis. Proposal of a new simple score. *J Hepatol.* 1997;26:642-49.
- (2) SRTR Inferential Analytic Request #3. UNOS , 264-268. 5-5-2005.
- (3) SRTR Inferential Analytic Request #3. UNOS , 264-268. 5-5-2005.
- (4) Yoo HY, Edwin D, Thuluvath PJ. Relationship of the model for end-stage liver disease (MELD) scale to hepatic encephalopathy, as defined by electroencephalography and neuropsychometric testing, and ascites. *Am J Gastroenterol.* 2003;98:1395-99.
- (5) Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL et al. A model to predict survival in patients with end-stage liver disease. *Hepatology.* 2001;33:464-70.
- (6) SRTR Inferential Analytic Request #3. UNOS , 264-268. 5-5-2005.
- (7) Said A, Williams J, Holden J, Remington P, Gangnon R, Musat A et al. Model for end stage liver disease score predicts mortality across a broad spectrum of liver disease. *J Hepatol.* 2004;40:897-903.
- (8) SRTR Inferential Analytic Request #3. UNOS , 264-268. 5-5-2005.
- (9) Cooper GS, Bellamy P, Dawson NV, Desbiens N, Fulkerson WJJ, Goldman L et al. A prognostic model for patients with end-stage liver disease. *Gastroenterology.* 1997;113:1278-88.
- (10) del Olmo JA, Pena A, Serra MA, Wassel AH, Benages A, Rodrigo JM. Predictors of morbidity and mortality after the first episode of upper gastrointestinal bleeding in liver cirrhosis. *J Hepatol.* 2000;32:19-24.
- (11) Donovan JP, Schafer DF, Shaw BWJ, Sorrell MF. Cerebral oedema and increased intracranial pressure in chronic liver disease. *Lancet.* 1998;351:719-21.
- (12) Jalan R, Dabos K, Redhead DN, Lee A, Hayes PC. Elevation of intracranial pressure following transjugular intrahepatic portosystemic stent-shunt for variceal haemorrhage [see comments]. *J Hepatol.* 1997;27:928-33.
- (13) Ong JP, Mullen KD. Hepatic encephalopathy. *Eur J Gastroenterol Hepatol.* 2001;13:325-34.
- (14) Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy--definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. *Hepatology.* 2002;35:716-21.

MELD Exception Guidelines for Candidates with Familial Amyloidotic Polyneuropathy (FAP)

Elizabeth Pomfret, M.D., Ph.D., Robert G. Gish, M.D., and David Brandhagen, M.D.

Familial amyloidotic polyneuropathy (FAP) is an autosomal dominant inherited disease, characterized by systemic deposition of amyloid fibrils in various tissues, resulting in organ dysfunction and ultimately leading to death(1). The clinical condition is characterized by peripheral and autonomic neuropathy, cardiomyopathy, nephropathy, malnutrition, and vitreous opacities. The disease generally begins between ages 25 and 35, and is ultimately fatal 7-10 years after onset of symptoms from progressive cardiac dysfunction, malnutrition, or other complications related to autonomic neuropathy(1, 2).

Transthyretin (TTR) or prealbumin is a 127-amino acid protein predominately synthesized in the liver that functions as a transport protein for thyroxin and saturated retinol-binding protein. A mutant, amyloidogenic TTR molecule is produced in patients with FAP as a result of a single amino acid substitution(1). More than 80 point mutations in the TTR gene have been reported; however, the most common worldwide defect is a substitution of valine by methionine at position 30 (Val30Met)(3).

Liver transplantation is the only definitive treatment for FAP and was first successfully performed in Sweden in 1990(4). The rationale for liver transplantation is to eliminate the main source of mutant TTR production, thereby arresting the progression of amyloid deposition. Since 1990, a total of 54 centers in 16 countries have performed orthotopic liver transplantation for FAP (3). According to the FAP World Transplant Registry (www.fapwtr.org), a total of 575 transplants have been performed in 539 patients, reaching a plateau of approximately 60 transplants per year. One and 5-year survival in patients transplanted early in the course of FAP are 90% and 82%, respectively. Causes of death in FAP patients correlate well with the causes of death in adult patients undergoing transplantation for chronic liver disease, with septicemia and infectious complications accounting for approximately 30% of the deaths. Cardiovascular death is higher in the patients with FAP (39% vs 9% in patients undergoing transplantation for chronic liver disease), reflecting the inherent cardiovascular risk of patients with this disease(3).

Because the FAP disease progresses so slowly, an innovative procedure called domino liver transplantation has been applied to these patients. The domino liver transplant involves removing the liver from the FAP patient and transplanting it into an older recipient with liver failure. FAP patients thus do not remove a liver from the donor pool, since their own liver may be transplanted into a patient on the list. To date, 22 centers in 12 countries have reported 131 recipients of domino liver grafts with a 1- and 5- year patient survival of 91.8% and 88.4%, respectively(3). Thus far there have been no reports of symptomatic FAP occurring in domino recipients.

Post transplant studies in patients with FAP show that mutant TTR levels become immeasurable in the serum(5). Reports indicate that the progression of FAP-related symptoms were halted in a significant proportion of patients and that clinical manifestations have even improved in approximately one third of the cases (5-7). In some patients ocular symptoms and cardiac dysfunction may continue to progress post-transplant (8). Successful orthotopic liver transplantation offers the only life-saving treatment for FAP.

Synthesis of Available Data

There is sufficient evidence to justify additional priority for candidates with FAP.

Proposal for Standardized MELD Exceptions for Candidates with FAP

Candidates with Familial Amyloidotic Polyneuropathy that satisfy all of the criteria below will receive an initial MELD score equivalent to a 15% mortality risk at 3 months. The MELD score will be increased by a 10% mortality equivalent every 3 months.

1. Biopsy confirmation of amyloid deposition from an involved organ.
2. Identification of the TTR gene mutation by DNA analysis or mass spectrometry (Val30Met vs Non-Val30Met).

Additional Guidelines

1. The patient should be ambulatory with a modified polyneuropathy disability (PND) score of less than IIIb (able to ambulate with 1 crutch or less).
2. Candidates should have a modified BMI (mBMI) greater than 700. $mBMI = (\text{weight in kg} / \text{length in m}^2) \times \text{serum albumin (g/L)}$.
3. FAP patients with obvious cardiac involvement and increased left ventricular wall thickness (mean wall thickness >12mm) should be considered for combined liver and heart transplantation or alternatively no transplantation at all. As there is no agreed upon consensus in the literature regarding features that constitute significant cardiac involvement we recommend that those patients with potentially life threatening cardiac dysrhythmia and/or cardiomyopathy with an ejection fraction < 40% ± NYHA Class II symptoms not be considered for liver transplantation alone.
4. The FAP liver should be domino transplanted into an appropriate patient awaiting liver transplantation whenever possible unless the variant of FAP is one that deposits amyloid in the liver (e.g. fibrinogen alpha chain amyloidosis).

The data elements described above should be collected prospectively through UNetSM on exceptional case applications with a diagnosis of FAP.

References

1. Lobato L. Portuguese-type amyloidosis (transthyretin amyloidosis, ATTR V30M). *J Nephrol* 2003; 16 (3): 438.
2. Suhr OB, Herlenius G, Friman S, Ericzon BG. Liver transplantation for hereditary transthyretin amyloidosis. *Liver Transpl* 2000; 6 (3): 263.
3. Herlenius G, Wilczek HE, Larsson M, Ericzon BG. Ten years of international experience with liver transplantation for familial amyloidotic polyneuropathy: results from the Familial Amyloidotic Polyneuropathy World Transplant Registry. *Transplantation* 2004; 77 (1): 64.
4. Holmgren G, Steen L, Ekstedt J, et al. Biochemical effect of liver transplantation in two Swedish patients with familial amyloidotic polyneuropathy (FAP-met30). *Clin Genet* 1991; 40 (3): 242.
5. Pomfret EA, Lewis WD, Jenkins RL, et al. Effect of orthotopic liver transplantation on the progression of familial amyloidotic polyneuropathy. *Transplantation* 1998; 65 (7): 918.
6. Adams D, Samuel D, Goulon-Goeau C, et al. The course and prognostic factors of familial amyloid polyneuropathy after liver transplantation. *Brain* 2000; 123 (Pt 7): 1495.
7. Sharma P, Perri RE, Sirven JE, et al. Outcome of liver transplantation for familial amyloidotic polyneuropathy. *Liver Transpl* 2003; 9 (12): 1273.
8. Hornsten R, Wiklund U, Olofsson BO, Jensen SM, Suhr OB. Liver transplantation does not prevent the development of life-threatening arrhythmia in familial amyloidotic polyneuropathy, Portuguese-type (ATTR Val30Met) patients. *Transplantation* 2004; 78 (1): 112.

MELD Exception Guidelines for Candidates with Hepato-pulmonary Syndrome **David C. Mulligan, M.D., Robert Gish M.D., and Michael J. Krowka, MD**

Background

The effects of hepato-pulmonary syndrome (HPS) on liver transplant waitlist mortality and patient outcome are not well understood (1;2). Studies of patients with pulmonary vascular disease are often limited and frequently lack diagnostic accuracy. Early results of orthotopic liver transplantation (OLT) in patients with significant HPS were poor and it was not until later small single center experiences that successful cases resulted in improved pulmonary vascular parameters post-OLT (3). It does not appear that not all patients with HPS benefit from OLT (3-7). Recently, specific diagnostic criteria and management recommendations for HPS have been proposed by the European Respiratory Society (ERS) Task Force on pulmonary-hepatic vascular disorders(7). This Task Force was comprised of international experts in hepatology, pulmonary, anesthesiology and transplant surgery.

The diagnosis of HPS rests is defined by the classic triad of severe liver disease, hypoxemia on room air, and intrapulmonary vascular dilatation(7). Up until the ERS peer-reviewed publication, some centers have used alveolar-arterial oxygen gradient rather than arterial hypoxemia (PaO₂) for definition of HPS, making the prevalence range from 15% to as high as 32%. In addition, variability has existed in the methods used to determine pulmonary vascular dilatation (microbubble echocardiography vs. radionuclide scanning with Tc99m- macroaggregated albumin). The echocardiography test is a qualitative test, yet is more sensitive in detecting pulmonary vascular shunts (dilatation) than the lung perfusion test. However, the lung perfusion study, by measuring uptake over the brain, provides a quantitative measure of the degree of pulmonary vascular dilatation. Importantly, 20-30% of HPS patients may have other comorbidities that can cause baseline or additional hypoxemia (i.e. ascites, hydrothorax, pneumonia, COPD, etc.) (8;9).

There are no proven medical treatments for HPS, other than simple O₂ supplementation followed by OLT (10). HPS alone is a risk factor for poor prognosis in patients with cirrhosis(10). Although some series have reported a 30 to 38% mortality within 12 months of OLT and 16% transplant hospitalization mortality (4;6), favorable long-term outcome (5 year survival of 76% vs 23% not transplanted) has been recently reported (11;12). HPS can be a reversible entity with favorable survival following OLT, especially if transplant is accomplished prior to the evolution of severe hypoxemia. Recent experience supports the anecdotal observations that PaO₂ < 60 mm Hg with or without OLT is associated with worse survival compared to those with PaO₂ > 60 mm Hg (12). In addition, lung perfusion scanning with brain uptake > 20% is associated with worse post-OLT outcome(13). Thus, HPS probably deserves a standard MELD exception (12).

Synthesis of Available Data

There are sufficient data to justify automatic additional priority for patients with HPS.

Proposal for standardized MELD Exceptions for Candidates with HPS

Patients with hepato-pulmonary syndrome that satisfy all four of the criteria below will receive a MELD score equivalent to a 15% mortality risk at 3 months. The MELD score will be increased by a 10% mortality equivalent every 3 months.

1. The patient must have evidence of liver disease
2. PaO₂ < 60 mmHg at rest (any position).
3. The presence of pulmonary vascular dilatation determined by "positive" contrast enhanced echocardiogram.
4. The absence of significant alternative pulmonary disease to explain hypoxemia.

The above described data should be collected prospectively by UNOS for each patient with the HPS diagnosis.

There are no data that permit extrapolation of this recommendation to pediatric patients

Reference List

- (1) Christensen E. Prognostic models in chronic liver disease: validity, usefulness and future role. *J Hepatol.* 1997;26:1414-24.
- (2) Krowka MJ, Porayko MK, Plevak DJ, Pappas SC, Steers JL, Krom RA et al. Hepatopulmonary syndrome with progressive hypoxemia as an indication for liver transplantation: case reports and literature review. *Mayo Clin Proc.* 1997;72:44-53.
- (3) Krowka MJ, Mandell MS, Ramsay MA, Kawut SM, Fallon MB, Manzarbeitia C et al. Hepatopulmonary syndrome and portopulmonary hypertension: a report of the multicenter liver transplant database. *Liver Transpl.* 2004;10:174-82.
- (4) Taille C, Cadranel J, Bellocq A, Thabut G, Soubrane O, Durand F et al. Liver transplantation for hepatopulmonary syndrome: a ten-year experience in Paris, France. *Transplantation.* 2003;75:1482-89.
- (5) Herve P, Lebrec D, Brenot F, Simonneau G, Humbert M, Sitbon O et al. Pulmonary vascular disorders in portal hypertension. *Eur Respir J.* 1998;11:1153-66.
- (6) Egawa H, Kasahara M, Inomata Y, Uemoto S, Asonuma K, Fujita S et al. Long-term outcome of living related liver transplantation for patients with intrapulmonary shunting and strategy for complications. *Transplantation.* 1999;67:712-17.
- (7) Rodriguez-Roisin R, Krowka MJ, Herve P, Fallon MB. Pulmonary-Hepatic vascular Disorders (PHD). *Eur Respir J.* 2004;24:861-80.
- (8) Krowka MJ, Wiseman GA, Burnett OL, Spivey JR, Therneau T, Porayko MK et al. Hepatopulmonary syndrome: a prospective study of relationships between severity of liver disease, PaO₂ response to 100% oxygen, and brain uptake after (99m)Tc MAA lung scanning. *Chest.* 2000;118:615-24.
- (9) Martinez G, Barbera JA, Navasa M, Roca J, Visa J, Rodriguez-Roisin R. Hepatopulmonary syndrome associated with cardiorespiratory disease. *J Hepatol.* 1999;30:882-89.
- (10) Schenk P, Schoniger-Hekele M, Fuhrmann V, Madl C, Silberhumer G, Muller C. Prognostic significance of the hepatopulmonary syndrome in patients with cirrhosis. *Gastroenterology.* 2003;125:1042-52.
- (11) Roberts MS, Angus DC, Bryce CL, Valenta Z, Weissfeld L. Survival after liver transplantation in the United States: a disease-specific analysis of the UNOS database. *Liver Transpl.* 2004;10:886-97.
- (13) Arguedas MR, Abrams GA, Krowka MJ, Fallon MB. Prospective evaluation of outcomes and predictors of mortality in patients with hepatopulmonary syndrome undergoing liver transplantation. *Hepatology.* 2003;37:192-97.
- (12) Swanson KL, Wiesner RH, Krowka MJ. Natural history of hepatopulmonary syndrome: Impact of liver transplantation. *Hepatology.* 2005;41:1122-29.

MELD Exception Guidelines for Candidates with Hereditary Hemorrhagic Telangiectasia
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Background

Hereditary hemorrhagic telangiectasia (HHT), also called Rendu-Osler-Weber's disease, is a rare autosomal dominant disease characterized by arterio-venous malformations involving the skin, mucous membranes, lungs, brain and the gastrointestinal tract. The genetic cause of this disease appears to be defects of transmembrane proteins that are components of the receptor complex for TGF (endoglin, activin receptor like-kinase 1). Hepatic involvement is frequent but in most cases is asymptomatic. It is characterized by diffuse vascular malformations throughout the liver that result in different types of shunting (hepatic artery to hepatic vein, hepatic artery to portal vein, portal vein to hepatic vein), with hepatic artery to hepatic vein shunting being the predominant. Symptomatic liver involvement can present as: 1) high output cardiac failure (most common presentation); 2) portal hypertension (from hepatic artery to portal vein shunting and/or from nodular regenerative hyperplasia); and/or 3) biliary abnormalities such as stricturing and necrosis (probably from ischemia) (6). A patient may have overlapping presentations and, with time, the predominant presentation may transition from one type to another(1). Although the diagnosis is not histological, the principal features of hepatic HHT are periportal telangiectases with accompanying fibrous tissue and sinusoidal congestion and dilatation (2). Liver transplantation may be indicated in cases of intractable heart failure, biliary sepsis and intrahepatic hemorrhage. The entity does not seem to progress to cirrhosis and even though patients may have portal hypertension (with varices and ascites) they generally do not develop liver insufficiency. Diagnosis is made radiographically, mostly with abdominal CAT scan. Histological examination is unnecessary and may be dangerous.

Liver transplantation for HHT is a difficult procedure. Embolization or operative hepatic artery ligation has been attempted for high output heart failure, however experience with these procedures is limited and results are inconsistent and not durable (3;4). More importantly, biliary and liver necrosis leading to acute liver failure has been reported following hepatic artery embolization and therefore this procedure is not recommended(4). Heart failure can be triggered during pregnancy and spontaneous post-partum regression of symptoms after delivery has been reported(5).

Most published accounts of liver transplantation for HHT are single case reports. The largest series in the literature from France describes six patients (6). From this experience, liver transplantation appears to be a difficult procedure in these patients due to the hypervascular nature of the liver. For example, the median blood loss was 59 units. Other cases of liver transplants that were unsuccessful because of fatal intra-operative hemorrhage have been described as well. Survival was 66% in this series, but at least 16 additional patients have been described that received transplants, all but one of whom survived. Therefore, liver transplantation is a reasonably successful option in this setting. Hemodynamic studies indicated that the hyperdynamic state resolved in all cases.

The natural history of hepatic involvement of HHT is unclear. The largest experience described by the Yale group includes 19 patients with hepatic HHT(1). Eight of the 19 patients had symptomatic high output cardiac failure. The condition of three patients improved, four were in stable condition with medical therapy, and one had died, after a median period of 24 months. Six patients had manifestations of portal hypertension such as ascites or variceal bleeding. After a median period of 19 months, the condition of two of the six patients had improved, and the other four had died. Five patients had manifestations of biliary disease. After a median period of 30 months, the condition of two of the five had improved, the condition of one was unchanged, heart failure had developed in one, and one had died after an unsuccessful attempt at liver transplantation. From this experience, it appears that progressive disease leading to mortality is frequent, but not universal.

Synthesis of available data:

There is insufficient objective evidence available to justify automatic additional priority for patients with HHT.

Proposal for Standardized MELD Exceptions for Candidates with HHT

At this time, we propose that patients with HHT should continue to be addressed by the Review Board and additional priority assigned on a case by case basis. Additional priority should not be automatically granted at this time.

Incremental Increases in MELD Score:

If an increase MELD score is provided, the MELD score should increase by an incremental 10% mortality risk score at 3 month intervals on a case by case basis after the RB has reviewed all of the information defined above for each 3 month cycle.

There are no data that permit extrapolation of this recommendation to pediatric patients

Reference List

- (1) Garcia-Tsao G, Korzenik JR, Young L, Henderson KJ, Jain D, Byrd B et al. Liver disease in patients with hereditary hemorrhagic telangiectasia. *N Engl J Med.* 2000;343:931-36.
- (2) Blewitt RW, Brown CM, Wyatt JI. The pathology of acute hepatic disintegration in hereditary haemorrhagic telangiectasia. *Histopathology.* 2003;42:265-69.
- (3) Neumann UP, Knoop M, Langrehr JM, Keck H, Bechstein WO, Lobeck H et al. Effective therapy for hepatic M. Osler with systemic hypercirculation by ligation of the hepatic artery and subsequent liver transplantation. *Transpl Int.* 1998;11:323-26.
- (4) Odorico JS, Hakim MN, Becker YT, Van Der WW, Musat A, Knechtle SJ et al. Liver transplantation as definitive therapy for complications after arterial embolization for hepatic manifestations of hereditary hemorrhagic telangiectasia. *Liver Transpl Surg.* 1998;4:483-90.
- (5) Livneh A, Langevitz P, Morag B, Catania A, Pras M. Functionally reversible hepatic arteriovenous fistulas during pregnancy in patients with hereditary hemorrhagic telangiectasia. *South Med J.* 1988;81:1047-49.
- (6) Azoulay D, Precetti S, Emile JF, Ichai P, Gillon MC, Duclos-Vallee JC et al. [Liver transplantation for intrahepatic Rendu-Osler-Weber's disease: the Paul Brousse hospital experience]. *Gastroenterol Clin Biol.* 2002;26:828-34.

MELD Exception Guidelines for Candidates with Primary Hyperoxaluria **Simon Horslen M.D., Robert G. Gish M.D., and Ruth McDonald, M.D.**

Background

Primary hyperoxaluria type 1 (PH1) results from a functional deficiency of the peroxisomal enzyme alanine:glyoxylate aminotransferase (AGT)(1;2). The metabolic defect leads to excessive oxalate production which injures the kidneys and subsequently accumulates in other tissues of the body(3). Renal injury results from deposition of calcium oxalate within the renal tubules or in the urinary tract as calculi. Renal failure is the end-result, but onset and progression is highly variable, from a severe neonatal presentation with rapid progression to renal failure, to adults with calculi but essentially preserved renal function(3). Severity of clinical disease is in part related to a spectrum of residual enzyme activity. Some patients have a form of the disease sensitive to pharmacological doses of pyridoxine. As renal function deteriorates oxalate accumulates in other tissues, of particular importance is cardiac deposition that leads to arrhythmias, heart block and death(4). This extrarenal accumulation rapidly progresses once the need for dialysis has been reached because current forms of dialysis remove oxalate very inefficiently(5).

Primary hyperoxaluria (PH2) is caused by a deficiency of glyoxylate reductase. Although the affected individuals are at risk for oxalate stones, PH2 is a milder disease and is not considered an indication for liver transplantation.

AGT is primarily expressed in hepatocytes and therefore liver transplantation is, in effect, enzyme replacement therapy. Urinary excretion of glyoxylate falls immediately to normal levels following liver transplantation, but oxaluria continues for a considerable time due to systemic accumulation and mobilization of oxalate. Renal transplantation alone in individuals with large systemic oxalate burdens tends to result in rapid injury to the allograft again from oxalate deposition, except perhaps in those pyridoxine sensitive cases(6). As a rule combined liver and kidney transplantation is required for long-term survival(7;8). Pre-emptive liver transplantation, i.e. prior to significant renal dysfunction has been advocated also(9), but decision-making is complicated by the variable progression of this disease(3;10). In the first 32 months following the introduction of MELD/PELD, 25 patients with a diagnosis of primary oxalosis/oxaluria received a liver transplant (17 liver kidney and 8 liver only). In this group liver transplantation was undertaken at a mean age of 25.4 years.

There are many case reports and reviews documenting the effectiveness of liver transplantation for PH 1. Undoubtedly AGT deficiency is an appropriate indication for liver transplantation, however, such an individual has no "liver disease" and therefore their calculated MELD/PELD score does not reflect their need. A search of available literature does not provide guidance on selecting optimal timing for liver transplantation in PH 1 patients, but it is clear that extrarenal accumulation of oxalate accelerates with end-stage renal failure once dialysis support is required. Irreversible and potentially lethal complications are therefore more likely once this stage has been reached. Survival for PH 1 in renal failure is approximately 50% by 2.5 years without transplantation (11;12). Outcome after transplantation is negatively affected by presence of systemic oxalate deposition i.e. outcomes are poor when transplantation is delayed until advanced systemic oxalosis has developed (13). In the severe infantile-onset form of PH1 death may occur from systemic oxalosis within the first year of life without combined liver and kidney transplantation.

Elevated urinary or plasma oxalate and glyoxylate, especially in patients with renal failure, do not reliably differentiate PH1 from PH 2 or secondary oxalosis. Approximately 25% of patients with proven AGT deficiency do not excrete excessive glyoxylate in their urine. Therefore an AGT deficiency on liver biopsy is essential to make the diagnosis of PH1.

Synthesis of Available Data

There are sufficient data to justify additional priority for patients with PH1.

Proposal for Standardized MELD Exceptions for Candidates with PH1

All candidates must have a proven deficiency of AGT by liver biopsy.

Candidates with that are (1) listed for preemptive isolated liver transplantation prior to significant renal injury or (2) listed for combination liver/ kidney transplantation prior to end-stage renal dysfunction will receive an initial MELD score equivalent to a 10 % mortality risk. The MELD score will be increased by a 10% mortality equivalent every 3 months.

Candidates that are more than one year old that listed for combination liver/ kidney transplantation that have developed end-stage renal dysfunction and are receiving extracorporeal renal replacement therapy will receive an initial MELD score equivalent to a 15 % mortality risk. The MELD score will be increased by a 10% mortality equivalent every 3 months.

Children younger than one year of age at the time of listing for combination liver/ kidney transplantation will receive a MELD score of 40.

The above described data elements should be collected by the RRB and UNOS for future analysis.

Reference List

- (1) Leumann E, Hoppe B. What is new in primary hyperoxaluria? *Nephrol Dial Transplant* 1999; 14(11):2556-2558.
- (2) Leumann E, Hoppe B. The primary hyperoxalurias. *J Am Soc Nephrol* 2001; 12(9):1986-1993.
- (3) Hoppe B, Langman CB. A United States survey on diagnosis, treatment, and outcome of primary hyperoxaluria. *Pediatr Nephrol* 2003; 18(10):986-991.
- (4) Hoppe B, Kemper MJ, Bokenkamp A, Portale AA, Cohn RA, Langman CB. Plasma calcium oxalate supersaturation in children with primary hyperoxaluria and end-stage renal failure. *Kidney Int* 1999; 56(1):268-274.
- (5) Diaz C, Catalinas FG, De Alvaro F, Torre A, Sanchez C, Costero O. Long daily hemodialysis sessions correct systemic complications of oxalosis prior to combined liver-kidney transplantation: case report. *Ther Apher Dial* 2004; 8(1):52-55.
- (6) Monico CG, Milliner DS. Combined liver-kidney and kidney-alone transplantation in primary hyperoxaluria. *Liver Transpl* 2001; 7(11):954-963.
- (7) Gagnadoux MF, Lacaille F, Niaudet P, Revillon Y, Jouvett P, Jan D et al. Long term results of liver-kidney transplantation in children with primary hyperoxaluria. *Pediatr Nephrol* 2001; 16(12):946-950.
- (8) Millan MT, Berquist WE, So SK, Sarwal MM, Wayman KI, Cox KL et al. One hundred percent patient and kidney allograft survival with simultaneous liver and kidney transplantation in infants with primary hyperoxaluria: a single-center experience. *Transplantation* 2003; 76(10):1458-1463.
- (9) Scheinman JJ. Primary hyperoxaluria type 1--liver transplantation before end-stage renal disease? *Pediatr Nephrol* 1993; 7(3):326-327.
- (10) Shapiro R, Weismann I, Mandel H, Eisenstein B, Ben Ari Z, Bar-Nathan N et al. Primary hyperoxaluria type 1: improved outcome with timely liver transplantation: a single-center report of 36 children. *Transplantation* 2001; 72(3):428-432.

- (11) Scheinman JI, Alexander M, Campbell ED, Chan JC, Latta K, Cochat P. Transplantation for primary hyperoxaluria in the USA. *Nephrol Dial Transplant* 1995; 10 Suppl 8:42-46.
- (12) Scheinman JI. Recent data on results of isolated kidney or combined kidney/liver transplantation in the U.S.A. for primary hyperoxaluria. *J Nephrol* 1998; 11 Suppl 1:42-45.
- (13) Jamieson NV. European PHI transplant registry report on the results of combined liver/kidney transplantation for primary hyperoxaluria 1984 to 1992. European PHI Transplantation Study Group. *Transplant Proc* 1995; 27(1):1234-1236.

MELD Exception Guidelines for Candidates with Polycystic Liver Disease **Luis Arrazola, M.D., Robert Gish M.D., and Gregory T. Everson, M.D.**

Background

Polycystic Liver Disease (PLD) is commonly associated with Polycystic Kidney Disease (PKD), but may rarely be exist in isolation. Symptomatic PLD is mainly limited to adults and rarely, if ever, presents in childhood. There is currently no effective medical therapy for polycystic disease. Most patients who have PLD require no medical or surgical intervention. Patients with PLD rarely, if ever, experience biochemical hepatic deterioration and classic symptoms of hepatic failure such as ascites, variceal hemorrhage, or encephalopathy are unusual(1-3). Although there is a typical decrease in the quality of life (QOL) in these patients, QOL (although not well studied) to date has not been associated with decreased survival. Serious, life-threatening, complications related to multiple hepatic cysts may occur including cyst infection, Budd-Chiari-like syndrome, portal hypertension, refractory ascites after cyst fenestration, cyst carcinoma, cholangiocarcinoma, and most importantly pain and or chronic wasting with malnutrition(2-4).

Symptomatic PLD only occurs in those with massive hepatic cystic disease where the total cyst:parenchyma ratio > 1(5). Patients with PLD and PKD on hemodialysis are at greatest risk of life-threatening complications due to hepatic cysts that include infection, hemorrhage, and carcinoma. In one center, 10% of mortality in patients with PLD and PKD on hemodialysis was attributed to these complications. However, this observation has not been confirmed by other centers. Non-transplant interventions which can relieve symptoms of massive hepatic cystic disease include: percutaneous cyst puncture and sclerotherapy, laparoscopic cyst decompression, open laparotomy with fenestration and liver resection(3;6-10). These interventions may provide temporary relief of symptoms but may also be associated with significant morbidity and even mortality. Open surgical decompression is associated with a very low mortality rate but is associated with substantial morbidity. Laparoscopic decompression reduces hospital stay, but has also significant morbidity(6). Liver resection is indicated only in highly selected patients and is associated with significant potential for mortality and frequent morbidity.

Liver transplantation, the ultimate treatment for this disease, eliminates the disease process itself and provides long-lasting relief of symptoms(11-14). Approximately 40% of those undergoing liver transplantation will require simultaneous kidney transplantation. Five year survival after liver or liver plus kidney transplantation is approximately 70 to 75%. Liver transplantation with or without kidney transplantation should be avoided in severely malnourished or debilitated patients. Patients with polycystic liver disease may be candidates for living donor liver transplantation. Patients with PLD that generally have preserved liver function and normal MELD scores if they do not have renal involvement.

Synthesis of Available Data

There are insufficient data to justify automatic priority for patients with PLD.

Proposal for Standardized MELD Exceptions for Candidates with PLD

We propose that PLD should continue to be addressed by the review boards using the following criteria, with data to be prospectively collected by UNOS and additional MELD priority assigned on a case by case basis. Additional MELD priority should not be no automatically granted at this time.

Criteria for Listing for Liver Transplantation (criteria 1, 2 and 3 must be satisfied in all patients)

1. Patients must satisfy criteria for massive PLD (total cyst / parenchyma > 1) and have a complication of the PLD that is likely to resolve after liver transplantation
2. Patients must have clinically significant manifestations of liver disease that can be attributed to massive PLD, which may include weight loss, ascites, and portal hypertension
3. Patients must have failed non-transplant interventions aimed at relieving symptoms or suffered complications related to these treatment, precluding additional attempts at non-transplant treatment.

4. Patients with contraindications for non-transplant interventions including surgical resection, shunts, and cystic unroofing meeting criteria 1 and 2.

If a patient meets listing criteria and any of the criteria for upgrade listed below:, the patient should qualify for a MELD score associated with a 10% 3-month mortality and increase equivalent to a 10% mortality risk every 3 months if there is progressive disease and an extension application is completed.

1. Development of any clinical feature of decompensation of liver function or portal hypertension: ascites or variceal hemorrhage.
2. Budd-Chiari-like syndrome due to cyst compression of hepatic venous outflow, not amenable to cyst decompression by radiologic or surgical approach. The hepatic venous outflow obstruction needs to be documented by CT scan, MRI or venography.
3. Ascites complicating cyst fenestration procedures that fail to respond to medical management, with or without peritoneovenous shunting.
4. Severe malnutrition reflected as a decrease in midarm circumference. Mid-arm circumference (lean body mass) is measured in the non-dominant arm mid-way between the acromion and the olecranon processes. The following descriptors are provided for women (and, in parentheses, for men) [if less than 23.1 cm (23.8cm), severe malnutrition; 23.1-25.5 cm (23.8-25.7 cm), intermediate malnutrition; 25.6-29.7cm (25.7-28.7cm), moderate malnutrition; and if greater than 29.7 (28.7 cm), no malnutrition or albumin <2 gm/dl.
5. Dialysis dependency and any of the section above criteria. This subgroup of polycystic patients appears to be at greatest risk of life-threatening complications arising in polycystic liver.
6. For patients not on dialysis, worsening renal function to the point of consideration of dialysis (**creatinine clearance 20-30ml/min**) who also meet the criteria listed in 1-5 above. Once again, the rationale for upgrading the patient is because the patient is moving toward a higher risk for mortality due to complications arising in hepatic cysts. Combined liver/kidney transplantation is indicated for those patients who are on dialysis or who have sufficient chronic renal failure to be considered “near-dialysis” (**creatinine clearance 20-30ml/min**). The latter patients will likely become dialysis dependent if given liver transplantation alone, since immunosuppressive therapy will further reduce glomerular filtration rate, precipitating overt renal failure.

The patients nutritional parameters and data should be submitted to the Review Board for special case consideration. Recurrent cyst infections should be documented by culture and must show that the infection is not responding to antibiotic therapy.

The Review Board must also require vascular studies (full reports of CT, MR or angiography) to be provided if vascular occlusion is claimed. In reference to complications of ascites, please see the proposed Guideline for Ascites. Transplantation for quality of life should not be a consideration to support upgrading patients to a higher MELD score.

Cyst carcinoma should not be used as an indication for liver transplantation since the prognosis of these patients is unknown or has a poor associated survival.

Incremental MELD score upgrades:

Patients meeting the criteria in items 1-6 should be eligible for a MELD score upgrade at 3 months intervals equivalent to 10 % mortality.

Reference List

- (1) Chauveau D, Grunfeld JP, Durand F, Belghiti J. Ascites in a polycystic patient. *Nephrol Dial Transplant.* 1997;12:228-30.

- (2) Chauveau D, Fakhouri F, Grunfeld JP. Liver involvement in autosomal-dominant polycystic kidney disease: therapeutic dilemma. *J Am Soc Nephrol.* 2000;11:1767-75.
- (3) Everson GT, Taylor MR, Doctor RB. Polycystic disease of the liver. *Hepatology.* 2004;40:774-82.
- (4) Chauveau D, Pirson Y, Le Moine A, Franco D, Belghiti J, Grunfeld JP. Extrarenal manifestations in autosomal dominant polycystic kidney disease. *Adv Nephrol Necker Hosp.* 1997;26:265-89.
- (5) Everson GT, Scherzinger A, Berger-Leff N, Reichen J, Lezotte D, Manco-Johnson M et al. Polycystic liver disease: quantitation of parenchymal and cyst volumes from computed tomography images and clinical correlates of hepatic cysts. *Hepatology.* 1988;8:1627-34.
- (6) Robinson TN, Stiegmann GV, Everson GT. Laparoscopic palliation of polycystic liver disease. *Surg Endosc.* 2004.
- (7) Gigot JF, Jadoul P, Que F, Van BB, Etienne J, Horsmans Y et al. Adult polycystic liver disease: is fenestration the most adequate operation for long-term management? *Ann Surg.* 1997;225:286-94.
- (8) Que F, Nagorney DM, Gross JB, Jr., Torres VE. Liver resection and cyst fenestration in the treatment of severe polycystic liver disease. *Gastroenterology.* 1995;108:487-94.
- (9) Robinson TN, Stiegmann GV, Everson GT. Laparoscopic palliation of polycystic liver disease. *Surg Endosc.* 2005;19:130-132.
- (10) Everson GT, Taylor MR. Management of polycystic liver disease. *Curr Gastroenterol Rep.* 2005;7:19-25.
- (11) Washburn WK, Johnson LB, Lewis WD, Jenkins RL. Liver transplantation for adult polycystic liver disease. *Liver Transpl Surg.* 1996;2:17-22.
- (12) Lang H, von Woellwarth J, Oldhafer KJ, Behrend M, Schlitt HJ, Nashan B et al. Liver transplantation in patients with polycystic liver disease. *Transplant Proc.* 1997;29:2832-33.
- (13) Swenson K, Seu P, Kinkhabwala M, Maggard M, Martin P, Goss J et al. Liver transplantation for adult polycystic liver disease. *Hepatology.* 1998;28:412-15.
- (14) Pirenne J, Aerts R, Yoong K, Gunson B, Koshiha T, Fourneau I et al. Liver transplantation for polycystic liver disease. *Liver Transpl.* 2001;7:238-45.

MELD Exception Guidelines for Candidates with Portopulmonary Hypertension

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Background

Patients with liver disease are predisposed to pulmonary arterial changes indistinguishable from those seen in idiopathic pulmonary artery hypertension. The effects of this abnormal liver-lung association, portopulmonary hypertension (POPH) on liver transplant waitlist mortality and patient outcome are not well understood, causing much debate over the appropriate allocation algorithms and the need for additional MELD priority(1). Studies of liver transplant candidates with pulmonary vascular disease are limited and frequently lack diagnostic accuracy. Early results of orthotopic liver transplantation (OLT) in patients with significant POPH were poor and it was not until later small single center experiences that successful cases resulted in improved pulmonary vascular parameters post-OLT (2,3). Recently, specific diagnostic criteria and management recommendations for POPH have been proposed by the European Respiratory Society (ERS) Task Force on pulmonary-hepatic vascular disorders(4).

The diagnosis of POPH is confirmed by right heart catheterization (RHC) criteria that includes measurements of mean pulmonary artery pressure (MPAP), pulmonary artery occlusion pressure (PAOP) cardiac output (CO), and calculated pulmonary vascular resistance (PVR)(4). It is likely that right heart function and other variables play an important role in patient outcome. Therefore, decisions regarding which patients to offer OLT and decisions regarding additional priority require full knowledge of the patient's right ventricular functional status in addition to pulmonary hemodynamics.

In the era prior to the availability of OLT and prostacyclin therapy, mean survival following diagnosis was 15 months, with half of the deaths related to pulmonary hypertension (5). In the current era of liver transplantation POPH has resulted in intraoperative death, and increased transplant hospitalization mortality (2,3). A literature review (n=43; 18 peer-reviewed studies) (2) and multicenter, prospective analysis (n=66; 10 centers) (3) indicated that a preoperative MPAP > 35 mmHg serves as a threshold for increased risk of death following OLT

Importantly, the literature review noted that the diagnosis of POPH was *initially made* in the operating room in 65% of patients who underwent OLT surgery (2). Mortality was significant with 10 of 14 deaths occurring within 21 days of OLT; 3 deaths were intraoperative. All deaths were associated with pre-OLT MPAP > 35 mm Hg. Fifteen of 29 survivors had MPAP > 35 mm Hg, but 12 had PVR < 400 dynes.s.cm⁻⁵.

In the multicenter study 30 (45%) POPH patients were excluded from OLT consideration due to severity of POPH (mean values: MPAP = 53±11 mm Hg; PVR = 616±288 dynes.s.cm⁻⁵) (3). Despite such screening, transplant hospitalization mortality following OLT was 36%; 13 died which included 5 intraoperative deaths. MPAP was similar between survivors and non survivors (45±14 vs 44±8 mm Hg), respectively), but only 1/13 non survivors had pre-OLT prostacyclin therapy (12/13 had MPAP > 35 mm Hg). Prostacyclin therapy was given to 5/23 survivors (18/23 had MPAP > 35 mm Hg) and 62% had PVR < 400 dynes.s.cm⁻⁵

Despite poor outcomes before and after liver transplantation, persistence of POPH and the development of de novo development of pulmonary artery hypertension after liver transplantation, there are also many reports of improvement in POPH after liver transplantation (6-13).

Case reports and small series suggest pre-OLT treatment with continuous intravenous infusions of prostacyclin may confer a long-term survival advantage post-OLT. In a recent series (n=28), the 5-year survival for POPH undergoing OLT was 56%; (43% had pre-OLT prostacyclin) Additional experience is needed to confirm the pre-OLT prostacyclin-OLT survival advantage hypothesis (14).

Reported experiences have yet to address whether candidates with POPH are at a higher risk of death while awaiting OLT compared to other patients with the same degree of liver dysfunction.

Synthesis of Available Data

There is sufficient evidence to justify automatic additional priority for selected patients with POPH.

Proposal for Standardized MELD Exceptions for Candidates with POPH

Patients with POPH that satisfy all of the criteria below will receive an initial MELD score equivalent to a 15% 3-month mortality risk at. The MELD score will be increased by a 10% mortality equivalent every 3 months.

1. The presence of liver disease.
2. Mean pulmonary artery pressure $25 < (\text{MPAP}) < 35$ mm Hg as measured by right heart catheterization.
3. The presence of pulmonary vascular resistance (PVR) ≥ 240 dynes.s.cm⁻⁵.
4. Pulmonary artery occlusion pressure (PAOP) ≤ 15 mmHg

Patients with MPAP > 35 mm Hg and/or PVR > 400 dynes.s.cm⁻⁵ should have pulmonary vasodilator therapy *and* hemodynamic improvement prior to receiving an increased addition MELD score and transplant consideration. Right heart function should be deemed acceptable.

Data on POPH concerning the above defined elements should be collected prospectively by UNOS for future re-evaluation of POPH as justification of additional MELD exception priority.

There are no data that permit extrapolation of this recommendation to pediatric patients

Reference List

- (1) Christensen E. Prognostic models in chronic liver disease: validity, usefulness and future role. *J Hepatol.* 1997; 26:1414-24.
- (2) Krowka MJ, Plevak DJ, Findlay JY, Rosen CB, Wiesner RH, Krom RA. Pulmonary hemodynamics and perioperative cardiopulmonary-related mortality in patients with portopulmonary hypertension undergoing liver transplantation. *Liver Transpl.* 2000;6:443-50.
- (3) Krowka MJ, Mandell MS, Ramsay MA, Kawut SM, Fallon MB, Manzarbeitia C et al. Hepatopulmonary syndrome and portopulmonary hypertension: a report of the multicenter liver transplant database. *Liver Transpl.* 2004;10:174-82.
- (4) Rodriguez-Roisin R, Krowka MJ, Herve P, Fallon MB. Pulmonary-Hepatic vascular Disorders (PHD). *Eur Respir J.* 2004;24:861-80.
- (5) Robalino BD, Moodie DS. Association between primary pulmonary hypertension and portal hypertension: analysis of its pathophysiology and clinical, laboratory and hemodynamic manifestations. *J Am Coll Cardiol.* 1991;17:492-98.
- (6) Ramsay MA, Simpson BR, Nguyen AT, Ramsay KJ, East C, Klintmalm GB. Severe pulmonary hypertension in liver transplant candidates. *Liver Transpl Surg.* 1997;3:494-500.
- (7) Plotkin JS, Kuo PC, Rubin LJ, Gaine S, Howell CD, Laurin J et al. Successful use of chronic epoprostenol as a bridge to liver transplantation in severe portopulmonary hypertension. *Transplantation.* 1998;65:457-59.

- (8) Krowka MJ, Frantz RP, McGoon MD, Severson C, Plevak DJ, Wiesner RH. Improvement in pulmonary hemodynamics during intravenous epoprostenol (prostacyclin): A study of 15 patients with moderate to severe portopulmonary hypertension. *Hepatology*. 1999;30:641-48.
- (9) Kuo PC, Johnson LB, Plotkin JS, Howell CD, Bartlett ST, Rubin LJ. Continuous intravenous infusion of epoprostenol for the treatment of portopulmonary hypertension. *Transplantation*. 1997;63:604-6.
- (10) Rafanan AL, Maurer J, Mehta AC, Schilz R. Progressive portopulmonary hypertension after liver transplantation treated with epoprostenol. *Chest*. 2000;118:1497-500.
- (11) Halank M, Wiemer M, Tschöpe C, Poller W, Schwimmbeck P, Horstkotte D et al. [Precapillary pulmonary hypertension of uncertain etiology]. *Dtsch Med Wochenschr*. 1998;123:861-65.
- (12) Koneru B, Ahmed S, Weisse AB, Grant GP, McKim KA. Resolution of pulmonary hypertension of cirrhosis after liver transplantation. *Transplantation*. 1994;58:1133-35.
- (13) Minder S, Fischler M, Muellhaupt B, Zalunardo MP, Jenni R, Clavien PA et al. Intravenous iloprost bridging to orthotopic liver transplantation in portopulmonary hypertension. *Eur Respir J*. 2004;24:703-7.
- (14) Swanson K, Burger C, Rosen C, Steers J, Wiesner R, Krowka M. Survival in portopulmonary hypertension and orthotopic liver transplantation. *Liver Transpl* 2005; 11: C-71 (Abstract).

MELD Exception Guidelines for Candidates with Severe Pruritus
W. Kenneth Washburn, M.D. and Robert Gish, M.D.

Background

Intractable pruritus is an extra hepatic manifestation of cholestatic liver disease. The exact etiology of this is not entirely clear. Some patients experience modest pruritus that can be controlled with simple pharmacologic interventions. A small minority of patients develop significant intractable pruritus that is refractory to many pharmacologic agents and may benefit from liver transplantation(1). Current medications used for the treatment of pruritus include ursodeoxycholic acid aimed at improving cholestasis. Other options aimed at eliminating or inactivating peripheral pruritogen through anion exchange include Cholestyramine or hepatic enzyme inducing agents such as Rifampin or phenobarbital. Other interventions may modulate central neurotransmission including opioid antagonist such as Naloxone or serotonin receptor agonist such as ondansetron or tropisetron. Extreme interventions for refractory pruritus include hemodialysis or plasmapheresis or albumin dialysis using molecular absorbent recirculation system(2;3). Refractory pruritus presents significant quality of life issues for patients experiencing this. The literature is void of any suggestion that refractory pruritus leads to additional mortality. There have been anecdotal reports of suicidal ideations as a consequence of pruritus, though there are no reports of this actually occurring. Based on the limited availability of published data, there does not appear to be a mortality risk associated with pruritus. Liver transplantation for refractory pruritus is not supported and would be based solely on quality of life issues and not on mortality risks(4;5).

Synthesis of Available Data

There are no data to justify additional priority for patients with pruritus.

Proposal for Standardized MELD Exceptions for Candidates with Pruritis

We propose that additional MELD priority should not be assigned by regional review boards because of pruritus and no further data should be collected at this time.

There are no data that permit extrapolation of this recommendation to pediatric patients.

Reference List

- (1) Neuberger J. Liver Transplantation for Cholestatic Liver Disease. *Curr Treat Options Gastroenterol.* 2003;6:113-21.
- (2) Bellmann R, Graziadei IW, Feistritz C, Schwaighofer H, Stellaard F, Sturm E et al. Treatment of refractory cholestatic pruritus after liver transplantation with albumin dialysis. *Liver Transpl.* 2004;10:107-14.
- (3) Bellmann R, Feistritz C, Zoller H, Graziadei IW, Schwaighofer H, Propst A et al. Treatment of intractable pruritus in drug induced cholestasis with albumin dialysis: a report of two cases. *ASAIO J.* 2004;50:387-91.
- (4) Bergasa NV. Pruritus in chronic liver disease: mechanisms and treatment. *Curr Gastroenterol Rep.* 2004;6:10-16.
- (5) Younossi ZM, Kiwi ML, Boparai N, Price LL, Guyatt G. Cholestatic liver diseases and health-related quality of life. *Am J Gastroenterol.* 2000;95:497-502.

MELD Exception Guidelines for Candidates with Recurrent Bacterial Cholangitis associated with Structural Biliary Disease
Greg Gores M.D., Robert Gish M.D., and Roshan Shrestha M.D.

Background

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease. The disease is progressive, ultimately leading to biliary sclerosis (secondary biliary cirrhosis); with portal hypertension; hepatic dysfunction; and, occasionally to cholangiocarcinoma. Although the pathogenesis of PSC is unclear it is commonly associated with inflammatory bowel disease, especially chronic ulcerative colitis. Median survival is 12 years (1). Although unusual, occasional patients with PSC will have repeated episodes of bacterial cholangitis. There are other patients with congenital cystic dilatation of intrahepatic biliary ducts often associated with congenital hepatic fibrosis called Caroli's syndrome manifested by portal hypertension and repeated bouts of intrahepatic cholangitis. Occasional patients with secondary sclerosing cholangitis, due to surgical mishap or bile duct injury, have repeated episodes of bacterial cholangitis. The natural history of these disorders has not been established in the medical literature. Finally there are patients who have undergone liver transplant who, shortly after surgery, develop a cholestatic pattern, abnormal liver enzymes evidenced by severe ischemic type biliary tract injury with biliary sludge, casts, ectasia and repeated bouts of cholangitis and graft failure while the hepatic artery is completely open. The exact mechanism of this type of injury is not entirely clear, although there are some risk factors have been identified (marginal graft, prolonged cold ischemic time and others).

The diagnosis of PSC is generally made by combination of symptoms, abnormal laboratory results, histopathology on liver biopsy and radiologic findings on various biliary imaging studies. Severe and diffuse intrahepatic strictures indicate a rapid course with short survival, whereas high-grade extrahepatic strictures are associated with early symptoms of cholangitis with pruritus, right upper quadrant abdominal pain, and fever. Approximately 50% of symptomatic patients eventually develop cirrhosis and liver failure. There are no effective medical therapies to date for advanced liver disease caused by PSC. Liver transplantation is an excellent treatment for PSC and is one of the earliest historic indications in the United States (2;3).

Patients with severe intrahepatic cholestatic liver disease due to sclerosing cholangitis or Caroli's syndrome may carry a significant risk of recurrent cholangitis and sepsis leading to higher morbidity and mortality. Since these patients generally have fairly well-preserved synthetic function, current organ allocation policy using MELD score alone may not prioritize these selected groups of patients appropriately to avoid such poor outcome. Given the excellent result of liver transplantation, lack of medical therapies, exceptional status of certain patients with severe sclerosing cholangitis and Caroli's syndrome should be provided. Similarly the ischemic biliary injury in the graft under immunosuppression carries a significant morbidity and mortality and may benefit by exceptional status for a timely transplant. However, at present the precise natural history of these conditions has not been defined.

Synthesis of Available Data

There are insufficient objective data to justify additional priority for patients with cholangitis in the setting of structural biliary disease.

Suggested data for submission to regional review boards

Exceptional case applications that are submitted to review boards for MELD exceptions on the basis of cholangitis should include the following documentation: 1) precise diagnosis (PSC, Caroli's post-transplant, etc.) 2) number of hospitalizations within the past 6 months for cholangitis 3) number of episodes of severe sepsis secondary to cholangitis requiring ICU management 4) number of episodes of positive blood cultures in the absence of other sources and 5) results of positive bacterial cultures on antibiotics or demonstrating resistance to antibiotics..

Proposal for Standardized MELD Exceptions for Candidates with Cholangitis

At this time, we propose that recurrent cholangitis should continue to be addressed by the review board and additional priority assigned after the above described data has been submitted on a case by case basis. Additional priority should not be automatically granted at this time.

The data elements defined above should be collected prospectively through UNetSM for future re-evaluation of cholangitis as justification of additional MELD priority.

There are no data that permit extrapolation of this recommendation to pediatric patients.

Reference List

- (1) Wiesner RH, Grambsch PM, Dickson ER, Ludwig J, MacCarty RL, Hunter EB et al. Primary sclerosing cholangitis: natural history, prognostic factors and survival analysis. *Hepatology*. 1989;10:430-436.
- (2) Abu-Elmagd KM, Malinchoc M, Dickson ER, Fung JJ, Murtaugh PA, Langworthy AL et al. Efficacy of hepatic transplantation in patients with primary sclerosing cholangitis. *Surg Gynecol Obstet*. 1993;177:335-44.
- (3) Marsh JW, Jr., Iwatsuki S, Makowka L, Esquivel CO, Gordon RD, Todo S et al. Orthotopic liver transplantation for primary sclerosing cholangitis. *Ann Surg*. 1988;207:21-25.
- (4) Lucey MR, Brown KA, Everson GT, Fung JJ, Gish R, Keeffe EB et al. Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. *Liver Transpl Surg*. 1997;3:628-37.

MELD Exception Guidelines for Candidates with Portal Hypertensive GI Bleeding Patricia Sheiner, M.D., Robert Gish, M.D., and Arun Sunyal, M.D.

Background

Portal hypertensive bleeding of the gastrointestinal tract is a complication of end stage liver disease. Bleeding can be controlled endoscopically and pharmacologically in up to 90% of patients(1). Transjugular intrahepatic portal systemic shunt (TIPS), or less often, surgery, are alternative treatments for patients with recurrent/refractory variceal bleeding or bleeding from portal hypertensive gastropathy (PHG) who have contraindication to TIPS or bleed despite a patent TIPS may have a mortality rate of close to 100%, yet these clinical situations are hard to quantify for the purpose of organ distribution.

TIPS may be contraindicated in a number of patients with end stage liver disease. Despite its minimally invasive nature, TIPS have been associated with a 30-day mortality of up to 48% (2). Many authors have looked at various factors associated with a poor prognosis after TIPS. These include bilirubin, serum creatinine, Childs-Pugh score, and encephalopathy. The development of the Model for End-Stage Liver Disease (MELD) was based on predicting mortality with a TIPS shunt. This system has now been modified and applied to liver organ distribution in the United States(3). Using this MELD system and multivariate analysis, the inclusion of gastrointestinal bleeding did not improve on the ability of the MELD score to predict mortality(4).

Bilirubin has been shown to be a good predictor of mortality after TIPS by a number of investigators. Rajan et al. have shown that an “elevated pre-TIPS bilirubin level is a powerful independent predictor of 30-day mortality after TIPS creation” with a 40% increased risk of death for each 1-mg/dl increase above 3.0 mg/dl(5). Patients with a bilirubin of > 5 mg/dl had increased odds of early death by a factor of 19 times(6). Bilirubin features predominantly in several other studies as an indicator of early mortality after a TIPS procedure. Other authors also found bilirubin to be one of the major factors predictive of early post TIPS mortality (2;7). Bilirubin, in the absence of an elevated creatinine or INR, often does not result in a MELD score that would allow timely transplant. Given the highly predictive nature of a bilirubin of >5 mg/dl of death after TIPS makes it an objective, reasonable and conservative cut off for a medical contraindication to TIPS. Anatomical variants, such as portal vein thrombosis, must also be considered as relative or absolute contraindications for TIPS shunt.

Data on liver waiting list candidates who develop GI bleeding should be collected to determine if there is an objective surrogate for increased mortality that can guide the Review Board or a quantitative factor that can improve the prediction of mortality risk calculated by the current MELD score. It will be necessary to develop definitions that are clear and quantifiable. Refractory variceal bleeding can be defined as acute severe variceal bleed requiring airway intubation and the insertion of a Minnesota or Blakemore tube in spite of optimal endoscopic treatment, coagulation support and pharmacologic management. This definition should also include blood transfusions requiring more than 6 units in 24 hours or more than 2 units per day over 3 days and that a TIPS is contraindicated as defined above. Each patient should be reassessed daily.

Chronic recurrent variceal or PHG bleeding can be defined as the requirement of more than 2 units of blood transfusion per week for more than 6 weeks in a patient with a TIPS or if a TIPS contraindicated. This terminology could be further refined to include documentation that the bleeding is not responsive to endoscopic and pharmacologic treatment.

Synthesis of Available Data

There are sufficient data to justify additional priority for patients with portal hypertensive GI bleeding.

Suggested data for submission to regional review boards

The following information should be required of all exceptional case applications for candidates with refractory GI bleeding: 1) The precise reason for contraindication to TIPS 2) The presence or absence of portal vein thrombosis, 3) The total GI blood loss for the previous 4 weeks, 3 days and 24 hours 4) The presence or absence of gastric varices, 5) The use of mechanical balloon tamponade and 6) The history of endotracheal intubation to stabilize the patient to aid in the control GI bleeding.

Proposal for Standardized MELD Exceptions for Candidates with Portal Hypertensive GI Bleeding

At this time, due to the lack of a quantifiable, verifiable, and reproducible method of documenting a mortality risk directly related to intractable GI bleeding, we propose that refractory portal hypertensive GI bleeding should continue to be addressed by the review board and additional priority assigned after the above described data has been submitted on a case by case basis. Additional priority should not be automatically granted at this time.

The data elements described above should be collected prospectively through UNetSM for future reevaluation of portal hypertensive GI bleeding as justification of additional MELD priority.

There are no data that permit extrapolation of this recommendation to pediatric patients.

Reference List

- (1) Comar KM, Sanyal AJ. Portal Hypertensive Bleeding. 32 ed. 2003: 1079-105.
- (2) Tyburski JG, Noorily MJ, Wilson RF. Prognostic factors with the use of the transjugular intrahepatic portosystemic shunt for bleeding varices. Arch Surg. 1997;132:626-30.
- (3) Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33:464-70.
- (4) Chalasani N, Kahi C, Francois F, Pinto A, Marathe A, Bini EJ et al. Model for end-stage liver disease (MELD) for predicting mortality in patients with acute variceal bleeding. Hepatology. 2002;35:1282-84.
- (5) Rajan DK, Haskal ZJ, Clark TW. Serum bilirubin and early mortality after transjugular intrahepatic portosystemic shunts: results of a multivariate analysis. J Vasc Interv Radiol. 2002;13:155-61.
- (6) Russo MW, Sood A, Jacobson IM, Brown RS, Jr. Transjugular intrahepatic portosystemic shunt for refractory ascites: an analysis of the literature on efficacy, morbidity, and mortality. Am J Gastroenterol. 2003;98:2521-27.
- (7) Chalasani N, Clark WS, Martin LG, Kamean J, Khan MA, Patel NH et al. Determinants of mortality in patients with advanced cirrhosis after transjugular intrahepatic portosystemic shunting. Gastroenterology. 2000;118:138-44.

**MELD Exception Guidelines for Candidates with Small for Size Syndrome after Liver Transplantation
Patricia Sheiner, M.D., Robert Gish, M.D., and Charles Miller, M.D.**

Background

Small for size graft failure syndrome is a significant problem after live donor transplant(1;2). This syndrome may occur either because the graft-recipient ratio was less than expected resulting in a graft recipient/weight ratio of less than 0.8 % (3) or because of a functional graft overflow from either outflow obstruction or increased portal perfusion to the liver(4). Although preservation or re-implantation of tributaries of the middle hepatic vein may help decrease the incidence of the small for size syndrome, when it occurs it has major impact on survival(5).

Small for size graft failure syndrome is characterized by severe cholestasis, ascites and coagulopathy. Over time, many livers do recover, however, not all do. Early graft dysfunction predisposes the patients to sepsis. Sagawa et al. reported a significantly decreased survival in patients receiving grafts that had a graft weight/recipient ratio of less than 1% (80% survival vs. 96%)(5). Other authors have shown similar survival disadvantages in graft volume/recipient body weight ratio <0.8% with some programs reporting survival results of less than 50% in this group(3;6).

Recipients who have “small for size” grafts characterized by hyperbilirubinemia, increased INR and less than 3 months after transplant appear to have a short window in order to be safely retransplanted(2). There are very few objective criteria at which a liver becomes irreversibly damaged. However, because of the risk of sepsis and death, patients who meet criteria for small for size need to be transplanted urgently within a 6 week period of time. One of the major issues is to expedite a second liver transplant to prevent infection in these patients.

Synthesis of Available Data

There are sufficient data to justify additional priority for patients with small for size graft failure syndrome.

Proposal for Standardized MELD Exceptions for Candidates with Small for Size Graft Failure Syndrome

Candidates that develop small for size graft failure syndrome, defined as meeting 4 of the following 6 criteria, will receive will receive an initial MELD score equivalent to a 50% mortality risk. The MELD score will be increased by a 10% mortality equivalent every 3 months.

1. Greater than three weeks post living donor transplant:
2. Hyperbilirubinemia $\rightarrow \geq 10\text{mg/dl}$ in the absence of rejection or common duct obstruction;
3. Bile duct ischemia (leak);
4. INR ≥ 1.5 ;
5. Ascites;
6. Biopsy with centio-lobular ballooning, necrosis and cholestasis.

The data elements described above should be collected prospectively through UNetSM for future reevaluation of small for size as justification of additional MELD priority.

Reference List

- (1) Goldstein MJ, Salame E, Kapur S, Kinkhabwala M, LaPointe-Rudow D, Harren NPP et al. Analysis of failure in living donor liver transplantation: differential outcomes in children and adults. World J Surg. 2003;27:356-64.

- (2) SRTR Inferential Analytic Request Small for Size. UNOS , 60-64. 5-5-2005.
Electronic Citation
- (3) Chui AK, Rao AR, Island ER, Lau WY. Critical graft size and functional recovery in living donor liver transplantation. *Transplant Proc.* 2004;36:2277-78.
- (4) Tanaka K, Ogura Y. "Small-for-size graft" and "small-for-size syndrome" in living donor liver transplantation. *Yonsei Med J.* 2004;45:1089-94.
- (5) Lee S, Park K, Hwang S, Lee Y, Choi D, Kim K et al. Congestion of right liver graft in living donor liver transplantation. *Transplantation.* 2001;71:812-14.
- (6) Kiuchi T, Kasahara M, Uryuhara K, Inomata Y, Uemoto S, Asonuma K et al. Impact of graft size mismatching on graft prognosis in liver transplantation from living donors. *Transplantation.* 1999;67:321-27.

MELD Exception Guidelines Candidates with Uncommon Hepatic Tumors **Jeffrey Punch, M.D., and Robert Gish, M.D.**

Background

Non-carcinoid neuroendocrine tumors

Hepatic metastases are present in approximately 75% of patients at the time a neuroendocrine tumor is diagnosed. Cure by transplantation appears to be rare, if it ever happens. It appears that the outcome for non-carcinoid tumors is inferior to the experience with patients that have carcinoid tumors limited to the liver(1). The largest series of patients with non-carcinoid patients from the French multi-center experience reports a survival rate of only 38%, 15%, and 8% at 1, 3, and 4 years, respectively with no disease free survivors at five years(1). Reports since then have failed to document an improvement in this outcome. Even in the absence of long term cure, liver transplantation probably offers substantial palliative benefit to selected patients. Nevertheless, given the dismal outcomes overall, it does not appear wise to offer liver transplantation to these patients as a standard MELD exception.

Carcinoid tumors

In the French experience, the survival rate for metastatic carcinoid tumors was 80%, 80%, and 69% at 1, 3, and 5 years, respectively(1). In comparison, the 5-year survival rate after non transplant treatment of NET ranges from 25 to 35%. This comparison is unfair for multiple reasons pertaining to selection bias, but it does suggest that selected patients with this disease may benefit from liver transplantation.

Patients should be excluded if they have evidence of extrahepatic tumor deposits, as these patients cannot be cured by liver transplantation. Ideally the primary tumor should have been removed, as tumor recurrence following upper abdominal exenteration is associated with high morbidity and has not been shown to improve tumor free survival. A bone scan and/or survey is important as the next most frequent site of distant metastasis after the liver is bone. It is suggested that transplantation should be considered when patients are symptomatic and have failed other available treatments after presentation to the Review Board.

Sarcoma

Although there are anecdotal cases of patients with long term survival following transplantation for primary angiosarcoma of the liver, the preponderance of the data indicates that cure is not possible and that results indicate very poor survival (2). These patients should not receive additional priority for liver transplants as a standard MELD exception.

Hepatic epithelioid hemangioendothelioma

These tumors arise from vascular endothelium. Patients are predominantly young adults, particularly females. The extent of the tumor is difficult to define radiologically. Diagnosis is confirmed by positive immunohistochemical staining for factor VIII. In the first year of the MELD/PELD policy 16 requests were made for MELD exceptions based on this diagnosis, 14 were granted.

Treatment can include observation alone, chemotherapy, resection, or transplantation, with long term survival reported with each treatment option. The results for liver transplantation are quite good despite the fact that the tumor is often widespread at the time of diagnosis. Five year tumor free survival rates of 60% are reported(3). Successful treatment of patients with extra-hepatic disease has been described, and metastatic spread at the time of transplant does not appear to correlate with post-transplant survival(4-6). Therefore, this tumor is one of the circumstances where transplantation in the presence of extra-hepatic disease may be justified. The highly variable clinical behavior makes it impossible to provide objective data on when transplant should be performed and how long the window of opportunity for transplantation is. Current opinion is that treatment should be individualized depending on symptoms, and the rate of disease progression.

Biliary Cystadenocarcinoma

This tumor must be distinguished from benign biliary cystadenoma. It can arise in association with Caroli's disease. It is usually multilocular, but unilocular cases have been reported. Generally this tumor is amenable to surgical resection. There are anecdotal cases of successful liver transplantation for this tumor. Long term follow-up is not available for patients that received transplants for this indication (2).

Hepatic adenoma in patients with glycogen storage disease (GSD)

Multiple hepatic adenomas are seen in approximately half of patients with Type I GSD, and in approximately one quarter of patients with Type III GSD. Rupture and malignant transformation of these tumors have both been reported, but the risk of these complications is unclear (7). Determining when malignant transformation has occurred can be problematic, making management of these patients difficult. Transplantation is indicated when malignant transformation is suspected or proven, and curative resection is not possible.

Synthesis of Available Data

There are insufficient data to justify additional priority for candidates with non-carcinoid neuroendocrine tumors, for hepatic sarcomas, or for biliary cystadenocarcinoma.

The available data justify additional priority for candidates with Carcinoid tumors that are limited to the liver, for hepatic epithelioid hemangioendotheliomas, and for candidates with hepatic adenomas in the setting of glycogen storage disease.

Proposal for Standardized MELD Exceptions for Candidates with Uncommon Tumors

At this time, we propose that candidates with uncommon tumors should continue to be addressed by the review board and additional MELD priority assigned on a case by case basis. Additional MELD priority should not be automatically granted at this time.

Reference List

- (1) Le Treut YP, Delpero JR, Dousset B, Cherqui D, Segol P, Manton G et al. Results of liver transplantation in the treatment of metastatic neuroendocrine tumors. A 31-case French multicentric report. *Ann Surg.* 1997;225:355-64.
- (2) O'Grady JG. Treatment options for other hepatic malignancies. *Liver Transpl.* 2000;6:S23-S29.
- (3) Madariaga JR, Marino IR, Karavias DD, Nalesnik MA, Doyle HR, Iwatsuki S et al. Long-term results after liver transplantation for primary hepatic epithelioid hemangioendothelioma. *Ann Surg Oncol.* 1995;2:483-87.
- (4) Makhoul HR, Ishak KG, Goodman ZD. Epithelioid hemangioendothelioma of the liver: a clinicopathologic study of 137 cases. *Cancer.* 1999;85:562-82.
- (5) Penn I. Hepatic transplantation for primary and metastatic cancers of the liver. *Surgery.* 1991;110:726-34; discussion 734-5.
- (6) Kayler LK, Merion RM, Arenas JD, Magee JC, Campbell DA, Rudich SM et al. Epithelioid hemangioendothelioma of the liver disseminated to the peritoneum treated with liver transplantation and interferon alpha-2B. *Transplantation.* 2002;74:128-30.
- (7) Labrune P, Trioche P, Duvaltier I, Chevalier P, Odievre M. Hepatocellular adenomas in glycogen storage disease type I and III: a series of 43 patients and review of the literature. *Journal of Pediatric Gastroenterology & Nutrition.* 1997;24(3):276-9.

Guidelines for MELD Score Upgrading in Candidates with Unusual Metabolic Liver Diseases That Would be Cured by Liver Transplantation
Sue McDiarmid M.D., Robert Gish, M.D., and Simon Horslen, M.D.

Metabolic liver disease makes up a small proportion of patients who undergo liver transplantation. For these patients liver transplantation is life-saving. These patients often do not present with typical findings of end stage liver disease and need to undergo special consideration and scrutiny concerning the appropriateness of liver transplantation and timing of transplantation.

Tyrosinemia type 1 (fumarylacetoacetate hydrolase deficiency) is a rare condition that results in fulminant liver disease, liver cancer and progressive liver failure. Standard treatment is now with NTBC [2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexenedione] and low tyrosine diet. Potential indications for liver transplantation include fulminant disease in infants, progression of liver disease on NTBC, presence or suspicion of HCC and possibly contraindications to the use of NTBC. Orthotopic liver transplantation corrects the metabolic liver disease and removes the risk for HCC. Renal dysfunction in later childhood or adulthood may develop. In most circumstances a PELD/MELD exception request is appropriate and each case should be individually reviewed with advice from a physician experienced in the care of patients with tyrosinemia(1-5)

Glycogen storage disease has at least 14 variants and subclassifications. Type 1 (1a Glucose-6-phosphatase deficiency and 1b Glucose-6-phosphate translocase deficiency) may result in metabolic instability or adenoma/HCC and is cured by liver transplantation. Type 3 debrancher enzyme deficiency can lead to cirrhosis in adult patients with and there is an increased risk for adenoma and HCC. OLT is an effective therapy for the liver disease. Currently, there are no data on which to base exception scores. Type 4 brancher enzyme deficiency can also result in cirrhosis in young children; for this case PELD scores currently probably reflect severity of liver disease and there are no data or supporting evidence to give additional PELD priority for these patients. If HCC or adenomas with malignant potential develop in these patients, standard HCC listing criteria can apply or an appeal to the review board can take place (6-14).

For alpha-1 antitrypsin deficiency without evidence of chronic liver disease there is no indication for additional MELD/PELD priority. Only one case has undergone OLT for COACH syndrome with portal hypertension due to hepatic fibrosis with concomitant CNS diseases. These patients can have severe cholestasis in addition to hepatic fibrosis but prognosis mostly determined by other features of syndrome. There are no data on which to advise review board to give additional PELD priority(15)

For Crigler-Najjar type 1, there is clear proven effectiveness of OLT for this condition. Since there is no coagulopathy, growth failure, hypoalbuminemia and the patients unconjugated bilirubin is reduced by phototherapy the patients, PELD score cannot be calculated thus exception scores score for OLT will be required. The 90-day death rate is probably negligible, but serious potential for brain injury is the major indication for liver replacement therapy. Currently there are no data to determine additional MELD/PELD priority, and the review board must discuss each case on an individual basis(16-19).

Hemophilias are genetic diseases associated with specific factor deficiencies. These include: Factor VIII deficiency – hemophilia A, Factor IX deficiency – hemophilia B, and Factor VII deficiency. Liver transplantation is an effective therapy but in general transplantation is reserved for other indications such as viral hepatitis with the development of end stage liver disease. These diseases, alone, are not considered indications for LT(3;20-22).

Methylmalonic academia has serious impact on renal and neurological function. Liver transplantation corrects the episodes of systemic metabolic decompensation complicating this disease. Unfortunately, renal and neurological complications of MMA have occurred late even after successful OLT. These patients must fulfill criteria for metabolic conditions associated with hyperammonemia to can be listed at Status 1B, thus no additional priority should be assigned through the review board(23-27).

Propionic academia results in a variety of metabolic problems for infants and children. Liver transplantation corrects episodes of systemic metabolic decompensation associated with this disease. These patients must fulfill criteria for metabolic conditions associated with hyperammonemia so they can be listed at Status 1B, thus no additional priority should be assigned through the regional review board(28).

Maple syrup urine disease results in multiorgan injury. Liver transplantation corrects these episodes of systemic metabolic decompensation associated with this metabolic disease. This condition is not associated with hyperammonemia as a rule. There is no liver dysfunction, therefore the calculated PELD score is not reflective of the patient's severity. Each case should be reviewed by the Review Board, with the help of a metabolic expert, and additional priority should be applied depending on the severity of the disease(29-31).

Homozygous familial hypercholesterolemia leads to childhood coronary artery disease and myocardial infarction. There is no structural liver disease the PELD score is not reflective of the patient's severity. There are no data to determine priority for a PELD score to assign for these patients and each case should be reviewed by the review board(32).

Biliary transport defects include: Byler's disease (progressive familial intrahepatic cholestasis type 1 - PFIC 1), Bile salt export protein deficiency (BSEP, PFIC 2), MDR3 deficiency (PFIC 3), These conditions have associated liver disease and the calculated PELD score is probably valid. Exceptions can be sought for the profound pruritus associated, and PELD exceptions should only be considered if there is clear evidence that the pruritus is impairing development and schooling. Each case should be considered with the aid of a metabolic expert and the input of the Review Board(33-36).

Other known metabolic diseases that may benefit from liver transplantation include:

1. Mitochondrial metabolic defects confined to the liver are very variable conditions(37-41): Each case will need to be individually assessed with the aid of metabolic experts and the Review Board;
2. Neonatal hemochromatosis which almost always fulfill criteria for fulminant hepatic failure(42-44);
3. Erythropoietic protoporphyria: liver transplantation is typically undertaken for acute liver failure or rapidly progressing chronic liver failure. Importantly in this disease, liver disease can recur in the allograft and no data on priority of listing is available(45-47);
4. Niemann-Pick type C, which can in a minority of patients present with severe neonatal hepatitis. Liver transplantation cures the liver disease but does nothing for late childhood dementia. Usual onset is 10-15 years of age, but timing of presentation may be very variable. The calculated PELD score probably reflects severity of liver disease and no additional PELD or MELD priority is advised (28;48;49);
5. Disorders of fatty acid metabolism which are mostly managed medically. Each case should be discussed individually with the review board(28);
6. Neonatal adrenal leukodystrophy, which is a peroxisomal biogenesis defect and as such is associated with significant neurodevelopmental concerns. There are no data that this is an indication for liver transplantation. No extra priority is advised for this condition(28),
7. Cholesterol ester storage disease results in cirrhosis and end-stage liver disease, thus the calculated MELD/PELD score will suffice(28),;
8. Protein C and/or S deficiency are genetic deficiencies of coagulation factors. Liver transplantation corrects hypercoagulable state, but transplantation usually undertaken for other indications(50-53);
9. Arginase deficiency is a urea cycle disorder that does not produce hyperammonemia. This disease is correctable with OLT but most managed medically. There are no data on this disease as an indication for transplant(54).

Reference List

- (1) Freese DK, Tuchman M, Schwarzenberg SJ, Sharp HL, Rank JM, Bloomer JR et al. Early liver transplantation is indicated for tyrosinemia type I. *J Pediatr Gastroenterol Nutr.* 1991;13:10-15.
- (2) Gordon RD, Shaw BW, Jr., Iwatsuki S, Esquivel CO, Starzl TE. Indications for liver transplantation in the cyclosporine era. *Surg Clin North Am.* 1986;66:541-56.
- (3) Kayler LK, Merion RM, Lee S, Sung RS, Punch JD, Rudich SM et al. Long-term survival after liver transplantation in children with metabolic disorders. *Pediatr Transplant.* 2002;6:295-300.

- (4) Manowski Z, Silver MM, Roberts EA, Superina RA, Phillips MJ. Liver cell dysplasia and early liver transplantation in hereditary tyrosinemia. *Mod Pathol.* 1990;3:694-701.
- (5) Murcia FJ, Vazquez J, Gamez M, Lopez SM, De l, V, Diaz MC et al. Liver transplantation in type I tyrosinemia. *Transplant Proc.* 1995;27:2301-2.
- (6) Lerut JP, Ciccarelli O, Sempoux C, Danse E, Deflandre J, Horsmans Y et al. Glycogenesis storage type I diseases and evolutive adenomatosis: an indication for liver transplantation. *Transpl Int.* 2003.
- (7) Labrune P. Glycogen storage disease type I: indications for liver and/or kidney transplantation. *Eur J Pediatr.* 2002;161 Suppl 1:S53-S55.
- (8) Moses SW, Parvari R. The variable presentations of glycogen storage disease type IV: a review of clinical, enzymatic and molecular studies. *Curr Mol Med.* 2002;2:177-88.
- (9) Martinez-Olmos MA, Lopez-Sanroman A, Martin-Vaquero P, Molina-Perez E, Barcena R, Vicente E et al. Liver transplantation for type Ib glycogenesis with reversal of cyclic neutropenia. *Clin Nutr.* 2001;20:375-77.
- (10) Faivre L, Houssin D, Valayer J, Brouard J, Hadchouel M, Bernard O. Long-term outcome of liver transplantation in patients with glycogen storage disease type Ia. *J Inher Metab Dis.* 1999;22:723-32.
- (11) Matern D, Starzl TE, Arnaout W, Barnard J, Bynon JS, Dhawan A et al. Liver transplantation for glycogen storage disease types I, III, and IV. *Eur J Pediatr.* 1999;158 Suppl 2:S43-S48.
- (12) Lachaux A, Boillot O, Stamm D, Canterino I, Regnier F, Regragui K et al. Orthotopic liver transplantation for glycogen storage disease type Ib--treatment with recombinant human granulocyte colony-stimulating factor. *Transplant Proc.* 1994;26:265.
- (13) Selby R, Starzl TE, Yunis E, Todo S, Tzakis AG, Brown BI et al. Liver transplantation for type I and type IV glycogen storage disease. *Eur J Pediatr.* 1993;152 Suppl 1:S71-S76.
- (14) Mowat AP. Orthotopic liver transplantation in liver-based metabolic disorders. *Eur J Pediatr.* 1992;151 Suppl 1:S32-S38.
- (15) Herzog D, Martin S, Yandza T, Alvarez F. Hepatic insufficiency and liver transplantation in a patient with COACH syndrome. *Pediatr Transplant.* 2002;6:443-46.
- (16) Schauer R, Stangl M, Lang T, Zimmermann A, Chouker A, Gerbes AL et al. Treatment of Crigler-Najjar type 1 disease: relevance of early liver transplantation. *J Pediatr Surg.* 2003;38:1227-31.
- (17) Kayler LK, Merion RM, Lee S, Sung RS, Punch JD, Rudich SM et al. Long-term survival after liver transplantation in children with metabolic disorders. *Pediatr Transplant.* 2002;6:295-300.
- (18) Al Shurafa HA, Bassas AF, Broering DC, Rogiers XG, Wali SH, Burdelski MM. Management of Crigler-Najjar Syndrome type I. *Saudi Med J.* 2001;22:486-89.
- (19) Gridelli B, Lucianetti A, Gatti S, Colledan M, Benti R, Bruno A et al. Orthotopic liver transplantation for Crigler-Najjar type I syndrome. *Transplant Proc.* 1997;29:440-441.
- (20) Punch JD, Merion RM, Turcotte JG. Hemophilia. *N Engl J Med.* 2001;345:1066-67.
- (21) Fung CH, Lo JW. Treatment for hemophilia: gene therapy vs transplantation. *JAMA.* 1994;271:1575-76.

- (22) Delorme MA, Adams PC, Grant D, Ghent CN, Walker IR, Wall WJ. Orthotopic liver transplantation in a patient with combined hemophilia A and B. *Am J Hematol.* 1990;33:136-38.
- (23) Hsui JY, Chien YH, Chu SY, Lu FL, Chen HL, Ho MJ et al. Living-related liver transplantation for methylmalonic acidemia: report of one case. *Acta Paediatr Taiwan.* 2003;44:171-73.
- (24) Nyhan WL, Gargus JJ, Boyle K, Selby R, Koch R. Progressive neurologic disability in methylmalonic acidemia despite transplantation of the liver. *Eur J Pediatr.* 2002;161:377-79.
- (25) Van't Hoff W, McKiernan PJ, Surtees RA, Leonard JV. Liver transplantation for methylmalonic acidemia. *Eur J Pediatr.* 1999;158 Suppl 2:S70-S74.
- (26) Van't Hoff WG, Dixon M, Taylor J, Mistry P, Rolles K, Rees L et al. Combined liver-kidney transplantation in methylmalonic acidemia. *J Pediatr.* 1998;132:1043-44.
- (27) Leonard JV. The management and outcome of propionic and methylmalonic acidemia. *J Inher Metab Dis.* 1995;18:430-434.
- (28) Groth CG, Ringden O. Transplantation in relation to the treatment of inherited disease. *Transplantation.* 1984;38:319-27.
- (29) Jan D, Poggi F, Laurent J, Rabier D, Jouvet P, Lacaille F et al. Liver transplantation: new indications in metabolic disorders? *Transplant Proc.* 1994;26:189-90.
- (30) Netter JC, Cossarizza G, Narcy C, Hubert P, Ogier H, Revillon Y et al. [Mid-term outcome of 2 cases with maple syrup urine disease: role of liver transplantation in the treatment]. *Arch Pediatr.* 1994;1:730-734.
- (31) Wendel U, Saudubray JM, Bodner A, Schadewaldt P. Liver transplantation in maple syrup urine disease. *Eur J Pediatr.* 1999;158 Suppl 2:S60-S64.
- (32) Alkofer BJ, Chiche L, Khayat A, Deshayes JP, Lepage A, Saloux E et al. Liver transplant combined with heart transplant in severe heterozygous hypercholesterolemia: report of the first case and review of the literature. *Transplant Proc.* 2005;37:2250-2252.
- (33) Bassas A, Chehab M, Heby H, Al Shahed M, Al Hussein H, Al Zahrani A et al. Living related liver transplantation in 13 cases of progressive familial intrahepatic cholestasis. *Transplant Proc.* 2003;35:3003-5.
- (34) Cohran VC, Heubi JE. Treatment of Pediatric Cholestatic Liver Disease. *Curr Treat Options Gastroenterol.* 2003;6:403-15.
- (35) Kalicinski PJ, Ismail H, Jankowska I, Kaminski A, Pawlowska J, Drewniak T et al. Surgical treatment of progressive familial intrahepatic cholestasis: comparison of partial external biliary diversion and ileal bypass. *Eur J Pediatr Surg.* 2003;13:307-11.
- (36) Cavestro GM, Frulloni L, Cerati E, Ribeiro LA, Corrente V, Sianesi M et al. Progressive familial intrahepatic cholestasis. *Acta Biomed Ateneo Parmense.* 2002;73:53-56.
- (37) Tamamori A, Okano Y, Ozaki H, Fujimoto A, Kajiwara M, Fukuda K et al. Neonatal intrahepatic cholestasis caused by citrin deficiency: severe hepatic dysfunction in an infant requiring liver transplantation. *Eur J Pediatr.* 2002;161:609-13.
- (38) Delarue A, Paut O, Guys JM, Montfort MF, Lethel V, Roquelaure B et al. Inappropriate liver transplantation in a child with Alpers-Huttenlocher syndrome misdiagnosed as valproate-induced acute liver failure. *Pediatr Transplant.* 2000;4:67-71.

- (39) Ducluzeau PH, Lachaux A, Bouvier R, Streichenberger N, Stepien G, Mousson B. Depletion of mitochondrial DNA associated with infantile cholestasis and progressive liver fibrosis. *J Hepatol.* 1999;30:149-55.
- (40) Sokal EM, Sokol R, Cormier V, Lacaille F, Mckiernan P, van Spronsen FJ et al. Liver transplantation in mitochondrial respiratory chain disorders. *Eur J Pediatr.* 1999;158 Suppl 2:S81-S84.
- (41) Sokol RJ, Treem WR. Mitochondria and childhood liver diseases. *J Pediatr Gastroenterol Nutr.* 1999;28:4-16.
- (42) Flynn DM, Mohan N, Mckiernan P, Beath S, Buckels J, Mayer D et al. Progress in treatment and outcome for children with neonatal haemochromatosis. *Arch Dis Child Fetal Neonatal Ed.* 2003;88:F124-F127.
- (43) Durand P, Debray D, Mandel R, Baujard C, Branchereau S, Gauthier F et al. Acute liver failure in infancy: a 14-year experience of a pediatric liver transplantation center. *J Pediatr.* 2001;139:871-76.
- (44) Murray KF, Kowdley KV. Neonatal hemochromatosis. *Pediatrics.* 2001;108:960-964.
- (45) Bonkovsky HL, Barnard GF. The Porphyrrias. *Curr Treat Options Gastroenterol.* 2000;3:487-500.
- (46) Kauppinen R, Timonen K, Mustajoki P. Treatment of the porphyrias. *Ann Med.* 1994;26:31-38.
- (47) Herbert A, Corbin D, Williams A, Thompson D, Buckels J, Elias E. Erythropoietic protoporphyria: unusual skin and neurological problems after liver transplantation. *Gastroenterology.* 1991;100:1753-57.
- (48) Yerushalmi B, Sokol RJ, Narkewicz MR, Smith D, Ashmead JW, Wenger DA. Niemann-pick disease type C in neonatal cholestasis at a North American Center. *J Pediatr Gastroenterol Nutr.* 2002;35:44-50.
- (49) Smanik EJ, Tavill AS, Jacobs GH, Schafer IA, Farquhar L, Weber FL, Jr. et al. Orthotopic liver transplantation in two adults with Niemann-Pick and Gaucher's diseases: implications for the treatment of inherited metabolic disease. *Hepatology.* 1993;17:42-49.
- (50) Angelis M, Pegelow CH, Khan FA, Verzaro R, Tzakis AG. En bloc heterotopic auxiliary liver and bilateral renal transplant in a patient with homozygous protein C deficiency. *J Pediatr.* 2001;138:120-122.
- (51) Pescatore SL. Clinical management of protein C deficiency. *Expert Opin Pharmacother.* 2001;2:431-39.
- (52) Schuetze SM, Linenberger M. Acquired protein S deficiency with multiple thrombotic complications after orthotopic liver transplant. *Transplantation.* 1999;67:1366-69.
- (53) Marlar RA, Montgomery RR, Broekmans AW. Diagnosis and treatment of homozygous protein C deficiency. Report of the Working Party on Homozygous Protein C Deficiency of the Subcommittee on Protein C and Protein S, International Committee on Thrombosis and Haemostasis. *J Pediatr.* 1989;114:528-34.
- (54) Santos SE, Martins E, Cardoso ML, Barbot C, Vilarinho L, Medina M. Liver transplantation in a case of argininaemia. *J Inherit Metab Dis.* 2001;24:885-87.

