Selection and Evaluation for Transplantation

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Disclosures:

Advisory Board: Mallinckrodt Pharmaceuticals
We have some material to cover in the next 20 minutes

MELD/PELD scoring systems
MELD/PELD exceptions
Multi-organ candidates
Co-morbidities
Impact of active infection, malignancy and malnutrition
Psychosocial issues

§ 121.8 of the Final Rule states that allocation policy should be based on “objective and measurable medical criteria, for patients or categories of patients who are medically suitable candidates for transplantation to receive transplants”

Patients should be rank ordered from most to least medically urgent on the waiting list
Adult candidate assignments

- Adult status 1A
- Calculated MELD-Na score
- Exception MELD score
- Inactive status

Pediatric candidate assignments

- Pediatric status 1A
- Pediatric status 1B
- Calculated MELD/PELD score
- Exception MELD/PELD score
- Inactive status
Adult status 1A requirements (1)

1. Fulminant liver failure in ICU, no pre-existing liver disease
   • HE within 56 days of onset AND one of:
     • Ventilator dependent or
     • On HD, CVVH, CVVHD or
     • INR > 2.0

2. Anhepatic

3. Primary non-function of allograft within 7d of txp
   • AST ≥ 3000 IU/L AND one of:
     • INR > 2.5
     • Arterial pH ≤ 7.3
     • Venous pH ≤ 7.25
     • Lactate ≥ 4 mmol/L

OPTN Policy 9, effective 5/21/20
Adult status 1A requirements (2)

4. HAT within 7 days of txp
   - AST > 3000 IU/L AND one of the following:
     - INR ≥ 2.5
     - Arterial pH ≤ 7.30
     - Venous pH ≤ 7.25
     - Lactate ≥ 4 mmol/L

5. Acute decompensated Wilson disease

Pediatric status 1A requirements (1)

1. Fulminant liver failure, no pre-existing liver disease
   - HE within 56 days of onset AND one of:
     - Ventilator dependent or
     - On HD, CVVH, CVVHD or
     - INR > 2.0

2. Primary non-function of allograft within 7 d of txp
   - AST ≥ 2000 IU/L AND one of:
     - INR ≥ 2.5
     - Arterial pH ≤ 7.3
     - Venous pH ≤ 7.25
     - Lactate ≥ 4 mmol/L
Pediatric status 1A requirements (2)

3. HAT within 14 days of txp
4. Acute decompensated Wilson disease

Pediatric status 1B requirements (1)

1. Hepatoblastoma without metastatic disease
2. Organic acidemia or urea cycle defect and has had an approved PELD exception for metabolic disease for > 30 days
3. Chronic liver disease with calculated MELD/PELD of greater than 25 AND one of:
   • Mechanical ventilation
   • GI bleeding with >30 mL/kg RBC transfusion in 24 hours
   • HD, CVVH, or CVVHD
   • Glasgow coma score of < 10, 48 hours prior to status 1B assignment
MELD and MELD-Na

- MELD = \(0.957 \times \log_e(Cr \text{ mg/dL}) + 0.378 \times \log_e(bili \text{ mg/dL}) + 1.120 \times \log_e(INR) + 0.643\)

- Cr set to 4 mg/dL when:
  - \(Cr > 4.0 \text{ mg/dL}\)
  - Two or more dialysis treatments in last 7 days
  - 24 hours of CVVHD in last 7 days

- MELD still used for candidates with MELD<11

6 Month wait list mortality as a function of serum sodium

Biggins SW et al, Gastroenterology 2006;130:1652-1660
MELD-Na

- Used for allocation if MELD $\geq 12$
- $\text{MELD-Na} = \text{MELD}_{(i)} + 1.32 (137-\text{Na}) - [0.033\times\text{MELD}_{(i)}\times(137-\text{Na})]$ 
- Sodium values less than 125 mmol/L are adjusted to 125 mmol/L

PELD score

- Used for candidates <12 years old
- $\text{PELD} = 0.436(\text{if age} < 1 \text{ yr}) - 0.687\times\log_e(\text{albumin g/dL}) + 0.480\times\log_e(\text{bili mg/dL}) + 1.857\times\log_e(\text{INR}) + 0.667(\text{growth failure})$
- Growth failure=2 standard deviations below expected growth for age and gender
Major changes to MELD exceptions effective 2019

- No longer a q 3 month MELD escalator
- MELD scores provided for standard exceptions are based on Median MELD at Transplant (MMaT)
- MMaT is calculated for geographic areas every 180 days
- Most adult exception scores are MMaT-3

Standard MELD exceptions (1)

- HAT < 14 days MELD=40, if not Status 1
- Primary hyperoxaluria= MMaT (SLK, biopsy or mutation proven, GFR<25mL/min by MDRD6)
  - 3 month escalator
- HCC= MMaT - 3 6 months after listing
- CCA=MMaT - 3
- FAP= (EF > 40%, ambulatory, identified mutation and biopsy proven)
  - MMaT - 3
Standard MELD exceptions (2)

- Cystic fibrosis = MMaT - 3 (FEV1 < 40%)
- HPS = MMaT – 3 (Evidence of shunt, PaO₂ < 60 mmHg, no underlying primary lung disease, clinical evidence of portal hypertension)
- PPH = MMaT – 3 (Post-treatment MPAP < 35 mmHg, Post-treatment PVR < 400 dynes/sec/cm⁻²)

Non-standard MELD/PELD exceptions

- Must go to National Liver Review Board
- Request a specific MELD/PELD score
- Justify why request is appropriate for score requested
- Majority vote of NLRB voters
Guidance to Liver Transplant Programs and the National Liver Review Board for:
Adult MELD Exception Review

https://optn.transplant.hrsa.gov/media/2847/liver_guidance_adult_meld_201706.pdf

- Ascites ................................................................. 3
- Budd Chiari .......................................................... 3
- Gastrointestinal Bleeding ....................................... 4
- Hepatic Encephalopathy ......................................... 4
- Hepatic Epithelioid Hemangioendothelioma .................. 5
- Hepatic Hydrothorax ................................................ 5
- Hereditary Hemorrhagic Telangietasia ......................... 6
- Multiple Hepatic Adenomas ...................................... 7
- Neuroendocrine Tumors (NET) ................................... 7
- Polycystic Liver Disease (PLD) .................................. 8
- Portopulmonary Hypertension ................................. 9
- Primary Sclerosing Cholangitis .................................. 10
- Post-Transplant Complications ................................. 10
  - Small for Size Syndrome ...................................... 10
  - Chronic Rejection .............................................. 10
  - Diffuse Ischemic Cholangiopathy ......................... 11
  - Late Vascular Complications .............................. 11
  - Pruritus ......................................................... 12
Standard pediatric MELD/PELD exceptions (1)

- HAT < 14 days MELD=40, if not Status 1
- Primary hyperoxaluria= MMat + 3 points at listing (SLK, biopsy or mutation proven, GFR<25mL/min by MDRD6)
- Urea cycle disorder or organic acidemia- MMaT
  - If no txp in 30 days, can go to Status 1B
- HCC=score of 40 points immediately
  - 3 month escalator, capped at 34
- CCA= MMaT
  - 3 month escalator

Standard pediatric MELD/PELD exceptions (2)

- CF= MMaT/MPaT
- HPS=MMaT/MPaT
- PPH=MMaT/MPaT
National Liver Review Board

- Implemented May 2019
- National anonymous review panels with waitlist mortality based guidance
- Expected to reduce non-standard exceptions
- Expected to eliminate regional variability in award of exceptions
- Each center may have two reviewers for adult non-HCC, pediatrics, and HCC boards

Simultaneous liver/kidney transplantation

- New policy in effect in August 2017 radically changed transplant options
- No real restriction on combined txp previously
- Rigorous rules in place now
- Safety net for recipients who do not undergo renal recovery after OLT
Simultaneous adult liver/kidney allocation requirements

<table>
<thead>
<tr>
<th>Diagnosis to qualify</th>
<th>Subsequent documentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic kidney disease&lt;br&gt;GFR &lt; 60 mL/min &gt; 90 consecutive days</td>
<td>Must have one of:&lt;br&gt;- Initiated regularly scheduled RRT&lt;br&gt;- GFR ≤ 30 mL/min&lt;br&gt; at time of registration for KT or after registration for KT</td>
</tr>
<tr>
<td>Sustained acute kidney injury&lt;br&gt;No pre-existing GFR requirement</td>
<td>Must have one, or combination of both, for at least 6 weeks:&lt;br&gt;- On dialysis at least once a week every 7 d&lt;br&gt;- Calculated CrCl or GFR of less than 25 mL/min every 7 d</td>
</tr>
<tr>
<td>Metabolic disease</td>
<td>Hyperoxaluria&lt;br&gt;Atypical hemolytic uremic syndrome</td>
</tr>
</tbody>
</table>

OPTN Policy 9.7.B

Other liver/SOT combinations

- No restrictions on simultaneous allocation
- Lung/liver transplantation
  - 2019-12 cases performed in US (largely CF)
- Heart liver transplantation
  - 2017-45 cases performed in the US (increasing, with more decompensated CHD with cirrhosis)
- All others liver combinations except liver intestine very rare
Comorbidities

- HIV
- Heart disease
- Pulmonary disease/tobacco abuse
- Skin malignancy
- Non-hepatic malignancy
- Frailty/sarcopenia
- Psychosocial support

HIV and liver transplantation

- Inclusion criteria:
  - CD4 count > 100 cells/μL without hx of OI
  - CD4 count > 200 cells/μL with prior resolved OI
  - Undetectable HIV viral load OR
    - Expectation of undetectable HIV viral load after txp
  - Documented compliance with ART regimen
  - Absence of chronic wasting/malnutrition

- HOPE Act permits HIV + organs into HIV + recipients at qualified centers

HIV and liver transplantation


Predictors of outcome in HIV liver transplant

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual Kidney-Liver</td>
<td>5.5 (1.8, 16.9)</td>
<td>0.003</td>
</tr>
<tr>
<td>HCV+ Donor</td>
<td>4.5 (1.8, 11.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI at Listing &lt;21</td>
<td>2.7 (1.0, 7.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>Treated Acute Rejection</td>
<td>2.9 (1.2, 7.0)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Solid Organ Transplantation in HIV: Multi-Site Study (Al052748)
Cardiovascular testing

- Echocardiogram with bubble study
  - Assess RV and LV function
  - r/o HPS
  - r/o pulmonary HTN (beware RVSP > 35 mmHg)

- EKG
  - Assess for long QT, dysrhythmia

- Pharmacologic stress testing
  - Largest data for dobutamine stress echo

- Cath as indicated by above (RHC or LHC, radial approach preferred in setting of coagulopathy)

Consensus recommendations for cardiac disease assessment

<table>
<thead>
<tr>
<th>Cardiac or pulmonary vascular condition</th>
<th>Absolute contraindications</th>
<th>Relative contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease</td>
<td>Nonrevascularized obstructive severe multivessel CAD</td>
<td>Nonrevascularized obstructive moderate CAD not involving left main or proximal LAD coronary arteries</td>
</tr>
<tr>
<td>Cardiomyopathy and heart failure</td>
<td>Left ventricular ejection fraction &lt;40% Moderate to severe right heart failure</td>
<td>Left ventricular ejection fraction &lt;50% Hypertrophic cardiomyopathy with resting left ventricular outflow tract obstruction</td>
</tr>
<tr>
<td>Poro-pulmonary hypertension</td>
<td>Severe pulmonary hypertension associated with right heart failure and/or not responsive to medical therapies</td>
<td>Moderate pulmonary hypertension with preserved right ventricular function not responsive to medical therapy</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>Recurrent ventricular arrhythmias</td>
<td>Recurrent unstable arrhythmias</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>Severe irreversible valvular disease</td>
<td>Moderate pulmonary hypertension with preserved right ventricular function not responsive to medical therapy</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>Congenital heart disease plus moderate to severe right heart failure not responsive to medical therapy</td>
<td>Congenital heart disease plus moderate pulmonary hypertension with preserved right ventricular function not responsive to medical therapy</td>
</tr>
</tbody>
</table>

*Expert consultation with a cardiologist or pulmonary hypertension specialist familiar with liver transplantation surgery is recommended prior to decision making in all situations.*

Lung disease pre-OLT

- Tobacco consumption should be prohibited in OLT candidates
  - Increased CV mortality
  - Increased risk of hepatic artery thrombosis
  - Increased risk of lung and oropharyngeal cancer post-OLT

- Impact of COPD not studied with FEV1<30%
  - Risk of death not worse with lesser degree of impaired FEV1

- No published precise guidelines about COPD
  - Presence of obstructive or restrictive lung disease associated with longer intubation and ICU but not post-op mortality


Skin malignancy pre-txp

<table>
<thead>
<tr>
<th>Skin malignancy</th>
<th>Appropriate treatment pre-txp</th>
<th>Wait time before txp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk squamous cell cancer (SCC)</td>
<td>Excision with clear margins</td>
<td>No delay</td>
</tr>
<tr>
<td>High risk SCC w/perineural invasion or ≥ 2 risk factors</td>
<td>Excision with clear margins +/- radiation therapy</td>
<td>2 years</td>
</tr>
<tr>
<td>SCC with nodal disease</td>
<td>Excision/LN resection/XRT</td>
<td>5 years</td>
</tr>
<tr>
<td>SCC with distant mets</td>
<td>Oncology</td>
<td>Not eligible for OLT</td>
</tr>
<tr>
<td>In situ melanoma</td>
<td>Wide local excision</td>
<td>No delay, f/u 3 mos post-txp</td>
</tr>
<tr>
<td>Stage Ia melanoma</td>
<td>Wide local excision</td>
<td>2 years</td>
</tr>
<tr>
<td>Stage Iib/IIa melanoma</td>
<td>Wide local excision +/- sentinel node biopsy</td>
<td>2-5 years</td>
</tr>
<tr>
<td>Stage Iib/Iic melanoma</td>
<td>Wide local excision +/- sentinel node biopsy</td>
<td>5 years</td>
</tr>
<tr>
<td>Stage III or IV melanoma</td>
<td>Oncology</td>
<td>Not eligible for OLT</td>
</tr>
</tbody>
</table>

Non-hepatic malignancy

- Age appropriate cancer screening recommended
  - Colonoscopy, mammography, Pap smear, prostate ca
- Candidates with prior extra-hepatic cancer should have definitive therapy with expected adequate tumor free survival
  - Oncology communication
  - Israel Penn International Transplant Tumor Registry
    - www.ipittr.uc.edu

Frailty, sarcopenia
Liver Frailty Index

Inputs:
1. Gender: ○ Male  ○ Female
2. Dominant hand grip strength (kg):
   attempt 1:  attempt 2:  attempt 3:  Avg: kg
3. Time to do 5 chair stands: sec
4. Seconds holding 3 position balance:
   Side:  Semi-Tandem:  Tandem:  Total: sec

Results:
The Liver Frailty Index is _______.
Decimal precision: 2

www.liverfrailtyindex.ucsf.edu

Lai, JC et al., Gastroenterology 2019;156:1682

Waitlist mortality

Not frail  Frail

*  *  *  *  *  *
9% 16% 25% 16% 23% 16% 20% 39% 39% 39% 39%
No ascites  No HE  No ascites  Ascites  No HE  HE  Both ascites and HE

* P < .02
Sarcopenia

- Better assessment of nutrition than BMI (ascites/edema)
- Predicts pre-transplant survival, post-OLT infection, LOS
- Failure to improve after transplant predicts mortality


Sarcopenic

Not Sarcopenic

Montano-Lopez AJ. Curr Opin in Clin Nutr & Metabol Care 2014;17:219-225
Psychosocial support

- Assessment of compliance
- Adequacy of support for perioperative recovery
- Absence of active psychiatric disease that could impact compliance, substance use
- Adequacy of financial coverage for post-operative care

Active infection and OLT

- Literature is sparse and observational
- Extrahepatic infection of more concern
  - Removal of infected PSC liver of low systemic risk
- SBP is a common issue
  - Waiting 48 hours from start of therapy reasonable
    - Negative blood cultures
    - Retap for evidence of improvement
- Bacteremia more challenging
  - Common recommendation for 48 hours of negative cultures and absence of deep seated infection (i.e. osteomyelitis, endocarditis, infected joint, etc.)
“Active” infection and OLT

- Less common organisms very difficult to manage, no clear guidelines, scattered case reports
- Cryptococcal meningitis
- MAC pulmonary infections
- Latent tb can be managed post-OLT
- Transplant ID input essential

Contraindications to OLT

- Driven by likelihood of survival and futility tradeoff
  - No actual policy that defines absolute contraindication
- Frailty
- Uncontrolled infection
- Uncontrollable extrahepatic organ disease
  - Heart, lung, neurologic disease
- Presence of extrahepatic malignancy with low chance of treatment
- Absence of appropriate caregiving plan for support during recovery
- Absence of financial means for follow-up and immunosuppression