Educational Objectives

• Examine the most recent data on kidney disease outcomes after liver transplantation, and identify criteria that are currently being investigated to guide patient selection for liver alone vs dual organ transplant
• Apply an up-to-date understanding of the mechanisms underlying antibody-mediated rejection to the initiation of evidence-based approaches to prevent rejection and minimize immunosuppressant-associated toxicity
• Identify strategies to maximize adherence in patients undergoing solid organ transplant

Case Report

• 62-year-old male with 5-year history of T2DM
• History of liver disease secondary to NASH
• Presented to local hospital with abdominal pain, nausea, and coffee ground emesis
• Transferred for liver transplant evaluation
• Work-up revealed decompensated liver failure; ultrasound showed a cirrhotic liver; EGD esophagitis with varices
Case Report: Laboratory Findings

- Upon transfer, Cr 2.4 mg/dL
  - On admission, Cr 1.5 mg/dL
  - 1 year earlier, Cr 0.6 mg/dL
- Urine output
  - 1.2 L at transfer
  - Over 3 days, decreased to 690 mL/day
- Patient became encephalopathic
  - Cr 3.2 mg/dL, Na+ 129 mEq/L, K+ 5.8 mEq/L
- Urinalysis bland
  - PCR 0.3 g/g, Urine Na+ 12 mEq/L
- Patient placed on active list for a liver transplant
  - MELD: 34

Case Report: Renal Ultrasound

Renal ultrasound showed mild echogenicity, but was otherwise normal

Polling question

Is this patient a dual liver/kidney transplant candidate?

1. Yes
2. No
3. I need more information
Consequences of MELD Allocation System

- Intended
  - Reduced waitlist mortality
- Unintended
  - Livers often allocated on basis of kidney disease severity
  - Compared to pre-MELD era:
    - SLK listings have increased
    - SLK transplants increased

Consequences of MELD Allocation System

Abnormal Kidney Function is More Common in Liver Candidates in MELD Era

<table>
<thead>
<tr>
<th>Pre-OLT creat (mg/dl)</th>
<th>% pts pre-MELD</th>
<th>% pts post-MELD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0.99</td>
<td>51.8</td>
<td>46.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1-1.99</td>
<td>36.6</td>
<td>38.5</td>
<td></td>
</tr>
<tr>
<td>≥ 2.0</td>
<td>7.9</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>Dialysis</td>
<td>3.7</td>
<td>5.3</td>
<td></td>
</tr>
</tbody>
</table>

Pre-MELD 1999-2002, n=11010; Post-MELD 2002-2004, n=13163, data from SRTR

Increasing Number of SLK in USA in MELD Era

From 2012 Annual Report of OPTN/SRTR.
Limited Utility of Estimating Equations in Candidates with eGFR <40 mL/min

<table>
<thead>
<tr>
<th>Method</th>
<th>GFR&lt;40 mL/min</th>
<th>GFR&gt;40 mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># pts</td>
<td>GFR</td>
</tr>
<tr>
<td>Iothalamate*</td>
<td>155</td>
<td>22.6</td>
</tr>
<tr>
<td>Cockcroft-Gault</td>
<td>151</td>
<td>46.1</td>
</tr>
<tr>
<td>Nankivell</td>
<td>148</td>
<td>58.0</td>
</tr>
<tr>
<td>MDRD 4</td>
<td>155</td>
<td>44.5</td>
</tr>
<tr>
<td>MDRD 5</td>
<td>155</td>
<td>43.9</td>
</tr>
<tr>
<td>MDRD 6</td>
<td>155</td>
<td>39.0</td>
</tr>
</tbody>
</table>

1447 OLT recipients, 1994–2001; *iothalamate GFR used as "gold-standard"

Reasons That Centers Consider SLK

- Avoid peri-operative dialysis
- Potential to prevent
  - Non-recovery of pre-operative AKI
  - Early post-transplant ESRD
  - Subsequent ESRD and need for later kidney from another donor
- May protect center from risk of being exposed to poor outcomes based on LTA

Wide Variation in Simultaneous Liver-Kidney Transplants Between Regions

Polling Question

Independent of eGFR, all of the following factors at the time of LTA have been associated with ESRD except:
1. Older age
2. Diabetes mellitus
3. Duration of dialysis
4. Presence of abnormalities on kidney biopsy

Renal Criteria Used to Determine Need for SLK vs LTA in Liver Candidates

Survey of 88 centers that perform SLK, 60% response

<table>
<thead>
<tr>
<th>AKI: minimum duration of dialysis for determining SLK</th>
<th>% of respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 weeks</td>
<td>32%</td>
</tr>
<tr>
<td>6 weeks</td>
<td>37%</td>
</tr>
<tr>
<td>8 weeks</td>
<td>32%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CKD (GFR)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR &lt;40 ml/min</td>
<td>24%</td>
</tr>
<tr>
<td>GFR &lt;30 ml/min</td>
<td>76%</td>
</tr>
</tbody>
</table>

Survey of 88 centers that perform SLK, 60% response

Risk of ESRD After LTA in Patients with Fluctuating eGFR Pre-transplant
New Challenges and Best Practices in Liver and Kidney Transplantation

ESRD by 6 Months Post-LTA and Pre-transplant Acute Dialysis Duration

Predictors of Non-recovery of Kidney Function Post-LTA

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of post-LTA RT (per day)</td>
<td>1.04 (1.02 to 1.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age at LT (per 5 yr)</td>
<td>1.03 (1.02 to 1.04)</td>
<td>0.02</td>
</tr>
<tr>
<td>Rec-LT</td>
<td>1.66 (1.30 to 2.25)</td>
<td>0.01</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>1.86 (1.27 to 2.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Donor factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1.27 (0.87 to 1.88)</td>
<td>0.25</td>
</tr>
<tr>
<td>Anemia</td>
<td>0.89 (0.55 to 1.44)</td>
<td>0.69</td>
</tr>
<tr>
<td>Other</td>
<td>1.67 (1.34 to 2.06)</td>
<td>0.01</td>
</tr>
<tr>
<td>Male donor</td>
<td>1.48 (1.03 to 2.10)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Association of Pre-transplant Dialysis Duration and Survival After SLK

Duration of Dialysis (mos)

Cox Proportional Hazard Analysis Comparing SLK and matched-control LTA recipients, matched for donor age, race, cause of death, recipient MELD and dialysis status

Adapted from Locke JE et al, Transplantation 2008
Poor Outcomes in Elderly Patients on Dialysis at Time of Liver Transplant

Distribution of LTA Patients Based on RIFLE Classification

- No AKI: 165
- Risk: 34
- Injury: 19
- Failure: 65
  - ATN: 30
  - HRS: 35

Recovery of Kidney Function After OLT

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Limitations with Comparing SLK and LTA Outcomes in MELD Era

- Only retrospective studies
- Lack of:
  - Appropriate control groups
  - Standardized selection criteria for SLK
  - Pre-LTA kidney and/or dialysis data
  - Data on pre-txp comorbidity
- Kidney outcomes after LTA not well characterized
- Misclassification with registry data
- Differences in liver disease severity?

Kidney Biopsy in Liver Transplant Candidates

- Pathological abnormalities common
- High risk of bleeding complications
- Not shown to be better than serum creatinine in predicting:
  - Post-bp reversibility
  - Post-bp kidney function
  - Rate of decline of GFR
  - Time to ESRD
- Should be considered a research tool for now


OPTN Policy Proposal

Listing Criteria for SLK
a. ESRD
b. CKD with GFR <30 (MDRD-6 or iothalamate) and proteinuria >3 g/day
c. Sustained AKI requiring dialysis for >6 weeks
d. Sustained AKI (GFR <25) for >6 weeks not on dialysis
e. Sustained AKI: combination of time in (c) and (d) >6 weeks
f. Metabolic disease

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New Challenges and Best Practices in Liver and Kidney Transplantation

OPTN Policy Proposal

Priority local listing for KAL
- If listed for SLK but received LTA

OR
- If required 2 weeks of pre-LTA dialysis and/or eGFR 30-40 mL/min for 4 weeks pre-LTA

AND
a. Continued maintenance dialysis for >90 days post-LTA
b. non-recoverable kidney function
c. between 90-180 days post-LTA

SLK Allocation in MELD Era

Summary of Issues
- Inadequate characterization of pre-kidney function has limited the establishment of uniform criteria
- 3 months duration of severe kidney disease is tipping point for worse outcomes after LTA
- CKD defined by impaired kidney function for >3 months
- Should restrict SLK to patients with stage 4-5 CKD
  - No clear benefit for patients not on dialysis
  - Selects patients with lowest likelihood of renal recovery

Proposed Algorithm:
SLK vs LTA in Liver Candidates with Kidney Dysfunction

Case Report: Liver Transplant

- Transplant nephrology consulted to initiate CRRT
- Decision made that patient did not require kidney transplant
- Patient had a GI bleed requiring multiple transfusions; transferred to ICU
- CRRT initiated
- Urine Na $<$10 mEq/L, urine output decreased to 200-300 mL
- 6 days later, underwent OLT
- Continued on CVVHD for 48 hours
- Remained oliguric on steroids and mycophenolate mofetil for 5 days, then started on tacrolimus 2 mg bid
- Discharged, eGFR 20mL/min

Polling Question

In LTA with GFR $<$25mL/min, which would you NOT consider?

1. Continue the present immunosuppressive regimen
2. Reduce the dose of tacrolimus
3. Convert tacrolimus to mTor

Everolimus in Liver Transplant

Case Report: Post-liver Transplantation

- 9 months post-liver transplant, kidneys failed and patient received a kidney transplant from his 33-year-old son
- T and B cell cytotoxicity crossmatches were negative
- Kidney functioned immediately
- At 1 month, Cr 1.3 mg/dL; on steroids, mycophenolate mofetil and tacrolimus

Case Report: Post-liver Transplantation

- At 3 months, Cr increased to 2.5 mg/dL
- Biopsy revealed Type Ib Banff acute T cell rejection; thymoglobulin begun
- Cr remained at 1.8 mg/dL
- Patient did not return for follow-up; compliance concerns
- Presented 9 months later complaining of fatigue and edema; Cr 2.6 mg/dL, a urine PCR 1.2 mg/g
Case Report: Biopsy

Case Report

- Blood sample sent for DSA
  - Moderate risk antibodies to the donor HLA DQ3 (7000 MFI)

Polling question

What is the most common cause of AMR?

1. Viral infection
2. Non-adherence to regimen
3. Age of recipient
New Challenges and Best Practices in Liver and Kidney Transplantation

**Causes of Kidney Transplant Failure**

- Antibody-Mediated Rejection 36 (64%)
- Glomerulonephritis 10 (18%)
- BK Virus 4 (7%)
- Other Causes 6 (11%)
- Nonadherent 17 (47%)
- Adherent 19 (53%)


---

**Early (<3 Months) vs Late Acute AMR after Kidney Transplant**

- Log-rank, p<0.001


---

**C1q Complement-binding Anti-HLA ab**

- 1,016 allograft kidney transplants recipients
- Five-year survival of the transplanted kidney:
  - 54% in patients with C1q anti-HLA ab
  - >93% in those with non-complement binding anti-HLA antibodies and those without donor-specific anti-HLA antibodies (P<0.001)
- AMR was the cause of rejection in 48% patients with C1q anti-HLA ab (vs 16% of patients without)

KDIGO Guideline Recommendation for Treatment of Acute AMR

6.4: We suggest treating antibody-mediated acute rejection with one or more of the following alternatives, with or without corticosteroids (2C):

- plasma exchange;
- intravenous immunoglobulin;
- anti-CD20 antibody;
- lymphocyte-depleting antibody.

Acute AMR Treatment after Kidney Transplant: A Systematic Review of Controlled Trials

- Searched treatment of AMR with IVIG, monoclonal antibodies (rituximab or eculizumab), proteasome inhibitors (bortezomib), and plasmapheresis/exchange
- Studies published 1950 – March 2011
- MEDLINE, EMBASE, Cochrane, and meeting abstracts
- 5 randomized and 7 non-randomized controlled trials
- GRADE quality low or very low

Acute AMR Treatment after Kidney Transplant: Results of 5 RCTs

<table>
<thead>
<tr>
<th>1st Author Year</th>
<th>Intervention</th>
<th>Number Treated/Con</th>
<th>Graft Failure Treated/Con</th>
<th>Benefit?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Böhmig 2007</td>
<td>Immunoadsorption</td>
<td>5/5</td>
<td>0/4</td>
<td>Yes</td>
</tr>
<tr>
<td>Boromini 1985</td>
<td>Plasmapheresis</td>
<td>23/21</td>
<td>7/17</td>
<td>Yes</td>
</tr>
<tr>
<td>Kudelakaran 1981</td>
<td>Plasmapheresis</td>
<td>12/12</td>
<td>6/3</td>
<td>No</td>
</tr>
<tr>
<td>Allen 1983</td>
<td>Plasmapheresis</td>
<td>13/14</td>
<td>3/4</td>
<td>No</td>
</tr>
<tr>
<td>Blake 1980</td>
<td>Plasmapheresis</td>
<td>19/19</td>
<td>4/6</td>
<td>No</td>
</tr>
</tbody>
</table>
Treatment of AMR after Kidney Transplant

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasmapheresis</td>
<td>Low, benefit not consistent</td>
</tr>
<tr>
<td>Immunoadsorption</td>
<td>Low, seems beneficial</td>
</tr>
<tr>
<td>IVIG</td>
<td>Very low</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Very low</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Very low</td>
</tr>
<tr>
<td>Antibody preparations</td>
<td>Very low</td>
</tr>
<tr>
<td>Eculizumab</td>
<td>Very low</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>Very low</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Very low</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Very low</td>
</tr>
<tr>
<td>Deoxypergualin</td>
<td>Very low</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>Very low</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Very low</td>
</tr>
</tbody>
</table>

Data describing the efficacy of treatments for AMR in renal allografts are of low or very low quality. Larger randomized controlled trials and dose-response studies are required.
Conservative Treatment of Early Mixed AMR

<table>
<thead>
<tr>
<th>Day of Biopsy</th>
<th>Banff '97 Grade</th>
<th>C4d/PG13 PFTN</th>
<th>Necrosis C/N/A</th>
<th>CSA Before (ng/mL)</th>
<th>TAC Before (ng/mL)</th>
<th>TAC After (ng/mL)</th>
<th>S Cr Before (mg/dL)</th>
<th>S Cr After (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>IA</td>
<td>+/-</td>
<td>Dac</td>
<td>10.9</td>
<td>10.0</td>
<td>4.17</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>IB</td>
<td>++/+</td>
<td>206</td>
<td>12.5</td>
<td>10.0</td>
<td>4.17</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>IB</td>
<td>++/+</td>
<td>146</td>
<td>14.5</td>
<td>6.97</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>IA</td>
<td>+/-</td>
<td>Dac</td>
<td>NA</td>
<td>10.4</td>
<td>6.97</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>IB</td>
<td>+/-</td>
<td>Bas</td>
<td>160</td>
<td>7.1</td>
<td>0.91</td>
<td>0.96</td>
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</tr>
<tr>
<td>10</td>
<td>IA</td>
<td>+++/+</td>
<td>Bas</td>
<td>103</td>
<td>10.9</td>
<td>0.91</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>IA</td>
<td>+/-</td>
<td>176</td>
<td>9.5</td>
<td>4.79</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>IB</td>
<td>+/-</td>
<td>Bas</td>
<td>12.8</td>
<td>11.2</td>
<td>9.04</td>
<td>1.74</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Brdrln</td>
<td>+/-</td>
<td>348</td>
<td>12.0</td>
<td>3.26</td>
<td>0.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>IB</td>
<td>+/-</td>
<td>5.7</td>
<td>9.2</td>
<td>1.24</td>
<td>1.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>IB</td>
<td>+++/+</td>
<td>8.3</td>
<td>9.5</td>
<td>0.79</td>
<td>0.79</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conservative Treatment of Early Mixed AMR

Conservative Treatment of Early Mixed AMR

Potential Treatments of AMR that Require Additional Study

- Intravenous immunoglobulin
- Rituximab (B-cell antibody)
- Bortezomib (proteasome inhibitor)
- Eculizumab (C5 inhibition)
- C1 Esterase Inhibitor
- BAFF inhibitors
- Plasmapheresis
Early vs Late Acute AMR

<table>
<thead>
<tr>
<th></th>
<th>Early AMR (n=40)</th>
<th>Late AMR (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low drug levels</td>
<td>0/40 (0%)</td>
<td>15/27 (56%)*</td>
</tr>
<tr>
<td>Low drug levels and non-adherent</td>
<td>0/0 (0%)</td>
<td>10/15 (75%)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>50.9±11.6</td>
<td>37.9±12.9*</td>
</tr>
<tr>
<td>Age (y) of those that were non-adherent</td>
<td>26.6±9.5</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.001 vs Early AMR

Addressing Late Graft Loss

• Shift in thinking about the causes of late graft rejection: insufficient immunosuppression and non-adherence to immunosuppressive medication are key factors.
• Insufficient immunosuppression may occur during immunosuppressive minimization (tapering) or calcineurin-inhibitor-avoidance
• Patients at high risk for non-adherence, specifically young adults who are in the transition phase from pediatric to adult renal services, should be identified.

Increasing Adherence in Transplant Patients

• Adherence to immunosuppressant regimens is challenging
  - Patients commonly take >8 medications/day at multiple specific times
  - Weekly clinic appointments for ~1 year post-transplantation
  - Laboratory visits between clinic visits
  - Significant lifestyle changes to incorporate healthy behaviors
• Physicians and other members of the transplant team can help improve adherence by providing education on treatment expectations, management of side effects, and strategies to improve adherence
  - Schedule of medication-taking
  - Simplified, more convenient medication regimens (reduced dosing, injectable)
  - Organizing pills (pill boxes, reminder systems)
  - Regularly scheduled visits with a provider, even when the patient feels well
  - Individualize regimen to reduce adverse events and side effects
Dosing Frequency, Persistence, and Adherence in Transplant Recipients

- 219 patients (45% male; 3±2 years post transplantation) randomized to tacrolimus 145 once daily or 74 twice daily
- Persistence at 6 months: 81.5% of the once-daily group vs 71.9% of the twice-daily group remained with the treatment ($P=0.0824$)
- Adherence: 88.2% of the once-daily group and 78.8% of the twice-daily group ($P=0.0009$)
- Doses were missed more frequently in the evening than in the morning (11.7% vs 14.2%; $P=0.0035$; twice daily regimen)


Case Report Management

- Patient was treated with steroid pulse, 3 doses of IVIG 70 g, and rituximab 1,000 mg X 2 over 2 weeks
- Liver function tests remained normal

Conclusions

- Candidates for SLK transplant include:
  - ESRD
  - Metabolic kidney diseases cured by liver transplant
  - Other?
- AMR is a common cause of death-censored transplant failure
- Currently, management of AMR must include maintenance of immunosuppression while optimizing patient adherence and minimizing side effects
  - Recognize those at risk for low-adherence
- Future therapies will address underlying pathophysiology of AMR