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Grant System Opens: September 7, 2021

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 Deadline: Friday, December 10, 2021

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Geoffrey C. Nguyen, MD, PhD, FRCPC
December 2, 2021 at Noon Eastern

Week 45, 2021
Acute Gastrointestinal Toxicity of Cancer Therapy: What Every Gastroenterologist Should Know
Shilpa Grover, MD, MPH
December 9, 2021 at Noon Eastern

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Disclosures:

Speaker:
Fredric D. Gordon, MD
Dr. Gordon, faculty for this educational event, has no relevant financial relationship(s) with ineligible companies to disclose.

Moderator:
Mark W. Russo, MD, MPH, FACG
Scientific Safety Committee: Moderna vaccine in liver transplant recipients

*All of the relevant financial relationships listed for these individuals have been mitigated
Primary Sclerosing Cholangitis in Liver Transplantation

Fredric D. Gordon, MD, FAASLD, FAST, AGAF
Professor of Medicine, Tufts School of Medicine
Vice Chair, Division of Transplantation and Hepatobiliary Diseases
Director of Hepatology
Lahey Hospital & Medical Center

Agenda

• Definition of PSC
• Pathogenetic mechanisms
• Cancer
• Treatment
  – Medical
  – Endoscopic
  – Surgical
• Transplantation
**Primary Sclerosing Cholangitis**

- **Definition**
  - Chronic, progressive, immune-mediated, inflammatory, cholestatic liver disease resulting in fibrostenotic strictures of the biliary tree

**Diagnosis of PSC**

- Index of suspicion
- Lab screening in at risk individuals
- ERCP vs. MRCP
  - AASLD/EASL – “MRC is the diagnostic modality of choice”
  - Sensitivity ≥ 80%, specificity ≥ 87%
  - ERC may have a role in early disease
PSC: Histology

PSC: Epidemiology

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>0.2-14 per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>M&gt;F, 2:1</td>
</tr>
<tr>
<td>Age at onset</td>
<td>30-40 years</td>
</tr>
<tr>
<td>Smoking</td>
<td>Decreased risk</td>
</tr>
<tr>
<td>Associated conditions</td>
<td>IBD, autoimmune hepatitis</td>
</tr>
</tbody>
</table>

PSC: Association with IBD

- 2-10% of pts with IBD have PSC
  - Up to 8% of pts with Ulcerative Colitis
    - 5.5% with pancolitis
    - 1% with distal colitis
  - 1-3% of pts with Crohn’s Disease
- Prevalence of IBD in pts with PSC
  - 80% have UC
  - 10% have CD


Laboratory Tests

- Alkaline phosphatase > 2x ULN
- Transaminases < 2x ULN
- Bilirubin may be elevated
- pANCA positive in 50-80%, not specific
Differential Diagnosis: Secondary Sclerosing Cholangitis

- Choledocholithiasis
- Cholangiocarcinoma
- Diffuse intrahepatic metastases
- Histiocytosis X
- Ischemic cholangiopathy
- AIDS cholangiopathy
- Mast cell cholangiopathy
- Recurrent pancreatitis
- Recurrent pyogenic cholangitis
- Surgical biliary trauma
- IgG4-related cholangitis

IgG4-related Cholangitis

- Cholangiographically identical to PSC
- Rapidly progressive
- Elevated IgG4 levels (typically ≥ 135)
- Often associated with autoimmune pancreatitis
- Associated with sialadenitis, retroperitoneal fibrosis, mediastinal lymphadenopathy
- Not linked to IBD
- Elderly males
- Responds to steroids
- Check IgG4 in all patients with PSC (AASLD recommendation)
Pathogenesis: Proposals

• Autoimmunity
• IBD connection
• Genetics

PSC and the Microbiome

• “Leaky gut hypothesis”
  – Pathogenic changes in gut microbiota
  – Endotoxin leakage
    • Enterohpetic circulation of lipopolysaccharides, lipoteichoic acid, peptidoglycan
    – Aberrant homing of intestinally activated lymphocytes to cholangiocytes

Translational Studies Supporting PSC-Microbiota Hypothesis

• Cholangiocytes from PSC patients are hypersensitive
  – Toll-like receptors and nucleotide-binding oligomerization domain expression are increased in PSC cholangiocytes
  – Lipopolysaccharides and other pathogen-associated molecular patterns (PAMPs) found in bile
  – Trigger increased expression of immune response genes, profibroinflammatory mediators


• Cellular senescence
  – G1 (replicative phase) arrest
  – Cells remain metabolically active and may transition to a pathologic state [senescence-associated secretory phenotype (SASP)]
  – SASP cells alter the microenvironment, reinforce senescence, initiate proinflammatory responses, and accelerate neoplastic transformation.

Translational Studies Supporting PSC-Microbiota Hypothesis

- SASP can be induced by exposure to LPS and flagellin
- Markers of SASP were increased in PSC pts

Microbiota Hypothesis and Antibiotics

- 3 prospective trials (Vancomycin, Metronidazole, Minocycline ± UDCA)
  - All showed reduction in alkaline phosphatase
  - No change in histology with short term f/u
- Probiotics
  - Small studies with divergent results
- Additional work ongoing
PSC and the Microbiome

- Gut inflammation $\rightarrow$ Portal venous bacterial translocation
- Severity of IBD $\approx$ Severity of PSC
- Changes in microbiota
- FMT - Safe but is it effective?
- More work needed


PSC and Genetics

- Familial studies
  - PBC: 63% in monozygotic twins. Approximately 10-fold increased risk in siblings
  - PSC: 11.5-fold increased risk in offspring but prevalence in 1st degree relatives is low (0.7%)
- Associated with extra-hepatic autoimmunity (71%, including IBD)

Lamberts et al, J Ital Soc Gastroenterol, 2011
PSC and Genetics

**Non-HLA**

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Lead SNP</th>
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<tr>
<td>1</td>
<td>rs3748816</td>
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<tr>
<td>2</td>
<td>rs6720394</td>
</tr>
<tr>
<td>2</td>
<td>rs7426056</td>
</tr>
<tr>
<td>2</td>
<td>rs3749171</td>
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<td>3</td>
<td>rs1397999</td>
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<td>4</td>
<td>rs13140464</td>
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<td>5</td>
<td>rs56258221</td>
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<td>6</td>
<td>rs4147359</td>
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<td>7</td>
<td>rs7937682</td>
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<td>8</td>
<td>rs11168249</td>
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<td>9</td>
<td>rs3184004</td>
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<td>10</td>
<td>rs1788097</td>
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<td>11</td>
<td>rs1452787</td>
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<tr>
<td>12</td>
<td>rs60652743</td>
</tr>
<tr>
<td>13</td>
<td>rs2836883</td>
</tr>
</tbody>
</table>

**HLA-associated**

- **PSC risk haplotypes**
  - B*08:01
  - DRB1*03:01-DQA1*05:01-DQB1*02:01
  - DRB1*13:01-DQA1*01:03-DQB1*06:03
  - DRB1*15:01-DQA1*01:02-DQB1*06:02
  - DRB1*01:01-DQA1*01:01

- **Protective haplotypes**
  - DRB4*01:03-DRB1*04:01-DQA1*03-DQB1*03:02
  - DRB4*01:01-DRB1*07:01-DQA1*02:03-DQB1*03:03
  - DRB4*02:02-DRB1*11:01-DQA1*05:03-DQB1*03:01
  - MICA*002

**Conclusions**

- Multiple HLA and non-HLA associations identified
- Cause-effect not verified in humans
- Interaction between genetics and environment
  - Microbiota hypothesis
- Additional work and insight needed
PSC: Cholangiocarcinoma

- Lifetime risk 10-15%
- Risk factors include: Elevated bilirubin, UC, colon Ca or dysplasia, variceal bleeding, proctocolectomy, and polymorphisms of NK group 2, member D gene.
- Duration of PSC is not a risk factor
- No evidence-based screening guidelines
  - Serial imaging
  - CA19-9
  - ERCP


<table>
<thead>
<tr>
<th>Method</th>
<th>Author</th>
<th>n=</th>
<th>Time Period</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
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<tr>
<td>Cytology</td>
<td>Lindberg</td>
<td>20</td>
<td>1997-2001</td>
<td>71</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Moreno Luna</td>
<td>86</td>
<td>2003-2004</td>
<td>18</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Boberg</td>
<td>121</td>
<td>2000-2004</td>
<td>76</td>
<td>95</td>
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<tr>
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<td>Charatcharo-enwitthaya</td>
<td>216</td>
<td>2000-2006</td>
<td>8</td>
<td>100</td>
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<td></td>
<td>Halme</td>
<td>186</td>
<td>2004-2007</td>
<td>48</td>
<td>88</td>
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<tr>
<td>FISH</td>
<td>Moreno Luna</td>
<td>86</td>
<td>2003-2004</td>
<td>60</td>
<td>87</td>
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<td>Charatcharo-enwitthaya</td>
<td>216</td>
<td>2000-2006</td>
<td>88</td>
<td>73</td>
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<tr>
<td></td>
<td>Bangarulingam</td>
<td>235</td>
<td>2003-0008</td>
<td>46</td>
<td>88</td>
</tr>
</tbody>
</table>

PSC: Colorectal Cancer

- Risk factors: Duration and extent of IBD, family history of CRC, PSC
- Mechanism: Unknown. ? Bile acids
- Milder/subclinical disease = longer duration

<table>
<thead>
<tr>
<th>Author</th>
<th>n=</th>
<th>5 year</th>
<th>10 year</th>
<th>20 year</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claessen</td>
<td>127 PSC/UC 84 PSC alone</td>
<td>14% 2.3%</td>
<td>31% 2.3%</td>
<td>Right colon</td>
<td></td>
</tr>
<tr>
<td>Fevery</td>
<td>200 PSC</td>
<td>2% 7%</td>
<td>15%</td>
<td>Age 49.5y</td>
<td></td>
</tr>
<tr>
<td>Terg</td>
<td>39 PSC/UC 1294 UC alone</td>
<td>11% 2%</td>
<td>18% 7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


PSC: Colorectal Cancer

- Screening: q1-2 years. Poor adherence.
- Effective prevention: Proctocolectomy
- Ineffective: Liver transplantation, UDCA

<table>
<thead>
<tr>
<th>Author</th>
<th>UDCA</th>
<th>CRN (%)</th>
<th>No UDCA</th>
<th>CRN (%)</th>
<th>Type</th>
<th>UDCA benefit?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pardi</td>
<td>29</td>
<td>3</td>
<td>23</td>
<td>8</td>
<td>RCT</td>
<td>Yes</td>
</tr>
<tr>
<td>Wolf</td>
<td>28</td>
<td>3</td>
<td>92</td>
<td>13</td>
<td>Retro</td>
<td>No</td>
</tr>
<tr>
<td>Lindstrom</td>
<td>37</td>
<td>13</td>
<td>40</td>
<td>15</td>
<td>RCT</td>
<td>No</td>
</tr>
<tr>
<td>Eaton</td>
<td>25</td>
<td>9</td>
<td>31</td>
<td>3</td>
<td>RCT</td>
<td>No-high dose</td>
</tr>
<tr>
<td>Rudolph</td>
<td>120</td>
<td>7</td>
<td>N/A</td>
<td>N/A</td>
<td>Prosp</td>
<td>No-short, Yes-long</td>
</tr>
</tbody>
</table>

Standard Dose UDCA for PSC

- 105 patients
- 13-15mg/kg/d UDCA
- 2-5 year f/u
- Improved LFTs
- No improvement
  - Survival
  - Progression to cirrhosis


High Dose UDCA for PSC

- 150 patients
- 28-30mg/kg/d UDCA
- Improved LFTs
- No improvement
  - Survival
  - Transplantation
  - Minimal listing criteria
- Study terminated after 6 years for futility

High Dose UDCA is Associated with Colorectal Neoplasia

- 56 patients
- 28-30mg/kg/d UDCA
- Increased risk of colorectal neoplasia (CRC, HGD, LGD)


Future Treatments for PSC

- Obeticholic acid – Phase II
  - Reduces alk phos
- nor-UDCA – Phase II
  - Reduces alk phos
- Lysyl oxidase-like 2 – antifibrotic – Phase II
  - Failed
- FMT

Non-UDCA Treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Year</th>
<th>Author</th>
<th>n=</th>
<th>Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillamine</td>
<td>1988</td>
<td>LaRusso</td>
<td>79</td>
<td>3 years</td>
<td>None</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>1994</td>
<td>Knox</td>
<td>24</td>
<td>2 years</td>
<td>Improved alkphos</td>
</tr>
<tr>
<td>Colchicine</td>
<td>1995</td>
<td>Olsson</td>
<td>84</td>
<td>3 years</td>
<td>None</td>
</tr>
<tr>
<td>MMF/UDCA</td>
<td>2004</td>
<td>Sterling</td>
<td>25</td>
<td>2 years</td>
<td>None</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>2004</td>
<td>Farkkila</td>
<td>80</td>
<td>3 years</td>
<td>Improved Mayo Risk</td>
</tr>
<tr>
<td>Infliximab</td>
<td>2008</td>
<td>Hommes</td>
<td>10</td>
<td>1 year</td>
<td>Stopped early</td>
</tr>
</tbody>
</table>

No study demonstrated improved histology or survival


Endoscopic Management

- German study
- 171 patients
  - 500 endoscopic dilations
- Median f/u 7.1 years
- All dominant strictures balloon dilated
- All received UDCA
- 22/96 (23%) required OLT

Transplant-free Survival

Liver Transplantation for PSC

- 5% of transplants in US
- Timing difficult
  - MELD score may not reflect risk
    - Cholangitis
    - "Early" portal hypertension
    - Pruritus

PSC: Waitlist Mortality
Hx of cholangitis vs. no infection

p=0.26
Recurrence of PSC in Live and Deceased Donor Liver Transplant Recipients

Recurrent PSC
Survival after Liver Transplantation
SRTR Data 2019


Post-transplant PSC Survival
UNOS Database

• July 1996 – Dec 2008
• 114 primary LDLT recipients
• 29 institutions
• Excluded: 8 HAT, 8 ABO incompatible, 2 ductopenic rejection
• n=96

Definition of Recurrence

• Abnormal cholestatic biochemical profile
• Graziadei Criteria (Hepatol 1999;30:1121-7)
  – Confirmed dx of PSC before Tx
  – Intrahepatic, multiple biliary strictures confirmed by cholangiography >90 days after Tx, OR
  – Biopsy findings showing fibrous cholangitis and/or fibro-obliterative lesions

Egawa et al., Am J Transplant, 2011.
Definition of Recurrence

- Exclusionary criteria
  - Other causes of multiple biliary strictures (secondary SC) such as HAT or stenosis, ductopenic rejection, ABO incompatibility
  - Unsuccessfully treated anastomotic stricture or no biliary-related-disease free period without any treatment until the development of biliary sclerosis

Egawa et al., Am J Transplant, 2011.

Recurrence

- 26/96 (27%) over 8-79 months
  - Bx only in 3, Bx and C-gram in 18, C-gram only in 5.

Egawa et al., Am J Transplant, 2011.
Survival

Recurrence-free Survival, all (n=96)

Graft Survival, recurrent PSC (n=26)

Risk Factors for Recurrence

- Multivariate
  - MELD > 24 (HR 3.16)
  - First degree relative donor (HR 3.12)
  - CMV antigenemia (HR 3.32)
  - Biliary anastomotic complication within 1 year (HR 4.19)

Egawa et al., Am J Transplant, 2011.
A2ALL PSC Study

Aims:

• Estimate the risk of recurrence of PSC in patients who have received a LDLT or DDLT
• Estimate the risk factors for recurrence of PSC, with focus on the degree of relatedness of the donor to the recipient


A2ALL PSC Study

• Study population
  – 1998-2013
  – 242 LDLT, 65 DDLT
  – Median follow-up 4.9 years

• Statistical methods
  – Kaplan-Meier curves
  – Cox regression models
Subject Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>mean (std.) or n (%)</th>
<th>Characteristic</th>
<th>mean (std.) or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient age</td>
<td>45 (13)</td>
<td>PSC type</td>
<td>152 (50%)</td>
</tr>
<tr>
<td>Male Recipient</td>
<td>215 (70%)</td>
<td>Intrahepatic</td>
<td>13 (4%)</td>
</tr>
<tr>
<td>Donor age</td>
<td>39 (13)</td>
<td>Extrahepatic</td>
<td>132 (43%)</td>
</tr>
<tr>
<td>Male Donor</td>
<td>168 (55%)</td>
<td>Intra and extrahepatic</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>MELD score</td>
<td>16 (8)</td>
<td>Small duct</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>LDLT</td>
<td>15*</td>
<td>Missing</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>DDLT</td>
<td>20*</td>
<td>Type of anastomoses</td>
<td>39 (13%)</td>
</tr>
<tr>
<td>Gender matched</td>
<td>180 (59%)</td>
<td>All duct to duct</td>
<td>39 (13%)</td>
</tr>
<tr>
<td>mismatched</td>
<td>127 (41%)</td>
<td>At least one Roux-en-Y</td>
<td>268 (87%)</td>
</tr>
</tbody>
</table>

* p<0.0001

Live Donor Relationships

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sibling</td>
<td>60 (24.7%)</td>
</tr>
<tr>
<td>Child</td>
<td>49 (20.2%)</td>
</tr>
<tr>
<td>Parent</td>
<td>11 (4.5%)</td>
</tr>
<tr>
<td>Total first-degree relatives</td>
<td>120 (49.6%)</td>
</tr>
<tr>
<td>Non-first-degree relative</td>
<td>23 (9.5%)</td>
</tr>
<tr>
<td>Non-biologic relative</td>
<td>36 (14.8%)</td>
</tr>
<tr>
<td>Unrelated</td>
<td>63 (26%)</td>
</tr>
<tr>
<td>Total non-first-degree donors</td>
<td>122 (50.4%)</td>
</tr>
</tbody>
</table>
### PSC Recurrence

<table>
<thead>
<tr>
<th>Recurrence % (n at risk)</th>
<th>Year 3</th>
<th>Year 5</th>
<th>Year 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>4.3% (190)</td>
<td>9.5% (136)</td>
<td>24.7% (37)</td>
</tr>
<tr>
<td>LDLT</td>
<td>5.0% (143)</td>
<td>9.5% (105)</td>
<td>21.1% (28)</td>
</tr>
<tr>
<td>DDLT</td>
<td>1.9% (47)</td>
<td>9.4% (31)</td>
<td>36.9% (9)</td>
</tr>
</tbody>
</table>

LDLT vs. DDLT, p=0.36


### PSC Recurrence by Donor Type

[Graph showing PSC recurrence over time for LDLT and DDLT, with Log-Rank p=0.36]

**Risk Factors for PSC Recurrence**

*(univariate models)*

**Significant:**
- Higher MELD at transplant
  - HR 1.04 per point, *p*=0.03
- Onset of biliary complication*
  - HR 2.1, *p*=0.04
- Donor age
  - HR 1.01 per year, *p*=0.01

**Not Significant:**
- Donor type
- First degree relative donor
- CMV infection
- Acute rejection
- Cholangiocarcinoma
- Race/Ethnicity
- PSC type
- Cold ischemia time
- Immunosuppression
- Colitis
- Pre-transplant colectomy

* Stricture, leak, or cast

---

**PSC Recurrence by Relatedness**

Multivariable Model of PSC Recurrence

Best 4 variable model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time dependent biliary complication</td>
<td>2.8 (1.3 – 6.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>4.00 (1.4 – 11.1)</td>
<td>0.008</td>
</tr>
<tr>
<td>MELD at transplant (per point)</td>
<td>1.06 (1.02 – 1.10)</td>
<td>0.002</td>
</tr>
<tr>
<td>Donor age (per 5 yrs)</td>
<td>1.17 (1.02 – 1.35)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Best 5 variable model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Time dependent biliary complication</td>
<td>2.8 (1.3 – 6.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>4.00 (1.3 – 10.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>MELD at transplant (per point)</td>
<td>1.06 (1.02 – 1.10)</td>
<td>0.001</td>
</tr>
<tr>
<td>Donor age (per 5 yrs)</td>
<td>1.20 (1.04 – 1.39)</td>
<td>0.01</td>
</tr>
</tbody>
</table>


Unadjusted Graft Loss and Mortality

<table>
<thead>
<tr>
<th></th>
<th>Year 3</th>
<th>Year 5</th>
<th>Year 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graft loss</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDLT</td>
<td>14%</td>
<td>16%</td>
<td>22%</td>
</tr>
<tr>
<td>DDLT</td>
<td>12%</td>
<td>14%</td>
<td>27%</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDLT</td>
<td>9%</td>
<td>11%</td>
<td>16%</td>
</tr>
<tr>
<td>DDLT</td>
<td>8%</td>
<td>9%</td>
<td>21%</td>
</tr>
</tbody>
</table>

Survival with Recurrent PSC


Overall Outcomes

Study Conclusions

- Risk of recurrent PSC was not different for LDLT vs. DDLT recipients
- Risk of recurrent PSC in a large North American LDLT cohort was considerably lower than the published Japanese cohort
- Degree of relatedness was “not significantly” associated with risk of recurrent PSC
- Biliary complications, cholangiocarcinoma, MELD score, and donor age were significantly associated with risk of PSC recurrence


Possible Explanations
Differences between NA and Japanese Data

- Definition of 1st degree relative
- Subjectivity in diagnosis of recurrent PSC
- Small number of events in NA data
- Genetics
- Microbiome
Summary

• Pathophysiology of PSC
  – Genetics
  – Microbiome

• Treatment

• Liver Transplantation
  – Living donor
  – Deceased donor

Questions?

Speaker:
Fredric D. Gordon, MD

Moderator:
Mark W. Russo, MD, MPH, FACG