Liver Transplantation: Expanding the Donor Pool

Anthony M. D’Alessandro M.D.
Division of Transplantation
University of Wisconsin
## UNOS Current Waiting List

<table>
<thead>
<tr>
<th>Type of Transplant</th>
<th># of Patients Waiting</th>
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<tbody>
<tr>
<td>Kidney</td>
<td>60,986</td>
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<tr>
<td>Liver</td>
<td>17,290</td>
</tr>
<tr>
<td>Lung</td>
<td>3,806</td>
</tr>
<tr>
<td>Heart</td>
<td>3,214</td>
</tr>
<tr>
<td>Heart-Lung</td>
<td>173</td>
</tr>
<tr>
<td>Kidney-Pancreas</td>
<td>2,434</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1,687</td>
</tr>
<tr>
<td>Intestine</td>
<td>191</td>
</tr>
</tbody>
</table>

**Total Patients:** 87,700
Deceased Organ Donors

DCD and DBD

Year

Number of Donors

Donation after Cardiac Death (DCD)
Donation after Brain Death (DBD)

UNOS data through 12/31/04

ASTS
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Expanded Criteria Donor (ECD) Livers

What is the definition of an ECD liver?

- UNOS kidney definition
  - Age > 60
  - Age 50-59 with 2/3: HTN, CVA, and Creat. 1.5
- Based on relative risk of graft loss
  - Feng S et al, Hepatology 2004;38 Suppl 1;S6
    - Age, cardiac arrest, CVA, Na > 170meq/L, split
  - Amin MG et al, Liver Transplantation 2004; Vol 10, No 12 pp 1468-1475
  - SRTR relative risk of graft loss > 1.7: age, CVA, race, split liver, DCD
- Based on Specific Donor Criteria
  - Numerous publications
Specific Donor Criteria of ECD Livers

- Age
- Steatosis
- Cold Ischemic Time
- DCD (NHBD)
- Hypotension/inotropic support
- Biochemical abnormalities
- Gender
- Hepatitis
- Donor malignancies
- Split livers
Deceased Donor Age 2000-2003


Percentage

Donors < 60
Donors > 60

![Graph showing the percentage of deceased donors aged less than 60 and more than 60 for the years 2000 to 2003.](chart.png)
Impact of Donor Age on Liver Function and Survival

- May be more immune to senescence
- More susceptible to endothelial cell injury
- Decreased synthetic and regenerative ability
- Increased delayed graft function and cholestasis
  - Yersiz et al, Transplantation 1995;60:790-794
- Increased steatosis
- Decreased tolerance to cold ischemia
Impact of Donor Age on Liver Function and Survival

- Rull R et al, Liver Transp, Vol 9, No 4 2003 389-393
  - 58/228 transplants > 65 years of age
    - Age < 65  2 year graft survival 85%
    - Age > 65  2 year graft survival 70%
    - Age > 65 and > 10U PRBC  2 year graft survival 48%

- Neipp M et al, Transp Int 2004 17:416-423
  - 67/1208 transplants > 60 years of age
    - No difference in 1, 3, and 5 year PS and GS, cholestasis, or vascular complications compared to < 60
    - However, PNF 12% and IPF 4%
Recommendations on Utilization of Older Donor Livers

- Donors > 60 suitable for transplantation
  - Keep CIT < 8 hours
  - Avoid combining multiple risk factors such as age, steatosis, and increased CIT
  - Avoid technically challenging recipients
  - Avoid transplanting into HCV+ recipients
  - Assess recipient based on MELD score
    - Allocate to MELD < 20 or > 20 despite increased incidence of graft failure
Steatotic Donor Livers: Impact on Graft Function

- Macrovesicular and Microvesicular
  - Steatosis may obstruct sinusoidal spaces
  - Reduced energy stores during preservation
  - Decreased capacity to regenerate ATP
  - Increased Kupffer cell dysfunction
  - Increased leukocyte adhesion, lipid peroxidation, and necrosis of endothelial cells
Steatotic Donor Livers: Impact on Graft Function

- Macrovesicular steatosis
    - 0-33% no difference
    - 33-66% increased IPF
    - > 66% increased PNF
    - Up to 30% steatosis, decreased 4 mo graft survival
    - Worse results if patient critically ill
Steatotic Donor Livers: Impact on Graft Function

- Microvesicular Steatosis
  - Safely expands the donor pool
    - Fishbein TM et al, Transplantation 1997;64:248-251
    - Scoring for marginal grafts
Recommendations for use of Steatotic Donor Livers

- Microvesicular Steatosis
  - May use with up to 100% microvesicular although there may be some increased IPF

- Macrovesicular Steatosis
  - Do not use if > 60%
  - Can use 30-60%, but avoid combining risk factors in the donor and recipient
  - < 30% safe to use in all recipients
Impact of Cold Ischemic Time on Liver Graft Function

- Cold ischemia independent risk factor for graft dysfunction
  - Ploeg RJ et al, Transplantation 1993;55:807-813
    - Increased DGF/PNF with preservation > 12 hrs
    - One of five factors including CIT, age, pressors, steatosis and ICU stay leading to preservation injury
Cold Ischemic Time and Risk of Liver Preservation Injury

Cold Ischemic Time and Probability of Dysfunction

Alti M et al, Transplantation 2004;77:411-416

- Formula for marginal liver
  - \((20.06 \times \text{Steatosis}) + (0.44 \times \text{Donor Age})\)
  - 23.6 is cutoff for marginal liver
Cold Ischemic Time and Probability of Dysfunction - Marginal Donors

Alti M et al, Transplantation 2004;77:411-416
Cold Ischemic Time and Probability of Dysfunction

Alti M et al, Transplantation 2004;77:411-416

Marginal
Non-marginal

Cold Ischemia Time (minutes)
Probability of Dysfunction

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Recommendations on CIT in Liver Transplantation

- CIT > 12-14 hours independent risk factor for graft dysfunction
  - Graft dysfunction worse when increased CIT combined with other risk factors such as age, inotropic support, steatosis, and ICU stay of the donor
  - CIT may be increased >12 hrs if other risk factors are not present
Donation after Cardiac Death (DCD)

The University of Wisconsin Experience with Liver Transplantation
DCD Liver Transplantation

Study Period

(1/1/93 – 7/31/02)

930 Organ donors

81 (8.7%) DCD

849 (91.3%) DBD

47 Multi-organ

1 Pancreas only

33 Kidney only

553 (65.1%) Liver transplants

36 (76.5%) Liver transplants

11 (23.4%) Livers not used
# DCD Liver Transplantation

## Donor Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DCD (n=36)</th>
<th>DBD (n=553)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>35.1±14.9</td>
<td>33.4±16.6</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>3.5:1</td>
<td>1.5:1*</td>
</tr>
<tr>
<td>Vasopressors, n(%)</td>
<td>12(33.3)</td>
<td>425(76.9)**</td>
</tr>
<tr>
<td>Warm ischemic time (min)</td>
<td>17.8</td>
<td>0.0**</td>
</tr>
<tr>
<td>Cold ischemic time (hr)</td>
<td>8.2</td>
<td>8.3</td>
</tr>
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</table>

*\(p=0.05\)

**\(p=0.0001\)
## Postoperative Laboratory Values

<table>
<thead>
<tr>
<th></th>
<th>Postoperative Day</th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>DCD</td>
<td>DBD</td>
<td>DCD</td>
<td>DBD</td>
</tr>
<tr>
<td>AST (u/L)</td>
<td>1034±838*</td>
<td>736±1114</td>
<td>202±226</td>
<td>258±453</td>
</tr>
<tr>
<td>ALT (u/L)</td>
<td>688±522*</td>
<td>542±522</td>
<td>442±339</td>
<td>562±339</td>
</tr>
<tr>
<td>LDH (u/L)</td>
<td>871±715*</td>
<td>783±715</td>
<td>305±129</td>
<td>352±129</td>
</tr>
<tr>
<td>GGT (u/L)</td>
<td>158±112*</td>
<td>124±141</td>
<td>236±214*</td>
<td>179±191</td>
</tr>
<tr>
<td>ALP (u/L)</td>
<td>117±69</td>
<td>121±99</td>
<td>138±60</td>
<td>131±85</td>
</tr>
<tr>
<td>PT/INR (sec)</td>
<td>14.4±1.1 / 1.4±.21</td>
<td>15.3±2.4 / 1.4±.25</td>
<td>13.0±1.3 / 1.2±.12</td>
<td>13.8±3.3 / 1.2±.18</td>
</tr>
</tbody>
</table>

*p<.001
## DCD Liver Transplantation

### Postoperative Laboratory Values

<table>
<thead>
<tr>
<th></th>
<th>Postoperative Day</th>
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<tbody>
<tr>
<td></td>
<td>7</td>
<td>Discharge</td>
<td>Discharge</td>
</tr>
<tr>
<td></td>
<td>DCD</td>
<td>DBD</td>
<td>DCD</td>
</tr>
<tr>
<td>AST (u/L)</td>
<td>53±32</td>
<td>96±310</td>
<td>46±40</td>
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<tr>
<td>ALT (u/L)</td>
<td>202±120</td>
<td>272±121</td>
<td>132±68</td>
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<tr>
<td>LDH (u/L)</td>
<td>251±79</td>
<td>272±79</td>
<td>201±56</td>
</tr>
<tr>
<td>GGT (u/L)</td>
<td>325±161*</td>
<td>276±225</td>
<td>447±380*</td>
</tr>
<tr>
<td>ALP (u/L)</td>
<td>156±63*</td>
<td>143±81</td>
<td>261±236*</td>
</tr>
<tr>
<td>PT/INR (sec)</td>
<td>13.3±1.4 /</td>
<td>13.3±1.9 /</td>
<td>12.9±1.7 /</td>
</tr>
<tr>
<td></td>
<td>1.2±.18</td>
<td>1.2±.21</td>
<td>1.14±.15</td>
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</table>

*\( p<0.001 \)
## DCD Liver Transplantation Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>DCD (n=36)</th>
<th>DBD (n=535)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
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<tr>
<td>Hepatic artery</td>
<td></td>
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<tr>
<td>Thrombosis (HAT)</td>
<td>2 (5.5)</td>
<td>64 (11.8)</td>
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<tr>
<td>Stenosis (HAS)</td>
<td>6 (16.6)</td>
<td>30 (5.4)*</td>
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<tr>
<td>Portal vein</td>
<td></td>
<td></td>
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<tr>
<td>Thrombosis (PVT)</td>
<td>1 (2.8)</td>
<td>18 (3.3)</td>
</tr>
<tr>
<td>Stenosis (PVS)</td>
<td>1 (2.8)</td>
<td>11 (2.0)</td>
</tr>
<tr>
<td>Primary nonfunction (PNF)</td>
<td>2 (5.5)</td>
<td>7 (1.3)</td>
</tr>
<tr>
<td>Hepatic abscess/biloma</td>
<td>6 (16.6)</td>
<td>46 (8.3)**</td>
</tr>
<tr>
<td>Ischemic-type biliary stricture (ITBS)</td>
<td>5 (13.8)</td>
<td>44 (8.0)</td>
</tr>
</tbody>
</table>

*p=0.001, **p=0.04.*
Patient Survival After Liver Transplantation

**DCD vs. DBD**

*% Patient Survival*

- **DBD (n=535)**
- **DCD (n=36)**

* *p=0.01*

**Years Post Transplantation**

<table>
<thead>
<tr>
<th>Years Post Transplantation</th>
<th>DBD(n=535)</th>
<th>DCD (n=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>90</td>
<td>80</td>
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<tr>
<td>2</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>60</td>
</tr>
</tbody>
</table>

*American Society of Transplant Surgeons*
Allograft Survival After Liver Transplantation

DCD vs. DBD

*p=0.006

% Graft Survival

Years Post Transplantation

DBD (n=510)
DCD (n=36)
Survival Following Liver Transplantation from Non-Heart-Beating Donors

Abt PL, Desai NM, Crawford MD, et al

<table>
<thead>
<tr>
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<th>NHBD</th>
<th>HBD</th>
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<tr>
<td>N</td>
<td>144</td>
<td>26,856</td>
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<tr>
<td>IPF</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>PNF</td>
<td>11.8%</td>
<td>6.4%*</td>
</tr>
<tr>
<td>HAT</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Biliary</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Retransplant</td>
<td>13.9%</td>
<td>8.3%**</td>
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<tr>
<td>3 yr PS</td>
<td>72.1%</td>
<td>77.4%</td>
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<tr>
<td>3 yr GS</td>
<td>63.3%</td>
<td>72.1%**</td>
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*p=.008, **p=.04
## Number of Transplants from DCD Donors

### University of Wisconsin

<table>
<thead>
<tr>
<th>Type of Transplant</th>
<th>Number of Transplants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney (1984)</td>
<td>537</td>
</tr>
<tr>
<td>Liver (1993)</td>
<td>59</td>
</tr>
<tr>
<td>Pancreas (1993)</td>
<td>49</td>
</tr>
<tr>
<td>Lung (1993)</td>
<td>18</td>
</tr>
</tbody>
</table>

**Total Transplants**

663*  

* As of 8/9/05

- Donor age < 50
- Warm ischemic time (WIT) < 30 min
- Cold ischemic time (CIT) < 8 preferably < 6 hours
- Avoid Retransplantation and technically difficult cases
- Careful surveillance for hepatic artery stenosis and biliary complications
Impact of Hypotension/Inotropic Support on Donor Liver Function

- Studies are variable on the effect of hypotension/inotropic support on graft loss
- No effect on graft loss
  - UNOS data with prolonged hypotension without increased graft loss
    - Only age > 55 was significant
    - Only age > 65 and steatosis impacted graft survival
Impact of Hypotension/Inotropic Support on Donor Liver Function

- Negative impact on graft function and survival
  - Opelz G, Wujciak T, NEJM 1994;330816-819
    - Use of norepinephrine
  - Markmann JF et al, Transplantation 2001;72:1113-1122
    - Dopamine > 10µg/kg/min
    - Dopamine > 15µg/kg/min
Recommendations on Donor Livers with Hypotension/Inotrope Support

- Take hypotension and vasopressor support into consideration with other known donor and recipient risk factors
Donor Liver Biochemical Abnormalities

- Serum Sodium > 155 meq/L
  - Literature variable, but overall low relative risk
    - Busuttil RW, Tanaka K  Liver Transp 2003;9:651-663
      - Increased AST, ALT, LDH with serum Na > 153 meq/L
  - No impact on graft function or survival
- Donor management with D5W to lower sodium below 155 meq/L
Donor Liver Biochemical Abnormalities

- Elevated hepatocellular enzymes secondary to cardiac arrest, hypotension and trauma
  - Evaluate other donor risk factors
  - Follow maximum elevation and if trend is downward consider recovery
  - CT scan to evaluate degree of trauma to donor liver
  - Visual inspection at time of recovery
  - Donor liver biopsy to assess for ischemic changes
Impact of Gender Mismatch on Liver Graft Survival

- Rustgi VK et al, Liver Transp;2002;8:514-518
  - Higher likelihood of graft failure when gender mismatched
  - Male to female no increased graft failure (11.5%)
  - Female to male increased graft failure (12.9%; p = .003)
- Gender matched allocation not practical in current allocation scheme
Transplantation of Donor Livers with Hepatitis B and C

- Transmission of HBV with HBcore(HBc) positive donor livers up to 78% if untreated
- Transmission of HBV with Hbsurface antibody(HBs) positive donor livers negligible
- Dickson RC et al, Gastroenterology 1997:113:1668-1674
Transplantation of Donor Livers with Hepatitis B and C

- Impact of treatment of HBc positive donor livers with HBIG and Lamivudine
  - Dodson SF et al, Transplantation 1999;68:1058-1061
    - 15/15 transplanted with HBc donor livers into recipients HbsAg- and Hbs- HBV free > 1yr
  - Manzarbeitia C et al, Liver Transplantation 2002;8: 556-561
    - 1 yr patient survival in recipients of HBc+ positive donor livers 88.6%
Impact of Transplanting HCV+ donor livers

- Avoid HCV+ donor livers to HCV- recipients except in extreme situations
- HCV+ donor livers into HCV+ recipients
  - Testa G et al, Transplantation 1999;65:925-929
    - 22 HCV+ grafts and recipients: no difference in rates of recurrence and 4 yr patient and graft survival
  - Marroquin CE et al, Liver Transplantation 2001;7:762-768
    - SRTR data: 96 HCV+ grafts and recipients vs. 2,287 HCV+recipients,HCV-grafts
    - Patient survival higher in recipients of HCV+ donor livers 2 yr after transplantation: 90% vs. 77% (p=.01)
Recommendations for Transplantation of Donor Livers with Hepatitis B and C

- HBs+ donor livers acceptable for transplantation
- HBc+ donor livers
  - High rate of false positive antibody testing
  - Nucleic acid testing (NAT) more accurate
  - If HBc+ and IgM- select patient that is HbsAg, Hbc, or HBs positive and possibly antibody – patient with higher MELD score and treat with HBIG and lamivudine until DNA testing finalized
  - If HBc+ and IgM+ select antibody + recipients and only very high MELD antibody – recipients and treat as above
  - Need to inform and consent antibody – recipients of Hbc+ donor livers
Recommendations for Transplantation of Donor Livers with Hepatitis B and C

- HCV+ donor livers
  - Only in extreme situations into HCV- recipients
  - Acceptable for transplantation into HCV+ recipients
    - Donor liver biopsy with minimal changes
Liver Donors with Malignancies

- Central Nervous System (CNS) Tumors
  - Overall risk of transmission is low
    - Kaufmann HM et al, Transplantation 2002;73:579-582
      - 293 recipients with livers from donors with CNS malignancy 1992-1999
      - No transmission of malignancy
  - Risk of transmission higher with craniotomy and ventriculo-peritoneal shunt
  - Glioblastoma and medulloblastoma have a higher risk of transmission and should be avoided except in risk-appropriate recipient
Liver Donors with Malignancies

Non-CNS Malignancies

- 17 documented cases of transmission
  - Melanoma(5), Choriocarcinoma(3), Glioblastoma(3), Adenocarcinoma(3), Kaposi’s sarcoma(1), neuroendocrine(1), squamous cell(1)

Consider type of malignancy and cancer-free interval

- Low risk: Hodgkins lymphoma, Seminoma
- High risk: Melanoma, Choriocarcinoma
- Unpredictable: Breast, colon, lung, renal cell carcinoma
Split Liver Transplantation (SLT)

- Benefits of SLT
  - Increase deceased donor liver supply
  - Decrease pediatric wait-list time with adult/pediatric SLT
  - Decrease pediatric wait-list morbidity and mortality
  - Decrease adult wait-list times with adult/adult SLT
  - Decrease utilization of live liver donation
Split Liver Transplantation (SLT)

- Adult/pediatric SLT
  - National survey of 83 teams reporting on 207 left lateral segments, 152 right trisegments, 15 left lobes and 13 right lobe transplants
  - Patient and graft survival worse with increased severity of illness, but comparable to whole organ transplants
  - Graft complications significantly higher
    - Left lateral segment- overall 32% complication rate
      Biliary and vascular most common complications
Split Liver Transplantation (SLT)

- **Adult/pediatric SLT**
  - Graft complications
    - Right trisegment results in regards to complications improved compared to LLS
    - Overall 26% complications: 11% biliary and 5% vascular
    - Segment 4 necrosis reported with RTS
  - Graft sharing between centers reported
    - Yersiz H et al; Annals of Surgery; 238(4):496-507
    - 25 grafts shared (22 RTS/3LLS) with 8 centers

[ASTS logo]
Split Liver Transplantation (SLT)

- **Adult/Adult**
    - 85 cases reported, primarily European
        - 34 cases
        - PS similar at one year
        - GS decreased at one year particularly in left-SLT
        - 22% biliary and 15% vascular complications
        - Biliary complications higher in left-SLT and vascular complications higher in right-SLT
Split Liver Transplantation (SLT)

- **Adult/Adult**
    - 18 adult/adult SLT
    - PS: R-SLT 89%; L-SLT 78%
    - Graft Complications: 27% Biliary and 11% vascular

- Overall results of Adult/Adult SLT
  - Complication rate similar between R-SLT and L-SLT
    - Biliary higher in L-SLT and vascular higher in R-SLT
    - Graft survival higher in R-SLT
  - Current allocation limits flexibility of adapting donors to optimal recipients
Other Potential Sources of Donor Livers

- Lopez-Navida A, Caballero F, Clinical Transplantation 2003;17:308-324
  - Poisoned Donors
    - Ethylene glycol, cyanide, acetaminophen, amanita phalloides, carbon monoxide and others
  - Grafts from transplant recipients
    - Liver, kidney, pancreas
  - Reuse of grafts
    - Liver and kidney
  - Domino transplants
    - Familial Amyloidosis
# Liver Transplantation: Expanding the Donor Pool

## Summary*

<table>
<thead>
<tr>
<th>Potential Donor Risk Factors</th>
<th>Potential Donor Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>CIT</td>
</tr>
<tr>
<td>Gender</td>
<td>Increased Na</td>
</tr>
<tr>
<td>Race</td>
<td>Steatosis</td>
</tr>
<tr>
<td>CVA</td>
<td>Split grafts</td>
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<tr>
<td>ICU stay</td>
<td>DCD</td>
</tr>
<tr>
<td>Inotropic support</td>
<td>Viral</td>
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</tbody>
</table>

*Modified from Busuttil RW, Liver Transp 2003;9(7):651-663*
Liver Transplantation: Expanding the Donor Pool

Summary

Potential Perioperative Risk Factors
- WIT
- Technical
- Blood Products

Potential Recipient Risk Factors
- Age
- Medical Status
- Renal Insufficiency
- Retransplantation
- Inotropics

*Modified from Busuttil RW Liver Transp 2003;9(7):651-663

ASTS
American Society of Transplant Surgeons
Liver Transplantation: Expanding the Donor Pool

Conclusions

- There are numerous ways to maximize the number of donor livers for transplantation.
- Awareness of potential donor risk factors as well as recipient risk factors is essential to maximizing outcomes.
- Expanded Criteria Liver Donors may have an increased relative risk of graft loss.
- However, use of ECD livers in appropriate recipients will decrease pre-transplant wait list mortality.