Liver Transplantation: Expanding the Donor Pool

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UNOS Current Waiting List

Type of Transplant	# of Patients Waiting
Kidney	60,986
Liver	17,290
Lung	3,806
Heart	3,214
Heart-Lung	173
Kidney-Pancreas	2,434
Pancreas	1,687
Intestine	191
Total Patients:	**87,700**

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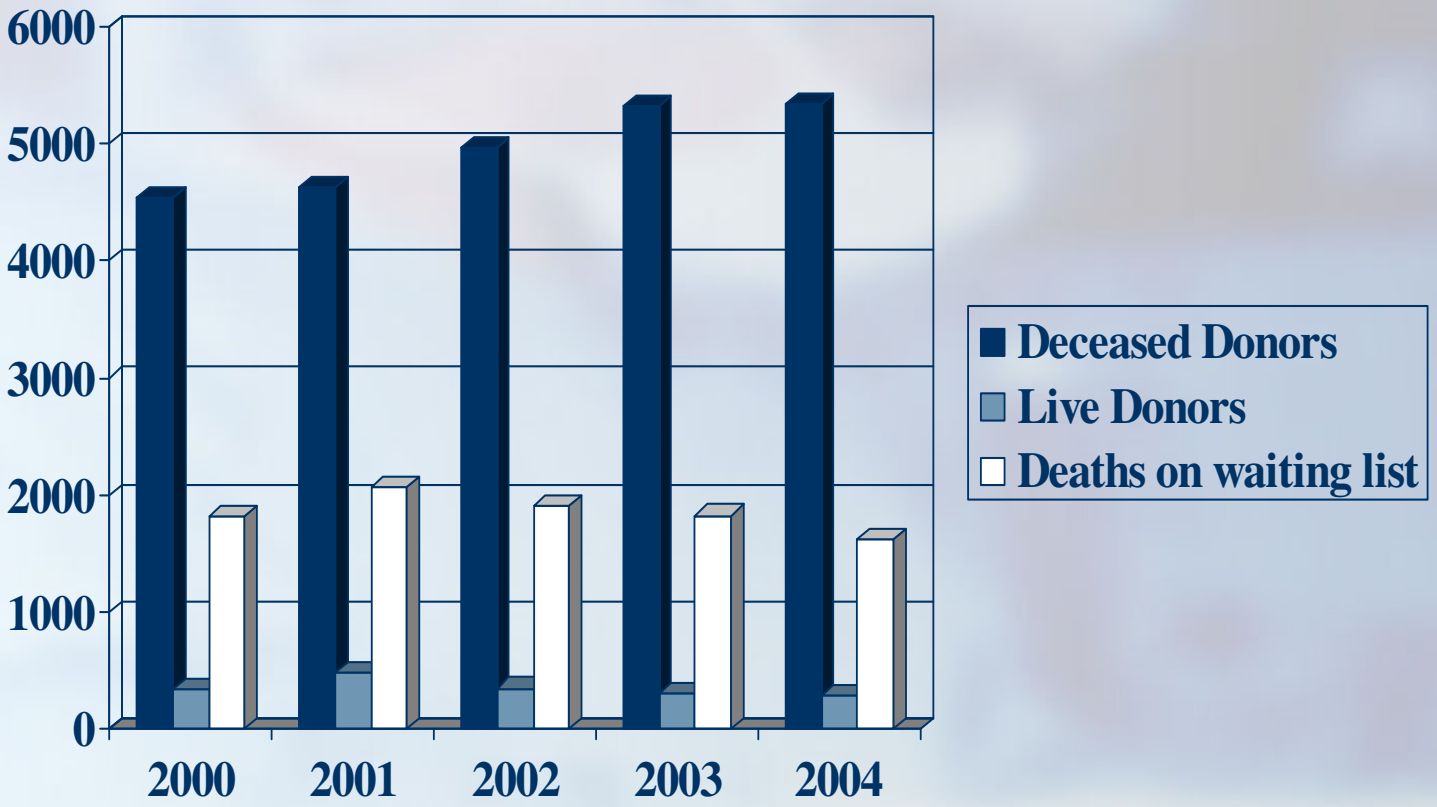
Deceased Donor and Live Liver Transplants 2000-2004



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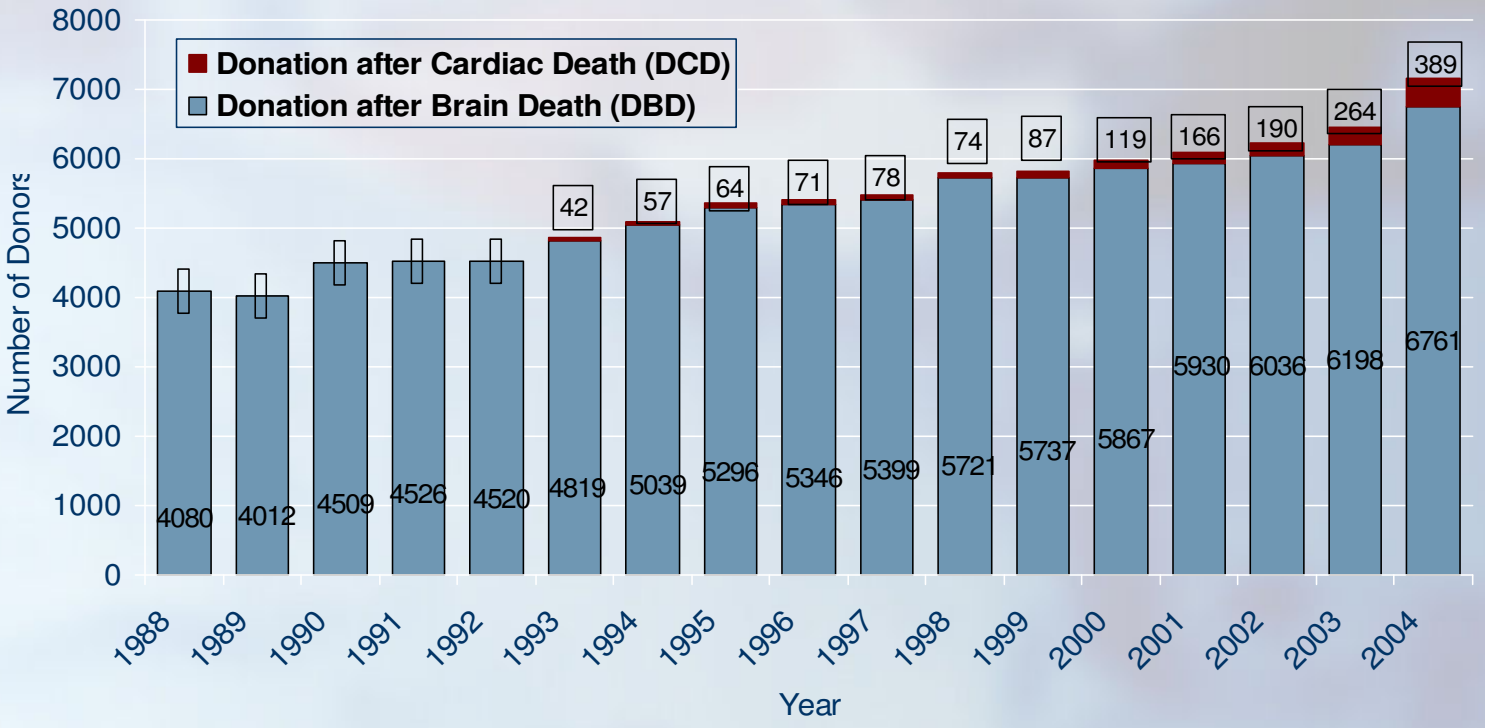
Deceased Organ Donors

DCD and DBD



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UNOS data through 12/31/04

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

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Specific Donor Criteria of ECD Livers

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

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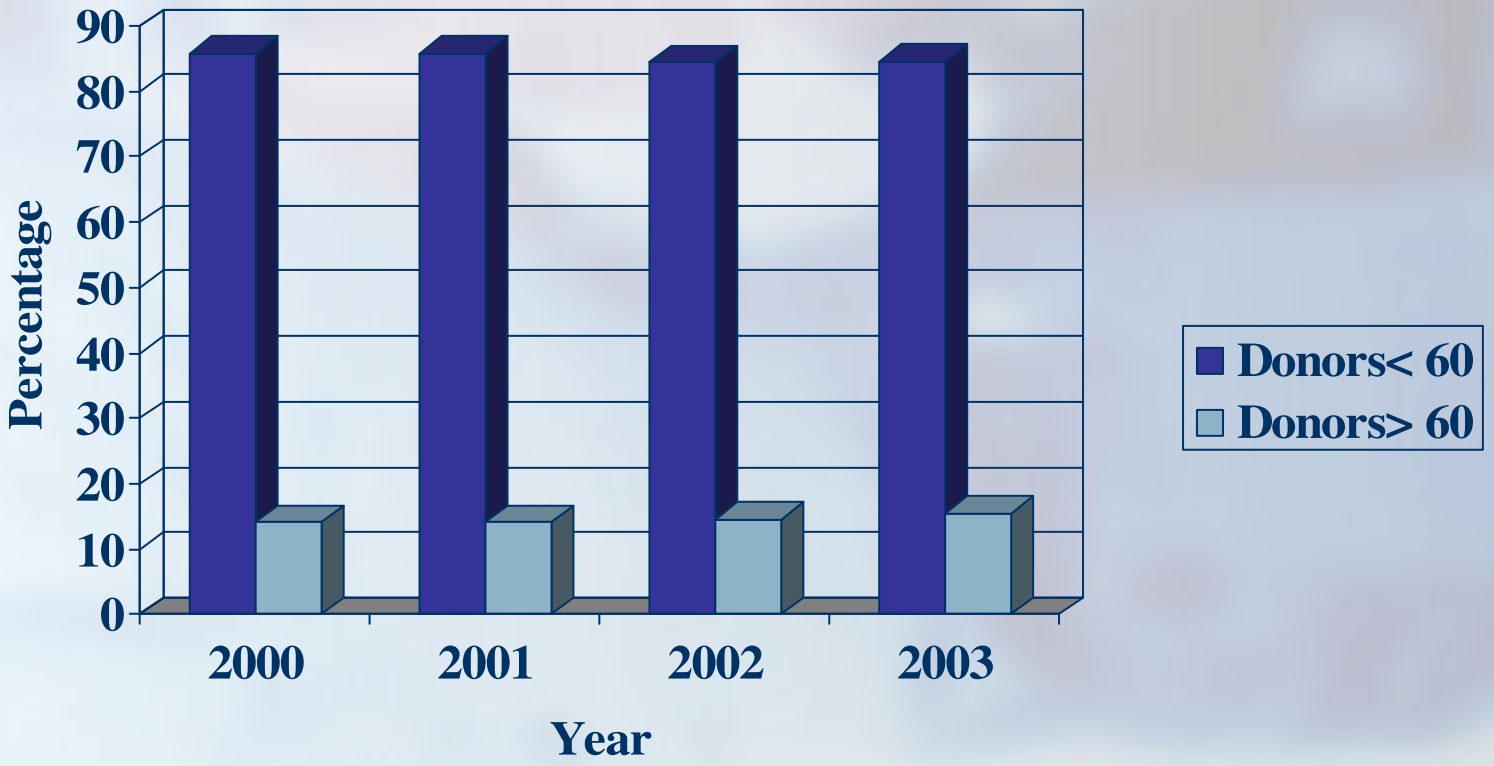
Deceased Donor Age 2000-2003



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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

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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%

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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

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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

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Steatotic Donor Livers: Impact on Graft Function

- Macrovesicular steatosis
  - D'Alessandro A et al, Transplantation 1991;51:157-163
    - 0-33% no difference
    - 33-66% increased IPF
    - > 66% increased PNF
  - Marsman WA et al, Transplantation 1996;62:1246-1251
    - Up to 30% steatosis, decreased 4 mo graft survival
    - Worse results if patient critically ill

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Steatotic Donor Livers: Impact on Graft Function

- Microvesicular Steatosis
  - Safely expands the donor pool
    - Fishbein TM et al, Transplantation 1997;64:248-251
    - Brinceno J et al, Transp Int 2000:32:2101-2102
      - Scoring for marginal grafts

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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

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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
  - Briceno J et al, Transplantation 2002;74:522-526
    - One of five factors including CIT, age, pressors, steatosis and ICU stay leading to preservation injury

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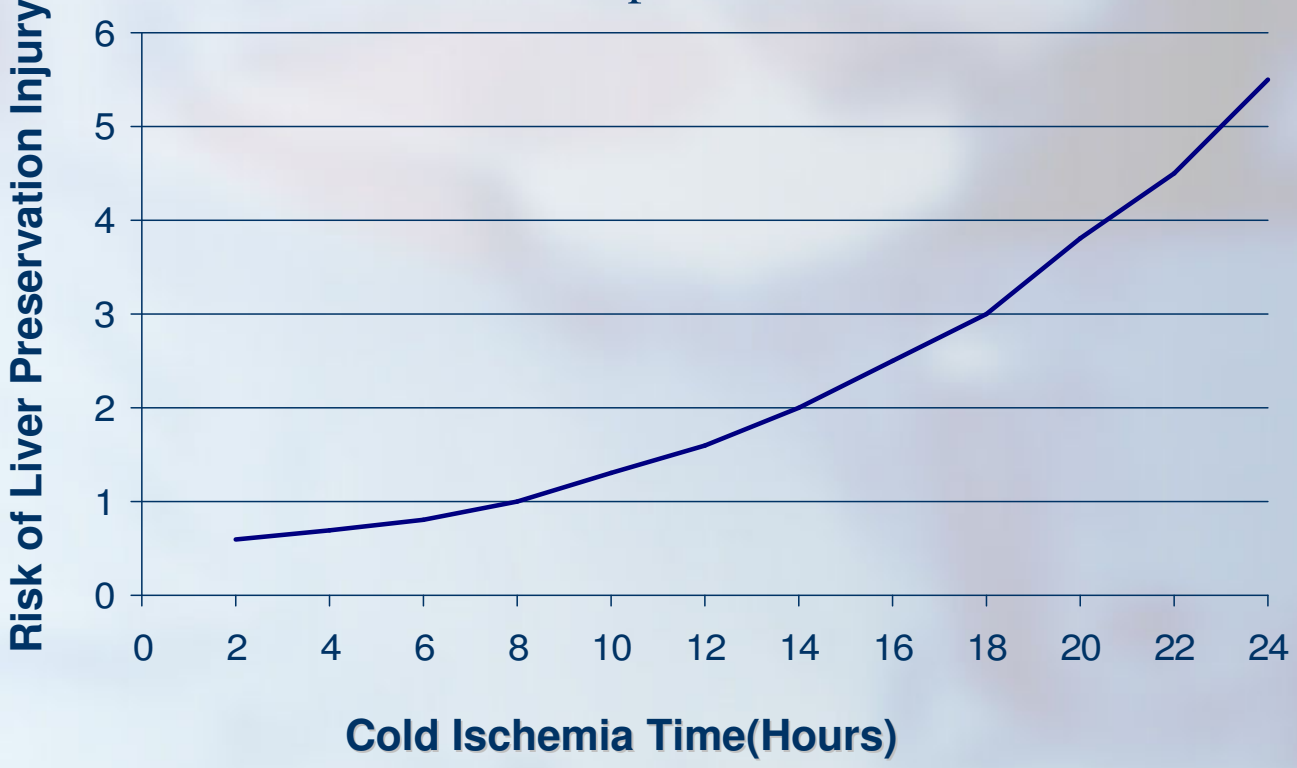
Cold Ischemic Time and Risk of Liver Preservation Injury

Bricano J et al, Transplantation 2002; 74:522-526



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Cold Ischemic Time and Probability of Dysfunction

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

- Formula for marginal liver
  - (20.06 X Steatosis) + (.44 X Donor Age)
  - 23.6 is cutoff for marginal liver

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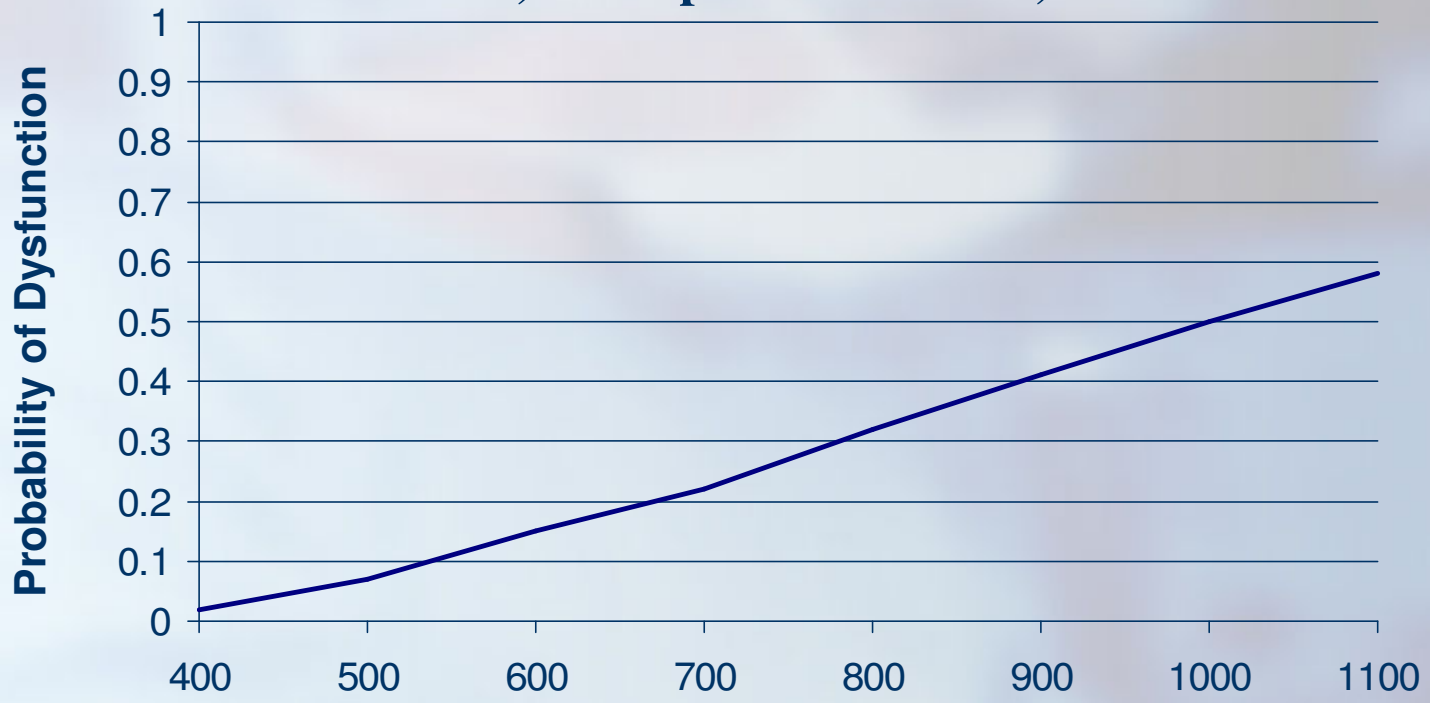
Cold Ischemic Time and Probability of Dysfunction-Marginal Donors

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



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Cold Ischemic Time and Probability of Dysfunction

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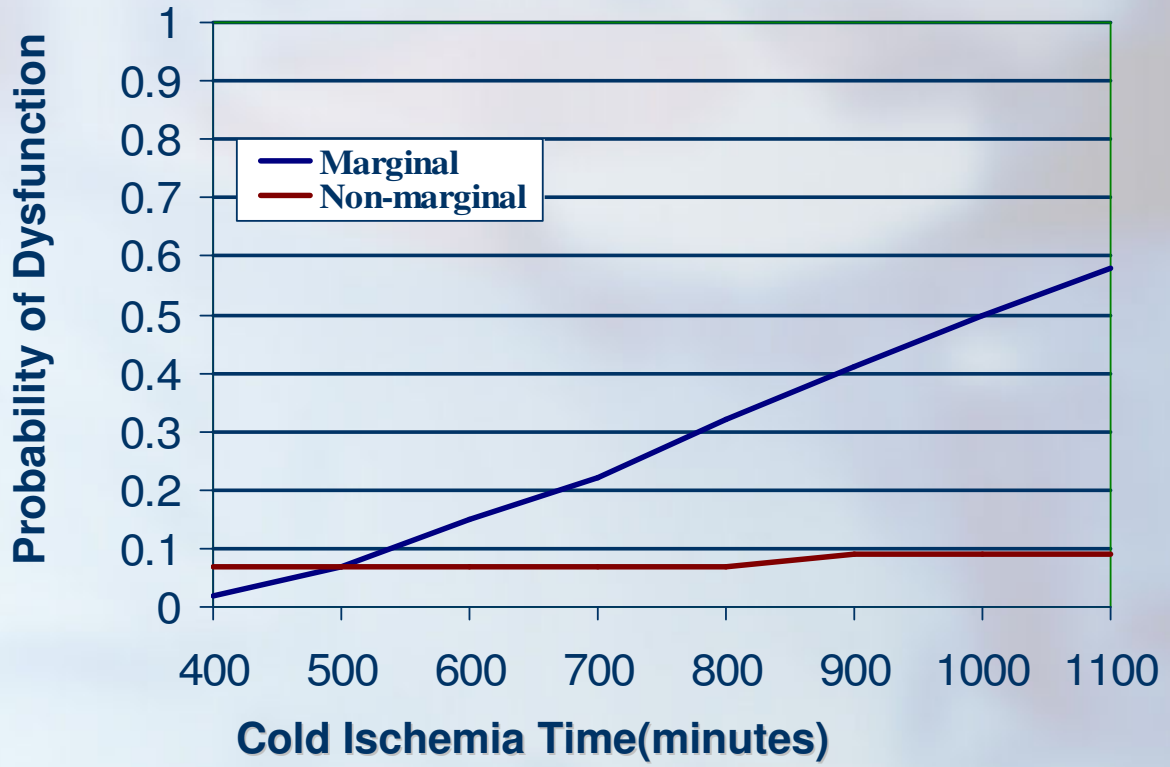

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Recommendations on CIT in Liver Transplantation

- 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

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Donation after Cardiac Death (DCD)

The University of Wisconsin Experience with Liver Transplantation

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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

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DCD Liver Transplantation

Donor Characteristics

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

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*p=0.05

**p=0.0001

DCD Liver Transplantation

Postoperative Laboratory Values

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

**p<.001*

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DCD Liver Transplantation

Postoperative Laboratory Values

	Postoperative Day			
	7		Discharge	
	DCD	DBD	DCD	DBD
AST (u/L)	53±32	96±310	46±40	37±34
ALT (u/L)	202±120	272±121	132±68	122±68
LDH (u/L)	251±79	272±79	201±56	192±56
GGT (u/L)	325±161*	276±225	447±380*	251±229
ALP (u/L)	156±63*	143±81	261±236*	119±131
PT/INR (sec)	13.3±1.4 / 1.2±.18	13.3±1.9 / 1.2±.21	12.9±1.7 / 1.14±.15	12.6±1.7 / 1.1±.34

*p<0.001

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DCD Liver Transplantation

Complications

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

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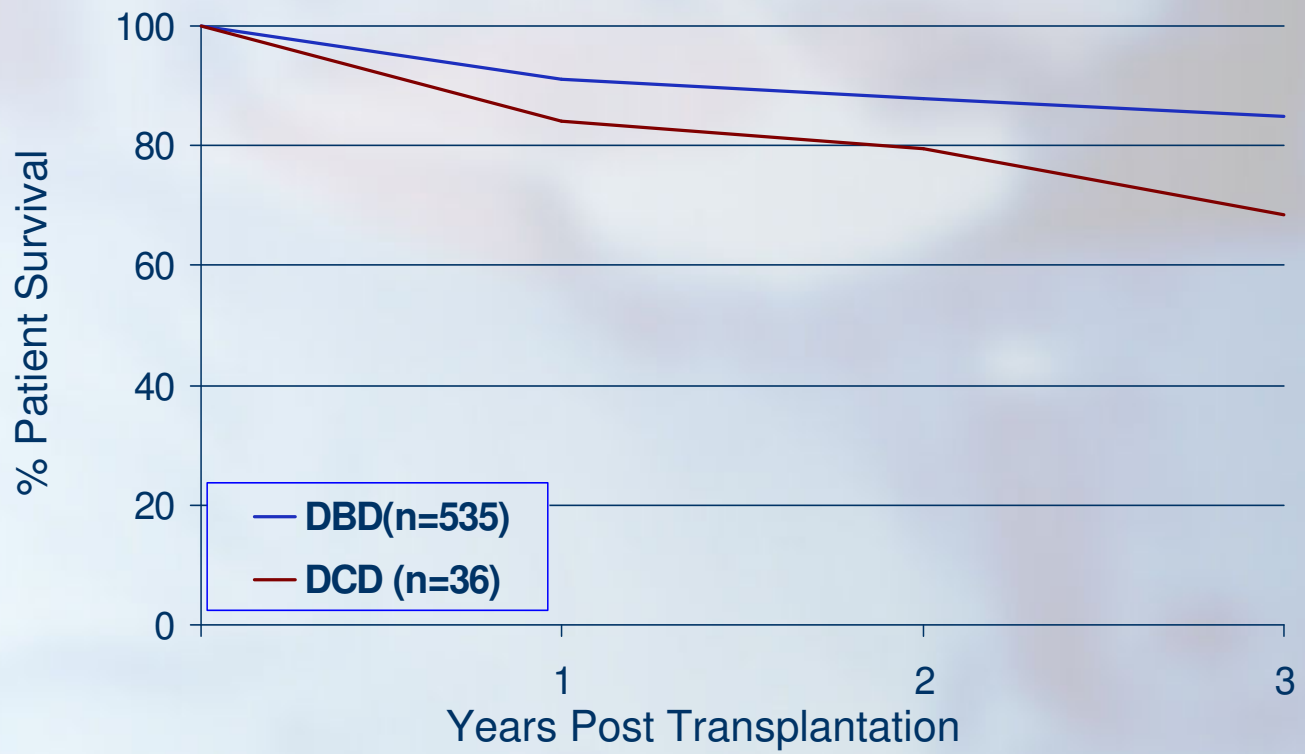
*p=0.001,**p=04.

Patient Survival After Liver Transplantation

DCD vs. DBD



*p=0.01

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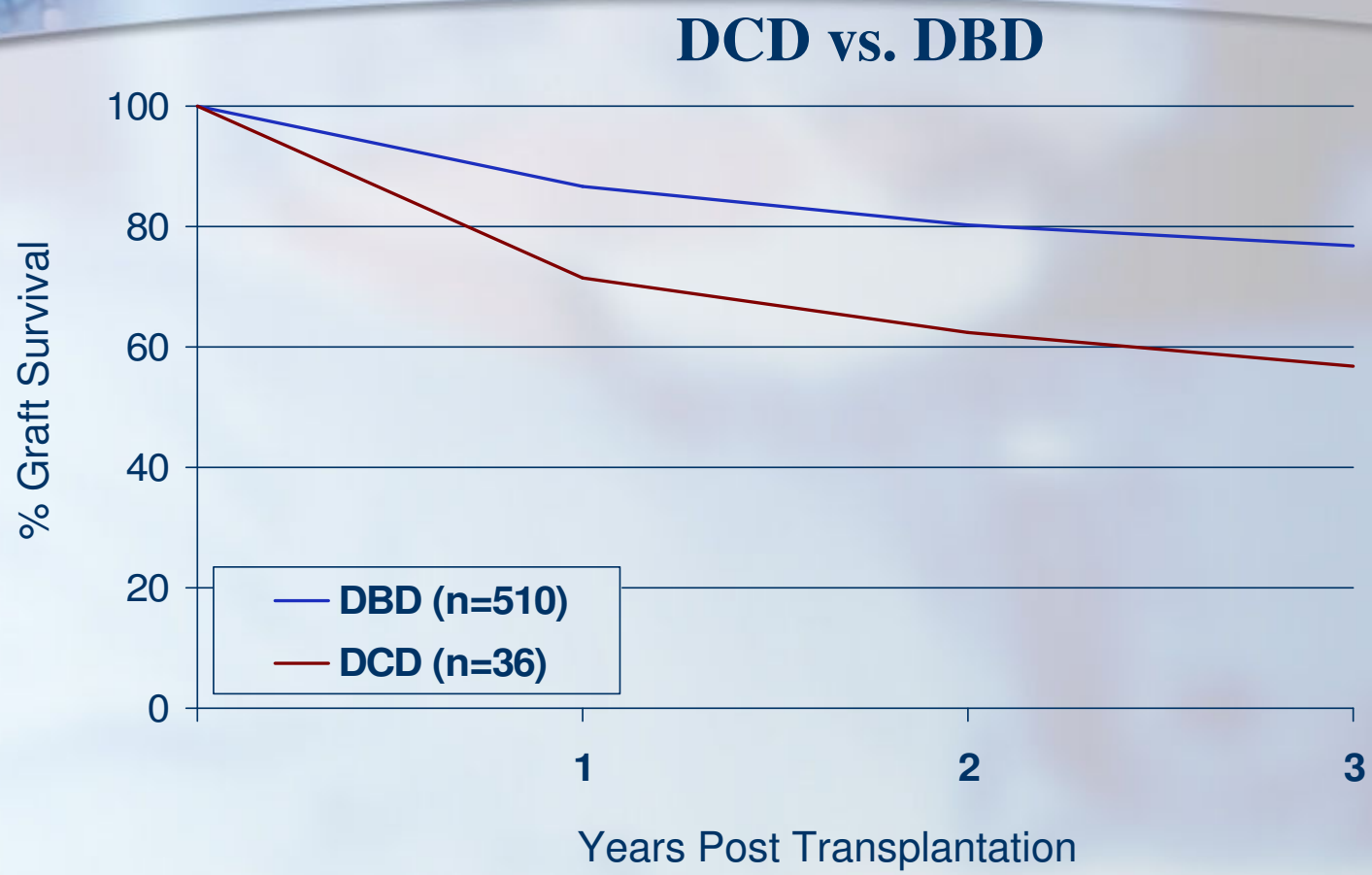
Allograft Survival After Liver Transplantation



*p=0.006

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Survival Following Liver Transplantation from Non-Heart- Beating Donors

Abt PL, Desai NM, Crawford MD, et. Al
Ann Surg 2004;239(1):87-92

	NHBD	HBD
N	144	26,856
IPF	--	--
PNF	11.8%	6.4%*
HAT	--	--
Biliary	--	--
Retransplant	13.9%	8.3%**
3 yr PS	72.1%	77.4%
3 yr GS	63.3%	72.1%**

p=.008, **p=.04

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Number of Transplants from DCD Donors

University of Wisconsin

Type of Transplant	Number of Transplants
Kidney (1984)	537
Liver (1993)	59
Pancreas (1993)	49
Lung (1993)	18
Total Transplants	**663***

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** As of 8\9\05*

Recommendations Regarding DCD Donor Liver Transplantation

- Foley DP et al, Annals of Surgery 2005 (in press)
  - 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

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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
  - Rocha MB et al, Transp Proc 2004;36:914-915
    - Only age > 55 was significant
  - Rull R et al, Transp Proc 2002;34:229-230
    - Only age > 65 and steatosis impacted graft survival

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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
  - Briceno J et al, Transplantation 2002;74:522-526
    - Dopamine > 15µg/kg/min

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Recommendations on Donor Livers with Hypotension/Inotropic Support

- Take hypotension and vasopressor support into consideration with other known donor and recipient risk factors

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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
    - Cieslak AA et al, Transp Proc 2003;35:2256-2259
      - Increased AST, ALT , LDH with serum Na > 153 meq/L
  - No impact on graft function or survival
    - Briceno J et al, Transplantation 2002;74:522-526
    - Rocha MB et al, Transp Proc 2004;36:914-915
- Donor management with D5W to lower sodium below 155 meq/L

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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

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Impact of Gender Mismatch on Liver Graft Survival

- Rustgi VK et al, Liver Transp;2002;8:514-518
  - UNOS data 1992-2000
  - 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

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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

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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%

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Transplantation of Donor Livers with Hepatitis B and C

- 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)

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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

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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

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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

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Liver Donors with Malignancies

- Non-CNS Malignancies
  - 17 documented cases of transmission
    - Kauffman HM et al, Transplantation 2002;74:358-362
      - 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

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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

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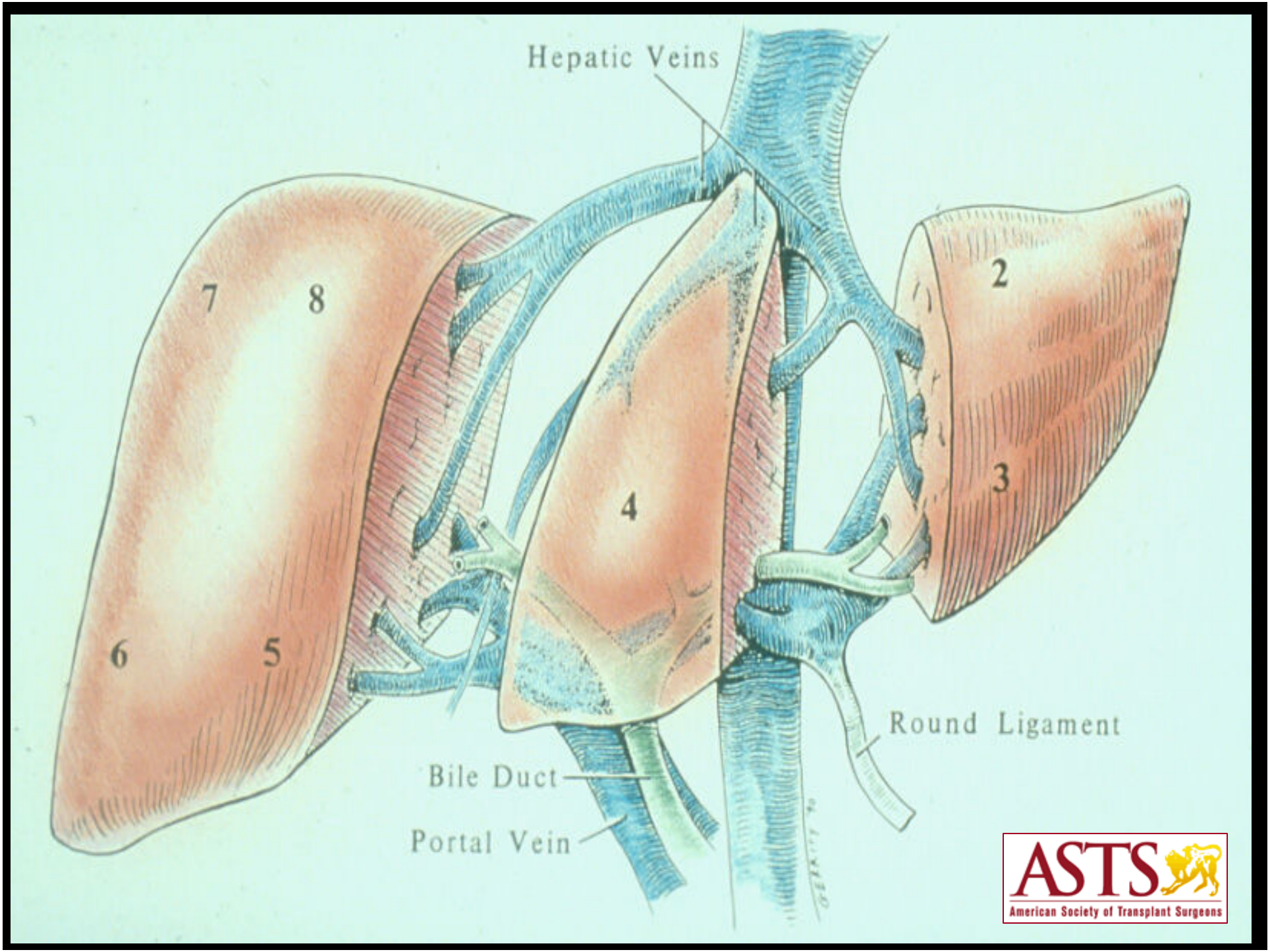
Hepatic Veins
7
8
2
4
3
6
5
Round Ligament
Bile Duct
Portal Vein
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Split Liver Transplantation (SLT)

- Adult/pediatric SLT
  - Renz JF et al, Annals of Surgery 2004;239(2):172-181
    - 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

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Split Liver Transplantation(SLT)

- Adult/pediatric SLT
  - Renz JF et al, Annals of Surgery 2004;239(2):172-181
    - 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

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Split Liver Transplantation(SLT)

- Adult/Adult
  - Renz JF et al, Annals of Surgery 2004;239(2):172-181
    - 85 cases reported, primarily European
      - Azoulay D et al, Annals of Surgery 2001;233:565-574
        - 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

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Split Liver Transplantation(SLT)

- Adult/Adult
  - Humar A et al, Am J Transplant 2001:1:366-372
  - Humar A et al, Transplant 2001, May12-16, 2001
    - 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

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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

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Liver Transplantation: Expanding the Donor Pool Summary*

- Potential Donor Risk Factors
  - Age
  - Gender
  - Race
  - CVA
  - ICU stay
  - Inotropic support
- Potential Donor Risk Factors
  - CIT
  - Increased Na
  - Steatosis
  - Split grafts
  - DCD
  - Viral

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

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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
  - Inotropic support

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

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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

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