参考資料１

レシピエント選択基準変更前後のシッピング

旧基準　（1995.4.1 ～ 2002.1.9　N=1,063）
新基準　（2002.1.10～2009.12.31　N=1,327）

	同一県内	ブロック内 県外	ブロック外	小児
旧基準	29.0 %	58.9%	12.1 %	2.7 %
新基準	81.5 %	18.3%	0.2%	6.6%

レシピエント選択基準変更前後の
HLA不適合抗原数・ドナー年齢・阻血時間

旧基準　（1995.4.1 ～ 2002.1.9　N=1,063）
新基準　（2002.1.10～2009.12.31　N=1,327）

	HLA不適合抗原数 （検索型）		ドナー 年齢	温阻血 時間	総阻血 時間
	DR	AB		（分）	（分）
旧基準	0.11 ± 0.34	1.28 ± 0.98	45.44 ± 17.11	7.94 ± 10.85	861.09 ± 402.95
新基準	0.51 ± 0.54	2.17 ± 0.97	48.94 ± 15.65	7.19 ± 8.97	731.01 ± 359.00
	（P<.001）	（P<.001）	（P<.001）		（P<.001）

レシピエント選択基準変更前後の
レシピエント年齢・待機期間・透析期間

旧基準　（1995.4.1 ～ 2002.1.9　N=1,063）
新基準　（2002.1.10～2009.12.31　N=1,327）

	レシピエント年齢（全体）	レシピエント年齢（16歳以上）	待機期間（年）	透析期間（年）
旧基準	44.60 ± 11.22	45.56 ± 9.80	6.76 ± 4.86	10.12 ± 6.21
新基準	47.44 ± 12.88	50.05 ± 8.58	14.27 ± 5.37	17.24 ± 6.70
	(P<.001)	(P<.001)	(P<.001)	(P<.001)

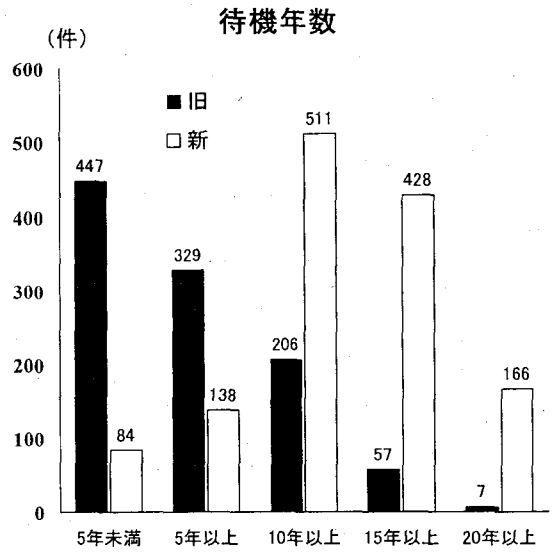
レシピエント選択基準変更前後の
レシピエント待機日数・透析日数

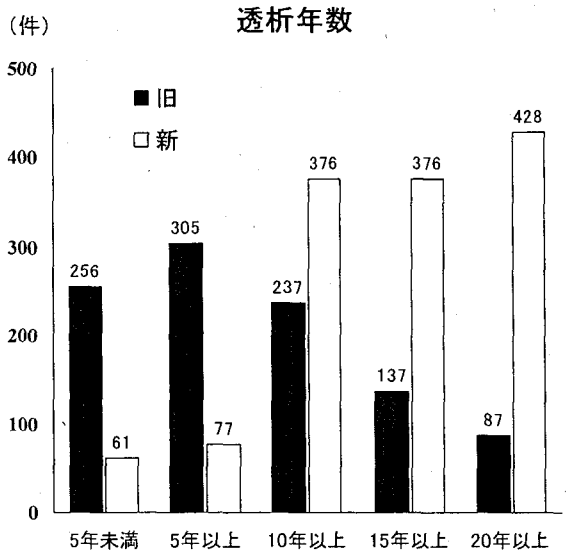
旧基準　（1995.4.1 ～ 2002.1.9　N=1,063）
新基準　（2002.1.10～2009.12.31　N=1,327）

		待機日数	透析日数	
旧基準		2467.04±1772.57	3694.26±2265.90	(P<.001)
新基準	全体	5207.99±1958.52	6292.61±2446.02	
	16歳以上	5521.06±1610.10	6631.28±2141.61	(P<.001)
	16歳未満	800.19±724.71	1489.00±1042.23	

選択基準変更前後の待機年数および透析年数
（腎単独移植のみ）

旧基準　（1995.4.1 ～ 2002.1.9　N=1,063）
新基準　（2002.1.10～2009.12.31　N=1,327）





レシピエント選択基準変更前後の生存率・生着率

旧基準　（1995.4.1 ～ 2002.1.9　N=1,063）
新基準　（2002.1.10～2009.12.31　N=1,327）

生存率（%）

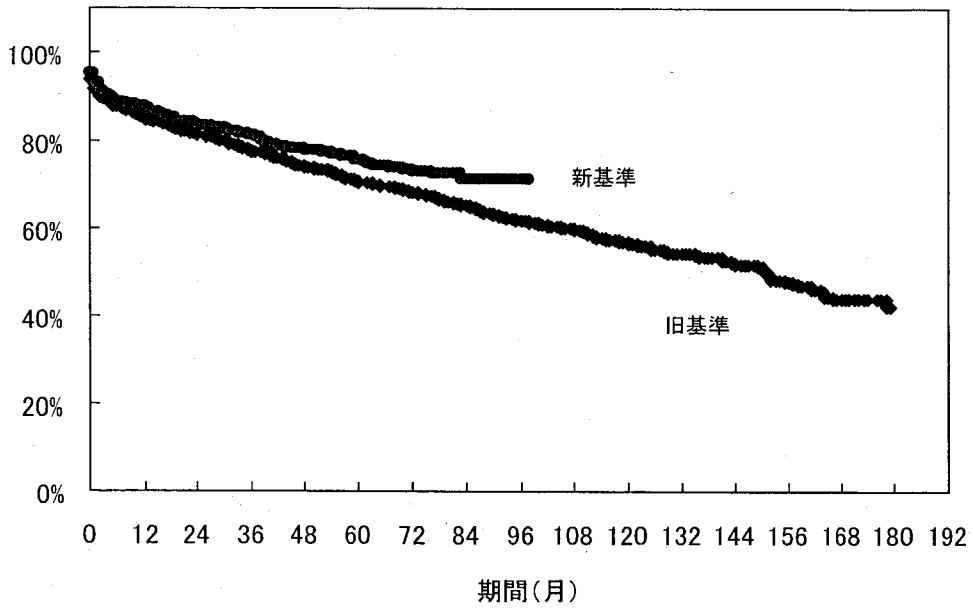
	1カ月	1年	3年	5年	(Logrank)
旧基準	98.2	95.3	91.5	89.3	p=0.135
新基準	98.0	96.1	93.7	91.7	

生着率（%）

	1カ月	1年	3年	5年	(Logrank)
旧基準	91.7	84.9	77.5	70.5	p=0.014
新基準	93.1	87.5	81.2	75.6	

生着率　選択基準別

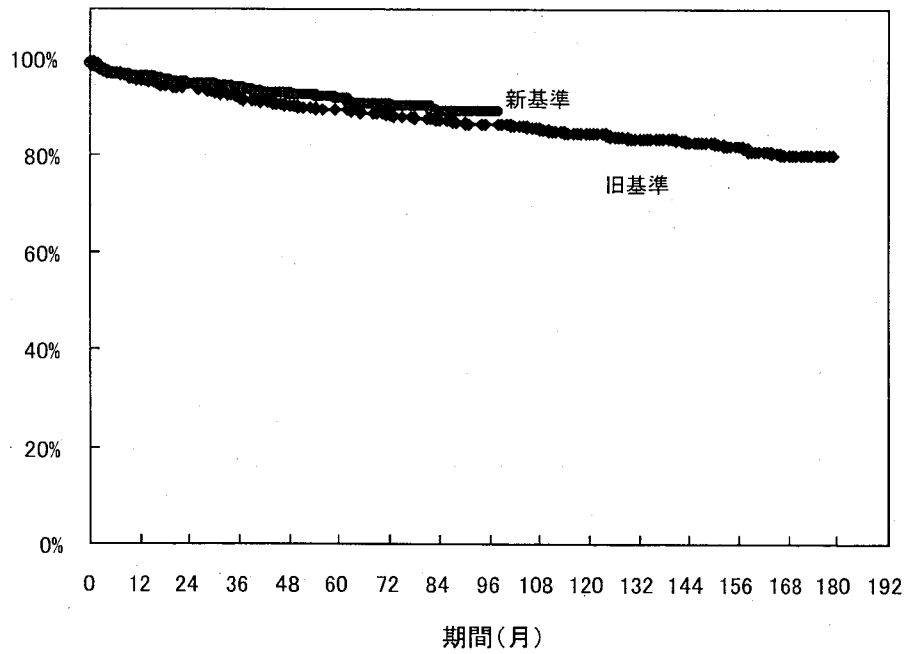
旧基準　　(1995.4.1 ～2002.1.9　　N=1,063)
新基準　　(2002.1.10～2009.12.31　N=1,327)



p=0.014

生存率　選択基準別

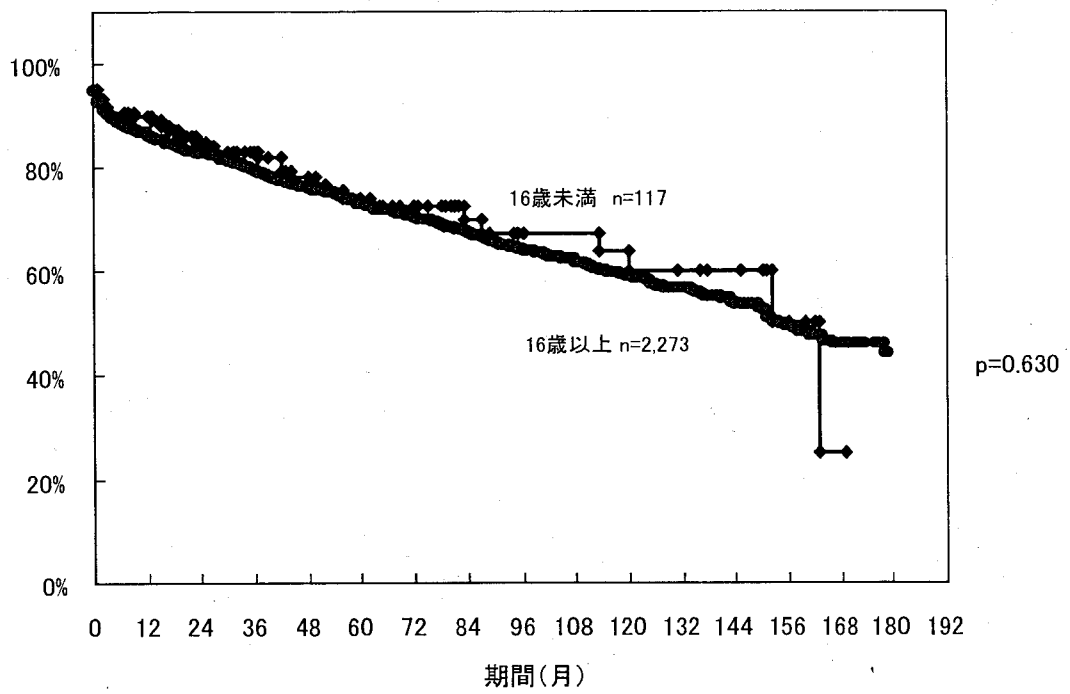
旧基準　　(1995.4.1 ～2002.1.9　　N=1,063)
新基準　　(2002.1.10～2009.12.31　N=1,327)



p=0.135

生着率　16歳未満・以上

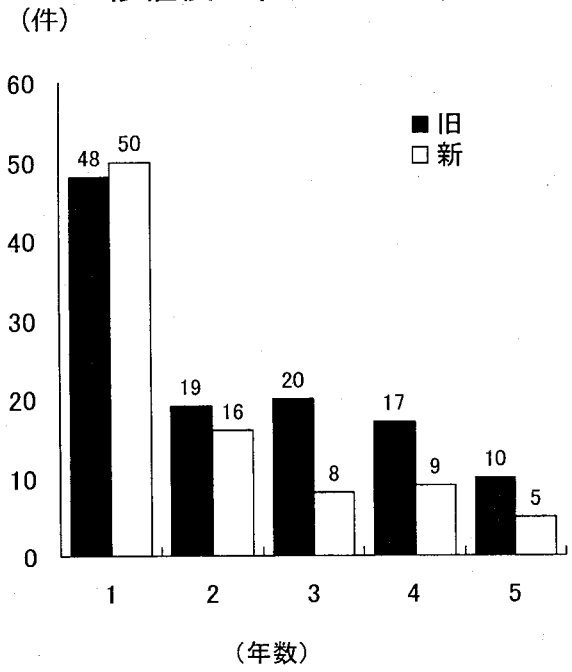
（1995.4.1～2009.12.31）



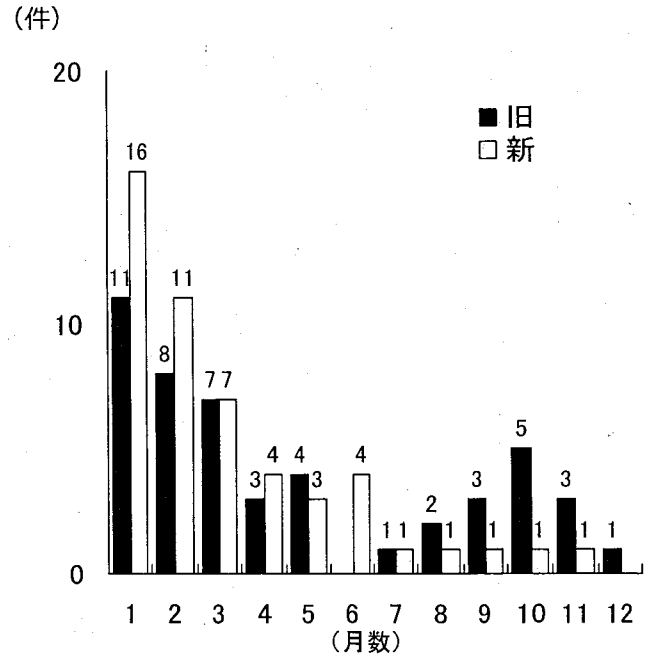
レシピエント選択基準変更前後の移植後死亡数

旧基準　（1995.4.1 ～ 2002.1.9　N=1,063）
新基準　（2002.1.10～2009.12.31　N=1,327）

移植後5年以内死亡数



移植後1年以内死亡数



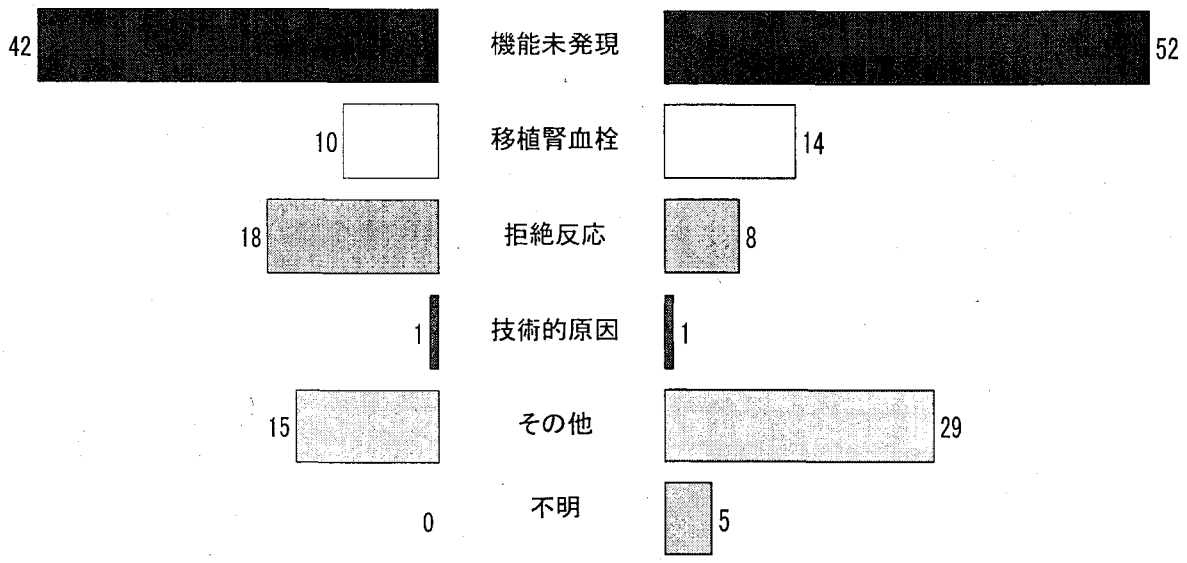
レシピエント選択基準変更前後の移植後無機能腎・術後透析期間・死亡・生着率

旧基準　（1995.4.1 ～ 2002.1.9　N=1,063）
新基準　（2002.1.10～2009.12.31　N=1,327）

	離脱不能（%）	機能未発現（%）	術後透析期間（日）	移植後死亡(%) 3カ月	6カ月	12カ月
旧基準	8.1	4.0	15.07±63.81	2.7	3.2	4.7
新基準	8.2	3.9	12.92±19.71	2.6	3.4	3.8

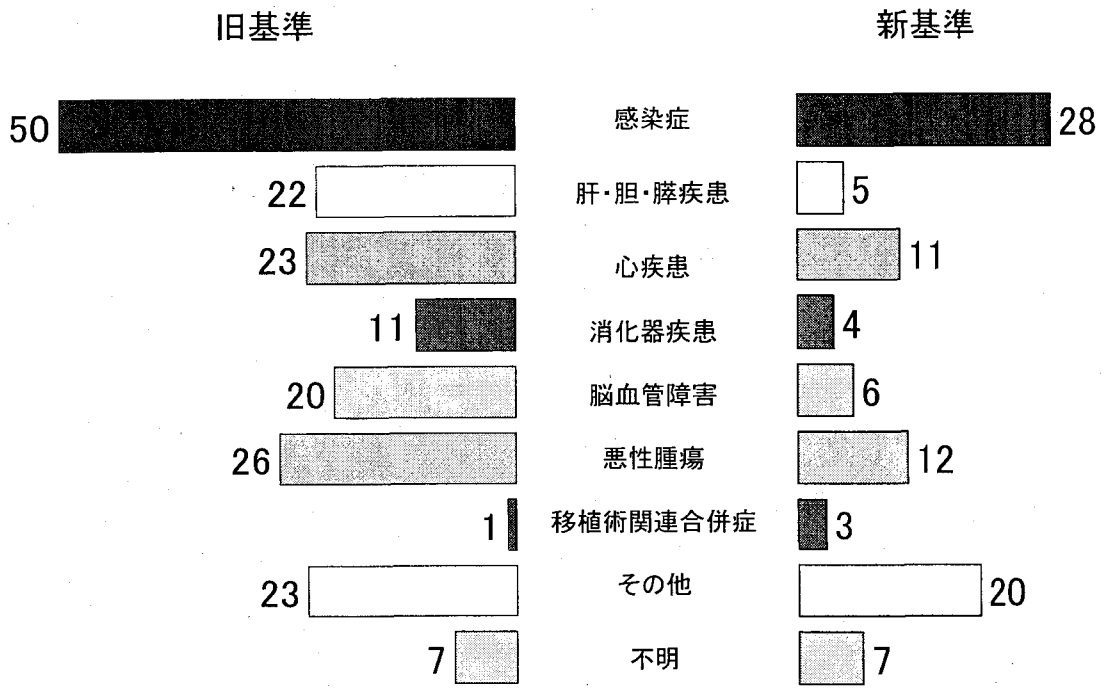
透析離脱不能例とその原因

旧基準		新基準
86/1063 (8.1%)	透析離脱不能例	109/1327(8.2%)
42/1063 (4.0%)	機能未発現	52/1327 (3.9%)

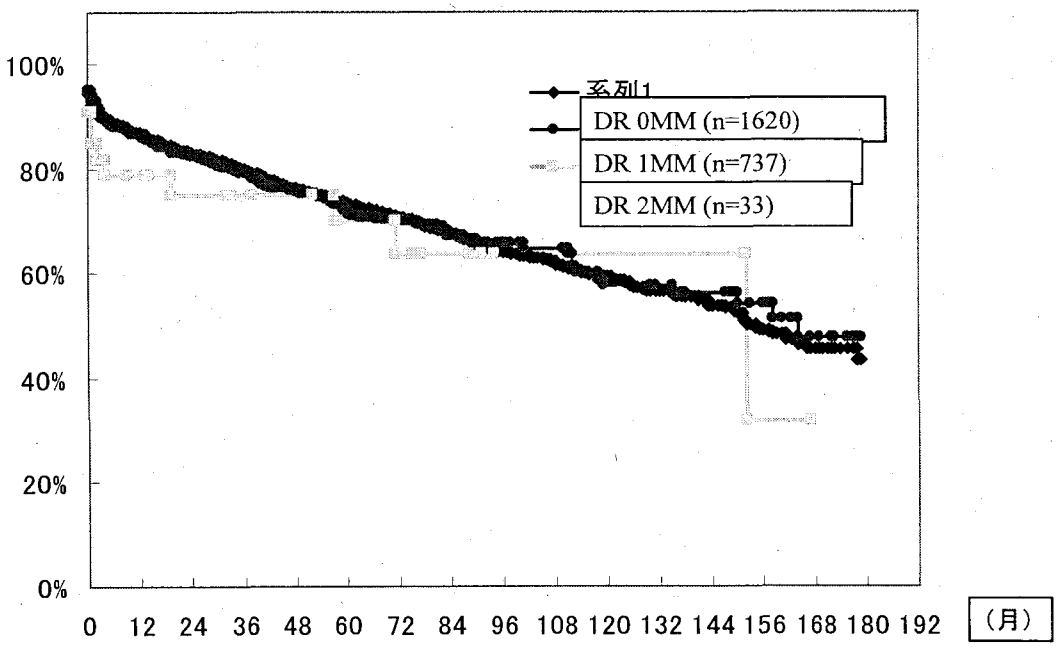


レシピエント選択基準変更前後の移植後死因

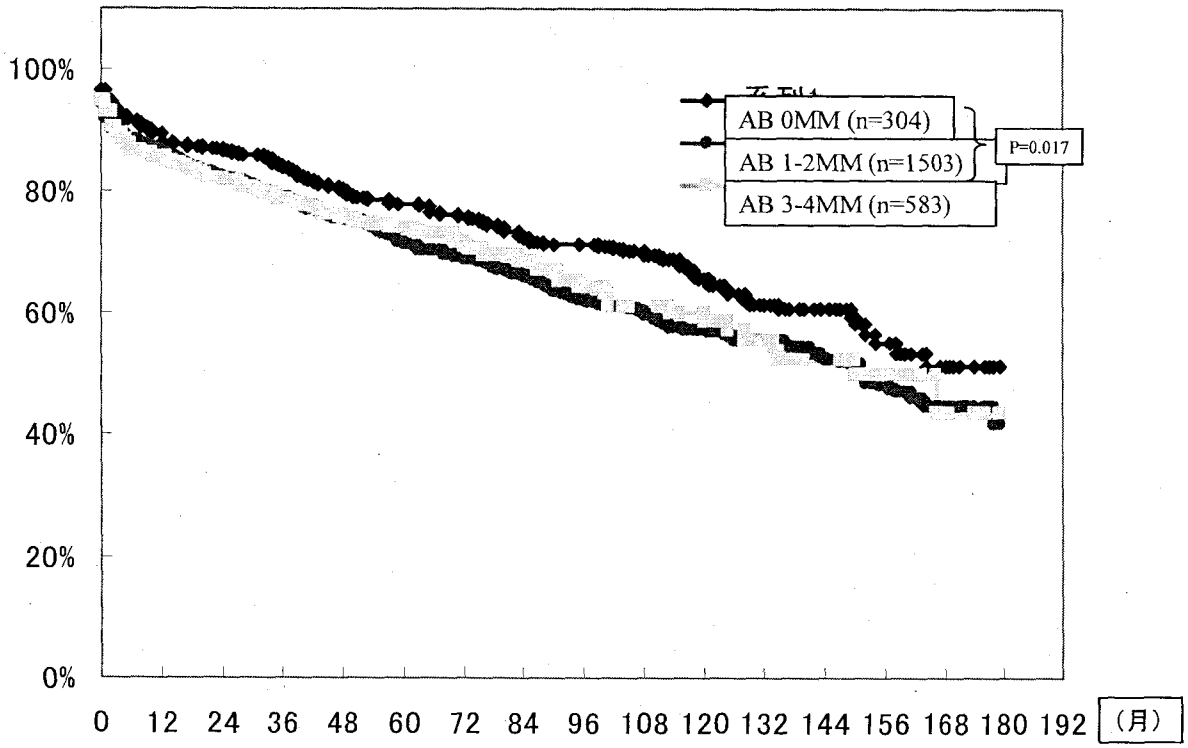
旧基準　（1995.4.1 ～ 2002.1.9　N=1,063）
新基準　（2002.1.10～2009.12.31　N=1,327）



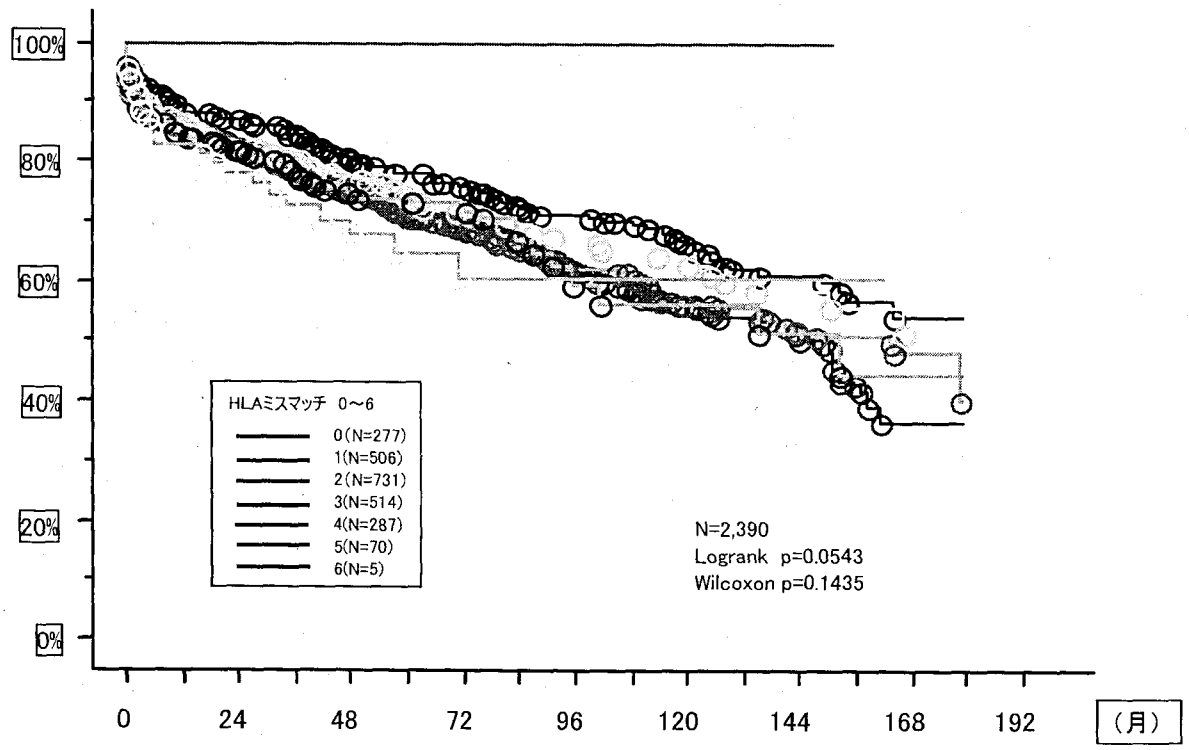
HLA不適合抗原数（検索型DR）生着率



HLA不適合抗原数(検索型A･B) 生着率



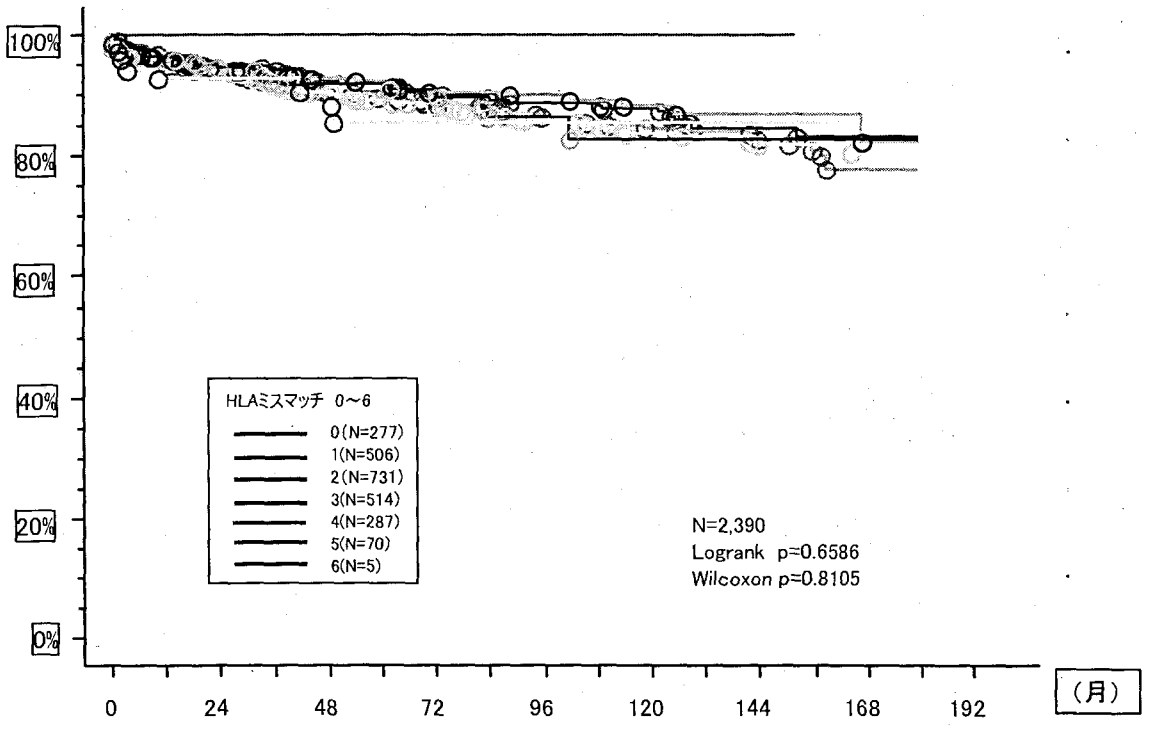
HLA不適合抗原数(検索型A･B･DR) 生着率



HLA不適合抗原数(検索型A･B･DR) 生着率

ミスマッチ数	1年	2年	3年	4年	5年	6年	7年	8年	9年	10年
0	88.4%	87.0%	84.4%	80.2%	77.9%	75.5%	72.3%	71.1%	69.4%	66.3%
1	86.1%	82.3%	78.5%	74.6%	71.5%	68.3%	66.3%	61.6%	58.4%	56.3%
2	86.0%	81.8%	78.6%	75.5%	70.8%	68.9%	65.3%	62.0%	60.5%	56.4%
3	86.9%	82.4%	80.2%	77.4%	74.0%	71.4%	69.7%	67.3%	65.2%	62.7%
4	85.3%	81.6%	77.8%	74.6%	73.9%	71.8%	66.9%	59.6%	55.9%	55.9%
5	82.8%	78.0%	72.5%	67.7%	64.9%	60.3%	60.3%	60.3%	60.3%	60.3%
6	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

HLA不適合抗原数(検索型A･B･DR) 生存率

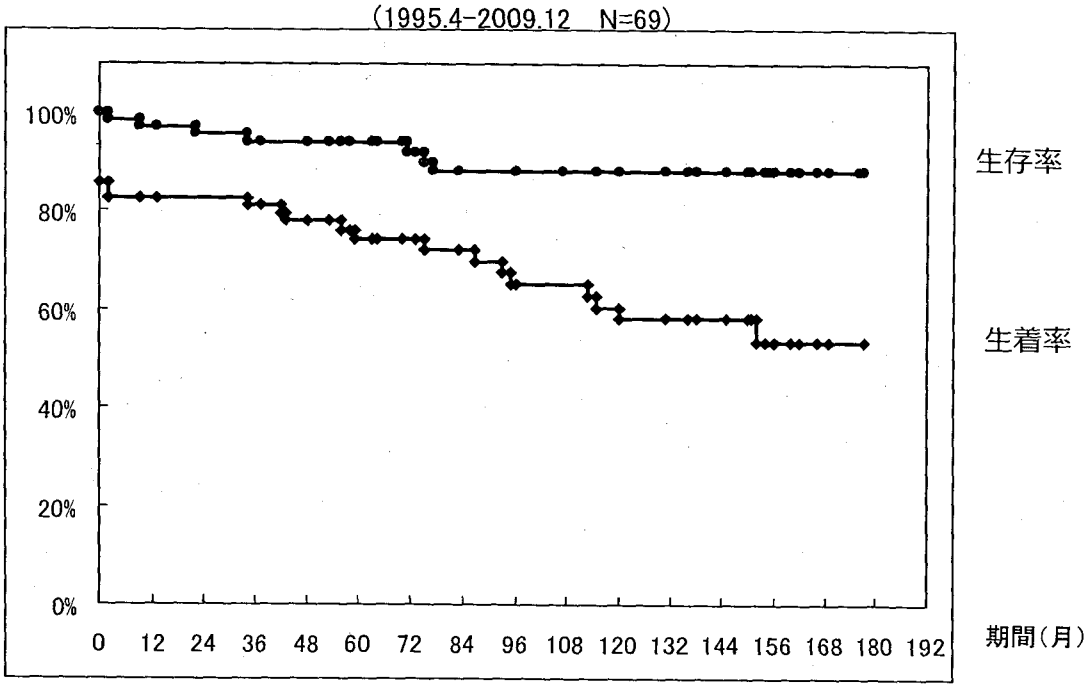


HLA不適合抗原数(検索型A･B･DR) 生存率

ミスマッチ数	1年	2年	3年	4年	5年	6年	7年	8年	9年	10年
0	96.0%	94.9%	94.2%	92.3%	91.5%	89.9%	89.1%	88.7%	88.3%	87.8%
1	95.2%	94.2%	91.7%	90.5%	89.8%	88.4%	87.6%	86.4%	85.5%	84.8%
2	95.7%	93.9%	91.9%	90.4%	89.0%	88.3%	86.7%	85.8%	84.8%	83.7%
3	96.3%	94.5%	93.7%	92.8%	92.4%	90.7%	90.7%	90.0%	89.1%	88.1%
4	96.2%	94.5%	92.3%	91.7%	91.7%	89.7%	86.2%	86.2%	82.8%	82.8%
5	92.8%	92.8%	92.8%	88.0%	85.5%	85.5%	85.5%	85.5%	85.5%	85.5%
6	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

小児提供者(16歳未満)からの(心臓停止後腎臓提供)
腎臓移植　生存･生着

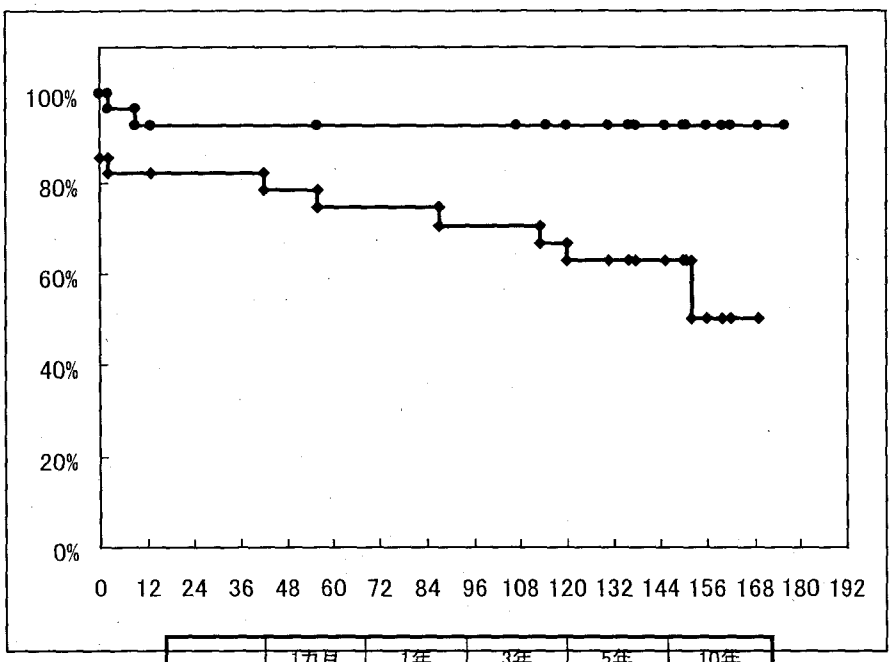
(1995.4-2009.12　N=69)



	1カ月	1年	3年	5年	10年
生存率	100%	98.6%	97.1%	94.0%	87.9%
生着率	85.5%	82.6%	81.1%	74.1%	60.4%

小児提供者(16歳未満)から小児(16歳未満)への(心臓停止後腎臓提供)腎臓移植　生存・生着

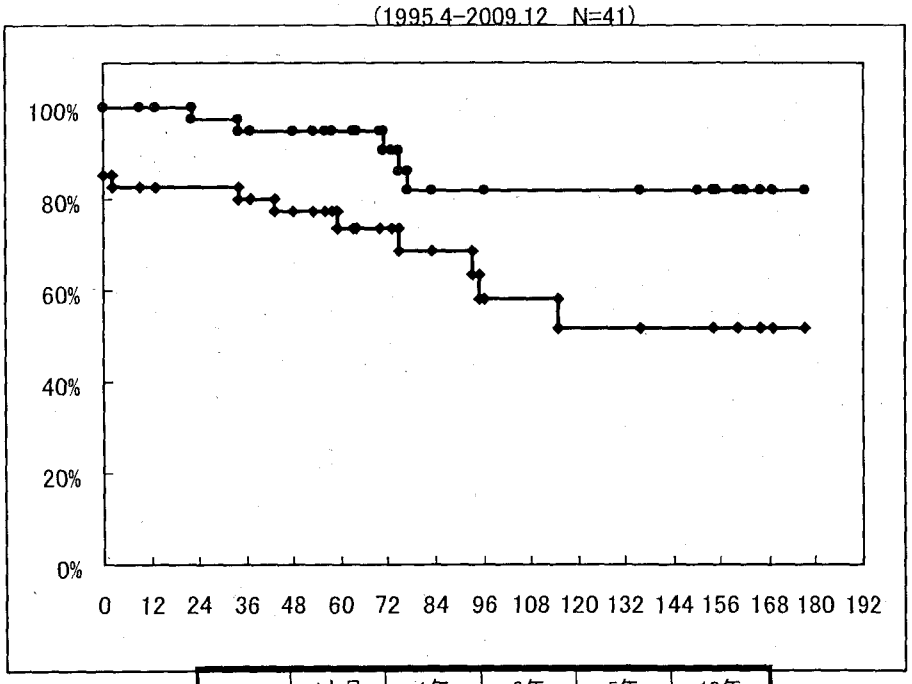
(1995.4-2009.12　N=28)



	1カ月	1年	3年	5年	10年
生存率	100%	92.9%	92.9%	92.9%	92.9%
生着率	85.7%	82.1%	82.1%	74.7%	66.8%

小児提供者(16歳未満)から16歳以上への(心臓停止後腎臓提供)腎臓移植　生存・生着

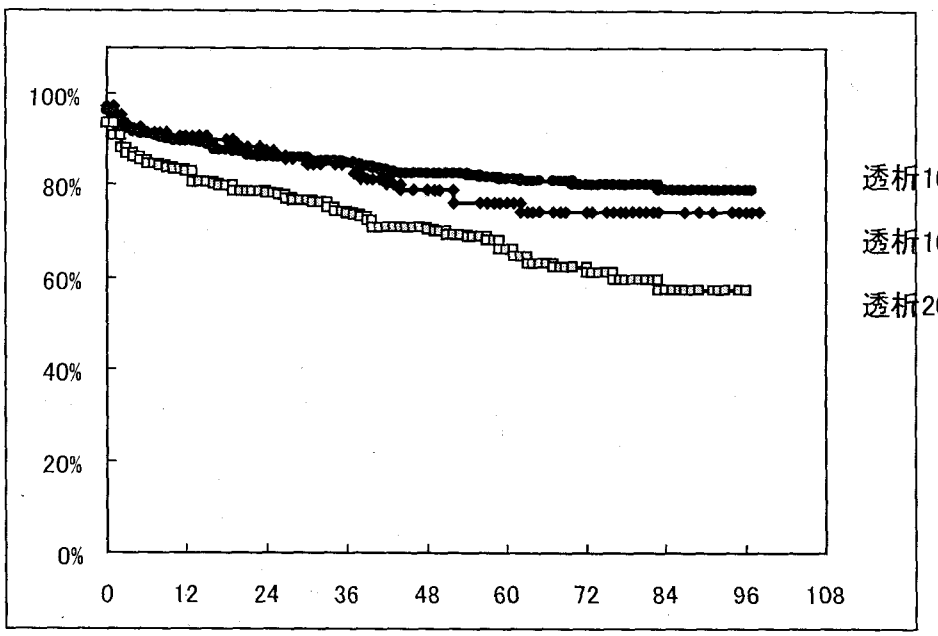
(1995.4-2009.12　N=41)



	1カ月	1年	3年	5年	10年
生存率	100%	100%	94.7%	94.7%	82.0%
生着率	82.9%	82.9%	80.3%	73.7%	51.7%

新基準による腎臓移植　生着率×透析期間

（透析導入日不明のデータを除く）



透析10年以上 n=741

透析10年未満 n=149

透析20年以上 n=426

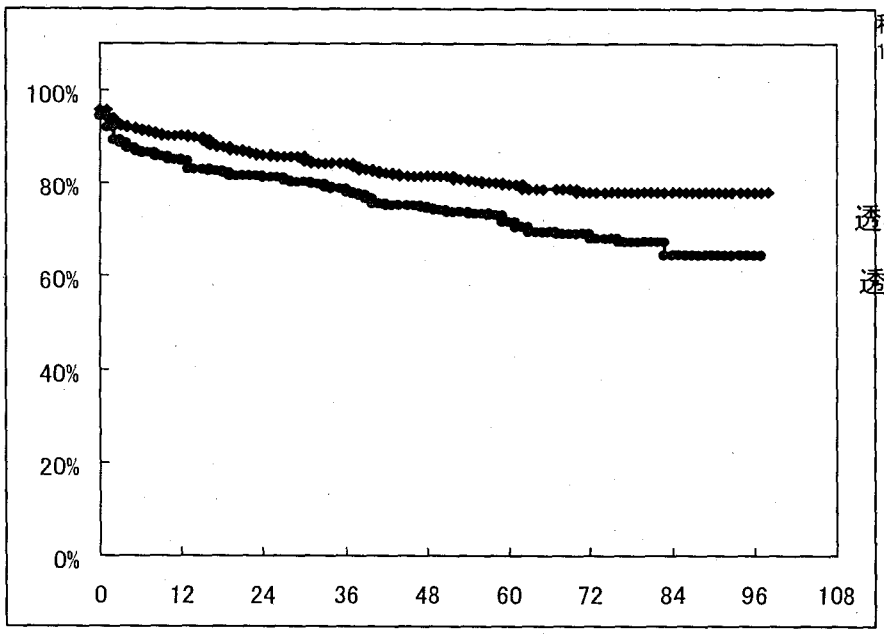
	1カ月	1年	3年	5年
10年未満	95.3%	90.5%	84.5%	76.0%
10年以上	94.1%	89.5%	84.9%	81.2%
20年以上	90.4%	83.0%	74.2%	65.9%

p<0.01

p<0.01

新基準による腎臓移植　生着率×透析期間

（透析導入日不明のデータを除く）



移植までの平均透析期間の17年で区別

p<0.01

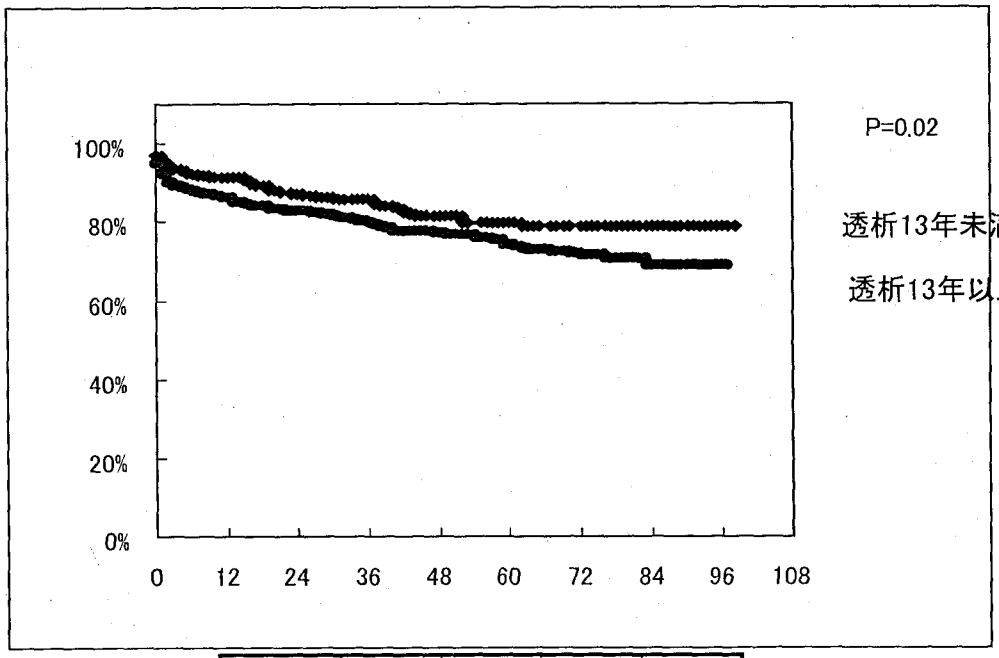
透析17年未満　n=682

透析17年以上 n=634

	1月	1年	3年	5年
17年未満	94.1%	90.1%	84.1%	79.5%
17年以上	91.8%	84.8%	78.4%	71.4%

新基準による腎臓移植　生着率×透析期間

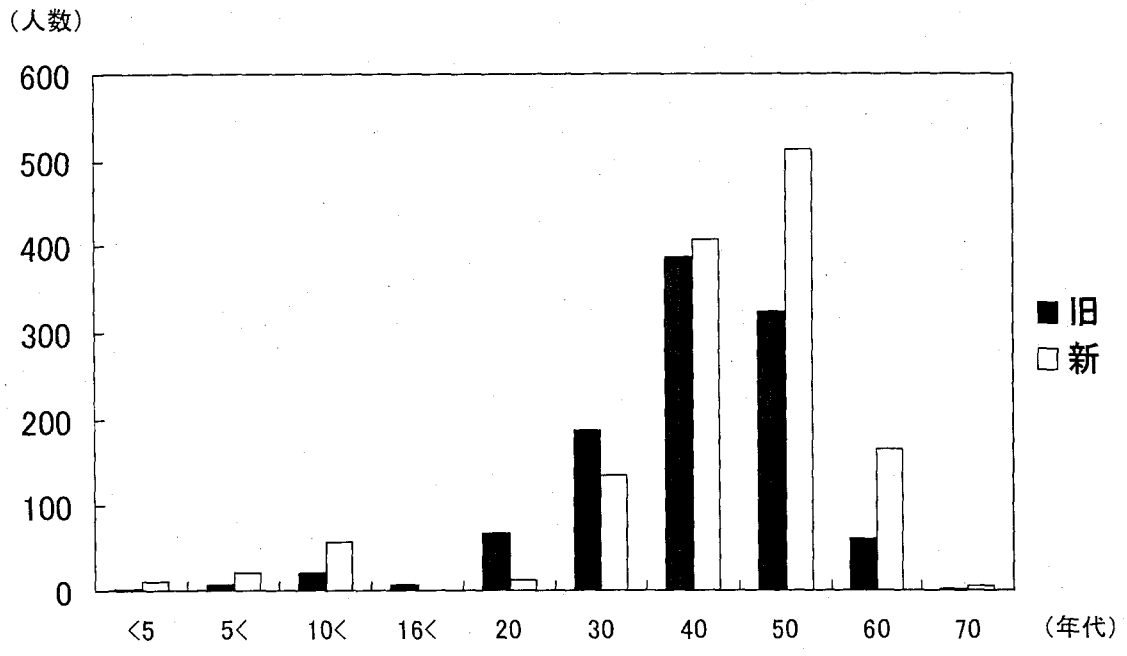
（透析導入日不明のデータを除く）



	1月	1年	3年	5年
13年未満	95.3%	91.1%	85.5%	79.8%
13年以上	92.2%	86.1%	79.5%	74.1%

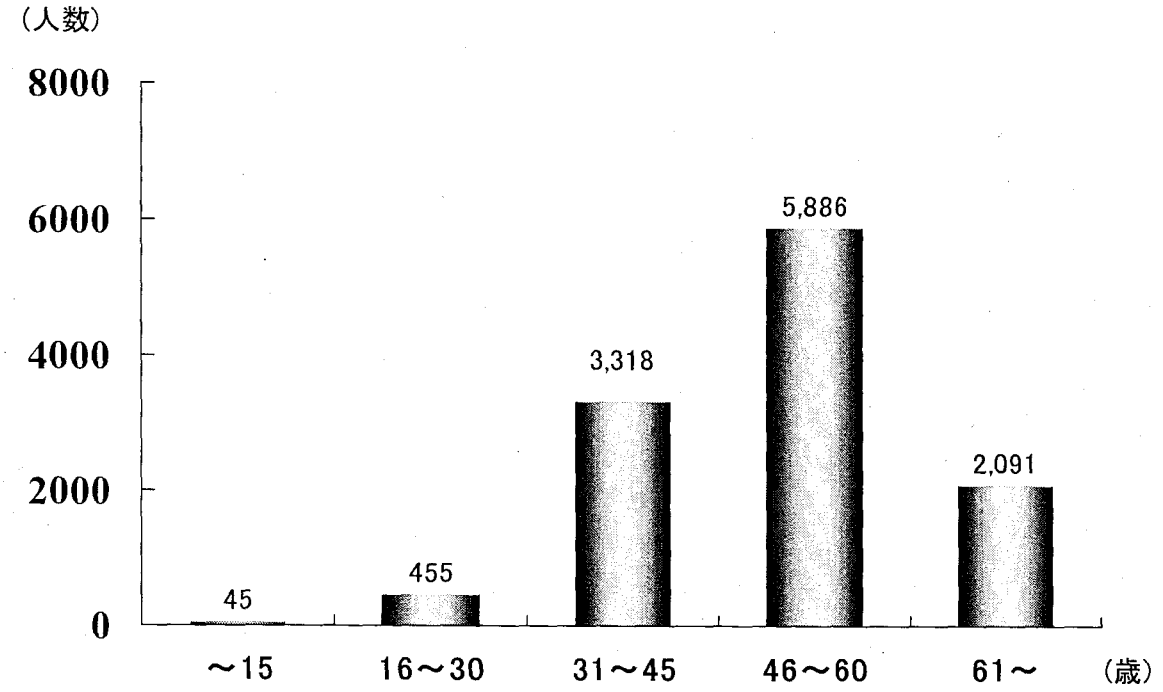
配分基準・年代別移植者数

旧基準　（1995.4.1 ～ 2002.1.9　N=1,063）
新基準　（2002.1.10～2009.12.31　N=1,327）



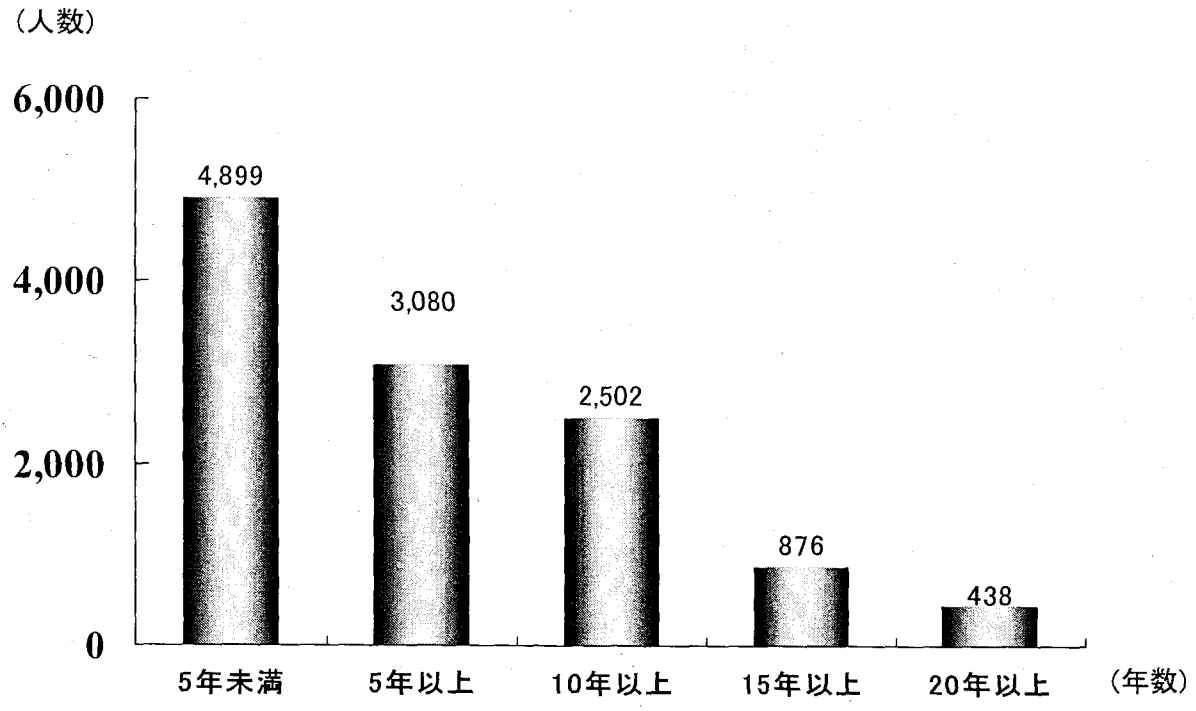
腎臓移植希望登録者　【年齢】

（2010.5.31現在　N=11,795）



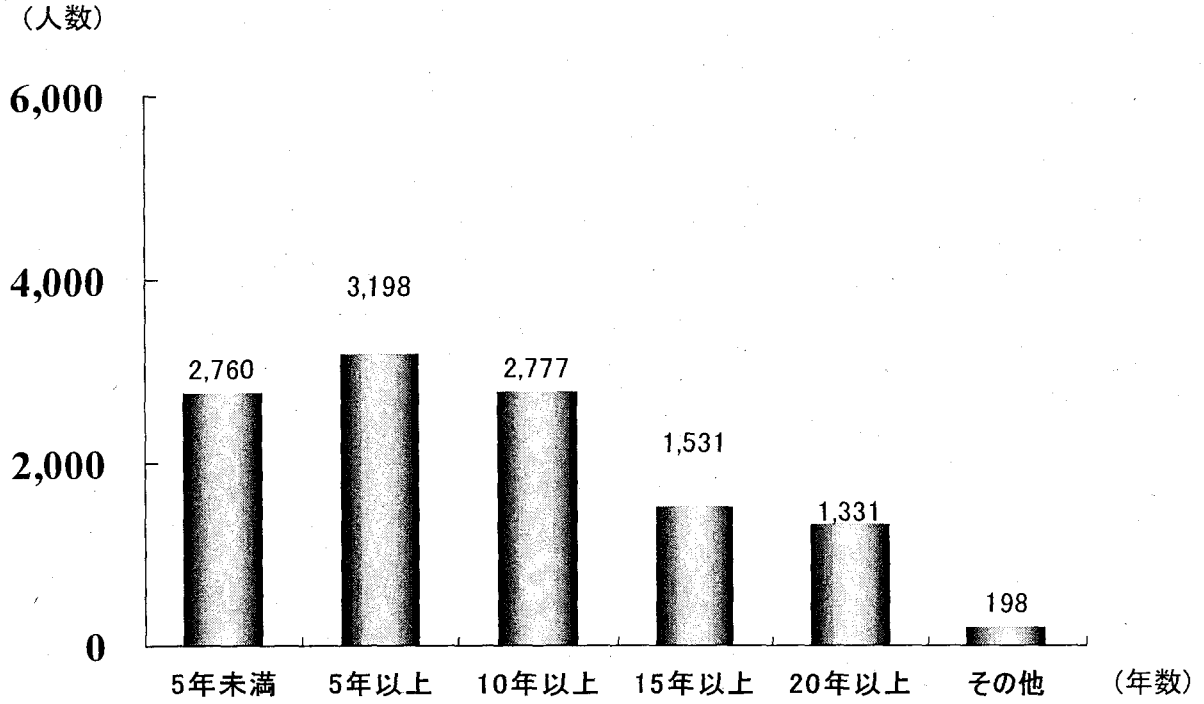
腎臓移植希望登録者 【待機年数】

（2010.5.31現在　N=11,795）



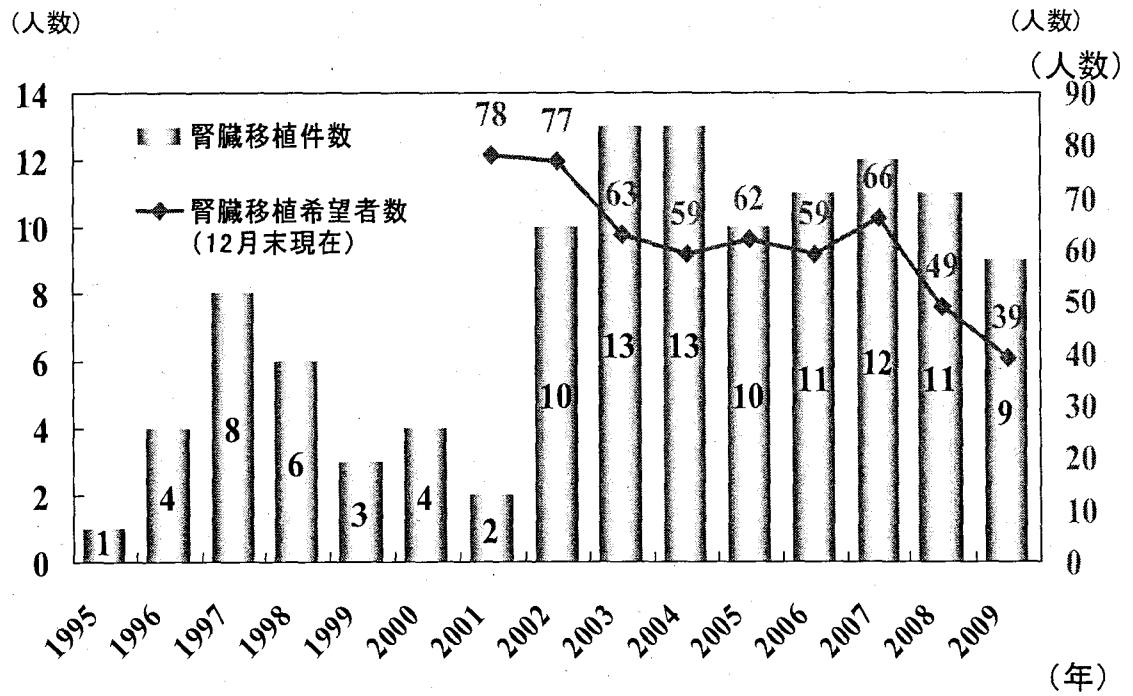
腎臓移植希望登録者 【透析年数】

（2010.5.31現在　N=11,795）



小児腎臓移植件数・腎臓移植希望者数の推移

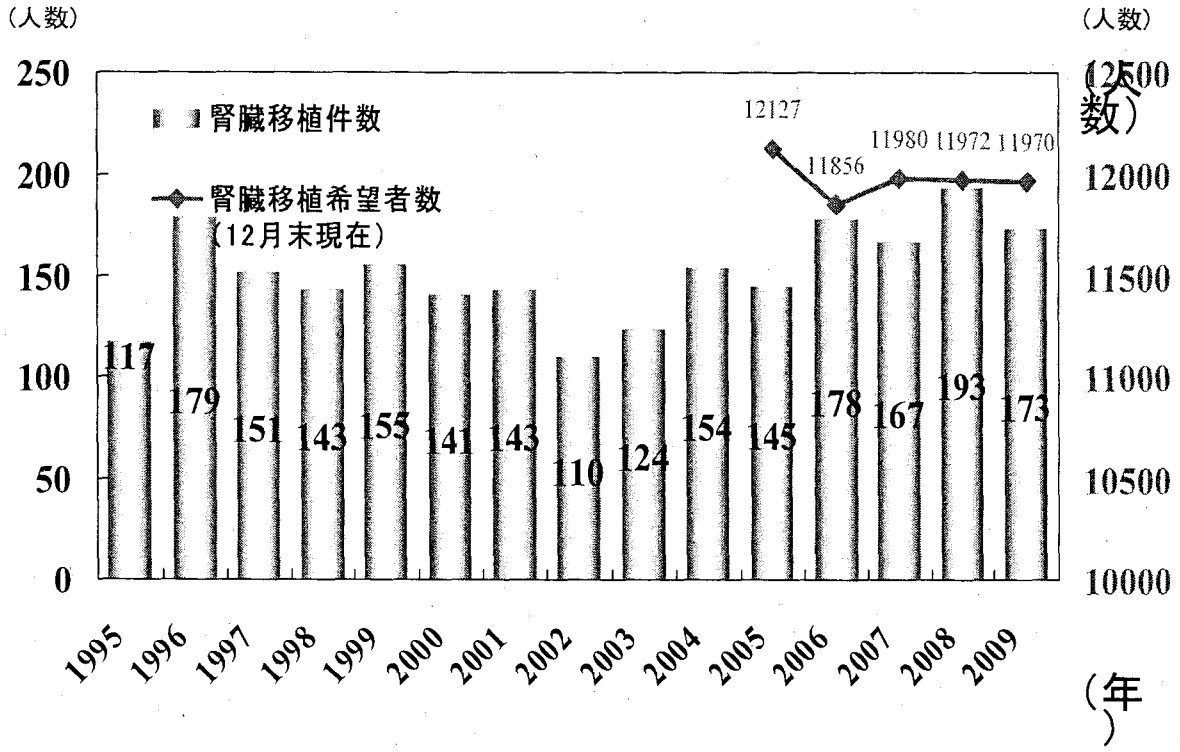
（16歳未満　1995年4月～2009年12月）



＊2002年1月10日より腎臓移植レシピエント選択基準が改正され、小児への移植が優先されるようになった

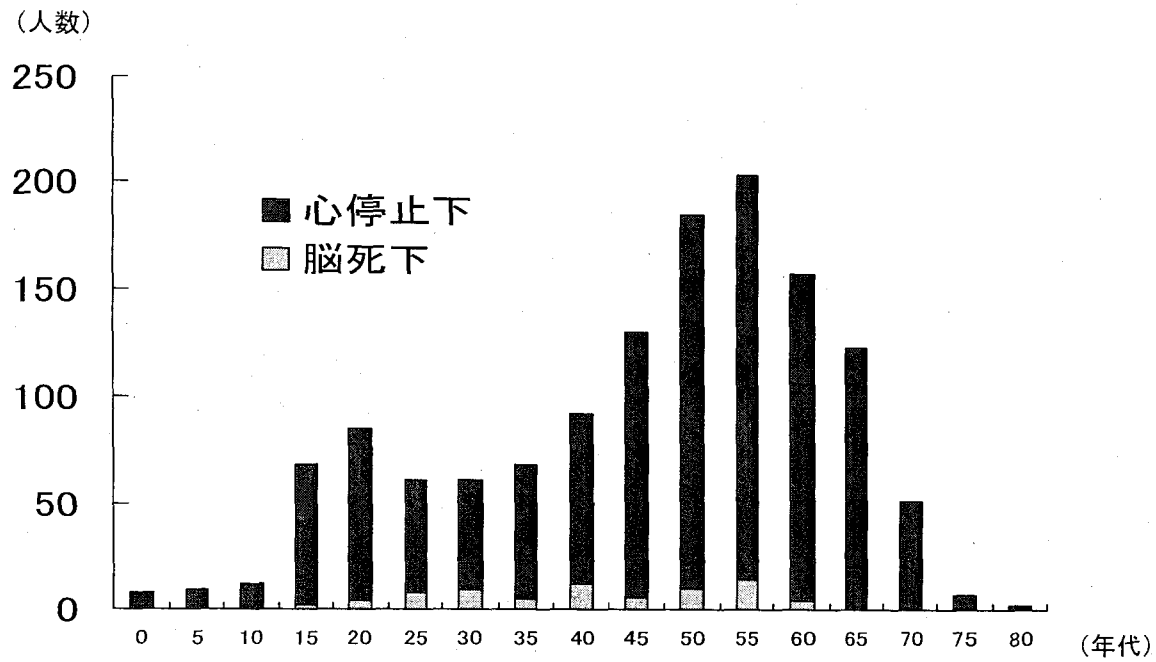
腎臓移植件数・腎臓移植希望者数の推移

（16歳以上　1995年4月～2009年12月）



腎臓提供者 【年代】

（1995/4～2009/12　脳死下N=76　心停止下N=1246）



参考資料２

全国の腎移植希望待機患者の分布

年代	待機患者数	%
0-15	50	0.43%
16-19	32	0.27%
20 代	343	2.93%
30 代	1539	13.14%
40 代	3248	27.74%
50 代	3971	33.92%
60 代	2312	19.75%
70 以上	213	1.82%
	11708	

平成 22 年 9 月 30 日現在

16 歳未満で登録した患者の現在の年齢分布

	現在の年齢(2010/11/10 現在)			
登録時年齢	0-15	16-19	20-	総計
0-5	16			1
6-10	15	1	10	1
11-15	19	14	57	4
総計	50	15	67	132

平成 22 年 11 月 10 日現在

参考資料３

腎臓移植希望者（レシピエント）選択基準改訂に係るシミュレーションの状況

次の観点からシミュレーションを行った。
＊16 歳～20 歳未満の加点により、この年齢層の候補者がどのように変化するか。
＊各年齢層への加点を加減することにより、長期待機患者等へのどのような影響が認められるか。

1 シミュレーションの前提条件

＊ ドナー条件：現行基準で行われた脳死下での提供事例 33 例（関東甲信越ブロック発生症例）
＊ 待機患者条件：平成 22 年 10 月 13 日現在の待機患者 4,567 名（関東甲信越地方のみ）

2 シミュレーションの方法

下記の条件ごとに、レシピエント候補者を選択し第 1 位及び第 2 位につき、検討した。(N=66)
若年者への加点は 20 歳を上限とした。

A：現行基準
B：待機期間の配点は現行基準：HLA×1.15※1　16 歳未満：14 点、16 歳～20 歳未満：12 点
C：待機日数の配点を概ね半減し※2、年齢加点を、
「16 歳未満：10 点、16 歳～20 歳未満：6 点、」とする。

※1 現行基準で行われた脳死下での腎提供事例 80 例について、レシピエント選択リストを作成し、そのリストの第 1 位のレシピエント 80 名の所在地、HLA、待機日数の平均換算点数の比は概ね 1.15：1：1.15 である。

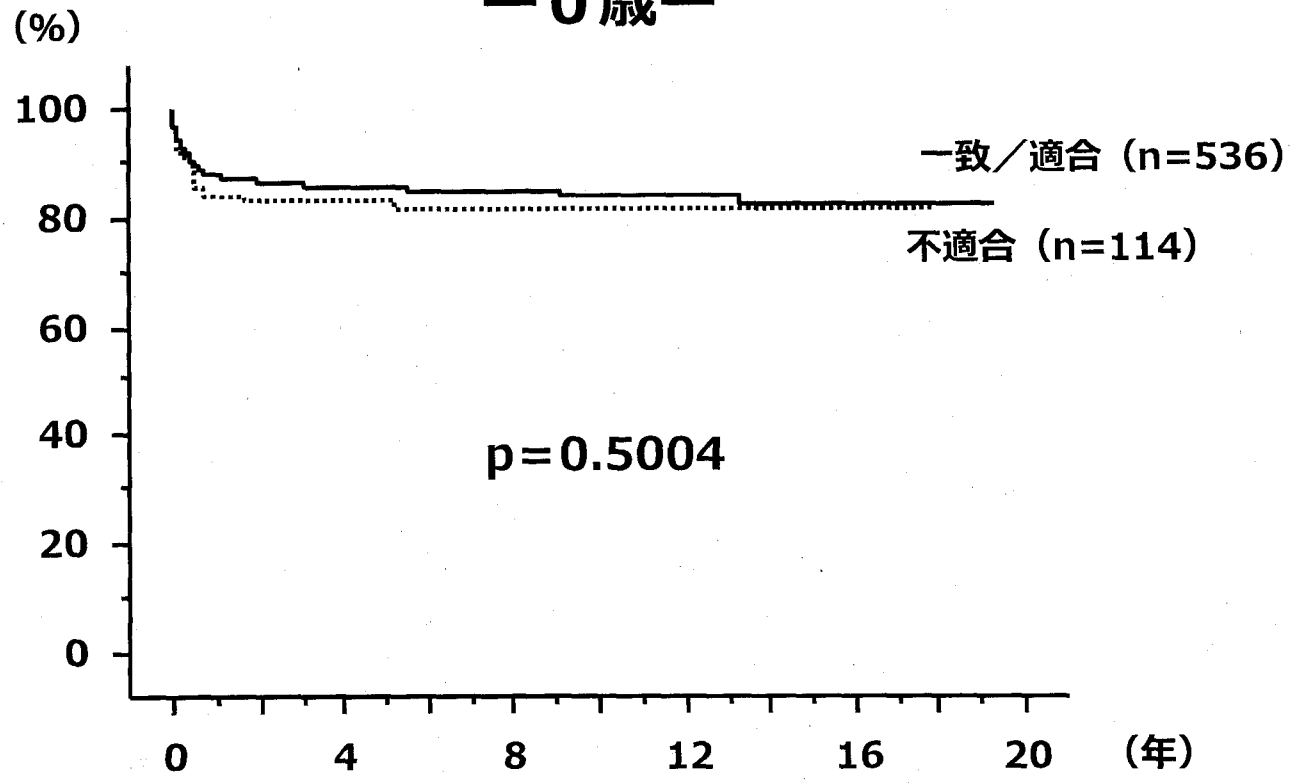
※2 待機期間が 10 年までは 0.5 点／年、11 年～20 年までは 0.25 点／年、20 年以上は 0.125 点／年となるような近似値を log 式とする。

3 シミュレーション結果

		A（現行基準）	B	C
待機日数（日）	全体	5289.4	5281.45	4274.7
	16 歳未満	997.25	937.08	1041.38
	16 歳～20 歳未満		983	983
	20 歳以上	6663	6496.04	6006.86
人数（%）	16 歳未満	16（24.2）	13（19.7）	21（31.8）
	16 歳～20 歳未満	0（0）	2（3）	2（3）
	20 歳以上待機期間10 年未満	1（1.5）	2（3）	4（6.1）
	その他	49（74.3）	49（74.2）	39（59.1）

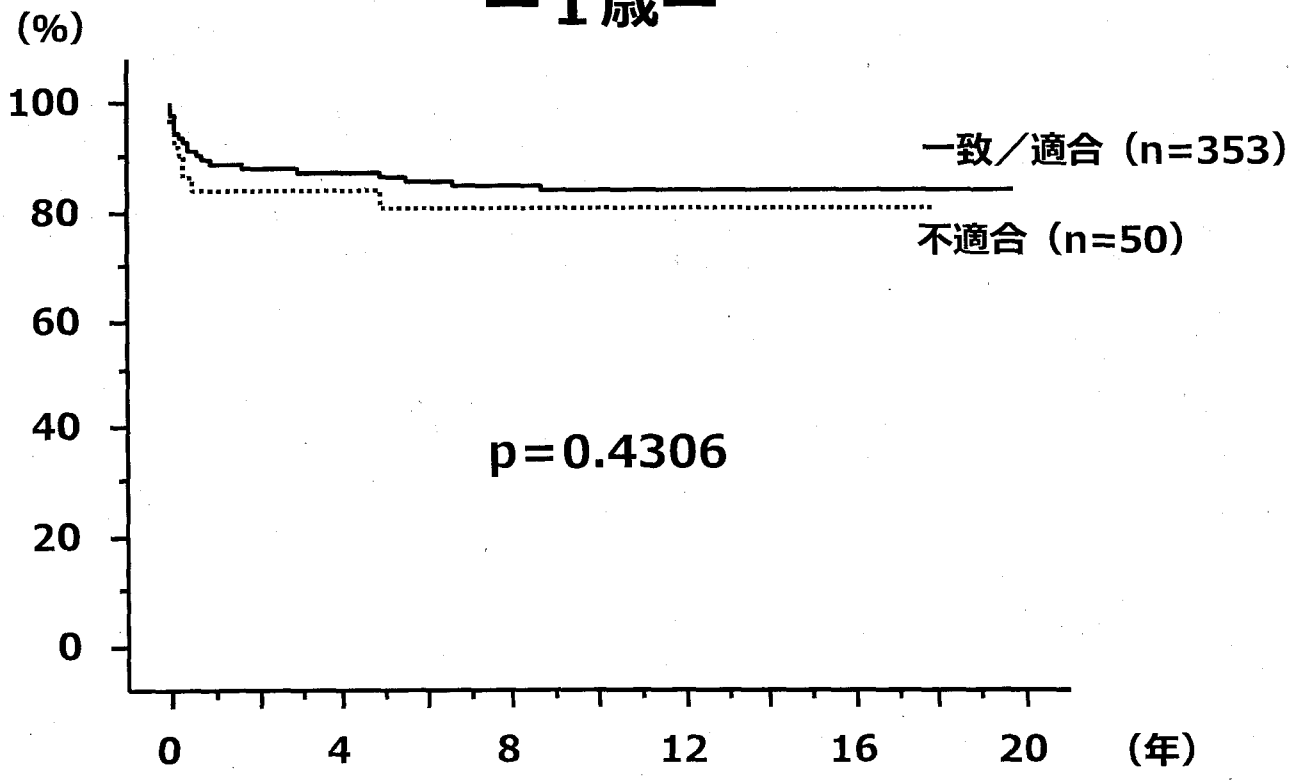
参考資料４

ＡＢＯ血液型適合度別の予後
－０歳－



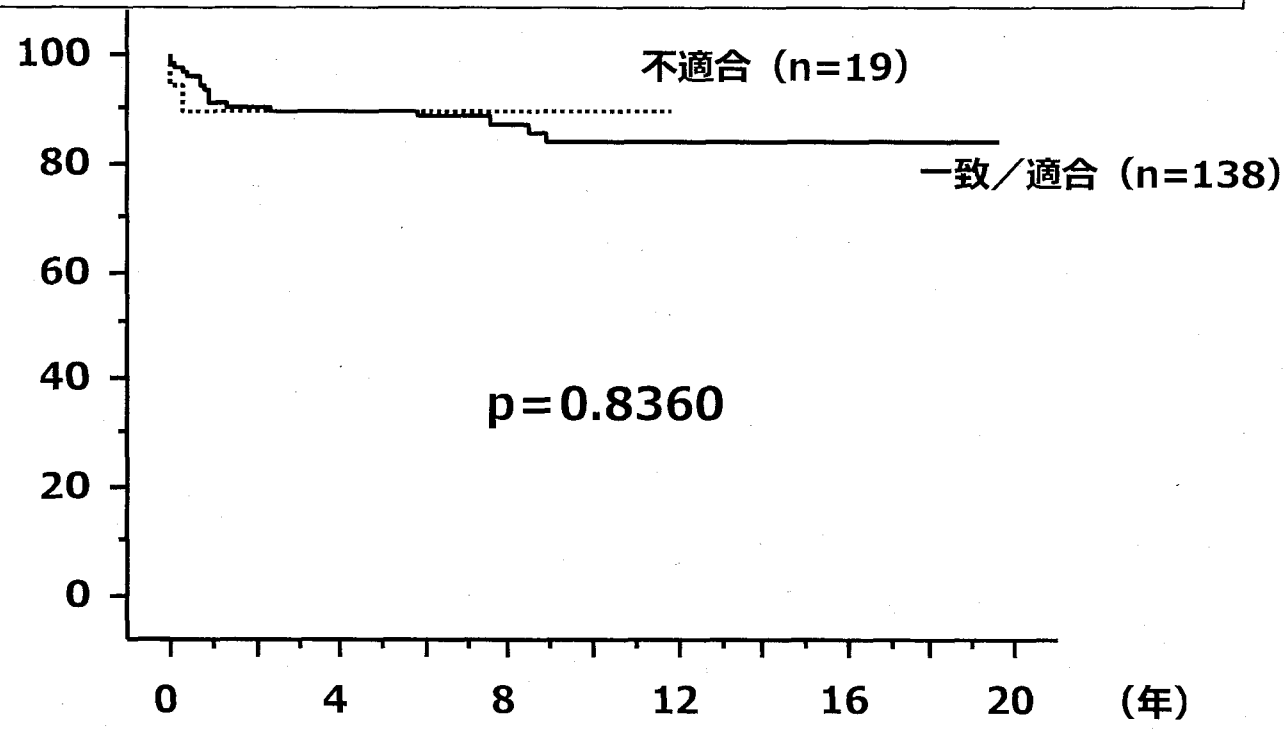
（日本肝移植研究会　2010.11.4）

ＡＢＯ血液型適合度別の予後
－１歳－



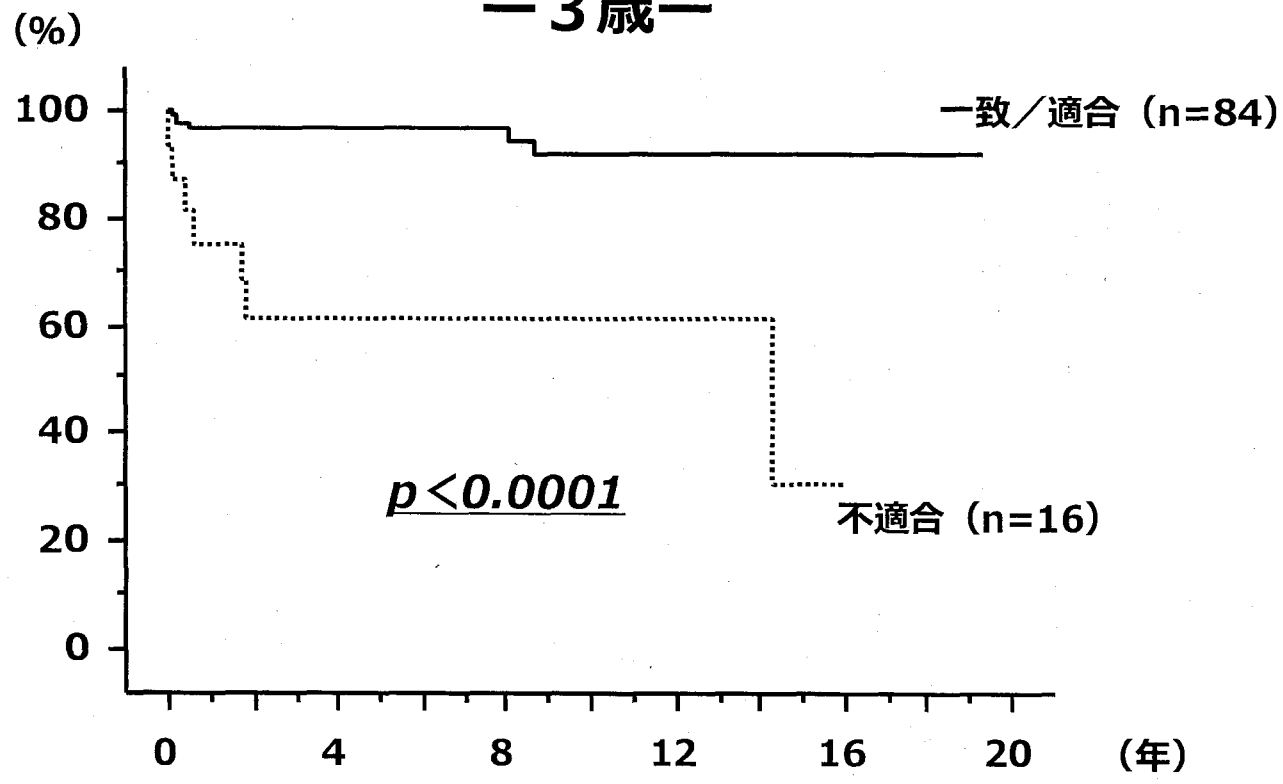
（日本肝移植研究会　2010.11.4）

ＡＢＯ血液型適合度別の予後
－２歳－



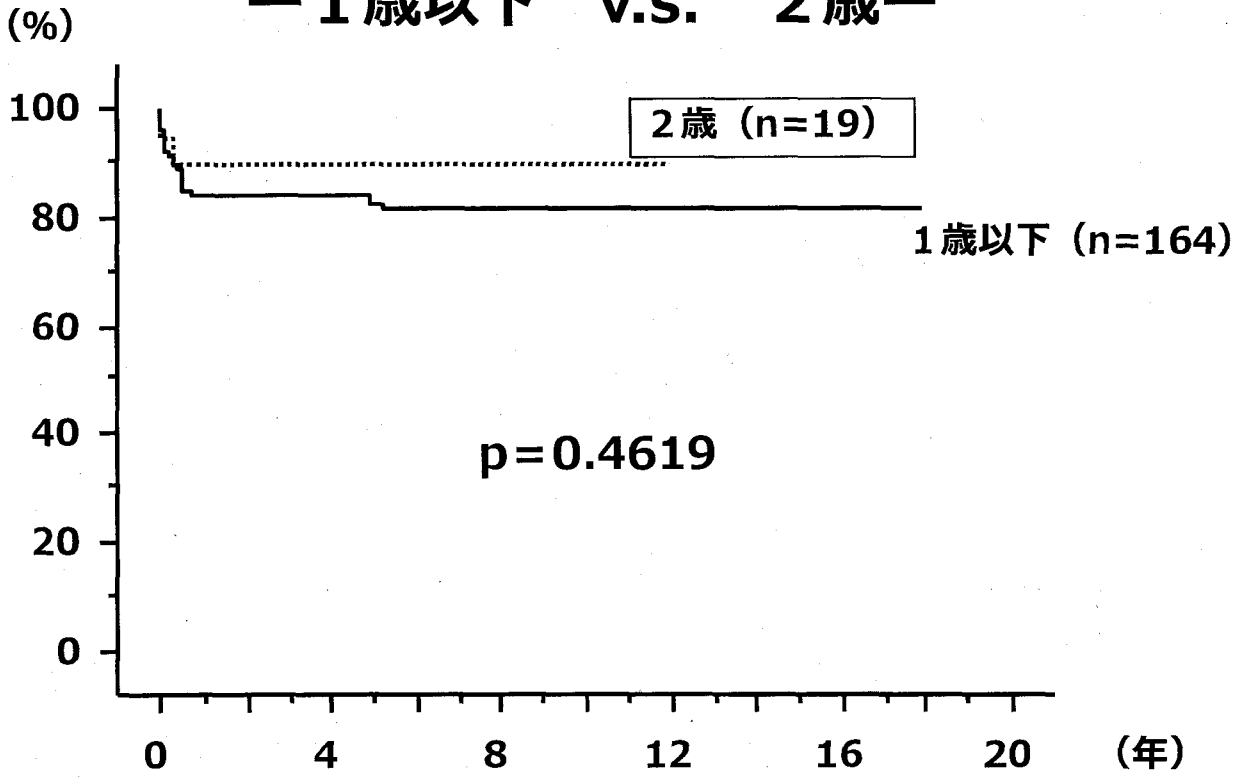
（日本肝移植研究会　2010.11.4）

ＡＢＯ血液型適合度別の予後
－３歳－



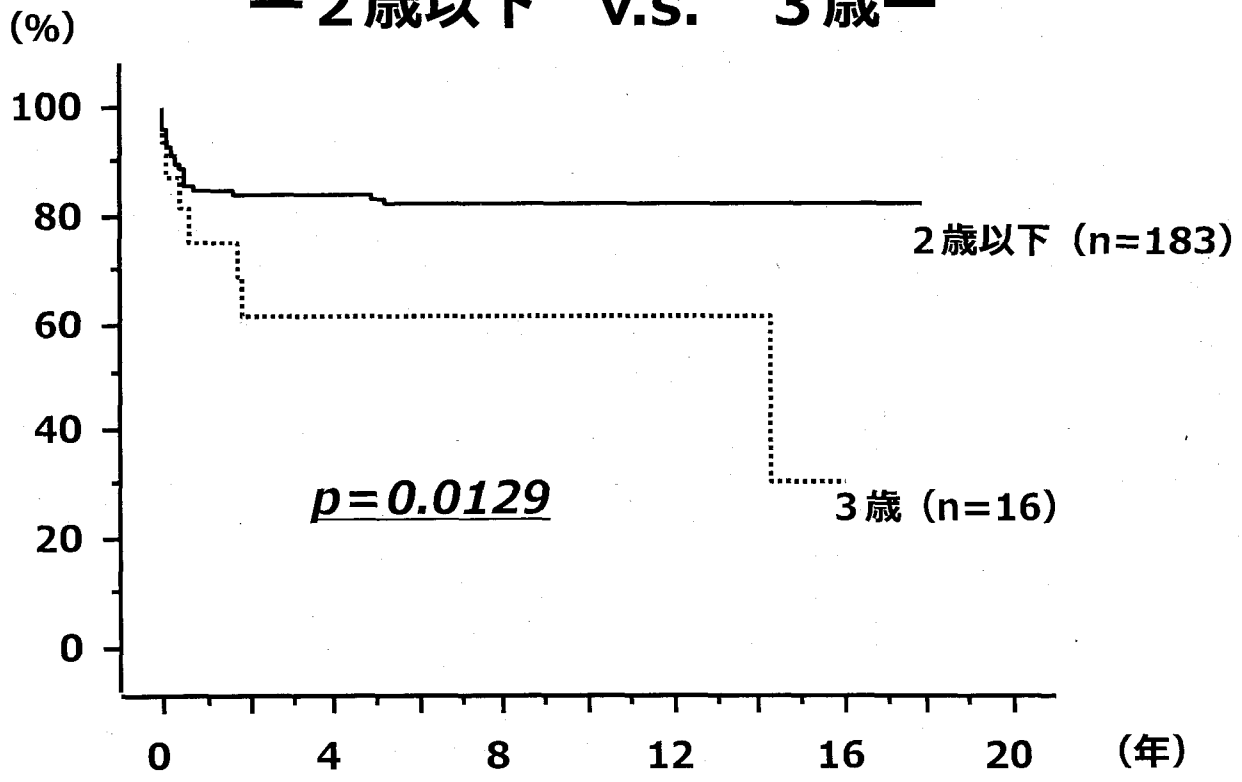
（日本肝移植研究会　2010.11.4）

ＡＢＯ不適合肝移植の予後
－１歳以下　v.s.　２歳－



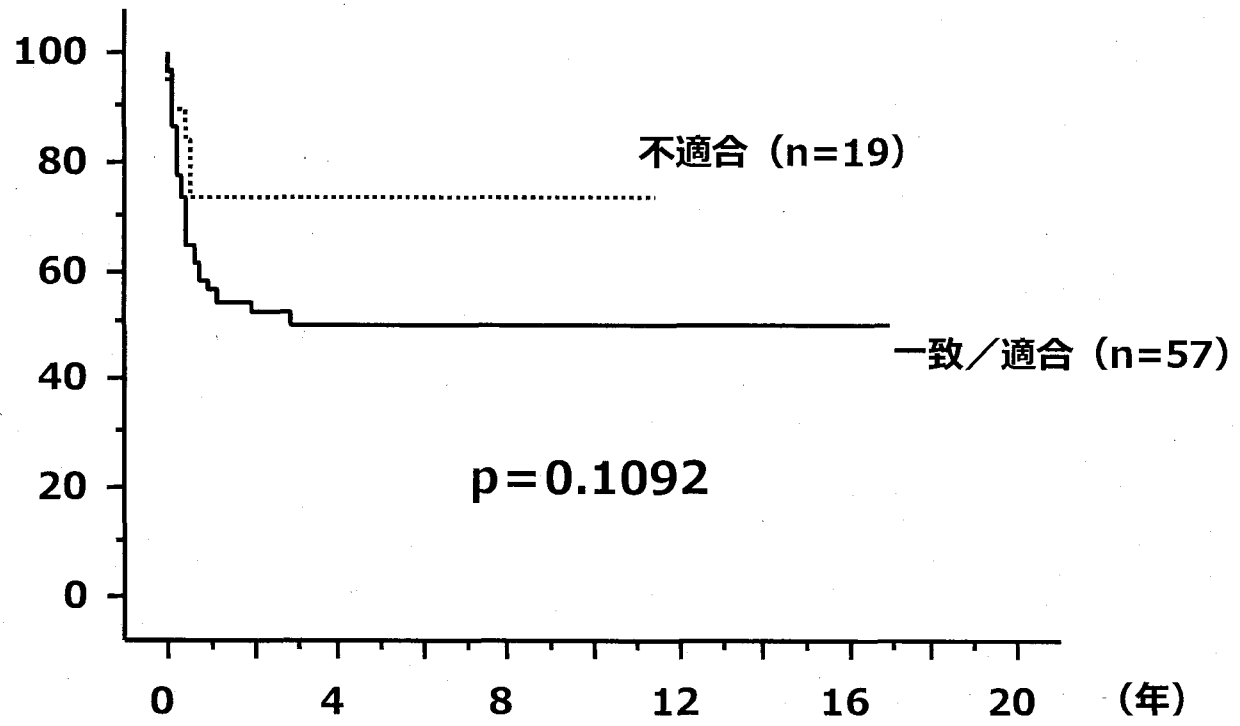
（日本肝移植研究会　2010.11.4）

ＡＢＯ不適合肝移植の予後
－２歳以下　v.s.　３歳－



（日本肝移植研究会　2010.11.4）

ＡＢＯ血液型適合度別の予後
－０歳、劇症肝炎のみ－



（日本肝移植研究会　2010.11.4）

参考資料５

TRANSPLANTATION Vol. 70, 1283–1291, No. 9, November 15, 2000

IMPROVED GRAFT SURVIVAL OF PEDIATRIC LIVER RECIPIENTS TRANSPLANTED WITH PEDIATRIC-AGED LIVER DONORS

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UNOS data 1992-1997の分析　(18歳未満を小児と定義)

小児ドナー中　35.6%が小児レシピエントに使用(1998年の小児、成人別登録後死亡率は小児7.4%、成人7.3%)

小児レシピ (n=2668)で、小児ドナーからと成人ドナーからの移植を比べると、３生率が81%対63%と有意に小児ドナーからの成績が良かった。成人レシピ (n=18525) で比べるとこのような差は見られなかった。

α-1,3-galactosyltransferase: expression cloning by gene transfer. Proc Natl Acad Sci USA 1989; 86: 8227.
9. Joziasse DH, Shaper NL, Kim D, Van den Eijinden DH, Shaper JH. Murine α1,3-galactosyltransferase. J Biol Chem 1992; 267: 5534.
10. Joziasse DH, Shaper JH, Van den Eijinden DH, Van Tunen AJ, Shaper NL. Bovine α1,3-galactosyltransferase: isolation and characterization of a cDNA clone. J Biol Chem 1989; 264: 14290.
11. Sandrin MS, Dekowski PL, Henning MM, Mouhtouris E, McKenzie IFC. Characterization of cDNA clones for porcine α(1,3)galactosyl transferase: the enzyme generating the Galα Gal epitope. Xenotransplantation 1994; 1: 81.
12. Starahan K, Gu F, Preece AF, Gustavsson I, Andersson L, Gustafsson K. cDNA sequence and chromosome localization of pig α1,3 galactosyltransferase. Immunogenetics 1995; 41: 101.
13. Vanhove B, Goret F, Soulillou JP, Pourcel C. Porcine α1,3-galactosyltransferase: tissue-specific and regulated expression of splicing isoforms. Biochim Biophys Acta 1997; 1356: 1.
14. Katayama A, Ogawa H, Kadomatsu K, et al. Porcine α-1,3-galactosyltransferase; full length cDNA cloning, genomic organization, and analysis of splicing variants. Glycoconj J 1998; 16: 583.
15. Shapiro MB, Senapathy P. RNA splice junction of different classes of eukaryotes: sequence statics and functional implications in gene expression. Nucleic Acids Res 1987; 15: 7155.
16. Shaper NL, Harduin-Lepers A, Shaper JH. Male germ cell expression of murine β4-galactosyltransferase. J Biol Chem 1994; 269: 25165.
17. Yamamoto F, McNeill PD, Hakomori S. Genomic organization of human histo-blood group ABO genes. Glycobiology 1995; 5: 51.
18. Svensson EC, Soreghan B, Paulson JC. Organization of β4-galactoside α2,6-sialyltransferase gene. J Biol Chem 1990; 265: 20863.
19. Soejima M, Koda Y, Wang B, Kimura H. Functional analysis of the 5'-flanking region of FTA for expression of rat GDP-L-fucose:β-D-galactoside 2-α-L-fucosyltransferase. Eur J Biochem 1999; 266: 274.
20. Loa NW, Lau JTY. Transcription of b-galactoside α2,6-sialyltransferase gene in B lymphocytes is directed by a separate and distinct promoter. Glycobiology 1996; 6: 271.
21. Svensson EC, Conley P, Paulson JC. Regulated expression of α2,6-sialyltransferase by the liver-enriched transcription factors HNF-1, DBP, and LAP. J Biol Chem 1992; 267: 3466.
22. Jones PA. The DNA methylation paradox. Trends Genet 1999; 15 (1): 34.

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IMPROVED GRAFT SURVIVAL OF PEDIATRIC LIVER RECIPIENTS TRANSPLANTED WITH PEDIATRIC-AGED LIVER DONORS

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Background. **Improving graft survival after liver transplantation is an important goal for the transplant community, particularly given the increasing donor shortage. We have examined graft survivals of livers procured from pediatric donors compared to adult donors.**

Methods. **The effect of donor age (<18 years or ≥18 years) on graft survivals for both pediatric and adult liver recipients was analyzed using data reported to the UNOS Scientific Registry from January 1, 1992 through December 31, 1997. Graft survival, stratified by age, status at listing, and type of transplant was computed using the Kaplan-Meier method. In addition, odds ratios of graft failure at 3 months, 1 year, and 3 years posttransplant were calculated using a multivariate logistic regression analysis controlling for several donor and recipient factors. Modeling, using the UNOS Liver Allocation Model investigated the impact of a proposed policy giving pediatric patients preference to pediatric donors.**

Results. **Between 1992 and 1997 pediatric recipients received 35.6% of pediatric aged donor livers. In 1998 the percent of children dying on the list was 7.4%, compared with 7.3% of adults. Kaplan-Meier graft survivals showed that pediatric patients receiving livers from pediatric aged donors had an 81% 3-year graft survival compared with 63% if children received livers from donors ≥18 years ($P<0.001$). In contrast, adult recipients had similar 3-year graft survivals irrespective of donor age. In the multivariate analysis, the odds of graft failure were reduced to 0.66 if pediatric recipients received livers from pediatric aged donors ($P<0.01$). The odds of graft failure were not affected at any time point for adults whether they received an adult or pediatric- aged donor. The modeling results showed that the number of pediatric patients trans-**

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planted increased by at most 59 transplants per year. This had no significant effect on the probability of pretransplant death for adults on the waiting list. Waiting time for children at status 2B was reduced by as much as 160 days whereas adult waiting time at status 2B was increased by at most 20 days.

Conclusion. **A policy that would direct some livers procured from pediatric- aged donors to children improves the graft survival of children after liver transplantation. The effect of this policy does not increase mortality of adults waiting. Such a policy should increase the practice of split liver transplantation, which remains an important method to increase the cadaveric donor supply.**

The nationwide donor shortage has forced scrutiny of our practices of organ allocation. In particular, liver allocation policies have been the subject of intense debate extending beyond the medical profession to the pages of the lay press and the corridors of the federal government (*1–4*).The issues of waiting time and mortality while waiting are amplified for liver transplant candidates (*5*) (and heart transplant candidates) because unlike kidney transplant candidates, no sustainable form of artificial organ support exists. In such patients allocation policies therefore take on a new urgency. If there were unlimited numbers of organs the justice of the argument "sickest first" is undisputed. However, given the limited organ supply, consideration must also be given to the question of how a scarce resource should be best utilized (*6*). In effect, which patients are likely to have the best graft survival?

Several investigators have identified factors that affect outcome after pediatric liver transplantation. Not surprisingly, as in adult liver recipients, the most important predictor is medical urgency (*7*). Although the technical challenges are considerable, young age itself is not a predictor of poor outcome in experienced centers (*8–11*). To date, donor factors considered have focused on whether the use of partial liver grafts affects the outcome of pediatric liver recipients. The use of split livers (one cadaveric donor divided to provide two transplantable segments), reduced livers (a cadaveric donor liver reduced in size to produce one transplantable segment), and living donor grafts, have already been shown to decrease the mortality of pediatric patients awaiting liver transplantation without decreasing patient and graft survivals (*12–14*). However, the effect of pediatric versus adult donor age on outcome has not been well studied. Our preliminary data showed that the majority of livers procured from pediatric-aged donors (<18 years of age) were transplanted into adults, although proportionately the same number of children die on the list as adults. This information caused to us question whether the outcome of pediatric or adult recipients was affected by the age of the donor. We postulated that if the results of this investigation showed that pediatric liver recipients benefited from receiving a donor of a pediatric age, as measured by improved graft and patient survival, without causing a negative impact on the adult population, then both utility and justice would suggest that pediatric recipients should receive at least some preference in receiving organs from pediatric donors.

METHODS

These analyses of posttransplant outcome were based on liver transplants reported to UNOS Scientific registry from January 1, 1992 through December 31, 1997. Odds ratios were calculated using a multivariate logistic regression analysis. This analysis controlled for several donor and recipient risk factors (e.g. donor race, donor cause of death, recipient race, diagnosis at time of transplant, previous transplant, medical condition at time of transplant, cold ischemia time, serum creatinine level and year of transplant). The outcome of interest was the odds of graft failure within 3 months, 1 year and 3 years posttransplant. PROC LOGISTIC, SAS version 6.3, was used to perform the logistic regression analysis. A stepwise regression technique, was used to determine the factors to be included in the final logistic regression model. Missing values for continuous variables were set to the mean, and for categorical variables, were set to the baseline value.

Acturial graft survival was computed using Kaplan-Meier method. These survival curves were stratified by age, status at transplant, type of transplant, and ICU group. A log-rank statistic was used to test the hypothesis of no difference in survival between groups.

For the median waiting times analyses, the cohort of patients included all registrations added to the UNOS Liver Waiting List between January 1, 1995 and December 31, 1997. Kaplan-Meier waiting times where calculated using PROC LIFETEST, SAS version 6.3. The actual probabilities on the waiting list of death, transplant, removed (not for reason of death or transplant), and still waiting, were computed using a competing risk method.

In April 1994 the UNOS liver data collection forms were amended. Among the information added to the forms was whether the transplanted liver was split or otherwise reduced in size. Therefore any information that specifies whole or split livers covers only the time period from April 1994 through December 31, 1997.

Modeling methods. Modeling results were generated by ULAM, the UNOS Liver Allocation Model. ULAM is a PC-based software package that simulates the current national and alternative liver allocation policies. Details of the construction of ULAM have been

TABLE 1. Distribution of pediatric and adult donor livers into pediatric and adult recipients, divided by age ranges: 1/1/92–12/31/97

Recipient age (yr)	Donor age (yr)				Total
	0–17		18+		
0–17	1786		882		2668
18+	3225		15300		18525
Total	5011		16182		21193
Recipient age	0–5	6–17	18–49	50+	
0–2	531	459	324	25	1339
3–17	263	533	449	84	1329
18–49	15	1712	5917	1989	9633
50+	13	1485	5224	2170	8892
Total	822	4189	11914	4268	21193

TABLE 2. Median waiting times for liver transplantation: by age and UNOS status: 1/1/92–12/31/97

Age group	Num Added	Status 1 95%			Status 2 95%			Status 3,4,7 95%	
		MWT	Conf limits	Num added	MWT	Conf limits	Num added	MWT	Conf limits
0–2 yr	295	23	(12,50)	178	51	(29,73)	815	189	(173,213)
3–5	75	10	(5,47)	36	35	(17,130)	211	231	(207,300)
6–10 yr	74	12	(5,40)	57	53	(22,246)	241	328	(235,428)
11–17 yr	153	10	(7,16)	77	46	(18,80)	382	409	(347,520)
18–49 yr	1236	9	(8,11)	834	28	(22,34)	8929	495	(472,517)
50+ yr	753	10	(8,12)	690	27	(22,32)	8757	460	(434,486)

TABLE 3. Mortality of patients on the UNOS liver waiting list for 1998 (Source UNOS OPTN Waiting List and Removal Files as of 9/7/1999)

Age (yr)	<1	1–5	6–10	11–17	18–34	35–49	50–64	65+
Patients	286	549	295	411	1143	6358	7411	1530
Deaths	50	34	15	16	84	445	556	117
Rate[a]	827.5	119.6	87.2	70.9	131.8	123.2	128.8	123.7
%	17.5	6.2	5.1	3.9	7.3	7.0	7.5	7.6

[a] Annual death rate per 1000 patient years at risk.

published elsewhere (*15*). In brief, ULAM is a discrete event simulation that matches individual donors and recipients using the same general algorithm as the UNOS match system. All statistical components of ULAM were derived from historical OPTN/SR data and the model has been validated against actual data from 1998–1999.

In our analysis, ULAM results were generated for the current national policy and the proposed policy giving pediatric patients preference to pediatric donors. For each policy, four independent simulations of 1998–2003 were generated with statistics collected from 1999–2003. A 1-year transition period allows the effects of the current policy to dissipate so that the impact of the proposed policy can be assessed more accurately. Output measures from the model represent the average of the four simulations of 1999–2003.

RESULTS

Current allocation of livers procured from donors <18 years. The first analysis determined how many livers procured from donors less than 18 years of age were transplanted into children (<18 years) compared to adults (18+ years). As seen in Table 1, which includes all cadaveric organs procured between 1/1/92 and 12/31/97 (including reduced and split grafts) pediatric recipients received 1786 of the total of 5011 (35.6% of pediatric-aged donor livers).

Analyzing these data further by dividing recipient and donor ages into subgroups, it can be seen that it is predominantly donors in the 6–17 age group that are transplanted into adults. Of donors aged 6–17 years, 1712 were transplanted into recipients aged 18–49, and 1485 into recipients aged greater than 50 years. Taken together, 3197 of 4189 (76.3%) 6- to 17-year-old donors were placed into adult recipients of which 46.4% were older than 50 years of age. In contrast, children received 882 of 16,182 adult liver donors (5.4%); this includes split and reduced size grafts (Table 2).

Current pediatric and adult mortality and waiting times on liver transplant list. The next questions examined were whether waiting time and mortality on the list differed between children and adults. Table 2 shows median waiting times for cadaveric liver transplants for pediatric and adult patients added to the liver waiting list between 1/1/95 to 12/31/97, divided according to age and UNOS status at time of listing. (Summary of Definitions of UNOS status codes: Up to and including 1997: status 1=In intensive care unit (ICU); status 2=hospitalized not in ICU; status 3=at home. 1998: status 1 adults=acute liver failure and in ICU; status 1 pediatrics=in ICU; status 2A (adults only)=chronic liver failure in ICU; status 2B=moderately urgent, defined by specific criteria; status 3=least urgent. Full definitions of status codes used can be found in the 1996 and 1998 UNOS Annual Reports.)

It can be seen that children 0–2 years waited longer in status 1 and status 2 than any other age range apart from status 2, 6- to 10-year-olds with an initial listing of status 2. At status 3, 4, and 7, adults waited longer than children. When this analysis was divided into years before and after split and reduced graft data were collected, i.e., 1/1/92 to 12/31/94 compared to 1/1/95 to 12/31/97 the same trends persisted (data not shown).

Mortality on the liver waiting list was also considered for different age ranges. For all patients on the liver waiting list during calendar year 1998 the number and percentage of patients dying is shown in Table 3. Note these numbers

TABLE 4. Patients listed on the liver waiting list between 1/1/95–12/31/97 (first 6 months after listing: probability of events)

Group	Initial status	Removed	Waiting	Transplanted	Died
Adult	1	0.151	0.082	0.448	0.319
	2	0.088	0.145	0.510	0.257
	3	0.032	0.690	0.197	0.082
Pediatric	1	0.179	0.118	0.433	0.270
	2	0.152	0.237	0.488	0.124
	3	0.088	0.573	0.283	0.056

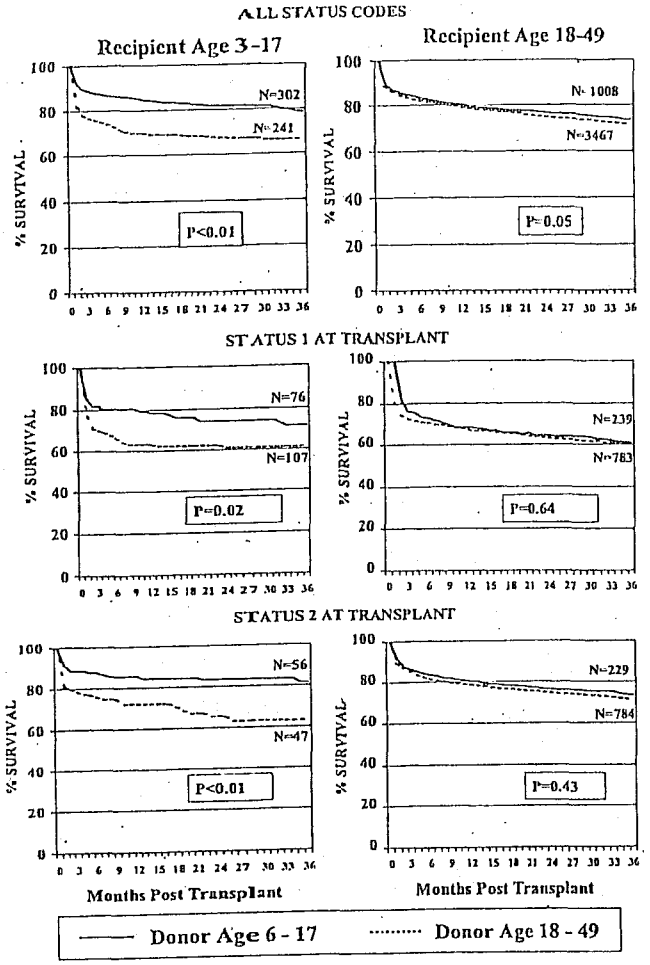

FIGURE 1. The unadjusted Kaplan-Meier 3-year survivals are shown for pediatric recipients (3–17 years) receiving livers from pediatric-aged donors (6–17 years) compared to adult donors (18–49 years) and adult recipients (18–49 years) receiving livers from pediatric aged donors (6–17 years). Results shown include retransplants, all UNOS statuses, and analyses for status 1 and status 2. Graphs on the left show the pediatric recipient data, graphs on the right show the adult recipient data.

exclude patients removed from the list because they became too ill to transplant. The percentage of patients dying was highest in the less than 1-year age range. Combining the <1 and 1- to 5-age groups, the percentage of patients dying is 10%, still higher than any other age range. From this data, the overall percent of children and adults dying in 1998 on the liver list was almost identical, 7.4%, the children (115 of 1541) and 7.3% adults (1202 of 16,442)

We also analyzed the probability of death on the waiting list, divided by status at time of listing and adjusted for race, ABO match, and repeat listing. For adult and pediatric liver recipients added to the waiting list between 1/1/95 and 12/31/97, four possible events could occur: 1) the patient was removed from the waiting list for reasons other than death or transplant, 2) the patient continued to wait, 3) the patient received a cadaveric organ, (living related transplants excluded, reduced and split grafts included), 4) the patient died before transplantation. Patients removed from the list because they were too ill to receive a transplant were counted as pretransplant deaths. Table 4 shows the estimates for the probability of these four possible outcomes in the first 6 months after listing for patients added to the list between 1/1/95 and 12/31/97. Both adult and pediatric patients at status 1 and 3 had similar probabilities of dying on the list. A total of 31% of adults and 27% of children initially listed in status 1, died waiting. In status 2, pediatric patients had a lower probability of dying but a longer waiting time compared to adults. A total of 25.7% of adults at status 2 died compared with 12.4% of children, whereas 14.5% of adults originally listed were still waiting at the end of 6 months compared to 23.7% of children at status 2. In the second 6 months after listing the probability for all four outcomes was similar between adults and children (data not shown).

Kaplan-Meier patient and graft survivals: effect of donor age on outcome of pediatric and adult liver recipients. Our first analysis attempted to answer this question by subdividing donor and recipient ages into several age ranges. However, the numbers in each subgroup became too small to allow for a meaningful statistical analysis. It was decided to eliminate several subdivisions of age ranges as well as extremes of donor and recipient age that might bias the results. Therefore, for the first analysis, the 0–5 age range for donors and the 0–2 age range for recipients was eliminated and the 3- to 5-year and 6- to 17-year age range for recipients was combined into one group, i.e., 3–17 years. It was also reasoned that pediatric recipients less than 3 years generally received whole organs from similar age donors based on size considerations. The upper limit of donor and recipient age was set at less than 50 years to exclude the possible negative effects of older donors and recipients. Figure 1, shows the unadjusted Kaplan-Meier 3-year graft survivals for pediatric recipients (3–17 years) receiving livers from pediatric-aged donors (6–17 years) compared to adult donors (18–49 years), and adult recipients receiving livers from pediatric aged donors. Results shown include retransplants, all UNOS statuses and a further analysis for status 1 and status 2. Excluded are reduced, split or living donor transplants. Pediatric recipients receiving livers from younger donors had a significantly improved graft survival, 81% compared with

TABLE 5. The odds of graft survival compared for adult and pediatric donors and recipient: whole grafts only

Recip age (yr)	Donor age (yr)	Num txd	Time points					
			3 Mo post-Tx		1-Yr post-Tx		3 Yr post-Tx	
			Odds ratio	*P*	Odds ratio	*P*	Odds ratio	*P*
3–17	6–17	496	0.62	0.02	0.50	<0.01	0.58	0.03
3–17	18–49	362	1.00	Ref.	1.00	Ref.	1.00	Ref.
18–49	6–17	1699	0.82	0.20	0.77	0.07	0.84	0.36
18–49	18–49	5879	0.78	0.08	0.77	.05	0.84	0.26

TABLE 6. Transplants performed 4/1/94–12/31/97, numbers of whole, reduced, split, and living donors by year 1994–1997

Yr	Type of transplant				
	Whole	Reduced	Split	Live	Total
1994	2669	108	26	45	2848
1995	3771	87	21	45	3924
1996	3865	84	62	46	4057
1997	3935	79	84	60	4158
Total	14240	358	193	196	14987

TABLE 7. Numbers of whole, reduced, split and living donors by age of recipient: 1994–1997

Age	Type of transplant				
	Whole	Reduced	Split	Live	Total
<1	254	131	39	106	530
1–2	304	102	35	47	488
3–5	192	42	13	15	262
6–10	223	35	13	14	285
11–17	375	21	13	7	416
18+	12892	27	80	7	13006
Total	14240	358	193	196	14987

63%, $P<0.001$. In contrast, adult recipients had similar graft survivals irrespective of donor age. These differences remained significant when status at time of listing was considered.

Multivariate analyses: effect of donor age or outcome of pediatric and adult liver recipients. The Kaplan-Meier survival curves were unadjusted for risk. Therefore a further multivariate regression analysis was performed to determine if placing younger donor livers into younger recipients reduced the odds of graft failure. As before, this analysis excluded living related donors and split and reduced grafts. Donor and recipient risk factors controlled for were: donor and recipient race, donor cause of death, recipient diagnosis at transplant, medical condition (UNOS status) at transplant, cold ischemia time, ABO match, donor creatinine level, and year of transplant. The odds of graft failure at three months, 1 and 3 years posttransplant were determined (Table 5). At all three time points, the odds of graft failure were significantly less if pediatric recipients (3–17 years) received livers from younger donors (6–17 years). In contrast the odds of graft failure at each time point for adult recipients were similar whether or not the donor was younger or older.

The same multivariate regression analysis was repeated but now applied to all pediatric and adult recipients, with no age exclusions and inclusive of split and reduced grafts. Table 6 shows the number of reduced and split organ transplants performed during the period of this analysis, and Table 7 the type of transplant according to age. During this time period 66 pediatric-aged donors were split, of which 24 segments were placed in adults.

The results of the unrestricted analysis (Table 8) remained very similar to the restricted analysis: pediatric patients have significantly reduced odds of graft failure if receiving a graft from a pediatric-aged donor whereas the age of the donor had little impact on the odds of graft failure to adult recipients.

An expected outcome of a policy that would direct more livers from pediatric donors to pediatric recipients would be an increased number of relatively large organs being directed to smaller recipients. This would encourage split liver transplantation whereby two recipients benefit from one organ. As well, reduced size transplantation, where part of the liver is discarded, might also occur. Therefore, we investigated the graft survivals of reduced and split size livers. For the time period 4/1/94–12/31/97 the Kaplan-Meier 3-year graft survival estimates for pediatric recipients of primary liver transplants subdivided by the type of organ received are shown (Fig. 2). It can be seen that reduced size grafts had a significantly lower 3-year graft survival compared to all other graft types. In comparison, split liver grafts had an overall 70% 3-year graft survival, not significantly different from either whole or living donor grafts. We were also interested in whether a split liver from a pediatric donor had a different patient and graft survival compared to that from an adult donor. Although the numbers were small, Kaplan-Meier three year adjusted patient survivals for split livers were not different if the liver was from an adult donor (n=51, patient survival 87%) or a pediatric donor (n=32, patient survival 89%). However, in comparison, the 3-year Kaplan-Meier graft survival was worse if the split liver was from an adult donor, 62%, as compared to a pediatric donor, 83%.

For all the above analyses of graft survivals, patient survivals were also examined (data not shown), and similar results were observed. Because of the complexity of the analyses derived from data accrued over several years, we did attempt to detect any possible center effects.

UNOS liver allocation model (ULAM) results. ULAM was used to investigate whether the proposal to allocate livers from pediatric donors preferentially to pediatric recipients, within urgency status and geographic areas, would have a detrimental impact on adult patients waiting on the list. In particular we believed it was important to investigate whether the number of adults dying either pretransplant or posttransplant would be effected by the proposed new policy. The proposed allocation sequence used in the model is shown in Table 9.

Two models were developed; the first defined a pediatric

TABLE 8. Odds of graft survival compared for pediatric and adult aged donors and recipients; including reduced and split grafts

Recip age (yr)	Donor age (yr)	Num txd	Time points					
			3 Mo post-Tx		1 Yr post-Tx		3 Yr post-Tx	
			Odds ratio	P	Odds ratio	P	Odds ratio	P
0–17	0 –17	1786	0.66	<0.01	0.62	<0.01	0.65	<0.01
0–17	18+	882	1.00	Ref.	1.00	Ref.	1.00	Ref.
18+	0 –17	3225	0.62	<0.01	0.84	0.29	1.06	0.75
18+	18+	15300	0.66	<0.01	0.86	0.33	1.06	0.75

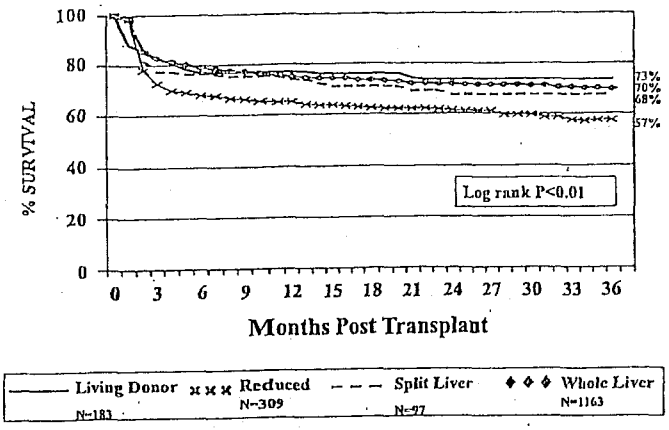

FIGURE 2. **The Kaplan-Meier 3-year graft survivals are shown for pediatric recipients of primary liver transplants subdivided by type of organ received.**

donor as <18 years, and the second defined a pediatric donor as <18 years and less than a specified weight range. Three weight ranges were investigated, <40, <45, and <50 kg. The second model was developed in response to concerns that small adult recipients might be disadvantaged by the proposed pediatric definition of <18 years without weight restrictions.

Neither model takes into account the data presented above which shows improved patient and graft survivals for children receiving livers from pediatric aged donors. Further, split liver transplant and outcomes were not considered.

Table 10 summarizes the most relevent data from the simulations comparing the current allocation policy to the four proposed pediatric donor definitions: 1) <18 years, 2) <18 years and <40 kg, 3) <18 years and <45 kg, 4) <18 years and <50 kg (Table 11).

The data presented in Table 12 represents the average of each measure for 5 years (1999–2003) and over four simulation runs. The data address: 1) the number of pediatric and adult patients transplanted by age (pediatric recipients divided 0 to 5 years, 6–11 years, 11–17 years) and by status, 2) median waiting time by status, and 3) probability of pretransplant death within 6 months of listing. The number of repeat transplants, and patient life years under the different proposals is not shown because the model did not account for expected improvements in pediatric graft survival should pediatrics recipients receive livers from pediatric aged donors.

In all of the proposed policies, slightly more pediatric patients were transplanted over the 5-year period. The increase over the current policy ranged from 151 over 5 years (30 per year) for the most restrictive policy with donors defined as <18 years and <40 kg, to 297 over 5 years (59 per year) the least restrictive policy defining a pediatric donor as <18 years. Consequently, each of the policies resulted in a corresponding decrease in the number of adult patients receiving transplants.

Investigating the change in the number of transplants by age and status showed that among pediatric patients fewer were transplanted in status 1 under the proposed policies. This is because more pediatric patients were transplanted at less urgent statuses under the proposed policies. In contrast about the same or slightly higher numbers of adult patients

TABLE 9. **Proposed order of allocation for a liver from a pediatric donor**

1. Local
Pediatric status 1
Adult status 1
2. Regional
Pediatric status 1
Adult status 1
3. Local
Adult status 2a
Pediatric status 2b
Adult status 2b
Pediatric status 3
Adult status 3
4. Regional
Adult status 2a
Pediatric status 2b
5. National
Pediatric status 1
Adult status 1
Adult status 2a
Adult status 2b
Pediatric status 3
Adult status 3

were transplanted in status 1 because there were fewer pediatric patients competing for organs while in status 1. This is reflected in the increased numbers of children transplanted at status 2B. This was most evident in the policy defining pediatric donors <18 years without weight restriction. The increase in pediatric status 2B patients transplanted was 304 over 5 years compared to current policies. This benefit was diluted as the more restrictive pediatric donor definitions by weight were applied. In contrast, the more stable pediatric patients at status 3 showed only a modest increase, approximately 4–10 more children per year. In examining the data by status for adults, it is also important to note that all of the proposed policies slightly increased the number of adult patients transplanted at status 2A. This effect ranged among 18 to 78 patients over 5 years.

Of all pediatric donor livers, the percent that went into adults was 68.8% under the current policy. Under the least restrictive proposed policy the percentage of adults still receiving pediatric donors was 59.2%, and ranged between 63–64% under the other pediatric donor proposals divided by weight. There was also a decrease in the percentage of adult livers that were transplanted into pediatric patients. This was most pronounced, 3.9%, in the policy defining pediatric donors <18 years, without weight restriction. Only a negligible increase in the percentage of adult livers that were transplanted into adults was demonstrated.

The percentage of local, regional, and national transplants was essentially unchanged as was the average and median distance the organ traveled. The percentage of organs that traveled greater than 1000 miles increased from 1.6 to 1.7%.

Deaths pretransplant and posttransplant and total deaths for the proposed policies was examined and no significant changes were noted with all four policies proposed as compared to the current policy.

When the probability of pre transplant death within 6 months of listing was analyzed, there were minimal differences, none of which was statistically significant, between

TABLE 10. ULAM comparison of current liver allocation policy to four proposed pediatric donor definitions: <18 yr and <40 kg; <18 yr and <50 kg; the model simulates 5 yr of transplant activity under the various definitions

	Current policy	<18 Yr	<40 kg	<45 kg	<50 kg
No. ped. txs	2132	2429	2283	2299	2307
Change from current policy		+297	+151	+167	+175
No. ped. txs by age					
0–5	1238	1417	1336	1339	1353
6–11	367	413	387	391	397
11–17	528	600	560	569	558
Txs by age and status					
Adult 1	4061	4085	4056	4100	4087
Adults 2A	4713	4731	4729	4733	4781
Ped 1	764	711	755	733	731
Ped 2B	1069	1372	1206	1246	1256
% of total/ped donor to adult recipient					
	69%	59%	64%	64%	63%
Med wait time					
Ped. 2B:2B	340.8	179.0	264.5	252.3	243.0
Ped. 3:2B	776.5	624.3	685.5	699.5	674.0
Adult 2A:2A	11.3	12.3	11.3	11.3	11.5
Adult 2B:2B	553.0	573.0	550.8	572.3	569.0
Adult 3:2B	947.5	968.5	958.5	963.0	965.5
Probability of pre-Tx death w/in 6 mo of listing					
Adult 1	11.8%	11.4%	11.7%	11.9%	11.6%
Ped 1	16.4%	15.5%	15.3%	15.4%	15.1%
Adult 2A	23.4%	22.2%	22.0%	21.9%	22.9%
Adult 2B	13.7%	14.0%	13.9%	13.6%	13.6%
Ped 2B	13.5%	12.3%	12.8%	12.0%	12.5%

the current and proposed policies among adult and pediatric recipients. Among pediatric patients, death rates decreased for patients listed initially in status 2B and status 3. Waiting time as measured by Kaplan-Meier estimates for most categories were reduced for pediatric patients and increased slightly for adult patients. Of importance, both pediatric and adult patients at status 1 had essentially no change in waiting time at status 1 although on average pediatric patients waited 2 days longer for transplant at status regardless of the policy. Of importance, children in status 2B had the most benefit from the policy defining pediatric <18 years without weight restriction, with median waiting time reduced by 160 days. In that same simulation adult waiting time at 2B was increased by only 20 days. When pediatric donors were further restricted by weight, the beneficial effect of decreased waiting time at status 2B for children continued to be evident but much less important ranging between 76 and 97 days, whereas the waiting time for adults was effected only slightly 2–16 days. Among adults waiting times increased the most for patients listed initially in status 3 with an ending status of 2B from 947 to 966 days and under the least restrictive policy.

DISCUSSION

We have shown that there is a significant beneficial effect on liver graft survival if pediatric recipients receive livers from pediatric-aged donors, whereas graft survival of adult recipients is not advantaged or disadvantaged by the age of the liver donor. This effect is seen at 3 months after liver transplantation, when donor factors are likely to have the strongest influence on outcome, but also persists at 3 years posttransplant. These findings hold true whether using a univariate or multivariate method of analysis or unadjusted Kaplan-Meier estimates of graft survival. Importantly, whether the analysis is performed on a restricted population of donor and recipients to decrease the potential impact of the extremes of donor and recipient age, and the possible influence of partial liver grafts, or the entire population of adult and pediatric recipients and donors, including partial liver grafts, the same benefit to pediatric patients receiving livers from younger donors persists. The improvement in graft survival for pediatric patients who receive younger donors compared to adults receiving younger donors, will have the greatest impact on the most medically urgent children, who we have shown wait longer to receive a donor, especially if aged less than 5 years, compared with adults of equivalent status.

We can only postulate why pediatric recipients have an improved survival if they receive a liver from a pediatric-aged donor. Donor quality, which is usually excellent in pediatric-aged donors, is a likely explanation. The recent research impetus studying the process of sensecence at the cellular level, may provide new insights in the future.

Should these results be utilized to change allocation policies to give children awaiting liver transplantation some preference in receiving younger donors? To answer this important question several related issues must first be considered. 1) Do children already hold an advantage over adults waiting liver transplantation, reflected either by shorter waiting times or a decreased mortality on the list? 2) Would redirecting some pediatric donors away from adults awaiting liver transplantation have a significant negative effect on the outcome of adults undergoing liver transplantation? 3) Could directing some adolescent donor livers to small children encourage split liver transplantation, which would increase the donor supply?

It has been argued that children already have an advantage over adult candidates awaiting liver transplantation because they have three possible options for receiving a liver:

a whole cadaveric graft, a partial cadaveric graft or a living donor organ (*16*). Despite this, an analysis of the last 3 years of the UNOS database show that children have similar mortalities and waiting times compared to adults on the transplant list. In fact, it is children less than 2 years of age at status 1 who waited significantly longer than any other age group. As well, in 1998, children less than 1 year had the highest mortality rate waiting for any age group, followed only by children in the 1- to 5-year age range. Therefore the data suggest that the availability of living related donors and partial liver grafts, which would most likely have benefited small children on the list, has not yet had a significant impact on pediatric mortality or waiting time as compared with adults. Furthermore, given that the results of liver transplantation in small pediatric patients in experienced centers are comparable to those of older children, there can be no justification for not providing young children with at least equal access to liver donors.

Although living related donation for children has been properly advocated as one means of alleviating the donor shortage for children (*17*), this modality should not be viewed as an excuse to divert cadaveric donors away from children (*18*). Because of the risk to the otherwise healthy donor, most often a parent (*18*), the ethically correct position is that living related donation should continue to be seen as last resort to try and alleviate the donor supply problem. Conversely, the split liver donor technique should become the first consideration for every suitable donor (*19*). The most recent reported results are comparable to whole graft transplantation (*20*). As well, a recent report suggests graft survival is better in infants who receive a split compared to a whole graft (*21*). However, reduced graft transplantation should be actively discouraged: not only are the results inferior, but a whole liver is diverted away from a more appropriately sized recipient.

The next question was more complex: would adults be disadvantaged by diversion of some pediatric donors to pediatric recipients? Fairness and balancing the conflicting notions of transplanting the most urgent first regardless of age versus best utilization of a scarce resource, would require that pediatric-aged donors should not always be placed in pediatric recipients. For example, it would seem inappropriate and unjust, either on a local or regional level that a status 1 adult should be bypassed for a status 2B child. For this reason, ULAM was programed to assign priority so that within each medical urgency status and within each geographic distribution level (local, regional, and national) pediatric candidates are prioritized.

The most important result of the modeling was that none of the proposed policies allocating livers from pediatric donors to pediatric recipients increased the probability of death for adults waiting on the transplant list. Although more children were transplanted per year (at most 59, less than 1 additional child per pediatric transplant center), and therefore proportionately less adults, the impact for the adults was on waiting time at the less urgent statuses, 2B and 3. Even then, the average wait was at most increased by 20 days. Importantly, the waiting time for the most medically urgent adults at status 2A and 1 was not affected by any of the proposed policies. In fact adults waited an average of 2 days less at status 1 compared to children, because more children were transplanted at status 2B. As well slightly more status 1 adult patients were transplanted under the proposed policies.

The decrease in waiting time for children at 2B was as much as 160 days. Clinically this is important as one of the most common criteria for listing children at status 2B is a growth failure, i.e., weight or height less than 5th percentile. The impact of decreasing waiting time by as much as half a year for the young, cholestatic, malnourished child is clinically highly relevant to the unique issues of growth and development in chronically ill children (*22*, *23*). It has already been shown that malnutrition has a negative effect on both pre- and posttransplant survival (*24*, *25*), and that age at transplant of <2 years in children is an important independent predictor of improved growth after transplantation (*26*). It should still be noted that even under the most liberal of the proposed policies, the majority of livers procured from pediatric aged donors will still be transplanted into adult recipients. As well, the percentage of transplants performed locally, regionally, and nationally would be affected only minimally.

The third question to be considered is how might a proposal to direct some livers from pediatric donors best encourage split liver transplantation. Our data show that split liver graft survival is significantly improved if the donor is in the pediatric age range. This result is most likely a reflection of the usually excellent quality of the adolescent donor and highlights the need for very careful donor selection if the split procedure is performed on adult-aged donors.

In comparing the four pediatric allocation proposals, with the least restrictive being any pediatric donor <18 years, and the most restrictive being <18 years as well as <40 kg, the data showed that the most positive effect occurred for the pediatric patients when the pediatric donor was defined <18 years. When the pediatric donor was further subdivided by weight, the potential benefit to pediatric patient was diminished without a substantial increase in benefit to adult patients. If the definition of the pediatric donor was restricted to weight <40 kg, the advantage of directing some of the larger pediatric donors to smaller pediatric recipients, which would promote split liver transplantation, would be lost. As can be seen from the data, most pediatric donor livers exported to adult recipients are in the donor age range of 11–17 years, are generally of excellent quality and ideal for splitting. In fact, UNOS recently approved a proposal that requires all participating centers to split suitable donor livers. If adolescent liver donors are preferentially offered to children waiting, many of whom would be too small to accept a whole graft, the center accepting such a liver should split the graft so that an adult patient would not be deprived of an organ. If the center was unwilling to split the donor liver, it should be returned to the donor pool for reassignment to the next eligible recipient. Such a policy could then be seen as a reason to improve the utilization of these excellent quality younger donors. The success of this concept will depend on centers being prepared to "share" split grafts. A recent report shows that "shipped" segments have an equivalent graft survival compared to locally procured segments (*27*). Given the demonstrated excellent results achievable both for the right and left split liver grafts (*28*), and the ongoing organ shortage, urgent priority should be assigned to any allocation policy that will encourage split liver transplantation (*29*). The onus will lie on the surgical transplant community to not

accept such livers for reduced size transplantation, a technique now in disrepute given the proven success of split livers, and the increasing donor shortage.

We have shown that an allocation policy giving some priority to children to receive livers from pediatric donors can improve the outcomes after liver transplantation, without a negative impact on adults. As well, such a policy would encourage split transplantation, the only method currently available to increase the cadaveric donor supply. Furthermore, this proposal strikes a balance between justice and utility; the sickest patients, whether adult or pediatric are still transplanted first, more grafts are made available by encouraging split transplantation, and patient and graft survival for children are improved without detriment to adult recipients outcome. As such this proposal is worthy of serious consideration by the community of transplant physicians, surgeons, and their patients.

REFERENCES

1. Cohen B, D'Amaro J. Some contemporary ethical considerations related to organ transplantation. Transpl Int 1995; 8: 238.
2. Bollinger RR. A UNOS perspective on donor liver allocation. United Network for Organ Sharing. Liver Transpl Surg 1995; 1: 47.
3. Yoshida EM. Selecting candidates for liver transplantation:a medical ethics perspective on the micro allocation of a scarce and rationed resource. Can J Gastroenterol 1998; 12: 209.
4. Neuberger J, Adams D, MacMaster P, Maidment A, Speed M. Assessing priorities for allocation of donor liver grafts: survey of public and clinicians. BMJ 1998; 317: 172.
5. Lucey MR, Brown KA, Everson GT, et al. Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. Liver Transplant Surg 1997; 3: 628.
6. Showstack J, Katz PP, Lake JR, et al. Resource utilization in liver transplantation: effects of patient characteristics and clinical practice. NIDDK Liver Transplantation Database Group. JAMA 1999; 281: 1381.
7. An update on liver transplantation in the United States: recipient characteristics and outcome. In: Belle SH, Beringer KC, Detre KM, eds. UNOS Liver Registry, Pittsburgh. Clinical Transplants 1995. Chapter 2, p. 18–32.
8. Colombani PM, Cigarroa FG, Schwarz K, Wise B, Maley WE, Klein AS. Liver transplantation in infants younger than 1 year of age. Ann Surg 1996; 223: 658.
9. Van der Werf WJ, D'Alessandro AM, Knechtle SJ, et al. Infant pediatric liver transplantation results equal those for older pediatric patients. J Pediatr Surg 1998; 33: 20.
10. Bonatti H, Muiesan P, Connelly S, et al. Hepatic transplantation in children under 3 months of age: a single centre's experience. J Pediatr Surg 1997; 32: 486.
11. Woodle ES, Millis JM, So SKS, et al. Liver transplantation in the first three months of life. Transplantation 1998; 66: 606.
12. Broelsch CE, Emond JC, Thistlethwaite JR, et al. Liver transplantation, including the concept of reduced-size liver transplants in children. Ann.Surg 1988; 208: 410.
13. Goyet Jd, Hausleithner V, Reding R, Lerut J, Janssen M, OTTE J-B. Impact of innovative techniques on the waiting list and results in pediatric liver transplantation. Transplantation 1993; 56: 1130.
14. Emond JC, Heffron TG, Thistlethwaite JR. Innovative approaches to donor scarcity: A critical comparison between split liver and living related liver transplantation. Hepatology 1991; 14: 92.
15. Pritsker AAB, Martin DL, Renst J, et al. Organ Transplantation Policy Evaluation: In Proceedings of the Winter Simulation Conference, 1995; 1314.
16. Slooff MJ. Reduced size liver transplantation, split liver transplantation, and living related liver transplantation in relation to the donor organ shortage. Transplant Int 1995; 8: 65.
17. Sindhi R, Rosendale J, Mundy D, et al. Impact of segmental grafts on pediatric liver transplantion-a review of the United Network for Organ Sharing Scientific Registry data (1990–1996), J Pediatr Surg 1999; 34: 107.
18. Broelsch CE, Burdelski M, Rogiers X, et al. Living donor for liver transplantation. Hepatology 1994; 20: 49S.
19. Busuttil RW, Goss JA. Split liver transplantation. Ann Surg 1999; 229: 313.
20. Goss JA, Yersiz H, Shackleton CR, et al. In situ splitting of the cadaveric liver for transplantation. Transplantation 1997; 64: 871.
21. Cacciarelli TV, Esquivel CO, Moore DH, et al. Factors affecting survival after orthotopic liver transplantation in infants. Transplantation 1997; 64: 242.
22. Moukarzel AA, Najm I, Vargas J, McDiarmid SV, Busuttil RW, Ament ME. Effect of nutritional status on outcome of orthotopic liver transplantation in pediatric patients. Transplant Proc 1990; 22: 1560.
23. Stewart S, Uauy R, Waller DA, Kennard B, Benser M, Andrews W. Mental and motor development, social competence, and growth one year after successful liver transplantation. J Pediatr 1989; 114: 574.
24. Moukarzel AA, Najm I, Vargas JV, McDiarmid SV, Busuttil RW, Ament ME. Effect of nutritional status on outcome of orthotopic liver transplantation in pediatric patients. Transplant Proc 1990; 22: 1560.
25. Shepherd RW, Chin SE, Cleghorn GJ, et al. Malnutrition in children with chronic liver disease accepted for liver transplantation: clinical profile and effect on outcome. J Paediatr.Child Health 1991; 27: 295.
26. McDiarmid SV, Gornbein JA, DeSilva P, et al. Factors affecting growth after pediatric liver transplantation. Transplantation 1999; 67: 404.
27. Hess UJ, Pattyn P, Kerremans I, et al. The course of shipped livers used as full size, reduced or split grafts. Acta Chir Belg 1997; 2: 76.
28. Rogiers X, Malago M, Gawad KA, et al. One year of experience with extended application and modified techniques of split liver transplantation. Transplantation 1996; 61: 1059.
29. Mirza DF, Achilles O, Pirenne J, Buckels JA, McMaster P, Mayer AD. Encouraging results of split-liver transplantation. Br J Surg 1998; 85: 494.

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参考資料６

Safety and Risk of Using Pediatric Donor Livers in Adult Liver Transplantation

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成人レシピエントで、小児（13歳未満）から(70例)と　19歳以上の成人から移植を受けた患者(1051例)の成績を比較した。肝動脈血栓症発症の率が、小児からの移植で12.9%と成人の3.8%より有意に高かった。特に、移植肝がレシピエント推定肝容積の40%未満の患者で発症率が高かった。よって、小児肝を成人に移植するにしても、40%以上が望ましい。

Safety and Risk of Using Pediatric Donor Livers in Adult Liver Transplantation

Sukru Emre, Yuji Soejima, Gulum Altaca, Marcelo Facciuto, Thomas M. Fishbein, Patricia A. Sheiner, Myron E. Schwartz, and Charles M. Miller

Pediatric donor (PD) livers have been allocated to adult transplant recipients in certain situations despite size discrepancies. We compared data on adults (age ≥ 19 years) who underwent primary liver transplantation using livers from either PDs (age < 13 years; n = 70) or adult donors (ADs; age ≥ 19 years; n = 1,051). We also investigated the risk factors and effect of prolonged cholestasis on survival in the PD group. In an attempt to determine the minimal graft volume requirement, we divided the PD group into 2 subgroups based on the ratio of donor liver weight (DLW) to estimated recipient liver weight (ERLW) at 2 different cutoff values: less than 0.4 (n = 5) versus 0.4 or greater (n = 56) and less than 0.5 (n = 21) versus 0.5 or greater (n = 40). The incidence of hepatic artery thrombosis (HAT) was significantly greater in the PD group (12.9%) compared with the AD group (3.8%; $P = .0003$). Multivariate analysis showed that preoperative prothrombin time of 16 seconds or greater (relative risk, 3.206; $P = .0115$) and absence of FK506 use as a primary immunosuppressant (relative risk, 4.477; $P = .0078$) were independent risk factors affecting 1-year graft survival in the PD group. In the PD group, transplant recipients who developed cholestasis (total bilirubin level ≥ 5 mg/dL on postoperative day 7) had longer warm (WITs) and cold ischemic times (CITs). Transplant recipients with a DLW/ERLW less than 0.4 had a trend toward a greater incidence of HAT (40%; $P < .06$), septicemia (60%), and decreased 1- and 5-year graft survival rates (40% and 20%; $P = .08$ and .07 *v* DLW/ERLW of 0.4 or greater, respectively). In conclusion, the use of PD livers for adult recipients was associated with a greater risk for developing HAT. The outcome of small-for-size grafts is more likely to be adversely affected by longer WITs and CITs. The safe limit of graft volume appeared to be a DLW/ERLW of 0.4 or greater. (*Liver Transpl 2001;7:41-47.*)

Although pediatric donor (PD) livers are ideally used for pediatric recipients, they are occasionally allocated to adult recipients, e.g., when only a pediatric liver is available for a critically ill adult or when an adult patient is listed with the weight range for a PD. In these circumstances, it is important to know the risks of using a small-for-size liver in an adult.

The main risk with such grafts is that they will fail secondary to inadequate liver volume. Experience with living related liver transplantation (LT) in adults has shown that grafts as small as 25% to 30% of ideal liver volume can be tolerated.[1,2] However, Emond et al[3] reported early functional impairment with grafts less than 50% of the expected liver volume. In addition, Kiuchi et al[4] reported that small-for-size grafts (<1% of recipient body weight) were associated with lower graft survival, probably because of enhanced parenchymal cell injury and reduced metabolic and synthetic capacity. Thus, in living donor LT, it is now accepted that grafts must be greater than 0.8% of the recipient body weight (or >40% of expected liver volume).[5]

Similar data on small-for-size cadaveric liver grafts are not available. In this study, we reviewed our large experience with the transplantation of pediatric livers into adult recipients and attempted to identify risk factors for poor graft survival and determine minimal graft volume requirements.

Patients and Methods

Study Population and Design

Between September 1988 and March 1999, 1,121 adults (age ≥ 19 years) underwent primary LT using full-size (whole) allografts from either PDs (age < 13 years; n = 70) or adult donors (ADs; age ≥ 19 years; n = 1,051). Patients who received primary transplants from donors aged between 13 and 18 years were excluded from analysis.

Mean post-LT follow-up was 1,830 days (median, 1,738 days; range, 78 to 3,664 days) in the PD group and 1,591 days (median, 1,477 days; range, 5 to 3,840 days) in the AD group. Donor liver weight (DLW) was measured at the end of the back-table procedure. Based on data from the first thousand LTs performed at our institution, estimated recipient liver weight (ERLW) was calculated using a formula developed at our center[6]:

$$\text{ERLW (cubic centimeters)} = 6 \times \text{weight (lb)} + 4 \times \text{age (years)} + 350$$

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In this study, DLW/ERLW ratio was used as an indicator of graft size matching.

Part 1: Comparison of outcomes in PD and AD groups. We compared the following factors between groups: recipient and donor age and sex, DLW/ERLW ratio, indication for LT, United Network for Organ Sharing (UNOS) status, and preoperative values for total bilirubin (TBil), prothrombin time (PT), and creatinine. Surgical data analyzed included cold (CIT) and warm ischemic time (WIT), total operative time, bypass use, type of caval reconstruction, and use of packed red blood cells and fresh frozen plasma. CIT was defined as the period from donor cross-clamping to the start of anastomosis in the recipient, and WIT was defined as the period from the start of anastomosis to allograft reperfusion. One- and 5-year patient and graft survival were also compared between groups, as was the incidence of postoperative complications, including primary nonfunction (PNF), hepatic artery thrombosis (HAT), portal vein thrombosis, bile leak, intrahepatic and extrahepatic bile duct stricture, septicemia, acute rejection, and post-LT ascites.

Part 2: Univariate and multivariate analysis. Univariate and multivariate analyses were performed in the PD group to determine the independent risk factors that adversely affected 1- and 5-year patient and graft survival. Continuous variables were dichotomized at clinically established cutoff points and presented as categorical. Diagnoses at primary LT were categorized into acute or chronic for statistical convenience. Variables found to predict 1-year graft survival on univariate analysis were further entered into multivariate analysis.

Part 3: Risk factors for prolonged cholestasis. To identify factors that predict and/or increase the risk for prolonged cholestasis in adults who receive small-for-size cadaveric livers, we compared PD recipients with and without prolonged cholestasis (TBil $\geq$ 5.0 mg/dL on postoperative day [POD] 7). Eighteen patients were excluded because of either graft loss within 7 days or inadequate data. Of the 52 patients remaining, TBil level was less than 5.0 mg/dL in 41 patients and 5.0 mg/dL or greater in 11 patients. Recipient and donor age, UNOS status, DLW/ERLW, CIT, WIT, use of packed red blood cells and fresh frozen plasma, and 1- and 5-year patient and graft survival were compared between the subgroups.

Part 4. To clarify minimal liver volume requirements, PD patients were divided on the basis of 2 different DLW/ERLW cutoff values (<0.4 or ≥ 0.4 and <0.5 or ≥ 0.5). Nine patients were excluded for lack of data on either DLW (n = 4) or recipient body weight (RBW) (n = 5); 61 patients were included in the analysis, as follows: DLW/ERLW less than 0.4 (n = 5) versus 0.4 or greater (n = 56) and DLW/ERLW less than 0.5 (n = 21) versus 0.5 or greater (n = 40).

Postoperative complications, including the incidence of PNF, HAT, portal vein thrombosis, bile leak, septicemia, and acute rejection, were compared at each cutoff point, as were 1- and 5-year patient and graft survival. TBil, glutamic-oxaloacetic transaminase, and PT values for PODs 2, 7, and 14 were also compared between the groups.

Statistical Analysis

Survival analysis was performed using the Kaplan-Meier method, and the groups were compared by means of the log-rank test. Continuous variables were compared using a 2-tailed, unpaired *t*-test for independent samples. Categorical data were compared using chi-squared test. For survival analysis, continuous variables were dichotomized at a clinically relevant cutoff point. Variables found to impact significantly on 1-year graft survival were analyzed by multivariate analysis. Multivariate analysis was performed using stepwise forward and backward Cox proportional-hazards models. *P* less than .05 is considered significant. All statistical analyses were performed with the StatView7 4.5 software for Macintosh (Abacus Concepts Inc, Berkeley, CA).

Results

Part 1

Groups were similar in terms of recipient age, cause of liver disease, UNOS status, and pre-LT liver function test results. There was also no difference between groups in terms of WIT or total ischemic time, bypass use, arterial anastomosis technique, blood product use, and initial immunosuppression. Preoperative demographics and surgical data, including initial immunosuppressive therapy, are listed in Table 1.

One- and 5-year patient survival rates were 82.9% and 70.0% in the PD group and 82.5% and 73.2% in the AD group (P = not significant). One- and 5-year graft survival rates tended to be less in the PD group than the AD group (68.6% *v* 75.0% for 1-year survival; $P = .17$; 52.6% *v* 65.8% for 5-year survival; $P = .051$), but did not reach statistical significance (Fig. 1).

Table 2 lists the incidence of postoperative complications and length of hospital and intensive care unit stays. The rate of HAT was 12.9% in the PD group compared with 3.8% in the AD group ($P = .0003$).

Figure 2 shows the causes of graft loss in the 2 groups. Thirty-five grafts were lost in the PD group and 361 grafts were lost in the AD group. Overall, causes of graft loss were similar between the groups.

Part 2

On univariate analysis, diagnosis at primary LT ($P = .01$), UNOS status ($P < .05$), pre-LT PT ($P = .005$), creatinine level ($P = .01$), DLW/RBW ($P = .01$), and primary immunosuppressive therapy ($P = .03$) reached statistical significance regarding 1-year graft survival in PD recipients. These variables were further evaluated in forward and backward stepwise Cox regression models. Independent risk factors were a high pre-LT PT and not using FK506 as primary immunosuppressive therapy (Table 3).

Table 1. Preoperative Demographics

Variables	Group		*P*
	PD (n = 70)	AD (n = 1,051)	
Recipient variables			
Sex (% female)	78.6	39.8	<.0001
RBW (kg)	65.3 ± 14.3	75.6 ± 16.9	<.0001
ERLW (g)	1,346 ± 319	1,511 ± 319	<.0001
Donor variables			
Donor age (yr)	8.9 ± 2.1	45.3 ± 17.3	<.0001
Sex (% female)	35.7	41.3	NS
Donor body weight (kg)	33.4 ± 11.7	72.9 ± 15.4	<.0001
DLW (g)	865 ± 267	1,477 ± 308	<.0001
DLW/ERLW	0.69 ± 0.44	1.05 ± 0.50	<.0001
CIT (h)	10.9 ± 3.4	10.0 ± 3.3	.04
Piggyback (%)	51.4	4.6	<.0001
Bile duct reconstruction (%)			.0006
Duct-to-duct with T-tube	49.3	44.5	
Duct-to-duct without T-tube	24.0	42.7	
Roux-en-Y	26.7	12.8	
ICU stay (d)	10.0 ± 11.7	8.9 ± 13.4	NS
Hospital stay (d)	36.7 ± 33.9	35.5 ± 32.8	NS

NOTE. Values expressed as mean ± SD unless otherwise noted.
Abbreviations: ICU, intensive care unit; NS, not significant.

Part 3

Table 4 shows the effect of post-LT cholestasis on patient and graft survival. One- and 5-year patient and graft survival were significantly worse in patients with a TBil level ≥5.0 mg/dL on POD 7. In these patients, WIT and CIT were significantly longer than those in patients with TBil levels less than 5 mg/dL on POD 7 (57.2 ± 13.0 *v* 45.5 ± 9.0 minutes; 13.1 ± 4.3 *v* 10.5 ± 3.0 hours, respectively).

Part 4

Table 5 lists postoperative complication rates and 1- and 5-year patient and graft survival rates, with special reference to DLW/ERLW. There was no statistical difference in diagnosis, UNOS status, or surgical variables (data not shown). Patients with a DLW/ERLW less than 0.4 had a trend toward a greater rate of HAT (40% *v* 10.7%; $P < .06$) and septicemia (60% *v* 25.0%). Furthermore, 1- and 5-year graft survival rates in this

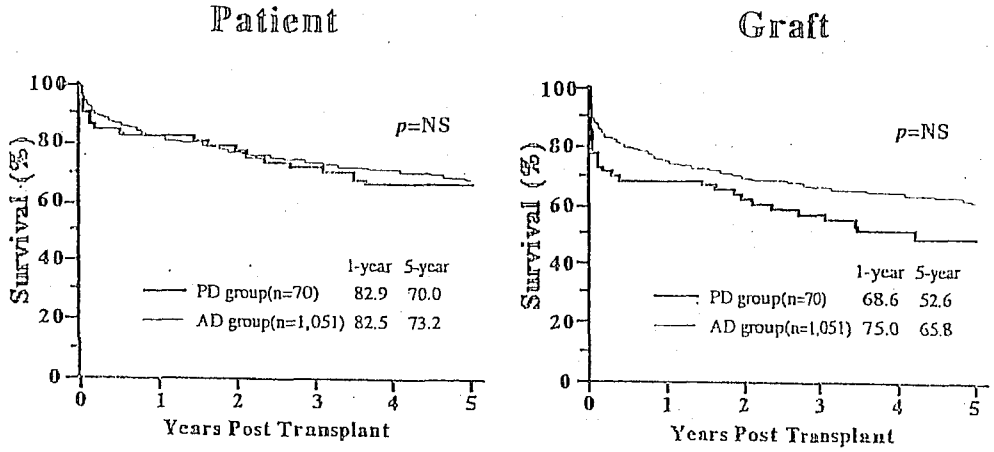

Figure 1. Comparison of patient and graft survival between the PD (n = 70) and AD groups (n = 1,051).

Table 2. Postoperative Complications

Variables	PD (n = 70)	AD (n = 1,051)	P
PNF (%)	7.1	6.3	NS
HAT (%)	12.9	3.8	.0003
Portal vein thrombosis (%)	2.1	1.5	NS
Bile leak (%)	5.7	3.8	NS
Bile duct stricture (%)*	5.7	5.8	NS
Septicemia (%)	28.6	19.8	NS
Acute rejection (%)	42.9	50.1	NS
Posttransplantation ascites (%)	7.1	10.5	NS

Abbreviation: NS, not significant.
* Intrahepatic and extrahepatic stricture.

Table 3. Independent Predictors of Inferior 1-Year Graft Survival in Recipients of PD Livers

Variables	Graft Survival (%)	Coefficient	Relative Risk	P
PT (s)				
<16	80.5	1		
≥16	51.7	1.165	3.206	.0115
FK506 use				
Yes	86.2	1		
No	57.5	1.499	4.477	.0078

group were only 40% and 20% compared with 73.2% and 57.1% in patients with a DLW/ERLW of 0.4 or greater. Although there was no statistical significance, probably because of the small sample size, diminished graft survival in this group of patients should be noted. When divided at a cutoff value of 0.5 for DLW/ERLW, postoperative complications and patient and graft survival were similar between the groups, except for a greater incidence of bile leak in patients with a DLW/ERLW less than 0.5.

Regarding chronological changes in serum TBil, glutamic-oxaloacetic transaminase, and PT values early after LT, we found that serum bilirubin levels tended to be greater in the group with a DLW/ERLW less than 0.4 at all points, but this did not reach statistical significance. PT POD 2 was significantly greater in the group with a DLW/ERLW less than 0.4 compared with the group with a DLW/ERLW of 0.4 or greater ($P < .05$).

Although females accounted for 39.8% of AD recipients, 78.6% of PD recipients were female. Primary biliary cirrhosis (21.4%) was a relatively frequent indication in the PD group compared with AD group (10.4%).

Table 1 lists surgical data. Mean CIT was significantly longer in PD recipients ($P < .04$). A piggyback procedure was used in 51.4% of PD recipients in contrast to only 4.6% of AD recipients ($P < .0001$). Patients in the PD group were significantly more likely to require Roux-en-Y hepaticojejunostomy than patients in the AD group because of the size discrepancy between donor and recipient ducts (26.7% *v* 12.7%).

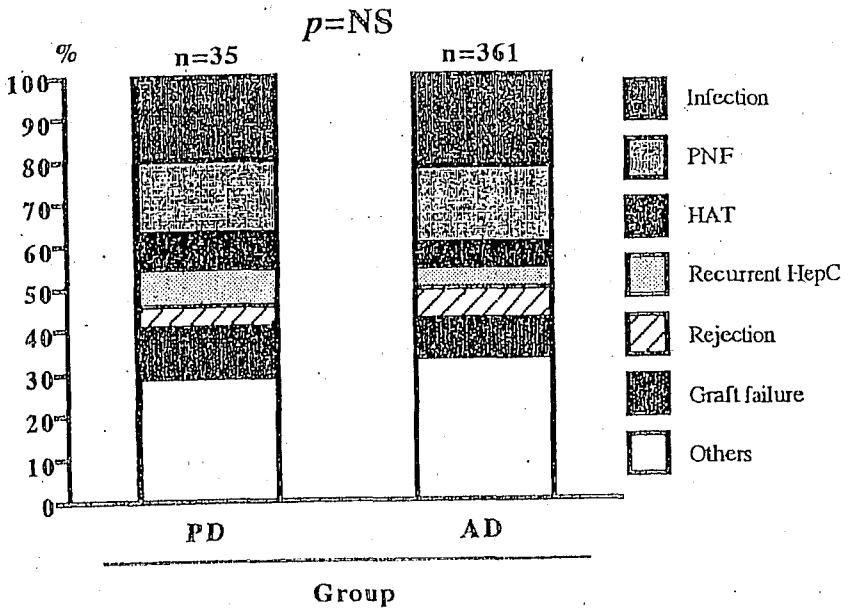

Figure 2. Comparison of causes of graft loss between the PD (n = 70) and AD groups (n = 1,051). (HepC, hepatitis C; NS, not significant.)

Table 4. Delayed Cholestasis After LT

Variables	TBil (mg/dL) POD 7 <5.0 (n = 41)	TBil (mg/dL) POD 7 ≥5.0 (n = 11)	*P*
Recipient age (yr)	51.1 ± 14.3	51.0 ± 14.5	NS
UNOS status (%)			NS
1	11.1	27.2	
2	36.1	18.2	
3	52.8	54.6	
Donor age (yr)	8.7 ± 2.1	9.7 ± 1.3	NS
DLW (kg)	855 ± 385	784 ± 147	NS
DLW/ERLW	0.63 ± 0.23	0.67 ± 0.49	NS
CIT (h)	10.5 ± 3.0	13.1 ± 4.3	.02
WIT (min)	45.5 ± 9.0	57.2 ± 13.0	.001
Intraoperative transfusions			
PRBCs (units)	10.9 ± 7.2	15.7 ± 14.9	NS
FFP (units)	17.9 ± 14.3	11.8 ± 8.7	NS
Patient/graft survival (%)			
1-yr	92.7*/80.5†	54.5*/36.4†	*†<.001
5-yr	80.5‡/65.9§	36.4‡/18.2§	‡§<.0001

NOTE. Values expressed as mean ± SD unless noted otherwise.
Abbreviations: PRBC, packed red blood cells; FFP, fresh frozen plasma; NS, not significant.
* 1-year patient survival.
† 1-year graft survival.
‡ 5-year patient survival.
§ 5-year graft survival.

Table 5. Preoperative Demographics and Postoperative Complications in the PD Group With Special Reference to DLW/ERLW at 2 Cutoff Points

Variables	DLW/ERLW <0.4 (n = 5)	DLW/ERLW ≥0.4 (n = 56)	*P*	DLW/ERLW <0.5 (n = 21)	DLW/ERLW ≥0.5 (n = 40)	*P*
Mean preoperative variables						
Recipient age (yr)	51.4	50.7	NS	51.5	50.4	NS
RBW (kg)	78.0	64.2	.04	69.0	63.4	NS
Donor age (yr)	8.6	8.7	NS	8.0	9.1	.06
Donor body weight (kg)	26.0	32.9	NS	26.6	35.2	.003
DLW (g)	555.6	883.2	.007	619.4	980.8	<.0001
DLW/ERLW	0.35	0.63	.001	0.42	0.71	NS
Postoperative complications						
PNF (%)	20.0	7.1	NS	5.8	10.0	NS
HAT (%)	40.0	10.7	.06	14.3	12.5	NS
Portal vein thrombosis (%)	0.0	3.6	NS	0.0	5.0	NS
Bile leak (%)	0.0	7.1	NS	19.0	0.0	.004
Septicemia (%)	60.0	25.0	NS	38.1	22.5	NS
Acute rejection (%)	40.0	44.6	NS	47.6	42.5	NS
Patient/graft survival (%)						
1-yr	80.0/40.0	85.7/73.2	NS	85.7/71.4	85.0/70.0	NS
5-yr	60.0/20.0	73.2/57.1	NS	66.7/52.4	75.0/55.0	NS

Abbreviation: NS, not significant.

Discussion

Currently, more than 14,000 patients are on the waiting list for liver transplants in the United States, with an expected supply of 4,500 donors per year.[7] The gap between the demand and supply of donor organs has been constantly increasing. As a result, centers have been expanding their donor acceptance criteria, including the use of small-for-size livers under certain conditions.

The use and allocation of pediatric livers in adult recipients is controversial. According to UNOS data,[7] approximately 20% of liver donors in the United States in 1997 were aged younger than 18 years, and 8.7% were aged younger than 10 years. Approximately 150 livers per year procured from PDs (defined as age < 13 years) were transplanted into adults (≥19 years; UNOS data request, 1999). According to Wight,[8] 28 pediatric livers were transplanted into adults in the United Kingdom in 1989, whereas 64 pediatric livers were transplanted into pediatric patients.

Because there was no UNOS policy for allocating PD livers to pediatric recipients during this study period, the use of pediatric livers in adult recipients was justified under certain urgent conditions. Recently, UNOS adopted a policy to allocate PD livers preferentially to pediatric recipients in the same region.

Our study showed that results with the use of pediatric livers in adults was similar to results with adult-to-adult combinations, although graft survival tended to be less in the former group. Of note, the incidence of HAT was significantly greater in the PD group compared with the AD group (12.9% *v* 3.8%). The incidence of HAT after primary LT varies from 1.6% to 8% in adults[9-13] and 5% to 38% in children.[14-16] Numerous factors have been implicated in HAT, including a prolonged CIT.[13,17-19] Not surprisingly, an increased incidence has been reported in pediatric recipients, in whom vessels are small.[14] It is also reported that size mismatching in vascular components could be problematic in LT using small-for-size grafts.[20] In our present study, CIT was longer in the PDs, and this may partly explain the high incidence of HAT. Furthermore, we believe the small size of the donor artery and inevitable size discrepancy between donor and recipient arteries might facilitate development of HAT. It is our policy to administer anticoagulation therapy with heparin to the recipient in this setting to prevent HAT.

Adam et al[21] reviewed their use of small donor livers in adult recipients and found that a very small graft size (<600 g), DRW ratio less than 0.5, and preservation time exceeding 12 hours were risk factors for complications. We did not confirm these findings in our patients (data not shown). Our multivariate analysis showed 2 independent risk factors for poor graft survival: preoperative PT greater than 16 seconds and no use of FK506 for primary immunosuppression. Patients with a preoperative PT less than 16 seconds who were administered FK506 had a 1-year graft survival rate of 94.1% (n = 17) versus a 37.5% (n = 16) 1-year graft survival rate in patients with a PT greater than 16 seconds preoperatively who were not administered FK506. The effect of a high preoperative PT on negative outcome can be explained by poor pre-LT patient condition and intraoperative blood loss (data not shown). These results suggest that restricting the use of small PD livers to relatively healthy adults may be the key to better graft and patient survivals. However, possibly because a cyclosporine-based immunosuppressive regimen was used earlier in our program, the improved graft survival in the FK506 era may reflect our learning curve related to increased surgical experience.

It is important to know the expected (or ideal) recipient liver weight before accepting a donor liver, especially when there is a size discrepancy between the donor and recipient. Urata et al[22] proposed a simple formula for predicting standard (or ideal) liver volume:

$$\text{Liver volume (milliliters)} = 706.2 \times \text{body surface area (square meters)} + 2.4$$

Since it was published in 1995, this formula has been widely used. However, we found that this formula tended to underestimate liver volume when we applied it to our donor population (data not shown). Heinemann et al[23] recently reported the same observation. The reason is not clear but is probably caused by the racial difference on which the formula was based. Thus, we adopted the formula developed at our institution:

$$\text{ERLW (grams)} = 6 \times \text{weight (lb)} + 4 \times \text{age (years)} + 350$$

Among 5 grafts with a DLW/ERLW less than 0.4, 1 graft (DLW/ERLW = 0.35) was lost to PNF, which was attributed to a small-for-size graft. The 2 smallest grafts (0.29 and 0.34) developed HAT on PODs 12 and 1. One graft (DLW/ERLW = 0.39) was lost to an unknown cause on POD 982. Thus, the 3 smallest of these 5 grafts were lost to causes attributable to the graft itself. Considering the high incidence of complications, including HAT (40%) and septicemia (60%), and the low graft survival, we currently believe we should not use grafts with a DLW/ERLW less than 0.4 in cadaveric LT.

In living related LT, small-for-size grafts are report-

edly associated with impaired graft function, indicated by prolonged hyperbilirubinemia, profuse ascites, and high PTs.[3] In our study, TBil levels in patients with a DLW/ERLW less than 0.4 tended to be greater, but the difference did not reach statistical significance. PT on POD 2 was significantly higher in patients with a DLW/ERLW less than 0.4. The incidence of post-LT ascites was similar between the PD and AD groups. In living related donor LTs, the development of increased ascites related to small-for-size livers may be caused by the large cut surface on the donor liver. This theory may explain why increased ascites was not seen in our transplant recipients, in whom the small-for-size livers were whole organs.

When we divided the PD liver recipients into 2 groups based on TBil level on POD 7, we found that graft volume (DLW/ERLW) was not associated with prolonged cholestasis (defined as TBil $\geq$ 5 mg/dL on POD 7). Conversely, grafts with long WITs and CITs developed cholestasis, suggesting that small-for-size livers were more vulnerable to ischemic insult. Furthermore, we found that graft and patient survival in patients who developed prolonged cholestasis were markedly inferior to those who did not.

In conclusion, the use of PD livers in adults was associated with a greater incidence of HAT, probably attributable to smaller donor vessel size and the inadequate capacity of the donor vessel for accommodating high arterial flow velocity in the recipient. Post-LT anticoagulation therapy is warranted when using PD livers in adults. The outcome of small-for-size grafts is more likely to be adversely affected by longer WITs and CITs. Grafts with a DLW/ERLW of 0.4 or greater (or $\geq$40% of ideal liver volume) can be used safely.

References

1. Lo CM, Fan ST, Chan JK, Wei W, Lo RJ, Lai CL. Minimum graft volume for successful adult-to-adult living donor liver transplantation for fulminant hepatic failure. Transplantation 1996;62:696-698.
2. Habib N, Tanaka K. Living-related liver transplantation in adult recipients: A hypothesis. Clin Transplant 1995;9:31-34.
3. Emond JC, Renz JF, Ferrell LD, Rosenthal P, Lim RC, Roberts JP, et al. Functional analysis of grafts from living donors. Implications for the treatment of older recipients. Ann Surg 1996;224: 544-552.
4. Kiuchi T, Kasahara M, Uryuhara K, Inomata Y, Uemoto S, Asonuma K, et al. Impact of graft size mismatching on graft prognosis in liver transplantation from living donors. Transplantation 1999;67:321-327.
5. Inomata Y, Kiuchi T, Kim I, Uemoto S, Egawa H, Asonuma K, et al. Auxiliary partial orthotopic living donor liver transplantation as an aid for small-for-size grafts in larger recipients. Transplantation 1999;67:1314-1319.
6. Schiano TD, Bodian C, Schwartz ME, Glajman N, Min A. Accuracy and significance of computed tomographic scan assessment of hepatic volume in patients undergoing liver transplantation. Transplantation 2000;69:545-550.
7. Annual Report of the US Scientific Registry for Organ Transplantation and the Organ Procurement and Transplantation Network—Transplant Data 1988-1999. UNOS, Richmond, VA, and the Division of Transplantation, Bureau of Health Resources and Services Administration, Rockville, MD, 1999.
8. Wight C. Utilization, paediatric donor livers: Failure to utilize available paediatric livers donated in the UK. Transplant Proc 1991;23:1561-1562.
9. Yanaga K, Makowka L, Starzl TE. Is hepatic artery thrombosis after liver transplantation really a surgical complication? Transplant Proc 1989;21:3511-3513.
10. Langnas AN, Marujo W, Stratta RJ, Wood RP, Li SJ, Shaw BW. Hepatic allograft rescue following arterial thrombosis. Role of urgent revascularization. Transplantation 1991;51:86-90.
11. D'Alessandro AM, Ploeg RJ, Knechtle SJ, Pirsch JD, Stegall MD, Hoffmann R, et al. Retransplantation of the liver—A seven-year experience. Transplantation 1993;55:1083-1087.
12. Drazan K, Shaked A, Olthoff KM, Imagawa D, Jurim O, Kiai K, et al. Etiology and management of symptomatic adult hepatic artery thrombosis after orthotopic liver transplantation (OLT). Am Surg 1996;62:237-240.
13. Langnas AN, Marujo W, Stratta RJ, Wood RP, Shaw BW Jr. Vascular complications after orthotopic liver transplantation. Am J Surg 1991;161:76-82; discussion 82-73.
14. Tan KC, Yandza T, de Hemptinne B, Clapuyt P, Claus D, Otte JB. Hepatic artery thrombosis in pediatric liver transplantation. J Pediatr Surg 1988;23:927-930.
15. Mazzaferro V, Esquivel CO, Makowka L, Belle S, Kahn D, Konern B, et al. Hepatic artery thrombosis after pediatric liver transplantation—A medical or surgical event? Transplantation 1989;47:971-977.
16. Busuttil RW, Seu P, Millis JM, Olthoff KM, Hiatt JR, Milewicz A, et al. Liver transplantation in children. Ann Surg 1991;213: 48-57.
17. Tisone G, Gunson BK, Buckels JA, McMaster P. Raised hematocrit—A contributing factor to hepatic artery thrombosis following liver transplantation. Transplantation 1988;46:162-163.
18. Rela M, Mutiesan P, Bhattagar V, Baker A, Mowat AP, Mieli-Vergani G, et al. Hepatic artery thrombosis after liver transplantation in children under 5 years of age. Transplantation 1996; 61:1355-1357.
19. Mor E, Schwartz ME, Sheiner PA, Meneses P, Hytiroglou P, Emre S, et al. Prolonged preservation in UW solution with hepatic artery thrombosis after orthotopic liver transplantation. Transplantation 1993;56:1399-1402.
20. Bismuth H, Castaing D, Sherlock DJ. Liver transplantation by "face-a-face" venacavaplasty. Surgery 1992;111:151-155.
21. Adam R, Castaing D, Bismuth H. Transplantation of small donor livers in adult recipients. Transplant Proc 1993;25:1105-1106.
22. Urata K, Kawasaki S, Matsunami H, Hashikura Y, Ikegami T, Ishizone S, et al. Calculation of child and adult standard liver volume for liver transplantation. Hepatology 1995;21:1317-1321.
23. Heinemann A, Wischhusen F, Puschel K, Rogiers X. Standard liver volume in the Caucasian population. Liver Transpl Surg 1999;5:366-368.

参考資料７

肝臓レシピエント新基準での優先順位

小児ドナー（18 歳未満）から提供があった場合に小児レシピエントに 1 点を加点するとした場合の優先順位

レシピエント年齢	生後 24 ヶ月未満			生後 24 ヶ月～18 歳未満		18 歳以上	
血液型	一致	適合	不適合	一致	適合	一致	適合
緊急性 9 点	① (11.5)				② (11)	③ (10.5)	④ (10)
緊急性 6 点	⑤ (8.5)	⑥ (8)		⑤ (8.5)	⑥ (8)	⑦ (7.5)	⑧ (7)
緊急性 3 点	⑨ (5.5)	⑩ (5)		⑨ (5.5)	⑩ (5)	⑪ (4.5)	⑫ (4)
緊急性 1 点	⑬ (3.5)	⑭ (3)		⑬ (3.5)	⑭ (3)	⑮ (2.5)	⑯ (2)

＊（ ）内は点数：例：生後 24 ヶ月未満、医学的緊急度 9 点の場合
医学的緊急度 9 点＋血液型 1.5 点＋小児ドナー１点＝11.5 点

ドナーが 18 歳以上の場合

レシピエント年齢	生後 24 ヶ月未満			24 ヶ月以上	
血液型	一致	適合	不適合	一致	適合
緊急性 9 点	① (10.5)				② (10)
緊急性 6 点	③ (7.5)	④ (7)		③ (7.5)	④ (7)
緊急性 3 点	⑤ (4.5)	⑥ (4)		⑤ (4.5)	⑥ (4)
緊急性 1 点	⑦ (2.5)	⑧ (2)		⑦ (2.5)	⑧ (2)

参考資料8

Review

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Liver grafts from anti-hepatitis B core positive donors: A systematic review

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Background & Aims: Although hepatitis B virus (HBV) transmission after liver transplantation of grafts from HBsAg-negative, anti-HBc positive donors is well established, the growing organ shortage favours the use of such marginal grafts. We systematically evaluated the risk of HBV infection after liver transplantation with such grafts and the effect of anti-HBV prophylaxis.

Methods: We performed a literature review over the last 15 years identifying 39 studies including 903 recipients of anti-HBc positive liver grafts.

Results: Recurrent HBV infection developed in 11% of HBsAg-positive liver transplant recipients of anti-HBc positive grafts, while survival was similar (67–100%) to HBsAg-positive recipients of anti-HBc negative grafts. *De novo* HBV infection developed in 19% of HBsAg-negative recipients being less frequent in anti-HBc/anti-HBs positive than HBV naive cases without prophylaxis (15% vs 48%, $p < 0.001$). Anti-HBV prophylaxis reduced *de novo* infection rates in both anti-HBc/anti-HBs positive (3%) and HBV naive recipients (12%). De novo infection rates were 19%, 2.6% and 2.8% in HBsAg-negative recipients under hepatitis B immunoglobulin, lamivudine and their combination, respectively.

Conclusions: Liver grafts from anti-HBc positive donors can be safely used, preferentially in HBsAg-positive or anti-HBc/anti-HBs positive recipients. HBsAg-negative recipients should receive prophylaxis with lamivudine, while both anti-HBc and anti-HBs positive recipients may need no prophylaxis at all.

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Introduction

despite the recent advances in liver transplantation (LT), there is a growing gap between the availability of donors and recipients on the waiting list. One of the current efforts to overcome the organ shortage is based on the use of grafts that are from donors with antibodies against the HBV core antigen (anti-HBc), but hepatitis B surface antigen (HBsAg) negative; the so called "anti-HBc positive donors" [1]. These grafts are rather common in countries with high or even intermediate prevalence of HBV infection, such as Asia and the Mediterranean basin. However, anti-HBc positive liver donors frequently have occult HBV infection, i.e. persistent liver and/or serum HBV DNA without serologic evidence of active HBV infection (negative HBsAg with or without positive anti-HBs). Indeed, several studies in HBsAg-negative subjects have shown that there is often the detection in the liver of covalently closed circular DNA (cccDNA) and pregenomic RNA, which is a marker of ongoing viral replication [2,3], and that may significantly increase with the use of post-LT immunosuppression and in particular with corticosteroids [4]. The liver grafts from anti-HBc positive donors are currently the main sources of *de novo* HBV infection after LT [5,6], which is usually defined by the development of positive HBsAg and/or detectable serum or liver HBV DNA in previously HBsAg recipients or even development of positive anti-HBc in previously HBV naive recipients. However, the literature documenting the risk of *de novo* HBV infection and the effects on the graft is scanty and conflicting.

The lack of definite data explains the wide variation in current clinical practice. In a survey in the USA in 2001, almost half of liver transplant physicians reported that they did not use anti-HBc positive donors in HBV naive recipients [7]. In a more recent international survey, the responders documented using prophylaxis with a nucleos(t)ide analogue (mostly lamivudine, but also entecavir and adefovir) in the majority of LT recipients of anti-HBc positive grafts, and 61% also used hepatitis B immunoglobulin (HBIG) (69% in US and 46% in non-US centres, $p = 0.03$) [8].

In this review, we systematically evaluated all the available data in order to quantify the impact of using liver grafts from anti-HBc positive donors and identify the optimal post-LT prophylaxis. We selected two types of recipients: (a) HBsAg-positive recipients and (b) HBsAg-negative recipients. In particular, we documented the rates of *de novo* HBV infection with or without anti-HBV prophylaxis relative to the donor–recipient HBV serological status, as well as data on the outcome of *de novo* post-LT HBV infection. Our search was based on Medline/PubMed from January 1994 to december 2008 using the search terms "hepatitis B core antibody" and "liver transplantation", in papers published in English. We also conducted a manual search of the reference lists in the review articles. In total, 133 articles were identified. Two authors (E.C., G.V.P.) reviewed the abstracts of these articles to identify potentially relevant articles. In total, 39 original

Keywords: *De novo* HBV infection; Liver transplantation; Marginal donors; Anti-HBc positive donors; Hepatitis B immunoglobulin; Lamivudine; Vaccination.

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Abbreviations: HBV, hepatitis B virus; LT, liver transplantation; anti-HBc, HBV core antigen; HBsAg, hepatitis B surface antigen; cccDNA, covalently closed circular DNA; HBIG, hepatitis B immunoglobulin; LAM, lamivudine.

Table 1. Published studies on the prevalence of anti-HBc positivity among liver donors in different countries.

First author, year [Ref.]	Donors, n/N anti-HBc		
	Country	Positive/total	Prevalence (%)
Wachs (1995) [42]	USA	25/1190	2
Douglas (1997) [12]	USA	3/332	3
Dodson (1997) [29]	USA	70/2578	3
Shinji (1998) [13]	Japan	16/171	9
Yu (2001) [19]	USA	15/169	9
Nery (2001) [40]	USA	48/724	6
Prieto (2001) [10]	Spain	33/268	12
Lee (2001) [14]	China	16/30	53
Roque-Alfonso (2002) [21]	France	22/315	7
Chen (2002) [16]	Taiwan	24/42	57
Lo (2003) [15]	China	28/51	55

articles evaluated the rate of *de novo* HBV infection from anti-HBc positive donors, were included in the final analysis. Data abstraction was done by one author (E.C.) and any conflicts in data abstraction were arbitrated by discussion with the senior authors (G.V.P., A.K.B.).

Prevalence of anti-HBc positive liver donors

The rate of anti-HBc positivity in liver donors varies substantially in different countries reflecting the local prevalence of HBV infection. Thus, the prevalence of anti-HBc is lower in developed countries ranging from 3% to 15% [9–13], but it may exceed 50% in highly endemic areas [14–16] (Table 1). The prevalence of anti-HBc may also vary in different areas of the same country and in specific ethnic populations (e.g. it is estimated that 25% of non-Hispanic black Americans in the USA are anti-HBc positive) [17], and it is usually higher in older age individuals, who are currently increasingly used as liver donors [10]. The latter could partly explain the increasing number of anti-HBc positive cadaveric livers transplanted in the USA (from 3.9% in 1998 to 4.9% in 2002) [18].

Liver grafts from anti-HBc positive donors to HBsAg-positive recipients

Nine studies [11,19–26] evaluated the recurrence of HBV infection in HBsAg-positive recipients of anti-HBc positive liver grafts (Table 2). During a median follow-up of 27 (19–42) months, post-transplant HBV infection was observed in 12 (10.5%) of 115 recipients, while median survival ranged from 67% to 100%. In the 12 cases with post-transplant HBV infection, the prophylaxis was: three with HBIG, three with lamivudine and six with HBIG and lamivudine (HBIG had been discontinued in one at HBV recurrence). In one retrospective cohort study [20], recipients of anti-HBc positive grafts ($n = 14$.5 with detectable serum HBV DNA at LT) were compared to recipients of anti-HBc negative grafts ($n = 65$). The 14 recipients of anti-HBc positive grafts developed HBV recurrence more frequently (69.2% vs 35.7%, $p = 0.034$) and earlier after LT (2.9 vs 6.4 years, $p < 0.005$). However, the patient and graft survival was not different between the two groups: 60-month survival: 67% vs 68%. In multivariate analysis, HBV recurrence was independently associated with anti-HBc donor status (RR: 2.796, $p = 0.02$) and the use of combined HBIG and lamivudine prophylaxis (RR: 0.249, $p = 0.021$), but not the recipients' pre-transplant HBeAg status [20].

Liver grafts from anti-HBc positive donors to HBsAg-negative recipients–risk of *de novo* HBV infection

We identified 38 relevant studies published as full papers [5,9–13,16,19,21–50] (Table 3). Nine did not have sufficient data regarding the serological HBV status in donors and/or recipients [12,13,23,31,39,43,45,49,50]. Four centres published two studies: one in Spain [36,37] and three in the USA [22,29,30,34,35,40] with two of these reports having overlap in study periods [29,35]. The indication for LT was recorded in 21 studies [10,19, 21–23,25,26,28,30,31,36,37,39,41–45,47,49,50]: HCV cirrhosis was the most common (25%), followed by alcoholic cirrhosis and cholestatic liver diseases. The cohort size ranged from 6 to 91 patients with only two studies reporting >50 patients [26,37]. The total number of patients that could be evaluated was 788.

The diagnosis of *de novo* HBV infection was based on the detection of HBsAg in previously HBsAg-negative recipients with or without compatible biochemical or histological findings in 14 studies [9,10,24,25,27–29,33,35,42,44,45,47,49], or the appearance of HBsAg and/or serum HBV DNA in 19 studies [5,11,13,19, 21,22,26,30–32,34,36–41,43,48]. The presence of HBV DNA was determined by a hybridization technique in three [10,16,37], branched-DNA assay in one [11] and polymerase chain reaction (PCR) assay in the remaining 20 studies [5,9,13,19,21,22,25, 26,28,30–32,34,36,39–41,47–49]. HBV DNA was evaluated in serum in 17 [9–11,16,22,25,26,30,37,39,40,43–45,47–49] and in both serum and liver tissue in nine studies [5,13,19,21,28, 31,32,34,41], while it was also evaluated in leukocytes in two studies [5,34]. In only one study, cccDNA was assessed in liver tissue [36].

Table 2. Published studies of liver transplantation using anti-HBc positive donors in HBsAg-positive recipients.

First author, year [Ref.]	HBsAg positive		Follow-up (months)	HBV recurrence, n (%)	Survival (%)
	Recipients, n	Anti-HBV prophylaxis			
Yu (2001) [19]	6	HBIG	20	0	100
Manzabeita (2002) [11]	3	HBIG + LAM	26	1 (33)	67
Joya-Varquez (2002) [20]	14	HBIG: 5, LAM: 3, HBIG + LAM: 5	42	9[a] (69)	
Roque-Afonso (2002) [21]	4	HBIG	19	0	75
Nery (2003) [22]	17	LAM: 12, HBIG + LAM: 5	29	0	
Montalti (2004) [23]	26	HBIG ± LAM	NA	0	
Donataccio (2006) [24]	4	HBIG: 3, HBIG + LAM: 1	38	1[b] (25)	100
Pracoso (2006) [25]	5	HBIG + LAM	29	0	67
Celebi-Kobak (2007) [26]	36	HBIG + LAM	19	1 (3)	92

HBIG, hepatitis B immunoglobulin; LAM, lamivudine; NA, not available.
[a] 2/5 patients under HBIG, 3/3 patients under LAM and 4/5 patients under HBIG + LAM.
[b] 1/3 patients under HBIG.

Table 3. Published studies[a] with liver transplantation using anti-HBc positive donors in HBsAg-negative recipients.[b]

First author, year [Ref.]	Anti-HBc (+), anti-HBs (−) recipients				Anti-HBc (+), anti-HBs (+) recipients				HBV naive recipients			
	Patients, *N*	Anti-HBV prophylaxis	Follow-up, months	*De novo* HBV, *n*	Patients, *N*	Anti-HBV prophylaxis	Follow-up, months	*De novo* HBV, *n*	Patients *N*	Anti-HBV prophylaxis	Follow-up, months	*De novo* HBV, *n*
Dickson (1997) [9]	2	None	22	0		None			18	None	22	15
Dodson (1997) [29]	15	None	56	2	7		56	0	25	None	56	18
Dodson (1999) [35]	8	HBIG + LAM	46	0		None			8	HBIG + LAM: 7, HBIG: 1	46	1
Prieto (2001) [10]	3	None	29	0	2	None	29	0	25	None	29	15
Manzabeita (2002) [11]	11	None	26	2	13		26	0	2	HBIG	26	2
Roque-Afonso (2002) [21]	4	HBIG	26	0					12	None: 4, HBIG: 8	22	5
Bacerna (2002) [37]					19	None	NA	0	64		NA	10
Chen (2002) [16]	2	LAM: 1, none: 1	40	0	3	LAM: 2, none:1	40	0	15	LAM: 13, none: 2	40	2
Nery (2003) [22]	13	HBIG + LAM: 4, LAM: 9	22	1	23	HBIG + LAM: 6, none: 17	21	0	8	HBIG + LAM: 2, LAM: 6	37	1
Loss (2003)[3] [32]									11	HBIG (bolus) + LAM + Vaccination	33	0
Suehiro (2005) [28]	4	HBIG + LAM	39	0	3	NA	39	0	15	HBIG + LAM	39	0
De Feo (2005)[2] [27]	NA	None	NA	0	NA	None	NA	0	14	None	NA	6
Donataccio (2006)[3] [24]	NA	HBIG	NA	NA	NA	HBIG	NA	NA	11	HBIG + LAM: 1,	57	7
Umeda (2006) [47]									38	HBIG	42	9
Celebi-Kobak (2007) [26]	4	LAM	17	0	3	LAM	28	0	4	LAM	23	0
Takemura (2007) [33]	2	LAM	31	0	5	HBIG	31	1	9	HBIG	31	1

HBIG, hepatitis B immunoglobulin; LAM, lamivudine; NA, not available.

De novo HBV infection also developed in (a) 1/3 anti-HBs positive recipients under HBIG + LAM + vaccination[1] [32]; (b) 0/35 anti-HBc positive and/or anti-HBs positive recipients under no anti-HBV prophylaxis[2] [27], (c) 0/1 anti-HBc positive recipient (unknown anti-HBs status) under HBIG during 11 months of follow-up[3] [24].

[a] Twenty-two studies with <10 patients each ($n = 13$) [5,19,25,30,34,36,38,40–42,44,46,48] or insufficient data ($n = 9$) on the serological HBV status of donors and/or recipients [12,13,23,31,39,43,45,49,50] are not included. *De novo* HBV infection developed in: (a) 15/57 HBV naive recipients [5,19,25,30,34,38,40–42,48] under no anti-HBV prophylaxis or LAM ± HBIG ± vaccination, (b) 2/51 anti-HBc positive recipients [anti-HBs negative (1/9), anti-HBs positive (1/20), anti-HBs unknown (0/22)] [5,19,25,36,38,40,44,46] under no anti-HBV prophylaxis or HBIG ± LAM ± vaccination and (d) 1/25 only anti-HBs positive recipients under LAM plus vaccination [44]. *De novo* HBV infection also developed in (a) 15/20 anti-HBc positive recipients (unknown anti-HBs status) under no anti-HBV prophylaxis (15/16) [13] or HBIG + LAM (0/1) [31] or HBIG plus vaccination (0/3) [49], (b) 0/11 anti-HBs positive recipients under HBIG plus vaccination [49] and (c) 14/95 recipients with unknown anti-HBs/anti-HBc status under HBIG ± LAM or no prophylaxis (9/67) [12,23,39,43] or HBIG ± vaccination (2/25) [45,50] or vaccination alone (3/3) [50].

[b] Thirty one recipients (from seven studies [11,16,21,22,24,36,37]) with successful pre-LT vaccination and no post-LT prophylaxis were not included; three (9.6%) of them developed *De novo* HBV infection. In addition, 34 recipients (from seven studies [19,24–26,31,33,34]) with successful pre-LT vaccination and HBIG and/or lamivudine post-LT prophylaxis were not included; none of them developed *de novo* HBV infection.

The immunosuppressive therapy after LT was reported in detail for each patient in only one study [32], while the immunosuppressive regimens with or without the number of patients in each regimen was reported in 19 studies [10,11,13,16,19,25,28,30,31,33,34,36,39,43–45,47–49] and no information on the immunosuppression was provided in 18 studies [5,9,12,21–24,26,27,29,35,37,38,40–42,46,50]. Tacrolimus or cyclosporine-based regimens were used in seven [10,11,25,28,34,36,39], only tacrolimus-based regimens in 10 [13,19,31–33,43,45,47–49] and only cyclosporine-based regimens in three studies [16,30,44]. In 18 studies [11,13,16,19,25,28,30–34,36,43–45,47–49] steroids were used as immunosuppressive regimen, while in two studies [10,39] steroid use was not reported. The plan of steroid withdrawal (usually tapered and stopped 3–12 months after LT) was only reported in 10 studies [16,19,31,32,34,44,45,47–49].

In total, *de novo* HBV infection was observed in 149 (18.9%) of 788 recipients at a median of 24 (5–54) months after LT. Post-transplant anti-HBV prophylaxis significantly affected the probability of *de novo* HBV infection, which developed in 28.2% (119/422) of recipients without, and 8.2% (30/366) of recipients with post-transplant prophylaxis ($p < 0.001$). Moreover, *de novo* HBV infection developed more rapidly in patients without than with post-transplant prophylaxis: median onset after LT: 19 vs 35 months ($p = 0.05$).

Probability of de novo HBV infection without post-transplant anti-HBV prophylaxis

De novo HBV infection after LT with grafts from anti-HBc positive donors developed in 47.8% (89/186) of HBV naive recipients compared to 15.2% (21/138) of recipients with serological markers of past HBV infection ($p < 0.001$) or 9.7% (3/31) of recipients with successful pre-LT vaccination ($p < 0.001$). *De novo* HBV infection also developed in 8.9% (6/67) of HBsAg-negative recipients with unknown pre-LT HBV status. The presence of anti-HBs in anti-HBc positive recipients, which was reported in 106 of 138 such cases, reduced the probability of *de novo* HBV infection but did not eliminate it (Fig. 1).

Anti-HBc positive liver grafts to HBsAg-negative recipients with past HBV infection. (a) HBsAg and anti-HBs negativity with anti-HBc positivity in recipients. In eight studies [5,9–11,16,29,36,38], *de novo* HBV infection developed in 13.1% (5/38) of such recipients with anti-HBc positive donors during a median follow-up of

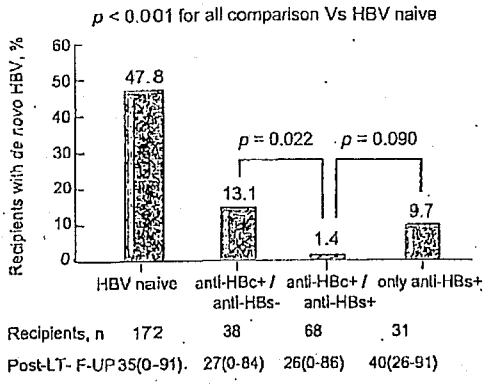

Fig. 1. Risk of *de novo* hepatitis B virus (HBV) infection in HBsAg-negative recipients who received liver grafts from anti-HBc positive donors and no HBV prophylaxis after liver transplantation (LT) in relation to their HBV serological status before transplant.

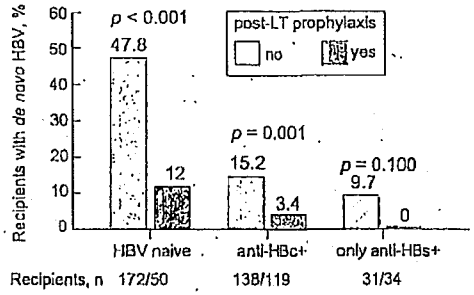

Fig. 2. Risk of *de novo* hepatitis B virus (HBV) infection in HBsAg-negative recipients of liver grafts from anti-HBc positive donors in relation to their pre-transplant HBV serological status and the use of HBV prophylaxis after liver transplantation (LT).

27 months (0.2–84). (b) HBsAg-negative recipients with anti-HBc positivity and anti-HBs positivity. In nine studies [5,10,11,16, 22,25,29,36,37], *de novo* HBV infection was documented in only 1.4% (1/68) of such recipients with anti-HBc positive donors during a median follow-up of 26 (0.2–86) months. The anti-HBs status of the donors was reported in only five studies including just 18 HBsAg-negative recipients positive for anti-HBc with or without positive anti-HBs [5,9,16,36,38], and therefore the impact of the anti-HBs donors' status could not be safely determined.

Anti-HBc positive liver grafts to HBsAg-negative recipients with successful pre-LT vaccination. Seven studies evaluated the development of *de novo* HBV infection in 31 HBsAg-negative recipients who developed anti-HBs after HBV vaccination before LT and received no post-LT prophylaxis [11,16,21,22,24,36,37]. *De novo* HBV infection developed in 3 (9.7%) of them during a median post-LT follow-up of 40 (26–91) months.

Anti-HBc positive liver grafts to HBV naive recipients. During a median follow-up of 35 months (range: 0.1–91), *de novo* HBV infection after LT with grafts from anti-HBc positive donors was detected in 47.8% (89/186) of HBV naive recipients included in 14 studies [5,9–11,16,21,24,27,29,30,37,38,41,42]. Interestingly, the presence of anti-HBs in the donors did not affect the probability of *de novo* HBV infection in HBV naive recipients. In particular, in eight studies [5,9,10,16,21,30,38,41] providing the anti-HBs status in the donor, *de novo* HBV infection developed in 71% (28/39) of recipients with both anti-HBc and anti-HBs positive donors during a follow-up of 37 (0.2–66) months, and in 65% (20/31) of recipients with anti-HBc positive but anti-HBs negative donors during a follow-up of 33 (0.1–91) months ($p = 0.70$) (Fig. 2).

Post-transplant prophylaxis against de novo HBV infection

Twenty five [5,11,16,19,21–26,28,31–35,40,43–50] studies reported data on post-transplant prophylaxis (HBIG and/or lamivudine and/or HBV vaccination) against *de novo* HBV infection in 366 patients who received liver grafts from anti-HBc positive donors. HBIG alone was used in 96, lamivudine alone in 75, HBIG and lamivudine in 104, HBIG and/or lamivudine in 7, post-LT vaccination with HBIG and/or lamivudine in 81 and post-LT vaccination alone in three cases. *De novo* HBV infection developed in 7.4% (27/363) of recipients who received HBIG and/or lamivudine after LT (combined with post-LT vaccination in 81 cases) and in all 3 cases who received post-LT vaccination alone ($p < 0.001$). In particular, *de novo* HBV infection under HBIG and/or lamivudine was observed significantly more frequently in HBV naive than anti-HBc and/or anti-HBs positive recipients (18/150 or 12% vs 4/153 or 2.6%, $p = 0.006$). *De novo* HBV infection also developed in 8.3% (5/60) of recipients with unknown pre-LT status who received HBIG and/or lamivudine with or without post-LT vaccination (Table 3).

HBIG monoprophylaxis. HBIG (5000 or 10,000 IU intravenously starting during the anhepatic phase) was used as monoprophylaxis for varying intervals after LT in eight studies [11,21,24,33, 35,46,47,50] (Table 3). During a median follow-up of 31 months (range: 3–86), *de novo* HBV infection developed in 18 (18.7%) of 96 recipients: five (27%) had discontinued HBIG and another two (11%) had low serum anti-HBs levels (<50 IU/mL) despite HIBG administration, at the diagnosis of *de novo* HBV infection. In particular, *de novo* HBV infection under HBIG monoprophylaxis developed in 27% (17/63) of HBV naive recipients and 5.8% (1/17) of recipients with past HBV infection ($p = 0.10$) during a median follow-up of 30 (3–86) and 19 (3–86) months, respectively. In addition, *de novo* HBV infection also developed in none of five recipients with successful pre-LT vaccination during a median follow-up of 35 (31–38) months and in none of 11 recipients with unknown pre-LT HBV status who received post-LT prophylaxis with HBIG alone. The impact of recipient's anti-HBs status could not be determined due to limited data.

Lamivudine monoprophylaxis. Since HBIG has several limitations, such as high cost, poor compliance and even low protection particularly in HBV naive recipients [11], lamivudine monoprophylaxis (100–150 mg/day for long periods) against *de novo* HBV infection was also evaluated in six studies [16,19,22,25,26,40] (Table 3). During a median follow-up of 25 (1–69) months, *de novo* HBV infection was observed in 2.6% (2/75) of recipients [1/25 (4.0%) recipients with past HBV infection, 1/33 (3.4%) HBV naive recipients, 0/17 recipients with successful pre-LT vaccination ($p = 0.72$)]. Interestingly, the HBV naive recipient with *de novo* HBV infection developed it after lamivudine discontinuation (Fig. 3).

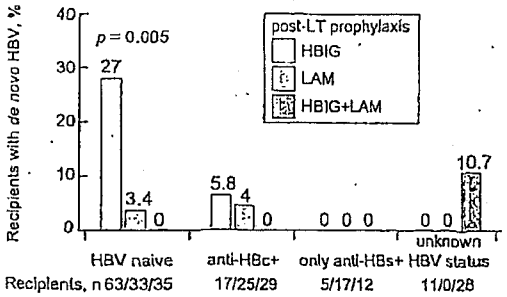

Fig. 3. Risk of *de novo* hepatitis B virus (HBV) infection in HBsAg-negative recipients who received liver grafts from anti-HBc positive donors and HBV prophylaxis after liver transplantation (LT) in relation to their pre-transplant HBV serological status and the type of post-transplant HBV prophylaxis. HBIG, hepatitis B immunoglobulin; LAM, lamivudine.

HBIG and lamivudine combined prophylaxis. Increasing periods of administration of lamivudine as monotherapy is associated with increasing rates of HBV resistance, particularly in patients under immunosuppressive therapy [51]. Thus, the effectiveness of HBIG and lamivudine combination was evaluated in eight studies [22,24,28,31,34,35,40,43] (Table 3). Lamivudine (100–300 mg/day) was given long-term, while HBIG was given short- or long-term at dosages ranging from 400 IU intramuscularly to 10,000 IU intravenously. During a mean follow-up of 39 (range: 1–86) months, *de novo* HBV infection was observed in 2.8% (3/104) of recipients [0/29 recipients with past HBV infection, 0/35 HBV naive recipients, 0/12 recipients with successful pre-LT vaccination, 3/28 (11%) recipients with unknown pre-LT HBV status]. Since the combination of HBIG with lamivudine is the most widely used approach for prevention of post-LT HBV recurrence in patients transplanted for HBV related liver disease, it is often used as prophylaxis against *de novo* HBV infection as well [8]. However, given the low probability of *de novo* HBV infection with lamivudine alone, the benefit of HBIG with lamivudine combined prophylaxis over monoprophylaxis with lamivudine or perhaps a more potent antiviral agent is not clear from the current literature.

HBV vaccination. HBV vaccination after LT has been evaluated as a strategy to prevent *de novo* HBV infection in recipients of grafts from anti-HBc donors in seven studies [5,32,44,45,48–50]. In six studies using post-LT vaccination combined with HBIG and/or lamivudine prophylaxis [5,32,44,45,48,49], *de novo* HBV infection developed in 5.7% (4/81) of recipients during a median post-LT follow-up of 33 months [22–85] (0/19 HBV naive, 2/48 anti-HBc and/or anti-HBs positive and 2/14 with unknown pre-LT HBV status, $p = 0.16$). In contrast, in the only study in which post-LT HBV vaccination was given alone, *de novo* HBV infection was observed in all three (100%) recipients at 14–20 months after transplant [50]. Thus, although data are very limited, monoprophylaxis with HBV vaccination after LT also does not appear to be an effective prophylactic strategy against *de novo* HBV infection in recipients of anti-HBc positive grafts.

Survival of recipients of grafts from anti-HBc positive donors

The 3-year survival of such recipients has been reported to range between 66% and 100%, if they were HBV naive, and between 89% and 100%, if they had past HBV infection [5,9–11,13,16,19,21–26,29–40,43–45,48,49]. The post-transplant survival of recipients of liver grafts from anti-HBc positive and anti-HBc negative donors has been comparatively evaluated in only two studies with contradictory results [9,10]: 4-year survival in recipients with anti-HBc positive donors was significantly lower compared to recipients with anti-HBc negative donors in a US study (56% vs 76%, $p = 0.005$) [9], whereas no significant difference in 4-year survival between these two groups was reported in a similar Spanish study (68% vs 76%, $p > 0.05$) [10].

Outcome of patients with *de novo* HBV infection

Histological characteristics

Histological characteristics were available in 13 studies including 68 patients [9,10,13,21,22,24,30,32,39,41,42,47,52], but liver biopsies at diagnosis of *de novo* HBV infection were performed in only six studies and only 41 patients [10,21,22,24,32,39] (Table 4). Mild inflammation without fibrosis was found in 33, mild to moderate inflammation with portal or bridging fibrosis in 12,

Table 4. Published studies[a] on the course of *de novo* hepatitis B virus (HBV) infection after liver transplantation.

First author, year [Ref.]	Patients with			Course of *de novo* HBV infection	Follow-up,[b] months
	De novo HBV, *n*	Histological findings	HBV therapy		
Prieto (2001) [10]	15	Chronic hepatitis: 12, mild/massive necrosis: 1/2	LAM	Survival: 80% – 3 deaths (recurrent HCV: 1, lymphoma: 1, sepsis: 1)	37
Segovia (2001) [52]	5	Cirrhosis: 1, moderate fibrosis: 1	LAM	Survival: 100%	8
Manzabeita (2002) [11]	4	Mild hepatitis: 1	HBIG ± LAM	LAM resistance: 1 (mild hepatitis)	19–63
Roque-Afonso (2002) [21]	5	Mild inflammation: 4	LAM	LAM resistance after 7–16 months: 5	12
Lee (2004) [50]	3	NA	LAM ± HBIG	Stable course	NA
Jain (2005) [43]	3	NA	ADV (YMDD mutation)	1 death (fulminant liver failure)	NA
Donataccio (2006) [24]	7	Cholestatic hepatitis: 2	LAM	2 deaths (cholestatic HBV: 1, sepsis: 1)	27
Umeda (2006) [47]	9	Mild inflammation/ fibrosis: 5	LAM (in six patients)	Disappearance of HBsAg in 5 patients after 4.6 months under LAM	21

HBIG, hepatitis B immunoglobulin; LAM, lamivudine; NA, not available.

[a] Seven reports of 1–2 cases with *de novo* HBV infection after liver transplantation were not included [22,32,33,36,38,39,44]. In total, 11 recipients (severe hepatitis: 1) received LAM ($n = 10$) or HBIG plus LAM ($n = 1$). All patients had an uneventful course, except for one patient [36] with poor response to LAM treated with addition of adefovir.

[b] After diagnosis of *de novo* HBV infection.

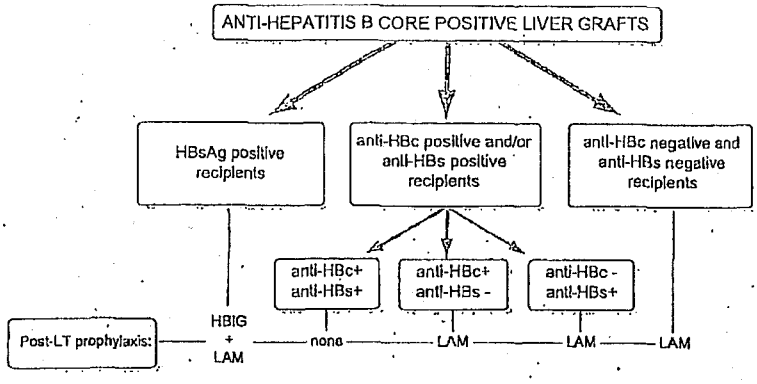

Fig. 4. Proposed algorithm for allocation and management of anti-HBc positive liver grafts. Such grafts should be first offered to HBsAg positive, then to anti-HBc and/or anti-HBs positive and lastly to HBV naive (both anti-HBc and anti-HBs negative) recipients. LT, liver transplantation; HBIG, hepatitis B immunoglobulin; LAM, lamivudine.

severe inflammation and/or cirrhosis in nine, cholestatic hepatitis in three, and non-specific findings in 11 patients.

Course of de novo HBV infection under antiviral therapy

The data on the treatment of *de novo* HBV infection is not well documented, but there are no grounds to expect the efficacy of treatment to be different from that of post-transplant HBV recurrence [51,53]. Only a total of 62 patients are reported. Lamivudine was used in the first 15 studies (combined with HBIG in three) with good initial response [10,11,21,22,24,32,33,36,38,39,43,44,47, 50,52], but lamivudine resistance developed in all five cases after 7–16 months in one study [21] (Table 4). Salvage adefovir therapy was effective in three patients with lamivudine resistance [36,43]. Given the poor resistance profile of long-term lamivudine monotherapy, newer and more potent nucleos(t)ide analogues with low probability of resistance need to be used in this setting despite the lack of data.

Survival of patients with de novo HBV infection

The survival has been reported to range between 66% and 100% during a median follow-up of 48 (3–80) months in 19 studies providing relevant data [5,10,13,16,21,24,30,32,33,35–39,41,42, 47,50,52]. In 14 studies, survival was 100% with a median follow-up of 32 (3–80) months [5,16,21,30,32,33,35–39,47,50,52]. In one study, the outcome of *de novo* HBV infection was significantly better than that of recurrent HBV infection: 3-year survival: 95% vs 60%, ($p = 0.03$) [41]. In the latter study, the causes of death were related to HBV infection in only 2 of 21 non-survivors with *de novo* HBV infection and two additional patients underwent re-LT due to HBV infection.

Conclusions

As the number of patients on LT waiting list continues to grow, the demand for donor organs increases. Thus, the expansion of donor criteria and the inclusion of marginal livers, such as those from anti-HBc positive individuals will be very helpful. In fact, such donors represent a significant source of transplantable organs, particularly in countries with high or intermediate HBV prevalence [54]. The risk of *de novo* post-LT HBV infection is the major limitation of using liver grafts from anti-HBc positive donors, since occult HBV infection in the donor liver may be reactivated in the recipient due to post-LT immunosuppressive therapy. Such liver grafts may be first offered to patients transplanted for HBV related liver disease, as they require life-long anti-HBV prophylaxis in any case (Fig. 4). Although in one study HBsAg-positive recipients of anti-HBc positive liver grafts were suggested to have more frequent and earlier HBV recurrence compared to those of anti-HBc negative liver grafts [20], the risk of HBV recurrence was not reported to be high in several other studies and the donor's anti-HBc status has not been found to affect the post-transplant survival.

Many centres now use grafts from anti-HBc positive donors for HBsAg-negative recipients. Since the probability of such *de novo* HBV infection is substantially lower in anti-HBc and/or anti-HBs positive compared to HBV naive recipients (15% vs 48%), it is reasonable to recommend that liver grafts from anti-HBc positive donors should be preferentially directed to HBV exposed LT candidates (Fig. 4). In the latter, the presence of anti-HBs seems to protect from *de novo* HBV infection and both anti-HBc and anti-HBs positive recipients seem to represent a group that can safely receive anti-HBc positive liver grafts without any post-transplant HBV prophylaxis (probability of *de novo* HBV infection <2%). Pre-LT vaccination alone does not appear to be an effective strategy, as *de novo* HBV infection after LT developed in 10% of successfully vaccinated recipients without any post-LT prophylaxis. However, HBV vaccination should be offered to all naive HBV patients early in the course of non-HBV chronic liver disease (i.e. in the pre-cirrhotic stage), even though additional anti-HBV prophylaxis will be needed in cases of LT with grafts from anti-HBc positive donors. Because of lack of data, no conclusions can be drawn on the effect of the donor's anti-HBs status, which could theoretically reduce the risk of transmission even further.

The use of post-transplant prophylaxis with HBIG and/or lamivudine reduces the overall probability of *de novo* HBV infection in both HBV naive (from 48% to 12%) and anti-HBc and/or anti-HBs positive recipients of anti-HBc positive grafts (from 15% to 3%). According to a recent survey reflecting current clinical practice, prophylaxis with lamivudine and often HBIG is usually used after LT with anti-HBc positive grafts, but it is less likely to be used in anti-HBs positive recipients [8]. Although there are no

good data from single studies on the optimal anti-HBV prophylaxis, several conclusions can be drawn based on all the studies we have reviewed. First, monoprophylaxis with HBIG or HBV vaccination after LT is an ineffective strategy, as it is associated with approximately 20% and 100% risk of *de novo* HBV infection. Monoprophylaxis with lamivudine appears to offer satisfactory protection with <3% risk of *de novo* HBV infection, although it should be noted that the number of reported cases is still small ($n=75$) and the follow-up relatively short (approximately 2 years). The combination of HBIG and lamivudine is often used empirically in this setting, because of its proven benefit in preventing HBV recurrence after LT for HBV related liver disease [51,55]. However, this combination does not seem to provide a clear benefit compared to lamivudine monoprophylaxis in liver transplant HBsAg-negative patients who receive anti-HBc positive grafts. In fact, the rationale for HBIG use is unclear, as there are no circulating HBsAg coated virions in HBsAg-negative recipients to be neutralised by HBIG. Whether monoprophylaxis with a new nucleos(t)ide analogue with better resistance profile might be a more cost-effective long-term approach in all or in subsets of such transplant patients also remains to be determined. Given the relatively low numbers of cases, the different subgroups of donor–recipient matching with anti-HBc/anti-HBs status and the varied prophylactic interventions, multicentre studies will be required in order to provide evidence-based data.

If *de novo* post-LT HBV infection develops, antiviral treatment is mandatory. Although documentation of transplant details and outcomes is scanty, it is reasonable to think that the efficacy of treatment is similar to that of post-transplant HBV recurrence. Given the poor resistance profile of long-term lamivudine monotherapy and the low potency of adefovir, both entecavir and tenofovir may be the agents of choice today, despite the current lack of relevant data. Entecavir has the advantage of not being nephrotoxic and tenofovir has the advantage of better long-term efficacy in cases of lamivudine resistance.

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References

[1] Nadig SN, Bratton CF, Karp SJ. Marginal donors in liver transplantation: expanding the donor pool. J Surg Educ 2007;64:46–50.

[2] Marusawa H, Uemoto S, Hijikata M, Ueda Y, Tanaka K, Shimotohno K, et al. Latent hepatitis B virus infection in healthy individuals with antibodies to hepatitis B core antigen. Hepatology 2000;31:488.

[3] Mason A, Xu L, Guo L, Kuhns M, Perrillo R. Molecular basis for persistent hepatitis B virus infection in the liver after clearance of serum hepatitis B surface antigen. Hepatology 1998;27:1736–1742.

[4] Scullard G, Smith C, Merigan T, Robinson W, Gregory P. Effects of immunosuppressive therapy on viral markers in chronic active hepatitis B. Gastroenterology 1981;81:987–991.

[5] Rokuhara A, Tanaka E, Yagi S, Mizokami M, Hasshikura Y, Kawasaki S, et al. De novo infection of hepatitis B virus in patients with orthotopic liver transplantation: analysis by determining complete sequence of the genome. J Med Virol 2000;62:471–478.

[6] Jilg W, Sieger E, Zachoval R, Schätzl H. Individuals with antibodies against hepatitis B core antigen as the only serological marker for hepatitis B infection: high percentage of carriers of hepatitis B and C virus. J Hepatol 1995;23:14–20.

[7] Burton J, Shaw-Stiffel T. Use of hepatitis B core antibody positive donors in recipients without evidence of hepatitis B infection: a survey of current practice in the United States. Liver Transpl 2003;9:837–842.

[8] Perrillo R. Hepatitis B virus prevention strategies for antibody to hepatitis B core antigen-positive liver donation: a survey of North American, European, and Asian-Pacific transplant programs. Liver Transpl 2009;15:223–232.

[9] Dickson RC, Everhart JE, Lake JR, Wei Y, Seaberg EC, Wiesner RH, et al. Transmission of hepatitis B by transplantation of livers from donors positive for antibody to hepatitis B core antigen. The National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database. Gastroenterology 1997;113:1668–1674.

[10] Prieto M, Gomez MD, Berenguer M, Cordoba J, Rayon JM, Pastor M, et al. *De novo* hepatitis B after liver transplantation from hepatitis B core antibody-positive donors in an area with high prevalence of anti-HBc positivity in the donor population. Liver Transpl 2001;7:51–58.

[11] Manzarbeitia C, Reich DJ, Ortiz JA, Rothstein KD, Araya VR, Munoz SJ. Safe use of livers from donors with positive hepatitis B core antibody. Liver Transpl 2002;8:556–561.

[12] Douglas D, Rakela J, Wright T, Krom RA, Wiesner RH. The clinical course of transplantation-associated *de novo* hepatitis B infection in the liver transplant recipient. Liver Transpl Surg 1997;3:105–111.

[13] Shinji U, Kohachiro S, Hiroyuki M, Yukihiro I, Katsuhiro A, Hiroto E, et al. Transmission of hepatitis B virus from hepatitis B core antibody-positive donors in living related liver transplants. Transplantation 1998;65:494–499.

[14] Lee K, Wai C, Lim S, Manjit K, Lee HL, Da Costa M, et al. Risk for *de novo* hepatitis B from antibody to hepatitis B core antigen-positive donors in liver transplantation in Singapore. Liver Transpl 2001;7:469.

[15] Lo C, Fan S, Liu C, Yong BH, Wong Y, Ng IO, et al. Safety and outcome of hepatitis B core antibody-positive donors in right-lobe living donor liver transplantation. Liver Transpl 2003;9:827–832.

[16] Chen YS, Wang CC, deVilla VH, Wang SH, Cheng YF, Huang TL, et al. Prevention of *de novo* hepatitis B virus infection in living donor liver transplantation using hepatitis B core antibody positive donors. Clin Transpl 2002;16:405–409.

[17] McQuillan G, Coleman P, Kruszon-Moran D, Moyer L, Lambert S, Margolis H. Prevalence of hepatitis B virus infection in the United States: The National Health and Nutrition Examination Survey, 1976 through 1994. Am J Public Health 1999;89:14–18.

[18] Fontana RJ, Merion RM. Are we ready for marginal hepatitis B core antibody-positive living liver donors? Liver Transpl 2003;9:833–836.

[19] Yu AS, Vierling JM, Colquhoun SD, Amaout WS, Chan CK, Khanafshar E, et al. Transmission of hepatitis B infection from hepatitis B core antibody-positive liver allografts is prevented by lamivudine therapy. Liver Transpl 2001;7:513–517.

[20] Joya-Vazquez FS, Dodson FS, Dvorchik I, Gray E, Chesky A, demetris AJ, et al. Impact of anti-hepatitis Bc-positive grafts on the outcome of liver transplantation for HBV-related cirrhosis. Transplantation 2002;73:1598–1602.

[21] Roque-Afonso AM, Feray C, Samuel D, Simoneau D, Roche B, Emile JF, et al. Antibodies to hepatitis B surface antigen prevent viral reactivation in recipients of liver grafts from anti-HBC positive donors. Gut 2002;50:95–99.

[22] Nery JR, Nery-Avila C, Reddy KR, Cirocco R, Weppler D, Levi DM, et al. Use of liver grafts from donors positive for anti-hepatitis B-core antibody (anti-HBc) in the era of prophylaxis with hepatitis-B immunoglobulin and lamivudine. Transplantation 2003;75:1179–1186.

[23] Montalti R, Nardo B, Bertelli R, Beltempo P, Puviani L, Vivarelli M, et al. Donor pool expansion in liver transplantation. Transplant Proc 2002;36:520–522.

[24] Donataccio D, Roggen F, de Reyck C, Verbaandert C, Bodeus M, Lerut J. Use of anti-HBc positive allografts in adult liver transplantation: toward a safer way to expand the donor pool. Transpl Int 2006;19:38–44.

[25] Prakoso E, Strasser SI, Koorey DJ, Verran D, McCaughan GW. Long-term lamivudine monotherapy prevents development of hepatitis B virus infection in hepatitis B surface-antigen negative liver transplant recipients from hepatitis B core-antibody-positive donors. Clin Transpl 2006;20:369–373.

[26] Celebi Kodak A, Karasu Z, Kilic M, Ozacar T, Tekin F, Gunsar F, et al. Living donor liver transplantation from hepatitis B core antibody positive donors. Transplant Proc 2007;39:1488–1490.

[27] de Feo T, Poli F, Mozzi F, Moretti MP, Scalamogna MCollaborative Kidney Liver and Heart North Italy Transplant Program Study Groups. Risk of transmission of hepatitis B virus from anti-HBC positive cadaveric organ donors: a collaborative study. Transplant Proc 2005;37:1238–1239.

[28] Suehiro T, Shimada M, Kishikawa K, Shimura T, Soejima Y, Yoshizumi T, et al. Prevention of hepatitis B virus infection from hepatitis B core antibody-positive donor graft using hepatitis B immune globulin and lamivudine in living donor liver transplantation. Liver Int 2005;25:1169–1174.

[29] Dodson SF, Issa S, Araya V, Gayowski T, Pinna A, Eghtesad B, et al. Infectivity of hepatic allografts with antibodies to hepatitis B virus. Transplantation 1997;64:1582–1584.
[30] Crespo J, Fábrega E, Casafont F, Rivero M, Heras G, de la Pepa J, et al. Severe clinical course of *de novo* hepatitis B infection after liver transplantation. Liver Transpl Surg 1999;5:175–183.
[31] Holt CD, Thomas R, van Thiel DH, Brems JJ. Use of hepatitis B core antibody-positive donors in orthotopic liver transplantation. Arch Surg 2002;137:572–575.
[32] Loss Jr G, Mason A, Nair S, Blazek J, Farr G, Guo L, et al. Does lamivudine prophylaxis eradicate persistent HBV DNA from allografts derived from anti-HBc-positive donors? Liver Transpl 2003;12:1258–1264.
[33] Takemura N, Sugawara Y, Tamura S, Makuuchi M. Liver transplantation using hepatitis B core antibody-positive grafts: review and university of Tokyo experience. Dig Dis Sci 2007;52:2472–2477.
[34] Fabrega E, Garcia-Suarez C, Guerra A, Orive A, Casafont F, Crespo J, et al. Liver transplantation with allografts from hepatitis B core antibody-positive donors: a new approach. Liver Transpl 2003;9:916–920.
[35] Dodson F, Bonham C, Geller D, Cacciarelli TV, Rakela J, Pung JJ. Prevention of *de novo* hepatitis B infection in recipients of hepatic allografts from anti-HBc positive donors. Transplantation 1999;68:1058–1061.
[36] Barcena R, Moraleda G, Moreno J, Dolore Martin M, de Vicente E, Nupo J, et al. Prevention of *de novo* HBV infection by the presence of anti-HBs in transplanted patients receiving core antibody-positive livers. World J Gastroenterol 2006;12:2070–2074.
[37] Barcena Marugan R, Garcia-Hoz F, Vazquez Romero M, Nash R, Mateos M, Gonzalez Alonso R, et al. Prevention of *de novo* hepatitis B infection in liver allograft recipients with previous hepatitis B infection or hepatitis B vaccination. Am J Gastroenterol 2002;97:2398–2401.
[38] Villamil I, Gonzalez-Quintela A, Aquilera A, Tome S, Otero E, Castroagudin FJ, et al. Truly *de novo* HBV infection after liver transplantation. Am J Gastroenterol 2004:767–768.
[39] Castells L, Vargas V, Rodrygez F, Allende H, Jardy R, Margarit C, et al. Transmission of hepatitis B virus by transplantation of livers from donors positive for antibody to hepatitis B core antigen. Transplant Proc 1999;31: 2464–2465.
[40] Nery JR, Gedaly R, Vianna R, Berho M, Weppler D, Levi DM, et al. Are liver grafts from hepatitis B surface antigen negative/anti-hepatitis B core antibody positive donors suitable for transplantation? Transplant Proc 2001;33:1521–1522.
[41] Chazouilleres O, Marnish D, Kim M, Carey K, Ferrell L, Roberts J, et al. "Occult" hepatitis B virus as source of infection in liver transplant recipients. Lancet 1994;343:142–146.
[42] Wachs ME, Amend WJ, Ascher NL, Bretan PN, Emond J, Lake JR, et al. The risk of transmission of hepatitis B from HBsAg(−), HBcAb(+), HBIgM(−) organ donors. Transplantation 1995;59:230–234.
[43] Jain A, Orloff M, Abt P, Kashyap R, Mohanka R, Lansing K, et al. Use of hepatitis B core antibody positive liver allograft in hepatitis C virus-positive and -negative recipients with use of short course of hepatitis B immunoglobulin and lamivudine. Transplant Proc 2005;37:3187–3189.
[44] Lin CC, Chen CL, Concejero A, Wang CC, Wang SH, Liu YW, et al. Active immunization to prevent *de novo* hepatitis B virus infection in pediatric live donor liver recipients. Am J Transplant 2007;7:195–200.
[45] Kwon C, Suh K, Yi N, Chang S, Cho Y, Lee H, et al. Long-term protection against hepatitis B in pediatric liver recipients can be achieved effectively with vaccination after transplantation. Pediatr Transplant 2006;10:479–486.
[46] Hwang S, Moon DB, Lee SG, Park KM, Kim KH, Ahn CS, et al. Safety of anti-hepatitis B core antibody-positive donors for living-donor liver transplantation. Transplantation 2003;75:S45–S48.
[47] Umeda M, Marusawa H, Ueda M, Takada Y, Egawa H, Uemoto S, et al. Beneficial effects of short-term lamivudine treatment for *de novo* hepatitis B virus reactivation after liver transplantation. Am J Transplant 2006;6:2680–2685.
[48] Soejima Y, Ikegami T, Taketomi A, Yoshizumi T, Uchiyama H, Harada N, et al. Hepatitis B vaccination after living donor liver transplantation. Liver Int 2007;27:977–982.
[49] Park JB, Kwon CH, Lee KW, Choi GS, Kim DJ, Seo JM, et al. Hepatitis B virus vaccine switch program for prevention of *de novo* hepatitis B virus infection in pediatric patients. Transpl Int 2008;21:346–352.
[50] Lee K, Lee D, Lee H. Prevention of *de novo* hepatitis B infection from HbcAb-positive donors in living donor liver transplantation. Transplant Proc 2004;36:2311–2312.
[51] Papatheodoridis GV, Sevastianos V, Burroughs AK. Prevention of and treatment for hepatitis B virus infection after liver transplantation in the nucleoside analogues era. Am J Transplant 2003;3:250–258.
[52] Segovia R, Sanchez-Fueyo A, Rimola A, Grande L, Bruguera M, Costa J, et al. Evidence of serious graft damage induced by *de novo* hepatitis B virus infection after liver transplantation. Liver Transpl 2001;7:106–112.
[53] Gish RG, McCashland T. Hepatitis B in liver transplant recipients. Liver Transpl 2006;12:S54–S64.
[54] Sung J. Hepatitis B virus infection and its sequelae in Taiwan. Gastroenterol Jpn 1984;19:363–366.
[55] Shouval D, Samuel D. Hepatitis B immune globulin to prevent hepatitis B virus graft reinfection following liver transplantation: a concise review. Hepatology 2000;32:1189–1195.

参考資料９

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REVIEW PAPER

Liver Transplantation Using Hepatitis B Core Antibody – Positive Grafts: Review and University of Tokyo Experience

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Abstract Hepatitis B surface antigen – negative and hepatitis B core antibody – positive grafts were considered unsuitable for transplantation. The number of potential recipients for liver transplantation now exceeds that of potential donor organs, which has led us to reevaluate the feasibility of these grafts. Several strategies involving prophylactic administration of hepatitis B immunoglobulin and/or lamivudine to transplant recipients have been proposed. At the University of Tokyo, we have continued to use hepatitis B immunoglobulin monoprophylaxis with zero recurrence.In this article we report our experience with the use of hepatitis B surface antigen – negative/hepatitis B core antibody – positive grafts with hepatitis B immunoglobulin monotherapy. We conducted a review of the literature regarding the feasibility of these grafts to reconfirm optimal prophylactic strategies for preventing *de novo* hepatitis B virus infection in transplant recipients.

Keywords Hepatitis B virus · *De novo* hepatitis · Living donor liver transplantation · Hepatitis B core antibody · Hepatitis B immunoglobulin

Abbreviations

HBV:	Hepatitis B virus
LDLT:	Living donor liver transplantation
HBcAb:	Hepatitis B core antibody
HBsAb:	Hepatitis B surface antibody
HBsAg:	Hepatitis B surface antigen
HBIG:	Hepatitis B immunoglobulin

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Introduction

Hepatitis B surface antigen (HBsAg) – negative and hepatitis B core antibody (HBcAb) – positive grafts are sources of *de novo* hepatitis B virus (HBV) infections. Therefore, they were considered unsuitable for transplantation during the early 1990s [1–3]. As shown in Table 1, the occurrence of *de novo* HBV hepatitis in recipients that received the grafts might be influenced by the pre-existing HBV immunity of the recipient [4–10].

The number of potential recipients for liver transplantation now exceeds that of potential donor organs, leading us to reevaluate the feasibility of using these grafts. Several strategies involving the prophylactic administration of hepatitis B immunoglobulin (HBIG) and/or lamivudine to the recipients have been proposed [7, 10–20]. Liver transplantation from live donors (LDLT) is currently the most effective alternative to overcome the organ shortage. Live donors are often restricted to the relatives of the recipient. In regions where HBV is prevalent, there is no choice other than a graft from a live donor who is HBsAg-negative/HBcAb-positive.

HBsAg-negative/HBcAb-positive grafts are now important topics in LDLT. The optimal prophylactic strategy remains a matter of debate. We conducted a review of the literature regarding the feasibility of HBsAg-negative/HBcAb-positive grafts to reconfirm optimal prophylactic strategies for preventing *de novo* HBV infection in recipients.

Table 1 Recipient's viral status and *de novo* HBV infection rates after transplant of HBcAb-positive grafts without prophylaxis

Author, year	Recipient viral status (HBsAb/HBcAb) +/+	+/−	−/+	−/−	Total (%)
Douglas, 1992 [1]	ND	ND	ND	ND	3/7 (43)
Chazouilleres, 1994 [2]				7/8	7/8 (88)
Wachs, 1995 [3]				3/6	3/6 (50)
Dickson, 1997 [5]	0/1	1/2	0/1	14/16	18/23 (78)
Dodson, 1997 [6]		0/7	2/15	18/25	20/47 (43)
Uemoto, 1998 [7]		1/1		14/15	15/16 (94)
Prieto, 2001 [8]	0/2	0/2	0/3	15/23	15/30 (50)
Manzarbeitia, 2002 [9]	0/13	1/1	2/11	2/2	3/27 (11)
Donataccio, 2006 [21]		0/1		3/4	3/5 (60)
Barcena, 2006 [40]	0/6		0/3		0/9 (0)

Note. HBsAb, hepatitis B surface antibody; HBcAb, hepatitis B core antibody; ND, not described.

Management protocols for prevention of *de novo* HBV Infection (Table 2)

HBIG monoprophylaxis

Uemoto et al. [7] first reported the successful prevention of *de novo* HBV infection using HBIG in recipients who received HBcAb-positive grafts from live donors. Although some authors followed their prophylaxis, the risk of reactivation remained high [4, 9, 11, 15, 21]. Decreased hepatitis B surface antibody (HBsAb) titer seems to be a significant risk factor for *de novo* infection [15]. More recent reports with satisfactory results targeted higher HBsAb levels for an indefinite period [19].

Lamivudine and HBIG

Dodson et al. [11] reported therapy using a combination of prophylactics: HBIG doses ranged from 10,000 IU only during the anhepatic phase [13] to 10,000 IU for seven days after transplantation [11, 14]. The minimum amount of HBIG required to prevent *de novo* infection is unclear. In either case, lamivudine was started after the initial HBIG administration or simultaneously. Suehiro et al. [22] reported that HBIG

Table 2 Prophylaxis for HBcAb-positive graft and infection rate

Author, year	*N*	Followup (months)	Protocols	Rate (%)
HBIG monotherapy				
Radomski, 1996 [4]	1	8	2000 IU/month	1/1 (100%)
Uemoto, 1998 [7]	3	13–24	100 IU/kg for 7 days and 1000 IU/m thereafter	0/3 (0%)
Dodson, 1999 [11]	1	11	10,000 IU for 7 days and monthly for 6 months, 1000 IU biweekly for 18 month	1/1 (100%)
Roque-Afonso, 2002 [15]	12	6–36	5000 IU for 7 days and subsequently to keep HbsAb > 100 IU/L	1/12 (8%)
Lee, 2004 [19]	18	13–80	10,000 IU for 7 days and subsequently to keep HbsAb > 200 IU/L	0/18 (0%)
Donataccio, 2006 [21]	6	18–62	10,000 IU for 7–10 days and stopped	4/6 (67%)
Donataccio, 2006 [21]	4	11–34	10,000 IU for 7–10 days and subsequently continued indefinitely	0/4 (0%)
Takemura, 2006	17	3–96	10,000 IU in anhepatic phase and subsequently to keep HbsAb > 200 IU/L for a year, then > 100 IU/L indefinitely	0/17 (0%)
HBIG + Lam				
Dodson, 1999 [11]	15	6–25	HBIG; 10,000 IU for 7 days and monthly for 6 months, 1000 IU biweekly for 18 months. LAM; 150 mg/day	0/15 (0%)
Holt, 2002 [14]	12	2–38	HBIG; 10,000 IU for 7 days, LAM; 300 mg/day	0/12 (0%)
Jain, 2005 [20]	28	36 ± 19[a]	HBIG; 10,000 IU for 4 days, LAM; 100 mg/day	3/28 (11%)
Suehiro, 2005 [22]	22	25–86	HBIG; 10,000 IU in anhepatic phase, 2000 IU for 7 days and subsequently to keep HbsAb > 100 IU/L, LAM; 100 mg/day	0/22 (0%)
Lam				
Yu, 2001 [12]	9	2–36	LAM; 100 or 150 mg/day	0/9 (0%)
Prakoso, 2006 [24]	10	2–69	LAM; 100 mg/day	0/10 (0%)

Note. HBIG, hepatitis B immunoglobulin; LAM, lamivudine.

[a] Mean ± standard error.

Table 3 Tailored approach based on graft HBVDNA and recipient HBV immunity

Author, Year	N	HBVDNA in donor		Recipient HBsAb	Protocols
		Graft	Serum		
Loss, 2001 [13][a]	1	–	–	ND	10,000 IU of HBIG in anhepatic phase + LAM 150 mg/day → discontinued after confirming the HBVDNA status (graft and donor serum)
	0	+	+	ND	HBIG + LAM → continued
	5	+	NA	ND	HBIG + LAM → LAM; 150 mg/day
Fabrega, 2003 [16][a]	7	–	–	ND	10,000 IU of HBIG for 7 days + Lam; 100 mg/day → discontinued after confirming the HBVDNA status (graft and donor serum)
	0	+	+	ND	HBIG + LAM → LAM; 100 mg/day
Nery, 2003 [17][a]	10	+	+	ND	10,000 IU HBIG for 7 days, weekly for 1 month, and monthly for 6 months + LAM; 100 mg/day
	13	–	–	–	LAM; 100 mg/day
	13	–	–	+	None
	2	NA	ND	–	LAM; 100 mg/day
	5	NA	ND	+	None

Note. HBVDNA, hepatitis B virus deoxyribonucleic acid; HBIG, hepatitis B immunoglobulin; NA, not available; ND, not described; LAM, lamivudine.

[a]No reinfection was seen in all the patients with these protocols.

use with lamivudine over an indefinite period of time might have prevented *de novo* infection in 22 patients receiving HBsAg-negative/HBcAb-positive grafts.

Long-term use of lamivudine is associated with the risk of mutated HBV infection. Jain et al. [20] reported 3 of 28 patients with *de novo* mutated HBV infection who used a protocol of short-term treatment with HBIG (10,000 IU HBIG for 4 days) and indefinite use of lamivudine (100 mg/day). Among these three infected patients, two had a YMDD mutation. Yen et al. [23] experienced a case complicated with a lamivudine-resistant mutation while using a similar protocol.

Lamivudine monoprophylaxis

Yu et al. [12] advocated lamivudine monoprophylaxis. HBV infection was prevented in nine patients who received HBsAg-negative/HBcAb-positive allografts. Six of the nine patients died of recurrent hepatocellular carcinoma (HCC) and sepsis, however, and the followup periods were limited (3–36 months). Prakoso et al. [24] reported that they successfully prevented HBV infection in ten HBsAg-negative patients with lamivudine monotherapy.

Tailored approach (Table 3)

Loss et al. [13] and Nery et al. [25] advocated that prophylaxis should be selected according to the serum and liver HBVDNA status of the donor or the recipient's preoperative serology. Loss et al. administered HBIG during the anhepatic phase and started lamivudine on postoperative day 1. If HBVDNA was detected in neither the donor liver nor serum, lamivudine was stopped. If HBVDNA was detected in the donor liver and serum, HBIG was continued with lamivudine. Fabrega et al. [16] started prophylaxis with a combination of HBIG and lamivudine on the first operative day until they obtained HBVDNA results from the donor samples. They stopped the prophylaxis when the donor's HBVDNA in serum and liver tissue was negative, even in a naïve recipient. None of their seven patients developed *de novo* hepatitis B with a mean followup period of 23 months.

The protocol of Nery et al. [17] was more complicated because the strategy was changed by not only the results of the donor HBV profile but also the recipient's HBV serology. The recipients of HBVDNA-positive grafts received HBIG and lamivudine combination therapy. If the donor serum and liver graft HBVDNA were both negative and the recipient was HbsAb-negative, lamivudine monotherapy was selected. If the recipient was HbsAb-positive, no therapy was administered. Their selective protocol successfully prevented 43 patients from reactivation of HBV, including 18 patients without prophylaxis. Two patients were excluded from their study because of low compliance; both recipients developed *de novo* hepatitis. Their allografts were HBVDNA-negative but they were infected with hepatitis. One was naïve and the other was only HBcAb-positive preoperatively.

A tailored approach is based on the results of testing for HBVDNA in the allografts. The sensitivity for HBVDNA detection, however, depends on the methodology [26]. Van Thiel et al. [27] reported that HBVDNA was detected in 11 (8%) of 133 livers from HBsAg-negative/HBcAb-positive donors. Marusawa et al. [28] reported that HBVDNA was detected in 14 of 17 grafts (82%) from HBcAb-positive donors.

Suehiro et al. [22] detected HBVDNA in 20 of 20 grafts. HBVDNA in all grafts was detected by polymerase chain reaction (PCR) methods, but the details of the methods differed. Van Thiel used primers targeting surface antigen sequences with a sensitivity of an approximately 600 HBV copies per milliliter serum sample. Marusawa used primers targeting the surface and pre-C/C region. The first PCR products were subjected to either Southern blotting analysis or to a second PCR amplification (seminested PCR for pre-C/C region and nested PCR for the surface region). The sensitivity of their assay was 10 copies per 20 μg DNA. Suehiro selected real-time PCR with a sensitivity of 10 copies per gram DNA.

Vaccination

The response rates to recombinant hepatitis B vaccine in liver transplantation candidates (with HBV unrelated liver failure) varied from 16% to 62% [29–38]. It is difficult to explain the variations in hepatitis B vaccine response rates. HBsAb titers rapidly decline and become undetectable in a significant proportion of patients after transplantation. HBsAb titers become undetectable in 37%–73% of the responders within one year after transplantation [33, 35, 38]. Dominguez et al. [30] reported a 62% response rate with 40-μg hepatitis B vaccinations three times preoperatively with a one-month interval and an additional three doses for nonresponders. Conventionally, patients with HBsAb titers of more than 10 IU/L are considered immunized [39].

Kaohsiung's group performed preoperative vaccination in all patients awaiting transplantation because approximately 80% of adults are HBcAb-positive in Taiwan [10]. They reported *de novo* HBV infection in three of eight preoperatively immunized patients who received an HBcAb-positive graft. They made a policy change [18] and began to use lamivudine after surgery with preoperative vaccination. Thereafter, none of 44 patients developed *de novo* hepatitis. Barcena et al. [40] vaccinated only those who were HBsAb- or HBcAb-negative and receiving an HBcAb-positive allograft. No postoperative prophylaxis against HBV was performed in their protocol. They immunized 14 recipients with 40-μg hepatitis B vaccinations three times with a 15-day interval, although the vaccine response rate was not described. One of the 14 recipients developed *de novo* HBV infection after receiving an HBcAb-positive liver; this might have occurred because of an immune escaped HBV mutant with a structural variation in the epitope of the surface antigen recognized by the HBsAb [41, 42].

University of Tokyo experience

From January 1996 to December 2005, 351 LDLT were performed at the University of Tokyo. All donors were HBsAg-negative and 34 (10%) were HBcAb-positive. Of the recipients of HBsAg-negative/HBcAb-positive grafts, 19 were HBV-unrelated recipients and the others had HBV-related cirrhosis. The 19 liver grafts were the subjects of the study. The serum HBV status included HbcAb- and HBsAb-negative ($n = 9$), HbcAb- and HBsAb-positive ($n = 5$), HBcAb-positive ($n = 2$), or HBsAb-positive ($n = 3$). There were 14 men and 5 women with a median age of 51 years [21–64]. The immunosuppression regimen for all recipients consisted of tacrolimus and corticosteroids.

Postoperative prophylaxis consisted of HBIG monotherapy. A total of 10,000 IU HBIG was administrated intravenously during the anhepatic phase. HBIG was administered once a month to maintain the HBsAb level above 200 IU/L during the first year and above 100 IU/L thereafter. We do not use nucleotide analogs for prophylactics to those who received HBcAb-positive graft to avoid the emergence of multidrug resistance.

Our strategy of anhepatic and low-dose HBIG monoprophylaxis prevented perioperative *de novo* HBV infection in all 19 patients that were preoperatively HBsAg-negative and received HBcAb-positive livers. Among the 19 patients, 3 patients died of HBV-unrelated causes between 2 and 13 months after transplantation without any evidence of HBV infection. Two patients were dropped from the prophylaxis protocol because of poor compliance. They skipped the monthly HBIG administration and as a result developed *de novo* HBV infection. Preoperatively, one was naïve and the other was HBsAb- and HBcAb-positive. HBsAb titers at the onset decreased to 10 and 15 IU/L. *De novo* hepatitis was defined as the development of positive serum HBsAg. Their HBsAg were detected 51 and 35 months after the operation. Hepatitis B e antigen became positive and serum HBVDNA was detected. They received antiviral therapy using lamivudine and their hepatitis B e antigen and HBVDNA became negative thereafter. The remaining 14 patients showed no evidence of HBV infection with followup periods of 3–86 months (median = 31 months).

The median amount of HBIG that was used during the first month of transplantation was 12,000 IU (10,000–18,000 IU) and that during the following 11 months was 14,000 IU (12,000–31,000 IU). After the first postoperative year, 10,000 IU HBIG (8000–22,000 IU) was required each year to keep HBsAb levels over 100 IU/L.

Future possible alternatives

Lamivudine is often used to treat a patient with chronic hepatitis B but antiviral drug-resistant mutation frequently develops. Resistance to adefovir dipivoxil is less common than for lamivudine [43]. Adefovir dipivoxil shows favorable outcome in patients with *de novo* hepatitis B after liver

transplantation [44] and in the patients with lamivudine-resistant hepatitis B [45, 46]. Recently, alternative nucleoside analogs adefovir dipivoxil, entecavir [47], telbivudine [48], and tenofovir [49] were administered efficiently in treating wild-type and/or mutated HBV. All of them also have the potential to be used for prophylaxis against *de novo* HBV infection from HBcAb-positive allograft. However, some reports revealed the emergence of mutated HBV which showed resistance not only to lamivudine but also to adefovir dipivoxil [43], entecavir [50], and telbivudine [48].

Conclusions

De novo HBV infection can be prevented with HBcAb-positive grafts when an adequate strategy is applied. HBIG monotherapy can prevent HBV infection from HBcAb-positive liver grafts. Lamivudine use can be reserved for *de novo* HBV infection. Lamivudine or preoperative vaccination monotherapy are still controversial therapies. Vaccination with lamivudine prophylaxis, however, is promising. A tailored approach might reduce the unnecessary administration of antiviral prophylaxis to a recipient. Further studies are needed to elucidate the optimal prophylactic treatment.

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References

1. Douglas DD, Rakela J, Mamish D, et al. (1992) Transmission of hepatitis B virus (HBV) infection from orthotopic donor livers. Hepatology 16:49
2. Chazouilleres O, Mamish D, Kim M, et al. (1994) Occult hepatitis B virus as source of infection in liver transplant recipients. Lancet 343:142–146
3. Wachs ME, Amend WJ, Ascher NL, et al. (1995) The risk of transmission of hepatitis B from HBsAg(−), HBcAb(+), HBIgM(−) organ donors. Transplantation 59:230–234
4. Radomski JS, Moritz MJ, Armenti VT, et al. (1996) Hepatitis B transmission from a liver donor who tested negative for hepatitis B surface antigen and positive for hepatitis B core antibody. Liver Transpl Surg 2:130–131
5. Dickson RC, Everhart JE, Lake JR, et al. (1997) Transmission of hepatitis B by transplantation of livers from donors positive for antibody to hepatitis B core antigen. Gastroenterology 113:1668–1674
6. Dodson SF, Issa S, Araya V, et al. (1997) Infectivity of hepatic allografts with antibodies to hepatitis B virus. Transplantation 64:1582–1584
7. Uemoto S, Sugiyama K, Marusawa H, et al. (1998) Transmission of hepatitis B virus from hepatitis B core antibody-positive donors in living related liver transplants. Transplantation 65:494–499
8. Prieto M, Gomez MD, Berenguer M, et al. (2001) De novo hepatitis B after liver transplantation from hepatitis B core antibody-positive donors in an area with high prevalence of anti-HBc positivity in the donor population. Liver Transpl 7:51–58
9. Manzarbeitia C, Reich DJ, Ortiz JA, et al. (2002) Safe use of livers from donors with positive hepatitis B core antibody. Liver Transpl 8:556–561
10. Chen YS, Wang CC, de Villa VH, et al. (2002) Prevention of *de novo* hepatitis B virus infection in living donor liver transplantation using hepatitis B core antibody positive donors. Clin Transplant 16:405–409
11. Dodson SF, Bonham CA, Geller DA, et al. (1999) Prevention of de novo hepatitis B infection in recipients of hepatic allografts from anti-HBc positive donors. Transplantation 68:1058–1061
12. Yu AS, Vierling JM, Colquhoun SD, et al. (2001) Transmission of hepatitis B infection from hepatitis B core antibody-positive liver allografts is prevented by lamivudine therapy. Liver Transpl 7:513–517
13. Loss GE, Mason AL, Blazek J, et al. (2001) Transplantation of livers from HBc Ab positive donors into HBc Ab negative recipients: a strategy and preliminary results. Clin Transplant 15:55–58
14. Holt D, Thomas R, Van Thiel D, et al. (2002) Use of hepatitis B core antibody-positive donors in orthotopic liver transplantation. Arch Surg 137:572–575
15. Roque-Afonso AM, Feray C, Samuel D, et al. (2002) Antibodies to hepatitis B surface antigen prevent viral reactivation in recipients of liver grafts from anti-HBC positive donors. Gut 50:95–99
16. Fabrega E, Garcia-Suarez C, Guerra A, et al. (2003) Liver transplantation with allografts from hepatitis B core antibody-positive donors: a new approach. Liver Transpl 9:916–920
17. Nery JR, Nery-Avila C, Reddy KR, et al. (2003) Use of liver grafts from donors positive for antihepatitis B-core antibody (anti-HBc) in the era of prophylaxis with hepatitis-B immunoglobulin and lamivudine. Transplantation 75:1179–1186
18. de Villa VH, Chen YS, Chen CL (2003) Hepatitis B core antibody-positive grafts: recipient's risk. Transplantation 75:49–53
19. Lee KW, Lee DS, Lee HH, et al. (2004) Prevention of *de novo* hepatitis B infection from HbcAb-positive donors in living donor liver transplantation. Transplant Proc 36:2311–2312
20. Jain A, Orloff M, Abt P, et al. (2005) Use of hepatitis B core antibody-positive liver allograft in hepatitis C virus-positive and -negative recipients with use of short course of hepatitis B immunoglobulin and lamivudine. Transplant Proc 37:3187–3189
21. Donataccio D, Roggen F, De Reyck C, et al. (2006) Use of anti-HBc positive allografts in adult liver transplantation: toward a safer way to expand the donor pool. Transpl Int 19:38–43
22. Suehiro T, Shimada M, Kishikawa K, et al. (2005) Prevention of hepatitis B virus infection from hepatitis B core antibody-positive donor graft using hepatitis B immune globulin and lamivudine in living donor liver transplantation. Liver Int 25:1169–1174
23. Yen RD, Bonatti H, Mendez J, et al. (2006) Case report of lamivudine-resistant hepatitis B virus infection post liver transplantation from a hepatitis B core antibody donor. Am J Transplant 6:1077–1083
24. Prakoso E, Strasser SI, Koorey DJ, Verran D, McCaughan GW (2006) Long-term lamivudine monotherapy prevents development of hepatitis B virus infection in hepatitis B surface-antigen negative liver transplant recipients from hepatitis B core-antibody-positive donors. Clin Transplant 20:369–373
25. Nery JR, Gedaly R, Vianna R, et al. (2001) Are liver grafts from hepatitis B surface antigen negative/anti-hepatitis B core antibody positive donors suitable for transplantation? Transplant Proc 33:1521–1522

26. Burton JR Jr, Shaw-Stiffel TA (2003) Use of hepatitis B core antibody-positive donors in recipients without evidence of hepatitis B infection: a survey of current practice in the United States. Liver Transpl 9:837–842
27. van Thiel DH, De Maria N, Colantoni A, et al. (1999) Can hepatitis B core antibody positive livers be used safely for transplantation: hepatitis B virus detection in the liver of individuals who are hepatitis B core antibody positive. Transplantation 68:519–522
28. Marusawa H, Uemoto S, Hijikata M, et al. (2000) Latent hepatitis B virus infection in healthy individuals with antibodies to hepatitis B core antigen. Hepatology 31:488–495
29. Chalasani N, Smallwood G, Halcomb J, et al. (1998) Is vaccination against hepatitis B infection indicated in patients waiting for or after orthotopic liver transplantation? Liver Transpl Surg 4:128–132
30. Dominguez M, Barcena R, Garcia M, et al. (2000) Vaccination against hepatitis B virus in cirrhotic patients on liver transplant waiting list. Liver Transpl 6:440–442
31. Carey W, Pimentel R, Westveer MK, et al. (1990) Failure of hepatitis B immunization in liver transplant recipients: results of a prospective trial. Am J Gastroenterol 85:1590–1592
32. van Thiel DH, El-Ashmawy L, Love K, et al. (1992) Response to hepatitis B vaccination by liver transplant candidates. Dig Dis Sci 37:1245–1249
33. Loinaz C, de Juanes JR, Gonzalez EM, et al. (1997) Hepatitis B vaccination results in 140 liver transplant recipients. Hepatogastroenterol 44:235–238
34. Chalasani N, Smallwood G, Halcomb J, et al. (1998) Is vaccination against hepatitis B infection indicated in patients waiting for or after orthotopic liver transplantation? Liver Transpl Surg 4:128–132
35. Horlander JC, Boyle N, Manam R, et al. (1999) Vaccination against hepatitis B in patients with chronic liver disease awaiting liver transplantation. Am J Med Sci 318:304–307
36. Dominguez M, Barcena R, Garcia M, et al. (2000) Vaccination against hepatitis B virus in cirrhotic patients on liver transplant waiting list. Liver Transpl 6:440–442
37. Villeneuve E, Vincelette J, Villeneuve JP (2000) Ineffectiveness of hepatitis B vaccination in cirrhotic patients waiting for liver transplantation. Can J Gastroenterol 14:59–62
38. Arslan M, Wiesner RH, Sievers C, et al. (2001) Double-dose accelerated hepatitis B vaccine in patients with end-stage liver disease. Liver Transpl 7:314–320
39. Centers for Disease Control (CDC) (1988) Update: universal precautions for prevention of transmission of human immunodeficiency virus, hepatitis B virus, and other bloodborne pathogens in health-care settings. MMWR Morb Mortal Wkly Rep 37:377–382
40. Barcena R, Moraleda G, Moreno J, et al. (2006) Prevention of de novo HBV infection by the presence of anti-HBs in transplanted patients receiving core antibody-positive livers. World J Gastroenterol 12:2070–2074
41. Moraleda G, Barcena R, Del Campo S, et al. (2006) De novo HBV infection caused by an anti-HBc positive donor in a vaccinated liver transplant recipient in spite of anti-HBs response. Am J Transplant 6:438–440
42. Carman WF, Zanetti AR, Karayiannis P, et al. (1990) Vaccine-induced escape mutant of hepatitis B virus. Lancet 336:325–329
43. Angus P, Vaughan R, Xiong S, et al. (2003) Resistance to adefovir dipivoxil therapy associated with the selection of a novel mutation in the HBV polymerase. Gastroenterology 125:292–297
44. Toniutto P, Fumo E, Caldato M, et al. (2004) Favourable outcome of adefovir-dipivoxil treatment in acute de novo hepatitis B after liver transplantation. Transplantation 77:472–473
45. Schiff ER, Lai CL, Hadziyannis S, Neuhaus P, et al. (2003) Adefovir dipivoxil therapy for lamivudine-resistant hepatitis B in pre- and post-liver transplantation patients. Hepatology 38:1419–1427
46. Lo CM, Liu CL, Lau GK, et al. (2005) Liver transplantation for chronic hepatitis B with lamivudine-resistant YMDD mutant using add-on adefovir dipivoxil plus lamivudine. Liver Transpl 11:807–813
47. Chang TT, Gish RG, de Man R, et al. (2006) A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med 354:1001–1010
48. Lai CL, Leung N, Teo EK, et al. (2005) A 1-year trial of telbivudine, lamivudine, and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B. Gastroenterology 129:528–536
49. van Bommel F, Zollner B, Sarrazin C, et al. (2006) Tenofovir for patients with lamivudine-resistant hepatitis B virus (HBV) infection and high HBVDNA level during adefovir therapy. Hepatology 44:318–325
50. Tenney DJ, Levine SM, Rose RE, et al. (2004) Clinical emergence of entecavir-resistant hepatitis B virus requires additional substitutions in virus already resistant to lamivudine. Antimicrob Agents Chemother 48:3498–3507