第37回 厚生科学審議会疾病対策部会臓器移植委員会
議事次第

日時：平成23年2月1日(火)
15:00 ～ 17:00
場所：厚生労働省共用第8会議室

1. 開 会

2. 議 事
（1） 改正法施行後の状況について
（2） 移植希望者(レシピエント)選択基準について
（3） 脳死下臓器提供事例の検証方法の見直しについて
（4） 今後の検討課題について
（5） その他

3. 閉 会

〈配布資料〉

資料１－１ 臓器提供者数の推移（年別）
１－２ 改正法施行後の脳死下での臓器提供事例について
１－３ 臓器移植の実施状況（過去３年間の状況）
１－４ 臓器提供施設の状況
１－５ 臓器移植に関する普及啓発の取り組み
１－６ 平成 23 年度臓器移植対策関係予算（案）について

資料２－１ 腎臓移植希望者(レシピエント)選択基準(案)
２－２ 肝臓移植希望者(レシピエント)選択基準(案)
２－３ 肝臓臓器提供者(ドナー)適応基準(案)

参考資料１ 腎臓移植希望者(レシピエント)選択基準の運用状況(NW 提出)
参考資料２ 全国腎移植希望待機患者の分布
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
参考資料４ ABO 血液型適合度別の予後
参考資料５ 文献：Transplantation vol70(9) 1283-1291
参考資料６ 文献：Liver Transplantation vol7(1) pp41-47
参考資料７ 肝臓レシピエント新基準での優先順位
参考資料８ 文献：Journal of Hepatology vol52 272-279
参考資料９ 文献:Dig Dis Sci vol52 2472-2477

資料３－１　前回の臓器移植委員会における検証方法の見直しに係る議論の概要
　３－２　脳死下の臓器提供事例に係る検証について
　３－３　前回の検証会議における検証方法の見直しに係る議論の概要

参考資料１　脳死下での臓器提供事例に係る検証会議
参考資料２－１　平成 12 年 6 月 14 日発出　通知
参考資料２－２　平成 17 年 11 月 2 日発出　通知
参考資料２－３　平成 19 年 8 月 1 日　発出　通知
参考資料２－４　平成 17 年 3 月 25 日発出　通知
参考資料２　検証の在り方の見直しの考え方
参考資料３　脳死下での臓器提供事例に係る検証作業進捗状況

資料４　日本脳神経外科学会の専門医訓練施設について

資料５　今後の検討課題について（案）

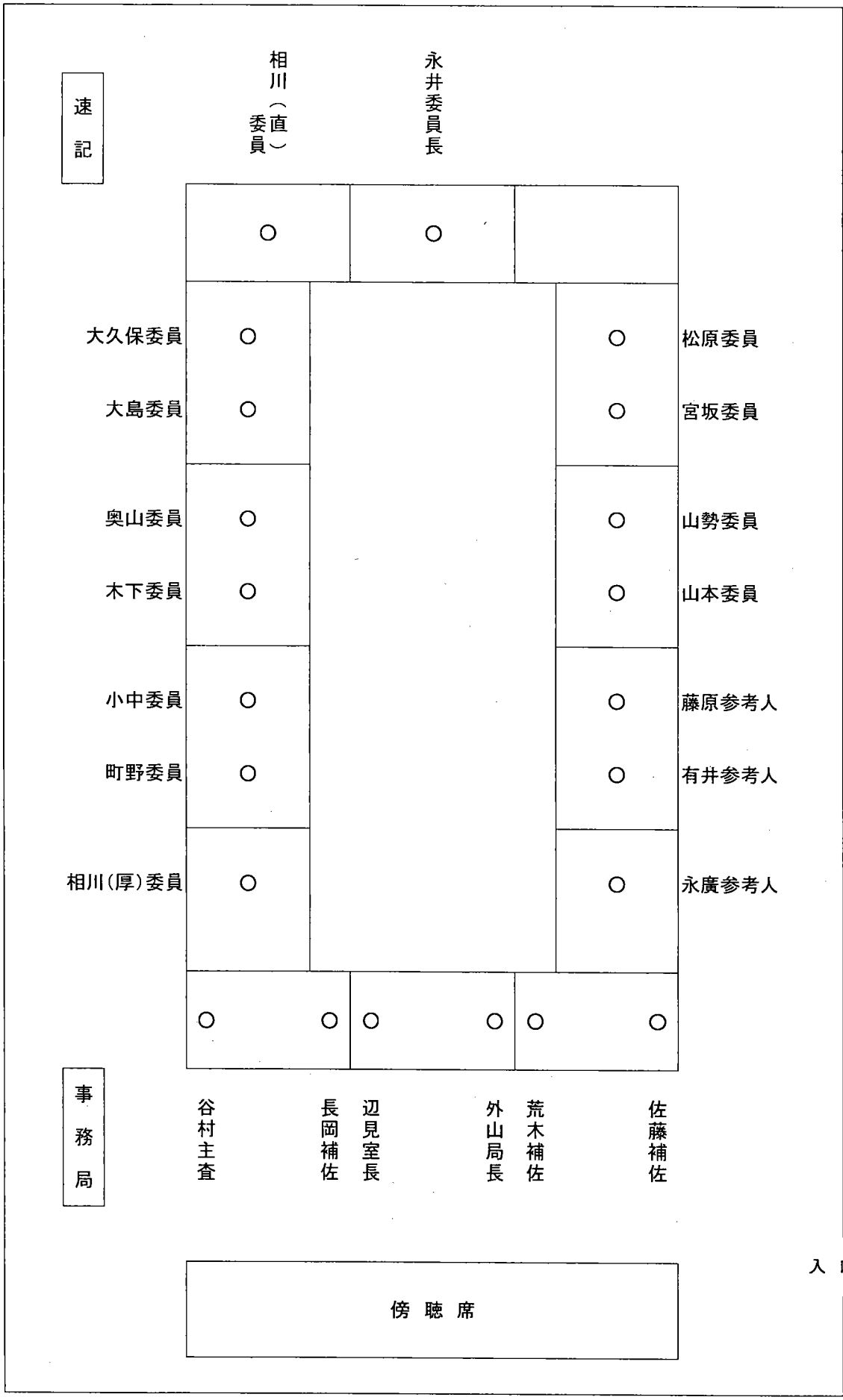
資料６－１　臓器提供者（ドナー）家族に対する心のケアについて
　６－２　JOTにおけるドナー家族対応・支援（小中委員提出資料）

参考資料１　JOT コーディネーターのドナー家族対応・支援
参考資料２　日本臓器移植ネットワークによる家族対応支援体制の強化

第37回厚生科学審議会疾病対策部会臓器移植委員会

日　時：平成23年2月1日（火）15：00～17：00

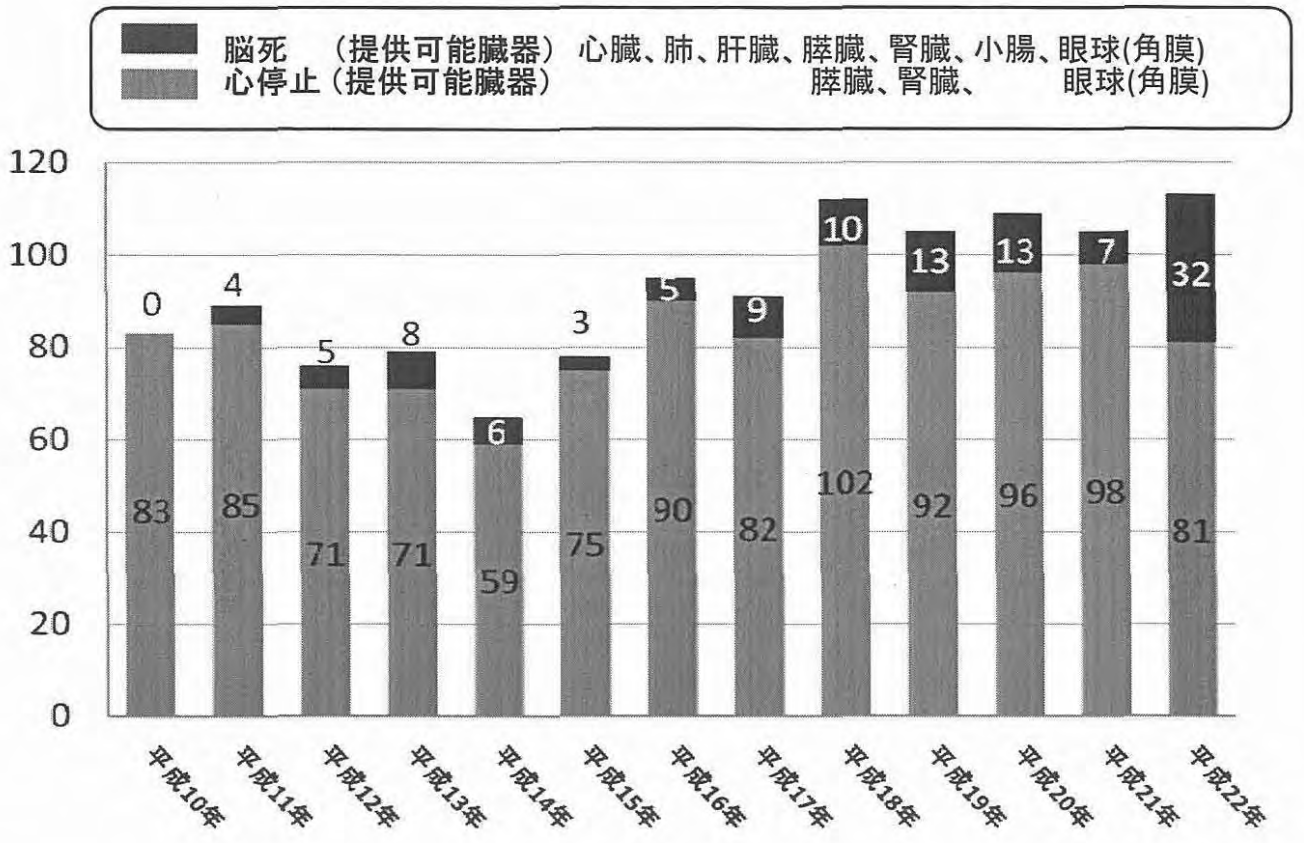
場　所：厚生労働省　共用第8会議室（6階）



資料1－1

臓器提供者数の推移（年別）

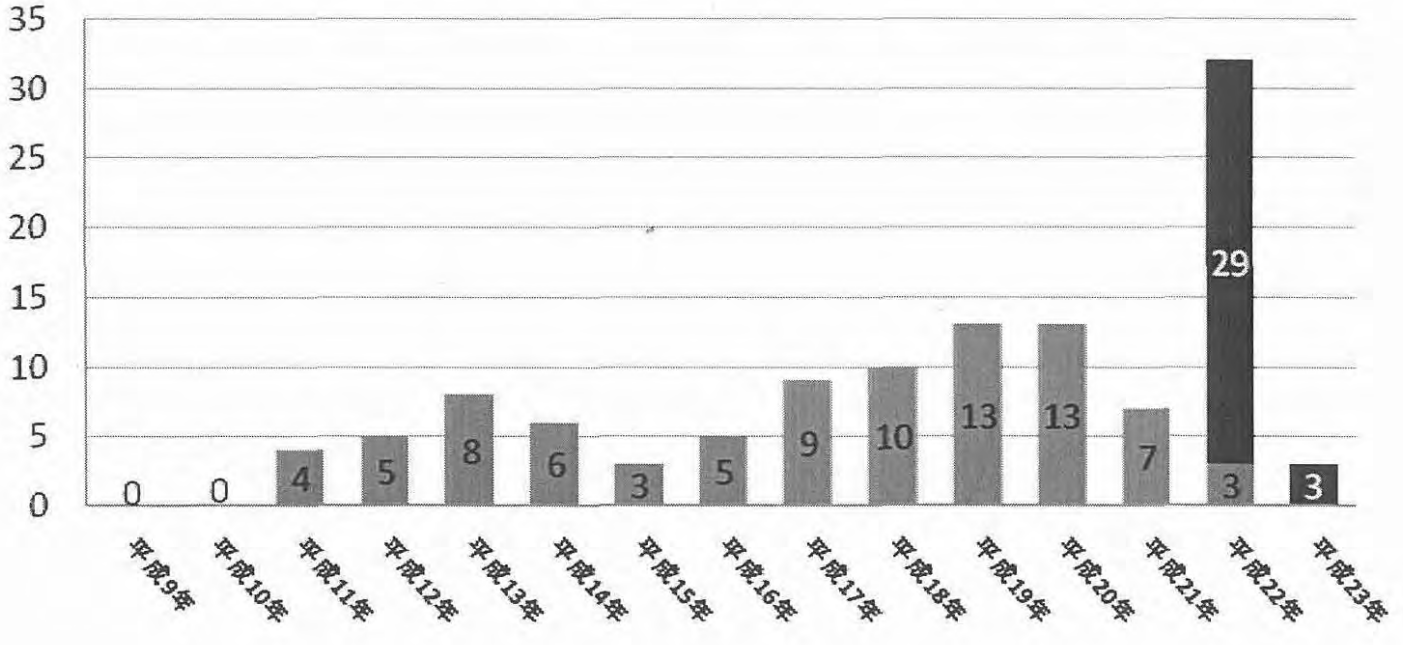
※平成22年まで



脳死下での臓器提供者数の推移（年別）

※平成23年1月27日現在

改正法施行(平成22年7月17日)以前　86例
改正法施行以降　32例（うち家族承諾30例）
} 累計118例(脳死判定数は119例)



資料1－2

改正法施行後の脳死下での臓器提供事例について(平成23年1月27日現在)

	脳死判定事例(提供事例)	提供日	原疾患	提供施設	書面による意思表示	心臓	肺	肝臓	膵臓	腎臓	小腸	眼球
1	第88例目(第87例目)	平成22年8月10日	20代 男性 交通外傷	関東甲信越	なし	国立循環器病研究センター	岡山大(両肺)	東大 －	藤田保健衛生大(膵腎同時)	群馬大	－	東京歯科大学市川総合病院 東京歯科大学市川総合病院
2	第89例目(第88例目)	平成22年8月19日	男性	近畿	なし	東大	阪大(両肺)	京大 －	名古屋第二赤十字(膵腎同時)	神戸大	－	－ －
3	第90例目(第89例目)	平成22年8月22日	50代 女性 脳血管障害	東海	なし	東北大	東北大(両肺)	阪大 －	名古屋第二赤十字(膵腎同時)	藤田保健衛生大	－	名古屋大 藤田保健衛生大
4	第91例目(第90例目)	平成22年8月27日	40代 女性 くも膜下出血	松山赤十字病院	あり	－	－	北海道大 －	東京女子医大(膵腎同時)	愛媛県立中央病院	－	愛媛大 愛媛大
5	第92例目(第91例目)	平成22年8月29日	40代 男性 蘇生後脳症	関東甲信越	なし	－	京大 京大	国立成育医療研究センター 京大	九州大(膵腎同時)	千葉大	東北大	東京歯科大学市川総合病院 東京歯科大学市川総合病院
6	第93例目(第92例目)	平成22年9月2日	40代 女性 くも膜下出血	北部九州	なし	国立循環器病研究センター	東北大(両肺)	名古屋大 －	－	東京女子医大 長崎医療センター	東北大	－ －
7	第94例目(第93例目)	平成22年9月4日	成人 男性 頭部外傷	東北	なし	東京女子医大	岡山大 京大	名古屋大 －	藤田保健衛生大	福島県立医大 福島県立医大	九州大	－ －
8	第95例目(第94例目)	平成22年9月7日	成人 男性 蘇生後脳症	関東甲信越	なし	国立循環器病研究センター	－	北海道大 －	東京女子医大(膵腎同時)	長野赤十字	－	長野赤十字 長野赤十字
9	第96例目(第95例目)	平成22年9月12日	40代 男性 心疾患	市立札幌病院	なし	－	岡山大(両肺)	東大 －	藤田保健衛生大(膵腎同時)	市立札幌	－	－ －
10	第97例目(第96例目)	平成22年9月18日	30代 男性	近畿	なし	国立循環器病研究センター	－	京大 岡山大	阪大(膵腎同時)	近江八幡市立総合医療センター	－	－ －
11	第98例目(第97例目)	平成22年9月25日	70代 男性 脳幹梗塞	北部九州	なし	－	－	－ －	－	熊本赤十字 熊本赤十字	－	－ －
12	第99例目(第98例目)	平成22年9月27日	50代 男性 脳血管障害	北海道	なし	埼玉医科大学国際医療センター	東北大 福岡大	京大 －	－	北海道大 市立札幌	－	－ －
13	第100例目(第99例目)	平成22年9月30日	50代 女性 くも膜下出血	市立札幌病院	なし	阪大	東北大	京大 －	東北大(膵腎同時)	札幌北楡	－	－ －
14	第101例目(第100例目)	平成22年9月30日	30代 男性 蘇生後脳症	東北大学病院	なし	国立循環器病研究センター	－	京大 －	阪大(膵腎同時)	仙台社会保険	－	東北大 東北大
15	第102例目(第101例目)	平成22年10月3日	70代 女性 脳出血	関東	なし	－	－	岡山大 －	－	東邦大医療センター大森病院 東京女子医大	－	－ －
16	第103例目(第102例目)	平成22年10月13日	18歳以上 男性 脳血管障害	西日本	なし	－	－	阪大 －	東京女子医大(膵腎同時)	日赤和歌山医療センター	－	－ －
17	第104例目(第103例目)	平成22年11月3日	30代 女性 くも膜下出血	九州大学病院	なし	阪大	岡山大(両肺)	広島大 －	藤田保健衛生大(膵腎同時)	福岡赤十字	－	－ －
18	第105例目(第104例目)	平成22年11月21日	50代 男性 脳血管疾患	高山赤十字病院	なし	東大	福岡大(左肺) －	東大 －	－	静岡県立総合病院 岐阜大	－	岐阜大 眼科杉田病院
19	第106例目(第105例目)	平成22年11月26日	60代 男性 低酸素脳症	福山市民病院	なし	阪大	岡山大(両肺)	－ －	－	県立広島 岡山医療センター	－	広島大 木村眼科内科病院
20	第107例目(第106例目)	平成22年11月26日	60代 女性 脳血管障害	札幌医科大学附属病院	なし	－	長崎大 東北大	国立成育医療研究センター －	東北大(膵腎同時)	市立札幌	－	－ －
21	第108例目(第107例目)	平成22年12月2日	40代 男性 脳血管障害	関東	なし	東大	京大(左肺) －	順天堂大医学部附属順天堂医院 －	国立病院機構千葉東(膵腎同時)	東京女子医大	－	－ －
22	第109例目(第108例目)	平成22年12月4日	30代 女性 脳血管障害	九州大学病院	なし	阪大	阪大 福岡大	－ －	藤田保健衛生大(膵腎同時)	九州大	－	－ －
23	第110例目(第109例目)	平成22年12月10日	60代 女性 くも膜下出血	大阪市立総合医療センター	なし	－	－ －	岡山大 －	国立病院機構千葉東(膵腎同時)	大阪市立大	－	－ －
24	第111例目(第110例目)	平成22年12月13日	60代 女性 脳血管障害	国立病院機構長崎医療センター	なし	東大	－ －	広島大 －	九州大(膵腎同時)	長崎大	－	－ －
25	第112例目(第111例目)	平成22年12月17日	18歳以上 男性 脳血管障害	北海道	なし	－	－ －	信州大 －	－	－ －	－	北海道大 札幌医科大
26	第113例目(第112例目)	平成22年12月18日	30代 男性 くも膜下出血	岐阜県総合医療センター	なし	東大	－ －	名古屋大 －	京都府立医科大 岐阜大	豊橋市民病院	－	－ －
27	第114例目(第113例目)	平成22年12月18日	30代 男性 脳血管障害	関東	なし	阪大	－ －	京大 －	香川大(膵腎同時)	北里大	－	－ －
28	第115例目(第114例目)	平成22年12月25日	成人 脳血管障害	藤田保健衛生大学病院	なし	九州大	京大(両肺)	阪大 －	東京女子医大(膵腎同時)	藤田保健衛生大	－	坂文種報徳會病院 坂文種報徳會病院
29	第116例目(第115例目)	平成22年12月29日	50代 男性 気管支喘息による低酸素脳症	大阪市立大学医学部附属病院	なし	東大	－ －	北海道大 －	千葉東(膵腎同時)	関西医科大附属枚方病院	－	福岡大 関西労災病院
30	第117例目(第116例目)	平成23年1月2日	20代 女性 頭部外傷	福井大学医学部附属病院	なし	東京女子医大	岡山大(両肺)	広島大 －	神戸大(膵腎同時)	福井大	－	－ －
31	第118例目(第117例目)	平成23年1月14日	50代 男性 心筋梗塞、蘇生後脳症	旭川医科大学病院	なし	－	－ －	北海道大 －	－	北海道大 市立札幌	－	旭川医科大 旭川医科大
32	第119例目(第118例目)	平成23年1月27日	30代 男性 くも膜下出血	前橋赤十字病院	あり	阪大	阪大 京大	京大 国立成育医療研究センター	北海道大(膵腎同時)	群馬大	－	－ －

資料1－3

臓器移植の実施状況（過去3年間の状況）

	平成20年	平成21年	平成22年	移植希望者数
心臓（単独）	11件 （11件）	6件 （6件）	23件 （23件）	158名
肺（単独）	14件 （14件）	9件 （9件）	25件 （25件）	142名
心肺同時	0件 （0件）	1件 （1件）	0件 （0件）	4名
肝臓（単独）	13件 （13件）	7件 （7件）	30件 （30件）	283名
膵臓（単独）	4件 （4件）	0件 （0件）	2件 （2件）	42名
腎臓（単独）	204件 （20件）	182件 （7件）	186件 （39件）	11，948名
肝腎同時	0件 （0件）	0件 （0件）	0件 （0件）	9名
膵腎同時	6件 （6件）	7件 （7件）	23件 （23件）	132名
小腸	1件 （1件）	1件 （1件）	4件 （4件）	4名
眼球（角膜）	1，641件 （11件）	1，595件 （12件）	1，694件 （24件）	2，600名

※1　移植希望者数は、平成23年1月4日（眼球（角膜）については平成22年12月31日）現在。
※2　（　）内は、脳死下での移植実施件数。

資料１－４

臓器提供施設の状況

〈概要〉

厚生労働省において、「臓器の移植に関する法律の運用に関する指針（ガイドライン）」に規定された下記の施設（合計４９２施設）を対象に、臓器提供施設としての体制整備状況等について、任意によるアンケートを行った（調査時期は平成２２年８月～９月）。

・大学附属病院
・日本救急医学会の指導医指定施設
・日本脳神経外科学会の専門医訓練施設（Ａ項）
※「Ａ項」とは、専門医訓練施設のうち、指導に当たる医師、症例数等において特に充実した施設。
・救命救急センターとして認定された施設
・日本小児総合医療施設協議会の会員施設

５類型該当施設数

合計	大学附属病院	日本救急医学会指導医指定施設	日本脳神経外科学会専門医訓練施設（A項）	救命救急センター	日本小児総合医療施設協議会の会員施設
492	128	89	342	213	31

＜体制整備の状況＞

アンケート有効回答数

合計	大学附属病院	日本救急医学会指導医指定施設	日本脳神経外科学会専門医訓練施設（A項）	救命救急センター	日本小児総合医療施設協議会の会員施設
487	128	89	337	212	31

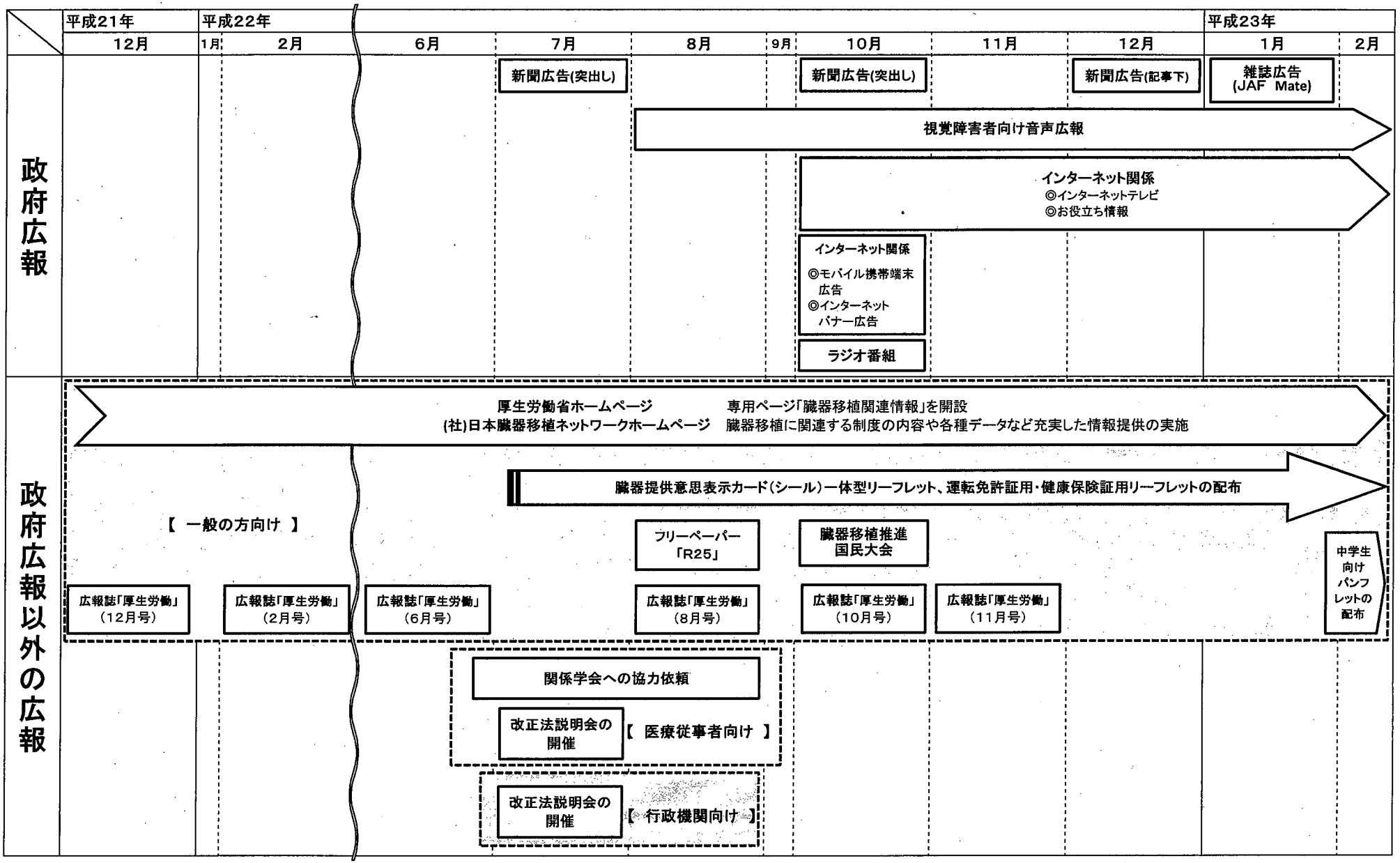
体制整備状況

	18 歳以上			18 歳未満		
	体制を整えている	今後整える予定	整えておらず、今後も整える予定がない	18 歳未満の児童からの臓器提供に協力可能	今後整える予定	整えておらず、今後も整える予定がない
合計	344	106	35	65	270	40

※　一部の項目に未回答の施設があるため、回答施設数の合計と回答内容の合計とは一致しない。

臓器移植に関する普及啓発の取り組み

資料1－5



別紙

臓器移植関連の普及啓発の取り組み状況

１．政府広報

【新聞広告】

◎突き出し広告

全国紙５紙、ブロック紙３紙、地方紙64紙

・平成22年 7月13日～18日：臓器移植法改正のお知らせ

・平成22年10月18日～24日：10月の臓器移植普及推進月間のお知らせ

◎記事下広告

全国紙５紙、ブロック紙３紙、地方紙64紙

・平成22年12月27日：運転免許証及び健康保険証に「臓器提供意思表示」の記入欄が設けられたことについてのお知らせ

【雑誌広告】

◎ JAF Mate：（期間）1、2月合併特別号（平成23年1月10日発行）

運転免許証に「臓器提供意思表示」の記入欄が設けられたことについて、社団法人日本自動車連盟（ＪＡＦ）の会員（個人・法人）向け月刊誌に広告を掲載

【視覚障害者向け資料】

◎音声広報「明日への声」：6分1200字程度で「改正臓器移植法への取り組み」を紹介

・音声ＣＤ 5000部を全国視覚障害者情報提供施設協会、日本盲人連合、全国盲人老人福祉施設連絡協議会、盲学校高等部、都道府県図書館、地方公共団体等に配布

・「政府広報オンラインホームページ」に音声ファイルを掲載

【インターネット関係】

◎政府広報インターネットテレビ「徳光＆木佐の知りたいニッポン！」

平成22年10月14日～掲載、20分番組、ゲスト（(社)日本臓器移植ネットワーク広報・普及啓発部長）を招き、臓器移植に関する情報等をわかりやすく紹介

◎政府広報オンライン「お役立ち情報」

国の行政施策の中から、暮らしにかかわりの深いテーマ、暮らしに役立つ情報を毎月４本程度掲出しわかりやすく解説

平成22年9月29日～約1年間掲載、約1ヶ月間トップページのタイトルに臓器移植に関する情報等を掲載

◎政府広報モバイル携帯端末

携帯端末用の無料ニュースサイト「Ｔｈｅ　ｎｅｗｓ」のトップページに約８０文字の文字広告を掲出、広報テーマは１週間毎に変更

臓器提供に関する意思表示への協力を呼びかける

◎政府広報インターネットバナー広告

「Yahoo! Japan ニュースネットワークプライムスプレイ」にバナー広告を掲出し、リンクにより関連サイトに誘導

平成22年10月25日～31日掲載、15秒間のアニメーション

臓器移植法が改正されたことについてのお知らせや臓器提供に関する意思表示への協力を呼びかける

【ラジオ番組】

◎政府広報ラジオ番組「中山秀征のジャパリズム」

政府の重要施策について、ゲストの解説と中山秀征氏とのトークによりわかりやすく説明

平成22年10月22日、16：30～16：55オンエア、25分番組、ＴＯＫＹＯ　ＦＭ（ＪＦＮ系全国15局ネット）

ゲスト（(社)日本臓器移植ネットワーク医療本部長）により、臓器移植法の改正や臓器移植に関する情報をわかりやすく解説

２．政府広報以外の広報

（１）一般方向け

【厚生労働省ＨＰ】

専用ページ「臓器移植関連情報」を開設（平成 22 年 7 月初旬～）

【日本臓器移植ネットワークＨＰ】

臓器移植に関連する制度の内容や各種データなど充実した情報提供の実施

【広報誌、雑誌関係】

◎広報誌「厚生労働」

・臓器移植法改正についての記事を掲載
（平成 21 年 12 月、平成 22 年 2 月、6 月及び 8 月の計 4 回）
・臓器移植普及推進月間についての記事を掲載
（平成 22 年 10 月）
・臓器移植の実施状況等に関する報告書（国会報告）についての記事を掲載
（平成 22 年 11 月）

◎フリーペーパー R25

・移植をテーマとして特集(2010.8.19 NO270)

【臓器移植推進国民大会の開催】

臓器移植に関する普及啓発等に功績のあった方への厚生労働大臣感謝状の贈呈やシンポジウム等を通じて啓発活動を実施（平成 22 年 10 月 3 日）
（主催：厚生労働省、熊本県、（社）日本臓器移植ネットワーク、（財）日本腎臓財団）

【新しい臓器提供意思表示カード、リーフレット等の配布】

・意思表示カード一体型リーフレット等の配布
・臓器提供意思表示欄が設けられた運転免許証や医療保険被保険者証の順次更新に伴い説明用リーフレットの配布

【中学生向けパンフレットの作成・配布（予定)】

全国の中学全学年を対象に教育用普及啓発パンフレットを作成し配布

（２）医療従事者向け

【関係学会への協力依頼】

◎医療現場への周知のため、8 つの学会に依頼し、機関誌や学会ＨＰに情報掲載

【説明会の開催】

◎改正臓器移植法説明会（(社)日本臓器移植ネットワーク主催）
臓器提供施設の医療従事者、都道府県コーディネーター向け
全国 3 カ所：中日本支部会場約 180 人（平成 22 年 7 月 15 日）
東日本支部会場約 400 人（平成 22 年 7 月 17 日）
西日本支部会場約 350 人（平成 22 年 7 月 24 日）

（３）行政機関向け

【説明会の開催】

◎臓器移植対策担当者会議（厚生労働省主催）
（都道府県、指定都市、中核市の担当者及び都道府県コーディネーター）
参加者数約 150 人（平成 22 年 7 月 13 日）

資料１－６

平成２３年度　臓器移植対策関係予算(案)について

１　臓器移植対策予算（案）

（平成 21 年度予算額）	（平成 22 年度予算額）	**（平成 23 年度予算(案)）**
537,693 千円 →	856,732 千円 →	**759,164 千円**
	（対前年度増減比 159.3%）	**（対前年度増減比　88.6%）**

２　主な事項

○ 臓器移植対策事業費（補助先：社団法人日本臓器移植ネットワーク）

（２３年度（案））　（２２年度予算）

７１９，３７４千円（８０７，７７８千円）

㊕ 意思表示の環境整備

〔**１４６，５３５千円**（１３５，３３７千円）〕

臓器提供意思表示カードと臓器移植に関する知識や意思の記入方法等の説明書きが一体となったリーフレットの作成配布

㊕ 臓器移植コーディネーター等研修の充実

〔　**３２，８４３千円**（　２４，７８５千円）〕

臓器移植コーディネーター及び臓器提供施設の医療従事者に対する研修の充実

㊐ 臓器提供施設の院内体制整備に対する支援

〔　**７，３９８千円**（　　０）〕

施設内の各部門間の連携及び外部の関係者との連携の下で院内体制を構築することを支援（全国６施設）

資料2－1

腎臓移植希望者（レシピエント）選択基準（案）

１．前提条件

（１）ＡＢＯ式血液型

ＡＢＯ式血液型の一致（identical）及び適合（compatible）の待機者を候補者とする。

（２）リンパ球~~直接~~交叉試験（全リンパ球又はＴリンパ球）陰性

２．優先順位

（１）搬送時間（阻血時間）

地　域	点　数
同一都道府県内（注）	１２点
同一ブロック内	６点

＊　移植希望者の登録地域は移植希望施設の所在地（都道府県）とする。

（２）ＨＬＡの適合度

ＤＲ座の適合 （ミスマッチ数）	Ａ座及びＢ座の適合 （ミスマッチ数）	点　数	
0	0	１４	
0	1	１３	
0	2	１２	
0	3	１１	
0	4	１０	
1	0	9	
1	1	8	
1	2	7	×１．１５点
1	3	6	
1	4	5	
2	0	4	
2	1	3	
2	2	2	
2	3	1	
2	4	０点	

（３）待機日数

待機日数（N）≦4014 日：待機日数ポイント＝N/365 点

待機日数（N）＞4014 日：待機日数ポイント＝10＋log1.74（N/365－9）点

（４）未成年者

１６歳未満については１４点を加算する。

１６歳～２０歳未満については１２点を加算する。

３．具体的選択法

適合条件に合致する移植希望者（レシピエント）が複数存在する場合には、優先順位は、以下の順に勘案して決定する。

（１）臓器の移植に関する法律第６条の２の規定に基づき、親族に対し臓器を優先的に提供する意思が表示されていた場合には、当該親族を優先する。

（２）ＡＢＯ式血液型が一致（identical）する者を適合（compatible）する者より優先する。

（３）２．の（１）～（４）の合計点数が高い順とする。ただし、これらの条件が同一の移植希望者（レシピエント）が複数存在した場合には、臓器搬送に要する時間、医学的条件に配慮する。

~~また、ＰＲＡ検査が可能な場合はＰＲＡ検査陰性を満たすこととする。~~

（注１）地域は、原則として、都道府県、ブロック内他都道府県とする。ただし、地域の実情を踏まえ、（社）日本臓器移植ネットワークにおいて複数の都道府県を統合したサブブロックを設置することも可能とする。

（注２）１年以内に移植希望者（レシピエント）の登録情報が更新されていることを必要条件とする。

（注３）Ｃ型肝炎抗体陽性ドナーからの移植は、Ｃ型肝炎抗体陽性レシピエントのみを対象とするが、リスクについては十分に説明し承諾を得られた場合にのみ移植可能とする。

（注４）　新ルール実施後１年を目途に新ルールの状況について検討を行うとともに、今後新たな医学的知見を踏まえ、PRA 検査の取り扱い等について適宜検討を行い、必要があれば、基準の見直しを行うこととする。

資料2－2

肝臓移植希望者（レシピエント）選択基準

１．適合条件

（１）ＡＢＯ式血液型

ＡＢＯ式血液型の一致（identical）及び適合（compatible）の待機者を候補者とする。

ただし、選択時２歳（生後 24 ヶ月）未満の場合には医学的緊急性９点の場合に限り、不適合（imcompatible）の待機者も候補として考慮する。

（２）前感作抗体

当面、選択基準にしないが、必ず検査し、登録する。

（３）ＨＬＡ型

当面、選択基準にしないが、必ず検査し、登録する。

（４）搬送時間（虚血許容時間）

臓器提供者（ドナー）の肝臓を摘出してから１２時間以内に血流再開することが望ましい。

２．優先順位

（１）医学的緊急性

予測余命が１ヶ月以内	９点
予測余命が１ヶ月～６ヶ月以内	６点
予測余命が６ヶ月～１年以内	３点
予測余命が１年を超えるもの	１点

ただし、先天性肝・胆道疾患及び先天性代謝異常症については、肝臓移植が治療的意義を持つ時期、患者の日常生活に障害が発生している状態及び成長障害がある状態を考慮の上、上表に規定する点数のいずれかを用いることがある。

（２）ＡＢＯ式血液型

ＡＢＯ式血液型が一致	１．５点
ＡＢＯ式血液型が適合	１．０点

ただし、選択時に２歳（生後 24 ヶ月）未満かつ医学的緊急性９点の待機者は、血液型を問わず、1.5 点を加点する。

（３）臓器提供者（ドナー）が 18 歳未満の場合には、選択時に 18 歳未満の移植希望者（レシピエント）に限り、１点を加点する。

３．具体的選択方法

適合条件に合致する移植希望者（レシピエント）が複数存在する場合には、優先順位は、以下の順に勘案して決定する。

（１）臓器の移植に関する法律第６条の２の規定に基づき、親族に対し臓器を優先的に提供する意思が表示されていた場合には、当該親族を優先する。

ただし、ＨＬＡの適合度を必ず確認し、臓器提供者（ドナー）のＨＬＡ－Ａ、ＨＬＡ－Ｂ、ＨＬＡ－ＤＲのすべてにホモ接合体が存在し、移植希望者（レシピエント）が臓器提供者（ドナー）のハプロタイプを共有するヘテロ接合体である場合には、移植片対宿主病（ＧＶＨＤ）の危険性が高いため、除く。

（２）２．の（１）、（２）、（３）の合計点数が高い順とする。ただし、これらの条件が同一の移植希望者（レシピエント）が複数存在した場合は、待機期間の長い者を優先する。

（３）（１）又は（２）で選ばれた移植希望者（レシピエント）が肝腎同時移植の待機者である場合であって、かつ、臓器提供者（ドナー）から肝臓及び腎臓の提供があったときには、当該待機者に優先的に肝臓及び腎臓を同時に配分する。また、選ばれた移植希望者（レシピエント）が肝腎同時移植の待機者の場合であって、かつ、臓器提供者（ドナー）から肝臓、膵臓及び腎臓の提供があったときには、膵臓移植希望者（レシピエント）選択基準で選ばれた移植希望者（レシピエント）が膵腎同時移植の待機者である場合であっても、当該肝腎同時移植の待機者に優先的に肝臓及び腎臓を同時に配分する。

なお、選ばれた肝腎同時移植の待機者が優先すべき親族でない場合であって、腎臓移植希望者（レシピエント）が優先すべき親族であるときや膵腎同時移植希望者（レシピエント）が優先すべき親族であるときは、当該腎臓移植希望者（レシピエント）や膵腎同時移植希望者（レシピエント）が優先される。

（４）（３）により、肝腎同時移植希望者（レシピエント）が選定されたものの、肝臓が移植に適さないことが判明した場合には、腎臓移植希望者（レシピエント）選択基準で選ばれた腎臓移植希望者（レシピエント）に腎臓を配分する。

（５）　（１）又は（２）で選ばれた移植希望者（レシピエント）が肝小腸同時移植の希望者である場合であって、かつ、臓器提供者（ドナー）から肝臓及び小腸の提供があった場合には当該待機者に優先的に肝臓及び小腸を同時に配分する。なお、

選ばれた肝小腸同時移植の待機者が優先すべき親族でない場合であって、小腸移植希望者（レシピエント）が優先すべき親族であるときには、当該小腸移植希望者（レシピエント）が優先される。

（６）（５）により、肝小腸同時移植希望者（レシピエント）が選定されたものの、肝臓が移植に適さないことが判明した場合には、小腸移植希望者（レシピエント）選択基準で選ばれた小腸移植希望者（レシピエント）に小腸を配分する。

４．その他

ＡＢＯ式血液型の取扱いや優先順位の点数付け等、当基準全般については、今後の移植医療の定着及び移植実績の評価を踏まえ、適宜見直すこととする。

また、将来ネットワークが整備され、組織的にも機能的にも十分機能した場合は、改めてブロックを考慮した優先順位を検討することが必要である。

資料２－３

＜肝臓＞臓器提供者（ドナー）適応基準（案）

１．以下の疾患又は状態を伴わないこととする。

（１）全身性の活動性感染症

（２）ＨＩＶ抗体、ＨＴＬＶ－１抗体、ＨＢｓ抗原などが陽性

（３）クロイツフェルト・ヤコブ病及びその疑い

（４）悪性腫瘍（原発性脳腫瘍及び治癒したと考えられるものを除く。）

２．以下の疾患又は状態を伴う場合は、慎重に適応を決定する。

（１）病理組織学的な肝臓の異常

（２）生化学的肝機能検査の異常

（３）１週間以内の腹部、消化管手術及び細菌感染を伴う腹部外傷

（４）胆道系手術の既往

~~（５）重度糖尿病~~

~~（６）過度の肥満~~

~~（７）重度の熱傷~~

（５）長期の低酸素状態

（６）高度の高血圧又は長期の低血圧

（７）ＨＣＶ抗体陽性

（８）ＨＢｃ抗体陽性

（９）先天性の代謝性肝疾患の保有の可能性がある者

（１０）重度糖尿病、過度の肥満、重症熱傷、その他の重度の全身性疾患

備考）摘出されたドナー肝については、移植前に肉眼的、組織学的に観察し、最終的に適応を検討することが望ましい(移植担当医の判断に委ねる)。

付記　上記の基準は適宜見直されること。

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)

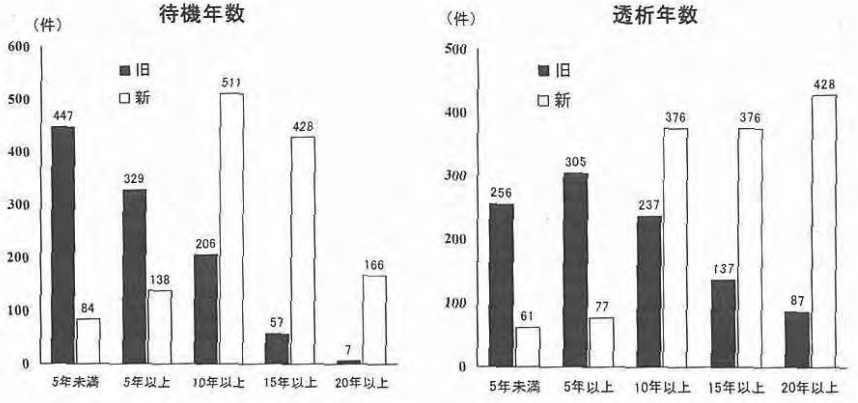
レシピエント選択基準変更前後の
レシピエント待機日数･透析日数

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（%）

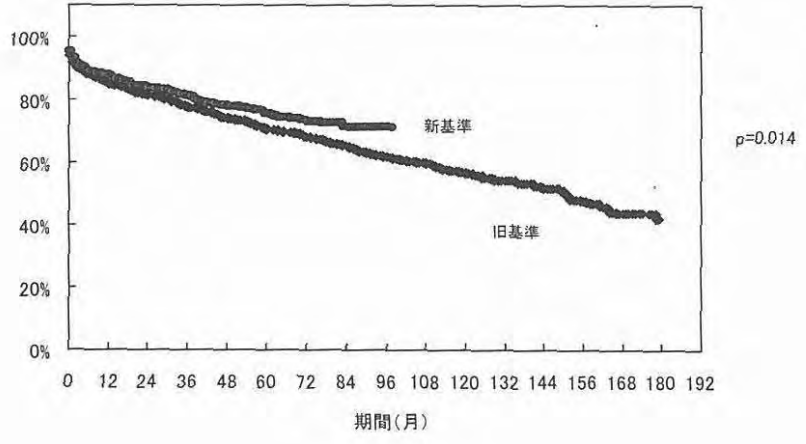
	1カ月	1年	3年	5年	(Logrank)
旧基準	98.2	95.3	91.5	89.3	p=0.135
新基準	98.0	96.1	93.7	91.7	

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	

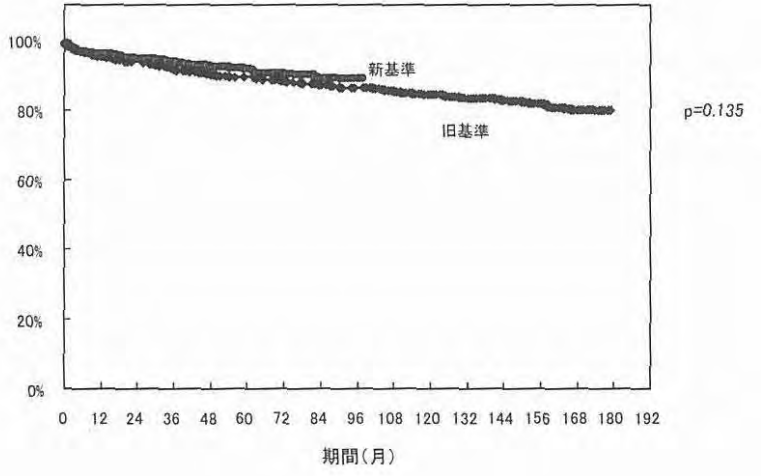
生着率　選択基準別

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

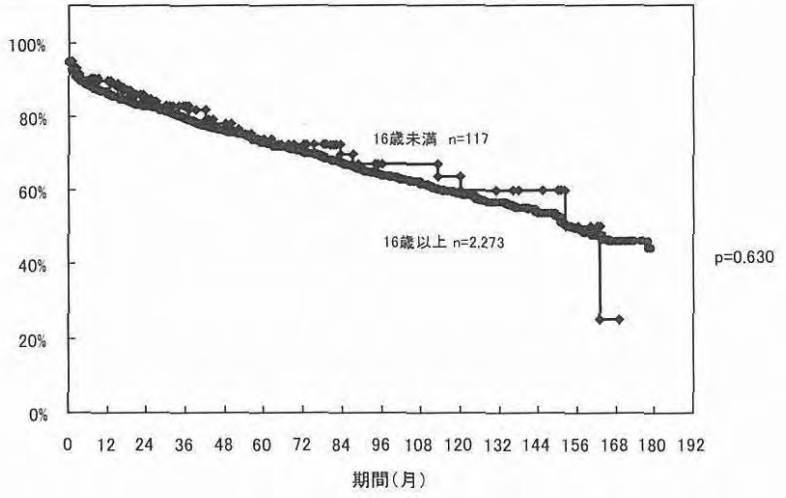


生存率　選択基準別

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

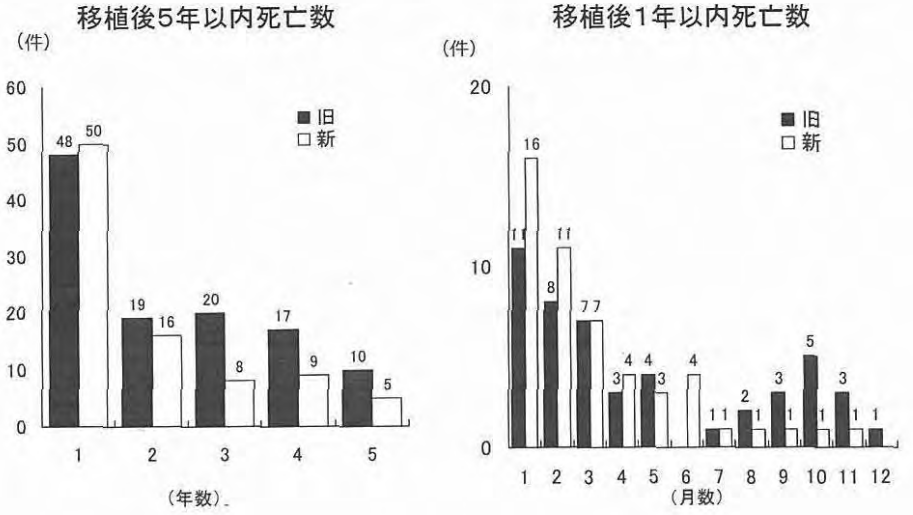


生着率　16歳未満・以上
（1995.4.1～2009.12.31）



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）



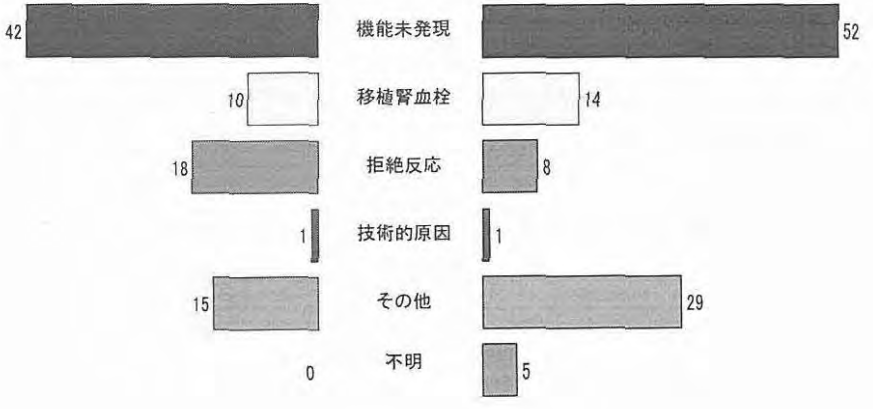
レシピエント選択基準変更前後の移植後無機能腎・術後透析期間・死亡・生着率

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

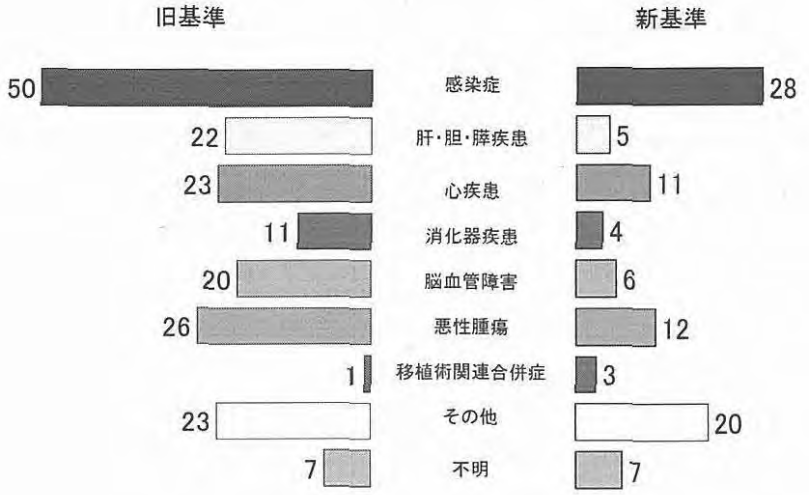
透析離脱不能例とその原因

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%)

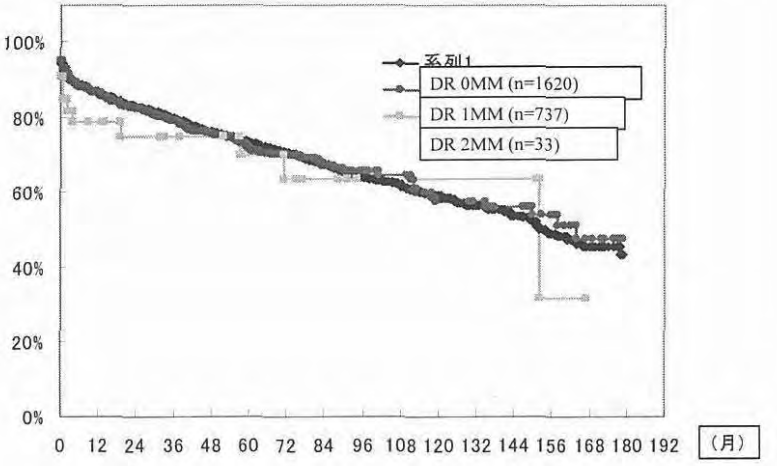


レシピエント選択基準変更前後の移植後死因

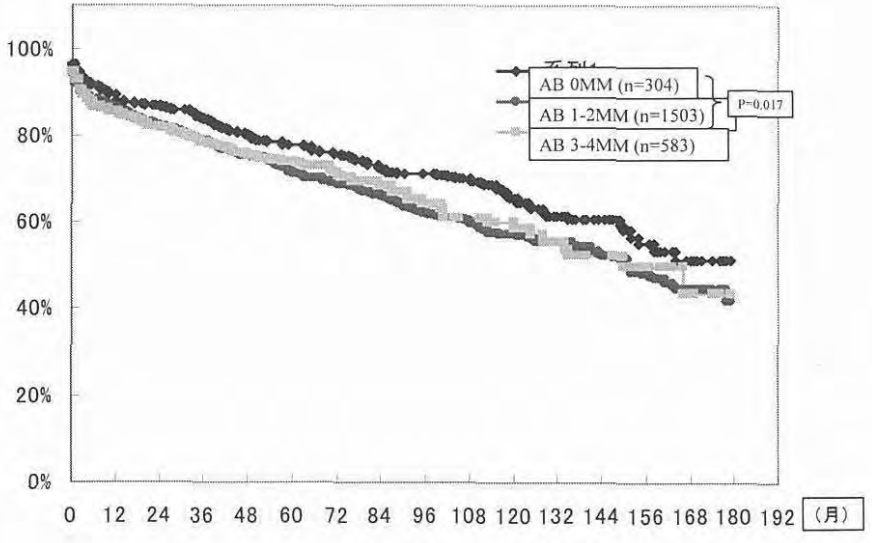
旧基準　(1995.4.1 ～ 2002.1.9　N=1,063)
新基準　(2002.1.10～2009.12.31　N=1,327)



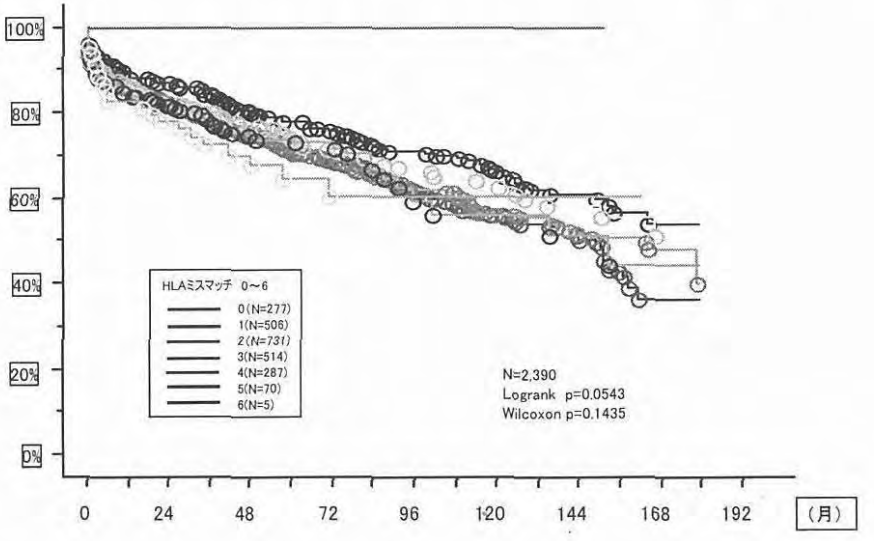
HLA不適合抗原数(検索型DR) 生着率



HLA不適合抗原数(検索型A･B) 生着率



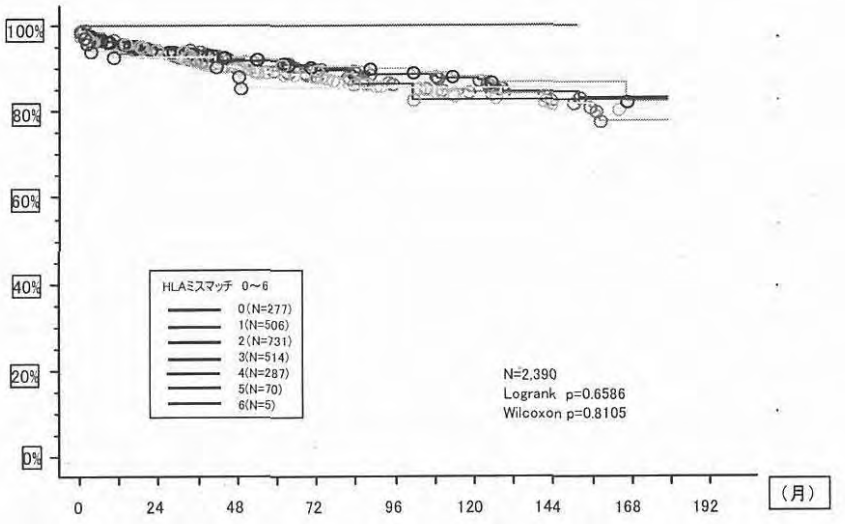
HLA不適合抗原数(検索型A･B･DR) 生着率



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

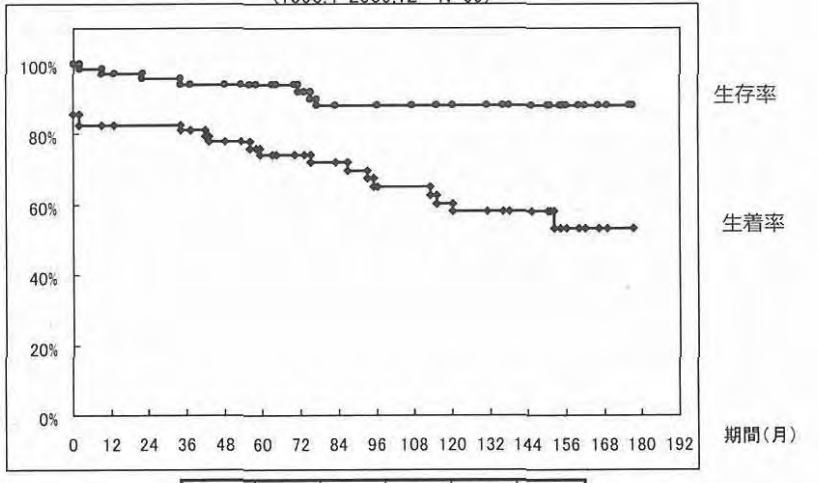


HLA不適合抗原数(検索型A・B・DR) 生存率

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

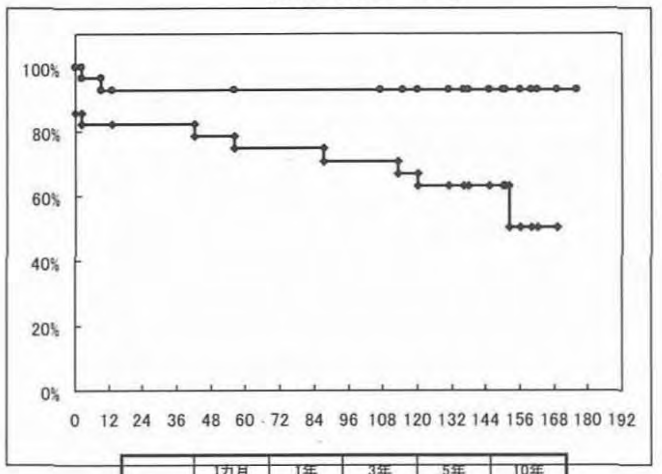
(1995.4-2009.12 N=69)



	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

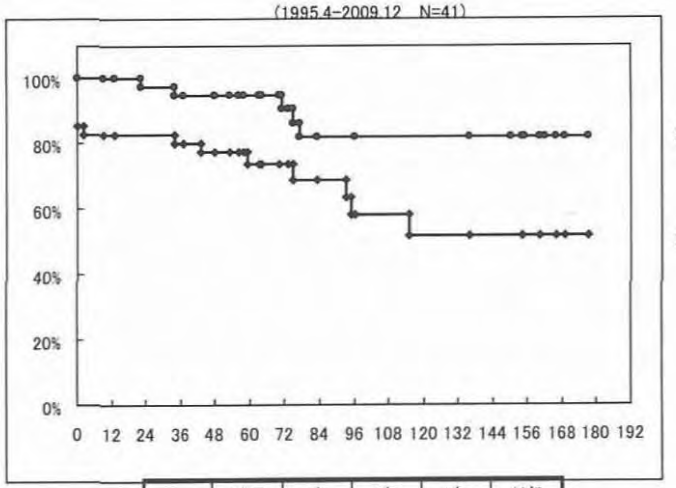
(1995.4-2009.12　N=28)



	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

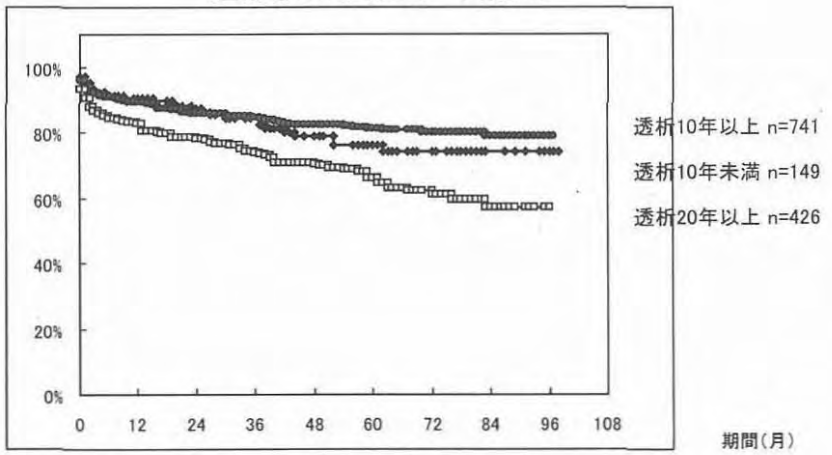
(1995.4-2009.12　N=41)



	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)



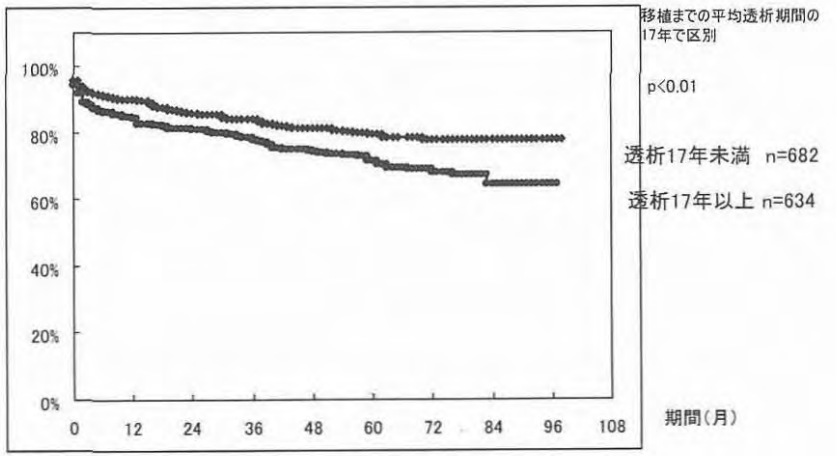
	1カ月	1年	3年	5年
10年未満	95.3%	90.5%	84.5%	76.0%
10年以上	94.1%	89.5%	84.9%	81.2%
20年以上	90.4%	83.0%	74.2%	65.9%

p<0.01

p<0.01

新基準による腎臓移植　生着率×透析期間

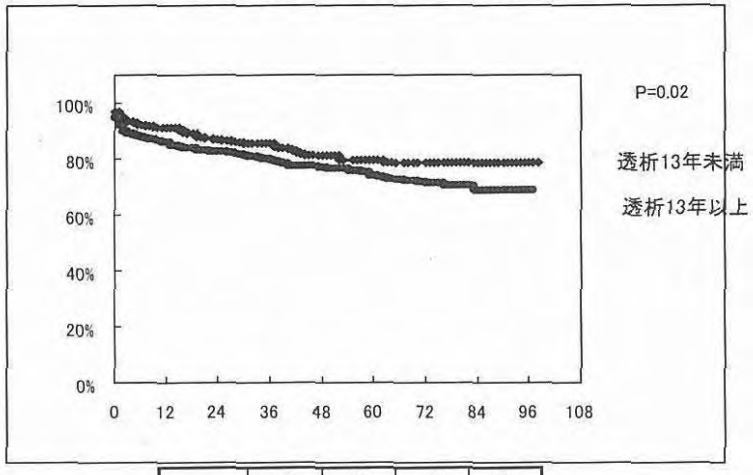
(透析導入日不明のデータを除く)



	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

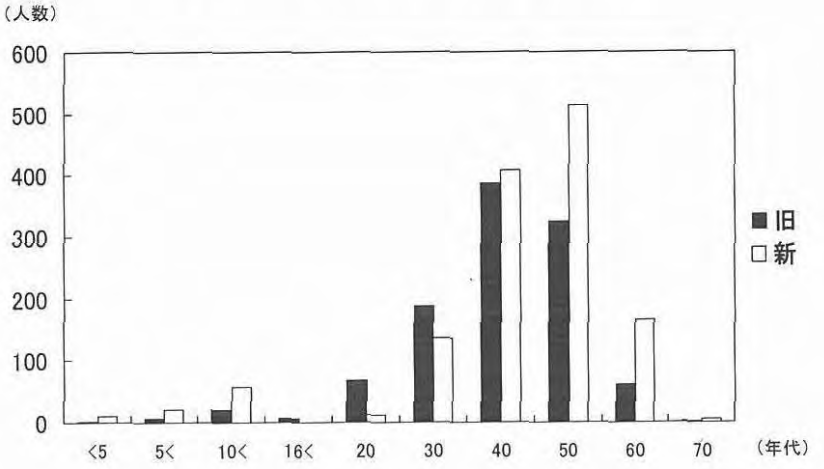
（透析導入日不明のデータを除く）



	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%

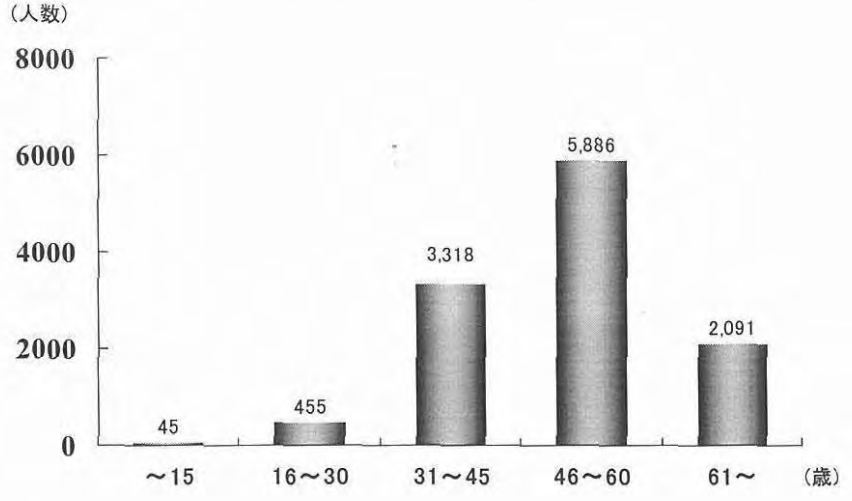
配分基準・年代別移植者数

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



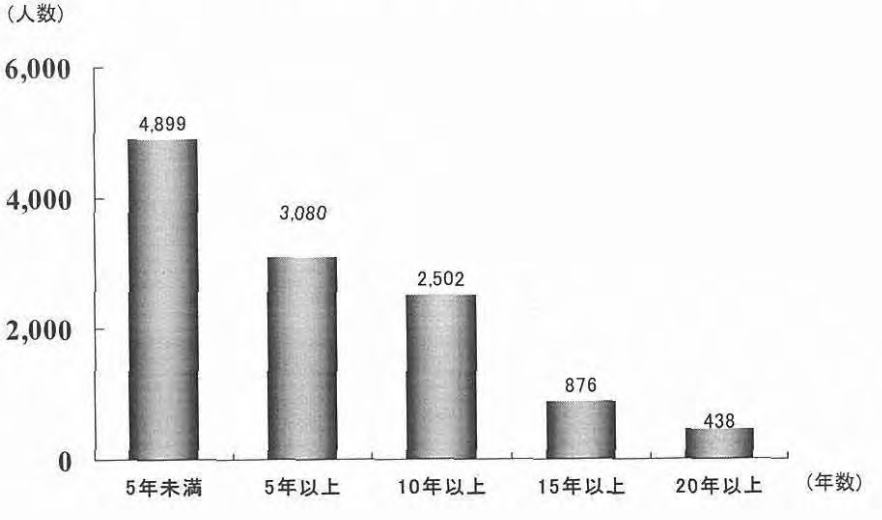
腎臓移植希望登録者　【年齢】

（2010.5.31現在　N=11,795）



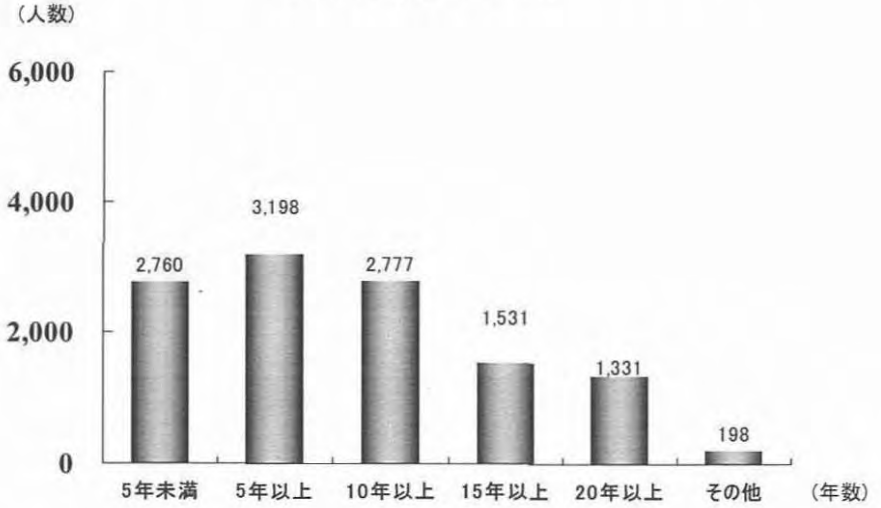
腎臓移植希望登録者【待機年数】

（2010.5.31現在　N=11,795）



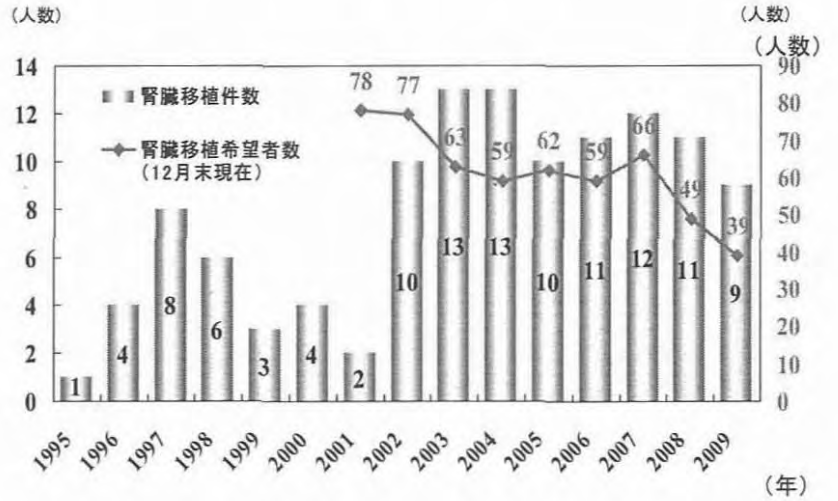
腎臓移植希望登録者【透析年数】

（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

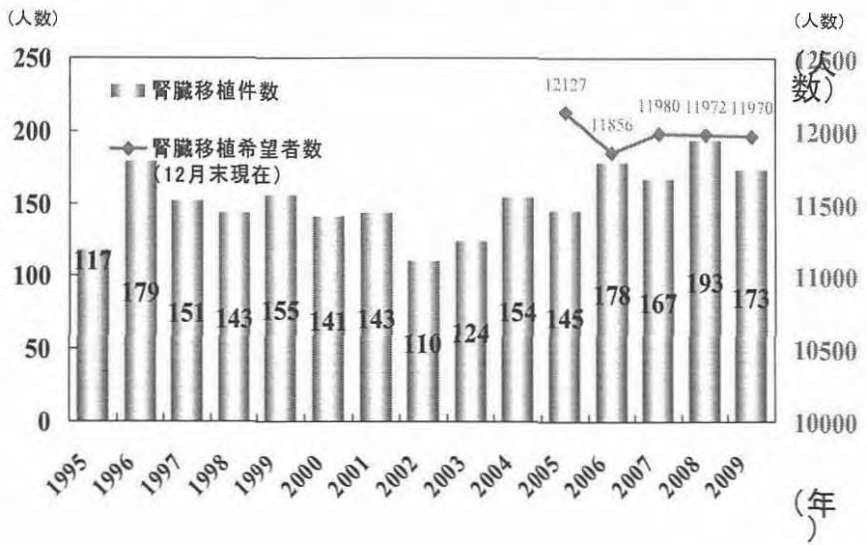
（16歳未満　1995年4月～2009年12月）



＊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

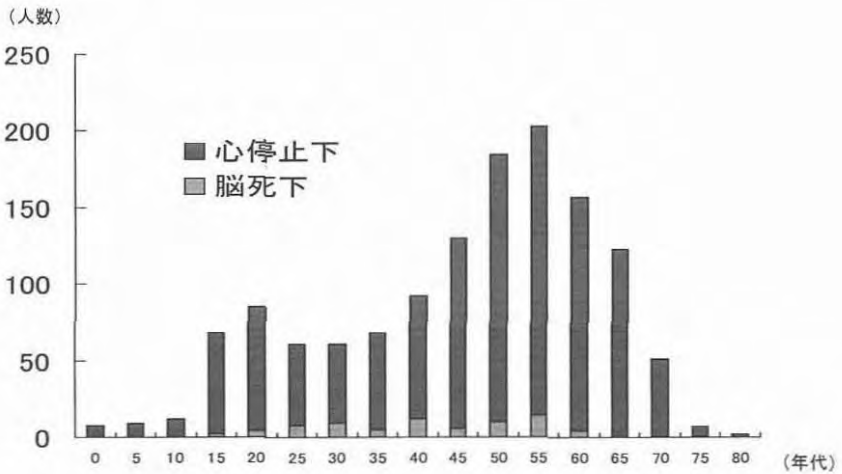
腎臓移植件数・腎臓移植希望者数の推移

（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。

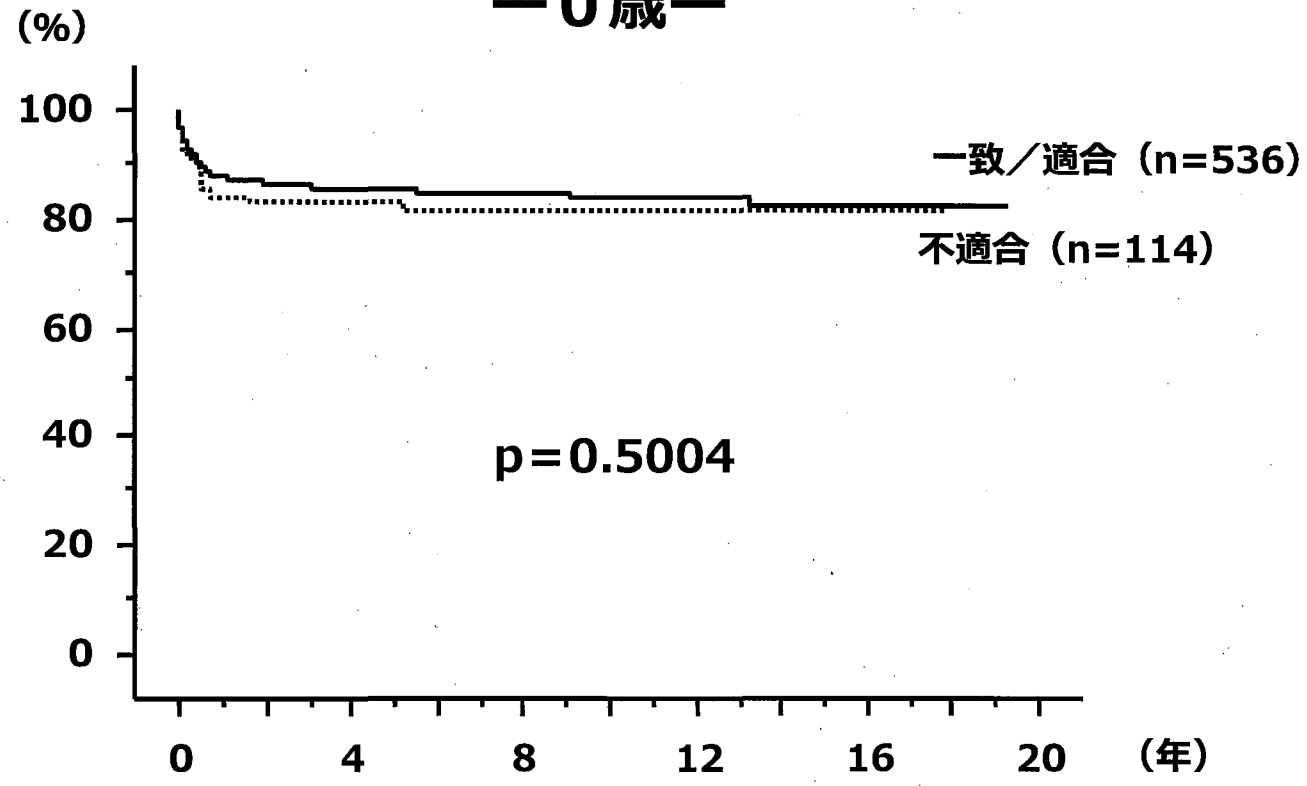
※2 待機期間が 10 年までは 0.5 点／年、11 年～20 年までは 0.25 点／年、20 年以上は 0.125 点／年となるような近似値を log 式とする。

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)

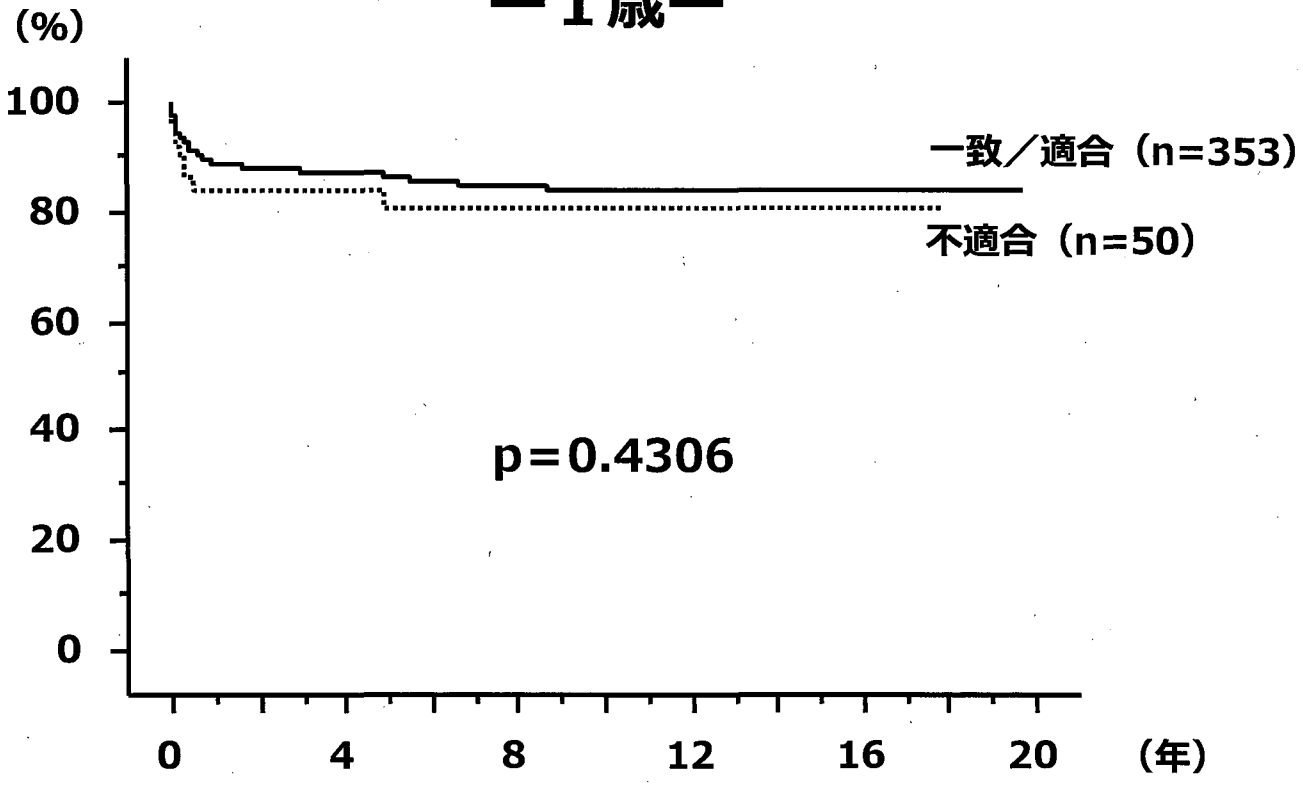
参考資料４

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）

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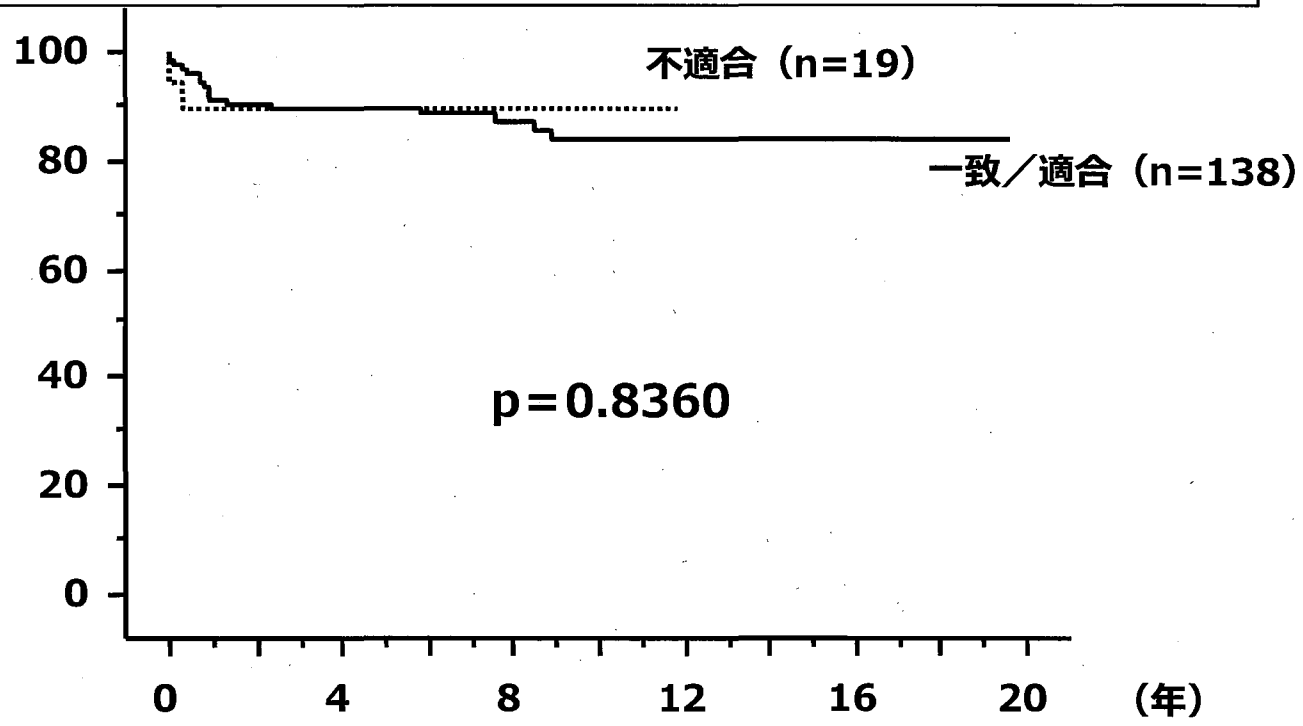

（日本肝移植研究会　2010.11.4）

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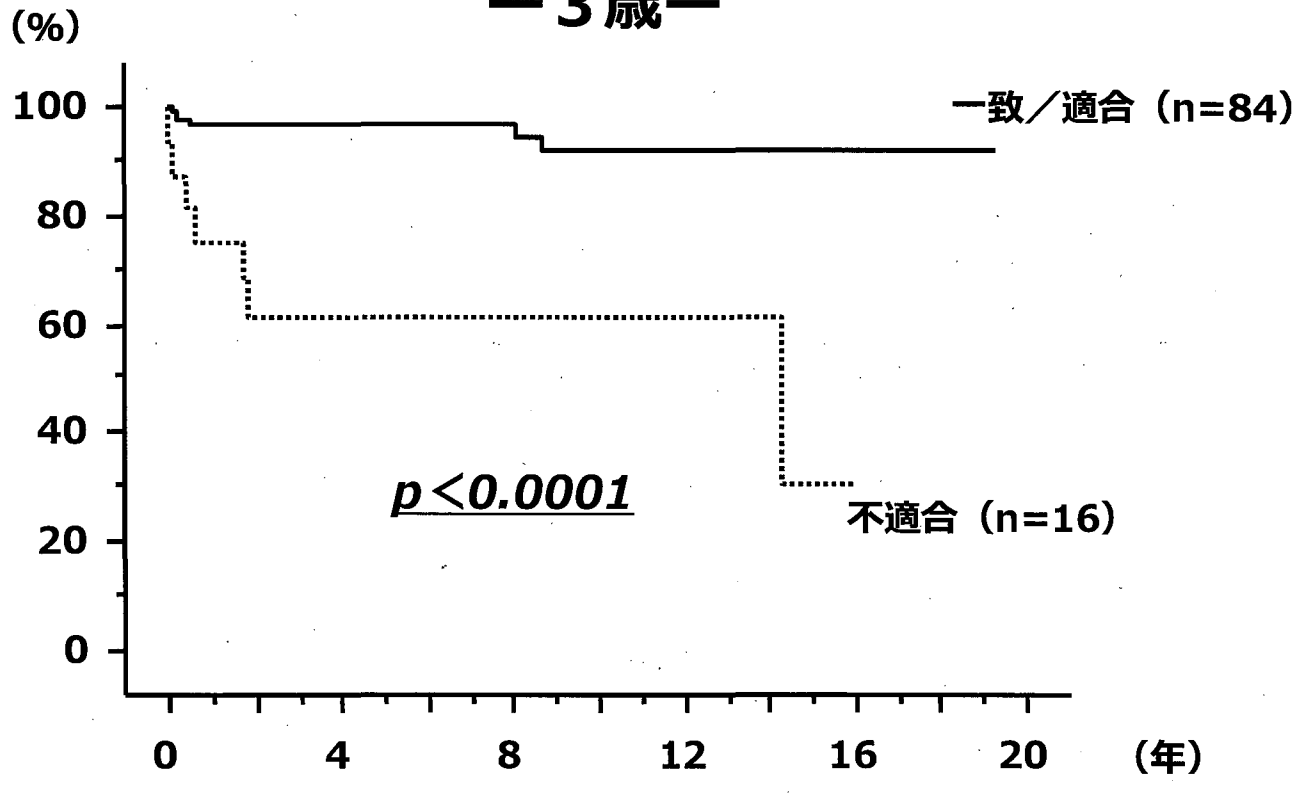
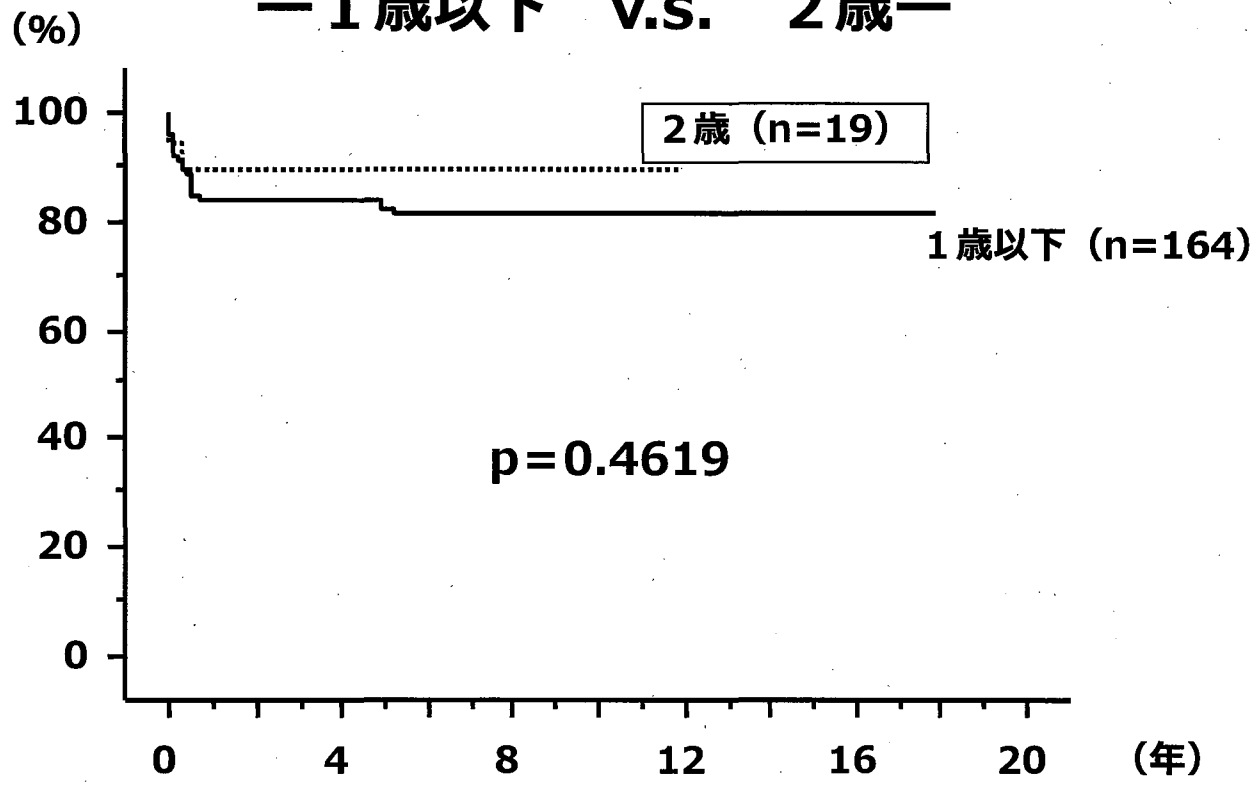


（日本肝移植研究会　2010.11.4）

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）

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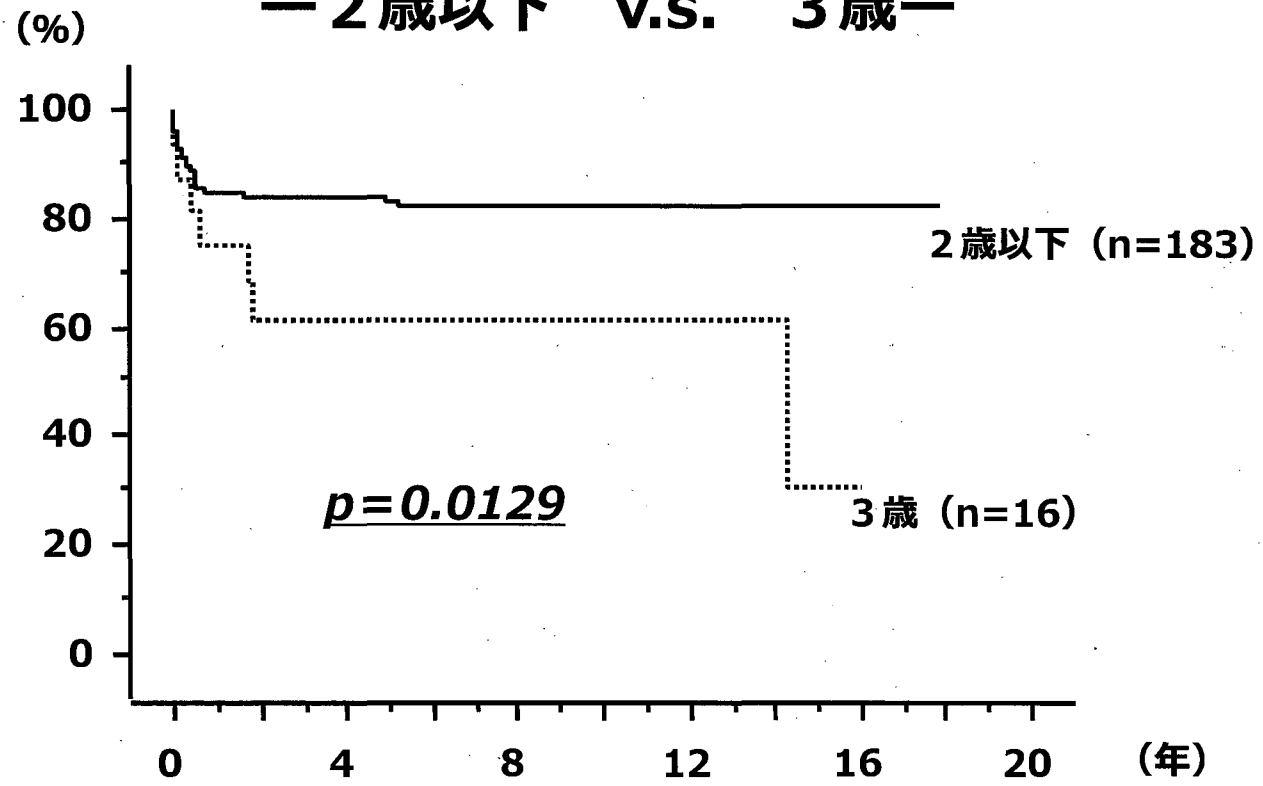
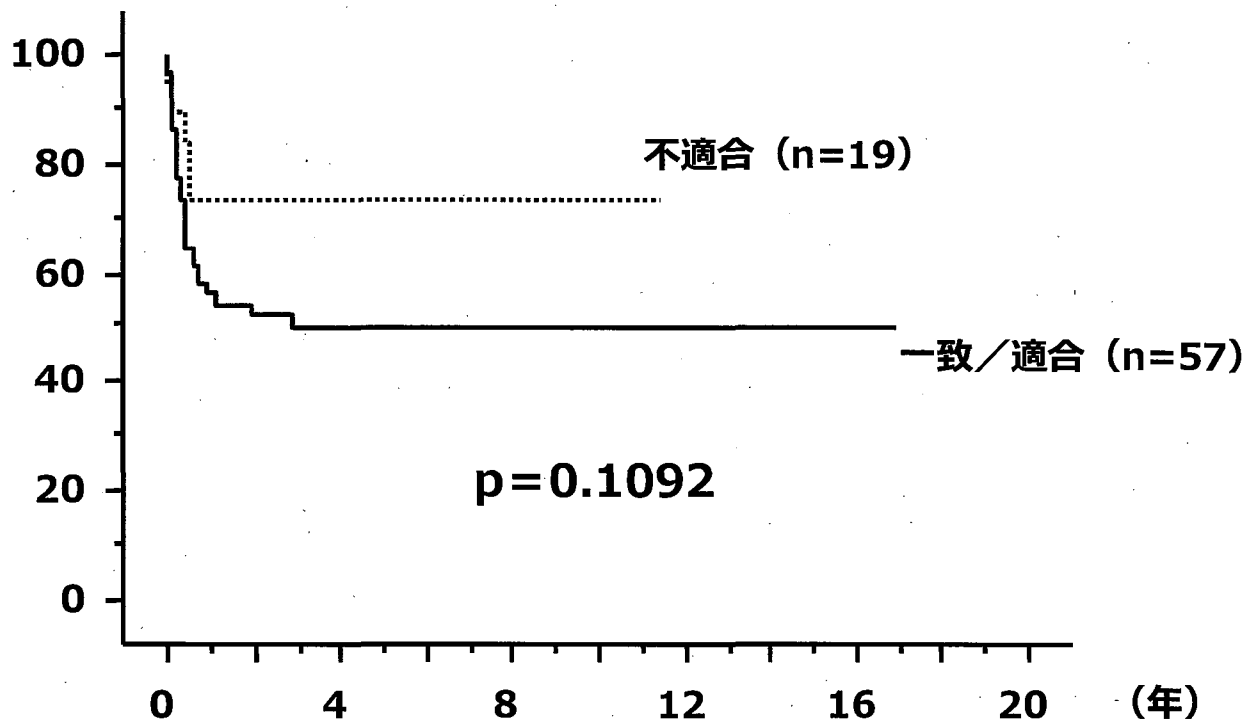


（日本肝移植研究会　2010.11.4）

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）

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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。

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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

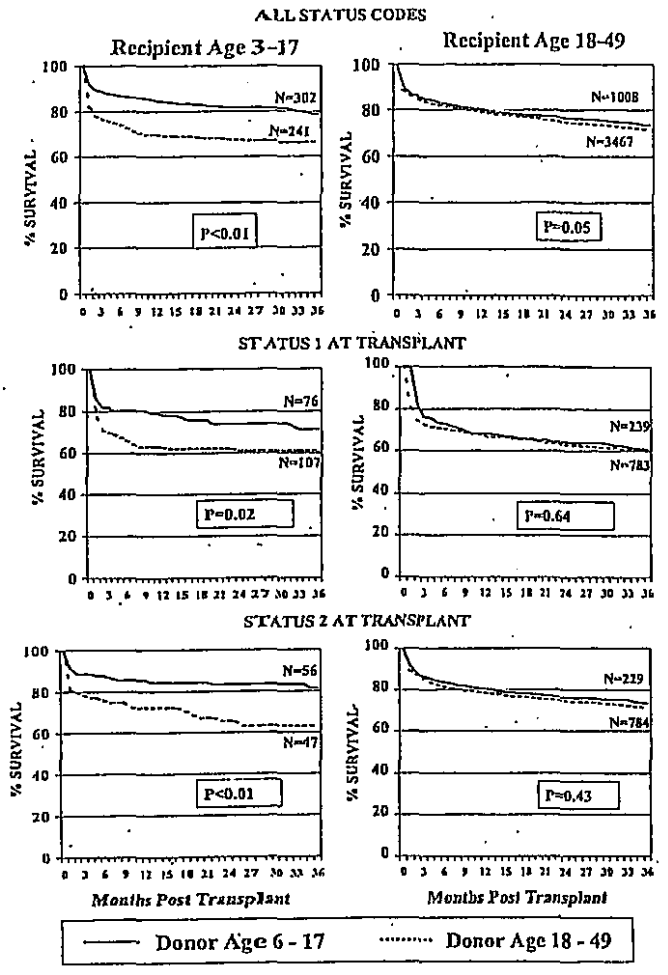

FIGURE 1. The unadjusted Kaplan-Meier 3-year survivals are shown for pediatric recipients (3–17 years) receiving livers from pediatric-aged donors (6–17 years) compared to adult donors (18–49 years) and adult recipients (18–49 years) receiving livers from pediatric aged donors (6–17 years). Results shown 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

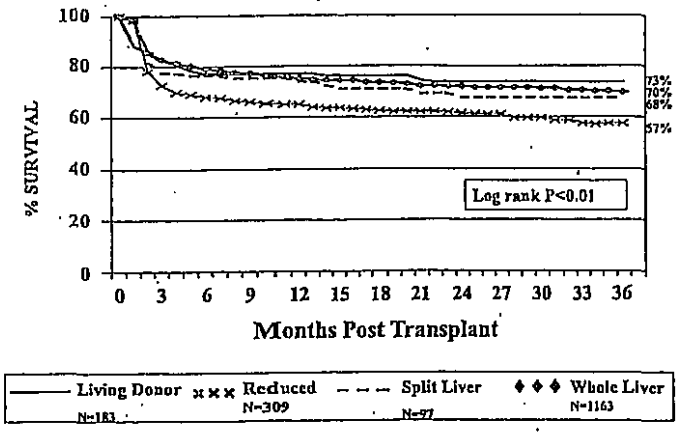

FIGURE 2. The Kaplan-Meier 3-year graft survivals are shown for pediatric recipients of primary liver transplants subdivided by type of organ received.

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.

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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

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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 ≥ 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

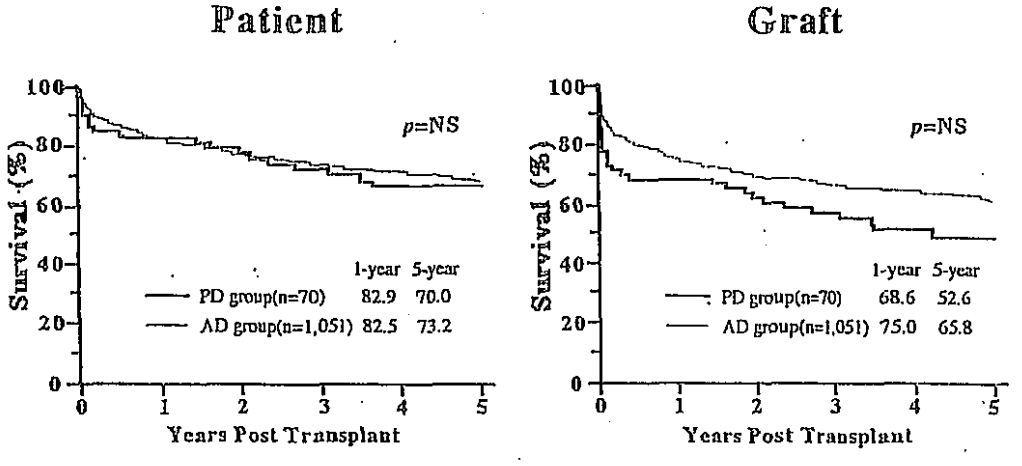

Figure 1. Comparison of patient and graft survival between the PD (n = 70) and AD groups (n = 1,051).

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%).

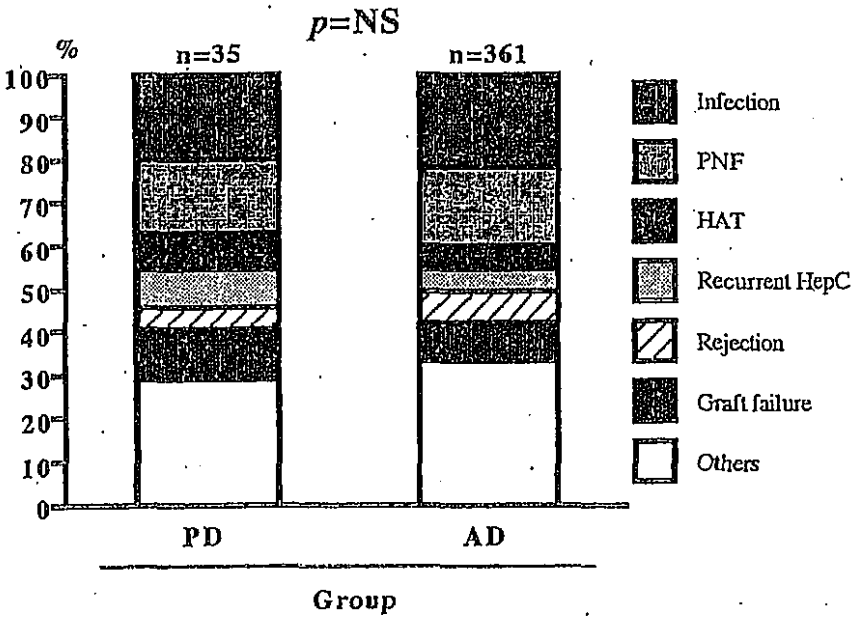

Figure 2. Comparison of causes of graft loss between the PD (n = 70) and AD groups (n = 1,051). (HepC, hepatitis C; NS, not significant.)

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.

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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

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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.

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
Manzabeitia (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		55	0	25	None	56	18
Dodson (1999) [35]	8	HBIG + LAM	46	0		None			8	HBIG + LAM: 7, HBIG: 1	46	1
Prietro (2001) [10]	3	None	29	0	2	None	29	0	25	None	29	15
Manzarbeita (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

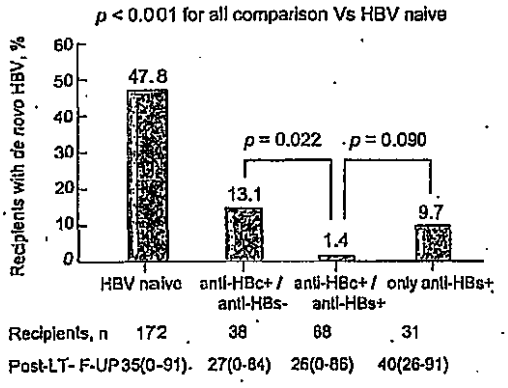

Fig. 1. Risk of *de novo* hepatitis B virus (HBV) infection in HBsAg-negative recipients who received liver grafts from anti-HBc positive donors and no HBV prophylaxis after liver transplantation (LT) in relation to their HBV serological status before transplant.

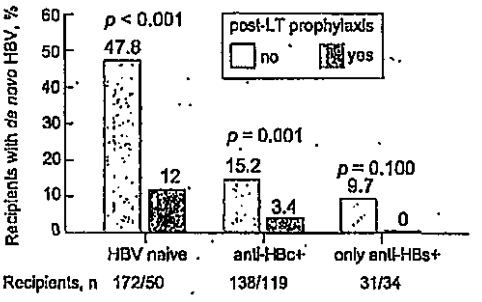

Fig. 2. Risk of *de novo* hepatitis B virus (HBV) infection in HBsAg-negative recipients of liver grafts from anti-HBc positive donors in relation to their pre-transplant HBV serological status and the use of HBV prophylaxis after liver transplantation (LT).

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).

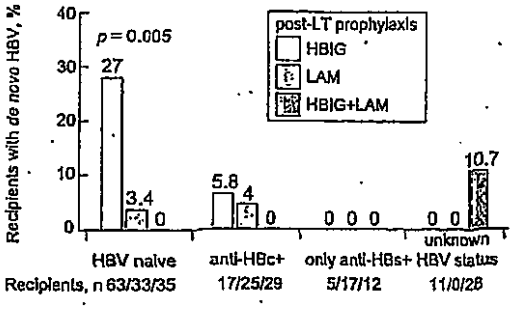

Fig. 3. Risk of *de novo* hepatitis B virus (HBV) infection in HBsAg-negative recipients who received liver grafts from anti-HBc positive donors and HBV prophylaxis after liver transplantation (LT) in relation to their pre-transplant HBV serological status and the type of post-transplant HBV prophylaxis.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

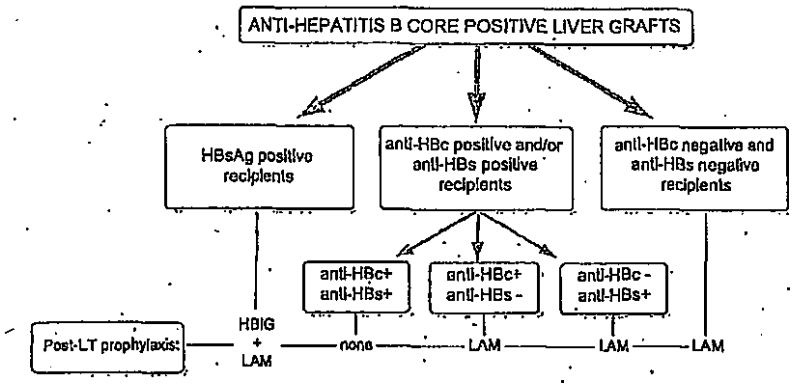

Fig. 4. Proposed algorithm for allocation and management of anti-HBc positive liver grafts. Such grafts should be first offered to HBsAg positive, then to anti-HBc and/or anti-HBs positive and lastly to HBV naive (both anti-HBc and anti-HBs negative) recipients. LT, liver transplantation; HBIG, hepatitis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

Suchiro 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. Suchiro 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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資料3－1

前回の臓器移植委員会（H22.9.6）における
検証方法の見直しに係る議論の概要

迅速化・効率化に係る主な意見

〇家族のグリーフケアの問題はあると思うが、もう少し迅速に対応して、現実に即した検証方法をとった方がよい。

〇検証委員会は1つしかないので、そこで全部をやっていくことは、とてもではないけれどもできないのではないか。もう少し絞ってやるべき。

〇実働部隊を増やさなければいけない。ただし、実働部隊は現場に出ている医者であるから、どのように増やすかというのは大変難しいことになると思う。

〇検証会議の人数を増やすのではなくて、新しい制度を含めて考えるなど、その辺がだいぶ問題になると思う。

〇各地域の3人全部集まって、それが同じ日、同じ時間に行かないと駄目というのは、これは現実的に難しいのではないでしょうか。

過去の経緯に係る主な意見

〇検証委員会というのは、もともと法律ができるときに患者団体として強く要望してつくっていただいた経緯がある。

〇30 例ぐらいを目途にやってはどうかという話があった。この先、いまと同じような形で検証委員会は検証をし続けるのか。

検証結果の分析に係る主な意見

〇全体を合わせていろいろなところに問題点がないか、あるいはこういうところを改善していったらもっとうまくいくのではないかというデータの蓄積が必要ではないか。

〇レスポンシビリティのところが非常にメインになっていましたが、今後はアナライシスのほうも非常に大事ではないか。

資料3－2

脳死下での臓器提供事例に係る検証について

１．これまでの検証結果について

2011 年 1 月末現在において、61 例※の脳死判定事例について検証が終了している。

これまでの検証結果から、初期救急及び全身管理については、全検証事例において、医学的に特に指摘を要するような例はなかった一方、脳死判定については、一部事例において、マニュアルが遵守されていない例や、法令に定める記録の保存年限に係る違反例などが見られた。いずれにしても、全検証事例において医学的な観点からは脳死と判断されたことに特に問題はないと考えられた。あっせん業務については、一部事例において、親族提供に係る本人の意思の確認に関する指摘やレシピエント選択手順の誤り等がみられたが、第 24 例目（H14.12 提供事例）の提供事例後、特に問題が指摘された事項はない。

※脳死下での臓器提供事例に係る検証会議における検証のほか、旧公衆衛生審議会臓器移植専門委員会において検証した 1～4 例目の 4 例を含む。

２．検証結果における具体的な指摘事項とそれを踏まえた対応

（１）医学的検証について

① 脳死下での臓器提供事例について第 1～10 例目まで検証結果を終えた時点で、法的脳死判定について、

ア）無呼吸テストが脳波測定に先立って行われた。(H11.3 提供事例)

イ）カロリックテストをエア・カロリック・テストで代用した。(H11.6 提供事例)

ウ）双極導出での脳波測定を実施しなかった。(H12.3 提供事例)

などといった適切でない手順等がみられた。こういった事例に対し、「法的脳死判定マニュアル」の作成等により、脳死判定手順の標準化を図った。(参考資料 2－1)

② 第 11 例目以降は、一部事例においては、

ア）器質的脳障害を診断するために CT 等による診断がなされていない。(H16.5 提供事例)（参考資料 2－2）

イ）脳死判定における脳波記録を紛失した。(H18.5 提供事例)（参考資料 2－3）

といったマニュアルに定められた手順等に反した事例もあり、その都度、脳死判定記録書等の改訂や、医療機関に対して注意を喚起する通知の発出にて対応を行った。

そのほか、マニュアル上では望ましいとされている範囲を外れるものとして、

ウ）無呼吸テストにおける PaO_2 が低かった。

エ）無呼吸テストの開始時の $PaCO_2$ が 35～45mmHg の範囲外であった。

オ）臨床的脳死判定の脳波測定時の記録時間が 30 分に満たなかった。　等といった点もみられたが、いずれの事例においても、総合的に判断して、医学的な妥当性が保たれていた。

（２）あっせん業務について

あっせん業務の検証については、

ア）レシピエント選定に移植実施施設側の連絡体制が整っておらず、レシピエント選定のための意思確認を終えるまでに長時間を要した。(H12.3 提供事例)

イ）親族に提供したいという本人の意思の確認について、疑問とされた。(H13.7 提供事例)

ウ）膵臓移植希望者（レシピエント）選択基準について、誤った運用が行われた。(H14.12 提供事例)（参考資料 2－4）

などの指摘がみられ、臓器移植委員会での議論を踏まえたガイドラインの改正や、日本臓器移植ネットワークに対して、原因の究明及び再発防止策の策定等により、あっせん機関としての信頼回復に努めることを求める通知発出等を行った。第 24 例目（H14.12 提供事例）後、特に問題は指摘されていない。

３．検証作業の見直しの経緯

1 例目から 4 例目は旧公衆衛生審議会疾病対策部会臓器移植専門員会において、5 例目から 10 例目は脳死下での臓器提供事例に係る検証会議において、一例ずつ、提供施設関係者の出席を得て検証作業を行った。

10 例目までの検証を終えたところで、平成 13 年 10 月 11 日の臓器移植委員会（参考資料 2）において、効果的・効率的、機動的で実務可能な検証システムとする必要があるとして、検証の手続きを改めることとされた。医学的検証については、提供施設で医学的検証作業グループメンバーを交えた検証を行うなど、提供施設とグループの双方の負担を軽減し、特に問題のない事例については検証会議への提供施設関係者の出席を求めないこととされ、より具体的な検証作業については検証会議において議論することとされた。なお、10 例目後のこれまでの検証事例については、全例について医学的検証作業グループのメンバーから初期治療、救命救急、脳死判定（脳波を含む）の 3 つの分野の専門家が提供施設を実地に訪問し検証を行ってきた。

資料3－3

前回の検証会議（H23.1.14）における
検証方法の見直しに係る議論の概要

○脳死判定の手順の標準化等が一定程度なされ、脳死判定マニュアルに定められた手順に反するような事例等が見られなくなってきたこと、及び改正法の施行後に脳死下での提供事例が増加していることに鑑みて、迅速かつ効率的に適切な検証を進めるための見直しが必要。

○医学的検証について

・法改正前からの要件である本人の書面による意思表示ありの事例については、医学的検証作業グループ会議において、事前に臓器提供施設から提供を受けた資料をもとに、実地訪問の必要性について検討し、必要がないと判断した事例については、実地訪問を行わず、提供資料を用いて検証を行う。

・法改正により新たに可能となった家族承諾による提供事例については、当面従来通りの方法で実地訪問を行った上で検証を行い、10 例程度検証を終えた時点で、改めて、その取り扱いについて再度検討する。

・小児（15 歳未満）からの提供事例については、当分の間、従来通りの方法で実地訪問を行った上で検証を行うこととする。

○なお、あっせん業務の検証については、当面従来通りの方法で、検証作業を行うこととする。

○マニュアルに反する事例等については、通知発出等の個別の対応に加え、今後は、1 年に 1 回程度、検証状況・結果のとりまとめを行い、臓器移植委員会へ報告し、検証作業の在り方等について必要に応じ、適宜見直しを行う。

　併せて、上記の検証状況・結果のとりまとめについて、広く臓器移植に関係する者に周知を図るため、新たに関係学会等に情報提供を行うことが望ましい。

参考資料１

脳死下での臓器提供事例に係る検証会議

１．開催趣旨

臓器移植が一般の医療として国民の間に定着するまでの暫定的措置として、厚生労働大臣が有識者に参集を求めて、脳死下での臓器提供に係る検証作業を行う検証会議を開催する。

２．検証事項

検証会議においては、以下の事項について検証を行う。

（１）　医学的検証

○臓器提供者に対する救命治療の状況

○臓器提供者に対する脳死とされうる状態の診断、法的脳死判定から臓器摘出に至るまでの状況

（２）　あっせん業務

（社）日本臓器移植ネットワークの行ったあっせん業務の状況（臓器提供者の家族に対するケアの状況を含む。）

３．開催実績

平成１２年３月の第１回開催以来、過去３３回開催し、第５例目から第６１例目の事例について検証。（直近開催：平成２３年１月１４日）

会議は非公開。報告書の公開はご遺族に確認し、承諾を得た場合に行う。

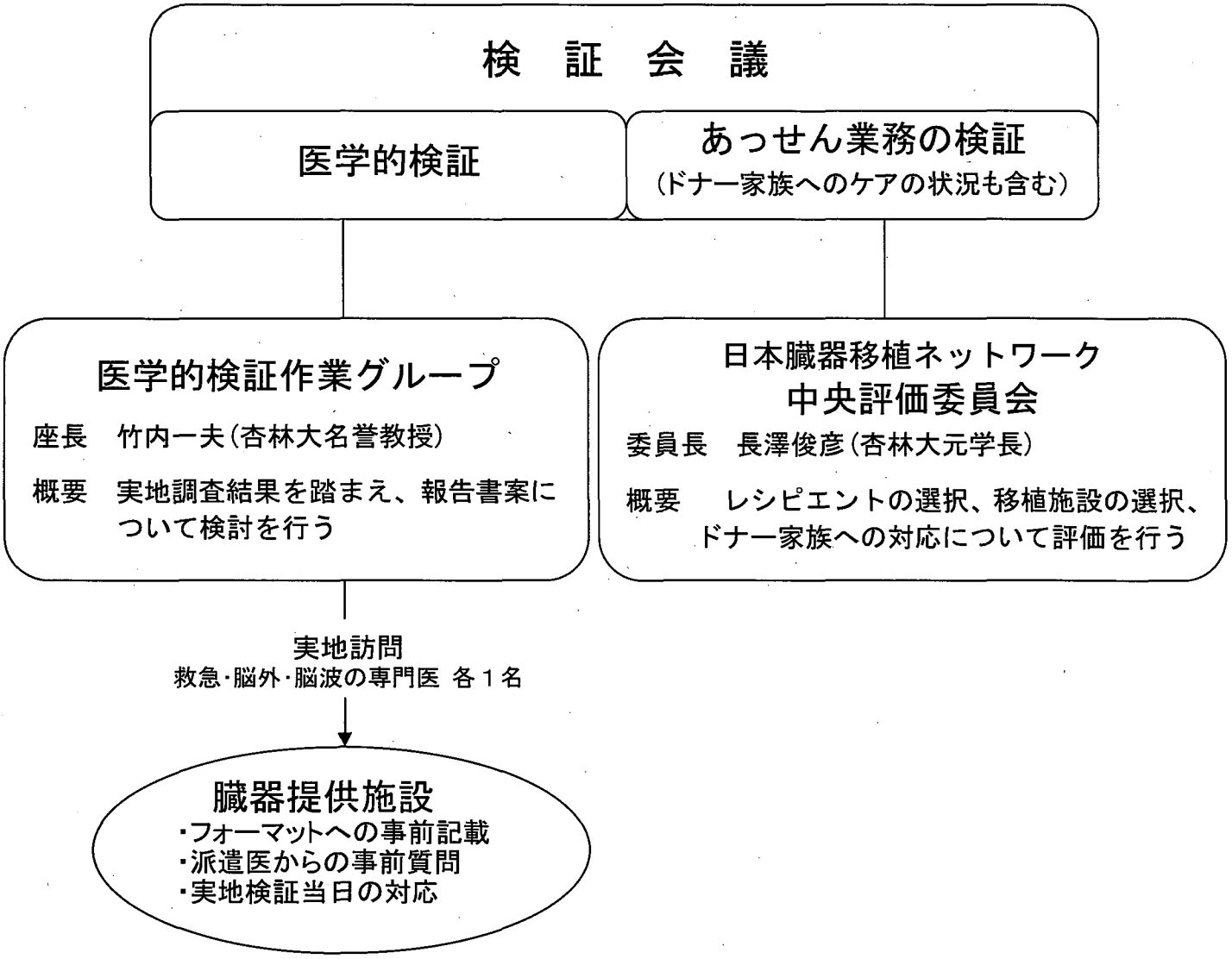
４．検証会議メンバー　（５０音順／敬称略。○：座長）

- 宇都木伸（東海大学法学部教授）
- 川口和子（全国心臓病の子供を守る会幹事）
- 吉川武彦（中部学院大学大学院研究科長・教授）
- 高杉敬久（（社）日本医師会常任理事）
- 島崎修次（杏林大学医学部教授）
- 竹内一夫（杏林大学名誉教授）
- アルフォンス・デーケン（上智大学名誉教授）
- 新美育文（明治大学法学部教授）
- 貫井英明（山梨大学名誉教授）
- 藤森和美（武蔵野大学人間関係学部教授）

○　藤原研司（（独）労働者健康福祉機構横浜労災病院名誉院長）

- 柳田邦男（作家・評論家）

（参考）　現行の検証作業


検　証　会　議
医学的検証
あっせん業務の検証
（ドナー家族へのケアの状況も含む）
医学的検証作業グループ
座長　竹内一夫（杏林大名誉教授）
概要　実地調査結果を踏まえ、報告書案について検討を行う
日本臓器移植ネットワーク
中央評価委員会
委員長　長澤俊彦（杏林大元学長）
概要　レシピエントの選択、移植施設の選択、ドナー家族への対応について評価を行う
実地訪問
救急・脳外・脳波の専門医 各１名
臓器提供施設
・フォーマットへの事前記載
・派遣医からの事前質問
・実地検証当日の対応

参考資料２－１

健医疾発第５８号
平成１２年６月１４日

各臓器提供施設長　殿

厚生省保健医療局エイズ疾病対策課長

臓器の移植に関する法律の規定による脳死判定のための検査の適正な実施について

臓器移植の推進につきましては平素から御高配を賜り、厚く御礼申し上げます。

さて、臓器の移植に関する法律（平成９年法律第１０９号）の規定による脳死判定（以下「法的脳死判定」という。）の個々の検査の手法につきましては、「『臓器の移植に関する法律』の運用に関する指針（ガイドライン）」において、「法的脳死判定マニュアル」（厚生省厚生科学研究費特別研究事業「脳死判定手順に関する研究班」平成１１年度報告書。以下「マニュアル」という。）に準拠して行うこととしております。

先般、第５例目の脳死下での臓器提供事例についての「脳死下での臓器提供事例に係る検証会議」（別紙参照）での検証過程において、法的脳死判定のために行うべき平坦脳波の確認のための脳波検査の方法が一部マニュアルに準拠していないことが判明したところです。

貴施設におかれましては、マニュアルに準拠した適正な法的脳死判定のための検査が行われるよう、個々の検査に際し実施すべき事項に係るチェックリストを作成し当該チェックリストに基づいて実施した検査を確認するなど検査の適正な実施を確保するための体制の整備を行うよう、よろしくお願い申し上げます。

「法的脳死判定マニュアル」（抜粋）

厚生省厚生科学研究費特別研究事業「脳死判定手順に関する研究班」平成１１年度報告書

X　脳死判定の順序

1 必要書面の確認

1）意思表示カード等、脳死の判定に従い、かつ臓器を提供する意思を示している本人の書面

2）脳死判定承諾書（家族がいない場合を除く）

3）臓器摘出承諾書（家族がいない場合を除く）

2 前提条件の確認

3 除外例の確認

4 生命徴候の確認

5 深昏睡の確認

6 瞳孔散大、固定の確認

7 脳幹反射消失の確認

8 平坦脳波の確認

➲聴性脳幹誘発反応消失の確認：必須条件ではないが行うことが望ましい。

➲6、7、8の相互の順序は問わない。

9 自発呼吸消失の確認（必ず5～8の確認の後に実施する）

10 脳死判定記録の確認

1）脳死判定の的確実施の証明書（☞参考資料4、本書p.215）

2）脳死判定記録書（☞参考資料5、本書p.217）

3）脳死判定の検査結果について、診療録に記載し又は当該記録の写しを貼付する。

5 前庭反射

1) 観察方法

①耳鏡により両側の鼓膜に損傷のないことを確認する。

②被験者の頭部を約30°挙上させる。

③被験側の耳の下に氷水を受けるための腎盆をあてる。

④50mℓの注射筒に氷水を吸引し、カテーテルを接続する。

⑤被験側外耳道内にカテーテルを挿入する。

⑥両側上眼瞼を挙上し、両眼の観察を可能にする。

⑦氷水の注入を開始する。

⑧氷水注入は20～30秒かけて行う。

⑨眼球が氷水注入側に偏位するか否かを観察する。

⑩50mℓの注入が終わるまで観察する。

⑪同様の操作を両側で行う。

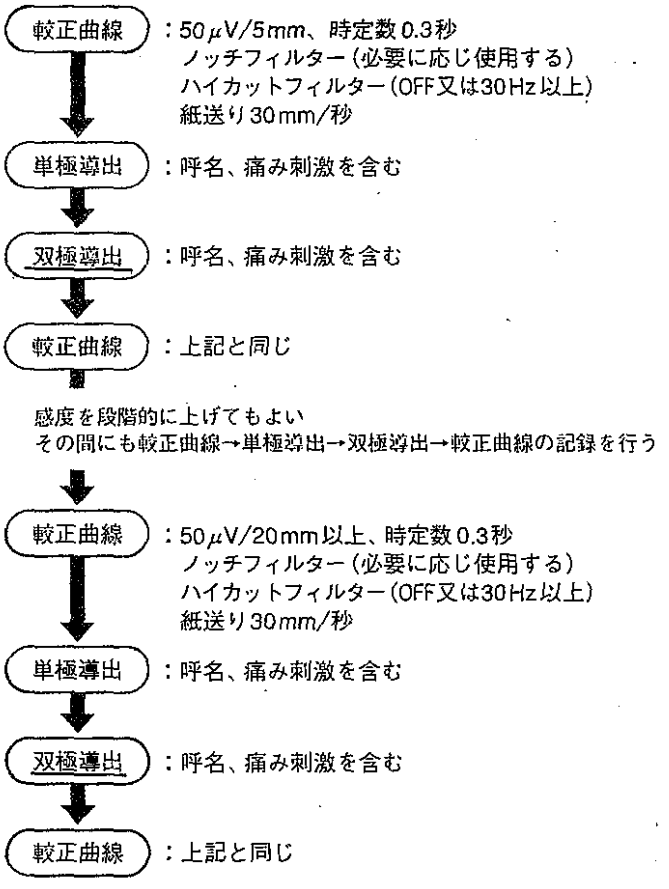
2) 判定方法

①両側の外耳道への刺激で、眼球偏位が認められない時のみ前庭反射なしと判定する。

②明らかな偏位ではなくても刺激に応じて眼球の動きが認められた場合は前庭反射ありと判定する。

備考

- 前庭反射の消失を確認する時は、氷水刺激によるものとし、通常耳鼻科領域等で用いられている20℃の冷水刺激検査、あるいは体温±7℃の温水と冷水を用いた冷温交互刺激検査とは異なる。
- 温度刺激検査において、冷風、温風を用いた「エアー・カロリック・テスト」については、現在承認されている機器では、温度刺激が十分でない可能性があるため、脳死判定には用いない。



※脳波の記録時間は全体で30分以上必要である。

図1-6　脳波記録の手順例

参考資料２－２

健臓発第1101002号
平成１７年１１月２日

各臓器提供施設長　殿

厚生労働省健康局疾病対策課
臓器移植対策室長

臓器の移植に関する法律の規定による脳死判定のための検査の適正な実施等について

臓器移植の推進につきましては、平素から御高配を賜り、厚く御礼申し上げます。

さて、臓器の移植に関する法律（平成９年法律第１０４号）の規定による脳死判定（以下「法的脳死判定」という。）の個々の検査の手法につきましては、「『臓器の移植に関する法律』の運用に関する指針（ガイドライン）」において、「法的脳死判定マニュアル」（厚生省厚生科学研究費特別研究事業「脳死判定手順に関する研究班」平成１１年度報告書。以下「マニュアル」という。）に準拠して行うこととしております。

先般、「第２２回脳死下での臓器提供事例に係る検証会議」における第３０例目の提供事例の検証過程において、ＣＴ等の画像診断が行われていない等、検査の方法が一部マニュアルに準拠していなかったことが判明しました。（別紙参照）

移植医療についての国民の理解を深めていくためには、法的脳死判定が適正に実施されることが不可欠であります。

つきましては、貴施設におかれては、マニュアルに準拠して法的脳死判定を実施されるよう、改めて万全を期されたくよろしくお願いします。

また、脳死判定の記録等について、これまで脳死判定の記録等に記載すべき内容を盛り込んだ書式例を参考として示してきたところですが、法的脳死判定の適正な実施に資する観点から、今般、脳死判定の的確実施の証明書書式例及び脳死判定記録書式例に、ＣＴ等の画像診断等の前提条件に関する事項を追加することとし、別添の通り改めましたので御活用下さい。

別紙

第２２回脳死下での臓器提供事例に係る検証会議
概要（平成17年９月30日）

第３０例目の提供事例に係る脳死判定について、

① 本事例については、経過中にＣＴ等の頭部の画像診断が行われておらず、「法的脳死判定マニュアル」においては器質的脳障害の診断等のためにＣＴ等が必須とされていることを踏まえれば、この手順が厳守されていなかったことは適切ではないが、臨床経過、症状から医学的に脳の二次性の器質的病変があることは間違いなく、法的に脳死と判定したことは妥当である。

しかしながら、法に基づく脳死判定の実施に際して満たすべき前提条件として、器質的脳障害の確認のためにＣＴ等の頭部画像診断が行われていなかったことは適切でなく、「法的脳死判定マニュアル」に則って行うべきである。

② また、無呼吸テストに関して、本事例では、テスト開始後の最初の動脈血ガス分析を１回目は９分後、２回目は７分後に行っている。SpO2、血圧ともに著変を認めず、不整脈等の出現も認めなかったものの、「法的脳死判定マニュアル」に定められたように、２～３分ごとの時間間隔で動脈血ガス分析を行うことが望ましかった。

参考資料２－３

健臓発0801002号
平成１９年８月１日

各臓器提供施設長　殿

厚生労働省健康局疾病対策課
臓器移植対策室長

臓器の移植に関する法律の規定による脳死判定に関する記録の管理等について

臓器移植の推進につきましては、平素から御高配を賜り、厚く御礼申し上げます。

さて、臓器の移植に関する法律（平成９年法律第１０４号）の規定による脳死判定（以下「法的脳死判定」という。）に関する記録につきましては、同法第１０条で医師による作成義務及び５年間の保存義務を規定しています。また、臓器の移植に関する法律施行規則（平成９年厚生省令第７８号）第５条では、法的脳死判定に当たって測定した脳波の記録は、脳死判定に関する記録に添付することが義務付けられています。

先般、「脳死下での臓器提供事例に係る検証会議」の検証過程で、第４６例目の臓器提供施設における脳波の記録の紛失が判明しました。

臓器の移植に関する法律では、法的脳死判定が適正に行われたか等について事後的に確認することができるよう、臓器の移植に関する一連の記録の作成及び保存を義務付けており、このような事態はあってはならないことです。

貴施設におかれては、脳死下での臓器提供に係る施設内の体制について改めて確認を行い、一連の記録の作成や保存に係る手順及び体制について万全を期すとともに、職員に対する徹底を図られるようお願いいたします。

（参考１）

第 46 例目の臓器提供施設が脳波記録の紛失に関して設置した調査委員会の報告では、法的脳死判定における脳波記録紛失の原因について、次のように指摘している。

・脳死判定委員会に関する要綱においては，脳波記録等の関係書類がどのように流れ，どの部署で保管するかが明記されておらず，今回の事件が発生したものと考察される。

・脳死判定委員会開催前までは，法的脳死判定の２回分の脳波記録は，集中治療部カンファレンスルームの机上に置かれていたことが確認されている。適切な管理がないまま，脳波記録が置かれていた場合，それが脳死下での臓器提供事例の際に記録されたものと理解されないまま，破棄された可能性が高いと推測された。

・平成１１年７月に脳死下での臓器提供事例におけるシミュレーションを実施したが，脳波記録の保管までは訓練していなかった。この点を補完するため，平成１８年度に脳死下での臓器提供事例におけるより詳細なシミュレーションを計画していた矢先に本件事例が発生し，関係者が不慣れであったことも原因の１つと推測される。

参考資料２－４

厚生労働省発健第 0325001 号
平成１７年３月２５日

社団法人日本臓器移植ネットワーク
理事長　筧　榮一　殿

厚生労働大臣

あっせん機関の業務に関する指示

貴社団法人日本臓器移植ネットワーク（以下「貴法人」という。）において、膵臓移植希望者（レシピエント）の選択について不適切な運用が行われていたとの報告を受けたところであるが、「臓器の移植に関する法律」（平成９年法律第１０４号）（以下「臓器移植法」という。）を適正に運用するために、貴法人の業務に関し下記のとおり改善の必要性が認められるので、必要な措置を講じた上で、改善状況を平成１７年４月２５日までに文書にて報告されたい。

記

平成１７年３月１７日に貴法人より、平成１４年１２月下旬に行われた第２４例目の脳死判定事例（第２３例目の脳死下臓器提供事例）の際、膵腎同時移植希望者が選択されたものの、臓器摘出手術の開始以降に膵臓が移植に適さないことが判明した場合には、まず、膵臓移植希望者（レシピエント）選択基準で選ばれた当該膵腎同時移植希望者に対して腎臓のみの移植の希望の有無を確認すべきであったにもかかわらず、当該膵腎同時移植希望者に対するこの確認を怠り、腎臓移植希望者（レシピエント）選択基準で選ばれた者に腎臓を提供していたことについて報告を受けたところである。

移植希望者の選択基準については、移植の実効性を担保し、移植機会の公平性を確保するために適正に運用しなければならないものであり、このような事態は、臓器移植法第２条に規定する臓器移植の基本理念に照らして非常に重大な問題である。

このため、今後は臓器移植法及び関係法令を遵守し、その趣旨を十分踏まえて業務を行うこととするとともに、以下の措置を講じられたい。

(1) 膵臓移植希望者（レシピエント）選択基準に関して不適切な運用が行われていたことについて、徹底した原因究明を行うこと

(2) 膵臓移植希望者（レシピエント）選択基準について熟知するとともに、職員に対する周知徹底を行うこと

(3) 今後、同様の事態が再び起こることがないよう、再発防止策を策定し、臓器のあっせん機関としての信頼回復に努めること

参考資料３
（第４回臓器移植委員会（H13.10.11）資料からの抜粋）

検証の在り方の見直しの考え方

＜基本的なスタンス＞

・　移植医療に対する国民の信頼を一層深める観点から、これまで「脳死下での臓器提供事例に係る検証会議」において行ってきた医学的検証、あっせん業務等の検証を総合的に、かつ、当該分野以外の有識者も加わる形で行えるよう、脳死下移植事例について引き続き同会議における検証を行う。

・　同時に、移植医療が徐々に定着しつつあること、今後移植数の増加が予想されるなか効果的・効率的、機動的で実務可能な検証システムとする必要があることから、今般、具体的な検証の手続き等については改める（より具体的な検証作業については検証会議において議論）。

・　今後、個別事例に係る検証結果や事例数の積重ね・動向等、必要に応じて適宜検証の在り方については見直すものとする。

＜個別見直し事項の考え方＞

１．　医学的検証について

・　臓器提供施設における事例関連データを当該施設以外の専門家が調査ができるよう、引き続き医学的検証作業グループ（竹内一夫班長）を置く。

・　なお、グループの増員を図り機動性を強化するとともに、あらかじめ検証会議への提出報告書（案）様式を提供施設に示し、例えば提供施設でグループメンバーを交えた検証を行うなど、提供施設とグループの双方の負担を軽減する。また、特に問題ない事例については検証会議への提供施設関係者の出席を求めない。

２．　あっせん業務の検証について

・　(社)日本臓器移植ネットワークの中央評価委員会における評価結果をも活用し、検証会議での作業の効率化を図る。

今後の脳死下での臓器提供に係る検証の在り方について（案）

これまでの検証会議についての考え方

医学的検証（参考１）	臓器あっせん業務の検証	ドナー家族の心理的ケア
① 昨今の事例においては、検証の成果もあり問題がほとんどなくなってきた。 ② しかし、事例が増加する中で、問題ケースの発生、又は脳死判定中止事例のような、手順検討が必要な事例が発生することがありうるのではないか。 ③ 国民の信頼を確保する必要性あり。	① 第15例目のようなあっせんに関する問題は起こりうる。 ② ネットワークが全事例の検証を行うが、別途、精査が必要な事例については、公平・公正の観点から検証を付加してはどうか。 ③ 国民の信頼を確保する必要性あり。	① ドナー家族の心情把握については、 a 事例発生後早速行うことが必ずしも適当でない。 b ある程度継続的フォローアップが必要。 ② 心理的ケアについては、精神医学的な研究、対応策も必要。

あらかじめ提供施設に報告書フォーマットを送付し、報告書（案）作成を依頼し、作業班メンバーで検証確認。

臓器提供施設と作業班メンバーで調整の上、提供病院内に作業班員が参加する形も。

（社）日本臓器移植ネットワークの中央評価委員会（参考２）であっせん業務に関する検証を行う。

評価委員会としての結論を報告

①臨床的アプローチについては「ドナー家族の心情把握等班」」（個別対応として問題事例は検証会議に報告）

②ドナー家族からの提言や研究班としての政策的示唆を臓器移植委員会に報告

検証会議（厚生労働大臣の検討会）

ドナー家族の心情把握等班

新たなルールの検討が必要な場合には検証会議から委員会へ提言

厚生科学審議会疾病対策部会臓器移植委員会

参考資料４

脳死下での臓器提供事例に係る検証作業進捗状況

○累積事例数　　平成23年1月19日現在

脳死下での臓器提供事例	117例
脳死判定事例	118例
検証会議終了事例	61例

○年別事例数　　平成23年1月19日現在

年	臓器提供数	検証実施数
平成9年	－	－
平成10年	－	－
平成11年	4	4（公衆衛生審議会）
平成12年	5	3
平成13年	8	3
平成14年	6	9
平成15年	3	2
平成16年	5	6
平成17年	9	4
平成18年	10	6
平成19年	13	11
平成20年	13	3
平成21年	7	4
平成22年	32	3
平成23年	2	3
合計	117	61

資料４

日本脳神経外科学会の専門医訓練施設について

１．臓器提供施設について

脳死下での臓器提供施設については、「「臓器の移植に関する法律」の運用に関する指針（ガイドライン）第４」において、その施設要件（５類型（※）その他の要件）を規定している。

※５類型

- 大学附属病院
- 日本救急医学会の指導医指定施設
- 日本脳神経外科学会の専門医訓練施設（Ａ項）

（注）Ａ項とは、専門医訓練施設のうち、指導に当たる医師、症例数等において特に充実した施設。

- 救命救急センターとして認定された施設
- 日本小児総合医療施設協議会の会員施設

２．日本脳神経外科学会の専門医研修に係る施設類型の変更について

日本脳神経外科学会の専門医制度の見直しに伴い、専門医訓練施設についても従来のＡ項及びＣ項の分類から、基幹施設、研修施設及び関連施設の３つの分類に改められた。なお、新しい制度は、平成２３年４月以降適用することとなり、新たなＡ項としての認定はなくなる。

（参考：施設数）　Ａ項：385 施設　Ｃ項：736 施設　（H22.10.4 現在）

３．暫定措置について

日本脳神経外科学会の専門医研修に係る施設類型の変更に伴い、今後臓器提供施設に係るガイドラインの規定ぶりを変更するまでの間、暫定的な措置として、以下のように取り扱ってはどうか。

≪暫定措置≫

平成２３年３月３１日現在において日本脳神経外科学会の専門医訓練施設（Ａ項）と認定されている施設については、当面の間、「「臓器の移植に関する法律」の運用に関する指針（ガイドライン）」における取扱いは、なお従前の例によることとする。

（参考）

専門医訓練施設について（日本脳神経外科学会ＨＰより抜粋）

　下記「指定の基準」のＡ，Ｂを満たす施設をＡ項、Ｃを満たす施設をＣ項としている。

指定の基準

Ａ　原則として年間脳神経外科手術１００例以上（そのうち中枢神経系の腫瘍・動脈瘤・動静脈奇形の直接手術、併せて３０例以上。その内訳は、少なくとも腫瘍１０例以上、動脈瘤・動静脈奇形１０例以上を含む）を行う施設。

Ｂ　当該施設においては専門医が２名以上おり、脳神経外科学的診断に必要な諸設備を有し、定期的にカンファレンス（臨床、C.P.C.（事務局注：臨床病理カンファレンス。病理解剖の後、主治医と剖検担当者を含めてカンファレンスを行うこと。）関連学科のセミナール等）を行い、原則として脳神経外科疾患の剖検率が３０％以上であることを要する。なお、専門医訓練場所として指定を受けようとするときには通算６年間の研修カリキュラムを専門医認定委員会に提出しなければならない。[註]

Ｃ　Ａの条件を満たし得ない施設も、専門医が１名以上おり、年間脳神経外科手術３０例以上行う施設は、すでに指定を受けた他の訓練場所における訓練の一環として指定訓練場所と同等の取扱いを受けることができる。ただしこの場合、すでに指定を受けた訓練場所の長は、当該施設の特色、同施設内での訓練の内容、期間等について専門医認定委員会の承認を得るものとする。

[註]Ａ項病院は単独または他のＡ項あるいはＣ項病院を関連施設として研修カリキュラムを組み訓練に当たることができる。

指定の方法

　上記訓練場所の指定は専門医認定委員会が毎年に行うのを原則とする。ただし指定
希望の申し出により随時審査を行うことができる。

基幹施設、研修施設及び関連施設について
（日本脳神経外科学会　専門医認定制度内規より抜粋）

第６条　研修プログラム（病院群）は第７条から第９条に定める基幹施設（単一）、研修施設（複数可）、関連施設（複数可）で構成され、研修プログラム審査委員会において審議のうえ認定委員会にて承認する。
２　（以下略）

第７条　基幹施設は特定機能病院または以下の条件を満たす施設とする。
（１）　原則として年間手術症例数が２００以上
（２）　１名のプログラム責任者（第 10 条で定める指導医の資格を持った部門長、診療責任者ないしはこれに準ずるもの）と３名以上の指導医がいる。ただし、プログラム責任者と指導医の兼務は不可とする。
（３）　他診療科とのカンファレンスを定期的に開催
２　基幹施設は、研修施設と関連施設を指導し、別に定める推奨カリキュラムに従った専門医研修教育を行う。
３　プログラム責任者はプログラム全体の指導体制、内容、評価に関し監督責任を持つと同時に、当該基幹施設においては指導管理責任者としてその指導体制、内容、評価に関しても責任を持つ。
４　基幹施設は他の研修プログラムへの参加は関連施設としてのみ認められ、研修施設として参加することはできない。

第８条　研修施設は、以下の条件を満たす施設とする。
（１）　１名の指導管理責任者（指導医の資格を持った診療科長ないしはこれに準ずるもの）と２名以上の指導医をおく。ただし指導管理責任者と指導医の兼務は可とする。
（２）　症例検討会を開催
２　指導管理責任者は当該研修施設での指導体制、内容、評価に関し責任を持つ。
３　研修施設は他の研修プログラムへの参加は関連施設としてのみ認められ、複数の研修プログラムに研修施設として参加することはできない。

第９条　関連施設はプログラム責任者が基幹施設・研修施設だけでは研修が不十分と判断した場合、これを補完するためにその責任をもって指定する。
２　関連施設の要件は特に定めないが、関連施設での研修は原則として１年を超えないものとする。

資料5

今後の検討課題について（案）

1　臓器提供施設に対する支援について

（1）体制整備に関する支援

・脳死判定マニュアル、提供施設マニュアルの整備（厚生労働科学研究）

・日本臓器移植ネットワーク等による支援

（2）臓器提供に係る手続きの負担軽減

・学会専門医によるコンサルト体制

2　ドナー家族の心のケアについて

（1）日本臓器移植ネットワークの体制強化

・コーディネーターの増員、研修の充実

・精神科医によるコーディネーターの支援

（2）ドナー家族ケアの充実

・家族ケア専任コーディネーターの設置

・ドナー家族専用の相談ダイヤルの設置

3　コーディネーターの教育等

（1）新しいコーディネーターの確保・育成

（2）コーディネーターの知識や技能の向上

4　普及啓発等

（1）対象者選定とアプローチ方法・内容

（2）意思表示を行っていただくための意思表示方法の普及方策

5　その他

（1）レシピエント選択基準等の定期的な見直し

（2）角膜移植に係る技術指針

資料6－1

臓器提供者（ドナー）家族に対する心のケアについて

1　これまでの取組状況

（1）（社）日本臓器移植ネットワークのコーディネーターによる対応
- 臓器提供を担当したコーディネーターが対応(原則提供後1年まで3～5回)
- 葬儀参列、自宅訪問（経過報告、大臣感謝状や手紙持参）、電話報告など
- コーディネーターには、毎年1回研修を行い、能力向上を図っている。

（2）厚生労働省における対応
- ドナー家族に対する感謝状（厚生労働大臣名）
- ドナー家族の集いにおける大臣挨拶（代読）

（3）脳死下での臓器提供に係る検証会議
あっせん業務に関する検証の中で「ドナー家族へのケアの状況」も取り扱う

2　法改正を踏まえた取組（平成２２年度予算）

（1）日本臓器移植ネットワークの医療専門職として、メンタルヘルスや患者遺族族のケアを専門とする精神科医を1名配置し、ドナー家族のケア等を担当。

（2）ドナー家族に直接向き合うコーディネーターの増員（22名→32名）

3　法改正を踏まえた追加取組（平成２３年度予算）

平成23年度の政府予算案において、コーディネーター等の能力向上を図るため、ドナー家族への対応などの研修メニューを追加するための予算を計上。

資料6－2

JOTにおけるドナー家族対応・支援

1．あっせんを担当するCoによる家族対応・支援

- ○ 臓器提供承諾時の家族対応・支援
- ○ 臓器提供承諾後から臓器摘出終了・退院までの家族対応・支援
- ○ 臓器提供後の家族対応・支援（詳細は2．参照）

2．臓器提供後の家族対応・支援

時期	担当	方法	内容	備考
1－2ヶ月	コーディネーター（各支部、都道府県）	訪問	お参り ご家族の近況を伺う。 移植後の経過報告 大臣感謝状・サンクスレターを届ける	
3－6ヶ月		訪問 手紙 メール 電話		
1年頃				ドナー家族の集いのご案内（地域ごとに1回／2－3年）
2年目以降			ご家族の希望により行う。	

JOTのドナー家族対応・支援体制の強化へ向けて

1．平成22年度

○　コーディネーター教育の一環として、家族心理に関して学ぶ機会を設けた。
○　医療専門職（精神科医師）の設置。

2．平成23年度以降

○　ドナー家族対応担当のコーディネーターの設置。
○　医療専門職とドナー家族対応コーディネーターによるWGを設置し、支援体制を構築。
○　ドナー家族専用ダイヤル（ホットライン）の設置。

参考資料１

JOTコーディネーターのドナー家族対応・支援

１）斡旋を担当するコーディネーターによる家族対応

○　臓器提供承諾時の家族対応（支援）を行う。（家族へ臓器提供に関する説明を行い、家族の自由な意思決定を担保し、意思確認を行う）

○　臓器提供承諾後から臓器摘出終了・退院までの家族対応（支援）を行う。

○　臓器提供後の家族対応（支援）を行う。

①　家族へのインフォームドコンセントまでの対応

・　ご家族への説明に際し、ご家族の状況に応じた対応を心がける。

②　家族へ臓器提供に関する説明と承諾

・　臓器提供に関する説明の前に、ご家族より患者様の病態と臓器提供に関するお考え等をお伺いし、ご家族の状況を把握するように努める。

・　ご家族の心情に配慮しながら、脳死の概要、臓器摘出の実際などの臓器提供に関する適切な説明を行い、ご家族が自由な意思決定ができるように支援する。又、ご本人の臓器提供に対する拒否の意思表示を意思登録システム等で慎重に確認する。

・　家族の承諾においては、任意性を担保し、承諾に関するご家族の総意には十分な時間を提供するように配慮する。

③　臓器提供承諾後の家族対応

・　ご家族に今後の手続き時間や内容をお伝えし、大切な家族との静かな面会時間の提供およびご家族の休養に配慮する。

・　ご家族の心情に配慮しつつ、情報公開時期・内容の再確認を行い、了承を得る

・　ご家族に応じた方法で、臓器摘出状況と臓器搬送状況の報告を行う

・　ご本人の退院時はお見送りする

④　退院後の対応

・お葬儀出席（承諾を得たコーディネーターがご家族の了承を得た場合）

・ご家族の近況や故人に関するお話を伺うと共に、移植後のﾚｼﾋﾟｴﾝﾄの経過を報告する。

・中央評価委員会や検証会議への情報提供了承と結果報告

・マスコミ報道・取材影響への配慮

・「ドナーファミリーの集い」開催

各支部において、１回/2・3年　開催

平成22年11月（大阪開催）　　平成23年2月（名古屋開催予定）

参考資料２

日本臓器移植ネットワークによる家族対応支援体制の強化

１）　平成 22 年度に行った家族対応に関する事項

①　移植コーディネーターに対して、家族関する研修を行った。

②　医療専門職（精神科医師）の設置

○　ドナー家族対応（臓器提供時、臓器提供後）についてのコーディネーターに対する助言・指導

○　ドナー家族への支援体制構築についての助言・指導

○　臓器斡旋を担うコーディネーターへの心理的支援

２）今後の家族対応に関する事項

①　ドナー家族対応の担当（23 年度からは専任設置）コーディネーターの設置

○　全ドナー家族への適切（標準的）なドナー家族対応の運営

○　臓器提供１年以降の当該（必要とする）ドナー家族の対応
（ドナー家族の必要に応じて移植後経過報告を行う）

○　ドナー家族専用電話の窓口対応

②　医療専門職とドナー家族対応コーディネーターによる、ドナー家族対応支援 WG を設置し、体制を構築する。

○　地域の専門家や支援施設との連携体制を構築し、必要時ドナー家族へ心理専門家やドナー家族支援施設等を紹介する。

○　ドナー家族支援冊子の作成

○「ドナー家族の集い」の在り方に関する検討

③　ドナー家族専用ダイヤル（ホットライン）の設置

○　ドナー家族専用ダイヤルは臓器提供承諾時に、ドナー家族へ紹介する

④　日本臓器移植ネットワーク・中央評価委員会に心理の専門家を加える。