

Impact of Pretransplant Renal Failure: When is Listing for Kidney-Liver Indicated?

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Renal and hepatic function are often intertwined both through the existence of associated primary organ diseases and hemodynamic interrelationships. This connection occasionally results in the chronic failure of both organs, necessitating the need for combined kidney-liver transplantation. Since 1990, over 1,790 patients in the United States have received such transplants with a patient survival somewhat less than that for patients receiving either organ alone. Patients with renal failure due to acute injury or to the hepatorenal syndrome have classically not been included as candidates for combined transplantation due to the reversibility of the renal dysfunction following liver transplantation. However, the rate and duration of renal failure prior to liver transplantation continues to be prolonged even with the new allocation scheme prioritizing liver transplants to those with renal failure. Thus the issue of when kidney transplantation should be offered and what evaluation is necessary prior to the decision continues to confront the transplant community. (*Liver Transpl* 2005;11:S35-44.)

Renal failure in the setting of liver disease occurs due to liver induced renal ischemia and processes that cause both liver and kidney disease such as hepatitis C and B infections and alpha-1 antitrypsin deficiency.^{1,2} The key to determining the need for renal replacement therapy (RRT) following liver transplantation and thus the need for a kidney transplant is the ability to predict irreversibility of renal injury or the progressive nature of primary renal disease. The patients with renal dysfunction to consider in this setting are those on dialysis with end-stage renal disease (ESRD), those with good renal function developing acute renal failure, those with multiple bouts of acute renal failure, and those with mild to moderate chronic renal disease who have acute renal failure. The decision to perform kidney-liver transplantation (KLT) is easy for the first 2 categories. Those with ESRD definitely require dual transplantation and those with initial episodes of acute renal failure do not if the primary reason for acute renal failure is treated successfully. The difficulty comes when acute on chronic renal dysfunction occurs and the acute renal failure adds permanent injury to the underlying renal damage. Additionally, there comes a time when a liver recipient may be so ill that there is an increased risk for primary nonfunction of the renal transplant in the hemodynamically unstable and inflammatory environment immediately after liver transplant. In these indi-

viduals, no matter the rationale for renal transplantation, a kidney should not be placed.

The decision-making process for dual transplantation can be difficult and has been hampered by the lack of a standardized evaluation and selection approach, the significant difficulty (until now) of treating the major cause of acute renal failure, the hepatorenal syndrome (HRS), and the increasing illness severity of those undergoing liver transplantation. However, it is fair to say that at this time there are a few key concepts and facts that can be used to start the process of building a protocol for the evaluation and selection of KLT candidates. The current key concepts governing the decision for KLT are the following:

HRS alone is not a reason for combined KLT.³ However, the length of dialysis treatment prior to development of irreversible renal failure from HRS is still not defined, and the impact of the slower development of renal failure with HRS type 2 still needs evaluation.

Treatment of HRS with vasopressin analogs or the combination of midodrine, octreotide, and albumin or initiation of the molecular adsorbents recirculation system (albumin dialysis) treatment may decrease the development of renal failure from HRS and improve post-liver transplant outcome.⁴⁻⁸

Abbreviations: RRT, renal replacement therapy; ESRD, end-stage renal disease; KLT, kidney-liver transplantation; HRS, hepatorenal syndrome; GFR, glomerular filtration rate; MELD, Model for End-Stage Liver Disease; KAT, kidney alone transplantation; LAT, liver alone transplantation; TIPS, transjugular intrahepatic portosystemic stent.

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Renal biopsy in those with liver failure is doable and helps to determine the cause of primary renal disease as well as the amount of permanent renal tissue destruction.^{1,2,9,10}

Kidney transplants should be given only to patients with irreversible renal failure—those who would require dialysis within 3 years of liver transplant. This includes patients with “prolonged” dialysis for HRS and/or a primary renal disease known to progress to ESRD.^{2,11} Prolonged dialysis for HRS or acute tubular injury of another etiology is defined as over 8 weeks. However, this may be shortened to 4-6 weeks in those with previous bouts of acute renal failure or other underlying renal disease. A glomerular filtration rate (GFR) of 20-30 mL/min in those with documented chronic kidney disease would suggest that combined transplant is needed.

Liver transplant recipients receiving a kidney transplant have a lower survival than recipients of kidney only transplants.¹² The severe medical condition of individuals with end-stage liver disease reduces survival.

Kidney transplants save the lives of people with ESRD, and there are over 62,000 currently on the kidney wait list.^{13,14}

The Model for End-Stage Liver Disease (MELD) score has prioritized liver transplantation since 2002 to those with renal dysfunction. The impact on renal outcome is still under review.¹⁵⁻¹⁷

The evaluation for a concurrent kidney transplant includes determination of GFR (iothalamate, EDTA, or iothexol), a urinalysis, quantification of urine protein excretion, renal ultrasound with duplex to assess renal anatomy and blood flow, other renal imaging (renal scan, computed tomography) as clinically indicated, and, if possible, a renal biopsy.^{2,11}

These key points are highlighted with the knowledge that (1) renal failure is a major determinant of liver transplant outcome, and poor renal function predicts decreased survival; (2) HRS of prolonged duration or in those with other underlying renal injury may not recover after liver transplant; (3) renal biopsy in those with coagulopathy and varices is riskier than in those with normal liver function; and (4) the MELD system is based upon the serum creatinine even though the serum creatinine and creatinine-based calculated GFR measurements are poor measures of renal function in liver disease.^{11,18-20} Questions remaining to be answered to refine the criteria for dual transplantation include: (1) What is the rate of primary nonfunction for KLT based upon liver disease severity at transplant? (2) What length of hemodialysis is still compatible with recovery

of renal function, and what parameters would help to determine recovery? (3) What determines responsiveness of HRS to vasopressin analogs (or other) treatment? (4) What other markers, treatments, or investigations can help identify the risk for renal failure in the setting of liver disease (e.g., cystatin C, ultrasound duplex, hemodynamic response to paracentesis, renal response to vasoconstrictors)? (5) What renal biopsy findings in liver failure help to determine future renal failure? (6) What is the impact of the current allocation system on long-term renal function in liver transplant recipients? (7) Should a marker of renal function other than the serum creatinine be used in the prioritization for liver transplant such as cystatin C or need for dialysis?

Kidney-Liver Transplantation Outcomes

KLT is increasing. Since 1990 and through 2004, 1,790 kidney-liver transplants have been performed (Table 1) for the renal disorders listed in Table 2.²¹ As of the end of July 2005, 323 individuals were listed for combined KLT. Patient, kidney, and liver allograft survival are shown in Table 3. Patient and liver allograft survival at 10 years is approximately 50%, while slightly fewer kidney transplants (44%) are still functioning. When Fong et al. compared kidneys in KLT (n = 899) from the Organ Procurement and Transplantation Network database (1987 to 2001) with the contralateral kidneys used for kidney alone transplantation (KAT, n = 628) or combined pancreas-kidney transplantation (n = 172), graft and patient survival rates were lower among LKT recipients compared with KAT ($P < 0.001$) and pancreas-kidney transplantation recipients ($P < 0.001$) (Fig. 1).¹² However, most of the graft loss was due to early KLT patient mortality. There was higher 1-year rejection-free survival among human leukocyte antigen–mismatched transplants (KLT 70%, KAT 61%, pancreas-kidney transplantation 57%) and lesser renal graft loss from chronic rejection among KLT recipients (KLT 2% vs. KAT 8% vs. pancreas-kidney transplantation 6%, $P < 0.0001$). Overall, several reviews of Organ Procurement and Transplantation Network data for deceased donor transplants performed from 1990 to 1995 from non–extended criteria donors reveal a kidney transplant half-life between 11 and 12 years while the recent data above suggests that the kidney half-life of KLT is somewhat less than 10 years.^{22,23} Thus, although there may be an immunologic advantage to transplanting the kidney with the liver, early graft loss is higher (due to recipient death) in KLT, and for some reason there also appears

Table 1. Number of Transplants and Serum Creatinine at Transplantation for Deceased Donor Kidney Alone, Liver Alone, and Combined Kidney-Liver Transplants Performed in the United States From 1990 to 2004²¹

Transplant Year	Kidney Alone Tx (n)	Average Creatinine at Tx (mg/dL)	Liver Alone Tx (n)	Average Creatinine at Tx (mg/dL)	K-L Tx (n)	Average Creatinine at Tx (mg/dL)
1990	7,264	9.6	2,618	1.3	45	4.9
1991	7,233	8.9	2,873	1.3	43	4.9
1992	7,137	8.7	2,955	1.3	57	5.0
1993	7,442	9.1	3,331	1.3	49	4.1
1994	7,533	7.7	3,487	1.3	86	4.9
1995	7,599	7.6	3,774	1.3	81	4.4
1996	7,596	7.9	3,870	1.2	112	4.3
1997	7,636	8.0	3,928	1.2	117	4.5
1998	7,895	8.4	4,277	1.2	98	4.6
1999	7,914	8.9	4,354	1.3	99	4.2
2000	7,958	9.1	4,408	1.2	135	3.7
2001	8,069	9.0	4,466	1.2	133	4.1
2002	8,287	8.7	4,698	1.3	209	4.6
2003	8,388	8.6	5,043	1.3	246	4.2
2004	9,030	8.6	5,457	1.4	280	4.6
Total	116,981	8.7	59,539	1.3	1,790	4.4

Abbreviations: Tx, transplant; K-L, kidney-liver.

to be a slightly higher long-term attrition rate. This needs to be reviewed in the context of medical comorbidities (hepatitis C virus, diabetes) and center effect.

Renal Function at Transplant

The serum creatinine at liver alone transplantation (LAT), KAT, and KLT from the Organ Procurement and Transplantation Network database from 1990 onward is shown in Table 1. As can be seen, the serum creatinine for kidney-only transplants is much higher than for the other 2 groups, but the creatinine is still

quite elevated for KLT. This indicates particularly poor renal function in KLT recipients, given the dismal sensitivity of serum or plasma creatinine in detecting reduced GFR.¹⁸⁻²⁰ Poor renal function at KLT is verified by the data in Table 4 detailing the number of recipients on dialysis at the time of transplant. Only 4%-5% of LAT recipients were receiving dialysis at transplant compared with 50%-60% of KLT recipients. Dialysis pretransplant has recently (as in the past) been associated with poor posttransplant outcome independent of the MELD score.^{15,24}

Table 2. Primary Renal Diagnosis of KLT Recipients Since 1990 Reported to the United Network for Organ Sharing²¹

	Transplant Year															Total
	'90	'91	'92	'93	'94	'95	'96	'97	'98	'99	'00	'01	'02	'03	'04	
Primary renal disease																
Not reported	4	6	2	3	12	5	4	5	4	1	1	4	3	3	1	58
Other	22	15	28	32	18	17	31	30	34	22	49	45	76	84	122	625
Glomerular diseases	5	5	6	3	13	16	18	19	19	11	20	14	23	36	35	243
Tubular interstitial	7	4	8	4	18	17	28	34	12	20	21	12	35	34	27	281
Polycystic kidney disease*	4	6	3	4	5	8	6	4	8	13	6	12	13	16	17	125
Diabetes	0	4	3	0	9	7	8	11	7	11	16	18	25	39	39	197
Congenital familial metabolic	1	0	2	0	0	0	0	0	0	0	1	0	0	3	2	9
Renovascular	1	1	0	0	0	2	5	4	4	3	2	4	2	4	3	35
Neoplasms	1	0	0	0	0	0	0	0	0	1	0	1	2	0	0	5
Retransplant/graft failure	0	1	3	3	8	6	9	9	7	14	12	16	22	15	20	145
Hypertensive nephrosclerosis	0	1	2	0	3	3	3	1	3	3	7	7	8	12	14	67
Total	45	43	57	49	86	81	112	117	98	99	135	133	209	246	280	1,790

Table 3. Combined Kidney-Liver Kaplan-Meier Patient Survival Rates for Transplants Performed 1990-2003²¹

Number of Transplants	Months Posttransplant	Patient Survival Rate	Kidney Survival Rate	Liver Survival Rate
1,510	12	78.61	74.51	75.13
	36	70.26	65.79	66.89
	60	65.29	60.00	61.70
	120	54.54	44.14	50.57

Liver Status at Transplant

Liver status at LAT and KLT is shown in Table 5. In general, before 1997, about the same percentage (20%-30%) of LAT and KLT recipients were severely ill at transplant (status 1, in the intensive care unit). With the introduction of the MELD score based upon the bilirubin, international normalized ratio of the prothrombin time, and serum creatinine level, renal failure became a major factor in the decision for more urgent liver transplant. Once implemented, indeed, the MELD score promoted more rapid transplantation for those with renal dysfunction, as shown in Table 6. However, although an elevated serum creatinine (over 3 mg/dL at transplant) is associated with a 30% decreased time to LAT and a MELD score over 25 resulted in an average time to transplant of 27 days in 2002 (95% confidence interval, 22,34), KLT (often with MELD scores at surgery over 30 and up to 60% on dialysis)

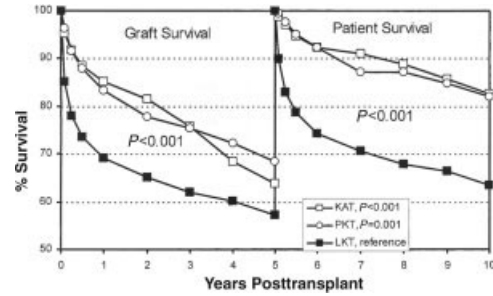


Figure 1. Survival of the patient and kidney allograft in recipients of KLT, KA (kidney alone), and SPK (simultaneous pancreas kidney).

have waiting times similar to the overall LAT list. Furthermore, the average waiting time for LAT with a creatinine over 3.0 mg/dL at transplant is still over 5 months.

Kidney After Liver Transplant

An alternative to simultaneous KLT is sequential liver and then kidney transplant. A retrospective review of KLT compared to sequential transplantation was performed by Becker et al.²⁵ Simultaneous recipients (n = 38) had a 74% survival rate at 6 months. Short-term survival was better in those transplanted for noncirrhotic liver disorders. Long-term (7-year) survival however, was similar in patients with cirrhosis and patients without cirrhosis (58.3% vs. 54.6%, respectively).

Table 4. Number and Percentage of Patients on Dialysis at Liver and Kidney-Liver Transplantation²¹

Year	Liver Alone					K-L Transplant				
	Yes		No		Unknown*	Yes		No		Unknown
	N	% of Patients	N	% of Patients		N	% of Patients	N	% of Patients	
1994	109	4.0	2,556	93.9	2.1	39	56.5	29	42.0	1.4
1995	186	4.9	3,493	92.6	2.4	46	56.8	29	35.8	4.9
1996	182	4.7	3,571	92.3	2.6	53	47.3	52	46.4	4.5
1997	159	4.0	3,614	92.0	3.4	60	51.3	52	44.4	3.4
1998	197	4.6	3,907	91.3	3.9	57	58.2	35	35.7	6.1
1999	191	4.4	3,863	88.7	6.5	50	50.5	41	41.4	8.1
2000	191	4.3	3,883	88.1	7.5	65	48.1	60	44.4	5.9
2001	101	2.3	2,004	44.9	2.3	28	21.1	28	21.1	1.5
2002	160	3.4	4,021	85.6	0	105	50.2	90	43.1	0
2003	201	4.0	4,771	94.6	0	128	52.0	118	48.0	0
2004	253	4.6	5,141	94.2	0	171	61.1	109	38.9	0

Abbreviation: N, number of transplants.

*Other categories not included reported from UNOS are not applicable and not reported. The total of Yes, No, Unknown, not applicable, and not reported is 100%.

Table 5. Liver Status at Transplantation for Liver Alone and Kidney-Liver Transplants for Selected Years Since 1990²¹

Year	Liver Status	Liver Alone		Combined Kidney-Liver	
		N	% of Patients	N	% of Patients
1990	1	757	28.9	18	40.0
	3	392	15	9	20
1991	1	621	21.6	9	20.9
	3	934	32.5	9	20.9
1992	1	685	23.2	21	36.8
	3	1,214	41.1	14	24.6
1993	1	746	22.4	15	30.6
	3	1,601	48.1	13	26.5
1994	1	768	22.0	21	24.4
	3	1,757	50.4	32	37.2
1995	1	729	19.3	15	18.5
	3	1,873	49.6	31	38.3
1996	1	814	21.0	30	26.8
	3	1,819	47.0	30	26.8
1997	1	735	18.7	24	20.5
	2A	183	4.7	12	10.3
	2B	565	14.4	27	23.1
	3	1,666	42.4	28	23.9
1998	1	482	11.3	6	6.1
	2A	686	16.0	32	32.7
	2B	2,347	54.9	50	51.0
	3	739	17.3	10	10.2
1999	1	515	11.8	8	8.1
	2A	845	19.4	30	30.3
	2B	2,553	58.6	56	56.6
	3	428	9.8	5	5.1
2000	1	555	12.6	15	11.1
	2A	909	20.6	47	34.8
	2B	2,563	58.1	68	50.4
	3	366	8.3	5	3.7
2001	1	576	12.9	7	5.3
	2A	1,092	24.5	68	51.1
	2B	2,397	53.7	52	39.1
	3	392	8.8	6	4.5
2002	1	461	9.8	3	1.4
	MP <10	182	3.9	3	1.4
	MP 10–14	396	8.4	0	0
	MP 15–30	2,389	50.9	114	54.5
	MP >30	575	12.2	67	32.1
2003	1	476	9.4	15	6.1
	MP <10	219	4.3	3	1.2
	MP 10–14	535	10.6	2	0.8
	MP 15–30	3,011	59.7	122	49.6
	MP >30	798	15.8	104	42.3
2004	1	498	9.1	7	2.5
	MP <10	172	3.2	1	0.4
	MP 10–14	423	7.8	0	0
	MP 15–30	3,485	63.9	144	51.4
	MP >30	876	16.1	128	45.7

NOTE: Pre-1997, status 1 was a patient in an intensive care unit because of acute or chronic liver failure with a life expectancy less than 7 days without a liver transplant. Status 3 patients were those defined as needing continuous care. After 1997 the status categories changed: status 1, an adult (age ≥ 18 years) with fulminant liver failure with a life expectancy without a transplant of less than 7 days, pediatric (<18 years) and in the intensive care unit because of acute liver failure or chronic liver failure with a life expectancy without a transplant of less than 7 days and meeting other medical criteria. Status 2A was a patient in the critical care unit because of chronic liver failure, with a life expectancy without a transplant of less than 7 days and a long-term prognosis with a successful liver transplant equivalent to that of a patient with fulminant liver failure. The patient also had a Child-Turcotte-Pugh score of 10 or greater and met other medical criteria. Status 2B is age 18 or older and has CTP score ≥ 10 , or a CTP score ≥ 7 and meets other medical criteria. Status 3 was a patient requiring continuous care and if ≥ 18 years had a Child-Turcotte-Pugh score of 7 or greater. The model for end-stage liver disease/pediatric end-stage liver disease scores started in 2002 and are calculated based upon the serum bilirubin, international normalized ratio, and creatinine values.

Abbreviations: N, number; A, B; MP, model for end-stage liver disease/pediatric end-stage liver disease.

Table 6. Average Number of Days Waiting for Transplant²¹

Year	Average Number of Days Awaiting Liver Only	Average Number of Days Awaiting K-L Transplant	Average Number of Days Awaiting Liver Alone, Creatinine >2.0 mg/dL	Average Number of Days Awaiting Liver Alone, Creatinine >3.0 mg/dL
1990	58.4	22.6	21.1	18.1
1991	67.3	101.7	33.2	25.1
1992	92.5	84.0	46.7	44.0
1993	122.6	104.3	49.8	39.0
1994	129.4	88.2	59.9	60.4
1995	148.8	120.8	65.7	62.9
1996	179.3	140.3	95.3	76.8
1997	216.1	201.3	111.4	95.8
1998	253.4	231.2	121.8	107.0
1999	264.9	327.0	149.0	135.8
2000	298.5	264.2	159.6	104.0
2001	305.9	344.4	162.8	136.7
2002	254.9	245.5	161.5	130.1
2003	249.1	254.2	170.1	174.2
2004	233.1	229.5	173.3	163.3
Total	206.5	217.0	117.4	100.2

Sequential transplant recipient ($n = 9$) survival was better when the kidney transplantation was performed after the liver transplantation ($n = 5$) than when the liver transplantation was performed after the kidney transplantation ($n = 4$). Kidney-after-liver recipients had a survival greater than 4 years in 4 of 5 recipients. Gonwa et al. reported earlier that liver transplant recipients developing ESRD have an overall improved survival with a kidney transplant (6-year survival, 71.4%) than if they remain on dialysis (6-year survival, 27%).²⁶ However, liver transplant recipients with hepatitis C virus may be at increased risk for complications after kidney transplant.^{27,28}

Hepatorenal Syndrome

HRS is a term for renal failure associated with liver failure. The etiology is partially ischemia and partially nephrotoxicity due to endotoxin, bile salts, and other unidentified substances present in the setting of liver disease.^{1,11} Classically, HRS type 1 or dialysis requiring acute renal failure for any reason has indicated a very poor prognosis without liver transplantation especially if associated with the need for mechanical ventilation.^{17,29} A recent review by Wong et al. of 102 liver transplant candidates receiving RRT for acute renal failure, including HRS, between 1999 and 2004 has verified these findings and shown that 35% survive to liver transplant or discharge (Fig. 2).³⁰ Mortality in patients not receiving a liver transplant was 94% and

was associated with a higher Acute Physiological and Chronic Health Evaluation II, lower mean arterial pressure, and the use of continuous RRT. Those receiving continuous RRT had a greater illness severity than those on intermittent treatment. The 1-year mortality of patients initiating RRT prior to liver transplant was 30% vs. 9.7% for all other liver recipients ($P < 0.0045$). United Network for Organ Sharing data in the 1990s seemed to favor renal transplantation for patients with HRS, as the 5-year survival of those undergoing KLT was 62.2% compared with 50.4% for patients with a serum creatinine >2.0 mg/dL receiving isolated liver transplants ($P = 0.0001$).³ However, the single center results from Baylor suggested otherwise, pointing to patient management strategies as a reason

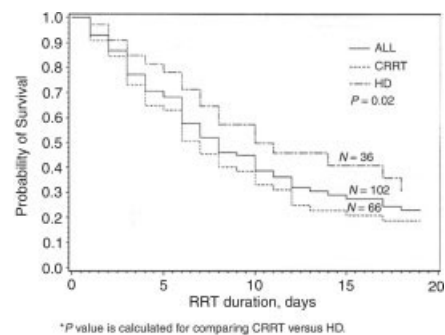


Figure 2. Kaplan-Meier plot of overall patient survival and survival by initial RRT modality. P value is calculated for comparing continuous RRT vs. hemodialysis.

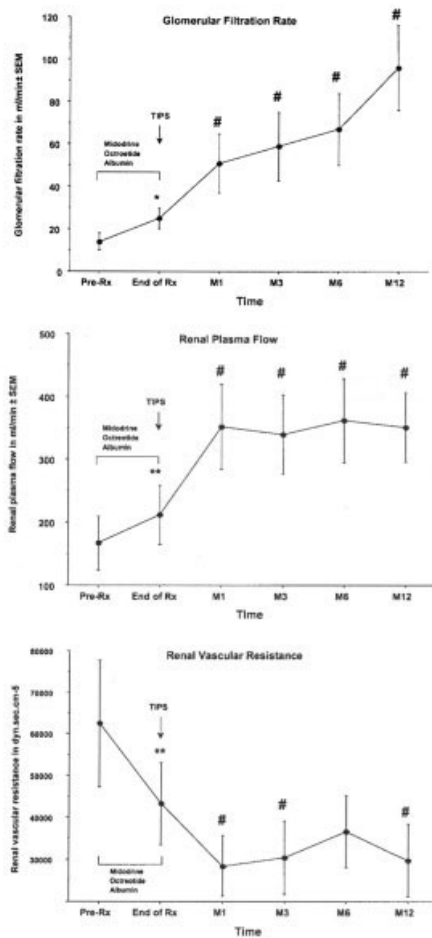


Figure 3. Renal hemodynamics in the 5 responders who received TIPS. * $P < 0.05$ vs. pretreatment, ** $P < 0.01$ vs. pretreatment; * $P < 0.05$ vs. pre-TIPS. Rx, medical treatment consisting of midodrine, octreotide and albumin; M, month.**

for the differential results. More recent advances in HRS treatment may further help to improve posttransplant outcome without renal transplantation.

Type 1 HRS (acute onset) has been shown in several studies to respond to a combination of midodrine, octreotide and albumin.^{30,31} Transjugular intrahepatic portosystemic stent (TIPS) shunt has also been shown to improve renal function in those with HRS; however, the impact on posttransplant outcome was only recently reported in a small number of very carefully evaluated patients. Consecutive patients presenting with type 1 HRS ($n = 14$) were all treated with midodrine, octreotide, and albumin infusions.³⁰ Responders were defined as those who improved renal function to a creatinine of less than $135 \mu\text{g/L}$ after 10 days of treatment ($n = 10$).

Responders without contraindications for TIPS underwent the procedure and were followed over the next year ($n = 5$). Those undergoing TIPS continued renal improvement over time (Fig. 3).³⁰ Of the 3 patients who underwent transplantation, 1 had undergone TIPS and 2 had not, and all were alive after transplant.

Recently, the impact of treating HRS with a vasopressin analog on post-liver transplant outcomes has been evaluated. The theory is that vasoconstriction of the overdilated splanchnic circulation by the analog will increase renal perfusion. Restuccia et al. reviewed 21 patients treated with vasopressin analogs as therapy for HRS.³² Of those treated, 16 responded to treatment with a reduction of the serum creatinine of greater than 25%. Nine of the 16 responders were transplanted compared to 1 of 5 of the nonresponders with the survival shown in Figure 4.³² The authors also compared the posttransplant survival of HRS responders with those who underwent transplantation without HRS; there was no difference. Likewise there was no difference in the 6-month posttransplant serum creatinine level between those with and without HRS. And there was no difference in the rate of severe infection. The conclusion of the paper was that HRS should be actively treated (with a vasopressin analog) prior to liver transplantation. Studies comparing the impact of the various approaches to the treatment of HRS on post-liver transplant outcome (e.g., vasopressin analog, molecular adsorbents recirculation system, pentoxifylline, midodrine, octreotide albumin, and TIPS) are awaited. From current treatment studies it appears that consideration for treatment prior to liver transplantation is warranted.

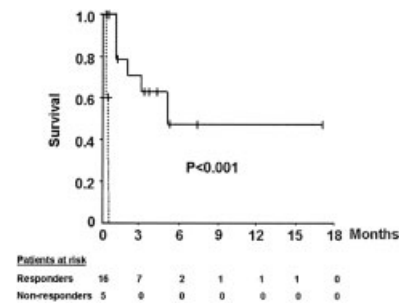


Figure 4. Probability of transplant-free survival in the 21 transplant candidates who received treatment with vasopressin analogs for HRS divided according to response to therapy: responders (continuous line) and nonresponders (discontinuous line). The small vertical lines in each curve represent the time of transplantation of the patients who were transplanted during follow-up.

Table 7. Evaluation for Kidney Liver Transplantation

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<ol style="list-style-type: none"> 1. Clinical Assessment <ol style="list-style-type: none"> A. History: nonsteroidal use, presence of diabetes, bleeding episodes, nausea, vomiting, diarrhea, paracentesis, infections, hypertension, diuretic use, lactulose use, contrast studies B. Physical: blood pressure, JVP, edema, tense ascites, cardiac rhythm, arterial integrity, neuropathy, bleeding, infection adenopathy, vasculitis, prostate enlargement, 24-hour urinary outputs C. Metabolic disease: Primary hyperoxaluria, polycystic disease, amyloidosis, familial hemolytic uremic syndrome, glycogen storage disease 2. General Laboratory Evaluation <ol style="list-style-type: none"> A. Electrolytes, glucose B. Disease specific antibodies, cryoglobulins, rheumatoid factor, antiglomerular basement membrane antibody 3. Renal Function Measure <ol style="list-style-type: none"> A. Serum creatinine, blood urea nitrogen B. Cystatin C 4. Glomerular Filtration Measure <ol style="list-style-type: none"> A. ¹²⁵I-iothalamate clearance B. ⁵²Cr-EDTA clearance C. Iohexol D. Inulin clearance E. ^{99m}Tc-DPTA 5. Urinalysis (repeat weekly while under evaluation) <ol style="list-style-type: none"> A. Measure sodium, creatinine, calculate fractional sodium excretion B. Measure protein:creatinine C. Microscopic evaluation 6. Protein Excretion Assessment (repeat weekly while under evaluation) <ol style="list-style-type: none"> A. [Protein:creatinine] or B. 24-hour urine protein excretion 7. Renal ultrasound with color flow Doppler (repeat weekly while under evaluation) or other measure of renal blood flow, renal plasma flow such as renal scan or para-aminohippuric acid clearance (repeat monthly if possible). 8. Renal biopsy depending upon safety as determined by coagulation parameters and the presence of varices 9. Biopsy Information Assessed According to: <ol style="list-style-type: none"> A. Renal disease: glomerular disease, tubular inflammation, tubular injury only or no abnormality B. Ischemia: wrinkled glomeruli, tubular injury C. Percentage of fibrosis, glomerular and interstitial fibrosis and arterial hyalinosis 10. Kidney-Liver Transplant if: <ol style="list-style-type: none"> A. Primary renal disease is expected to cause renal failure within 3 years of transplant B. HRS with dialysis dependent renal failure lasting over 8 weeks C. Perhaps HRS with dialysis dependent renal failure of 4-6 weeks' duration if previous episodes of acute renal failure have occurred or other underlying renal disease is present D. Renal biopsy shows over 30% tubulointerstitial fibrosis or $\geq 40\%$ glomerulosclerosis or moderate or more arteriosclerosis <p>Do Not Perform Kidney Transplant if:</p> <ol style="list-style-type: none"> A. There is still a low sodium excretion B. There is no permanent fibrosis on biopsy C. There is still fair renal blood flow without a progressive renal disease or only minor amounts of fibrosis on biopsy

Evaluation and Selection

The evaluation of individuals with liver and kidney function should start with a complete history and physical and be followed by an accurate measure of renal function (Table 7). An easy and accurate marker of renal function is not available for those with liver disease, but there is evidence that cystatin C levels are more accurate than the serum creatinine.^{19,20} Cystatin C is a low-molecular-weight protein produced at a constant rate by all nucleated cells, freely filtered and not secreted nor reabsorbed along the nephron. The serum level is

independent of sex, muscle mass, and age. More helpful, however, in making the decision for kidney transplantation is an actual measurement of GFR by clearance techniques.³³ A renal ultrasound should be performed to rule out anatomic abnormalities. Because liver disease causes renal ischemia and the degree of renal ischemia has been associated with an increased risk of renal failure, an evaluation of renal perfusion should be performed.³⁴⁻³⁶ This may be accomplished by duplex ultrasound, renal scan or paraamino hippurate clearance.^{2,34-36} Of note, the duplex is the easiest to

perform and a high intrarenal resistive index (>0.78) on duplex Doppler is evidence of impending HRS. Evidence for primary renal disease may be found through the urinalysis (microscopic evaluation, protein-creatinine ratio), 24-hour protein excretion or renal biopsy. Renal biopsy should be performed for the evaluation of urinary abnormalities (hematuria >6 cells/hpf, RBC casts, pyuria, WBC casts, proteinuria >500 mg/d) or acute renal failure not explainable by history (e.g., drug exposure, bleeding, sepsis culture) or criteria for HRS. Biopsy may be performed percutaneously if the coagulation status is intact or via the transjugular route if impaired; those with primary renal disease with a GFR less than 30 cc/min should receive dual transplantation. Those diseases known to progress rapidly or individuals whose biopsies show over 40% glomerulosclerosis or 30% of the interstitium as fibrosis should receive a kidney transplant with the liver.^{2,11} Treatment of patients with HRS is now advisable, as outlined previously. If patients become dialysis dependent as a consequence of toxic or ischemic tubular injury, predicting renal recovery in the setting of liver disease is difficult. However, if there is no recovery after 8 weeks (the usual recovery time for acute renal failure), then combined transplantation may be considered. In those with prior renal injury or chronic kidney disease predating dialysis, 4-6 weeks may be enough time to make the decision for KLT. No matter the cause, the earlier the liver transplant can be performed the better. Furthermore, there is a great need to collect more specific data on such patients to help modify future KLT criteria. Posttransplant management should be geared toward promoting renal recovery (limit nephrotoxin exposure, limit calcineurin inhibitor dosing and sirolimus loading, and use strategies to prevent infection and gastrointestinal bleeding).

Conclusion

Renal disease impacts liver transplant outcomes and should remain an important determinant in priority for liver transplant. Kidney transplants save the lives of those with ESRD on dialysis. The renal evaluation in liver failure needs to be comprehensive and standardized. Only those with permanent renal failure should receive KLT. HRS is not an indication for kidney transplantation unless prolonged and severe. HRS should be treated at presentation to try to limit renal injury. The results of decisions based upon established evaluation criteria need to be periodically reviewed, especially in the context of the time to liver transplantation.

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References

- Davis CL, Gonwa TA, Wilkinson AH. Pathophysiology of renal disease associated with liver disorders: Implications for liver transplantation. *Liver Transpl* 2002;8:91-109.
- Davis CL, Gonwa TA, Wilkinson AH. Identification of patients best suited for combined liver-kidney transplantation: Part II. *Liver Transpl* 2002;8:193-211.
- Jeyarajah DR, Gonwa TA, McBride M, Testa G, Abbasoglu O, Husberg BS, et al. Hepatorenal syndrome: Combined liver kidney transplants versus isolated liver transplant. *Transplantation* 1997;64:1760-1765.
- Cardenas A. Hepatorenal syndrome: A dreaded complication of end-stage liver disease. *Am J Gastroenterol* 2005;100:460-467.
- Steiner C, Mitzner S. Experiences with MARS liver support therapy in liver failure: Analysis of 176 patients of the International MARS Registry. *Liver* 2002;22(Suppl 2):20-25.
- Stange J, Mitzner SR, Risler T, Erley CM, Lauchart W, Goehl H, et al. Molecular adsorbent recycling system (MARS): Clinical results of a new membrane-based blood purification system for bioartificial liver support. *Artif Organs* 1999;23:319-330.
- Sen S, Davies NA, Mookerjee RP, Cheshire LM, Hodges SJ, Williams R, Jalan R. Pathophysiological effects of albumin dialysis in acute-on-chronic liver failure: A randomized controlled study. *Liver Transpl* 2004;10:1109-1119.
- Mullhaupt B, Kullak-Ublick GA, Ambuhl P, Maggiorini M, Stocker R, Kadry Z, et al. First clinical experience with molecular adsorbent recirculating system (MARS) in six patients with severe acute on chronic liver failure. *Liver* 2002;22(Suppl 2):59-62.
- Jouet P, Meyrier JP, Mal F, Callard P, Guettier C, Stordeur D, et al. Transjugular renal biopsy in the treatment of patients with cirrhosis and renal abnormalities. *Hepatology* 1996;24:1143-1147.
- Sam R, Leehey DJ, Picken MM. Transjugular renal biopsy in patients with liver disease. *Am J Kidney Dis* 2001;37:1304-1307.
- Pham PT, Pham PC, Rastogi A, Wilkinson AH. Review article: Current management of renal dysfunction in the cirrhotic patient. *Aliment Pharmacol Ther* 2005;21:949-961.
- Fong TL, Bunnapradist S, Jordan SC, Selby RR, Cho YW. Analysis of the United Network for Organ Sharing database comparing renal allografts and patient survival in combined liver-kidney transplantation with the contralateral allografts in kidney alone or kidney-pancreas transplantation. *Transplantation* 2003;76:348-353.
- Meier-Kriesche HU, Kaplan B. Waiting time on dialysis as the strongest modifiable risk factor for renal transplant outcomes: A paired donor kidney analysis. *Transplantation* 2002;74:1377-1381.
- Schaubel D, Desmeules M, Mao Y, Jeffery JR, Fenton S. Survival experience among elderly end stage renal disease patients. A controlled comparison of transplantation and dialysis. *Transplantation* 1995;60:1389-1394.
- Narayanan Menon KV, Nyberg SL, Harmsen WS, DeSouza NF, Rosen CB, Krom RA, et al. MELD and other factors associated

- with survival after liver transplantation. *Am J Transplant* 2004;4:819-825.
16. Wong LP, Blackley MP, Andreoni KA, Chin H, Falk RJ, Klemmer PJ. Survival of liver transplant candidates with acute renal failure receiving renal replacement therapy. *Kidney Int* 2005;68:362-370.
 17. Alessandria C, Ozdogan O, Guevara M, Restuccia T, Jimenez W, Arroyo V, et al. MELD score and clinical type predict prognosis in hepatorenal syndrome: Relevance to liver transplantation. *Hepatology* 2005;41:1282-1289.
 18. Caregaro L, Menon F, Angeli P, Amodio P, Merkel C, Borluzzi A, et al. Limitations of serum creatinine level and creatinine clearance as filtration markers in cirrhosis. *Arch Intern Med* 1994;154:201-205.
 19. Samyn M, Cheeseman P, Bevis L, Taylor R, Samaroo B, Buxton-Thomas M, et al. Cystatin C, an easy and reliable marker for assessment of renal dysfunction in children with liver disease and after liver transplantation. *Liver Transpl* 2005;11:344-349.
 20. Orlando R, Mussap M, Plebani M, Piccoli P, De Martin S, Floreani M, et al. Diagnostic value of plasma cystatin C as a glomerular filtration marker in decompensated liver cirrhosis. *Clin Chem* 2002;48:850-858.
 21. Organ Procurement and Transplantation Network data as of August 19, 2005.
 22. Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D. Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Engl J Med* 2000;342:605-612.
 23. Cecka JM. The OPTN/UNOS Renal Transplant Registry 2003. *Clin Transpl* 2003;1-12.
 24. Desai NM, Mange KC, Crawford MD, Abt PL, Frank AM, Markmann JW, et al. Predicting outcome after liver transplantation: Utility of the model for end-stage liver disease and a newly derived discrimination function. *Transplantation* 2004;77:99-106.
 25. Becker T, Nyibata M, Lueck R, Bektas H, Demirci G, Lehner F, et al. Results of combined and sequential liver-kidney transplantation. *Liver Transpl* 2003;9:1067-1078.
 26. Gonwa TA, Mai ML, Melton LB, Hays SR, Goldstein RM, Levy MF, et al. End stage renal disease (ESRD) following orthotopic liver transplantation (OLT) utilizing calcineurin based immunotherapy: Risk of development and treatment. *Transplantation* 2001;72:1934-1939.
 27. Molmenti EP, Jain AB, Shapiro R, Scantlebury V, Lee R, Tot-suka E, et al. Kidney transplantation for end-stage renal failure in liver transplant recipients with hepatitis C viral infection. *Transplantation* 2001;71:267-271.
 28. Singh N, Gayowski T, Ndimbie OK, Nedjar S, Wagener MM, Yu VL. Recurrent hepatitis C virus hepatitis in liver transplant recipients receiving tacrolimus: Association with rejection and increased immunosuppression after transplantation. *Surgery* 1996;119:452-456.
 29. Witzke O, Baumann M, Patschan D, Patschan S, Mitchell A, Treichel U, et al. Which patients benefit from hemodialysis therapy in hepatorenal syndrome? *J Gastroenterol Hepatol* 2004;19:1369-1373.
 30. Wong F, Pantea L, Sniderman K. Midodrine, octreotide, albumin, and TIPS in selected patients with cirrhosis and type 1 hepatorenal syndrome. *Hepatology* 2004;40:55-64.
 31. Moreau R, Lebrec D. Acute renal failure in patients with cirrhosis: Perspectives in the age of MELD. *Hepatology* 2003;37:233-243.
 32. Restuccia T, Ortega R, Guevara M, Gines P, Alessandria C, Ozdogan O, et al. Effects of treatment of hepatorenal syndrome before transplantation on posttransplantation outcome. A case-control study. *J Hepatol* 2004;40:140-146.
 33. Skluzacek PA, Szewc RG, Nolan CR 3rd, Riley DJ, Lee S, Pergola PE. Prediction of GFR in liver transplant candidates. *Am J Kidney Dis* 2003;42:1169-1176.
 34. Platt JF, Ellis JH, Rubin JM, Merion RM, Lucey MR. Renal duplex doppler ultrasonography: A noninvasive predictor of kidney dysfunction and hepatorenal failure in liver disease. *Hepatology* 1994;20:362-369.
 35. Kastelan S, Ljubicic N, Kastelan Z, Ostojic R, Uravic M. The role of duplex doppler ultrasonography in the diagnosis of renal dysfunction and hepatorenal syndrome in patients with liver cirrhosis. *Hepatogastroenterolgy* 2004;51:1408-1412.
 36. Al-Kareemy EA, Sobh MA, Muhammad AM, Saber RA. Renal dysfunction in liver cirrhosis: Renal duplex Doppler US vs. scintigraphy for early identification. *Clin Radiol* 1998;53:44-48.