Chronic Renal Allograft Dysfunction

Rebecca Rojas MD

Assistant Professor of Internal Medicine

Division of Nephrology

University of Texas Southwestern Medical Center at Dallas

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Introduction

Almost 30 million Americans have chronic kidney disease and over half a million have kidney failure. Unfortunately a significant number of dialysis patients die within just a few years of initiating treatment (Foundation, 2011). Though options such as peritoneal dialysis and hemodialysis are available to our patients, there is no doubt that transplantation is the most optimal treatment for our patients with ESRD. Despite a well known increased risk of death in transplant patients in the early post transplant period, patient survival rates long term are far superior to those patients remaining on dialysis (Figure 1) (Wolfe, Ashby et al. 1999) (Ojo, Hanson et al. 2001).

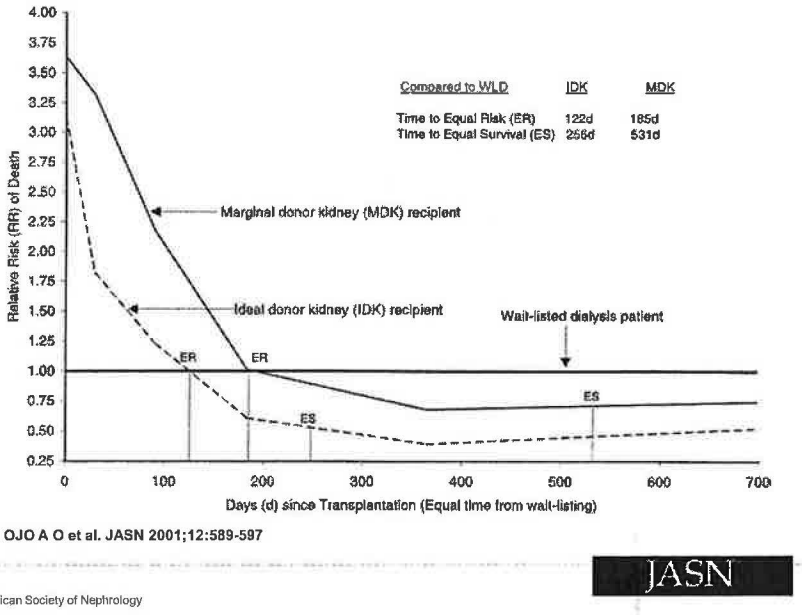


Figure 1

There were 15,429 kidney transplants in the United States in 2010. Kidney transplants utilizing deceased donors remain the most common transplant performed in the United States. There are three types of deceased donors, 1) Standard criteria donor (SCD), 2) Extended criteria donor (ECD), 3) Donation after cardiac death donor (DCD). Amongst deceased donation, standard criteria donors (SCD) remain the most highly utilized organs, followed by ECD/DCD kidneys. Unfortunately, there are a significant number of patients awaiting a kidney transplant. As of the completion of this manuscript a

little over 88,000 patients were noted to be on the kidney transplant waiting list (2009 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1999-2008. U.S. Department of Health and Human Services, Health Resources and Services Administration, Healt).

Unfortunately, and despite our best efforts the survival of our renal allograft is limited. Despite what appears to be more potent immunosuppression with less rejection episodes occurring in the first year (less than 10%) with improved first year graft survival rates, rates of chronic allograft loss after the first year have not significantly improved. In 1987, the half life of a living donor kidney was noted to be about 10 years. Fast forward ten years the half still remains a little over ten years. Similar findings are seen with deceased donor kidneys (Table 1, 2) (2009 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1999-2008. U.S. Department of Health and Human Services, Health Resources and Services Administration, Healt).

Chronic deterioration of the renal allograft is thought to be a multifactorial process. The two most common causes of allograft loss after the first post transplant year remain chronic allograft nephropathy and death with a functioning allograft. CAN describe a clinical syndrome which is the final common pathway of many different pathophysiologic processes. At one point, the term "chronic allograft nephropathy" was also used to describe the *pathological* changes we viewed on biopsies of flailing allografts....typical wear and tear, or so we thought. The "its run its course" type attitude is no longer prevalent in the transplant community and recent literature has argued vehemently against *not* searching for a definitive cause of allograft dysfunction. El-Zoghby and colleagues looked at over 1300 post transplant patients and their histological data. Of the patients that lost their allografts, a specific cause for failure was determined in nearly all cases and an immunologic cause as the reason for failure was noted in about 40% of patients, implicating an ongoing chronic immunologic process in chronic allograft dysfunction (El-Zoghby, Stegall et al. 2009). Most recently, prelimary results of DeKAF have become available. The goal of DeKAF was to attempt to identify and cluster specific histologic findings on biopsy with no identifiable diagnosis. The study was able to demonstrate six distinct clusters based on Banff criteria. The six clusters identified were also found to have significantly different survival rates. With this information, the study attempted to argue that search for the specific clinic diagnosis associated with the various clusters was key (Matas, Leduc et al. 2010).

Table 1

Adjusted Graft Survival by Year of Transplant at 3 Months, 1 Year,

3 Years, 5 Years and 10 Years

Living Donor Kidney Transplants

		3 Months		1 Year		3 Years		5 Years		10 Years	
		Surv.	Std. Err.	Surv.	Std. Err.	Surv.	Std. Err.	Surv.	Std. Err.	Surv.	Std. Err.
Transplant Year	# Transplants	91.20%	1.40%	88.40%	1.60%	75.50%	2.20%	66.50%	2.40%	49.20%	2.60%
1987	399										
1988	1,817	92.60%	0.60%	88.30%	0.80%	80.00%	1.00%	71.80%	1.10%	51.50%	1.20%
1989	1,901	93.50%	0.60%	90.50%	0.70%	83.30%	0.90%	75.70%	1.00%	54.20%	1.20%
1990	2,091	93.60%	0.50%	91.00%	0.60%	84.60%	0.80%	75.80%	1.00%	55.00%	1.20%
1991	2,395	95.10%	0.40%	92.80%	0.50%	85.30%	0.70%	76.20%	0.90%	56.10%	1.10%
1992	2,534	94.10%	0.50%	91.40%	0.60%	84.90%	0.70%	75.90%	0.90%	53.90%	1.10%
1993	2,851	94.80%	0.40%	91.70%	0.50%	84.00%	0.70%	75.20%	0.80%	53.90%	1.00%
1994	3,005	95.10%	0.40%	92.60%	0.50%	85.80%	0.60%	76.60%	0.80%	53.60%	1.00%
1995	3,389	95.00%	0.40%	92.50%	0.50%	85.60%	0.60%	77.60%	0.70%	54.70%	0.90%
1996	3,672	95.80%	0.30%	93.60%	0.40%	86.50%	0.60%	77.80%	0.70%	56.50%	0.90%
1997	3,930	96.40%	0.30%	94.20%	0.40%	87.80%	0.50%	79.10%	0.70%	57.30%	0.80%
1998	4,409	97.10%	0.30%	94.70%	0.30%	88.20%	0.50%	80.30%	0.60%	58.70%	0.80%
1999	4,688	96.60%	0.30%	94.60%	0.30%	87.90%	0.50%	80.40%	0.60%	+	+
2000	5,471	96.70%	0.20%	94.30%	0.30%	87.60%	0.40%	79.90%	0.60%	+	+
2001	6,016	96.90%	0.20%	94.60%	0.30%	88.30%	0.40%	80.50%	0.50%	+	+
2002	6,227	97.40%	0.20%	95.20%	0.30%	88.90%	0.40%	81.40%	0.50%	+	+
2003	6,458	97.30%	0.20%	95.60%	0.30%	88.80%	0.40%	81.40%	0.50%	+	+
2004	6,636	97.60%	0.20%	95.40%	0.30%	89.50%	0.40%	+	+	+	+
2005	6,567	97.40%	0.20%	95.40%	0.30%	89.60%	0.40%	+	+	+	+
2006	6,429	98.10%	0.20%	96.30%	0.20%	+	+	+	+	+	+
2007	6,033	98.20%	0.20%	96.80%	0.20%	+	+	+	+	+	+

Source: OPTN/SRTR Data as of May 4, 2009.

Table 2

Adjusted Graft Survival by Year of Transplant at 3 Months, 1 Year, 3 Years, 5 Years and 10 Years

Deceased Donor Kidney Transplants

		3 Months		1 Year		3 Years		5 Years		10 Years	
		Surv.	Std. Err.	Surv.	Std. Err.	Surv.	Std. Err.	Surv.	Std. Err.	Surv.	Std. Err.
Transplant Year	# Transplants	82.60%	1.00%	74.80%	1.10%	61.60%	1.20%	50.80%	1.30%	30.30%	1.20%
1987	1,629										
1988	7,035	82.10%	0.50%	74.70%	0.50%	62.10%	0.60%	51.90%	0.60%	31.00%	0.60%
1989	6,717	84.20%	0.50%	77.40%	0.50%	65.10%	0.60%	55.20%	0.60%	32.80%	0.60%
1990	7,265	85.60%	0.40%	79.20%	0.50%	67.40%	0.60%	56.80%	0.60%	34.30%	0.60%
1991	7,234	88.20%	0.40%	82.80%	0.50%	71.70%	0.50%	60.00%	0.60%	35.30%	0.60%
1992	7,138	88.70%	0.40%	83.00%	0.50%	71.60%	0.50%	59.90%	0.60%	34.00%	0.60%
1993	7,442	88.40%	0.40%	82.60%	0.40%	71.40%	0.50%	60.40%	0.60%	36.70%	0.60%
1994	7,533	89.80%	0.30%	84.10%	0.40%	73.50%	0.50%	61.60%	0.60%	37.00%	0.60%
1995	7,598	91.10%	0.30%	85.70%	0.40%	75.20%	0.50%	63.50%	0.60%	39.60%	0.60%
1996	7,596	92.00%	0.30%	87.40%	0.40%	77.00%	0.50%	64.90%	0.60%	40.30%	0.60%
1997	7,634	93.20%	0.30%	88.60%	0.40%	77.60%	0.50%	66.20%	0.50%	41.20%	0.60%
1998	7,898	93.50%	0.30%	89.00%	0.30%	78.40%	0.50%	67.00%	0.50%	42.50%	0.60%
1999	7,916	93.20%	0.30%	88.20%	0.40%	78.10%	0.50%	67.40%	0.50%	+	+
2000	7,958	93.50%	0.30%	88.20%	0.40%	77.40%	0.50%	66.40%	0.50%	+	+
2001	8,071	94.20%	0.30%	89.30%	0.30%	79.10%	0.40%	68.20%	0.50%	+	+
2002	8,287	94.10%	0.30%	89.50%	0.30%	79.00%	0.40%	68.70%	0.50%	+	+
2003	8,388	94.50%	0.20%	89.80%	0.30%	79.50%	0.40%	69.80%	0.50%	+	+
2004	9,029	95.00%	0.20%	90.50%	0.30%	80.20%	0.40%	+	+	+	+
2005	9,511	95.30%	0.20%	90.70%	0.30%	81.40%	0.40%	+	+	+	+
2006	10,215	95.40%	0.20%	91.20%	0.30%	+	+	+	+	+	+
2007	10,083	95.80%	0.20%	92.10%	0.30%	+	+	+	+	+	+

Factors in the immediate post transplant period

Though all attempts should be made to identify and address a specific cause of dysfunction, the overall health of the renal allograft is affected by numerous processes that can be seen as early as day one. Following implantation of an ideal kidney, immediate function is expected with urine outputs exceeding more than 100ml/hour and falls in creatinine over 20% not uncommonly seen. When this is not seen, there is a broad yet known differential of allograft dysfunction that physicians are keenly aware of.

To better understand some of the potential factors that may influence allograft function during this early post transplant period, one simply has to understand the surgery itself and the anatomy involved (Fig 2). Whether as a result of technical or patient related issues, arterial or venous thrombosis or occlusion are included in the differential of renal allograft dysfunction in this early post transplant period. Some of the technical/patient related issues include endothelial damage, dissection/kinking of the vessels, external compression by fluid collections i.e. hematoma/lymphocoele and recipients with a thrombotic tendency (anticoagulation is then sometimes considered given the allografts inability to tolerate any extended amount of warm ischemia time if thrombosis does occur).

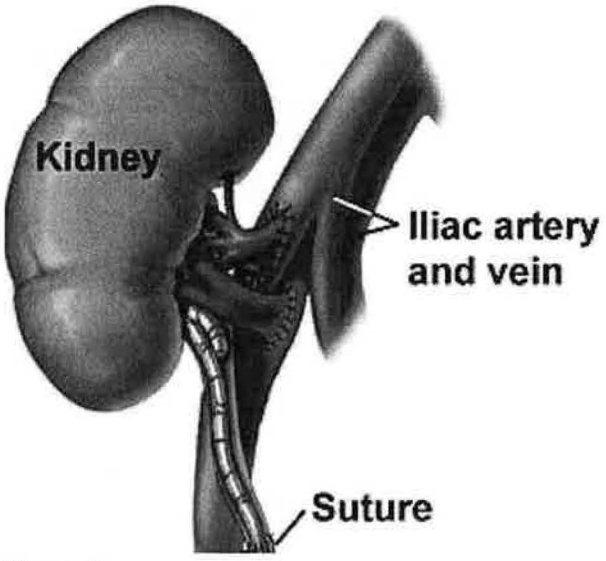
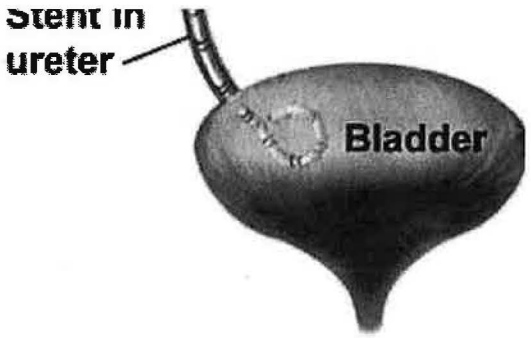


Figure 2



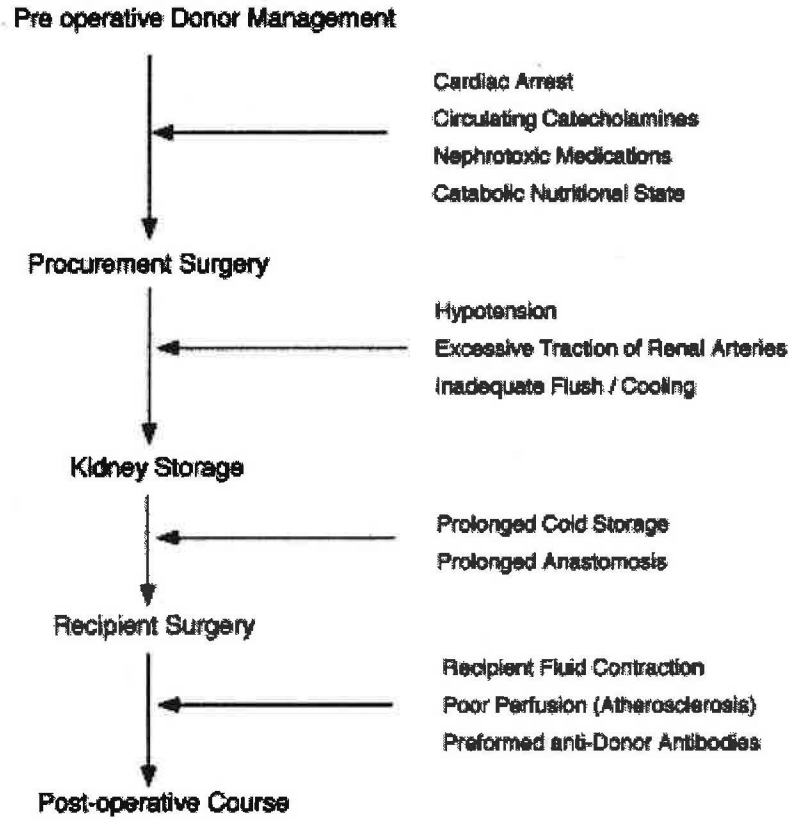
Urine leaks or obstruction are also known causes of allograft dysfunction during this time. Surgical complications with implantation and disruption of blood supply are risk factors for complications involving the ureter. Hyperacute antibody rejection occurs in the presence of preformed antibodies directed at donor HLA antigens and typically results in the allograft being destroyed in a matter of minutes. The presence of more effective cross matching techniques that identify important cytotoxic antibodies to donor HLA antigens and more potent immunosuppressive medications have essentially lead to the near eradication of this entity. And as with all other hospitalized patients, infections, medications and hemodynamic factors such as hypovolemia remain important contributors to allograft dysfunction in this early post transplant period. Most importantly, an entity known as

delayed graft function (DGF) has been seen to have a very important on chronic allograft survival and dysfunction and can be seen during this time.

Delayed graft function

Delayed graft function (DGF) is clinically defined as the need for dialysis within the first post-transplant week. Its effect on the renal allograft and chronic allograft dysfunction is well known. OPTN/SRTR Data as of May 4, 2009 demonstrated unadjusted graft survival data of deceased donor kidney transplants at 3months, 1 year, 5 years and 10 years with and without DGF of 97 vs. 88%, 93 vs. 82%, 73 vs. 55% and 70 vs. 30% respectively. Unadjusted graft survival data of living donor kidney transplants again at 3months, 1 year, 5 years and 10 years with and without DGF of 98 vs. 78%, 97 vs. 73%, 82 vs. 50% and 60 vs. 32% (2009 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1999-2008. U.S. Department of Health and Human Services, Health Resources and Services Administration, Healt). It is believed the majority of DGF is due to acute tubular necrosis as a result of ischemic injury. Given not all donor kidneys experience DGF, the donor kidney seems to be able to tolerate a certain amount of ischemic injury. Whether patients exposed to more severe ischemic injury are at highest risk for DGF remains unknown but appears reasonable to conclude. This being said, there is no question that any ischemic injury likely has some impact on the donor kidney several years post transplant. Though written almost fifteen year ago, Shoskes and Halloran very nicely described the various risk factors for ischemia that the donor kidney is exposed to at every step along the path from procurement to reperfusion (Figure 3) (Shoskes and Halloran 1996). Especially important to deceased donor kidneys, management of a critically ill patient prior to procurement may have an impact on graft survival and be another point at which further ischemic injury can occur. Other risk factors for ischemia can be seen at the time of organ procurement and preservation. At procurement, complete transection of the donor renal artery, vein, ureter along with denervation of the kidney occurs. Until reperfusion, there is obvious ongoing ischemia which can be referred to as either cold or warm ischemia. Warm ischemic time is defined as the time from cross clamping of the donor vessels until the commencement of cold storage (kidney is flushed with preservation solution and put into cold storage). Cold ischemia time begins when the organ is flushed with preservation solution and ends once reperfusion is begun and the donor kidney reaches physiological temperatures. Ideal CITs should be limited to less than 19 hours and WIT to less than 20 minutes (Table 3). Pulsatile perfusion involves ex vivo perfusion of the donor kidney. As compared to

cold storage, the literature has supported its use in high risk donor kidneys but its use and potential benefit in all donor kidneys has yet to be defined (Moers, Smits et al. 2009). Interestingly, patients who are highly sensitized and who have a greater degree HLA mismatching are at an increased risk for DGF, indicating another point at which an immunologic factor appears to have a role in chronic allograft dysfunction.



Possible etiologies of ischemic injury in cadaveric renal transplantation.

Figure 3

(Shoskes and Halloran 1996)

Table 3

Unadjusted Graft Survival, Deceased Donor Kidney Transplants Survival at 3 Months, 1 Year, 5 Years, and 10 Years

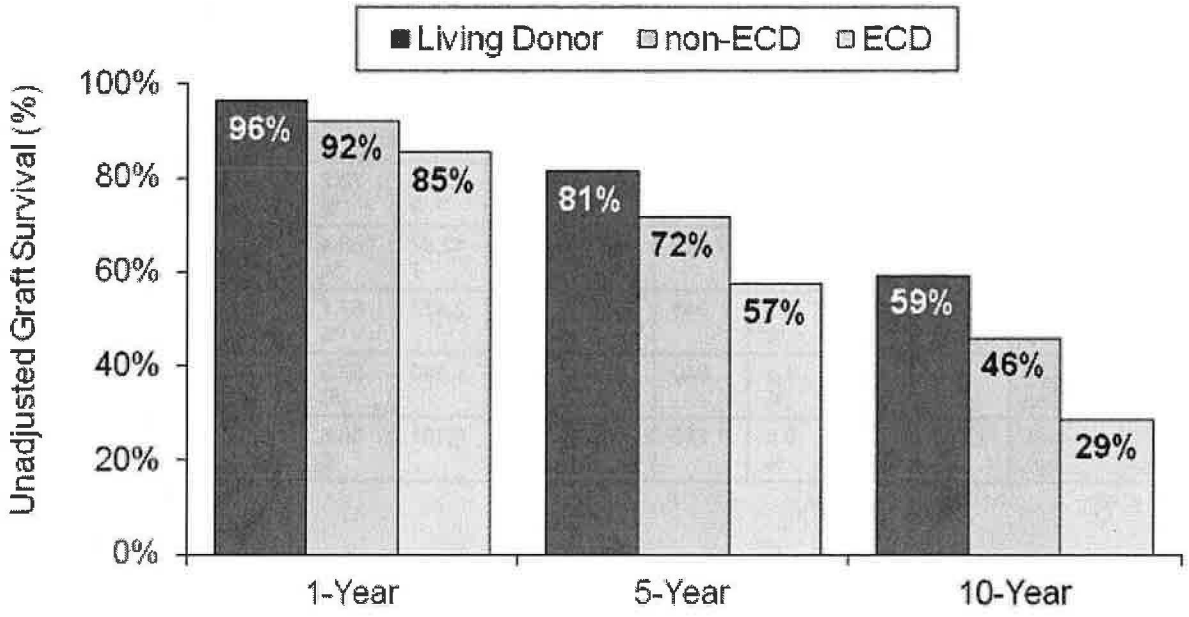
		3 Months (Tx 2006 - 2007)			1 Year (Tx 2006 - 2007)			5 Years (Tx 2002 - 2007)			10 Years (Tx 1997 - 2007)		
		N	%	Std. Err.	N	%	Std. Err.	N	%	Std. Err.	N	%	Std. Err.
Total	All	20,298	95.3 %	0.1 %	20,298	91.0 %	0.2 %	55,513	69.3 %	0.3 %	94,990	43.3 %	0.3 %
Cold Ischemic Time	0-11 Hours	4,421	96.6 %	0.3 %	4,421	92.7 %	0.4 %	10,749	70.9 %	0.6 %	15,727	45.3 %	0.8 %
	12-21 Hours	8,349	95.2 %	0.2 %	8,349	91.1 %	0.3 %	22,739	70.2 %	0.4 %	38,756	43.5 %	0.4 %
	22-31 Hours	4,519	95.3 %	0.3 %	4,519	90.6 %	0.4 %	12,677	68.4 %	0.6 %	23,822	43.3 %	0.5 %
	32-41 Hours	943	94.7 %	0.7 %	943	89.7 %	1.0 %	2,477	67.7 %	1.3 %	5,120	38.3 %	1.1 %
	42+ Hours	340	94.1 %	1.3 %	340	87.3 %	1.8 %	680	57.3 %	3.0 %	1,115	36.6 %	2.5 %
	Unknown	1,726	93.2 %	0.6 %	1,726	88.6 %	0.8 %	6,191	66.8 %	0.8 %	10,450	43.4 %	1.0 %

Impact of the donor kidney/recipient factors

We have two types of donors, deceased and living donors. We have three types of deceased donor kidneys which include, 1) standard criteria donor (SCD), expanded criteria donor (ECD) and donation after cardiac death (DCD) donor (previously known as the "non heart beating donor"). SCD and ECD donors are defined by conventional brain death criteria and an ECD donor is a donor over the age of 60 or over the age of 50 with two of the following additional risk factors: a history of high blood pressure, a creatinine greater than or equal to 1.5, or death resulting from a stroke. DCD donor does not meet criteria for conventional brain death but is determined to have no hope for any viable recovery and death is determined using cardiopulmonary criteria. The type of donor kidney plays a very important role on chronic allograft survival. Understanding how the allograft is procured and stored prior to surgery, it is easy to see why there is a definite survival advantage of recipients of living donors. Most recent 2009 SRTR/OPTN data reveals a 1, 5 and 10 year allograft survival of living donor, non-ECD and ECD kidneys of 96, 92, 85% and 81, 72, 57% and 59, 46, 29% respectively (Figure 4). On average, graft

survival remains about 15-20 years for a live donor kidney and about 10-15 years for a deceased donor kidney.

Figure III-7. Unadjusted 1-Year (2006-2007), 5-Year (2002-2007), and 10-Year (1997-2007) Kidney Graft Survival*, by Donor Type



*Death is included as an event.

Source: *2009 OPTN/SRTR Annual Report*, Tables 5.10a, b, d.

Figure 4

Which patients benefit from receiving ECD versus SCD kidneys? Schold and colleagues were able to show that for patients aged 18 to 39 years, there was a longer life expectancy when receiving a living donor (27.6 years) or standard criteria donor (26.4 years) kidney after four years of dialysis versus an extended criteria donor kidney (17.6 years) after two years of dialysis. By comparison, for those patients greater than 65 years of age, life expectancy was slightly higher with an extended criteria donor (ECD) kidney (5.6 years) after two years of dialysis versus a standard (5.3 years) or living donor (5.5 years) kidney after four years of dialysis. In general, for younger patients it is worth waiting for a higher quality kidney, whereas for older patients the additional wait time does not make any significant

amount of difference (Nephsap 2008, JD Schold 2006). Donor age has also been shown to impact allograft survival, with younger donors aged 18-34 having an overall better survival advantage over older donor kidneys >50 (Table 4,5) (JD Schold 2006) (2009 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1999-2008. U.S. Department of Health and Human Services, Health Resources and Services Administration, Healt). 2009 SRTR data was also able to demonstrate a survival advantage of the allograft in those patients younger than 65 years of age. The adjusted graft survival of a DDKT at 5 years being 70%+ versus 58.5% and at 10 years 40%+ versus 25.2% in those 64 and younger versus those >/= 65+ respectively. Adjusted graft survival at 5 and 10 years for living related kidney transplants in those 64 and younger versus those patients >/+65 was 80%+ versus 73.9% and 50%+ versus 38.1% respectively. Teenagers were shown to demonstrate a lower graft survival, reasons possibly attributed to questionable adherence and newly known independence (Table 6, 7) (2009 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1999-2008. U.S. Department of Health and Human Services, Health Resources and Services Administration, Healt).

The quality/pathology of the implanted donor kidney at the time of transplantation also plays a very significant role on chronic allograft dysfunction, with an abundance of literature demonstrating the impact of interstitial fibrosis and vascular changes on allograft survival. Most recently, the presence of glomerulosclerosis on biopsy was found to be an important factor playing a role on chronic allograft survival (Bajwa, Cho et al. 2007) (Cockfield, Moore et al. 2010).

Table 4

Unadjusted Graft Survival, Living Donor Kidney Transplants
Survival at 3 Months, 1 Year, 5 Years, and 10 Years

		3 Months (Tx 2006 - 2007)			1 Year (Tx 2006 - 2007)			5 Years (Tx 2002 - 2007)			10 Years (Tx 1997 - 2007)		
		N	%	Std. Err.	N	%	Std. Err.	N	%	Std. Err.	N	%	Std. Err.
Total	All	12,462	98.10%	0.10%	12,462	96.30%	0.20%	38,350	81.40%	0.30%	62,864	59.40%	0.40%
Donor Age	6-11 Years	0	-	-	0	-	-	0	-	-	1	0.00%	.
	12-17 Years	3	100.00%	0.00%	3	100.00%	0.00%	5	100.00%	0.00%	12	66.70%	27.20%
	18-34 Years	3,900	98.30%	0.20%	3,900	97.10%	0.30%	12,331	82.80%	0.50%	20,801	61.90%	0.60%
	35-49 Years	5,604	98.00%	0.20%	5,604	96.40%	0.30%	17,782	81.70%	0.40%	29,206	59.40%	0.60%
	50-64 Years	2,802	98.00%	0.30%	2,802	95.50%	0.40%	7,842	79.40%	0.70%	12,191	56.30%	1.00%
	65+ Years	152	96.70%	1.40%	152	92.60%	2.10%	389	60.90%	3.70%	644	29.20%	3.70%
	Unknown	1	0.00%	.	1	0.00%	.	1	0.00%	.	9	+	+

Table 5

Unadjusted Graft Survival, Deceased Donor Kidney Transplants
Survival at 3 Months, 1 Year, 5 Years, and 10 Years

		3 Months (Tx 2006 - 2007)			1 Year (Tx 2006 - 2007)			5 Years (Tx 2002 - 2007)			10 Years (Tx 1997 - 2007)		
		N	%	Std. Err.	N	%	Std. Err.	N	%	Std. Err.	N	%	Std. Err.
Total	All	20,298	95.30%	0.10%	20,298	91.00%	0.20%	55,513	69.30%	0.30%	94,990	43.30%	0.30%
Donor Age	<1 Year	107	84.10%	3.50%	107	80.40%	3.80%	190	60.80%	4.80%	344	47.10%	4.60%
	1-5 Years	464	94.60%	1.00%	464	90.20%	1.40%	1,292	72.50%	1.60%	2,398	54.00%	1.60%
	6-11 Years	462	96.80%	0.80%	462	91.70%	1.30%	1,431	74.30%	1.50%	2,992	47.70%	1.50%
	12-17 Years	1,411	96.90%	0.50%	1,411	94.00%	0.60%	4,339	75.40%	0.90%	8,281	51.60%	0.90%
	18-34 Years	6,065	96.90%	0.20%	6,065	93.90%	0.30%	16,484	75.10%	0.50%	27,654	50.00%	0.50%
	35-49 Years	5,994	95.50%	0.30%	5,994	91.30%	0.40%	16,258	68.80%	0.50%	27,622	42.30%	0.50%
	50-64 Years	4,949	93.50%	0.40%	4,949	87.80%	0.50%	13,282	62.30%	0.60%	21,900	33.80%	0.60%
	65+ Years	846	91.80%	0.90%	846	83.00%	1.30%	2,237	53.20%	1.50%	3,799	22.40%	1.20%

(2009 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1999-2008. U.S. Department of Health and Human Services, Health Resources and Services Administration, Healt)

Table 6

Adjusted Graft Survival, Living Donor Kidney Transplants

Survival at 3 Months, 1 Year, 5 Years, and 10 Years

		3 Months (Tx 2006 - 2007)			1 Year (Tx 2006 - 2007)			5 Years (Tx 2002 - 2007)			10 Years (Tx 1997 - 2007)		
		N	%	Std. Err.	N	%	Std. Err.	N	%	Std. Err.	N	%	Std. Err.
Total	**All**	12,462	98.10%	0.10%	12,462	96.40%	0.20%	38,350	81.40%	0.30%	62,864	58.90%	0.40%
Age at Tx	**<1 Year**	6	83.70%	13.80%	6	83.70%	13.80%	15	87.20%	8.20%	36	87.30%	6.00%
	1-5 Years	158	99.40%	0.60%	158	98.70%	0.90%	552	92.30%	1.30%	979	80.50%	2.10%
	6-11 Years	133	96.30%	1.60%	133	96.30%	1.60%	514	85.30%	2.00%	1,005	66.50%	2.70%
	12-17 Years	312	97.80%	0.80%	312	96.10%	1.10%	1,208	75.50%	1.70%	2,200	52.90%	2.10%
	18-34 Years	2,468	98.00%	0.30%	2,468	96.20%	0.40%	7,975	79.30%	0.60%	14,300	59.00%	0.70%
	35-49 Years	3,857	98.20%	0.20%	3,857	96.80%	0.30%	12,044	84.60%	0.50%	20,372	64.40%	0.70%
	50-64 Years	4,282	98.10%	0.20%	4,282	96.30%	0.30%	12,580	81.90%	0.50%	19,227	56.90%	0.80%
	65+ Years	1,246	98.00%	0.40%	1,246	95.40%	0.60%	3,462	73.90%	1.10%	4,745	38.10%	2.00%

Table 7

Adjusted Graft Survival, Deceased Donor Kidney Transplants

Survival at 3 Months, 1 Year, 5 Years, and 10 Years

		3 Months (Tx 2006 - 2007)			1 Year (Tx 2006 - 2007)			5 Years (Tx 2002 - 2007)			10 Years (Tx 1997 - 2007)		
		N	%	Std. Err.	N	%	Std. Err.	N	%	Std. Err.	N	%	Std. Err.
Total	All	20,298	95.40%	0.10%	20,298	91.20%	0.20%	55,513	69.10%	0.30%	94,990	41.80%	0.30%
Age at Tx	<1 Year	2	51.40%	22.80%	2	51.40%	22.80%	4	76.30%	17.30%	5	81.70%	14.50%
	1-5 Years	159	95.00%	1.70%	159	91.80%	2.20%	358	78.80%	3.00%	562	64.20%	3.40%
	6-11 Years	216	97.40%	1.10%	216	95.20%	1.40%	575	75.60%	2.50%	955	51.00%	2.90%
	12-17 Years	672	96.70%	0.70%	672	93.60%	1.00%	1,618	65.90%	1.90%	2,501	40.10%	2.00%
	18-34 Years	2,267	95.70%	0.40%	2,267	92.60%	0.60%	6,919	69.60%	0.80%	13,450	45.90%	0.70%
	35-49 Years	5,402	96.20%	0.30%	5,402	93.00%	0.30%	15,777	73.00%	0.50%	29,285	48.10%	0.50%
	50-64 Years	8,161	95.20%	0.20%	8,161	90.60%	0.30%	21,909	70.30%	0.40%	36,126	40.80%	0.50%
	65+ Years	3,419	93.50%	0.40%	3,419	87.20%	0.60%	8,353	58.50%	0.80%	12,106	25.20%	0.90%

HLA match

Tissue typing is a process used to identify proteins in our blood called antigens. Antigens are markers on the cells in our body which help our body differentiate self from non self. There are many different proteins but the HLA A, B and DR antigens are the most important in renal transplantation. These antigens are inherited from our parents, three from our mother and three from our father (Figure 5). Our HLA system remains the most important barrier to acceptance of the renal allograft. The degree of HLA matching affects long term allograft survival. The increased degree of HLA mismatching is associated with increased allograft loss likely as a result of some ongoing chronic immunology injury (Table 8,9) (Opelz and Dohler 2007) (2009 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1999-2008. U.S. Department of Health and Human Services, Health Resources and Services Administration, Healt).

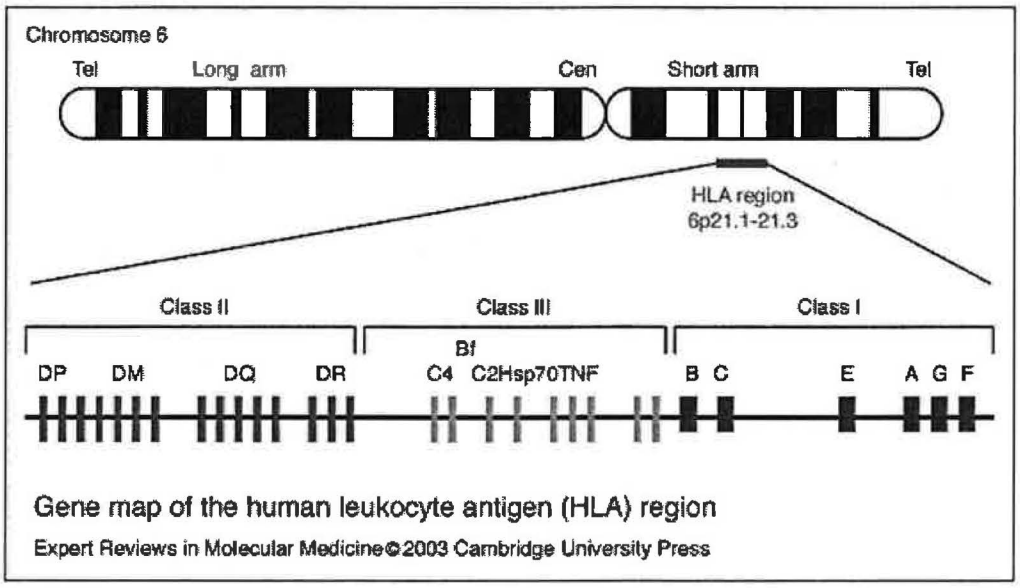

Chromosome 6
Tel
Long arm
Cen
Short arm
Tel
HLA region
6p21.1-21.3
Class II
Class III
Class I
Bf
DP
DM
DQ
DR
C4
C2Hsp70TNF
B
C
E
A
G
F
Gene map of the human leukocyte antigen (HLA) region
Expert Reviews in Molecular Medicine©2003 Cambridge University Press

Figure 5

Table 8

Unadjusted Graft Survival. Deceased Donor Kidney Transplants
Survival at 3 Months, 1 Year, 5 Years, and 10 Years

Level of HLA Mismatch		3 Months (Tx 2006 - 2007)			1 Year (Tx 2006 - 2007)			5 Years (Tx 2002 - 2007)			10 Years (Tx 1997 - 2007)		
		N	%	Std. Err.	N	%	Std. Err.	N	%	Std. Err.	N	%	Std. Err.
Total	All	20,298	95.30%	0.10%	20,298	91.00%	0.20%	55,513	69.30%	0.30%	94,990	43.30%	0.30%
A Locus Mismatch	0	4,009	96.20%	0.30%	4,009	93.00%	0.40%	11,366	73.90%	0.60%	20,485	47.70%	0.60%
	1	7,147	95.10%	0.30%	7,147	90.20%	0.40%	19,386	68.80%	0.50%	33,762	43.50%	0.50%
	2	9,139	95.10%	0.20%	9,139	90.70%	0.30%	24,754	67.50%	0.40%	40,684	40.80%	0.40%
	Unknown	3	100.00%	0.00%	3	100.00%	0.00%	7	68.60%	18.60%	69	33.60%	6.40%
B Locus Mismatch	0	3,235	96.60%	0.30%	3,235	93.60%	0.40%	9,738	74.10%	0.60%	18,999	48.00%	0.60%
	1	4,519	94.90%	0.30%	4,519	90.60%	0.40%	13,774	70.00%	0.50%	28,403	43.30%	0.50%
	2	12,541	95.10%	0.20%	12,541	90.40%	0.30%	31,994	67.30%	0.40%	47,519	41.00%	0.50%
	Unknown	3	100.00%	0.00%	3	100.00%	0.00%	7	68.60%	18.60%	69	33.60%	6.40%
DR Locus Mismatch	0	4,838	96.50%	0.30%	4,838	93.00%	0.40%	14,416	73.70%	0.50%	27,212	47.60%	0.50%
	1	8,634	95.40%	0.20%	8,634	91.10%	0.30%	23,226	69.20%	0.40%	39,919	42.70%	0.40%
	2	6,816	94.40%	0.30%	6,816	89.40%	0.40%	17,841	65.60%	0.50%	27,742	39.40%	0.60%
	Unknown	10	100.00%	0.00%	10	100.00%	0.00%	28	71.60%	9.60%	117	30.90%	5.50%
Total Mismatch	0	2,865	96.70%	0.30%	2,865	93.70%	0.50%	8,162	74.90%	0.70%	13,939	49.60%	0.80%
	1	161	96.30%	1.50%	161	92.50%	2.10%	555	75.40%	2.00%	2,315	47.40%	1.40%
	2	709	95.90%	0.70%	709	92.50%	1.00%	2,508	71.80%	1.10%	6,381	45.30%	0.90%
	3	2,329	95.20%	0.40%	2,329	91.10%	0.60%	7,228	70.90%	0.70%	15,274	44.30%	0.60%
	4	5,261	95.30%	0.30%	5,261	90.90%	0.40%	13,923	69.40%	0.50%	22,926	42.40%	0.60%
	5	5,109	94.90%	0.30%	5,109	90.10%	0.40%	15,581	66.60%	0.50%	22,938	39.90%	0.70%
	6	2,854	94.50%	0.40%	2,854	89.70%	0.60%	7,426	64.60%	0.90%	11,081	38.20%	0.90%
	Unknown	10	100.00%	0.00%	10	100.00%	0.00%	30	70.40%	9.20%	136	34.40%	5.00%

Source: OPTN/SRTR Data as of May 4, 2009.

(2009 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1999-2008. U.S. Department of Health and Human Services, Health Resources and Services Administration, Healt)

Table 9

Unadjusted Graft Survival, Living Donor Kidney Transplants
Survival at 3 Months, 1 Year, 5 Years, and 10 Years

Level of HLA Mismatch		3 Months (Tx 2006 - 2007)			1 Year (Tx 2006 - 2007)			5 Years (Tx 2002 - 2007)			10 Years (Tx 1997 - 2007)		
		N	%	Std. Err.	N	%	Std. Err.	N	%	Std. Err.	N	%	Std. Err.
Total	All	12,462	98.10%	0.10%	12,462	96.30%	0.20%	38,350	81.40%	0.30%	52,864	59.40%	0.40%
A Locus Mismatch	0	2,824	98.30%	0.20%	2,824	95.80%	0.30%	9,154	84.50%	0.50%	16,113	65.40%	0.70%
	1	6,624	98.10%	0.20%	6,624	96.30%	0.20%	20,575	80.60%	0.40%	33,661	57.60%	0.50%
	2	2,982	97.90%	0.30%	2,982	95.80%	0.40%	8,306	80.30%	0.60%	12,239	55.60%	1.10%
	Unknown	132	98.90%	1.50%	132	96.10%	1.70%	315	79.70%	3.20%	851	53.40%	2.70%
B Locus Mismatch	0	1,933	98.10%	0.30%	1,933	96.90%	0.40%	6,366	86.00%	0.60%	11,608	67.20%	0.80%
	1	6,341	98.30%	0.20%	6,341	96.70%	0.20%	19,853	80.80%	0.40%	32,991	58.10%	0.50%
	2	4,056	97.70%	0.20%	4,056	95.60%	0.30%	11,815	79.90%	0.50%	17,514	55.70%	0.90%
	Unknown	132	98.90%	1.50%	132	96.10%	1.70%	315	79.70%	3.20%	851	53.40%	2.70%
DR Locus Mismatch	0	2,678	98.50%	0.20%	2,678	97.20%	0.30%	8,565	84.60%	0.50%	15,065	66.60%	0.70%
	1	6,666	97.90%	0.20%	6,666	96.30%	0.20%	20,547	80.90%	0.40%	33,787	57.10%	0.50%
	2	3,067	98.00%	0.30%	3,067	95.60%	0.40%	8,915	79.40%	0.60%	13,106	55.00%	1.00%
	Unknown	131	98.90%	1.50%	131	96.10%	1.70%	323	80.90%	3.00%	906	54.40%	2.50%
Total Mismatch	0	1,067	98.10%	0.40%	1,067	97.10%	0.50%	3,458	89.20%	0.70%	6,429	73.10%	1.00%
	1	573	98.80%	0.40%	573	97.00%	0.70%	2,281	82.40%	1.10%	4,032	61.50%	1.50%
	2	2,108	98.30%	0.30%	2,108	97.00%	0.40%	6,878	81.30%	0.60%	11,855	59.30%	0.80%
	3	3,515	98.10%	0.20%	3,515	96.80%	0.30%	11,054	80.50%	0.50%	18,306	56.80%	0.70%
	4	1,802	98.10%	0.30%	1,802	95.80%	0.50%	5,147	81.00%	0.80%	7,844	58.70%	1.30%
	5	2,050	97.90%	0.30%	2,050	95.60%	0.50%	6,001	79.50%	0.70%	8,910	55.80%	1.20%
	6	1,114	97.40%	0.50%	1,114	95.30%	0.60%	3,205	79.40%	1.00%	4,575	52.50%	1.90%
	Unknown	133	97.00%	1.50%	133	96.20%	1.70%	326	80.80%	3.00%	914	54.50%	2.50%

Source: OPTN/SRTR Data as of May 4, 2009.

(2009 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1999-2008. U.S. Department of Health and Human Services, Health Resources and Services Administration, Healt)

Rejection and outcomes

Rejection still remains a dreaded complication of transplantation. Thought the incidence of acute rejection episodes in the first year of transplantation has declined to less than 10%, its presence still has a very impact on the renal allograft. The use of more potent immunosuppression has resulted in a significant reduction in both acute t cell and antibody mediated rejection. Cellular rejection is mediated by T lymphocytes and other inflammatory cells activated against donor histocompatibility antigens. Chronic cellular rejection is not as clearly defined clinically but most recently acknowledged in Banff. Antibody mediated rejection remains somewhat of an enigma but its presence is becoming more and more realized and its long term impact on the renal allograft better understood. Antibody mediated rejection occurs as a result of antibodies to HLA antigens. The proposed pathogenesis of antibody

mediated rejection is thought to involve many steps, with binding of antibody to HLA antigens on the endothelium initiating a series of important events, the most important of which is activation of the complement cascade with the end product being complement C4d binding to the endothelium (Figure 6, 7). It should not come as any surprise that C4d then is stated to be the footprint of antibody mediated rejection and its presence the main criteria needed for the diagnosis of both acute and chronic antibody mediated rejection.

Acute cellular rejection itself has been associated with as high as a 10% one year graft loss. The presence of both a cellular and antibody mediated rejection is even more detrimental to the allograft with one year graft loss being as high as 40% (Crespo, Pascual et al. 2001). Rejection itself, the number of rejections, severity of rejection and reversibility after treatment are all important factors that impact chronic renal allograft survival as well (Meier-Kriesche, Ojo et al. 2000). Most recently, the time of rejection has also been determined to be an important factor, with late acute rejection episodes having more of a negative impact on graft survival (Joseph, Kingsmore et al. 2001) (Opelz and Dohler 2008).

Anti-donor HLA IgG antibodies against either class I or class II antigens are associated with an increased risk of antibody mediated rejection and an increased risk for graft loss. More specifically, antibodies against donor HLA antigens DR, A, B (highly expressed on kidney) put the allograft at the most risk for acute antibody mediated rejection. What is now being recognized is that the presence of HLA antibodies to likely any of the HLA antigens and whether present before transplantation or de novo after transplantation appear to have an important impact on chronic allograft nephropathy. Both the 13th and 14th International Histocompatability Workshops were able to demonstrate that most chronic failures were preceded by de novo antibody development, whether they were donor specific or not (Terasaki, Ozawa et al. 2007) (Terasaki and Ozawa 2005; Terasaki and Cai 2008) (Lefaucheur, Suberbielle-Boissel et al. 2008). In addition, highly sensitized patients are also noted to have reduced long term graft survival rates, again demonstrating the importance of antibody with regards to long term allograft survival (Table 10) (Opelz 2005). A histologic finding, transplant glomerulopathy (double contours of glomerular basement membranes) is thought to likely represent the process of chronic antibody mediated rejection especially given its strong association with class II HLA donor specific antibodies (Cosio, Gloor et al. 2008; Issa, Cosio et al. 2008).

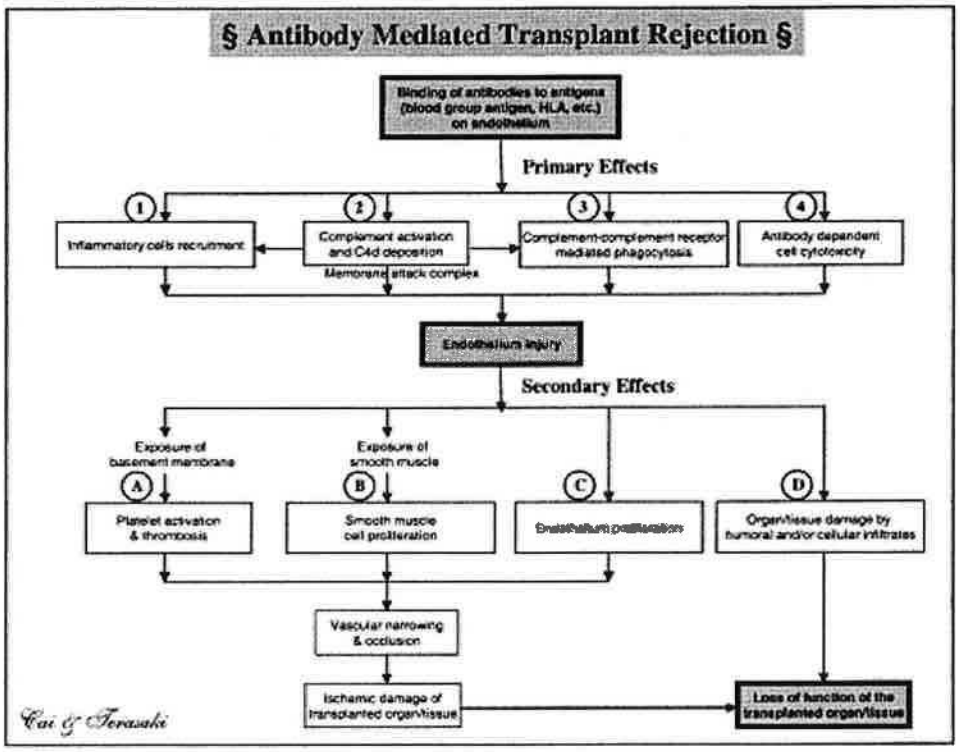


Figure 6

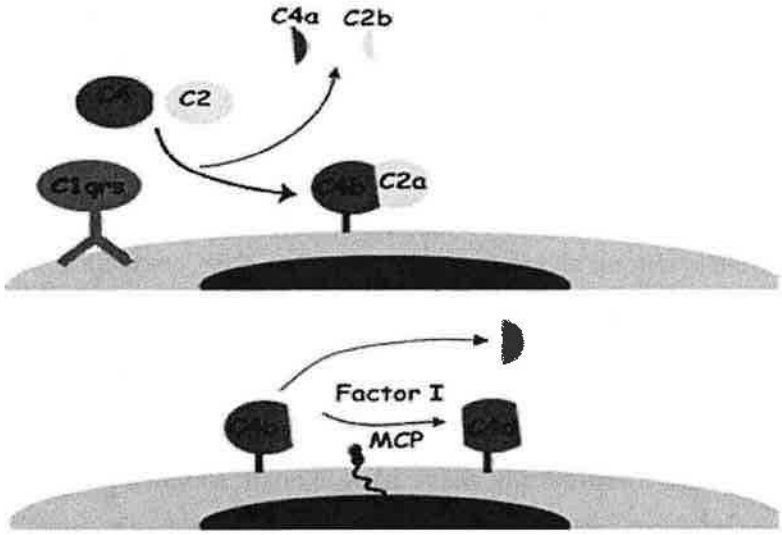


Figure 7

- Increases in sensitization to lymphocyte antigens, incrementally augment risk of graft loss

	PRA at Tspt	5 Yrs	10 Yrs
DD-ECD	0-9%	58.2	28.9
	10-79%	52.4	26.5
	80%+	48.4	20.1
DD-nECD	0-9%	72.1	46.5
	10-79%	70.1	42.7
	80%+	70.2	42.8
Living donor	0-9%	81.7	58.4
	10-79%	79.9	53.5
	80%+	69.2	52.9

Source: OPTN/SRTR Data as of May 4, 2009.

Table 10

Calcineurin Inhibitor Toxicity

Although it is evident that chronic deterioration is a multifactorial process, immunosuppressant nephrotoxicity continues to play a major role in chronic allograft dysfunction. As a class, calcineurin inhibitors cause vasoconstriction of the afferent and efferent glomerular arterioles with a subsequent reduction in renal blood flow and GFR. The exact mechanism of vasoconstriction remains unclear but endothelial cell dysfunction has been proposed. Acutely, CNIs can cause a functional nephrotoxicity, tubular vacuolization and arteriolar hyalinization. Theoretically, these acute changes should improve with dose adjustment of the calcineurin inhibitor. Chronically, all compartments seem to be affected with glomerulosclerosis, arteriolar hyalinosis, interstitial fibrosis and tubular atrophy all being seen. Calcium channel blockers, ace inhibitors, angiotensin II receptor antagonists and even fish oil have all been proposed as medications that could potentially mitigate the effects of calcineurin inhibitor nephrotoxicity. There are no definitive answers. Numerous studies have looked at withdrawal, minimization and even conversion of calcineurin inhibitors to other less nephrotoxic medications.

Sirolimus was in particular looked at because of its reported ability at inhibiting renal fibrosis. The CAESAR (Cyclosporine Avoidance Eliminates Serious Adverse Renal Toxicity) study looked at CNI withdrawal. It randomized over 500 patients into one of three groups: 1) Daclizumab, MMF, steroid and low dose CSA (trough 50-100)/wean to off by 6 months 2) daclizumab, MMF, steroids and low dose CSA (trough 50-100), 3) MMF, steroids, standard dose CSA with no induction therapy(target trough 150-300 then at month 4 and after 100-200 ng/ml). Kidney function at 1 year was similar between the two groups but the incidence of rejection was unacceptably higher in the complete withdrawal group at almost 38%. Most importantly, low dose CSA was well tolerated. (Ekberg, Grinyo et al. 2007) The ELITE-SYMPHONY study (Efficacy Limiting Toxicity Elimination-Symphony) took a look at minimization of CNIs. This study compared four regimens in a randomized, controlled, prospective trial of almost 1600 patients. The patients were assigned to either 1) conventional dose CSA, steroids and MMF or daclizumab induction, mmf and steroids plus either low dose CSA (trough 50-100 ng/ml), low dose sirolimus (4-8 ng/ml) or low dose tacrolimus (trough 3-7). Mean GFR and allograft survival at one year was higher for the low dose tacrolimus compared to all others and biopsy confirmed acute rejection rates were the lowest in the low dose tacrolimus group compared to all other groups. Of note, those patients on low dose Sirolimus fared worse in all aspects with the lowest allograft survival rates and highest acute rejection rates. Another important point to make from this study is that the low dose prograf group seemed to fair better overall as compared to the low dose cyclosporine group. The Convert trial was a large prospective randomized study that enrolled over 800 patients that asked the question we have all been seeking an answer to. Can sirolimus replace the use of CNI. Unfortunately, the bottom line of the CONVERT trial was that the use of Sirolimus in place of CNI in patients with GFRs <40ml/min was unsafe and that in those patient with a GFR of >40ml/min with >110mg/d of protein there was no advantage with worse adverse events, in particular worsening proteinuria, being seen in those patients who were converted to Sirolimus (Schena, Pascoe et al. 2009).

BK Polyoma Virus

There are numerous infections that the transplant nephrologist should be aware of. BK nephropathy can have a very important impact on the donor kidney. It is a polyomavirus. The majority of adults have been exposed and are seropositive for BK. In immunocompetent individuals, the virus remains latent in the urinary epithelium. It is only when a patient becomes immunosuppressed that viral replication/nephropathy can occur and unfortunately, this virus has a preference for the transplanted

kidney. Many other potential risk factors also include recipient of a female donor kidney, older age of recipient at the time of transplant, and renal injury (i.e. rejection, ischemia/reperfusion injury/stent placement) (Khamash, Wadei et al. 2007) (Thomas, Dropulic et al. 2007). Further, as with CMV a few studies have shown an increased risk in recipients of BK seropositive donor kidneys (Shah 2000; Bohl, Storch et al. 2005). BK viremia is seen in approximately 15% of kidney transplant patients and polyomavirus-associated nephropathy (PVAN) in 2-10% of patients. Graft loss can be exceedingly high when PVAN is present. It is generally believed that the presence of BK in the allograft must be preceded by the presence of BK in the blood and viremia must be preceded by viruria. For this reason, many centers use BK plasma viral loads to screen for the presence of BK. The PPV for the presence of BK increases with BKV loads >10 (4^{th}) copies/ml in the plasma (>10 (7^{th}) copies/ml in urine). Urine decoy cells can be seen with BK but lack sensitivity and specificity for screening purposes. The definitive diagnosis of PVAN requires a renal biopsy. The treatment of BK essentially involves minimization of immunosuppression. Other options for the treatment of BK include cidofovir, quinolones and even IVIG (Kuypers, Vandooren et al. 2005; Gabardi, Waikar et al. 2010). Leflunamide (Arava) has in vitro activity against the virus (Josephson, Gillen et al. 2006). Retransplantation in patients with BK nephropathy is routinely done. There is very little data at present time with regards to this subject matter but the general consensus is that patients should be transplanted (at the very least) with negligible levels in the blood (Ramos, Vincenti et al. 2004).

Recurrent disease

All forms of glomerulonephritis can recur in the renal allograft. Glomerular diseases account for a significant number of patients undergoing transplantation. Recurrent disease is the third most common cause of allograft loss at ten years following chronic allograft dysfunction and death with a functioning allograft. The incidence of recurrence has been seen in some reports as 3-5% within 5 years and 15-20% at ten. The four most frequent forms of primary idiopathic GN that can recur after transplantation include FSGS, MPGN, idiopathic membranous and IgA. FSGS can recur in 30% of cases in first transplants and its recurrence associated with inferior graft outcomes (Hickson, Gera et al. 2009). However, recurrence is almost 100% in patients who had recurrence in a previous allograft. Other risk factors for recurrence include young age at presentation, rapid loss of kidney function in the native kidneys (typically less than 3 years), and those with the collapsing variant of FSGS. Recurrence of FSGS is bimodal and can occur within a few hours to days after after transplant or months to years later.

Caution should be undertaken when living related donors in patients with a known genetic variant of the NPHS2 gene (Bertelli, Ginevri et al. 2003) (Ruf, Lichtenberger et al. 2004). Though slim, recurrence has been reported. A permeability factor or humoral factor has been proposed as the underlying pathogenesis. Not surprising then, plasmapheresis remains the mainstay of treatment in patients with recurrent idiopathic FSGS. The use of plasma-exchange prophylactically in patients thought to be at high risk for recurrence has not consistently been shown to be of benefit (Ponticelli and Glassock 2010) (Hariharan, Adams et al. 1999; Gohh, Yango et al. 2005; Golgert, Appel et al. 2008; Hickson, Gera et al. 2009). MPGN recurs in 30% of cases. The subtype most important in renal transplantation is MPGN type II (dense deposit disease) which can recur histologically in >60% of cases. Outcomes of DDD (dense deposit disease) are typically unfavorable. Underlying pathogenesis appears to involve abnormalities involving the complement system. Patients with autoantibodies towards C3B or CfH mutations seem to have the highest risk of recurrence (Braun, Stablein et al. 2005; West and Bissler 2008). The type I subtype of MPGN is also of clinical importance. Idiopathic membranous recurs in 20-30% of patients and is the most common GN lesion found de novo after transplantation (not uncommonly in association with hepatitis C). The pathogenesis is thought to potentially involve autoantibodies to podocyte proteins. The diagnosis is typically made several years post transplant and the prognosis better than other GNs, as can also be said of IgA. Histologically, IgA likely recurs in a significant number of patients. Clinically, various studies have documented recurrence in 18-25% of patients. The underlying pathogenesis is currently unknown but unlike the underlying pathogenesis in native IgA, abnormal glycosylation of IgA1 is not likely involved. There are numerous proposed risk factors for recurrence: 1) young age at diagnosis of original disease, 2) more rapid progression to ESRD after original diagnosis (typically less than 3-5 years) 3) ?IgA in donor kidney 4) certain TNF and Il-10 polymorphisms 5) native kidney biopsy crescents, 6) living donor or zero mismatched donor kidney (Coppo, Amore et al. 2007). Graft loss occurs in only a minority of patients (Ponticelli and Glassock 2010) (Hariharan, Adams et al. 1999; Gohh, Yango et al. 2005; Golgert, Appel et al. 2008).

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