Monitoring and Managing Chronic Graft Health in the Kidney Recipient

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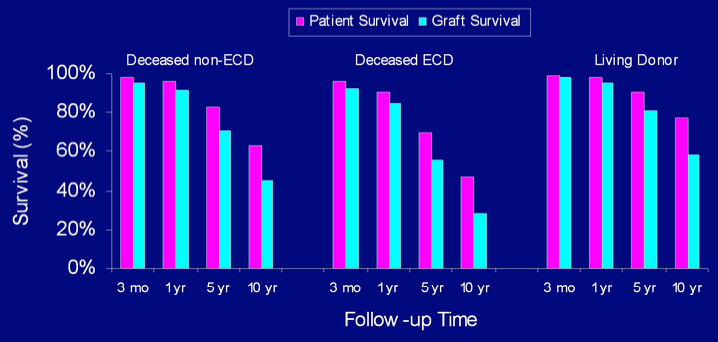
How Effective Are We In Maintaining Chronic Graft Health?

- Many benchmarks to evaluate

How long do grafts last?

Figure I-3. Unadjusted Patient and Graft Survival.



Five-year patient survival percentages (based on transplants during 2001-2006) and 10-year patient survival (based on transplants during 1996-2006) were clearly higher for recipients of living donor organs than for those of deceased donor organs. Similarly, living donor organs had the highest five- and 10-year graft survival.

Source: *2008 OPTN/SRTR Annual Report*, Tables 5.10a, 5.10b, 5.10d, 5.14a, 5.14b, 5.14d.

SRTR

So…despite our monitoring and managing

- Grafts don't last a lifetime
- In other words we are not managing graft health as successfully as our patients…or we would like

Why not?

Are we allowing acute rejection to destroy our patient's allograft?

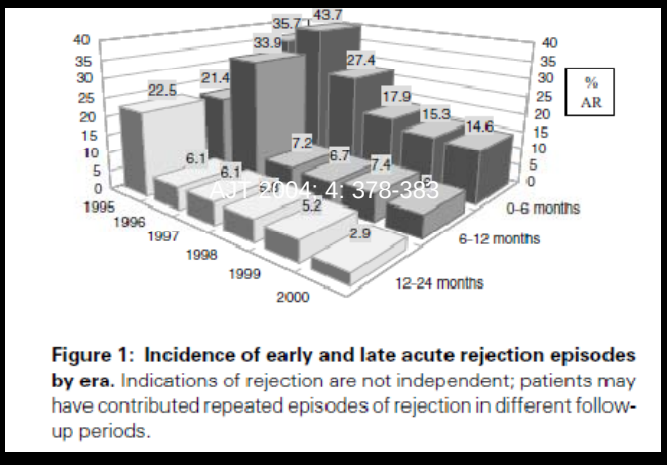


Figure 1: Incidence of early and late acute rejection episodes by era. Indications of rejection are not independent; patients may have contributed repeated episodes of rejection in different follow-up periods.

AJT 2004; 4: 378-383

If acute rejection was the principal culprit

- you would anticipate improvements in long term graft survival…

Not the case

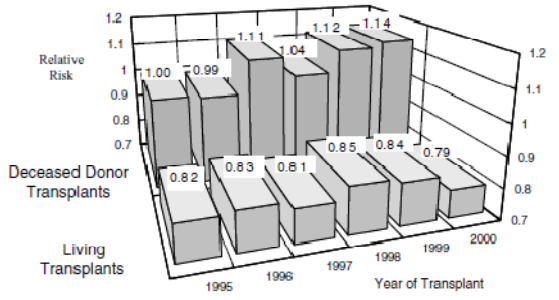


Figure 2: Relative risk for overall graft loss by donor type. Model corrected for induction, antiproliferative, and inhibitor medication regiments at baseline, cold ischemia time, PRA level, HLA-A, -B, and -DR mismatches, recipient and donor gender, ethnicity, and age, presence of delayed graft function, primary diagnosis, and waiting time on dialysis.

AJT 2004; 4: 378-383

What causes most graft loss now?

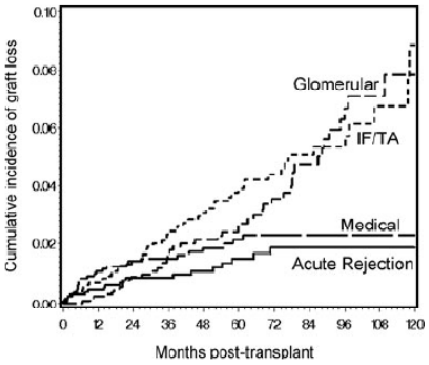


Figure 3: Cumulative incidence of graft loss due to acute rejection, glomerular disease, IF/TA and medical conditions (accounting for the competing risks of death and losses due to other causes such as primary nonfunction).

AJT 2009; 9: 527-535

What does this all mean?

- Our monitoring approach is not working and/or
- Our management approach is failing

Let’s consider the monitoring aspect of the equation

Why Do We Monitor?

- As a management tool
- To evaluate whether the kidney is stable
  - If it is we assume that there is no intrinsic ongoing process
- If the kidney is not stable we ask:
  - Is there an underlying acute or chronic process?
  - Can that process be reversed?
  - How will the process affect long term survival?
- We also monitor for prognosis and planning

How can we diagnose kidney transplant trouble

- And make the diagnosis before it is too late

Evaluate kidney function

- Check the creatinine

What does an increase in creatinine mean in the chronic patient?

- Still can be acute rejection
- More likely:
  - Chronic allograft injury
  - Recurrence of original disease
  - De novo kidney disease

You may argue

- Serum creatinine is not the most sensitive or specific measure to assess kidney dysfunction and the processes that affect graft health long term
- Do we have better measures?

Other measures of kidney function

- Inulin
- Iothalamate
- Iohxol
- Pros: most accurate measure of allograft function
- Cons: cost, low patient acceptance, lack of availability

How about?

- Cystatin C?

- Pros: independence from body weight
- Paucity of studies in the transplant setting

Overall What Do We Want to Know

- Kidney function
- Kidney parenchyma
- Immunologic status

How Might We Get this Information?

- Kidney function
  - Creatinine
- Kidney parenchyma
  - Protocol biopsies
- Immunologic status
  - Development of donor specific antibodies

Donor Specific Antibodies?

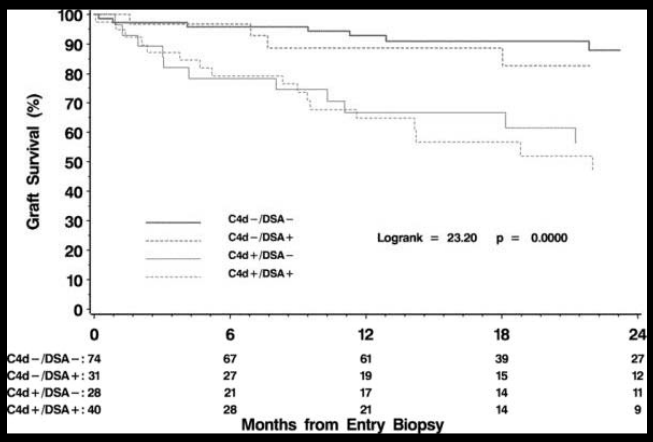


FIGURE 2. Kaplan-Meier analysis of the impact of presence or absence of C4d and donor-specific antibody (DSA) on allograft survival after for cause biopsy, by group.

Transplantation. 90(1):68-74, July 15, 2010.

Parenchyma: Biopsies?

- Protocol biopsies have shown inflammation below the Banff threshold if persistent may result in decreased renal function after 1 and 2 years

AJT 2007: 7: 356-365

On the other hand…

- Slight risk of morbidity
- Decreasing prevalence of inflammation found on biopsies from patients given tacrolimus/MMF combination
  - No benefit in a group undergoing biopsies within first 6 months. (AJT 2007: 7: 2538)
- Sampling error
- Cost

KDIGO

- How do these guidelines suggest monitoring?

Table 4: Routine screening after kidney transplantation

	Screening intervals by time after transplantation					
Screening test	1 week	1 month	2–3 months	4–6 months	7–12 months	>12 months
Creatinine[a]	Daily	2–3 per week	Weekly	Every 2 weeks	Monthly	Every 2–3 months
Urine protein[b]	.....	Once	.....	Every 3 months	.....	Annually
Complete blood count[c]	Daily	2–3 per week	Weekly	.....	Monthly	Annually
Diabetes[d]	.....	Weekly	.....	Every 3 months	.....	Annually
Lipid profile[e]	–	–	Once	–	–	Annually
Tobacco use[f]	Prior to discharge		–	–	–	Annually
BKV NAT[g]	.....	Monthly	.....	.....	Every 3 months	–
EBV NAT (seronegative)[h]	Once	.....	Monthly	.....	Every 3 months	–
Blood pressure, pulse, height, body weight	Each clinic visit					

AJT 2009; 9 (suppl 3): S29

So for now…

- Most of us monitor with creatinine
- Let’s put creatinine measurements in context

How well do most grafts function?

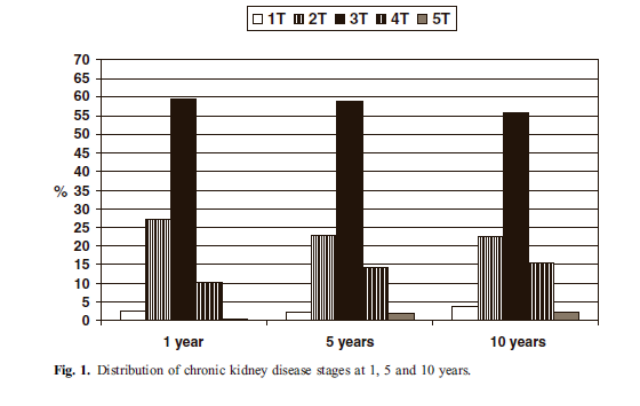
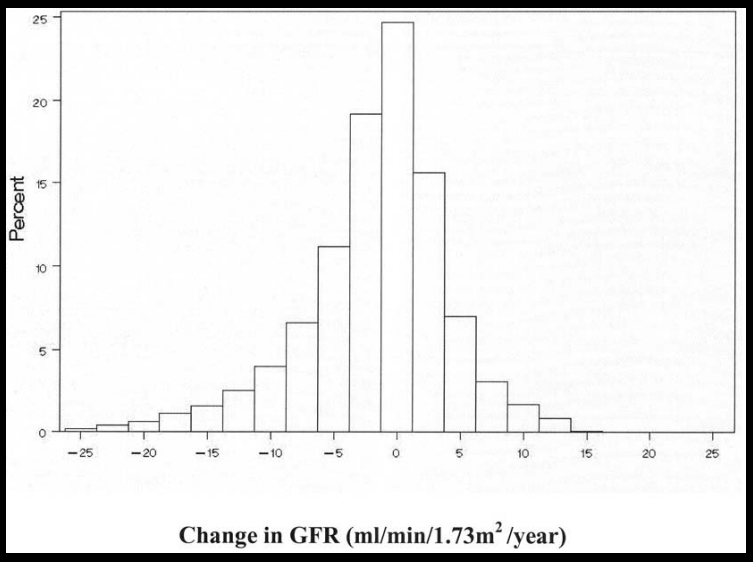


Fig. 1. Distribution of chronic kidney disease stages at 1, 5 and 10 years.

NDT plus 2010; 3 (suppl 2): ii2-ii8

How stable are most grafts?

Figure 1. Change in GFR after kidney transplantation



Gill, J. S. et al. J Am Soc Nephrol 2003;14:1636-1642

Table 2. Annualized change in GFR (ml/min per 1.73 m^2 per year) before and 2 yr after transplantation (piece-wise regression)

Overall	-1.66 ± 6.51
During first 2 posttransplant years	-0.33 ± 8.87
After first 2 posttransplant years	-2.68 ± 9.44

JASN 2003; 14: 1636-1642

What can we do about late graft deterioration?

- Depends on the cause and whether the process is reversible
- Often even if we do something…we are not sure that our interventions have long term benefit

This brings us to the management side of the equation

Though before we can manage

- We need to know what we are managing
- We need to clarify what needs management
  - i.e. what portends a bad prognosis
- We need to identify effective management

We are starting to get a sense of histologic features associated with poor prognosis

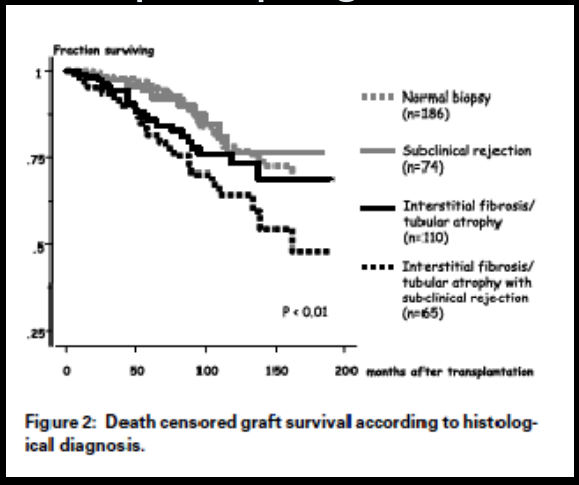


Figure 2: Death censored graft survival according to histological diagnosis.

AJT 2006l 6: 747

DeKAF

- Identifying those at risk for graft loss
- Testing management of dysfunction in order to identify how to improve long term graft health

DeKAF

- Multi-center observational study at 7 centers in US and Canada
  - Identify and characterize the cause of late (> 90 d) kidney allograft dysfunction and failure
    - define individual phenotypes leading to dysfunction
    - For each phenotype identify risk factors and expected outcomes
    - Use these categories to test potential interventions

DeKAF APPROACHES

- 2 cohorts
  - cross-sectional, transplanted prior to Oct 1 2005, developing late graft dysfunction leading to biopsy
  - Prospective cohort entered at time of transplant

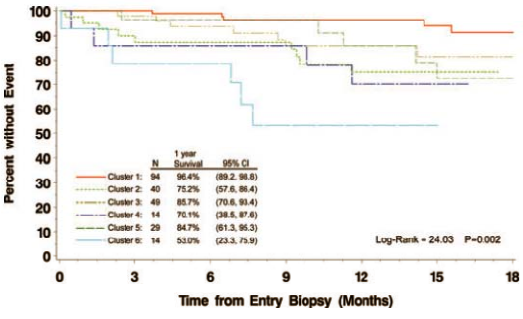


Figure 4: Death-censored graft survival (postbiopsy) by cluster ($p = 0.0072$).

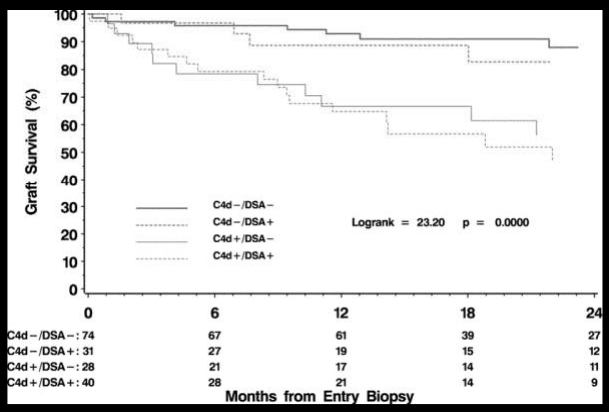
AJT 2010; 10: 315-323

What else have we learned from DeKAF?

- Antibody-mediated injury (as indicated by C4d staining and circulating DSA) in patients with new-onset late graft dysfunction often leads to graft failure
- Grafts from similar recipients without evidence for antibody-mediated injury remain well preserved

DeKAF

- Bottom line: nonimmunologic issues may take a back seat to immunologic insult



Evidence for Antibody-Mediated Injury as a Major Determinant of Late Kidney Allograft Failure.
Gaston, Robert; Cecka, J; Kasiske, Bert; Fieberg, Ann; Leduc, Robert; Cosio, Fernando; Gourishankar, Sita; Grande, Joseph; Halloran, Philip; Hunsicker, Lawrence; Mannon, Roslyn; Rush, David; Matas, Arthur

Transplantation. 90(1):68-74, July 15, 2010.
DOI: 10.1097/TP.0b013e3181e065de

FIGURE 2. Kaplan-Meier analysis of the impact of presence or absence of C4d and donor-specific antibody (DSA) on allograft survival after for cause biopsy, by group.

These findings bring up provocative management questions

- Are current immunosuppressant practices successful in the long term?
  - Aggressive early immunosuppression to decrease acute rejection followed by long term minimization and late immunologic injury
- Do any currently available immunosuppressants minimize development of late post-transplant donor specific humoral immunity?
- Could it be that immunosuppressant toxicities limit our ability to provide best long term treatment?

In the future we may be able to

- Monitor more effectively
  - Non-invasively diagnose inflammation and the presence of fibrosis
- Better manage immunologic perturbations
  - Tailor the intensity of immunosuppression to the inflammatory status of the graft or use other strategies that have yet to be defined by DeKAF or other studies

In the meantime…

- We will all continue to monitor serum creatinine and some of us will perform protocol biopsies
- And although this session won't address BK…I want to remind you to remember to monitor for BK to prevent nephropathy
  - a cause of graft inflammation and tubular atrophy

Thank You!

Let’s Define Chronic Graft Health

- After one year