

Managing Immunosuppression After Transplant Failure

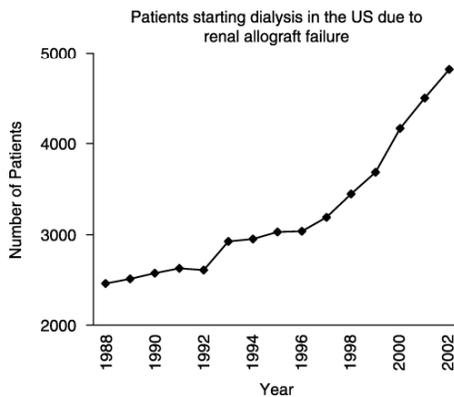
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Another day in the transplant clinic...

- “My patient Kurt Cobain’s kidney graft has failed and he has started back on hemodialysis. What should I do with his immunosuppression medication?”
 - »Or
- “Mr. Roethke, nice to see you again to discuss another transplant. You have been back on PD for a year? Let’s talk about your medications.”

What happens to the patient after graft failure?

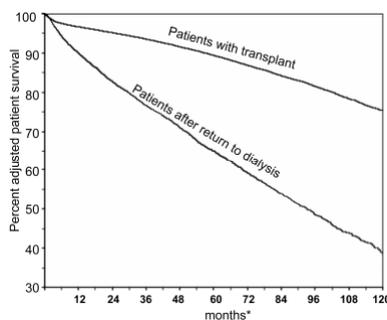


- 10-15% dialysis population made up of patients with failed grafts returning to dialysis
- Five percent of transplant wait list made up of patients with prior transplant

UNOS Renal Transplant Registry

Outcomes after renal graft failure

- Kaplan and Meier-Kriesche, AJT, 2002



- Decreased patient survival after graft loss
 - 10 yr patient survival 40% graft loss vs 75% functioning transplant
- Rao et al, NDT, 2005: mortality HR
 - Transplant naïve 1
 - Cad donor transplant 0.25
 - Living donor transplant 0.13
 - Graft failure on dialysis 0.90

What is the impact of continued immunosuppression after renal graft failure?

- *How much does immunosuppression contribute to mortality risk?*
- *Taper vs continuing immunosuppression*
- *Does the cause, timing, and course of graft failure matter?*
- *Implications for future retransplant?*
- *Relationship of transplant patient with the transplant center after graft failure*

To Stop or Not To Stop

- | | |
|---|--|
| <ul style="list-style-type: none">• <i>Potentially favors discontinuation</i>• Infection risk• Adverse metabolic effects (glucose, lipids), HTN• Cost | <ul style="list-style-type: none">• <i>Potentially favors continuation</i>• Preservation residual renal function• Prevention graft intolerance syndrome• Reduce sensitization?• Prevent reactivation systemic disease• Prevent adrenal insufficiency |
|---|--|



Infections after renal allograft failure with or without immunosuppression

	Immunosuppression continued	Immunosuppression discontinued
Time periods	19	29
Female:Male	9:10	14:15
Age n (yr) ^a	42.5 (12.2)	41.7 (12.9)
Duration of graft function (yr) ^a	3.1 (2.7)	1.8 (3.0) ^b
Follow-up after graft failure (yr) ^a	1.3 (0.8)	3.1 (3.1) ^b
Total follow-up (patient yrs)	25.4	91.2
Infections	58	62
Lethal infections	5	0

^a Mean (SD).

^b $P < 0.05$.

- 37 patients receiving 42 transplants 1975-95
- Low dose immunosuppression (prednisone avg 9.75 mg or pred avg 13mg + AZA 75 mg) vs discontinuation (nephrectomy)

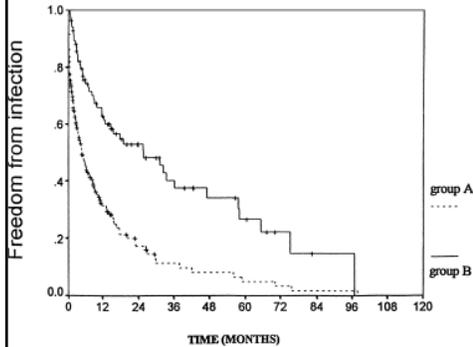
Gregoor, Transplantation, 1997

Increase in infections with continuation of immunosuppression

	Group A (infection/ patient-year) (n=19)	Group B (infection/ patient-year) (n=29)
Viral infections		
Cytomegalovirus	1 (0.04)	3 (0.03)
Herpes zoster	1 (0.04)	0
Herpes simplex I	1 (0.04)	0
Bacterial infections		
Urinary tract	12 (0.47)	6 (0.07)
Bronchitis/pneumonia	18 (0.71)	27 (0.30)
Skin	3 (0.12)	17 (0.19)
Opportunistic infections		
Histoplasma capsulatum	1 (0.04)	0
Tuberculosis	1 (0.04)	0
Sepsis	10 (0.39)	1 (0.01)
Continuous ambulatory peritoneal dialysis-related peritonitis	7 (2 patients)	4 (4 patients)
Other infections	3 (0.12)	4 (0.04)
Total infections	58 (2.28)	62 (0.68)

Gregoor, Transplantation, 1997

Continuation of immunosuppression increases risk of infection after failed graft



- 197 pts with failed transplants >3 mo function (1972-1996)
- Group A with (192 time periods) and group B without immunosuppression (90 time periods)
- Group A avg prednisone 7.13, AZA 56, CsA 232
- Avg f/u 147d grp A, 590d grp B

Gregoor, Clinical Transplantation, 2001

Continuation of immunosuppression increases risk of infection after failed graft: Incidence per patient year

	Group A	Group B	OR	p
Viral infections	0.10	0.01	7.7	0.0002
Bacterial infections	1.16	0.35	3.3	<0.0001
sepsis	0.18	0.04	4.3	<0.0001
urinary tract	0.29	0.06	5.2	<0.0001
lung	0.28	0.09	3.2	<0.0001
skin	0.31	0.14	2.2	0.0009
opportunistic	0.10	0	45.3	<0.0001
PD peritonitis	0.36	0.14	2.6	<0.0001
TOTAL	1.7	0.51	3.4	<0.0001

Gregoor, Clinical Transplantation, 2001

Increase in morbidity and mortality associated with continued immunosuppression

	Group A	Group B	p
Cardiovascular disease	19	5	0.001
myocardial	17	3	
cerebral	0	2	
other	2	0	
Infectious disease	15	7	0.03
sepsis	6	4	
opportunistic	3	1	
other	6	2	
Malignancies	1	0	
Other	4	3	
TOTAL	39	15	<0.0001

Gregoor, Clinical Transplantation, 2001

Non-Immunologic factors impact mortality after kidney transplant failure

- Study of 4741 pts initiating dialysis after renal graft failure (USRDS) 1995-98
- Majority of 1016 deaths due to cardiac (36%) or infectious (17%) causes
- Risk of death not associated with prior antibody induction, acute rejection treatment, or continuation of CNI

Predictors of cardiac and infectious death after kidney transplant failure

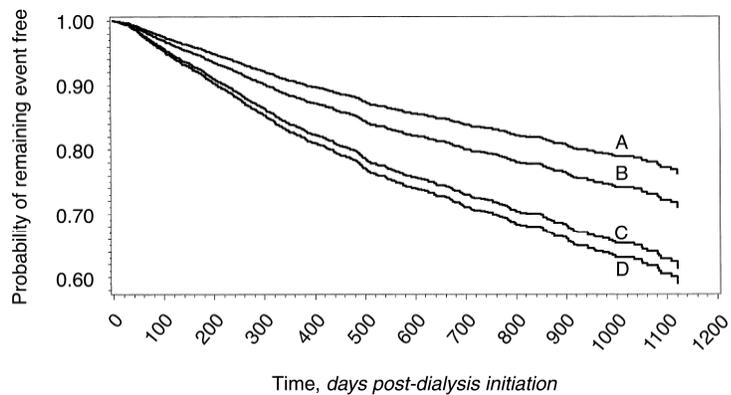
- **Cardiac death:**
 - Age (per year) RR 1.03
 - Diabetes 1.75
 - PVD 1.80
 - CHF 1.40
 - Cadaveric donor 1.6
- **Infectious death:**
 - Age RR 1.03
 - Female 1.48
 - Diabetes 2.17
 - PVD 2.01

» p<0.05

Gill et al, Kidney International,
2002

Non-Immunologic factors impact mortality after kidney transplant failure

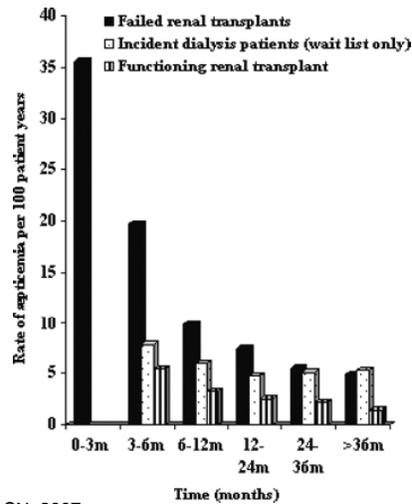
- A=no diabetes, CHF, PVD; B=CHF, C=DM, D=PVD



Gill et al; Kidney International
2002

Sepsis after failed renal transplant

- 5117 pts returning to dialysis (USRDS 1995-2004)
- Not able to determine type of immunosuppression continued after graft failure



Johnston, JASN, 2007

Factors associated with sepsis after renal graft failure

	HR
Age > 60 yrs	1.31
BMI >30	1.17
Diabetes	1.76
Hemodialysis (vs PD)	1.70
PVD	1.44
CHF	1.25
Induction therapy: depleting	0.91
nondepleting	0.86 p=NS

Johnston et al, JASN, 2007

Advantages of discontinuation of immunosuppression

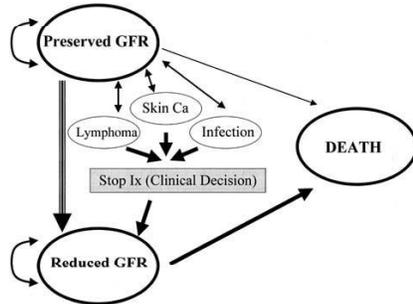
- Some evidence that it reduces morbidity and mortality due to infectious complications
- Highest ID risk first 3-6 months after dialysis initiation; i.e. period of immuno taper; lack of controlled studies
- Unclear contribution immunologic vs non-immunologic factors to adverse outcomes
- Potential benefit to decrease CV risk factors

Should immunosuppression be continued to preserve residual renal function?

- Residual renal function has a beneficial effect on survival of dialysis patients
- Little data on course of residual renal graft function after return to dialysis
- RRF declined faster in a group of 28 pts returning to PD (Davies, Proceedings of the ISPD, 2001) ; survival was unaffected vs native ESRD PD pts

Should immunosuppression be continued to preserve RRF?

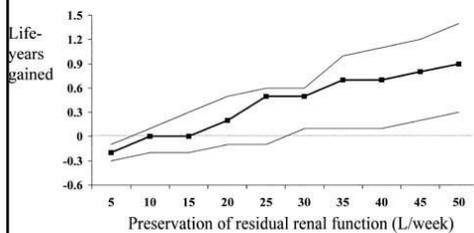
A decision analysis model



- Assumed continued immuno after return to PD until urine volume <100ml/day vs. gradual steroid taper and other immuno stopped at time of PD start
- Introduced probabilities:
 - PD survival based on CANUSA
 - Probabilities of infection/cancer and associated mortality
 - Probabilities of losing graft function with/without immunosuppression

Jassal et al, AJKD, 2002

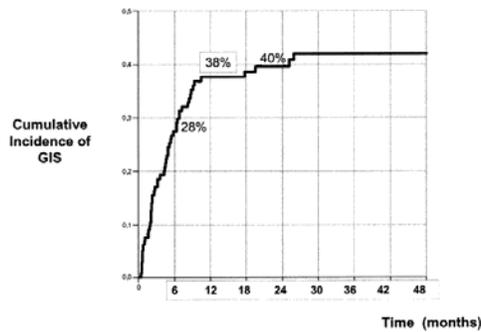
Should immunosuppression be continued to preserve RRF?



- Model shows a potential survival benefit to preserving RRF with continued immunosuppression
- Effect of immuno on CV risk, DM not included; effect of use of immunosuppression in uremia

Jassal et al, AJKD, 2002

Continuation of immunosuppression to avoid acute rejection?



- Graft intolerance syndrome: fever, graft pain, hematuria, enlarged graft, malaise
- Prednisone reduced by 2.5 to 5 mg q 1-2 weeks, CNI reduced by 25% q week, antimetabolite stopped immediately
- Retrospective observational study of 149 transplant patients returning to dialysis 6/89 through 12/01

Delgado et al, AJKD, 2005

Continuation of immunosuppression to avoid acute rejection?

- Incidence of graft intolerance syndrome 30-40% despite different immunosuppression withdrawal protocols
- Pediatric transplant recipients reported to have a higher incidence (61%) despite 3 month withdrawal of immuno Krause et al, NDT, 2008
- No difference in rates of graft intolerance immuno continuation vs withdrawal Gregoor et al, Clinical Transplantation, 2001

Does continued immunosuppression impact patient sensitization

- High frequency of anti-donor antibodies found in patients with chronic rejection:
- 100% of 29 pts developed HLA antibodies prior to diagnosis of chronic rejection (Lee et al, Transplantation, 2002)
- 96% of 826 patients listed after a failed transplant had HLA antibodies (El-Awar et al, Transplant Proceedings, 2002)
- Elevated PRA ranges 30-70% in observational studies of transplant pts returning to dialysis (Mao et al, Transplantation, 2007)

HLA antibodies after graft failure

- Retrospective review 192 patients receiving a primary and subsequent transplant between 1980-92
- Group A: retransplant without dialysis
- Group B: dialysis for some time prior to retransplant

	Group A	Group B
Peak PRA >10%	33%	78%
Current PRA >10%	17%	55%

High risk of sensitization after failed islet transplantation

- 98 patients receiving 191 islet infusions March 1999-January 2007
- 17 patients discontinued immunosuppression
- 8/17 had de novo antibodies prior to immuno discontinuation
- 2 more developed antibodies after discontinuation
- Broadening of sensitization after discontinuation of immunosuppression:
- Class I PRA >20% in 5/15 patients on immunosuppression, increased to 11/14 after discontinuation; Class II 3/15, increasing to 10/14

Campbell et al, AJT, 2007

- Some evidence continuation of immunosuppression after graft failure increases incidence infections
- Whether continuation beneficial to preserve residual graft function not well studied
- Whether continuation can forestall graft intolerance: should consider adverse effects chronic inflammatory state
- Some suggestion immunosuppression withdrawal can increase sensitization

Recommended management of immunosuppression after transplant failure:

Failed graft in situ

- Majority of authors recommend discontinuation after initiating dialysis; minimization with advanced graft CKD
- Reduce infection risk (level C evidence, opinion based)
- Theoretical benefits of continuation not well studied or documented (i.e. preservation RRF, risk of greater sensitization): if so, how much, with or without CNI?
- Continuation as a bridge to retx with living donor; bridge to graft nephrectomy high risk for graft intolerance syndrome (?pediatric)



Immunosuppression withdrawal algorithms

- Recommendations limited by lack of head to head comparisons
- Rapid withdrawal may induce acute rejection, risk of graft rupture, hemorrhage
- Published center protocols generally taper over 3-6 months
- Initial step is to discontinue antimetabolite immediately (AZA, MMF, Sirolimus)
 - Bone marrow suppression effects

Immunosuppression withdrawal algorithms: calcineurin inhibitors

“Taper and withdrawal over brief period (1-3 wks) if graft failure was chronic and slow; 4-8 weeks if graft failure followed more acute immunologic events”

“Maintain low plasma levels of CNI until dialysis commences at which time they are stopped completely over several weeks”

“Reduce CNI to once a day and then go down slowly over 3-6 months”

“Decrease CNI by 25% weekly”

Steroid withdrawal algorithm

“Steroid dose should be minimized at time of graft failure and then discontinued slowly over several months because the patient may be adrenally suppressed”

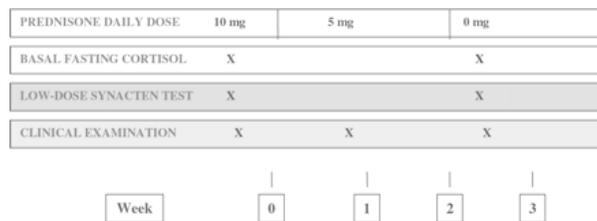
“Maintain the same dose of steroids taken when dialysis is initiated for 1 month; then halve steroid dose every month until complete withdrawal”

“Reduce prednisone to 5 mg a day and go down slowly over 3-6 months”

“Decrease prednisone by 2.5 to 5 mg every 1-2 weeks”

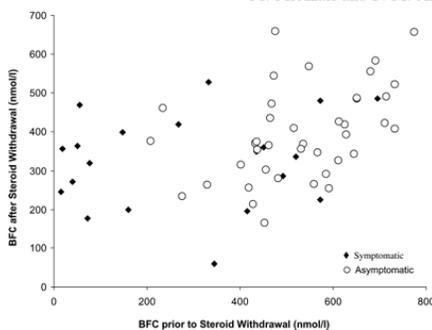
Steroid withdrawal after long-term medication for immunosuppressive therapy in renal transplant patients: adrenal response and clinical implications

- 63 renal transplant patients with functioning grafts
- Prednisone withdrawal after long term steroids (mean 36 months)
- Monitored for clinical symptoms withdrawal, basal cortisol(BFC), stimulated cortisol



Miozzari and Ambuhl, NDT, 2004

Risk of symptoms with steroid withdrawal



- 20 of 63 patients had symptoms of steroid withdrawal(SW)
- 9 of 9 patients with BFC <171 nmol/l had SW symptoms
- 11 of 54 patient with BFC >171 nmol/l had symptoms
- Symptomatic group on steroids longer (58 m vs 25 m)

- Early/acute graft failure (within 1 year) generally requires graft nephrectomy; allows for rapid discontinuation of immunosuppression
- Risks of continuation of immunosuppression after graft failure appear to outweigh benefits
- Graft intolerance syndrome can occur even with slow tapering of immunosuppression
- Steroids should be tapered slowly to avoid symptoms of adrenal insufficiency
- Recommendations/standardization hampered by lack of controlled studies