Current Trends in Kidney Transplantation: The Role of Nonadherence

Donald E. Hricik, MD
Professor of Medicine
Case Western Reserve University
Chief of the Division of Nephrology and Hypertension
Medical Director Kidney and Pancreas Transplantation
University Hospitals Case Medical Center
Cleveland, Ohio

Disclosures:
Grants from:
Novartis Pharmaceuticals Corporation, Oxford Immunotec Ltd., Bristol Myers Squibb
Current Themes in Kidney Transplantation

• Continued shortage of donors

• Increasing use of marginal donors
  – Higher rates of delayed graft function
  – Decreased long-term graft survival rates

• Emerging role of antibodies in acute and chronic rejection

• Decreased concerns about calcineurin inhibitor nephrotoxicity
The widely perceived success of renal transplantation must be tempered by the realization that organ demand far exceeds organ supply; in addition, despite significant improvements in 1-year graft survival, the rate of chronic graft loss after the first year remains substantial.

Cumulative Graft Failure (Measured by Yearly Attrition Rate) of First-Time Kidney Transplants

Etiology of Allograft Failure: Changing the Way We Think\(^1\)

<table>
<thead>
<tr>
<th>Past</th>
<th>Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Primarily a T-cell–mediated process</td>
<td>• Insufficient control of the humoral arm of a recipient’s immune system by current immunosuppressive regimens</td>
</tr>
</tbody>
</table>

Progressively superseding the historical dogma that such allograft losses were caused by CNI toxicity and CAN

CAN: chronic allograft nephropathy; CNI: calcineurin inhibitor.
~ 1990s – early 2000’s: Avoid CNI nephrotoxicity!

Nephrotoxicity of calcineurin inhibitors: native kidneys

(Ojo AO et al NEJM 349:10, 2003)
CNI Sparing Strategies

- CNI avoidance
- CNI withdrawal
  - Without conversion to another agent
  - With conversion to another agent
- CNI dose reduction

## CNI-Sparing Prospective Clinical Trials: CNI Avoidance Protocols

<table>
<thead>
<tr>
<th>Study [N]</th>
<th>Comparison Groups</th>
<th>Follow-Up</th>
<th>Incidence of AR</th>
<th>Graft Function</th>
<th>Graft Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ekberg et al (ELITE-Symphony)&lt;sup&gt;1&lt;/sup&gt; [1,645]</td>
<td>CsA-MMF-pred vs DAC-MMF-pred with: •Low-dose TAC •Low-dose CsA •Low-dose SRL</td>
<td>12 mo</td>
<td>↓ in low-dose TAC-MMF-pred</td>
<td>↑ in low-dose TAC-MMF-pred</td>
<td>↑ in low-dose TAC-MMF-pred</td>
</tr>
<tr>
<td>Larson et al&lt;sup&gt;2&lt;/sup&gt; [165]</td>
<td>TAC-MMF-pred vs SRL-MMF-pred</td>
<td>33 mo</td>
<td>Similar</td>
<td>Similar</td>
<td>Similar</td>
</tr>
<tr>
<td>Flechner et al (ORION)&lt;sup&gt;3&lt;/sup&gt; [443]</td>
<td>SRL-TAC (elimination at 13 wk)-pred vs SRL-MMF-pred vs TAC-MMF-pred</td>
<td>24 mo</td>
<td>↑ SRL-MMF-pred</td>
<td>Similar</td>
<td>Similar</td>
</tr>
<tr>
<td>Vincenti et al (BENEFIT)&lt;sup&gt;4&lt;/sup&gt; [666]</td>
<td>bela*-MMF-pred vs bela†-MMF-pred vs CsA-MMF-pred</td>
<td>12 mo</td>
<td>↑ bela*†-MMF-pred</td>
<td>↑ bela*†-MMF-pred</td>
<td>Similar</td>
</tr>
<tr>
<td>Durrbach et al (BENEFIT-EXT)&lt;sup&gt;5&lt;/sup&gt; [543]</td>
<td>bela*-MMF-pred vs bela†-MMF-pred vs CsA-MMF-pred (ECD)</td>
<td>12 mo</td>
<td>Similar</td>
<td>↑ bela*†-MMF-pred</td>
<td>Similar</td>
</tr>
</tbody>
</table>

* More intensive; † Less intensive.

bela: belatacept; DAC: daclizumab; ECD: extended-criteria donor; pred: prednisone; SRL: sirolimus.

### CNI-Sparing Prospective Clinical Trials: CNI Elimination Protocols

<table>
<thead>
<tr>
<th>Study [N]</th>
<th>Comparison Groups</th>
<th>Follow-Up</th>
<th>Incidence of AR</th>
<th>Graft Function</th>
<th>Graft Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conversion to SRL-Based Regimen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lebranchu et al (CONCEPT)	extsuperscript{1} [193]</td>
<td>CsA-MMF-pred vs SRL-MMF-pred</td>
<td>13 mo</td>
<td>Similar</td>
<td>↑ SRL-MMF-pred</td>
<td>Similar</td>
</tr>
<tr>
<td>Weir et al (Spare-the-Nephron)	extsuperscript{2} [299]</td>
<td>CsA or TAC-MMF vs SRL-MMF</td>
<td>24 mo</td>
<td>Similar</td>
<td>↑ SRL-MMF</td>
<td>Similar</td>
</tr>
<tr>
<td>Schena et al (CONVERT)	extsuperscript{3} [275]</td>
<td>CsA or TAC-MMF or AZA-pred vs SRL-MMF-pred</td>
<td>24 mo</td>
<td>Similar</td>
<td>↑ SRL-MMF-pred for GFR &gt;40 mL/min/1.73 m(^2)</td>
<td>Similar</td>
</tr>
</tbody>
</table>

Retrospective analysis of long-term outcome of kidney grafts related to biopsy at 1 yr (N = 292)

- 6 patients with inflammation and no fibrosis

Pathologic diagnoses
  - Acute rejection (n = 3)
  - BK nephropathy (n = 1)
  - Pyelonephritis (n = 1)
  - Nonspecific findings (n = 1)

In patients with fibrosis, level of inflammation associated with worse outcome

Graft Survival in DeKAF

Impact of Diagnosis of CAN or CNI Nephrotoxicity

CAN Does not Predict Subsequent Graft Failure: DEKAF Study

- n=440 “troubled grafts”
- Baseline creatinine <2 mg/dL
- Creatinine increase >25%

![Graph showing graft survival](image)

No kidney allograft lost in 10 years!

Is Immune Monitoring the Key to Safe CNI Minimization? CTOT-09

- Tacrolimus withdrawal in stable kidney transplant recipients
- Living donors, DSA negative, peak PRA < 20%
- Thymo, MMF, Tac, low dose prednisone for 6 mo
- Eligible for randomization (2:1 withdrawal) at 6 mo if
  - Absence of AR within first 6 mo
  - Absence of anti HLA antibody
  - 6 mo biopsy no rejection
- Withdraw tacrolimus over 3 months, serial urine for chemokines
- Biopsies driven by elevated urinary MIG (CXCL9) or IP10 (CXCL10) on 2 consecutive repeat studies

Timing of Adverse Outcomes (DSA and/or ACR) in Control Patients (upper panel) vs Patients Randomized to Tacrolimus Withdrawal (lower panel)

Selective Efficacy of Calcineurin Inhibitors in Preventing Memory Cell Activation

Kirk, et al, 2004
1996-2006: 330 of 1317 KTX with graft loss at mean 50-month follow-up
138 (43.4%) due to death
39 (11.8%) due to 1° non-function
153 (46.3%) due to graft failure (biopsies mean 4.7 months prior to graft loss):

• Of “IF/TA”
• 1/4 history of acute rejection
• Acute rejection (12%)

• Glomerular disease (37%)
• Of “glomerular disease”
• 40% “transplant glomerulopathy” (~HLA Ab?)

• ONLY 1 GRAFT LOSS ATTRIBUTED SOLELY TO CNI TOXICITY

Distribution of Histologic Diagnoses by Time

- No major abnormalities
- Borderline
- Polyoma virus nephropathy
- Antibody-mediated rejection
- Glomerulonephritis
- Atrophy-fibrosis
- Mixed rejection
- Other

Days post-transplantation

Sellares et al, AJT, 12:368, 2012
Donor Specific Antibodies (DSAs) as Mediators of Allograft Injury

- In addition to DSAs existing prior to transplant (e.g., due to pregnancy, blood product transfusions, or previous transplants), they can emerge at any time after transplantation and may occur in 20%-30% of transplant patients.
  - Recent observations indicate de novo DSAs are mainly class II and that DSAs against class II HLAs are associated with a worse prognosis than DSAs to class I HLAs.

- DSAs are responsible for a complex array of types of ABMR, including a particularly ominous form of chronic rejection termed “transplant glomerulopathy”.

ABMR: antibody-mediated rejection; DSA: donor-specific antibody.
Natural History of Antibody-Mediated Allograft Deterioration

ENDAT: endothelial activation and injury transcript; IFTA: interstitial fibrosis/tubular atrophy.

Once DSAs develop, they result in ongoing injury to the allograft that limits the half-life and results in a sensitized patient who will be very difficult to re-transplant.

AT1R: angiotensin II receptor, type 1; HLA-DQ: human leukocyte antigen, DQ subregion; HLA-DR: human leukocyte antigen-D–related.
The Role of ABMR and Nonadherence in Kidney Transplant Failure¹

Almost half of ABMR is due to nonadherence

Distribution of Attributed Causes of Graft Failure

- ABMR: antibody-mediated rejection
- Polyoma virus nephropathy: 7%
- Medical/surgical conditions: 11%
- Glomerulonephritis: 18%
- Probable ABMR: 9%
- Mixed rejection: 5%
- 64% ABMR, probable ABMR, or mixed rejection
- Non-adherent: 47%
- Adherent: 53%

ABMR: antibody-mediated rejection.
Late Graft Loss: A Changing Paradigm

- Chronic rejection is the most frequent cause of death-censored graft loss
- Chronic rejection is commonly due to insufficient immunosuppression
  - Inappropriate prescription (minimizing or avoidance strategies)
  - Patient non-adherence

Impact of Compliance on Graft Failure and Survival

- Medicare claims for immunosuppression in 15,525 KTRs with ≥1 year of graft function were used to calculate compliance via medication possession ratio.

Poor and fair compliance groups had inferior allograft and patient outcomes, as well as an increase in medical costs.

Transplant Outcomes and Economic Costs Associated With Noncompliance to Immunosuppression

- $12,840 increase in individual 3-year medical costs for patients with persistently low compliance

- Low compliance associated with
  - Younger age
  - GI symptoms
  - Rejection in first year
  - CNI with AZA or SRL

SRL: serolimus.
Risk Factors for Nonadherence in Transplant Patients\(^1,2\)

<table>
<thead>
<tr>
<th>Social/Economic Factors</th>
<th>Therapy-Related Factors</th>
<th>Condition-Related Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger patient ((&lt;25) years)</td>
<td>Complex medical regimens</td>
<td>High symptom distress</td>
</tr>
<tr>
<td>Male gender</td>
<td>Higher medication toxicity/side effects</td>
<td>Patient without diabetes</td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td></td>
<td>Increased period of time since transplantation</td>
</tr>
<tr>
<td>Non-US resident</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor social support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor transportation access</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiteracy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Health System/HCT Factors</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor provider–patient rapport</td>
<td>Lack of healthcare coverage</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Impediments to cost of medication, including unemployment/copayments</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Greater geographic distance to travel</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor aftercare/discharge planning</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient-Related Factors</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor illness insight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poorly perceived treatment benefits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of education about illness and treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of psychological or psychiatric illness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substance abuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of abuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of nonadherence</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Red Flags That Should Increase the Level of Suspicion for Nonadherence\textsuperscript{1}

- Frequent cancellation or rescheduling of appointments
- Failure to respond to treatment
- Patient acknowledgment of difficulties in following the prescribed therapeutic regimen
Difficulty for Both Prediction and Intervention

• There is not one single cause for non-adherence
  – Examples
    • Lack of understanding of the regimen
    • Forgetfulness
    • Financial problems with co-pays
    • Difficulty with regimen (work schedule/travel)
• Therefore, it is difficult to have a single effective intervention
Screening for Nonadherence

- Open a non-threatening dialogue

- Patient triage/check-in questions
  - “How many times in the last month did you miss a medication?”
  - “What time do you take your medications?”
  - “Have you had any problems filling your prescriptions?”

- Red flags
  - Frequent cancellation or rescheduling of appointments
  - Failure to respond to treatment
  - Acknowledgment of difficulties in following the prescribed therapeutic regimen
How can we measure adherence?

- **Objective measures**
  - Direct observation that medication was consumed
  - Serum drug levels, biological markers/tracers, electronic monitoring
  - Pill counts, refill records

- **Subjective measures**
  - Patient self-reporting

No perfect measure of adherence in clinical practice—need to incorporate more than one approach
MEMS: A microprocessor embedded in cap of a medication bottle records every opening and closing of the cap.

195 patients: 44 (22.6%) decreased adherence by 7% or more in month 2 post-transplant
- AR
- Early graft loss

MEMS: Medication Event Monitoring System.
Drug Level Monitoring (Intra-Patient Variability) to Assess Under-Immunosuppression/Adherence\textsuperscript{1}

- N = 356
- Measured TAC variability while on stable dose; median follow-up: 3.72 y
- Composite endpoint: late allograft rejection, transplant glomerulopathy, or graft loss (including death)

For every one-unit increase in TAC SD, there was a 27% increase in composite endpoint (HR = 1.27; 95% CI, 1.03-1.56)

NS: not specified; SD: standard deviation.
Strategies to Optimize Adherence

- Monitoring drug levels
- Tracking pharmacy refills
- Supervised medication administration
- Electronic notification (patient, center, other)
  - Bottle caps
  - Pill dispensers
  - Apps
  - Alarms/reminders
- Simplified regimens
Randomized, multicenter, controlled trial of 219 patients 3 ± 2 years post-transplant to evaluate adherence between QD and BID tacrolimus using electronic monitoring.

In patients receiving the BID regimen, the average percentage of missed doses was 11.7% in the morning and 14.2% in the evening ($P = .0035$).

BID: twice daily; QD: once daily.
Changing immunosuppression: risk/benefit poorly defined

- **CNI:** Change CNI? Reduce dose? Discontinue?
- **Antimetabolite:** Decrease MPA? Change to AZA or mTOR?
- **Steroid:** Consider late withdrawal?

ADMIRAD: Can Adherence Be Improved With Simplified Dosing?1

6-month electronic monitoring data

**Persistence with medication**: Kaplan-Meier estimates of the % of pts continuing with treatment over time

**Implementation of dosing regimen**: Day-to-day % of pts with correct dosing relative to patients who were still engaged with treatment

<table>
<thead>
<tr>
<th>Dosing Schedule</th>
<th>Pts Engaged With Regimen, 6 mo</th>
<th>Pts Engaged With Regimen Who Took Prescribed Number of Daily Doses, 6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>QD (n = 145)</td>
<td>81.5%</td>
<td>88.2%</td>
</tr>
<tr>
<td>BID (n = 74)</td>
<td>71.9%</td>
<td>78.8%</td>
</tr>
<tr>
<td><em>P</em></td>
<td>.0824</td>
<td>.0009</td>
</tr>
</tbody>
</table>

Efficacy of Once-daily Tacrolimus

- Phase III, open-label, comparative, non-inferiority study
- 638 subjects receiving de novo kidney transplants were randomized to one of three treatment arms: daily tacrolimus extended-release, twice-daily tacrolimus, or twice-daily cyclosporine
- All subjects received basiliximab induction, mycophenolate mofetil, and corticosteroids

**Efficacy of LCP-Tacrolimus**

- Phase III, RCT, double-blind, double-dummy; primary endpoint: treatment failure
- 543 subjects receiving de novo kidney transplants were randomized to one of two treatment arms: daily LCP-tacrolimus, twice daily tacrolimus
- All subjects received basiliximab induction, mycophenolate mofetil; corticosteroids per local practice

Table: Comparison of Tac-MR* and LCP-Tac*

<table>
<thead>
<tr>
<th>Metric</th>
<th>Tac-MR*</th>
<th>LCP-Tac*</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_0$</td>
<td>Similar</td>
<td>Similar</td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>Similar</td>
<td>Lower</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>Similar</td>
<td>Delayed</td>
</tr>
<tr>
<td>AUC</td>
<td>Lower</td>
<td>Higher</td>
</tr>
<tr>
<td>Required dose</td>
<td>Higher</td>
<td>Lower</td>
</tr>
</tbody>
</table>

*compared to twice-daily tacrolimus
## Interventions

<table>
<thead>
<tr>
<th>Domain</th>
<th>Suggestions</th>
</tr>
</thead>
</table>
| Communication and consultation| • Inquire about life events (if necessary, refer to psychological or counseling services)  
• Remind recipients of short- and long-term consequences of nonadherence  
• Identify people in the recipient's social support network to share accountability  
• Encourage open discussion and problem solving to counteract medication side effects  
• Discuss how the medication schedule can be integrated into daily living                                                                      |
| Patient education and resources| • Emphasize the benefits of sustained and successful transplantation  
• Facilitate networking with donors and families (eg, highlight donor journey)  
• Provide patient stories about kidney rejection and consequences due to nonadherence                                                        |
| Practical devices and tools    | • Pill counters  
• Alarms (phones, clocks, watches)  
• Prescription refill reminders (mail, e-mails, phone calls, text messages)  
• Visual cues (calendars, stickers with information updated as prescriptions change)  
• Travel medication packs  
• Contingency packs (extra supply of medications)                                                                                         |
| Healthcare system             | • Ensure clinic appointments do not conflict with medication schedules  
• Provide easy access to local pharmacy services (automated online orders)  
• Facilitate access to financial support                                                                                                      |

Adherence-Enhancing Interventions

![Box plot showing differences in adherence outcome measures by intervention component.](image)

- TRT simpl: n=18, p=0.37
- Cogn-Educ: n=36, p=0.14
- Behav-Counsel: n=47, p=0.07
- Soc-Psych: n=13, p=0.50
- EM-feedback: n=22, p=0.02
- Tech rem: n=20, p=0.22
- Tech equip: n=11, p=0.59
- Rewards: n=4, p=0.44

Results of a Behavioral Contract Intervention to Improve Adherence and Healthcare Outcomes Among RTRs

A 12-month randomized-controlled trial of an intervention using behavioral contracts to improve immunosuppressant therapy adherence and associated outcomes among RTRs

1. Intervention group had improved compliance from baseline to 1-year mark and continued to maintain higher adherence in 1-year follow-up
2. Fewer emergency department visits and hospitalizations in intervention group

Behavioral contracts make the patient part of the solution and are an effective adherence intervention in RTRs, positively impacting healthcare outcomes and costs

Continuous Self-Improvement Interventions for Patients


- **Plan**
  - Identify life routines
  - Identify optimal steps for medication taking and how life routines impact these steps
  - Identify important people in medication-taking process

- **Do**
  - Incorporate change into existing routines
  - Implement more than one system-wide solution

- **Check**
  - Evaluate compliance data to see whether outcome was met

- **Act**
  - Track compliance
Involving the patient/caregivers in the process

Communicating nonadherent behavior to the patient care team

Catching nonadherence early

Monitoring for signs of potential nonadherence

Considering comorbidities and dosing regimens

Educating patients on the importance of lifelong adherence

Ongoing reinforcement

Opportunities to Improve Long-Term Adherence