Best Practices in Care to Improve Outcomes for Transplant Recipients

Educational Objectives

• Describe strategies to leverage center-specific data and best practices from transplant quality-improvement initiatives to improve processes of care
• Discuss the importance of regular monitoring strategies that can allow early identification of graft rejection and allow for appropriate changes in immunosuppressant regimen
• Identify patient barriers to adherence to improve implementation of strategies to engage patients and maximize adherence after transplantation

Case Presentation

• 66-year-old male with T2DM for 16 years, hypertension for 20 years
• ESRD on hemodialysis for 4 years
• BMI = 36
• Single vessel coronary disease with PCI and stent 2 years ago
• Mitral valve replacement, on warfarin
• CPRA 0%
• Medicaid insurance
• ½ PPD smoker currently

Case Presentation (2)

• Deceased donor offer becomes available
• 62-year-old, hypertension, died of a cerebrovascular accident
• Terminal creatinine 1.4 mg/dL
• KDPI = 93%
• HLA matching: 1B and 1DR match

KDPI and Graft Survival

Estimated Graft Survival Rates by KDPI

How Do We Assess Risk and Effects on Program Outcomes?
### SRTR Program Specific Reports (PSRs)

**Tools to Monitor and Improve Your Program**

The PSR contains:
- Program summary
- Waiting-list information
- Waiting-list activity
- Candidate characteristics
- Candidate outcomes
- Transplant information
- Donor and recipient characteristics
- Patient and graft survival
- Living donor follow-up summary (if applicable)

### How Does SRTR Risk Adjust Outcomes?

1 year Deceased Donor Graft Survival Risk Adjustment Factors

- Any Previous Malignancy
- Candidate characteristics
- Candidate outcomes
- Transplant information
- Donor and recipient characteristics
- Patient and graft survival
- Living donor follow-up summary (if applicable)

### SRTR Timelines for Evaluation

- The SRTR examines 2.5 year cohorts for outcomes – and determines the number of observed events (graft or patient loss) vs the number of expected events.
- But reports lag behind real time up to a year to allow events to accrue – so it’s old news in some cases.

#### Cohorts Evaluated in the Fall 2017 PSR Cycle

- Graft survival (1-Year Cohort): January 1, 2012 - June 30, 2014
- Graft survival (3-Year Cohort): January 1, 2010 - June 30, 2012
- Patient survival (5-Year Cohort): January 1, 2012 - June 30, 2016

### 1-Year Patient Survival Deceased Donor-Recipient Factors

**Not the Same List as for Graft Survival**

- Candidate (at listing) Ethnicity
- Candidate (at listing) Race
- Candidate (at listing) Disease (other than insrurance)
- Candidate (at listing) Disability
- Candidate (at listing) Age at Transplant (years)
- Candidate (at listing) History of Cancer
- Candidate (at listing) Donor BUN (mg/dL)
- Candidate (at listing) Donor eGFR (mL/min/1.72m2, calculated from SCr, age, gender, race)
- Candidate (at listing) Donor Drug-Treated Systemic Hypertension
- Candidate (at listing) Donor Diuretics
- Candidate (at listing) Donor Clinical Infection of the Lung (Confirmed or Unconfirmed)
- Candidate (at listing) Donor Cigarette Use (>20 pack years) Ever
- Candidate (at listing) Donor T4
- Candidate (at listing) Donor Serum Creatinine (g/dL)
- Candidate (at listing) Donor Local vs Regional/National Share
- Candidate (at listing) Donor Kidney Donor Risk Index (KDRI, calculated*)
- Candidate (at listing) Donor History of Cancer
- Candidate (at listing) Donor Ethnicity

### 1-Year Graft Survival and Patient Survival

**Donor Factors**

#### GRAFT SURVIVAL

<table>
<thead>
<tr>
<th>Donor</th>
<th>MBO Blood Group</th>
<th>Age (years)</th>
<th>Any Previous Malignancy</th>
<th>Candidate characteristics</th>
<th>Candidate outcomes</th>
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#### PATIENT SURVIVAL

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<th>Candidate outcomes</th>
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### Criteria Used by MPSC to Identify Transplant Programs that Require Further Scrutiny

- **Large Centers** (≥15 transplants in 2.5-year period)
  - Probability >75% that the HR is >1.2
  - Probability >10% that the HR is >1.5

- **Small Centers** (≤9 transplants in 2.5-year period)
  - Probability >10% that the HR is >1.2
  - Probability >10% that the HR is >1.5

* Events are defined as any death or graft loss within 1 year of transplant.
Best Practices in Care to Improve Outcomes for Transplant Recipients

Bayesian Methods for Assessing Transplant Program Performance

Large Program – HR = 1.67 (death rate 67% higher than expected; O/E = 1 is as expected)

299 transplants in 2.5 year cohort

13 patient deaths in 1 year (6.97 expected based on risk adjustment)

Small Program – HR = 1.37 (death rate 37% higher than expected; O/E = 1 is as expected)

6 transplants in 2.5 year cohort

1 patient death in 1 year


Cumulative Sum – CUSUM Reports

CUSUM reports are better suited to ongoing quality improvement because they:
1. Show actual events in the time they occurred, rather than an average that can mask periods of high or low events
2. Cover a 3 year period up to 2 months prior to release date, so are more relevant to a program’s current practice and quality efforts


Quality Improvement Methods and Strategies

What CMS Expects

• Quality Assessment and Performance Improvement
• An effective transplant quality assurance and performance improvement (QAPI) program is ongoing and comprehensive, dealing with the full range of services offered by the transplant program, including patient safety, clinical care, quality of life, and those services provided under contract or arrangement
• The hospital leadership and governing body must be clearly engaged in QAPI oversight
• The transplant program must have systems in place to monitor care and services in all phases and settings of transplant and living donation, drawing from multiple sources
• The transplant QAPI program uses a methodical approach to determine when in-depth analysis is needed to fully understand improvement opportunities, causes, and implications of change for care and services delivered
• The transplant QAPI program must define, implement, and evaluate performance improvement interventions with the objective of improving quality of care


Case Presentation

• Patient accepts the kidney, basiliximab induction, followed by tacrolimus-MMF-prednisone
• Delayed graft function, 10 days; serum creatinine declines to 1.8-2.1 mg/dL range; BP 138/84 on metoprolol, amlodipine
• Week 4: BK serum viral load 11,300, MMF discontinued, tacrolimus dose reduced to target level 6-8 ng/mL
• Week 8: BK viral load 2,800, new DSA to HLA B3 at 1,800 MFI

• Week 12: BK viral load, 975; serum creatinine, 2.1; tacrolimus level, 3.3; patient admits to missing his nighttime dose
• Week 15: serum creatinine, 2.4; tacrolimus level, 5.1; BP 142/86; HLA B3 DSA now at 2,600 MFI; urine P/Cr, 0.3
• Week 16: serum creatinine, 2.5; tacrolimus level, 5.2; BP 140/88; remains on warfarin, metoprolol, amlodipine. Ultrasound of transplant kidney unremarkable except for elevated resistive indices (0.85)

Subclinical Injury and Graft Loss

Our patient’s known risk factors are circled in red

Best Practices in Care to Improve Outcomes for Transplant Recipients

Graft Survival in DeKAF
Diagnosis of CNI Nephrotoxicity Does Not Predict Allograft Survival

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

Subclinical Acute Rejection

- Defined as histologic acute rejection (cellular or antibody-mediated) with stable renal allograft function (stable creatinine)
- Currently diagnosed on a “protocol” or surveillance biopsy
- Only about half of transplant programs perform surveillance biopsies
  - Logistics, cost, risk of biopsy the most frequently reported reasons why not

Currently Used Biomarkers in Kidney Transplantation

- Gold standard:
  - Serum creatinine, urine protein/creatinine, immunosuppressive drug levels
  - Indication kidney biopsy
- Commonly used adjuncts
  - Viral monitoring (BK, CMV, EBV)
  - Donor-specific HLA antibody testing
  - Protocol kidney biopsy (various time points)
- Developing biomarkers
  - Donor-derived cell-free DNA (dd-cfDNA, Allsure)
  - Blood gene expression profiles (Trugraf, kSORT)
  - Urine biomarkers (CXCL9, gene expression profiles)

Need for Improved Detection of Under- and Over-Immunosuppression and Differential Diagnosis

Personalized Medicine

- The ideal biomarker is non-invasive, inexpensive and provides a diagnosis with high accuracy and in a subclinical setting (before creatinine goes up)
- Ideal biomarkers do not exist in medicine, but development moves towards better biomarkers
- Serum creatinine is not sensitive or specific to renal allograft injury or the cause – a lagging indicator of injury

Biomarkers in Development

Donor-Derived Cell-Free DNA as a Biomarker in Transplantation

Call-Free DNA (cfDNA)

- Fragments of DNA in the blood that originate from cells undergoing cell injury and death
- DNA degrades into nucleosomal units consisting of ~166 bases
- cfDNA is cleared from the blood by the liver and kidney, and has a short half-life of ~30 minutes

Donor-Derived Cell-Free DNA (dd-cfDNA)

- Assay DNA is very late in viable transplant rejection
  - dd-cfDNA is very late in viable transplant rejection
  - dd-cfDNA is elevated at the time of rejection
    - De Vlaminck, Sci Transl Med. 2014 (heart)
    - Grskovic, J Mol Diagn. 2016 (heart)
    - Schutz, PLOS Med. 2017 (liver)
  - dd-cfDNA decreases following successful treatment
    - De Vlaminck, Sci Transl Med. 2014 (heart)
    - Grskovic, J Mol Diagn. 2016 (heart)
dd-cfDNA Is Very Sensitive But Not Specific for ABMR in Patients with Graft Dysfunction

Low dd-cfDNA (<1%) in Patients with Graft Dysfunction has a Very Low Probability to be ABMR

<table>
<thead>
<tr>
<th>Performance metric</th>
<th>AllSure test performance at 1% threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROC/AUC</td>
<td>0.87 (95% CI 0.75-0.97)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>81%</td>
</tr>
<tr>
<td>Specificity</td>
<td>83%</td>
</tr>
<tr>
<td>NPV</td>
<td>96%</td>
</tr>
<tr>
<td>PPV</td>
<td>44%</td>
</tr>
</tbody>
</table>

Molecular Classifiers for Acute Kidney Transplant Rejection
In Peripheral Blood by Whole Genome Gene Expression Profiling

Differentiates normal (TX) from acute rejection (AR) from acute dysfunction without rejection (ADNR)

A Peripheral Blood Diagnostic Test for Acute Rejection in Renal Transplantation – kSORT

Urinary-cell mRNA Profile and Acute Cellular Rejection: Kidney Allografts

Multicenter Validation of Urinary CXCL9 as a Risk-Stratifying Biomarker for Kidney Transplant Injury
Case Presentation, continued

- Biopsy is performed – Banff 1A acute cellular rejection, no features of AMR (c4d negative, minimal capillaritis) and SV40 negative, treated with pulse methylprednisone
- Donor-derived cell-free DNA level is 0.21%
- Tacrolimus dose is increased to target a level of 6-8, MMF restarted at reduced dose
- Week 20: BK viral load undetectable, serum creatinine, 2.3; tacrolimus level, 8.9
- Week 24: BK viral load undetectable; DSA to HLA B3 at 2.800 MFI; serum creatinine, 2.3; tacrolimus level, 2.9. Patient admits to frequently forgetting to take his nighttime dose

Adjusted Rate of Allograft Failure in the US

Why Do Kidneys Fail? Mayo Experience

1996-2000: 330 of 1317 KTX with graft loss at mean 50-month follow-up
138 (4 safer) due to death
30 (9.1%) due to """"no-function"
162 (46.3%) death graft failure (biopsy mean 4.7 months prior to graft loss)
- Of """"IP/TA"""
- 1/4 history of acute rejection
- 40% """"transplant glomerulopathy"""" (HLA A/B28)
- ONLY 1 GRAFT LOSS ATTRIBUTED SOLELY TO CNI TOXICITY

Antibody-mediated Rejection and Non-adherence

ABMR = antibody-mediated rejection

Non-adherence Predicts DSA Development

- 315 consecutive recipients without donor-specific antibody (DSA)
  - Mean follow-up: 6 years
  - 47 (15%) developed de novo DSA
- Adherent recipients
  - n=268
  - 8% de novo DSA
- Nonadherent
  - n=47
  - 49% de novo DSA

Health Care Non-adherence and Graft Survival

Adjusted for age, gender, race, marital status, co-morbidities, donor characteristics, immunologic risks and baseline immunosuppression, rejection and delayed graft function.
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

Risk Factors for Non-adherence

- **Health system/health care provider factors**
  - Insurance issues
  - Organ failure
  - Inflammation
  - Tobacco use (addiction program specialists)

- **Genetic/related factors**
  - Chronically related patients

- **Patient-related factors**
  - Nonadherence to medication

- **Treatment-related factors**
  - Longer time to next transplant
  - More hospital days
  - Better-controlled health
  - Physical limitations


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

Strategies to Improve Adherence

- **Provider level**
  - Avoid under-dosing (no margin for missed doses)
  - Simplified regimens

Time in Therapeutic Range (TTR)

- n=538 Tac-treated patients, target level 6-9 ng/ml (0-3 mos); 5-8 ng/ml (4-12 mos); MMF 90%, rATG 50%
- TTR<60% considered high-risk from data with warfarin


TIME IN THERAPEUTIC RANGE (5-10 NG/ML) IN FIRST YEAR

dnDSA Development is Preceded by Drop in Tacrolimus Levels

- 492 patients; 96% 1st transplant, <10% CPRA>80, follow up 87 mos, mean of 97 tacrolimus levels/patient
- Tacrol level CV: dnDSA (39.7) vs no dnDSA (33.8), P=0.001


SYMPHONY: “Low Dose” Tacrolimus 4-7 ng/mL
12-month randomized open-label multicenter tria (n=1645)
4 arms (IL2R induction in “low” arms, MMF/Prednisone for all)

<table>
<thead>
<tr>
<th>Month</th>
<th>Tacrolimus level</th>
<th>Dose reduction (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>4.4</td>
<td>1.0</td>
</tr>
<tr>
<td>24</td>
<td>6.3</td>
<td>1.5</td>
</tr>
</tbody>
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"Low-dose" Tacrolimus Results in More Rejection and DSA

- Phase IV 2-arm RCT, n=186 low-risk, basiliximab-tacrolimus (level 8-12), MMF-steroids withdrawn by 10 wks.
- At 4 mos: Arm 1: 50% tacrolimus ER dose reduction (level >3 mcg/L); Arm 2: Tacrolimus ER, level 7-12 mcg/L
- dnDSA in 6/87 Arm 1 pts; 0 in Arm 2 pts
- No difference in eGFR at 12 months post-transplant


P=0.016

Target Tacrolimus Levels at 12-months Post-transplant

RECENT RCTs

<table>
<thead>
<tr>
<th>Trial</th>
<th>Achieved 12-mos Tac levels (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SYMPHONY</td>
<td>6.4</td>
</tr>
<tr>
<td>OPTICEPT</td>
<td>6-7.5</td>
</tr>
<tr>
<td>HARMONY</td>
<td>6-7</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>6-8 (24 wk)</td>
</tr>
<tr>
<td>De Graauw, 2017</td>
<td>6.8</td>
</tr>
<tr>
<td>Gatault, 2017</td>
<td>5.6 vs 7.4</td>
</tr>
</tbody>
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* Low-dose arm: increased rejection

Once-daily Formulations of Tacrolimus

<table>
<thead>
<tr>
<th>Tac-ER*</th>
<th>Tac-ER*</th>
<th>GCP-Tac*</th>
</tr>
</thead>
<tbody>
<tr>
<td>C0</td>
<td>Similar</td>
<td>Similar</td>
</tr>
<tr>
<td>Cmax</td>
<td>Similar</td>
<td>Lower</td>
</tr>
<tr>
<td>T1/2</td>
<td>Similar</td>
<td>Delayed</td>
</tr>
<tr>
<td>AUC</td>
<td>Lower</td>
<td>Higher</td>
</tr>
<tr>
<td>Dose change</td>
<td>40%</td>
<td>30% lower</td>
</tr>
</tbody>
</table>

*Compared to twice-daily IR tacrolimus


Extended-Release Tacrolimus vs Twice-Daily Tacrolimus RCTs

- Basiliximab, MMF, and corticosteroids in all subjects, both studies
- No difference compared to twice-daily tacrolimus

Persistence and Adherence in Kidney Recipients

Effect of Dosing Frequency

- 219 patients randomized to once-daily or twice-daily tacrolimus

<table>
<thead>
<tr>
<th></th>
<th>Once-daily (n=146)</th>
<th>Twice-daily (n=74)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistence, 6 mos</td>
<td>82%</td>
<td>72%</td>
<td>0.08</td>
</tr>
<tr>
<td>Adherence, 6 mos</td>
<td>88%</td>
<td>79%</td>
<td>0.0009</td>
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- Doses were missed more frequently in the evening than in the morning (11.7% vs 14.2%; P=0.0035)

**Best Practices in Care to Improve Outcomes for Transplant Recipients**

**What Can Centers Do?**
- Multidisciplinary approach
- Electronic monitoring and notification
- Personalize education programs
  - Culturally and content appropriate
  - Reinforce but don’t confuse
  - More face-time
- Engage patients and their family
- Track pharmacy refills

**Use of Electronic Monitoring to Predict Patterns of Early Medication Adherence in Renal Transplantation**

**Synergistic Effect of Epitope-Mismatch and Non-adherence on Graft Survival**
- 195 patients monitored with MEMS
- Mean follow-up: 6 years

**Eplet Mismatch Modulates Effect of Tacrolimus Trough Levels on the Development of dnDSA**

**Interventions for Medication Non-Adherence**
- Relative few trials, mainly in adults
  - Limited effectiveness
  - Multi-component interventions are more efficacious but not feasible on large scale
  - Efficacy evaluated primarily during intervention period
  - Since no permanent cure, intervention should ideally be given for as long as medical therapy is needed
- Most practical intervention is modifying immunosuppression regimen from twice-a-day to daily dosing
Case Presentation, continued

- Patient switches to a once-daily tacrolimus formulation
- He immediately notes that it is much easier for him to adhere to this tacrolimus regimen
- Tacrolimus levels consistently remain between 6-8 for the remainder of the first post-transplant year, 5-7 thereafter
- Serum creatinine remains stable between 2.2-2.6 mg/dL, no significant proteinuria, BK viral load remains undetectable, low level class I DSA persists

Summary

- Transplant centers should have effective quality assurance and performance improvement programs in order to optimize patient outcomes and to help achieve acceptable program-specific reports
- Adoption of one of the newer approaches to better risk stratify and mitigate chronic under-immunosuppression due to provider under-dosing and patient non-adherence may help improve allograft survival
- Novel non-invasive biomarkers to evaluate alloimmune injury are emerging and may represent a valuable adjunctive tool in the management of kidney recipients