Evidence to Inform Transplant Policy and Practice

John S. Gill MD, MS, FAST
Professor of Medicine
University of British Columbia Division of Nephrology
St. Paul’s Hospital, Vancouver
jgill@providencehealth.bc.ca
Disclosures

- Treasurer – American Society of Transplantation
  - Opinions do not necessarily reflect official policy of the AST

- Grant Support – Astellas

- Consultant – Astellas

- Consultant – Sanofi

- Canadian

- Nephrologist
# Overview

<table>
<thead>
<tr>
<th>Issue</th>
<th>Policy / Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cessation of coverage for immunosuppressant drugs</td>
<td>“Immuno-Bill”</td>
</tr>
<tr>
<td>Fragmentation of dialysis and transplant care</td>
<td>Patients Demonstration Act</td>
</tr>
<tr>
<td>Access to transplantation</td>
<td>Referral for kidney transplantation</td>
</tr>
<tr>
<td>Care of wait-list patients</td>
<td>Screening for coronary artery disease</td>
</tr>
</tbody>
</table>
Cessation of coverage for immunosuppressant drugs

- For patients insured by ESRD Medicare
  - Immunosuppressant drug coverage ceases three years after transplantation
  - Cessation of drug coverage is associated with transplant failure
Kidney-Transplant Survival and Immunosuppressive Coverage Policies for Selected Countries (for Recipients of a First Kidney-Only Transplant from a Deceased Donor).*

<table>
<thead>
<tr>
<th>Country</th>
<th>5-Yr Survival</th>
<th>10-Yr Survival</th>
<th>Government-Funded Immunosuppressive Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>81 percent</td>
<td>59 percent</td>
<td>Lifetime for all recipients</td>
</tr>
<tr>
<td>Canada</td>
<td>80 percent</td>
<td>58 percent</td>
<td>Lifetime for all recipients</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>78 percent</td>
<td>56 percent</td>
<td>Lifetime for all recipients</td>
</tr>
<tr>
<td>United States</td>
<td>69 percent</td>
<td>43 percent</td>
<td>Lifetime for recipients $&gt;65$ yr of age or with work-related disability; 3 yr for all other recipients</td>
</tr>
</tbody>
</table>
Opinions

Our Medicare policy for kidney transplants is totally irrational

Doctors perform a kidney transplant. (Linda Davidson/The Washington Post)

By Marcello Tonelli and John Gill
December 6, 2017

Marcello Tonelli is associate vice president of research at the University of Calgary. John Gill is a clinician scientist and professor of medicine at the University of British Columbia and a member of the board of directors for the American Society of Transplantation. They are both former presidents of the Canadian Society of Nephrology.
Estimated 10 year cost savings of $73 million
Extending Immunosuppressant Coverage is likely cost saving but definitely cost-effective

Kadatz and Gill – manuscript under review
Varying factors that could affect cost within a plausible range did not alter cost savings

Kadatz and Gill manuscript under review
Fragmentation of Dialysis and Transplant Care
Transitions Between Dialysis and Transplantation and Risk of Death

Post-transplant Patient Survival In Canada and United States

Patient Survival > Canada

Higher risk of death in U.S. patients related to duration of dialysis before transplant

Kim SJ et al. AJT 2006; 6: 109-114
Dialysis Exposure and Kidney Transplant Survival In Canada

ATC 2010

N = 6191 Adult First Deceased Donor Kidney Transplant Recipients 95-05
Geographic variation in dialysis mortality in United States
(hazard ratio for death on dialysis, 2010-2014)

Cox model output, adjusted for: age (18-49 or 50+), gender, race, cause of ESRD, and dialysis vintage (<2, 2-5, or >5 years).

Clark and Gill – Unpublished Data
Post-Transplant Survival Associated with Duration of Pre-transplant Dialysis and Death rate on dialysis in state of residence

Clarke and Gill – Unpublished data
The impact of longer pre-transplant dialysis exposure was greater in regions with higher dialysis mortality.

Cox model adjusted for: Age, gender, cause of ESRD, race, BMI, year of transplant, PRA, PVD, CHF, CVA, ASHD, diabetes, non-ambulatory state, COPD and tobacco use.
Policy Implications

- Post transplant dialysis outcomes are impacted by pre-transplant dialysis care
- Silos of care are inappropriate
- Integrated care models including dialysis and transplantation are needed to ensure optimal patient outcomes
Access to kidney transplantation
Kidney Transplant Wait-List Is Shrinking
Why is the waiting-list decreasing?

### Waiting list state

<table>
<thead>
<tr>
<th></th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients at start of year</td>
<td>99,322</td>
<td>98,018</td>
<td>95,658</td>
</tr>
<tr>
<td>Patients added during year</td>
<td>30,215</td>
<td>30,854</td>
<td>30,918</td>
</tr>
<tr>
<td>Patients removed during year</td>
<td>31,466</td>
<td>33,167</td>
<td>33,891</td>
</tr>
<tr>
<td>Patients at end of year</td>
<td>98,071</td>
<td>95,706</td>
<td>92,685</td>
</tr>
</tbody>
</table>

### Removal reason

<table>
<thead>
<tr>
<th>Removal reason</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deceased donor transplant</td>
<td>12,279</td>
<td>13,501</td>
<td>14,077</td>
</tr>
<tr>
<td>Living donor transplant</td>
<td>5331</td>
<td>5334</td>
<td>5536</td>
</tr>
<tr>
<td>Transplant outside US</td>
<td>49</td>
<td>77</td>
<td>67</td>
</tr>
<tr>
<td>Patient died</td>
<td>4983</td>
<td>4862</td>
<td>4414</td>
</tr>
<tr>
<td>Patient refused transplant</td>
<td>518</td>
<td>471</td>
<td>524</td>
</tr>
<tr>
<td>Improved, transplant not needed</td>
<td>208</td>
<td>193</td>
<td>212</td>
</tr>
<tr>
<td>Too sick for transplant</td>
<td>4078</td>
<td>4345</td>
<td>4505</td>
</tr>
<tr>
<td>Other</td>
<td>4020</td>
<td>4384</td>
<td>4556</td>
</tr>
</tbody>
</table>
Why is the waiting-list decreasing?

<table>
<thead>
<tr>
<th>Waiting list state</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients at start of year</td>
<td>99,322</td>
<td>98,018</td>
<td>95,658</td>
</tr>
<tr>
<td>Patients added during year</td>
<td>30,215</td>
<td>30,854</td>
<td>30,918</td>
</tr>
<tr>
<td>Patients removed during year</td>
<td>31,466</td>
<td>33,167</td>
<td>33,891</td>
</tr>
<tr>
<td>Patients at end of year</td>
<td>98,071</td>
<td>95,706</td>
<td>92,685</td>
</tr>
</tbody>
</table>
Access to transplantation
Percentage of dialysis patients who were wait-listed

USRDS 2018 Annual Data Report
Proportion of incident dialysis patients who were wait-listed or received a kidney transplant within one year

USRDS 2018 Annual Data Report
Wait-list provides an incomplete picture of the need for transplantation
Steps to access transplantation

1. Referral to transplant center
2. Complete transplant work up
3. Accepted onto wait-list
4. Survive the list
5. Transplant

No National Data
Referral for kidney transplantation in Canadian provinces

**METHODS**
Prospective ascertainment of referral for transplantation in 12 Transplant Centers

**Outcome:** Referral for kidney transplantation (per 100 patient years of dialysis)

**CONCLUSION:** Referrals varied more than 3 fold between provincial regions in which deceased donor kidneys are routinely shared suggesting the need for standardization of referral practices and national reporting of referral

Linked to national data (Canadian Organ Replacement Register) on incident dialysis patients to determine incidence of referral

**doi:** 10.1681/ASN. Kim SJ*, Gill JS*, Knoll G, Campbell P, Cantarovich M, Cole EH, Kiberd B. (co-first authors)
Implications – policy and practice

- National reporting of referral for transplantation is needed
- Standardization of referral is needed
Management of wait-listed patients
When Do Our Patients Die?
Gill et al KI 2007; 71(5): 442-7
Incidence of Myocardial Infarction

Kasiske et al, JASN 2006; 17:900

Cumulative Incidence

On the Waiting List
Post-transplant: Deceased Donor
Post-transplant: Living Donor

Incidence of Myocardial Infarction for Medicare beneficiaries listed 1995-2002 (N=53,297)
Transplant Guidelines
What are we supposed to be doing?

**Before Listing**

**AST 2001**
- High-risk $\rightarrow$ stress test
- Diabetes
- Prior IHD
- $\geq 2$ traditional risk factors
- Positive test $\rightarrow$ angiography
- Critical lesions $\rightarrow$ revascularize

*Am J Transplant 2001;1:S3*

**During Wait-listing**

**KDOQI 2005**
- Annual stress tests in wait-listed patients who have:
  - Diabetes
  - Prior IHD, PVD or EF $\leq 40$
- $\geq 2$ traditional risk factors

*Am J Kidney Dis 2005;45:S1*
Transplant Guidelines differ from General Guidelines

**AST 2001**
High-risk $\rightarrow$ stress test
  - Diabetes
  - Prior IHD
  - $\geq$2 traditional risk factors
Positive test $\rightarrow$ angiography
Critical lesions $\rightarrow$ revascularize

*Am J Transplant 2001;1:S3*

**KDOQI 2005**
Annual stress tests in waitlisted patients who have:
  - Diabetes
  - Prior IHD, PVD or EF$\leq$40%
  - $\geq$2 traditional risk factors

*Am J Kidney Dis 2005;45:S1*

**AHA/ACC 2007**
Intermediate Risk Surgery
$\geq$1 Risk Factor

- No Symptoms
  - Functional Capacity $\geq$4 METS
    - Yes
    - Proceed to Surgery
  - No/Unknown
    - Surgery with HR Control
    - Stress testing “if it will change management” (Class IIb)

*J Am Col Cardiol 2007;50:1707*
Cardiac Disease Evaluation and Management Among Kidney and Liver Transplantation Candidates

A Scientific Statement From the American Heart Association and the American College of Cardiology Foundation

Endorsed by the American Society of Transplant Surgeons, American Society of Transplantation, and National Kidney Foundation

Krista L. Lentine, MD, MS, Co-Chair; Salvatore P. Costa, MD, Co-Chair; Matthew R. Weir, MD, FAHA; John F. Robb, MD, FAHA; Lee A. Fleisher, MD, FAHA; Bertram L. Kasiske, MD; Robert L. Carithers, MD; Michael Ragosta, MD; Kline Bolton, MD; Andrew D. Auerbach, MD; Kim A. Eagle, MD, FAHA, Chair; on behalf of the American Heart Association Council on the Kidney in Cardiovascular Disease and Council on Peripheral Vascular Disease

JACC Vol. 60, No. 5, 2012
July 31, 2012:434–80
What did AHA recommend for screening after wait-listing?

- The usefulness of periodically screening asymptomatic WL patients for myocardial ischemia while on the transplant waiting list to reduce the risk of MACEs is uncertain
- Class IIIB Level C
Now What?
Is a trial of screening ethical?

Strategy of testing/ intervention is not risk free/ and may be harmful

- Risk of loss of residual renal function with angiography
- Risk of in hospital mortality following coronary revascularization is about 3 times higher in dialysis patients vs non-ESRD
- Risk of blood transfusion and CVA in ESRD patients
- Abnormal screening tests may unnecessarily delay transplantation or exclude patients from consideration of transplantation
CARSK
Canadian Australasian Randomized Trial of Screening Kidney Transplant Candidates for Coronary Artery Disease
Hypothesis

- After screening for wait list entry, non use of cardiac screening tests is non-inferior versus the current standard care which is screening all asymptomatic wait-listed patients for coronary artery disease (CAD) at regular intervals.

- We will also compare the benefits and costs of screening and subsequent treatment versus not screening from a health system perspective.
Inclusion Criteria:
At least 18 years of Age
No symptoms of active cardiac disease
Actively Wait-listed For Kidney Only Transplant
No previous extra-renal transplant
Anticipated date of transplantation > 12 months from date of enrollment
Anticipated to require cardiac screening before transplantation

Informed Consent

Randomization

Regular Screening During Wait-listing

No Screening after Wait-listing

Note patients in both groups may be investigated for symptoms

Annual from date of last test
- Diabetes
- Angiographic CAD not revascularized
- PTCA
- Incomplete CABG
- CABG > 3 yrs ago

Every 24 months for all others

Management of a positive non-invasive test irrespective of whether it was done for screening or symptoms will be managed as per center protocol
It’s a trial about “NOTHING”

SEINFELD says it's the "show about nothing."

So I watch it with the t.v. off.
The trial will enroll 3300 patients in Canada, Australasia, Spain, Germany (trial results will be disseminated to US transplant physicians in a knowledge translation partnership with United Health Group).

Irrespective of the outcome – the trial will either:

- a) make better use of scarce deceased donor kidneys by informing better management of wait-list patients (n = 175,000 world-wide),
- and/or b) save valuable resources (estimated $300 million/year) by averting needless and potentially harmful tests.
## Summary

<table>
<thead>
<tr>
<th>Issue</th>
<th>Policy / Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cessation of coverage for immunosuppressant drugs</td>
<td>“Immuno- Bill”</td>
</tr>
<tr>
<td>Fragmentation of dialysis and transplant care</td>
<td>Patients Demonstration Act</td>
</tr>
<tr>
<td>Access to transplantation</td>
<td>Referral for kidney transplantation</td>
</tr>
<tr>
<td>Care of wait-list patients</td>
<td>Screening for coronary artery disease</td>
</tr>
</tbody>
</table>
Thank You!

- Please address any questions to
  - jgill@providencehealth.bc.ca