Back to dialysis after graft failure: Transplantectomy or not? Stop immunosuppression?

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CHU Sart-Tilman

Layout

- Introduction
- Epidemiology
- A note of caution on causality and bias
- Patient survival after failed KTx
- Immunization after failed transplant
- Immunosuppression
- Transplantectomy
- An integrated approach
Introduction

The aim of a successful transplantation:
- To die in one’s bed at the 85 years of age with a functioning transplant
- Yet (almost) every study on transplant outcome consider **return to dialysis AND death with a functioning transplant** as the metrics for failure

Challenges we are faced when dealing with patients with failed kidney transplant:

1. (When to initiate RRT?)
2. What to do with immunosuppression?
3. To perform a transplantectomy or not?
3.13 TREATMENT OF A FAILED TRANSPLANT KIDNEY
There are no evidence-based guidelines on how failed transplanted kidneys should be managed. The management very much depends on the clinical situation of the individual patient.


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EPIDEMIOLGY
A few figures,…

- Allograft failure is the 5th cause of admission to RRT
- Patients with a failed kidney transplant represent 6-7% of patients on RRT (USRDS data)
- 15% of patients on the waiting lost for KTx are re-transplant candidates USRDS data (14% in our center)

Epidemiology in Belgium

Distribution of ESRD patients between modalities

Recent evolution of treatment modalities

41 to 43% of ESRD pts are KTx

Rise over 9 years:
- 26% for RRT
- 39% for KTx

https://eservice.chu-tivoli.be/GNFB/PAGE_PRESENTATION_PUBLIC/
Flow between treatment modalities

A WORD OF CAUTIOUS ON CAUSALITY & BIAS IN OBSERVATIONAL STUDIES
Causality?

Hill’s criteria

Association is not causality

<table>
<thead>
<tr>
<th>Causal Association</th>
<th>Exposure → Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spurious Association</td>
<td>Exposure ↔ Disease</td>
</tr>
<tr>
<td>Reverse Causality</td>
<td>Exposure ← Disease</td>
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</tbody>
</table>

PATIENT SURVIVAL AFTER FAILED KTX
Mortality: Meta-analysis

Annual mortality 1st year post return to RRT

<table>
<thead>
<tr>
<th>Study</th>
<th>RR</th>
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</thead>
<tbody>
<tr>
<td>Aletirn 1975</td>
<td>0.40 [0.28, 0.52]</td>
</tr>
<tr>
<td>Henkin 1977</td>
<td>0.19 [0.62, 0.73]</td>
</tr>
<tr>
<td>Curtis 1981</td>
<td>0.12 [0.02, 0.51]</td>
</tr>
<tr>
<td>Maltas 1985</td>
<td>0.13 [0.04, 0.35]</td>
</tr>
<tr>
<td>Coombi 1992</td>
<td>0.15 [0.57, 0.32]</td>
</tr>
<tr>
<td>Donn 1997</td>
<td>0.15 [0.56, 0.27]</td>
</tr>
<tr>
<td>Ojo 1998</td>
<td>0.15 [0.05, 0.23]</td>
</tr>
<tr>
<td>Santos 2000</td>
<td>0.14 [0.09, 0.22]</td>
</tr>
<tr>
<td>Davies 2001</td>
<td>0.15 [0.08, 0.20]</td>
</tr>
<tr>
<td>Howard 2001</td>
<td>0.15 [0.09, 0.19]</td>
</tr>
<tr>
<td>Meier-K 2001</td>
<td>0.15 [0.11, 0.20]</td>
</tr>
<tr>
<td>Sasal 2001</td>
<td>0.14 [0.10, 0.18]</td>
</tr>
<tr>
<td>Duman 2004</td>
<td>0.15 [0.10, 0.18]</td>
</tr>
<tr>
<td>de Jonge 2006</td>
<td>0.14 [0.10, 0.18]</td>
</tr>
<tr>
<td>Chin 2010</td>
<td>0.12 [0.09, 0.16]</td>
</tr>
<tr>
<td>Chung 2011</td>
<td>0.12 [0.09, 0.15]</td>
</tr>
<tr>
<td>Peri 2011</td>
<td>0.11 [0.08, 0.14]</td>
</tr>
<tr>
<td>Buturovic-P 2013</td>
<td>12</td>
</tr>
</tbody>
</table>

Decline in mortality rate beyond one year post RRT initiation

Kabani et al, NDT 2014, pp1778-1786

Mortality

- Higher than in the « naïve-transplant patients » in most studies
- Essentially in the first year post RRT initiation
- Causes:
  - Infection: 75 % in old studies =>16-17% in more recent ones
  - Cardio-vascular: 35-45% recent studies

Gill et al, KI 2007, pp1778-1786
Mortality: DOPPS analysis

Mortality: « Transplant Failure » vs « Transplant Naïve »

Bias?

- All-cause mortality
  - Unadjusted
  - Adjusted
- Cardiovascular-related
  - Unadjusted
  - Adjusted
- Infection-related
  - Unadjusted
  - Adjusted

Adjusted for age, sex, race, BMI, time since initiation of HD or TX failure, 13 summary comorbid conditions, albumin and catheter use.

Perl et al, NDT 2012, pp 4464-4472

Is there a way to “adjust” for this residual confounders?

Adjust for “Dialysis vintage” or “time spent in CKD”

40 years of functional KTx after living donation

Dan Med J 2014;61(3):A4796
Key messages about morbi-mortality associated with failed KTx

• Transition problem
  – Accumulating co-morbidity
  – Acceptance and preparation issues

• Hope for the best, prepare for the worst (both to be kept in mind when eGFR < 20 ml/min)
  – Pre-emptive re-transplantation often the best option
  – Be ready for RRT anyhow

IMMUNIZATION AFTER FAILED KTX
Immunization after failed KTx and its consequences on future transplantation

Percentage of anti-HLA immunization after various immunizing events

<table>
<thead>
<tr>
<th></th>
<th>Class I and/or II</th>
</tr>
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<tbody>
<tr>
<td>Pas d'El</td>
<td>51.2%</td>
</tr>
<tr>
<td>Tf</td>
<td>51.2%</td>
</tr>
<tr>
<td>G</td>
<td>66.7%</td>
</tr>
<tr>
<td>Tx</td>
<td><strong>94.7%</strong></td>
</tr>
</tbody>
</table>

Pernin et al, OP-80, SFT Liège 2016

Effect of transplantectomy on Donor specific immunization

Del Bello et al, CJASN 2012, pp 1310-1319

<table>
<thead>
<tr>
<th>Time after Tx</th>
<th>N</th>
<th>Nephrology</th>
<th>Immunosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>30</td>
<td>31</td>
<td>28</td>
</tr>
<tr>
<td>No</td>
<td>31</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>%</td>
<td>55</td>
<td>70</td>
<td>66</td>
</tr>
</tbody>
</table>

Scornik et al, Hum Immunol, 2011 pp 398-401

Lachmann et al, NDT 2016 pp 1351-1359
Key messages about immunization after failed KTx

- Most studies found a positive association between transplantectomy and development of de novo DSA
- Confounding effect of immunosuppression withdrawal difficult to take into account
- Two theories to explain this rise in antibodies after transplantectomy:
  - Sponge effect: antibodies are adsorbed on endothelial class I antigens
  - On going immunization due to persistence of donor tissue after kidney removal
- Immunosuppression can help to prevent antibody development even after failed KTx
- Importance of documenting anti-HLA antibodies early after transplantectomy and/or immunosuppression withdrawal

IMMUNOSUPPRESSIVE TREATMENT WITHDRAWAL AFTER FAILED KTX
To withdraw IS?

**PRO**
- Infection risk associated with IS
- Cardiovascular risk associated with IS
- Cancer risk associated with IS
- Metabolic AE associated with IS
- Reduction of direct cost

**CONS**
- Residual kidney function (especially in PD patients)
- Minimization of allosensitization
- Prevention of “*graft intolerance syndrome*”* and acute rejection
- Prevention of adrenal insufficiency
- Prevention of reactivation of systemic disease (eg. SLE, vasculitis)

Graft intolerance syndrome

- Low grade fever
- Flu-like symptoms
- Pain in the graft region
- Hematuria
- Tenderness and swelling of KTx

=> In extreme and rare cases can lead to transplant rupture
To withdraw IS?

"Immunosuppression should be stopped in patients with renal allograft failure" Smak Gregoor Clin Transplant 2001

Groupe A: 192 patients on IS
Groupe B: 90 patients off IS

"Continued transplant immunosuppression may prolong survival after return to peritoneal dialysis" Jassal AJKD 2002

- Decision analytic model
- 2 assumptions:
  - survival benefit of better GFR naïve Tx = failed KTx
  - risks of carcinoma and opportunistic infection failed KTx after IS w/d = general pop w/o IS
- Life expectancy was prolonged from 5.3 years to 5.8 years when immunosuppression was continued

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<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract</td>
<td>0.10</td>
<td>0.00</td>
<td>7.7 (1.3-46.6)</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>0.03</td>
<td>0.00</td>
<td>6.6 (1.3-36.9)</td>
</tr>
<tr>
<td>Hepatic abscess</td>
<td>0.03</td>
<td>0.00</td>
<td>1.8 (0.3-40.2)</td>
</tr>
<tr>
<td>Pseudoaneurysm</td>
<td>0.02</td>
<td>0.00</td>
<td>9.1 (1.1-72.6)</td>
</tr>
<tr>
<td>Renal infarction</td>
<td>1.19</td>
<td>0.26</td>
<td>2.3 (1.2-4.4)</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>0.10</td>
<td>0.00</td>
<td>3.9 (1.1-14.2)</td>
</tr>
<tr>
<td>Invasive tumor</td>
<td>0.09</td>
<td>0.00</td>
<td>5.7 (3.2-10.5)</td>
</tr>
<tr>
<td>Enteritis pseudomembranous</td>
<td>0.19</td>
<td>0.00</td>
<td>1.0 (0.2-2.1)</td>
</tr>
<tr>
<td>Other bacterial infection</td>
<td>0.21</td>
<td>0.02</td>
<td>2.9 (1.4-5.4)</td>
</tr>
<tr>
<td>Opportunistic infection</td>
<td>0.10</td>
<td>0.00</td>
<td>4.3 (1.0-16.6)</td>
</tr>
<tr>
<td>Tx-related failure</td>
<td>0.05</td>
<td>0.14</td>
<td>2.0 (1.0-4.9)</td>
</tr>
<tr>
<td>Total infections</td>
<td>1.20</td>
<td>0.31</td>
<td>3.4 (1.0-10.5)</td>
</tr>
</tbody>
</table>

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How to withdraw IS?

- No consensus, but...
- All IS drug can be withdrawn immediately after transplantectomy except for steroids (consider risk of adrenal insufficiency)
- Two approaches to the weaning of IS:
  - Stop antimetabolites at RRT initiation, taper CNI over several weeks
  - Stop CNI at RRT initiation taper antimetabolite
- In case of severe acute rejection start steroid again and performe transplantectomy when acute inflammation has settled
Key messages about immunosuppressive treatment withdrawal after failed KTx

- IS should be maintained only for patients with living donor (or deceased?) transplantation foreseen in the short term (<1 year)
- For all other cases weaning process must be considered at various speed according to individual situation (balance the risks and benefits for each patient)
- Special situation: Multi-organ Tx: do not forget the still functioning Tx (liver, pancreas, heart,...) => keep on monitoring IS
Transplantectomy?

**PRO**
- Increased mortality if failed KTx is retained (?)
- Infection risk associated with IS
- Cardiovascular risk associated with IS
- Cancer risk associated with IS
- Metabolic AE associated with IS
- Removal of infection source (chronic pyelonephritis, BK-VAN)

**CONS**
- Residual kidney function (especially in PD patients)
- Risk of surgery (morbidity 17-60% and mortality 1.5-14%)
- More immunization after transplantectomy

“Transplant Nephrectomy Improves Survival following a Failed Renal Allograft”
Aysus et al JASN 2010

- USRDS 1994-2004
- 10.951 adults with failed KTx
- 31% with transplantectomy 1.66 years post RRT
- Pts with transplantectomy:
  - 4.6 years younger
  - Less smokers
  - Less often males
  - Less MACE
  - Less peripheral vascular disease
  - Less diabetes
  - Less COPD
  - Less cancer

Adj HR: 0.68 (0.63-0.74)
Surgical techniques and complications

Extra-capsular
- Mostly in the 3 first month
- Allow for almost complete removal of the transplanted tissue
- In rare selected cases can be used later to allow retransplantation in the same site.

Sub-capsular
- Preferred technique for late nephrectomy
- More often complicated with bleeding
- Leave more allograft tissue in situ (immunological trigger?)

- Morbidity 17-60% (bleeding, sepsis, wound infection, hematoma, lymphocele, …)
- Mortality: 1,5 to 14% (earlier post-Tx and urgent indication being associated with the worst outcome)

Transplantectomy: indications

**Absolute**
- Primary non-function
- Hyper-acute rejection
- Early recalcitrant rejection
- Early graft lost (<1 year)
- Arterial or venous thrombosis
- Graft intolerance syndrome
- Recurrent urinary tract infection or sepsis
- Multiple retained failed transplant before repeat transplant
- Cancer

**Relative**
- Chronic inflammation state:
  - EPO resistant anemia
  - Elevated ferritin level
  - Elevated CRP
  - Elevated erythrocyte sedimentation rate
  - Low (pre-)albumin
- Graft lost due to BKAN with high level BK viremia

Pham et al, World J Nephrol 2015, pp 148-159
On-going RCT

Systematic Transplantectomy Versus Conventional Care After Kidney Graft Failure (DESYRE)

- Intervention: early (<2 month) transplantectomy under immunosuppression vs progressive immunosuppression weaning
- Primary outcome: anti-HLA immunization (measured by Luminex test) a year after graft-loss and return to dialysis in the renal transplant patient.
- Secondary outcome:
  - Morbidity and mortality after transplantectomy
  - Measuring the impact of systematic transplantectomy on mortality, inflammation, nutritional status, anemia, hypertension and cardiovascular risk factor
  - Infectious comorbidity
- Multi-center. N=118

ClinicalTrials.gov
Late allograft failure

Candidate for new KTx

Moderate to severe IS treatment AE

Yes

Moderate to severe IS treatment AE

No

Living donor or KTx < 1 year

Yes

Keep IS until KTx

No

Wean IS off

Graft intolerance

Yes

Wean IS off

No

HD

Urine output>500 ml/d

Yes

Keep KTx

No

Moderate to severe IS treatment AE

Keep IS and IS

PD

Urine output<500 ml/d

Yes

Keep KTx

No

Wean off IS

* Idem supra ...