Living Donor Evaluation, Unique Aspects of the Evaluation, and Management of ADPKD Transplant Recipients

Presenter:
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Disclosure of Interests

KB have/had consultancy agreements with Bristol-Myers Squibb, Chiesi, Effimune, Hexal, Novartis, Pfizer, and Veloxis and has received research grants for clinical studies, speaker’s fees, honoraria, travel expenses, and payment for development of educational presentations from AiCuris, Astellas, BmT GmbH, Bristol-Myers Squibb, Chiesi, Hexal, Novartis, Otsuka, Roche, Pfizer, Siemens, and Veloxis
1. Optimal Choice of renal replacement therapy

Relative Risk of death after Transplantation in comparison to non-transplanted waitlisted patients

Wolfe et al. NEJM 1999

4-16 years longer life expectancy, depending on age
Kidney transplantation prolongs life in ADPKD patients

Multivariate Cox regression analysis in 693 Danish patients who had ADPKD and reached ESRD between 1990 and 2007. n = 330 events, mean follow-up 5.1 years.

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time periods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1996 to 2001 versus 1990 to 1995</td>
<td>0.62 (0.49 to 0.80)</td>
<td>&lt;0.001</td>
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<tr>
<td>2002 to 2007 versus 1996 to 2001</td>
<td>0.80 (0.56 to 1.15)</td>
<td>NS</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
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<tr>
<td>male versus female</td>
<td>1.34 (1.07 to 1.68)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>transplantation versus dialysis</td>
<td>0.30 (0.22 to 0.42)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age at onset of ESRD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>age per year</td>
<td>1.05 (1.04 to 1.07)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Orskov B CJASN 2010

Controversies Conference on ADPKD | January 17-19, 2014 | Edinburgh, United Kingdom
Long Waiting time on dialysis is bad!

Pre-emptive transplantation is best
Waiting time is the most important modifiable factor for outcome
Kaplan-Meier graft survival curves: donor type

Living donation ist better, irrespective of match!

Percent surviving

Cadaveric ($t_{1/2}=9.7$)
Living related ($t_{1/2}=15.2$)
Living distant/unrelated ($t_{1/2}=15.5$)
ADPKD patients have at least similar outcomes after kidney transplantation.

Patient survival after transplant of 1,554 nondiabetic control and 3,170 ADPKD pts

\[ P = 0.23, \text{ log-rank test} \]

Perrone RD AJKD 2001
ADPKD patients have at least similar outcomes after kidney transplantation.

Patient survival:
534 ADPKD vs. 4779 controls

Jacquet A Transplant Int 2011

Graft survival

P = 0.46, log rank test

P = 0.013, log rank test
1. Optimal Choice of renal replacement therapy

Renal transplantation is the optimal RRT for ADPKD. Timely transplantation is crucial for outcome. Best results are obtained from preemptive transplantation from a living donor.
2. what post-transplant complications occur more frequent in ADPKD than in non-PKD patients

potential risks discussed in the literature with partially controversial results (problems in retrospective study design and control groups)

related to polycystic kidney
  - size
  - infection (cysts, UTI)
  - bleeding
  - malignancy

related to extrarenal disease manifestation
  - cerebral aneurysm, stroke
  - diverticulosis
  - cardiac disease
  - liver cysts

related to other causes/associations
  - post-transplant diabetes
  - hypertension
  - erythrocytosis
  - malignancies (skin)
  - hyperlipidemia
  - coagulation disorder
## Post-transplant Complications in ADPKD Compared to Non-PKD Patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>ADPKD Group (n = 534)</th>
<th>Control Group (n = 4779)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy-proven acute rejection (%)</td>
<td>24.3</td>
<td>27.4</td>
<td>0.13</td>
</tr>
<tr>
<td>NODAT (%)</td>
<td>12.4</td>
<td>9.6</td>
<td>0.06</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>49.7</td>
<td>39.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipid-lowering drug use (%)</td>
<td>48</td>
<td>37.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>49.7</td>
<td>42.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>1.1</td>
<td>1.7</td>
<td>0.31</td>
</tr>
<tr>
<td>Cutaneous cancer (%)</td>
<td>7.9</td>
<td>7.4</td>
<td>0.71</td>
</tr>
<tr>
<td>Kidney cancer (%)</td>
<td>0.4</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Thromboembolic disease %</td>
<td>8.6</td>
<td>5.8</td>
<td>0.009</td>
</tr>
</tbody>
</table>

NODAT, new onset diabetes after transplantation.
post-transplant infections in ADPKD compared to non-PKD patients

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<th>Control group (n = 4779)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>All types (%)</td>
<td>67.7</td>
<td>70.4</td>
<td>&lt;0.18</td>
</tr>
<tr>
<td>Lower urinary tract infections (%)</td>
<td>48.4</td>
<td>44.9</td>
<td>0.12</td>
</tr>
<tr>
<td>Pyelonephritis (%)</td>
<td>6.2</td>
<td>7.6</td>
<td>0.22</td>
</tr>
<tr>
<td>Abdominal (%)</td>
<td>6.5</td>
<td>5.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Pulmonary (%)</td>
<td>15.9</td>
<td>18</td>
<td>0.25</td>
</tr>
<tr>
<td>Bacteriemia (%)</td>
<td>7.5</td>
<td>5.6</td>
<td>0.07</td>
</tr>
<tr>
<td>Others (%)</td>
<td>15.5</td>
<td>18.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Jacquet A Transplant Int 2011
Controversies Conference on ADPKD | January 17-19, 2014 | Edinburgh, United Kingdom
3. What evaluations should ADPKD transplant candidates undergo to minimize the risk?

- Related to polycystic kidney:
  - Size
  - Infection (cysts)
  - Bleeding
  - Malignancy

- Imaging
- Nephrectomy

- Related to extrarenal disease manifestation:
  - Cerebral aneurysm, stroke
  - Diverticulosis
  - Cardiac disease
  - Liver cysts

- Imaging
- Intervention

- Related to other causes:
  - Post-transplant diabetes
  - Hypertension
  - Erythrocytosis
  - Malignancies (skin)
  - Hyperlipidemia
  - Coagulation disorder

- Dermatology
- Lab investigation
What evaluations are specifically recommended for ADPKD patients by current guidelines?

**British guidelines 2008**
no specific recommendations for ADPKD patients

**Canadian guidelines 2005**
not sufficient evidence to support screening for cerebral aneurysm of all patients or to deny access to KTX without screening
no recommendation for routine screening for diverticular disease

**KDIGO 2009 Transplant guidelines**
no evidence that the benefits of screening for RCC after Tx outweigh harm

**Canadian guidelines 2005, ERBP 2013, and EAU 2009:**
nephrectomy (before transplantation) in case of severe recurrent symptomatic complications (e.g. bleeding, infection, stones)
unilateral nephrectomy for space reasons
What about nephrectomy?

Data and procedures for nephrectomy are highly controversial occurring in 10-100%:

- in Italy (1):
  - 83% of centers before Tx, mainly for abdominal space

- in France (2): 33% of pts with nephrectomy
  - prophylactic: 71%
  - infection (cysts): 15%
  - bleeding: 8%
  - malignancy: 1.5%

Controversial issues:

- Imaging (CT vs. MRI vs. ultrasound, no imaging = only clinical)
- Indication (prophylactic vs only for problems
  - which problems? what severity?, what size? iliac crest?)
- Timing (before vs. simultaneous vs. after Tx)
- Uni- or bilateral
- Method (open vs. laparoscopic (hand assistet vs. transperitoneal) vs. embolisation)

3. How should native kidneys be monitored after renal transplantation? increased risk of kidney cancer?

Risk of kidney cancer in ADPKD controversial depending on patient cohorts, and controls in some studies up to 8% in nephrectomy specimens clinical consequences of small (<1.5cm) incidental tumors unclear

Renal cancer is associated with acquired cystic kidneys

Screening modality unclear (ultrasound vs. MRI vs. CT)

no apparent higher mortality due to kidney cancer

**KDIGO post-Tx 2009**

Higher incidence of kidney tumors after Tx no evidence that benefits of screening for kidney tumors outweigh harm

5. Can ADPKD kidneys be used as donor organs under specific circumstances?

so far around n=12 case reports of donors with ADPKD
donor age 20-55 years (mean 30 years)
normal renal function
most kidneys < 15cm
up to 15 years of follow-up with good results

informed consent of recipient?!
++ What is the work up for related living donors?

British guidelines (2011)
...reasonable steps should be taken to exclude genetic disease in the potential donor.

- record family history
- routine work-up
- screening for ADPKD by ultrasound
  using revised ultrasound criteria (Pei Y et al JASN 2009)
  - proceed with donation
    - if donor >40 years of age and ≤2 cysts
  - 20-40 years: additional CT or MRI (criteria?)
- eventually additional genetic testing according to guidelines for genetic testing
  - linkage analysis
  - or DNA sequencing of recipient and donor for pathogenic variant
  (Huang E. Transplantation 2009)
7. What is the optimal timing of preemptive renal transplantation in ADPKD?

Instead of dialysis or within 6 months after initiation of RRT.
8. Should native nephrectomy be done and at what point related to transplantation: pre, concurrent, or post Tx?

Already discussed
9. What immunosuppressive therapies should be utilized in a transplanted ADPKD patient?

Immunosuppressive treatment according to current guidelines, unless new data demonstrate specific benefits for ADPKD patients.
9. Should hepatic cystic disease impact on choice of immunosuppression?

Immunosuppressive treatment according to current guidelines, unless new data demonstrate specific benefits for ADPKD patients.
Thank you for your attention!
10. What are the indications for combined kidney-liver transplantation?

Combined kidney – liver transplantation is rare
Italy 40/1709 (0.023%) transplanted ADPKD pts

Indications: severe clinical symptom burden
e.g. due compression syndrome, severe malnutrition
liver failure (e.g. HBV or HCV infection)
Budd-Chiari-like-Syndrome with hepato-venous outflow obstruction
Cyst infection?

Eurotransplant waitlisting criteria:
Massive PLD (total Cysts/Parenchyma >1) and complication(s), that can exclusively be treated by liver Tx
clinically apparent liver disease due to massive PLD, incl. weight loss, ascites, portal hypertension

Failure or contraindications of non-transplant related interventions
9. What immunosuppressive therapies should be utilized in a transplanted ADPKD patient?

mTOR inhibitors may have beneficial effects on kidney and liver cysts

mTOR inhibitors are approved immunosuppressants after kidney transplantation

however

mTOR inhibitors have several contraindications and side effects and are not considered standard of care according to KDIGO 2009

Excellent outcomes and quality of life with current standard of care

Cyst growth is not a major concern for the vast majority of patients, especially after nephrectomy

Potential benefits of mTOR inhibitor for ADPKD patients were not clearly demonstrated in large clinical trials

**Immunosuppressive treatment according to current guidelines, unless new data demonstrate specific benefits for ADPKD patients**
9. Should hepatic cystic disease impact on choice of immunosuppression?

mTOR inhibitors may have beneficial effects on liver cysts

mTOR inhibitors are approved immunosuppressants after kidney transplantation however

mTOR inhibitors have several contraindications and side effects and are not considered standard of care according to KDIGO 2009

Excellent outcomes and quality of life with current standard of care

Cyst growth is not a major concern for the vast majority of patients,

Potential benefits of mTOR inhibitor for liver cysts were not clearly demonstrated

Immunosuppressive treatment according to current guidelines, unless new data demonstrate specific benefits for ADPKD patients