Innovations in Evaluations & Management of Renal Complications in ADPKD

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• Investigator of TEMPO study, research funding from Otsuka
Challenges in the Evaluations & Management of Renal Complications in ADPKD

• Kidney cyst infections
• Chronic Pain
Challenges of kidney cyst infections in ADPKD

Difficulty in diagnosis

• Fever and abdominal pain carries a broad differential.
• Conventional imaging may not be definitive in
  – isolating the location of infection
  – differentiating cyst infection from cyst hemorrhage or pyelonephritis.
• Blood and Urine culture is often negative.
  – Urine and blood cultures were found to be respectively positive in 39 and 24% episodes.

Challenges of kidney cyst infections in ADPKD

Difficulty in Treatment

• Empiric therapy with antibiotics that is widely known to penetrate cyst
• Infection recurs after antibiotic treatment discontinuation
• Percutaneous or surgical drainage of infected cysts required
  – 5/33 pts for cyst drainage, 4/33 extirpation (nephrectomy or partial hepatectomy)

Case 19F

Present illness:

• 5 episodes of high fever within 6 months.
• Treated with antibiotics and puncture/drainage of the cysts.
• Referred to us after the last episode of fever.
  - WBC 11700/mm³, Cr 0.66 mg/dl, CRP 7.12 mg/dl
  - Urine WBC 50-99/HPF, RBC 20-29/HPF
  - Urine culture from previous hospital: Citrobacter diversus

Family History: Father: ESRE with ADPKD
Case 19F

1. Her temperature went down with carbapenem, although her infection recurred after the discontinuation of the treatment.

2. Laparoscopic marsupialization of the infected cysts were planned.
   i. Construct 3D image and 3D model of the kidney
   ii. CT-guided puncture of the cyst and instillation of methylene blue
   iii. Laparoscopic marsupialization
$^{18}$FDG PET/CT for the diagnosis of infectious cysts

Dec 2012
3D navigation of renal cysts
3D model of the kidney made of 3D printer
Laparoscopic marsupialization
Construction of 3D model has advantages in

- Explanation of the disease and the procedure to the patient and family
- Identifying the precise location of the cysts and the simulation of surgery
Challenges in the Evaluations & Management of Chronic Pain in ADPKD

- Chronic pain is a common complaint..., with a negative impact on sleep, activity, mental status, and social relationships.

- Chronic pain is one of the most difficult symptoms to treat.
A sequential approach to pain management in ADPKD

- Non-pharmacologic therapies
- Systemic, non-narcotic analgesics
- Low-dose opioids
- Transcutaneous electrical nerve stimulation
- Acupuncture
- Spinal cord stimulation (neuromodulation)
- Neuraxial opioids and local anesthetics
- Surgical decortication
- Renal denervation
- Transcatheter arterial embolization

*Advances in Chronic Kidney Disease, Vol 17, No 3 (May), 2010: pp e1-e16*
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# Surgical Cyst Decortication in ADPKD; review of literature

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>n</th>
<th>Follow-up periods</th>
<th>50% pain relief</th>
<th>100% pain relief</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haseebuddin (2012)</td>
<td>18</td>
<td>Mean; 130 M</td>
<td>8/12 (67%)</td>
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<tr>
<td>McNally (2003)</td>
<td>7</td>
<td>Mean; 14 M</td>
<td>5/7 (71%)</td>
<td>2/7 (29%)</td>
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<tr>
<td>Lee (2003)</td>
<td>29</td>
<td>Mean; 32 M</td>
<td>73% (at 12 months)</td>
<td>52% (at 24 months)</td>
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<tr>
<td>Lifson (1998)</td>
<td>7</td>
<td>Mean; 26 M</td>
<td></td>
<td>5 (71%)</td>
</tr>
<tr>
<td>Elashry (1996)</td>
<td>5</td>
<td>3-15 M</td>
<td>5/5 (100%)</td>
<td>1/5 (20%)</td>
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<tr>
<td>Brown (1996)</td>
<td>8</td>
<td>12-28 M</td>
<td>5/8 (63%)</td>
<td>5/8 (63%)</td>
</tr>
<tr>
<td>Teichman (1995)</td>
<td>6</td>
<td>6-40 M</td>
<td></td>
<td>5/6 (83%)</td>
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<tr>
<td>Elzinga (1992)</td>
<td>26</td>
<td>21±2</td>
<td>80% (at 12 months)</td>
<td></td>
</tr>
<tr>
<td>Chehval (1995)</td>
<td>3</td>
<td>16 M</td>
<td></td>
<td>3/3 (100%)</td>
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</table>
Surgical Cyst Decortication in ADPKD

- Cyst decortication in patients with ADPKD has a long history.

- Cyst decortication is highly effective in the management of disease-related chronic pain for the majority of patients with ADPKD, providing durable pain relief.
Robotic Surgical Cyst Decortication in ADPKD
Renal denervation for chronic pain in ADPKD

- Sensory innervation of the kidney is mediated predominantly via sympathetic afferents derived from spinal segments T10 through T12.
- Afferent C fibers from the renal parenchyma and A delta fibers from the renal pelvis and calices travel along the renal artery to the renal plexus, which is composed of fibers from the celiac plexus, celiac ganglion aorticorenal ganglion, lowest splanchnic nerve, first lumbar nerve and aortic.
Renal denervation inhibits cyst growth in Cy/+ rats

Control

sham

bil RND

Renal denervation (RND) for chronic pain in ADPKD

- Renal denervation for Loin pain haematuria syndrome (LPHS) related pain, with a success rate of approximately 25%.
  - BJU Int, 93: 818, 2004
  - Br J Urol, 80: 6, 1997

- Laparoscopic renal denervation made 4 adolescent ADPKD pts pain free
  - J Urol 175, 2274-2276, June 2006
Renal denervation (RND) by percutaneous radiofrequency ablation (RF) for refractory hypertension

- RND by RF has been associated with reductions in blood pressure.
  - *Circulation* 2012; **126**: 2976–82.

Figure 3. Innervation of kidney. Abbreviation: n., n. rami. Reproduced from Bajwa et al. with permission of Macmillan Publishers Ltd.
Percutaneous RND by RF for chronic kidney pain

- A 40-year-old hypertensive lady with Loin pain haematuria syndrome (LPHS)
- Refractory pain symptoms despite the use of non-steroidal anti-inflammatory drugs, adjuvant antidepressants and opioid-like agents.
- Percutaneous RF applied only to the right renal artery.
- After a 6-month follow-up, the patient is pain free and normotensive with all drugs withdrawn.


? Clinical trials for chronic pain +HTN with ADPKD
Transcatheter arterial embolization (TAE) of the renal artery

- Transcatheter arterial embolization (TAE) of the renal artery with metallic coils
- Effective and less invasive renal contraction therapy for ADPKD
- Requirements of many metallic coils (31.2±11.2)
- Recurrence caused by recanalization and/or revascularization by collateral vessels
- Practice limited in Japan and Korea

A 60-year old woman with abdominal distention

Right renal arteriogram

A. Right renal arteriogram before TAE shows narrowed and stretched renal arteries.

B. After TAE with absolute ethanol, the right renal artery is occluded.
Change in kidney volume after TAE

Percent shrinkage of kidneys after TAE (%)

Time after TAE

60.9 ± 16.7 % at 3m after TAE (range, 26.4 – 89.6%) (30 kidneys)

46.4 ± 20.8 % at 6m after TAE (range, 11.5 – 85.8%) (26 kidneys)

34.6 ± 16.7 % at 12m after TAE (range, 10.9 – 77.4%) (23 kidneys)

29.7 ± 13.6 % at 24m after TAE (range, 9.6 – 67.8%) (16 kidneys)

Hokkaido University Graduate School of Medicine, Department of Radiology
New embolic material, Embosphere®

- Embosphere Microspheres are made from trisacryl cross linked with gelatin.
Assessment of QOL

VAS: visual analog scale (abdominal fullness),
FANLTC: Functional Assessment of Non-Life Threatening Conditions,
FACT-Hep: Functional Assessment of Cancer Therapy-Hepatobiliary
Transcatheter arterial embolization (TAE) of the renal artery

- Significant volume reduction
- New embolic material
- ? Pain control
Innovations in the Evaluations & Management of Renal Complications in ADPKD

- Kidney cyst infections
  - Imaging; PET/CT
  - Surgical intervention; navigation for procedures

- Chronic Pain
  - Surgical decortication; minimally invasive surgery
  - Renal denervation; ? Percutaneous RND
Challenges in the Evaluations of Health-related Quality of Life in ADPKD

- HALT-PKD Study; SF-36 scores
- SF-36 lower for patients with lower eGFRs than higher eGFRs
- No decrease in SF-36 in ADPKD with eGFRs >60 than the age-matched general population
- No report on HrQOL specific for ADPKD

Miskulin, et al. AJKD in press
HrQOL of liver cyst

- Prospective study by Japanese consortium of PKD study, Ministry of Welfare and Health
- Case-control study (N=111)
  - Case: liver cysts occupied $\geq 25\%$ of liver volume
  - Control: liver cysts $< 25\%$
- Comparison of general (FANLTC) and liver specific QOL (FACT-Hep)
General QOL by CKD stage

CKD stageによるFANLTCの一元配置分析

一元配置の分散分析

<table>
<thead>
<tr>
<th>分散分析</th>
<th>要因</th>
<th>自由度</th>
<th>平方和</th>
<th>平均平方</th>
<th>F値</th>
<th>p値(Prob&gt;F)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>CKD stage</td>
<td>2</td>
<td>538.454</td>
<td>269.227</td>
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<td>108</td>
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<td></td>
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<td>21311.408</td>
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</table>
Liver specific QOL by CKD stage

CKD stageによるHepの一元配置分析

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<tr>
<td>全体(修正済み)</td>
<td>110</td>
<td>13526.491</td>
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</table>
General QOL by % of liver cysts occupancy

![Graph showing general QOL by % of liver cysts occupancy](image)

### One-Way ANOVA Analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Degrees of Freedom</th>
<th>Sum of Squares</th>
<th>Mean Square</th>
<th>F Value</th>
<th>p Value (Prob&gt;F)</th>
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<tbody>
<tr>
<td>Liver Cyst Ratio</td>
<td>3</td>
<td>1599.378</td>
<td>533.126</td>
<td>2.8939</td>
<td>0.0387*</td>
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<td>Error</td>
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<td>19712.030</td>
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<td>Overall (Adjusted)</td>
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<td>21311.408</td>
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Liver specific QOL by % of liver cysts occupancy

一元配置の分散分析

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<th>p値(Prob&gt;F)</th>
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<td>肝嚢胞割合</td>
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<td>全体(修正済み)</td>
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<td>13526.491</td>
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HrQOL study of liver cysts

• Specific HrQOL questionnaires reflects cysts volume occupancy.
• Burden of disease should be measured by specific HrQOL questionnaires.
• Development of kidney specific HrQOL questionnaires for ADPKD needed