Biomarkers in Obstructive Uropathies

Brian Becknell, MD, PhD
Disclosures

None.
Goals for this presentation

• Define the clinical problem and need for biomarkers.
• Can fetal biomarkers predict ESRD risk in PUV?
• Can urinary biomarkers identify patients with UPJO who require surgery?
What’s obstructive uropathy?

- *Merck Manual*: Obstructive uropathy is structural or functional hindrance of normal urine flow, sometimes leading to renal dysfunction (obstructive nephropathy).
What’s a biomarker?

*Biomarker:* A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.

Why are biomarkers needed for patients with obstructive uropathy?

• Accurate patient / family counseling about ESRD risk
• Better risk stratification = more homogeneous patient cohort for intervention
• Timing surgical intervention
Severe obstruction can lead to fetal and perinatal demise.

~20% of boys with PUV will develop ESRD in childhood.
Chronic kidney disease in children: the global perspective

Bradley A. Warady • Vimal Chadha

<table>
<thead>
<tr>
<th>Distributions by diagnosis</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive uropathy</td>
<td>1,385</td>
</tr>
<tr>
<td>Aplastic/hypoplastic/dysplastic kidney</td>
<td>1,125</td>
</tr>
<tr>
<td>Other</td>
<td>913</td>
</tr>
<tr>
<td>FSGS</td>
<td>557</td>
</tr>
<tr>
<td>Reflux nephropathy</td>
<td>536</td>
</tr>
<tr>
<td>Polycystic disease</td>
<td>257</td>
</tr>
<tr>
<td>Prune belly</td>
<td>185</td>
</tr>
<tr>
<td>Renal infarct</td>
<td>155</td>
</tr>
<tr>
<td>Unknown</td>
<td>168</td>
</tr>
<tr>
<td>HUS</td>
<td>134</td>
</tr>
<tr>
<td>SLE nephritis</td>
<td>96</td>
</tr>
<tr>
<td>Cystinosis</td>
<td>97</td>
</tr>
<tr>
<td>Familial nephritis</td>
<td>99</td>
</tr>
<tr>
<td>Pyelo/interstitial nephritis</td>
<td>87</td>
</tr>
<tr>
<td>Medullary cystic disease</td>
<td>82</td>
</tr>
<tr>
<td>Chronic GN</td>
<td>76</td>
</tr>
<tr>
<td>MPGN-type I</td>
<td>67</td>
</tr>
<tr>
<td>Berger’s (IgA) nephritis</td>
<td>64</td>
</tr>
<tr>
<td>Congenital nephrotic syndrome</td>
<td>68</td>
</tr>
</tbody>
</table>

Renal outcome in patients with congenital anomalies of the kidney and urinary tract

Simone Sanna-Cherchi¹,²,⁹, Pietro Ravani³,⁹, Valentina Corbani²,⁹, Stefano Parodi⁴, Riccardo Haupt⁴, Giorgio Piaggio⁵, Maria L. Degli Innocenti⁵, Danio Somenzi², Antonella Trivelli⁵, Gianluca Caridi⁶, Claudia Izzi⁷, Francesco Scolari⁷, Girolamo Mattioli⁸, Landino Allegri² and Gian Marco Ghiggeri⁵,⁶
Report on The Society for Fetal Urology panel discussion on the selection criteria and intervention for fetal bladder outlet obstruction

M.K. Farrugia a, M.C. Braun b, C.A. Peters c, R. Ruano d, C.D. Herndon e

Biomarkers for LUTO

<table>
<thead>
<tr>
<th>Stage I (mild LUTO)</th>
<th>Stage II (severe LUTO, with prenatal findings suggestive of preserved fetal renal function)</th>
<th>Stage III (severe LUTO, with prenatal findings suggestive of fetal abnormal renal function)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount of amniotic fluid</td>
<td>Normal</td>
<td>Oligohydramnios or anhydramnios</td>
</tr>
<tr>
<td>Echogenicity of fetal kidneys</td>
<td>Normal</td>
<td>Hyperechogenic</td>
</tr>
<tr>
<td>Renal cortical cysts</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Renal dysplasia</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Fetal urinary biochemistry</td>
<td>Favorable</td>
<td>Favorable within three consecutive evaluations</td>
</tr>
<tr>
<td>Fetal intervention</td>
<td>Not indicated</td>
<td>Indicated to prevent pulmonary hypoplasia and severe renal impairment</td>
</tr>
</tbody>
</table>

The disease can progress from Stage I to Stage II and then to Stage III during pregnancy. LUTO, lower urinary tract obstruction.
RRT in PUV: Predictive Role of Serum Nadir Cr during the first year of life (SNC1)

- Retrospective cohort study
- 274 consecutive male infants with confirmed PUV
- Underwent intervention for PUV within 90 days of life
- 15% required RRT

Renal Parenchymal Area and Risk of ESRD in Boys with Posterior Urethral Valves

Jose E. Pulido,* Susan L. Furth,** Stephen A. Zderic,§ Douglas A. Canning,§ and Gregory E. Tasian§

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Number at risk
Total RPA $\geq 12.4 \text{ cm}^2$ 46
Total RPA $< 12.4 \text{ cm}^2$ 14

<table>
<thead>
<tr>
<th>Analysis Time (months)</th>
<th>Total RPA $\geq 12.4 \text{ cm}^2$</th>
<th>Total RPA $&lt; 12.4 \text{ cm}^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>46</td>
<td>14</td>
</tr>
<tr>
<td>50</td>
<td>28</td>
<td>8</td>
</tr>
<tr>
<td>100</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>150</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>200</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>250</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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Total RPA $\geq 12.4 \text{ cm}^2$ — Total RPA $< 12.4 \text{ cm}^2$
Baseline GFR, ACR, and PCR predict RRT risk for patients with obstructive uropathy in the CKiD Cohort

<table>
<thead>
<tr>
<th></th>
<th>Cases (n = 27)</th>
<th>Controls (n = 41)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline (years)</td>
<td>10.0 (9–13)</td>
<td>10.0 (9–13)</td>
<td>0.950</td>
</tr>
<tr>
<td>Age at outcome (years)</td>
<td>15.9 (12.7, 16.9)</td>
<td>15.8 (12.7, 16.6)</td>
<td>0.821</td>
</tr>
<tr>
<td>Male sex</td>
<td>23 (85.2)</td>
<td>33 (80.5)</td>
<td>0.751</td>
</tr>
<tr>
<td>Nonwhite race</td>
<td>7 (25.9)</td>
<td>18 (43.9)</td>
<td>0.133</td>
</tr>
<tr>
<td>GFR (mL/min per 1.73 m²)</td>
<td>36.9 (28.6, 42.2)</td>
<td>53.5 (44.5, 64.6)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Urine protein/Cr (mg/mg)</td>
<td>0.40 (0.23, 0.84)</td>
<td>0.22 (0.11, 0.47)</td>
<td>0.010*</td>
</tr>
<tr>
<td>Urine microalbumin/Cr** (mg/mg)</td>
<td>0.58 (0.27, 1.68)</td>
<td>0.03 (0.01, 0.14)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Serum CO₂ (mmol/L)</td>
<td>20 (18, 20)</td>
<td>22 (20, 25)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Serum phosphate (mg/dL)</td>
<td>4.6 (4.3, 5.1)</td>
<td>4.5 (3.9, 4.8)</td>
<td>0.125</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>4.3 (4.2, 4.4)</td>
<td>4.4 (4.3, 4.5)</td>
<td>0.270</td>
</tr>
<tr>
<td>Serum hemoglobin (g/dL)</td>
<td>12.4 (11.4, 13.3)</td>
<td>13.2 (12.3, 14.3)</td>
<td>0.020*</td>
</tr>
</tbody>
</table>
Change in GFR, ACR, and PCR anticipates need for RRT
Can fetal urine biomarkers improve prediction of renal outcomes in PUV?

<table>
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<tr>
<th>Table 1 Standardized multidisciplinary prenatal management based on disease severity [6].</th>
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<td><strong>Fetal urinary biochemistry</strong></td>
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<td><strong>Fetal intervention</strong></td>
</tr>
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The disease can progress from Stage I to Stage II and then to Stage III during pregnancy. LUTO, lower urinary tract obstruction.
Biomarker Discovery

Genomics
The potential

Proteomics
The current status

Metabolomics
The left-over
Proteomics: A Promising Approach for CKD progression in DN

A. Controls versus established CKD

- Discovery
  - (n=230 CKD, 379 HC)
  - Good et al. 2010

- Validation
  - (n=110 CKD, 34 HC)
  - (n=22 DN)
  - Good et al. 2010, Andersen et al. 2012
  - (n=62 CKD, n=75 HC)
  - (n=165 DN)

B. Prediction of progression of CKD?

- (n=35 DN)
  - Zürbig et al. 2012

- (n=44 DN, 44 HC)
  - Roscioni et al. 2013

- (n=552 CKD)
  - (n=76 CKD)
  - Schanstra, Zürbig et al., Argiles et al. 2013

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Joost P. Schanstra et al. JASN 2015;26:1999-2010
Proteomics: A Promising Approach for CKD progression in DN

A) Controls versus established CKD

- Discovery
  - (n=230 CKD, 379 HC)
  - Good et al 2010
- Validation
  - (n=110 CKD, 34 HC)
    - Good et al 2010
  - (n=62 CKD, n=75 HC)
    - Molin et al 2012

B) Prediction of progression of CKD?

- (n=35 DN)
  - Zürbig et al 2012
- (n=44 DN, 44 HC)
  - Roscioni et al 2013
- (n=552 CKD)
  - Schanstra, Zürbig et al
- (n=76 CKD)
  - Argiles et al 2013

C) Large scale interventional trial (n=3280)
   "PRIORITY"

Joost P. Schanstra et al. JASN 2015;26:1999-2010
Proteomics for biomarker discovery in PUV

Fetal Urinary Peptides to Predict Postnatal Outcome of Renal Disease in Fetuses with Posterior Urethral Valves (PUV)

Julie Klein,¹,²* Chrystelle Lacroix,²,³* Cécile Caubet,¹,²* Justyna Siwy,⁴,⁵ Petra Zürbig,⁴ Mohammed Dakna,⁴ Françoise Muller,⁶ Benjamin Breuil,²,⁷ Angelique Stalmach,⁸ William Mullen,⁸ Harald Mischak,⁴,⁸ Flavio Bandin,¹,⁹,¹⁰ Bernard Monsarrat,²,³ Jean-Loup Bascands,¹,² Stéphane Decramer,¹,⁹,¹⁰ Joost P. Schanstra¹,²†
Blinded validation of 12PUV score in a separate PUV population

- AUC 0.94 [95% CI: 0.82-0.99]
- Linear model
  AUC 0.93 [95% CI: 0.80-0.99]
- KNN model
  AUC 0.90 [95% CI: 0.76-0.97]

Comparison of 12PUV score distribution between noESRD and ESRD groups (n = 22 vs n = 16)
Combining proteomics and metabolomics may be superior to 12PUV alone

Buffin-Meyer et al. (2018)
*J. Proteomics*. PMID: 29929039
Fetal urine proteomics in PUV

- Currently exploratory with limited validation
- Assays are run by one lab
- Cost and regulatory concerns
- Limited application – performance of postnatal PUV12 measurement in predicting ESRD remains untested
Ureteropelvic junction obstruction (UPJO)

Most common cause of congenital obstruction
Incidence: 1 in 500 live births
  • Boys > girls; L > R
  • Bilateral involvement 10-40%
Presentation:
  • Antenatal imaging
  • Symptoms
  • Incidental
Diagnosis: Imaging
Treatment: Observation vs. Surgery
Hydronephrosis ≠ Obstruction

- Presence of hydronephrosis is readily identifiable…
  … but whether clinically significant and how it impacts need for intervention is controversial
Potential Indications for Surgery

• Worsening hydronephrosis/thinning of renal cortex
• Prolonged washout on diuretic renogram ($T_{1/2} > 15-20$ min)
• Poor or worsening split renal function
• Pyelonephritis, hypertension, hematuria, stones, pain
Do urinary biomarkers predict need for pyeloplasty?

- Distinguish surgical candidates vs. those well suited for non-operative management
- Guide timing of pyeloplasty
Urinary NGAL Levels Correlate with Differential Renal Function in Patients with Ureteropelvic Junction Obstruction Undergoing Pyeloplasty

Nicholas G. Cost, Paul H. Noh, Prasad Devarajan, Vesna Ivancic, Pramod P. Reddy, Eugene Minevich, Michael Bennett, Christopher Haffner, Marion Schulte, and W. Robert DeFoor Jr.

<table>
<thead>
<tr>
<th>Differential Function</th>
<th>Spearman $\rho$</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalized $^*$ NGAL:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>$-0.359$</td>
<td>0.004</td>
</tr>
<tr>
<td>Renal pelvis</td>
<td>$-0.383$</td>
<td>0.002</td>
</tr>
<tr>
<td>Renal pelvis/bladder</td>
<td>$-0.166$</td>
<td>0.20</td>
</tr>
<tr>
<td>$T_{1/2}$</td>
<td>$-0.363$</td>
<td>0.007</td>
</tr>
</tbody>
</table>

$^*$ Correction to creatinine in same specimen.
Potential Novel Biomarkers of Obstructive Nephropathy in Children with Hydronephrosis

Beata Bieniaś and Przemysław Sikora

Disease Markers (2018)
Potential Novel Biomarkers of Obstructive Nephropathy in Children with Hydronephrosis

Beata Bienias and Przemyslaw Sikora

$r = 0.5, p < 0.05$

Urine NGAL/Cr

Sensitivity

1 - specificity

0.544

Disease Markers (2018)
Peptidomics in UPJO

**Discovery**
- Spontaneous Resolution
- Intermediate obstruction
- Relief surgery (pyeloplasty)
- + Healthy controls
- Urinary proteome analysis
- Differentially secreted proteins/peptides

**Validation**
- Urinary proteome analysis
- Classification
- Pyeloplasty
- Spontaneous resolution
- Comparison of proteome-based prediction with clinical situation 1-2 years

Predicting the clinical outcome of congenital unilateral ureteropelvic junction obstruction in newborn by urinary proteome analysis

Stephane Decramer1−3, Stefan Wittke4, Harald Mischak4, Petra Zürbig4, Michael Walden4, François Bouissou1−3, Jean-Loup Bascands1,2 & Joost P Schanstra1,2

… but these results were not further validated

Summary

- Early evidence points to value of biomarkers in predicting CKD progression in patients with obstructive uropathy
- Initial observations need to be replicated in independent cohorts
- Still in discovery / initial validation phase
- Lack of a diagnostic gold standard for UPJO is a barrier to biomarker studies
Acknowledgements

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Nephrology and Urology Research Affinity Group
Center for Clinical and Translational Research