CKD Screening and Treatment in Pediatric Urology Clinics

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Nationwide Children’s Hospital
Disclosure Statement

I have nothing to disclose.
2 weeks ago in Columbus…
NCH Spina Bifida Clinic

- 18 year old female with MM, shunted hydrocephalus, neurogenic bowel/bladder, LE deficits
- Routine appointment in multidisciplinary clinic
- CIC Q3H, no UTI recently. Not taking her Ditropan XL.
- HS Senior
- BP 126/72 mmHg, baseline physical exam
- Last serum Cr in 2011 (1.07)
- Renal ultrasound, renal lengths 9 and 10 cm. “Echogenic with loss of corticomedullary differentiation, consistent with medical renal disease, correlate clinically.” No hydronephrosis.
- You check serum Cr as it’s been awhile …
Ultrasound changes: “Medical renal disease”

- Non-specific changes in kidney echotexture
- Hypoechoic → Isoechoic → Hyperechoic
- Renal size may distinguish acute (bigger) or chronic (smaller) process

Generally, kidneys of patients with advanced CKD are small and echogenic (bright).

Lab calls you with a critical value ...

K 7.2, BUN 80, Cr 4 mg/dL.
As you send her to the ED, you wonder, how did this happen? Could this have been identified sooner/prevented?
The challenge(s)

- CKD is not an obvious diagnosis.
- And most patients with urologic disorders do NOT have significant CKD.
- Can we identify these patients by screening?
- What treatment(s) can we offer them?
Outline

• Definition of CKD
• Signs/symptoms of CKD
• Causes of CKD / Screening
• Complications / Treatment of CKD
• Improving care for children with CKD and urologic disease
Definitions of CKD

CKD classification:

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR (mL/min/1.73m²)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&gt; 90 + kidney damage</td>
<td>Reduced kidney function</td>
</tr>
<tr>
<td>II</td>
<td>60 – 89 + kidney damage</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>30 – 59</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>15 – 29</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>&lt; 15</td>
<td></td>
</tr>
</tbody>
</table>

GFR = Glomerular filtration rate
Kidney damage = Abnormality on blood, urine, imaging or biopsy (≥ 3 months)
Definition of CKD

Estimating Glomerular Filtration Rate (GFR):

- Serum studies
  1. Creatinine
  2. Cystatin C
- 24 hour urine for creatinine clearance
- Single injection plasma disappearance curves
Definitions of CKD

Estimating GFR

Serum Creatinine

- Released from skeletal muscle at a relatively constant rate
- Influenced by muscle mass, gender, body composition, and age
- Rough estimate of normal Cr for age in children (beware of “normal” adult values):
  \[ \text{Age (years)} / 30 + 0.3 = \text{Normal Cr for age (mg/dL)} \]
Definitions of CKD

Estimating GFR - Serum Cystatin C

- Endogenous protein produced by all nucleated cells at a relatively constant rate
- Not influenced by muscle mass, gender, body composition, or age (between 1 – 50 years)
- Normal value ~ 0.8 – 1 mg/L
- May affect cystatin C: Inflammation, proteinuria, smoking, diabetes, AKI
Definitions of CKD

Estimating GFR: Bedside Schwartz formula

• \[ \frac{0.413 \times \text{height (cm)}}{\text{SCr (mg/dL)}} \]
• Developed using data from children ages 1 – 16 with mild to moderate CKD
Definitions of CKD

Estimating GFR in adults

MDRD (1999)
Underestimates GFR in healthy adults with GFR > 60 ml/min

CKD-EPI (May 2009)
More precise and accurate than MDRD equation, especially at higher GFR
Definitions of CKD

Estimating GFR: 24 hour urine for creatinine clearance

- \( \text{CrCl} = \frac{U \times V_U}{P} = \left( \frac{U_{Cr} \times [V_U \text{ (mL)/T \text{ (min)}]/P_{Cr}}\right) \times 1.73/\text{BSA} \)
- Limitation with low baseline GFR due to tubular secretion of Cr
- May overestimate true GFR by up to 67%
Definitions of CKD

Estimating GFR: Single injection plasma disappearance curves

Radioisotopes

Can also estimate GFR by measuring renal uptake of tracer using a gamma camera

\(^{99m}\)Tc-DTPA

\(^{51}\)Cr-EDTA

\(^{125}\)I-iothalamate – some tubular secretion occurs

Nonradioisotopes

Inulin – gold standard

Iothalamate – some tubular secretion occurs

Iohexol
Summary

• Many ways to estimate GFR: all have their limitations
• Pick one, usually this is SCr.
• In SB or patients with low muscle mass, consider monitoring Cystatin C instead.
Outline

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CKD Presentation

- Signs/symptoms of uremia
- Signs/symptoms of CKD complications
- Signs/symptoms of the underlying cause of CKD
CKD Presentation

<table>
<thead>
<tr>
<th>Signs/Symptoms</th>
<th>CKD class</th>
</tr>
</thead>
<tbody>
<tr>
<td>S/Sx and labs related to underlying cause of CKD</td>
<td>1 – 5</td>
</tr>
<tr>
<td>S/Sx and labs related to CKD complications</td>
<td>3 – 5</td>
</tr>
<tr>
<td>S/Sx related to uremia</td>
<td>Late 4 – 5</td>
</tr>
</tbody>
</table>
CKD Presentation: Uremia

• Decreased energy/fatigue
• Increased sleepiness
• Decreased appetite
• Nausea/vomiting: Worse in am
• Poor concentration
• Worsening school performance
CKD Presentation: Underlying Cause of CKD

- Polyuria/polydipsia/nocturia
- Recurrent UTI
- Enlarged kidneys
- Hematuria/proteinuria
- Hypertension
CKD Presentation: Complications

- Anemia
- Bone Disease
- Cardiovascular Disease
- Developmental delay
- Electrolyte abnormalities
- Fluid abnormalities
- Growth failure
- Infections
Summary

CKD presentation varies according to:
- underlying cause
- extent
- complications

Your history taking / review of systems can really help!
- This is part of effective screening.
Outline

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• Causes of CKD / Screening
• Complications / Treatment of CKD
• Improving care for children with CKD and urologic disease
# Causes of CKD – adults

| Cause                                      | Percent of Cases
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>44.9</td>
</tr>
<tr>
<td>Type 1</td>
<td>3.9</td>
</tr>
<tr>
<td>Type 2</td>
<td>41.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>27.2</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>8.2</td>
</tr>
<tr>
<td>Chronic interstitial nephritis or obstruction</td>
<td>3.6</td>
</tr>
<tr>
<td>Hereditary or cystic disease</td>
<td>3.1</td>
</tr>
<tr>
<td>Secondary glomerulonephritis or vasculitis</td>
<td>2.1</td>
</tr>
<tr>
<td>Neoplasms or plasma-cell dyscrasias</td>
<td>2.1</td>
</tr>
<tr>
<td>Miscellaneous conditions‡</td>
<td>4.6</td>
</tr>
<tr>
<td>Uncertain or unrecorded cause</td>
<td>5.2</td>
</tr>
</tbody>
</table>

* Data are from the U.S. Renal Data System.³
Causes of CKD - Pediatrics

- Cong. structural disorders 49%
- Glomerulonephritis 16.5%
- Congenital kidney disease 10%
- Acquired kidney disease 6.5%
- Other 16%
- Unknown 2.6%

NAPRTCS 2008 Annual Report
Congenital Structural Disorders

- Obstructive uropathy 20.7%
- Aplasia/dysplasia/hypoplasia 17.3%
- Reflux nephropathy 8.4%
- Prune belly 2.7%

Total 49.1%
CKD screening guidelines in adults

• 11% incidence in adults but usually early stage
• Primary risk factors for CKD: hypertension, diabetes
• In asymptomatic adults, the USPSTF concluded there is insufficient evidence to assess benefits vs harm of routine CKD screening
• American College of Physicians (ACP) recommends against CKD screening in asymptomatic adults without risk factors
• ASN strongly recommends routine screening for CKD in all adults. Early recognition of asymptomatic stage 1-3 CKD may reduce incidence of AKI from nephrotoxic medications, contrast dyes for medical imaging. AKI accelerates CKD.

Ann Intern Med 2012;157:567-570
CKD screening

- **BP measurement** (usually 3 separate occasions)
- **Urine protein**
  - Ideally a first morning sample (rule out orthostatic proteinuria)
  - Dipstick protein ≥ 1+ (can be hard to interpret)
  - Urine albumin/Cr ratio > 30 mg/g
- **Serum Cr**
UK guidelines for CKD screening

• Annual SCr in patients with “high risk of obstructive nephropathy”:
  • Known/suspected bladder outlet obstruction
  • Neurogenic bladder (SCr may overestimate true GFR)
  • Urinary diversion surgery
  • Urinary stone disease due to primary hyperoxaluria, cystinuria, Dent’s disease, struvite stones, anatomic abnormalities, > 1 stone/year

http://www.nice.org.uk/guidance/cg148/chapter/guidance
AUA Guideline: Evaluation of Child with VUR

- Monitoring BP, height, weight annually
- UA for proteinuria and bacteriuria annually, Ucx and sensitivity if suggestive of infection
- US q12months to monitor renal growth / parenchymal scarring.
AUA guideline: Following VUR resolution

- **Optional:** If both kidneys are normal by US or DMSA, monitor BP, height, weight and UA for protein/UTI annually through adolescence.

- **Recommendation:** If either kidney is abnormal by US or DMSA, do this.

- **Recommendation:** Long-term concerns of HTN (especially during pregnancy), renal functional loss, recurrent UTI, and familial VUR in siblings and offsprings should be discussed with family and communicated to child at appropriate age.
CKD surveillance in SB patients

- GFR monitoring. Avoid Cr based methods to estimate GFR. Use Cystatin C instead.
- Unilateral renal damage may only be appreciated by nuclear medicine scans ($^{99m}$Tc DMSA).
- Monitor Albuminuria
- Check BP

Filler et al. (2012) Int Urol Nephrol
Risk Factors for End Stage Renal Disease in Children With Posterior Urethral Valves

William DeFoor,* Curtis Clark, Elizabeth Jackson, Pramod Reddy, Eugene Minevich and Curtis Sheldon

From the Division of Pediatric Urology, Cincinnati Children’s Hospital, Cincinnati, Ohio

15/119 pts with ESRD, mean interval from dx to ESRD 8.1 yr

<table>
<thead>
<tr>
<th>TABLE 3. Multivariate logistic regression analysis of ESRD risk factors in patients with posterior urethral valves</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Factor</td>
</tr>
<tr>
<td>VUR</td>
</tr>
<tr>
<td>Bladder dysfunction</td>
</tr>
<tr>
<td>Nadir creatinine greater than 1.0 mg/dl</td>
</tr>
</tbody>
</table>

* Controlling for other risk factors (1 equals no increased risk).

DeFoor et al. (2008) J Urology
```
Risk Factors Associated With Chronic Kidney Disease in Patients With Posterior Urethral Valves Without Prenatal Hydronephrosis

Dena L. Engel, John C. Pope, IV, Mark C. Adams, John W. Brock, III, John C. Thomas and Stacy T. Tanaka*

From the Division of Pediatric Urology, Monroe Carell Jr. Children’s Hospital at Vanderbilt, Nashville, Tennessee

- preoperative bilateral hydronephrosis
- increased hydronephrosis severity
- bilateral VUR

“Importantly CKD can require decades to manifest, such that transition to adult care can complicate care continuity. All should be counseled on potential loss of renal function.”

Figure 2. Kaplan-Meier estimate of survival without chronic kidney disease in 141 boys with posterior urethral valves with postnatal presentation.

Engel et al. (2011) J Urology
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Who develops Significant CKD? PUV experience

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*

Table 1. Characteristics of 60 patients with posterior urethral valves according to kidney function

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Non-ESRD (n=52)</th>
<th>ESRD (n=8)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation, wk (IQR)</td>
<td>2 (1–11)</td>
<td>1 (0.5–1.5)</td>
<td>0.11</td>
</tr>
<tr>
<td>Total RPA, cm² (IQR)</td>
<td>17.05 (13.69–21.74)</td>
<td>10.37 (8.21–13.61)</td>
<td>0.01</td>
</tr>
<tr>
<td>Nadir 1-mo creatinine, mg/dl (IQR)</td>
<td>0.5 (0.4–0.8)</td>
<td>1.6 (1.4–3.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VUR≥4 bilaterally (%)</td>
<td>6/52 (13)</td>
<td>4/8 (37.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>UTI (IQR)</td>
<td>0 (0–1)</td>
<td>1 (0–2)</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Group characteristics: significance tested using Wilcoxon rank sum or Fisher exact test. IQR, interquartile range; RPA, renal parenchymal area; VUR, vesicoureteral reflux; UTI, urinary tract infection.

Pulido et al. (2014) CJASN
Who develops Significant CKD? PUV experience

Combined creatinine velocity and nadir creatinine: A reliable predictor of renal outcome in neonatally diagnosed posterior urethral valves

Robert Coleman, Thomas King, Cezar-Doru Nicoara, Muhammad Bader, Liam McCarthy, Harish Chandran, Karan Parashar

Table 2  Risk scores for each prognostic indicator.

<table>
<thead>
<tr>
<th>Nadir creat score Result (µmol/L)</th>
<th>Score</th>
<th>C_{vel} score Result (µmol/L/day)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>1</td>
<td>≤3</td>
<td>1</td>
</tr>
<tr>
<td>35–75</td>
<td>2</td>
<td>3 to 3</td>
<td>2</td>
</tr>
<tr>
<td>&gt;75</td>
<td>3</td>
<td>&gt;3</td>
<td>3</td>
</tr>
</tbody>
</table>

Figure 1  Simple linear regression PUV Risk Score versus CRI risk.
CKD Progression in SB

- Febrile UTI (pyelonephritis)
- Detrusor instability / dyssynergia / VUR
- Co-morbidities: congenital kidney and urinary tract anomalies, diabetes, hypertension
- Prematurity (Brenner hypothesis: decreased nephron mass)
- Exposure to nephrotoxins: NSAIDs, radiocontrast
- Kidney stones
Summary – CKD Screening

• Recognize CKD complications (Stage 3-5)
• Screen patients with bladder outlet obstruction, renal scarring, neurogenic bladder, urinary diversion for CKD:
  - BP
  - urine albumin/Cr
  - serum Cr (or Cystatin C in SB patients)
Outline

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Complications of CKD

- Anemia
- Bone disease
- Cardiovascular disease
- Development
- Electrolyte abnormalities
- Fluid abnormalities
- Growth
- Infection
- Proteinuria
- Psychiatric disorders
Anemia

Treatment: Iron, Erythropoietin, Antibiotics (if infected)

Nat. Rev. Nephrol. doi:10.1038/nrneph.2015.82
Bone Disease

- Bone pain
- Skeletal deformities
  - e.g. rickets, genu valgum
- Extraskeletal calcifications
- Increased risk for SCFE
- Muscle weakness
- Poor growth
Treatment of CKD-Mineral Bone Disorders

• Treat vitamin D deficiency
• Use active vitamin D analogs, calcimimetics to suppress parathyroid gland
• Phosphorus reduction: low-phos diet, phos binders
• Optimize Ca level if low with supplements
• Control acidosis
• Parathyroidectomy
Cardiovascular Disease

- Early detection and treatment of hypertension
- Recognize peripheral vascular disease/coronary artery disease
- Dysrhythmias
CKD Treatment - Hypertension

ESCAPE Trial

Age 3 – 18 yr with CKD stage 2 – 4 & HTN
n = 385

RCT
High fixed dose ramipril with strict (24-hr MAP < 50\textsuperscript{th}%) vs standard (24-hr MAP 50 – 90\textsuperscript{th}%) BP goal
Non RAS inhibitors used to lower BP prn

Outcomes (5 yr follow-up)
1\textdegree: 50% drop in GFR or ESRD
2\textdegree: Changes in BP, GFR, proteinuria
Developmental Delay

- Related to underlying diagnosis
- Those with moderate to severe CKD more severely affected
  - ~25% of infants with more severe CKD show developmental delay
- Often subtle
- Cognitive deficits
  - Cognitive function of school-age children with CKD usually within normal limits, but lower than healthy children (total, verbal, and performance IQ)
  - May benefit from IEP
  - Variable improvement (if any) with kidney transplant
  - Persist into adulthood
Electrolyte Abnormalities

Potassium

Treatments for life-threatening hyperkalemia:
- Dialysis
- Calcium
- Insulin/glucose, bicarbonate, β-agonist (albuterol)

Treatment for non life-threatening hyperkalemia:
- Limit intake, avoid meds which may increase K⁺ (like spironolactone, β-blockers, KCl supplements)
- Treat acidosis
- Kayexalate, Lasix
Electrolyte Abnormalities

Hyponatremia: Rx Sodium supplement
  Usually seen in infants with congenital anomalies
Hypocalcemia: Rx Ca$^{2+}$ supplement and 1,25-vitamin D
  Due to decreased 1,25-OH vit D and high phos
Hyperphosphatemia: Rx Low Phos diet / Phos binders
  Due to decreased renal clearance
Metabolic Acidosis in CKD

Causes

- Decreased renal acid excretion
- Decrease renal bicarbonate reabsorption
- Increased protein catabolism
Complications of Acidosis

Complications

“Uremic” symptoms (e.g. malaise, weakness)
Poor growth
Resistance to IGF-1
Worsening bone disease
Bone used to buffer acid load in chronic acidosis
Increased PTH

Therapy: alkali replacement
Bicitra, sodium bicarbonate
Goal: HCO$_3^-$ > 22 mEq/L (K/DOQI)
Fluid Requirements

• Abnormalities in urine output (polyuria / oliguria):
  - Underlying diagnosis
  - Degree of renal failure
• Fluid requirements depends on patient’s usual urine output
  - Fluid needs can be similar, more, or less than those without renal failure
Growth: Short Stature in CKD

Height SDS for children at the time of CRI registration

<table>
<thead>
<tr>
<th>Height SDS</th>
<th>All Patients</th>
<th>Age at CKD Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Total</td>
<td>6907</td>
<td>100.0</td>
</tr>
<tr>
<td>-1.88 or worse</td>
<td>2455</td>
<td>35.5</td>
</tr>
<tr>
<td>-1.88 to 0</td>
<td>3233</td>
<td>46.8</td>
</tr>
<tr>
<td>Better than 0</td>
<td>1219</td>
<td>17.6</td>
</tr>
</tbody>
</table>

NAPRTCS 2008 Annual Report
Poor Linear Growth in CKD

- Growth hormone resistance
- Protein and calorie malnutrition
- Bone disease (renal osteodystrophy)
- Electrolyte abnormalities (e.g., hyponatremia)
- Metabolic acidosis

Recombinant GH is indicated for children with persistent short stature in CKD
Complications of CKD: Infection

• Patients with CKD have some degree of immunosuppression

• After cardiovascular disease, infections are the leading cause of death in pediatric CKD patients
CKD: Proteinuria

• Renal scarring leads to glomerular hyperfiltration, and passage of plasma protein into the urinary space.
• Detect proteinuria by dipstick or urine albumin/Cr ratio.
• Treat with ACEi/ARB
• Generally we do not restrict dietary protein in kids, to promote growth.
Heavy proteinuria predicts 50% GFR decline or RRT in children with non-glomerular disease

Warady et al. (2015) AJKD
Normal 25-Hydroxyvitamin D Levels Are Associated with Less Proteinuria and Attenuate Renal Failure Progression in Children with CKD

Figure 2. Diastolic BP is inversely associated with serum 25(OH)D at baseline. Expressed in three ranges of 25(OH)D levels (<50, 50-75, >75 nmol/L).

Figure 3. Annual change in eGFR (ml/min/1.73 m²)

Shroff et al. (2015) JASN
CKD: Psychiatric Disorders

Prevalence of psychiatric disorders in children with CKD (n=19) or on HD (n=19)

- Total prevalence: 52.6%
  - Adjustment disorder: 18.4%
  - Depression: 10.3%
  - Neurocognitive disorder: 7.7%
  - Anxiety disorder: 5.1%

Disorders more prevalent in HD group (68.4%) vs predialysis group (36.8%)

CKD Progression Relative to GFR
Variable Rates of CKD Progression

- Depends on type and severity of underlying disease
- Factors associated with faster rate of decline
  - Glomerular disease
  - Puberty (metabolic demand)
  - Acute kidney injury
  - Heavy proteinuria (P:Cr ratio > 2)
  - Hypertension
  - Diabetes mellitus
  - Decreased renal mass (e.g., LBW infant ↓nephron number)
Summary

• Recognize and treat CKD complications.
• Slow CKD progression by treating proteinuria and hypertension, and by preventing further kidney injury.
Outline

- Definition of CKD
- Signs/symptoms of CKD
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Improving CKD care in urologic disease

• Treat underlying cause (*when possible*)
• Recognize and treat CKD complications (*in collaboration with nephrology*)
• **Constant vigilance** to prevent further kidney injury
  - Includes communication with other providers
  - Patient / family education
• Prevent CKD progression
  - Treat hypertension and proteinuria: ACEi / ARB
When to consider nephrology referral?

- CKD: Stage 3 or higher
- More than 1 antihypertensive
- Suspect glomerular disease (hematuria/proteinuria, HTN, elevated Cr)
- Not comfortable with prescribing ACEi/ARB for hypertension and/or albuminuria
CKD Treatment: Multidisciplinary approach

- Nursing
- Dietitian
- Psychologist/psychiatrist
- Social worker
- Pediatrician
- Urologist / Nephrologist

Uro/Neph Clinic
Summary

• CKD in children is usually due to congenital structural renal disease
• Presentation is variable according to cause and severity
• Monitor regularly for complications
• CKD progression may be slowed by addressing underlying cause, good control of BP and proteinuria
• For best results, use a multidisciplinary approach
Selected Readings


Selected Readings


