DE-MYSTIFYING CAKUT: APPROACH TO CKD AND RENAL TRANSPLANT

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Objectives

- Define the renal spectrum of disorders encompassing CAKUT
- Review in utero kidney-bladder development
- Approach to antenatal hydronephrosis
- Renal function review: general principles
- Review of common CAKUT disorders leading to chronic kidney disease (CKD)
- Role of ACE inhibitors in mitigating progression of CKD
- CAKUT and Renal Transplantation
- Surgical approach to CAKUT
 - Preparation for renal transplant

What is CAKUT?

- C : Congenital
- A : Anomalies
- K: Kidney
- U: Urinary
- T: Tract

CAKUT : spectrum

- Abnormalities in renal parenchyma development
 - Renal dysplasia, hypoplasia, renal agenesis, renal tubular dysgenesis
- Abnormalities in migration of the kidneys
 - Renal ectopy, fusion abnormalities such as Horshoe Kidney
- Abnormalities in the urinary collecting system
 - Posterior Urethral Valves, Uretero-pelvic and Uretero-vesical obstructions, vesicoureteral reflux, urogenital sinus
- Part of a clinical syndrome

CAKUT

- Higher incidence with family history of CAKUT, renal disease, or mothers with diabetes mellitus
- Overall rate:
 - affects 0.3-1.6/1000 live and stillborn infants
 - Variable incidence with different forms of CAKUT
- Genetic Factors/Mutations in CAKUT (examples)
 - EYA1 and SIX1 (Branchio-Oto-Renal Syndrome)
 - FRAS1 (Fraser Syndrome)
 - PAX2 (Papillo-renal syndrome)
 - SALL1 (Townes-Brocks syndrome)
 - WT1

Additional Factors in CAKUT

- Prematurity
- Maternal:
 - Diabetes
 - Alcohol use
- Radiation exposure
 - Link to Bladder extrophy
- Proximal renal tubular dysgenesis
 - Twin-twin transfusion
 - ACE-inhibitor use in pregnancy

Renal Embryogenesis



URETERIC BUDDING



Nature Clinical Practice Nephrology June 2008

Renal Development In Utero



Wein: Campbell-Walsh Urology, 10th. ed. A. Kidney development

Kidney/Bladder: Normal View



Pre-natal CAKUT Clinical Presentation



Focus on Pre-natal Hydronephrosis

- Transient or physiologic hydronephrosis (41%-88%)

 resolves during pregnancy
 or within the first year after birth especially if the APD is mild in the second and
 third trimester
- VUR) (10%-30%): Magnitude of ultrasound dilation does not correlate with the grade of VUR
- CAKUT
 - UPJ obstruction (10%-30%)
 - UVJ obstruction/megaureter (5%-10%)
 - Ureteral atresia/PUV/ureterocele, prune belly syndrome, ectopic ureter, etc (-4%-7%)

CAKUT = Congenital anomalies of the kidney and urinary tract; PUV = posterior urethral valves; UPJ = ureteropelvic junction; UVJ = ureterovesical junction; VUR = vesicoureteral reflux

Post-natal management: Hydronephrosis

- Unilateral renal involvement:
 - Renal/bladder US after 48 hours- 1 week of life
 - This allows for intravascular volume repletion, given changes with expected extracellular fluid losses
 - Prophylactic abx (Amoxicillin <3 months of age)
 - If mod-severe Hydro and/or vesico-ureteral reflux
 - Consider Voiding cystourethrogram (VCUG)
 - Serial follow up ultrasounds 3-6 month intervals for hydro
 - Consider MAG3 diuretic renogram scan with lasix if concerns for ureter-pelvic (UPJ) obstruction
- If no hydro on post-natal imaging, consider one repeat q6 months until age 2.

Post-natal Management: Hydronephrosis

- Bilateral renal involvement
 - Renal/bladder US within 24-48 hours max
 - Prophylactic antibiotics (Amoxicillin)
 - VCUG
 - Consider MAG3 if concerns for obstruction
 - Urology/Nephrology inpatient consultation
 - Fluid/electrolyte management

Renal Function: Quick Review

SERUM CREATININE

- Initial neonate values reflective of "maternal creatinine"
- Infants born at term:
 - ~1 week to reach expected baseline
- Infants born pre-term:
 - ~ 2-3 weeks to reach expected baseline

- Serum creatinine value can be utilized to evaluate Glomerular Filtration Rate (GFR)
 - Indicator of renal function

GFR in infancy

AGE	AVERAGE GFR ML/MIN/1.73 M ²	RANGE ML/MIN/1.73 M ²
2-8 days	39	17-60
4-28 days	47	26-68
37-95 days	58	30-86
1-6 months	77	39-114
6-12 months	103	49-157
12-19 months	127	62-191
2-12 years	127	89-165

Reproduced with permission from Heilbron DC, Holliday MA, al-Dahwi A, Kogan BA. Expressing glomerular filtration rate in children, Pediatr Nephrol. 1991; 5:5-11.

Heilbron et al, Pediatric Nephrology 1991

Overview of common CAKUT disorders

Vesico-ureteral reflux: VUR

Ureter Insertion



 Affects 1% of newborns

Primary: Incomplete closure of ureterovesicle junction (UVJ)

Possible reflux

Secondary: due to high pressure bladder during voiding

Grades of VUR



- Evaluation with VCUG, consider DMSA scan for renal scarring
- Spontaneous Resolution by 5 years
 - Grade 1-2: 80%
 - Grade 3-4: 10-20% (bilateral disease)
 - Grade 5: rare

VCUG with VUR



Duplex Collecting System

- Most common CAKUT disorder
- Complete: kidney has 2 collecting systems and 2 ureters
- Partial: 2 collecting systems with one ureter or unification prior to bladder
- Maybe assymptomatic/normal variant



Renal Dysplasia

- Malformed kidney tissue elements, filtering units
- Renal ultrasound:
 - Increased echogenicity or "brightness" compared to the liver
 - Cysts
 - Kidneys may be small in size
- Usually associates with ureter/bladder anomaly
- May present with urinary tract infections, failure to thrive
- If Bilateral: expected renal failure progression



Dysplastic



Renal Hypoplasia

- Small number of working nephrons (renal filtering units)
 - Reduction of renal size by 2 standard deviations per age
 - DMSA scan rules out renal scarring
- Presentation:
 - Failure to thrive
 - Proteinuria from secondary focal segmental glomerulosclerosis (FSGS)
 - Progression to chronic kidney disease

Syndromes associated with hypoplasia



Branchio-Oto-renal syndrome: EYA1 and SIX1 mutation



Papilla-renal syndrome: PAX2 mutation

Posterior Urethral Valves (PUV)

• Etiology for pre-natal Lower Urinary Tract Obstruction (LUTO)



VCUG



PUV

- Affects 1:5000 to 1:8000 pregnancies
- Even after surgical ablation, creatinine may still be elevated
 - Relationship between PUV and renal dysplasia
 - High risk of progression to chronic kidney disease (~20%)
 - CKD: Risk factor Cr nadir ≥ 1mg/dl by 1 yr of age
- VUR is present in 1/3 1/5 of affected patients
- Bladder outlet dysfunction:
 - Muscular hypertrophy of the bladder lifelong poorly fx bladder
 - Imaging with thickened bladder wall, trabecular, diverticula
- Sever cases:
 - Neonates may progress to end-stage renal disease

Renal Ectopy (i.e. pelvic kidney)

- Kidneys do not ascend properly to retroperitoneal fossa
 - Gestational weeks 6-9
- Reported as 1:1000 autopsies
- Simple Ectopy: kidney lies in correct side of body, but abnormal position (pelvic kidney)
- Crossed Renal Ectopy: kidney that crosses the midline
- Associations with VUR: 20-70% (single \rightarrow bilateral)
- Associations with UPJ obstruction (hydronephrosis)
- Girls: associates with vagina/uterus abnormalities

Renal Ectopy

- Renal ultrasound serial exams at least yearly
- Initial serum creatinine
- VCUG to evaluate for VUR
- DMSA scan to evaluate for differential function/scarring
- MAG -3 scan for evaluation of obstruction



Renal fusion: Horseshoe Kidney

- **Horsehoe kidney** (renal ectopy/fusion)
 - Risk of UTI/stones/hypertension/ UPJ obstruction/Wilm's tumor
 - Most common fusion anomaly
 - 90% of cases: fusion at the lower poles of the kidney



Horsehoe kidney

MAG 3 scan – UPJ obstruction



Right kidney: green Left kidney: red

DMSA scan - Horseshoe Kidney



Considerations for Patients with CAKUT with CKD

Early Diagnosis and Monitoring

Multidisciplinary Approach

Urology – bladder management
Nephrology – hypertension, proteinuria, fluid management
Gynecology – associates with vaginal/ureterus
Orthopedics – renal osteodystrophy
Infectious Disease – pyelonephritis/chronic infections
Medical Home

Nutrition and Growth Management

Sequelae: Risks for CKD

- End-stage renal disease
 - Hypertension
 - Urinary tract infections and pyleonephritis→ renal scarring + uro sepsis
 - Increased risk with inadequate bladder emptying
 - Failure to thrive
 - Urinary concentrating defect leading to dilute urine and polyuria
 - Proteinuria

The Nephron: ~1million per kidney



Calculation of GFR

- Children <16 years
 - Pediatric Schwartz equation
 - Constant : based on age
 - Constant: 0.41 for modified Schwartz
 - (eGFR) (new enzymatic method)



MDRD: teenagers and adults (www.mdrd.com)



Urine Concentrating Defect

- Decreased removal of solute from nephron
 - Principally in the thick ascending loop of henle
 - Lead to solute diuresis \rightarrow water losses in the urine
- Relative increase in blood flow to the papilla increases washout of solute.
 - \rightarrow Decreased solute content of papillary interstitium
 - \rightarrow Reduces urinary concentrating capacity
- Reduced response of the cortical collecting duct to vasopressin.

Relation Between Kidney Function, Proteinuria, and Adverse Outcomes

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URRENT GUIDELINES CLASSIFY chronic kidney disease (CKD) into 5 stages, based chiefly on estimated glomerular filtration rate (eGFR) (eTable 1, available at http://www.jama.com).1 Adoption of the scheme has facilitated large-scale estimates of CKD prevalence, led to multiple studies examining the relation between CKD severity and clinical outcomes, and permitted a global effort to educate physicians and the public about the implications of CKD.2 Despite these benefits, the guidelines have been criticized because they do not incorporate information about the presence and severity of proteinuria, an im-COURS 1

Context The current staging system for chronic kidney disease is based primarily on estimated glomerular filtration rate (eGFR) with lower eGFR associated with higher risk of adverse outcomes. Although proteinuria is also associated with adverse outcomes, it is not used to refine risk estimates of adverse events in this current system.

Objective To determine the association between reduced GFR, proteinuria, and adverse clinical outcomes.

Design, Setting, and Participants Community-based cohort study with participants identified from a province-wide laboratory registry that includes eGFR and proteinuria measurements from Alberta, Canada, between 2002 and 2007. There were 920 985 adults who had at least 1 outpatient serum creatinine measurement and who did not require renal replacement treatment at baseline. Proteinuria was assessed by urine dipstick or albumin-creatinine ratio (ACR).

Main Outcome Measures All-cause mortality, myocardial infarction, and progression to kidney failure.

Results The majority of individuals (89.1%) had an eGFR of 60 mL/min/1.73 m² or greater. Over median follow-up of 35 months (range, 0-59 months), 27 959 participants (3.0%) died. The fully adjusted rate of all-cause mortality was higher in study participants with lower eGFRs or heavier proteinuria. Adjusted mortality rates were more than 2-fold higher among individuals with heavy proteinuria measured by urine dipstick and eGFR of 60 mL/min/1.73 m² or greater, as compared with those with eGFR of 45 to 59.9 mL/min/ 1.73 m² and normal protein excretion (rate, 7.2 [95% CI, 6.6-7.8] vs 2.9 [95% CI, 2.7-3.0] per 1000 person-years, respectively; rate ratio, 2.5 [95% CI, 2.3-2.7]). Similar results were observed when proteinuria was measured by ACR (15.9 [95% CI, 14.0-18.1] and 7.0 [95% CI, 6.4-7.6] per 1000 person-years for heavy and absent proteinuria, respectively; rate ratio, 2.3 [95% CI, 2.0-2.6]) and for the outcomes of hospitalization with acute myocardial infarction, end-stage renal disease, and doubling of serum creatinine level.

Conclusion The risks of mortality, myocardial infarction, and progression to kidney failure associated with a given level of eGFR are independently increased in patients with higher levels of proteinuria.

JAMA. 2010;303(5):423-429

JAMA, 2010

www.jama.com

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Strict Blood-Pressure Control and Progression of Renal Failure in Children

The ESCAPE Trial Group*

ABSTRACT

- Published 2009
- 6 month trial period with Ramipril (ACE inhibitor), with 5 year follow up
- 385 children with CKD: GFR range 15-80 ml/min/1.73m²
- Primary endpoints: time to 50% decline In GFR or progression to ESRD
- Trial group 29.9% reached endpoint versus 41.7% in control group
- Proteinuria initial decreased 50% then rebounded despite BP control

Surgical Approaches to CAKUT: Preparation for Renal Transplantation Journal of Pediatric Urology (2013) 9, 217-222



Pediatric Urology

Hydronephrosis in pediatric kidney transplant: Clinical relevance to graft outcome

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Pre-Renal Transplant Management

- Normal drainage from the kidney into a reservoir
- A urinary reservoir that permits low-pressure storage for a socially acceptable time
- Absence of infection
- Imaging: VCUG
 Consider urodynamics

Post-Kidney Transplant Management

Bladder Management

- VCUG 2-3 months post transplant
- Consider Urodynamic Testing

Continued Co-Management

- Urologist
- Renal Transplant Team
- Infectious Disease Specialist
- Gynecology

Multidisciplinary Care

- Nephrologist/Urologist/Fetal Care team/Neonatalolgist must plan and coordinate from beginning
- This could be a prenatal assessment or post-natal assessment
- The team must be in place for either scenario

Why Urology?

- 20-25% pediatric patients transplanted or on dialysis with CAKUT spectrum. (NAPRTC's 2010,2011)
- This is consistent with European experience

CAKUT: Prenatal Diagnosis

- GU anomalies 1:250-1:1000 pregnancies
- Prenatal US detects 73-82% of these anamolies¹
- Fetal Urinalysis and anatomy help to define a role for intervention
 - Early second trimester urine isotonic
 - As they mature they become hypotonic
 - Fetal Urine Sodium and B-microglobulin decreases
 - Urine Ca stays the same
 - Sequential analysis the best

Fetal Intervention: PUV

- Open Surgery
 - Select centers with high volume experience
 - Crombleholme et al- 5 patients with LUTO
 - 3 dead
 - 1 ESRD
 - 1 Renal function preserved
- Vesicoamniotic Shunt: performed to increase AFI
 - US guided at gestation 19-20 weeks
 - May require amnioinfusion for a window
 - No survival benefit if amniotic fluid volume does not improve
 - 45% complication rate (meta-analysis)
 - Death
 - Shunt blockage and migration

Fetal Cystoscopy

- 1995 described by Quintero
- Allows visualization pathology
- No head to head comparisons with Shunt placement
- Requires Access to fetal bladder
- Difficult to access urethra
- Size of instrumentation remains a limitation
- Limited Data

Postnatal management

- Decompression bladder and upper tracts is key
- GFR may still improve if can stop continued injury
- Fixed urine output is a concern and must be addressed

Management of the Bladder

- Immediate decompression and stabilization renal function
- Avoidance of a "balloon" catheter as this may cause further bladder injury.
- Recommend starting oxybutinin at 0.1mg/kg Q8H
- Ablation of valves after Cr stabilizes
- Consideration for clean Intermittent catheterization (CIC) especially if fixed urine output and VUR
- If Prune Belly Syndrome and stasis consider diversion
 - Vesicostomy if minimal ureteral dilation and urethral atresia
 - Ureterostomy or pyelostomy if massive upper tract dilation

Avoid Unnecessary Surgery

- Preserve the peritoneal cavity for PD
- If fixed urine output and ESRD consider G-tube
- Simultaneous Gtube and PD not advised if PD is "urgent"
- Consider Feeding NG and PD if this is the case
- Avoid ureteral reconstruction and nephrectomy in newborn period especially if transplant is being considered
- Avoid any bladder reconstruction procedures without medical management (CIC and Oxybutinin)

Infant with PUV and ESRD: no surgery intervention



DOL #2 VCUG: VUR b/l and diverticulum

1 year later only CIC and Oxybutinin

Take Home Points

- Promote Growth and development
- Preserve all anatomy- don't "burn" bridges
- Allow for best success for transplant
- Medical management is the mainstay of initial therapy
- GFR my improve: low pressure drainage is critical
- CIC is advisable as allows one to manipulate bladder to a low pressure storage organ
 - Normal neonatal voids are High Pressure which can hurt these diseased kidneys
- Preserves ability to "void" in the future
- Preserving voids in the beginning may not have same outcome

Summary

- Try to think outside the box
- You are trying to allow successful transplant
- GFR may improve with time
- Avoid unnecessary interventions
- Coordinated care and multidisciplinary care may be the best way to prepare the families and the patients.

Thank You