Renal Review

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The speaker has signed a disclosure form and indicated she has no significant financial interest or relationship with the companies or the manufacturer(s) of any commercial product and/or service that will be discussed as part of this presentation.

Session Summary

This session will provide a general overview of neonatal renal function and disorders to help prepare for certification exams.

Session Objectives

Upon completion of this presentation, the participant will:

- be able to briefly discuss the embryology of the kidney and renal system
- be familiar with renal function in the preterm and term neonate
  - how to evaluate renal function in the neonate
  - how this effects medications
  - how to protect renal function
- identify acute renal injury and its clinical management
- understand long term consequences of renal dysfunction in the preterm and term neonate
  - hypertension
- identify renal anomalies and GU anomalies

Test Questions

1. Nephrogenesis is complete by ______ weeks EGA.
   a. 30
   b. 32
   c. 34
   d. 36

2. Prostaglandins produced by the kidneys have (a) __________ effect on renal vascular system.
   a. Vasoconstrictor
   b. Vasodilation
   c. Synergistic
   d. No
3. Newborns with spina bifida are at risk for ________:
   a. Intrinsic renal failure
   b. Post-renal failure
   c. Pre-renal failure
   d. Transcellular failure

4. The most common risk factor for renal failure in the newborn period is:
   a. Placental abruption
   b. Low Apgar
   c. Prematurity
   d. Neonatal sepsis

5. Baby B is a FT delivered by C/S for severe fetal distress associated with placenta abruption. Apgars were 2 & 4. Vigorous resuscitation, including intubation, ventilation and volume expansion for hypotension. At 24 hours of age, she is severely oliguric, edematous, and urine is grossly bloody.
   a. Post renal disease
   b. Prerenal renal disease
   c. Intrinsic renal disease

References

Brodsky, D. & Martin, C. (2010). Neonatology review (2nd ed.).


Objectives:

Renal Review
Tami Wallace DNP APRN NNP-BC

The many functions of the kidney

- Maintains plasma osmolarity, electrolyte balance, excretes nitrogenous end products
- Produces renin
- Produces erythropoietin
- Metabolizes vitamin D
- Degrades insulin
- Produces prostaglandins

Embryology (Brodsky and Martin)

- 3 mesodermic structures
  - Pronephros (little function)
  - Mesonephros-epididymis
    - Vas deferens, seminal vesicles
  - Metanephros-pelvicalyceal
    - 5th week of gestation, first nephron at 8 wks
Nephrogenesis

- Nephron is the functional unit of the kidney
  - Filtration, reabsorption, secretion
- Deep nephrons form first
- Number of nephrons increases until 34-35 weeks and then size increases
- Fetal growth restriction may reduce number of nephrons
- Preterm birth may reduce the number of nephrons

Urine

- Production first seen at 10-12 weeks
- A major component of amniotic fluid, increases with gest age
- Fetal urine is hypotonic (increase with gest age), limited concentrating ability puts the preterm infant at risk for dehydration
  - Limited sensitivity to vasopressin
  - Short loop of Henle
  - Low osmolality of medullary interstitium (limited Na reabsorption in thick ascending loop)
  - Low serum urea
- Further reduced in infants with low GFR

Glomerular Filtration Rate (GFR)

- Increases with number and size of nephrons
- Doubles by 2 weeks of age
- Adult levels at one year of age (term healthy newborn)
- Serum creatinine is a reflection of GFR
- Newborn normal <2mg/dL (if serum creat doubles the GFR falls by approx 50%)
- ** creat of limited value in the neonate

Other Measures of GFR

- Creatinine exchanged thru placenta
- Back filtration of creatinine in preterms
- No other good markers currently clinically available
- Research:
  - Inulin (Hoseini, 2012)
  - Cystatin C and B-trace protein (Filler, 2016)
Glomerular and Tubular Function
Brodsky and Martin, 2010

• Sodium:
  – 2/3 filter Na+ reabsorbed in the prox tubule, 20% in ascending loop of Henle and 10% in distal tubule
  – Capacity to reabsorb Na is low until 34 weeks gestation...in severely ill infants Na loss can be high
  – FENA = urinary fractional excretion of Na
    • FENA(%) = Urine Na+ x Plasma Creatinine / x 100
    • <1% is normal, 1-2.5% is prerenal, >3% is intrinsic renal failure
    • **because preterm infants waste Na, their fractional excretions may be elevated even in the face of intravascular depletion.

• Bicarbonate:
  – Low serum bicarb threshold in proximal tubule (improves with gest age). Once threshold is surpassed, bicarb is excreted in urine
  – Limited ability to excrete acid load (decreased ability to acidify urine)

• Magnesium
  – Passive reabsorption in proximal tubule and thick ascending loop
  – This is established early and fractional excretion is low

• Potassium:
  – Reabsorbed in the proximal Tublule and ascending loop of Henle
  – Excreted in distal tubule and collecting ducts
  – Limited number of Potassium channels, limits ability to excrete K+

• Calcium
  – Reabsorption in proximal tubule and loop of Henle (passive and limited by Na+), distal tubule and collecting ducts
  – Neonatal not so trivia
    • What drug works in the loop and causes Ca++ excretion?
  • Phosphorous
    – 80% of phos reabsorbed in proximal tubule (some in distal tubule and some is excreted, but infants usually have a high level of reabsorption
    – **Low serum phos usually due to inadequate intake
    – Neonatal not so trivia
      • Why would an early preterm infant on TPN have a low Phos?

• Glucose
  – Renal glucose threshold increases with gestational age
  – When plasma glucose exceeds the renal transport ability the infant will develop glucosuria

☆ Glucosuria causes?
  An unhappy NNP.........
Mark Menster’s Laws of Nephrology (retrieved only from my memory)

1. When in doubt answer proximal tubule, you will be right the majority of the time
2. Remember that the stupidest kidney is still smarter that the smartest doctor.

Hormonal Control of Renal Function

- Renin: secreted when there is decreased renal perfusion (hypotension, hypovolemia) and increased sympathetic tone
- Angiotensinogen (liver)
- Angiotensin I
- ACE (angiotensin converting enzyme...in lung)
- Angiotensin II
  - Active octapeptide: \( \text{Na, H}_2\text{O reabsorption, arteriolar vasoconstriction, stim release of ADH and aldosterone} \)
  - Adrenal cortex: stimulates release of Aldosterone which acts on kidney to increase Na reabsorption (CI follows), increase K secretion, increase H+ secretion.

Evaluation of Renal Function

- Family history
- Physical exam
- Lab

Family and Pregnancy History

- Family history of renal anomalies or disease?
- Oligo or anhydramnios
  - Renal agenesis or dysplasia, obstructive uropathy
- Polyhydramnios?
- Renal causes are: fetal DI, tubular dysfunction
- Large placenta?
  - Nephrotic syndrome
- Clinical event or medications?
  - Asphyxia, infection, volume loss, indomethacin (risk for ATN and ARF)
- Maternal drugs?
  - Captopril or indomethacin
- Increased alpha-fetoprotein
  - Congenital nephrotic syndrome

Physical Exam

- Urine output
  - Majority of infants void by 24 hours of life
  - Normal urine out 1-3 ml/kg/hr
  - Oliguria <1 ml/kg/hr consider eval
- Polyuria
  - Central DI, hypervolemia, structural kidney disease, infections, polyuric phase of ATN
  - Transient diuretic phase in preterm infant
- Abd Mass
  - Most freq abd mass in newborn
  - Hydrenephrosis, renal anomalies, structural urologic anomalies
  - Also look for edema, abnormal genitalia, hypertension, other associated anomalies (myelo, pneumothorax, anal atresia, abnormal ears, vertebral anomalies, etc.)
Laboratory

- Newborn labs are reflective of Mom’s renal function
- Creatinine: norms are higher in preterm and drop over first weeks
  - Preterm 0.8-1.8, drops to < 0.7 (all in mg/dL)
  - Term 1.2 +/- 0.5, drops to < 0.7
- BUN
  - Increased by dehydration, protein intake, etc.
- Urinalysis
  - How best to obtain?
  - Specific gravity, proteinuria, hematuria, sediment, etc.

Radiology

- Ultrasound
  - Assess anatomy
  - Include Doppler’s to evaluate for thrombus
- VCUG: voiding cystourethrogram
  - Anatomical and functional evaluation of lower urinary tract (example: reflux in recurrent UTI)
- Radionuclide renal imaging
  - Uses isotopes to allow visualization, determines blood flow distribution and function, scarring

Congenital Disease

Anomalies

- Renal Agenesis and dysplasia
- Potters sequence or Oligohydramnios sequence

Obstructive Uropathies

Obstruction leads to dilation above the lesion
May have abnormal development or function of kidney
Possible oligohydramnios

Hydronephrosis

- Most common obstruction is at ureteropelvic junction
- Bladder outlet or urethral obstruction
- Graded by severity
### Prenatal Hydronephrosis
- Mildly dilated renal pelvis is frequently reported and often normal (high urine output)
- Check for renal structure and amniotic fluid volume, other anomalies
- Follow
- Postnatal ultrasound
- If mod or severe, VCUG +/- antibiotic prophylaxis
- Posterior urethral valves
  - Males, bilateral hydronephrosis, hydroureter and thick walled large bladder
  - VCUG to confirm
  - Surgical ablation of valves
  - Many have progressive renal disease

### Prune belly Syndrome (Eagle-Barrett)
- Abnormal kidneys from obstructive uropathy
- Deficient abd muscles
- Cryptorchidism
- Patent Urachus (for decompression—may be protective)

### Other Developmental Anomalies
- Ectopic Kidney, horseshoe kidney
  - Abnormal positions
- Urachal sinus or patent urachus

### Hypospadias and epispadias (Brodsky, 2010)
- Hypospadius
  - Most frequent disorder of external genitalia, increasing in incidence
  - Closure disorder of urethral groove
  - If assoc with bilateral undescended testes rule out CAH
  - Delay circumcision
  - Timing of repair is controversial (usually prior to 18 months)
- Epispadias
  - Rare
  - Also can occur in girls
  - Cell migrational disorder, may be associated with extrophy of bladder

### Other Developmental Anomalies
- Exstrophy of the bladder
  - More freq occurs in males
  - Surgical repair in first days
  - Genital function usually satisfactory
- Exstrophy of the cloaca
  - Frequent other anomalies (vertebral, no anal opening, other genitourinary anomalies, omphalocele
  - Complex, multidisciplinary care

### Cryptorchidism (Brodsky, 2010)
- Failure of testicular descent (usually occurs in 7th month of gest)
- Assoc with maternal diethylstilbestrol, abnormal hypothalamic-pituitary-testicular axis, low intra-abdominal pressures (gastroschisis, etc), chromosomal anomalies, familial
Cryptorchidism

- 2/3 unilateral R>L
- Majority are inguinal
- Higher incidence in preterm
- If both hypospadias and cryptorchidism, increased risk of CAH

**Evaluation**
- Determine position
- Assess need for chromosomes, CAH, LH, FSH, testosterone, etc.

Treatment and outcome of Cryptorchidism

- **Management:**
  - Pediatric urologist in first 2-3 months
  - Surgery delayed until 6-9 months to allow testes to descend. Orchiopexy by 1 year
  - ? Hormonal therapy if bilateral
- **Outcome:**
  - Majority descend by 9 months (90% preterm and 75% term)
  - If not repaired there is a 10x increase in incidence of carcinoma
  - Risk of infertility with bilateral

Inguinal Hernia

- 3-5% term infants, 13% of preterm infant
- 90% boys
- 60% are on right
- Testis descend between 25-35 weeks gest, preterm this is interrupted
- Risks: incarceration, damage to vas deferens, testicular atrophy

**Repair:**
- Methods and timing are controversial
  - Mesh, no mesh?, contralateral exploration?, laparoscopic? What type of anesthesia?
  - One study 2030 pts, 32.9% delayed repair, 8.2% had incarceration at repair. Early repair increased chance of reoperation (Sulkowski, et al. 2015)
  - Randomized controlled trial underway! (Clinical trials.gov)

Ambiguous genitalia (Houk, 2016)

- AKA Disorder of Sex Development (DSD)
- Discrepancy between external genitalia and chromosomal sex. Atypical genital appearance “ambiguous genitalia”
- 2006 consensus: terms pseudo hermaphrodite, hermaphrodite and intersex are potentially pejorative and should be replaced by DSD. This is controversial to some patients and support groups. DSD is a broad term that includes things like Turner, trisomy X, females with CAH, etc. where no problem with gender disruption is expected.

DSD diagnostic approach (Houk, 2016)

- History, physical exam, karyotype (with probe for SRY...sex determining region on the Y chromosome). Pelvic/abd ultrasound, assessment of adrenal and gonadal function
- **Categorize:**
  - Virilized XX, undervirilized XY. Mixed sex chromosome pattern
- **Initial evaluation should be undertaken quickly:** Congenital adrenal hyperplasia can be a medical emergency (salt wasting form of CAH)
  - 17-hydroxyprogesterone
DSD treatment (Houk, 2016)

- Multidisciplinary
- Both medical and psychosocial issues
- Family psychosocial EMERGENCY
- Gender decisions
  - Historically gender was “assigned”
  - Current trends toward waiting for surgical intervention until sexual identity is firmly established.
- Preservation of fertility
- Functional outcomes
  - Ongoing potential for malignancy in gonadal tissues
    - Routine MRI or ultrasound, patients with XY gonadal dysgenesis need evaluation for renal failure and Wilms
  - CAH have extensive and life long medical needs, replacement steroids, hormones, electrolytes, psychosocial support

Psychosocial outcomes

- Infant and family specific
- Need long-term support
  - Psychosexual adjustment
  - Decision making.

Acquired Kidney Disease

- Renal vascular thrombosis
- Nephrocalcinosis
- Hypertension
- Acute Renal Failure
- Chronic Renal Failure

Renal Vascular Thrombosis (Brodsky & Martin, 2010)

- Clinical Triad Diagnosis
  - Enlargement of kidney + Hematuria + renal failure
- Diagnosis
  - Renal ultrasound with Doppler’s
- Management
  - Controversial
  - Conservative: remove indwelling catheters, treat hypertension
  - Aggressive: antithrombolytic medications, surgery

Renal Vessel Thrombosis (Brodsky & Martin, 2010)

- Renal artery
  - Risks: indwelling UAC, hyper viscosity, thrombophilia
- Renal Vein
  - Risks: polycythemia (SGA, IDDM), hypovolemia, hypercoagulable states
  - Often unilateral

Nephrocalcinosis (Skeith, 2015)

- Deposits of Calcium salts in renal parenchyma. Occurs more frequently in preterm due to tubular immaturity
- Incidence in preterm infants is 7-41%
- Risk factors: prematurity, loop diuretics, increased Ca and vit D supplementation. Some genetic causes.
- Neonates with Nephrocalcinosis are asymptomatic
**Nephrocalcinosis** (Mattoo, 2015)

- Diagnosis is usually by ultrasound (occasionally seen on plain films)
- Treatment: directed toward treating cause
  - If due to loop diuretics, trial a thiazide
- Resolves in majority of non genetic cases. Unclear whether it results in significant chronic kidney injury
- Follow up long term

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**Hypertension** (Flynn, 2015)

- Incidence
  - Risk factors: UAC placement with thromboembolism (most common), BPD, and renal parenchymal disease.
  - Diagnosis: repeat accurate measures > 95th percentile

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**Hypertension in Preterm**

- Evaluation
  - History: look for risk factors
  - Physical: 4 extremity BP to r/o coarc or thrombus, look for abd mass, signs of peripheral thrombi, hyperthyroidism, dysmorphic features
  - Urinalysis, urine culture, electrolytes, BUN and creat, Ca
  - Renal ultrasound with Doppler eval
  - Radionuclide imaging recommended when ultrasound not diagnostic (defer if possible until infant 44 weeks PMA due to immature renal fcn)
  - Angiography rare, but is the gold standard for renal vascular disease
  - Echocardiography to rule out LV hypertrophy or LV dysfunction

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**Acute Renal Failure AKA Acute Kidney Injury**

- “abrupt reduction in kidney function measured by a rapid decline in GFR” (Mattoo, 2015)
- AKI
  - Impairment of nitrogenous waste product excretion
  - Loss of water and electrolyte regulation
  - Loss of acid-base regulation
- Incidence of AKI is high in sick neonates (may be as high as 8% of NICU admissions, highest in preterm and critically ill)

(Mattoo, 2015)
Normal Renal Function

<table>
<thead>
<tr>
<th>Gestation</th>
<th>Day of life</th>
<th>GFR in ml/min per 1.73 m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>27 weeks</td>
<td>Day 7</td>
<td>13.4 (7.9 to 18.9)</td>
</tr>
<tr>
<td></td>
<td>Day 28</td>
<td>21 (15.5 to 26.5)</td>
</tr>
<tr>
<td>30 weeks</td>
<td>Day 7</td>
<td>21.9 (16.4 to 27.4)</td>
</tr>
<tr>
<td></td>
<td>Day 28</td>
<td>29.6 (24-35)</td>
</tr>
</tbody>
</table>

AKI

- Serum Creatinine: newborns considered to have renal failure is serum creatinine is > 1.5 mg/dL (133 micromol/L)
- AKI
  - Oliguric (<1 ml/kg/hr)
  - Non oliguric

Pathophysiology

- Risk factors: developmental immaturity, hemodynamic changes (hypotension and hypoxia), hypovolemia (due to reversible losses)
- Changes in Renal Blood Flow
  - 20% of adult cardiac output goes to kidney
  - 2-4% of fetus CO, 10% by one week of life
  - Impaired auto regulation of renal blood flow
  - Limited ability to concentrate urine
  - Elevated FENa (reduced responsiveness to aldosterone, as high as 5% in preterm)
- Causes
  - Asphyxia is most common cause
  - Prerenal: due to inadequate renal perfusion 85%
    - Can decrease GFR without renal disease or can case ATN (damage to tubules)
  - Intrinsic: due to intrarenal pathology 11%
  - Post renal failure: due to obstruction 3%

Clinical Presentation AKI

- Oliguria or anuria
- Rising serum creatinine
- Hyponatremia (almost always dilutional), hyperkalemia, metabolic acidosis, hyperphosphatemia, hypocalcemia, edema

Evaluate Cause AKI

- History, physical
- CBC
- Urine Na excretion
  - Can distinguish prerenal from intrinsic. Prerenal low Na excretion (< 20-30 mEq/L), above 30-40 mEq/L in intrinsic
- FENa
  - Less helpful in preterm
  - Don’t use if diuretics given
- Urine osmolality (urine SG too variable)
- Some newer biomarkers
- Renal Ultrasound
- VCU?
### Treatment AKI (Mattoo, 2015)

- **Initial approach**
  - Catheterize bladder
  - Fluid challenge (unless infant has hypertension or other signs of intravascular volume overload)
    - 10-20 ml/kg of isotonic saline over 1-2 hours
  - Do not use colloid

- **Conservative management**
  - Fluid restriction, monitoring fluid and electrolytes
  - Furosemide for signs of fluid overload (limited value in using for simple diuresis)
  - Dopamine: may increase RBF by increasing systemic BP, despite wide spread use of “renal dose” dopamine there is little evidence of a renal protective effect

### Treatment of AKI (Mattoo, 2015)

- **Maintenance of fluid and electrolyte balance**
  - Fluid: estimated insensible water losses + urine output
  - Treat hyperkalemia (in another lecture)
  - Metabolic acidosis: treat cause, sodium bicarb probably worsens outcomes

- **Avoiding complications**
- **Adequate nutrition**
  - Ideal 100kcal/kg/d low renal solute load formula
  - TPN: AA up to 1.5gm/kg/d, IL 2 gm/kg/d

- **Treatment of underlying cause**

### Renal Replacement Therapy (Mattoo, 2015)

- **Hemodialysis**
  - Most rapid method, may cause instability
  - Technically challenging in newborns

- **Peritoneal dialysis**
  - Less efficient at fluid removal, heparinization not needed
  - Hernias, leaking, infections

- **Hemofiltration**
  - CVVHD: more precise fluid and metabolic control

### Theophylline (Mattoo, 2015)

- Nonspecific adenosine receptor antagonist
- Inhibits renal vasoconstriction produced adenosine. Some evidence that it reduces risk of renal dysfunction in asphyxiated full terms.
- Not recommended for prophylactic or routine use as studies were pre cooling era. Lack of information about long term renal and neurodevelopmental outcome.

### Prognosis (Mattoo, 2015)

- Depends on underlying cause
- Mortality is high and risk of chronic renal failure is substantial

### Treatments for Renal Disease

For your interest, probably not on your exam 😊

- At least one team is looking at miniaturization of the hemodialysis circuit that would allow it’s use in smaller infants.
- **Future:**
  - Stem cells to prolong/enhance nephrogenesis (Watorek, 2006)
Chronic Renal Failure (Brodsky, 2010)

- GRF of < 25% for > 3 months
- Complications:
  - Failure to thrive
    - Inadeq calories, abnl lytes, hormonal abnormalities, use of steroids
    - Increase caloric intake, limit Na+ and Phosphate
    - If severe limit protein
  - Bone disease
    - Decrease Vit D hydroxylation, increase PTH, excess aluminum
    - Provide 1,25(OH) Vitamin D
  - Neurologic
    - Encephalopathy, motor delays, due to excess aluminum, hypertension, primary disease, etc.
- Management: Dialysis or transplant
- Prognosis: depends on underlying etiology, transplant patients do better

Medication dosing

- Neonates have a large volume of distribution and a decreased (and ever changing) GFR
- Extensive interindividual variability
- Know which drugs are eliminated by the kidney and adjust dosing!