NEONATAL RENAL PHYSIOLOGY

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3RD PAEDIATRIC NEPHROLOGY WORKSHOP AND CONFERENCE
WORKSHOP ON NEONATAL FLUID AND ELECTROLYTE BALANCE
OCTOBER 20TH 2018
Plan

- Definitions
- Anatomical development of the kidney
- Evolution of renal function in the neonate
- Summary
Basic terms

- Renal function assessment
  - Blood creatinine and urea
  - Biomarkers
    - Serum **Cystatin C**
    - **N Gal** (Neutrophil gelatinase-associated lipocalin (NGAL)):
  - GFR ml/min/1.73m²
    - Schwartz formula – \[ \text{Ht (cm)} \times k \times \frac{\text{pCr (umol/l or mg/dl)}}{} \]
  - Neonatal normal values differ from older children
## Definitions

<table>
<thead>
<tr>
<th>TERMINIOLOGY</th>
<th>GESTATIONAL AGE/ WT</th>
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<tbody>
<tr>
<td>TERM</td>
<td>≥ 37/40</td>
</tr>
<tr>
<td>PRETERM</td>
<td>&lt; 37/40</td>
</tr>
<tr>
<td>LATE PRE TERM</td>
<td>32-36&lt;6/40</td>
</tr>
<tr>
<td>VERY PRE TERM</td>
<td>28-31&lt;6/40</td>
</tr>
<tr>
<td>EXTREME PRETERM</td>
<td>&lt;28/40</td>
</tr>
<tr>
<td>VERY LOW BIRTH WEIGHT</td>
<td>&lt;1500G</td>
</tr>
<tr>
<td>EXTREMELY LOW BIRTH WEIGHT</td>
<td>&lt;1000G</td>
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</table>
ANATOMICAL DEVELOPMENT
Development

Intermediate mesoderm
Nephrotome

Pronephros
Mesonephros
Metanephros

regresses
5th week urine
11th-12th week involutes
Mesonephric duct outgrowth
Ureteric bud
Metanephric blastema

Caudal tubules form part of male genital tract

Urogenital sinus
Allantois
Mesonephros
Gonad
Caudal
Cloacal
Metanephric tissue
The kidney

Ureteric bud
- Ureters
- Pelvis
- Collecting tubules
- Drainage system

Metanephric blastema
- Nephrons
  - Glomeruli
- Filters
The placental “dialysis” system

- Amniotic fluid - stage 1
  - diffusion of water and solute through placenta and fetal skin
  - dialysate of maternal and fetal plasma
  - 25/40 – skin diffusion stops

- Amniotic fluid - stage 2
  - fetal urine by 11 weeks
The kidney

- First glomeruli: 9/40
- Urine production: 11/40
- Nephrogenesis ends: 34-35/40
- Preterm infants <35/40 do not have full nephron quota
- Most nephrons form in 3rd trimester
- Then…glomeruli – become larger and their functions mature
- Mature by 18-24 months post natal life
FUNCTIONAL DEVELOPMENT
Effective renal plasma flow

- Increases towards term and up to age 2 years
- Premature 20ml/min/1.73m²
- Term 83ml/min/1.83m²
- Age 2 years (adult value) 650ml/min/1.73m²
- Renal perfusion pressure increases
- Renal vascular resistance falls
- Autoregulation improves
GFR

- Intrauterine: placental filter
- At birth: active glomerular filtration
- GFR increases with age
  - Neonate: 40m/min/1.73m²
  - 2 years: 100-125 m/min/1.73m² = adult levels
  - Premature infants:
    - Slower rise in GFR – normal values achieved later
    - VLBW – normal values at age 8 years
- Important for drug dosing / assessing renal function
Creatinine

- At birth, sCr = maternal values
  - Usually falls slowly to baseline
- But filtered creatinine is absorbed by neonatal tubules in the first few days of life
- Serum creatinine may actually rise briefly after birth
Creatinine

- The greater the prematurity the higher plasma creatinine will rise
- Serum creatinine in the first few days of life may not truly reflect infants renal function
- **Cystatin C** may be better measure of GFR
  - Freely filtered across capillaries and completely reabsorbed by proximal tubules
WATER BALANCE
Urinary concentrating ability

- Max urinary concentrating ability low in neonate
  - Term 700mOsm – low
  - 6-12 months – adult levels – 1400mOsm

- Immature tubules

- Relative tubular insensitivity to ADH, aldosterone
Fluid balance in the neonate

In foetus

- fluid balance – amniotic fluid
- total body water (ICF + ECF) is 95% total body weight
- large interstitial volume

ECF = interstitial fluid + intravascular fluid
Water balance – Immediate postnatal changes

- Foetus: High ECF + interstitial fluid (ISF)
- ECF + ISF loss
- ANP
- Na + H2O loss
  - Wt loss: 10-15% Prem, 5-10% term

Graph showing body water content (%):
- TBW: 92%, 86%, 77%, 72%, 66%, 62%
- ECF: 60%, 45%, 32%, 30%, 28%, 26%
- ICF: 26%, 32%, 30%, 38%, 36%

Age (months):
- Fetus: 0
- Newborn: 3-6, 9/0
Implications of postnatal changes

- Weight gain in first week of life - Na retention
- Fluid management should allow isotonic ECF loss (less fluid intake initially then graduated increase)
- Avoid sodium intake until
  - postnatal diuresis / natriuresis end
  - Or till weight loss of 7% of birth weight
- Premature infants –
  - risk of initial hypernatraemia – as very dilute urine
  - Later hyponatremia – high urinary sodium losses
Fluid balance regulation

Immature urinary Na and water conservation

Risk of dehydration  *  High insensible losses
Urine production postnatally

- 99% pass urine in the first day
- Day 1-2 urine output 13-30cc/kg/day
- Oliguria < 1cc/kg/hr
- If postnatal weight loss is > 10% investigate
ELECTROLYTES
Renin-Angiotensin-Aldosterone System (RAAS)

- Blood pressure regulation
- Intrarenal blood flow
- Fluid and electrolyte balance

Water and Sodium retention. Increased circulating volume. Increased renal perfusion.
RAAS

- Fetus
  - Relative insensitivity of adrenal to angiotensin >>
  - >> reduced aldosterone secretion
- In premature infant
  - Insensitivity and immaturity of nephron development >>
    negative Na and H20 balance
Sodium balance
Sodium balance

- Distal tubule – site of most sodium exchange
- Premature infants have
  - Higher Na delivery to the tubules
  - Lower Na resorption in DCT and Intestine vs. term
  - Higher sodium losses

After initial post natal diuresis
- Thriving term infants have positive Na balance
- Preterm infants < 35/40 continue to have negative Na balance in first 3 weeks after birth
Sodium balance

- Prems
  - At risk for hyponatraemia
  - Age < 33/40 need 3-5mEq/kg/day for initial weeks after birth
- Excessive Na to term infants
  - Fluid retention, oedema, hypernatraemia
- FeNa – fractional excretion of Na
  - Highest in first 10 days of life
  - < 0.4% by age 1 month (adult values)
Sodium balance

- Na excretion increased by
  - Hypoxia, diuretics, jaundice, high fluid or salt intake, respiratory distress
- Modulators of Na excretion
  - RAS – **Renin Angiotensin Aldosterone System**
  - ANP – **Atrial Natriuretic Peptide**
  - prostaglandins, catecholamines
Potassium

- K filtered at glomerulus – reabsorbed in proximal tubules
- Reabsorption in ascending loop (slight)
- Secreted in distal convoluted tubule
Potassium

- Neonatal hyperkalemia (especially prems)
  - Immaturity of distal tubules
  - Reduced sensitivity of cortical collecting duct to aldosterone
- In premature infants
  - Immediately after birth, K shifts from intracellular to extracellular compartment
  - During the diuresis K is lost and serum K gradually returns to normal
Calcium

- Last trimester – calcium actively transported from mom to foetus
- Maternal PTH does not cross placenta
- After birth – calcium levels in newborn depend on
  - intrinsic PTH secretion
  - dietary calcium intake
  - renal calcium reabsorption, bone stores and Vit D status
Calcium

- Active and passive reabsorption throughout nephron
- Ionized Ca is the active portion – PTH regulated
- Ca levels stabilize and reach adult levels by first week of life
Early neonatal hypocalcaemia

- Normally after birth calcium levels fall (faster in the premature)
- Hypocalcaemia
  - In first 3 days of life
  - Ca < 2mmol/l (8mg/dl) (term)
  - Ca < 1.75 mmol/l (7mg/dl) (premature)
- Term, prems, low and N bwt
- Rarely symptomatic
Early neonatal hypocalcaemia

Causes:

- Hypo-parathyroidism –
  - fall in PTH levels in first 48 hrs
  - end organ unresponsiveness to PTH
- Hypercalciuria
- Hyperphosphataemia
- Excessive Na intake >> hypercalciuria
Phosphate

- Phosphate levels higher in the newborn and young children

- Causes:
  - Lower GFR – less PO4 secretion
  - Relative tubular unresponsiveness – to PTH less phosphaturia
Albumin

- Albumin levels are low in neonates especially premature infants
- Albumin levels rise throughout gestation
  - Some albumin from placenta
  - Increased hepatic albumin production
  - Mean serum albumin 19g/l <30/40
  - Rises to mean of 31g/l at term
- Post natal rise at term ? related to ECF volume contraction postnatally
ACID BASE BALANCE
Acid base balance - antenatally

- Foetal carbonic and organic acids – neutralized by blood buffers bicarbonate and Hb
- Organic acids, uric acid, lactate, keto-acids lactate
  - Eliminated via placenta and maternal kidneys
Acid base balance postnatally

- Respiratory / buffer / renal
- Buffers – first line
  - bicarbonate / carbonic acid
  - Hb oxy Hb
  - Protein
  - Phosphate buffer
- Respiratory – respiratory acidosis limiting compensation
- Renal – tubular immaturity
Acid base

- Premature infants often acidotic
  - BUT usually **do not** need bicarbonate
  - Reduced bicarbonate reabsorption
  - Reduced H+ secretion

- Regulation of acid / base balance improves with advancing gestational age
## Normal Acid – Base Values

<table>
<thead>
<tr>
<th>Age</th>
<th>pH</th>
<th>$\text{HCO}_3$ (mmol/L)</th>
<th>$\text{PaCO}_2$ (mmHg)</th>
<th>Base excess (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>7.24 (7.14–7.34)</td>
<td>20 (14–26)</td>
<td>49 (29–69)</td>
<td>-14 to -4</td>
</tr>
<tr>
<td>Newborn</td>
<td>7.37 (7.18–7.50)</td>
<td>20 (17–24)</td>
<td>34 (27–40)</td>
<td>-10 to -2</td>
</tr>
<tr>
<td>Infant</td>
<td>7.39 (7.20–7.50)</td>
<td>22 (19–24)</td>
<td>35 (27–41)</td>
<td>-7 to -1</td>
</tr>
<tr>
<td>Toddler</td>
<td>7.40 (7.27–7.49)</td>
<td>22 (19–24)</td>
<td>36 (29–41)</td>
<td>-5 to 0</td>
</tr>
<tr>
<td>Child</td>
<td>7.40 (7.34–7.46)</td>
<td>23 (18–25)</td>
<td>37 (32–48)</td>
<td>-4 to +2</td>
</tr>
<tr>
<td>Adolescent</td>
<td>7.38 (7.32–7.44)</td>
<td>24 (20–26)</td>
<td>41 (35–47)</td>
<td>-3 to +2</td>
</tr>
<tr>
<td>Adult</td>
<td>7.39 (7.37–7.41)</td>
<td>25 (20–28)</td>
<td>41 (37–45)</td>
<td>-3 to +3</td>
</tr>
</tbody>
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SUMMARY
Progressive maturation of glomerular and tubular function with age

Immaturity of glomerular filtration
  - Implications for drug elimination

Immaturity of salt, water and acid base balance
  - Risk of dehydration
  - Electrolyte disturbance
  - Acid base disorders

Be aware of neonatal normal values
Caution

Handle with care