DISCLOSURES

Dr. Lorenz has no relevant financial relationships to disclose or conflict of interests to resolve.

Dr. Lorenz has disclosed that his presentation involves discussion of the off-label uses of insulin and albuterol.
OUTLINE

- Briefly review functional limitations of the immature kidney
- Discuss challenges of early fluid, electrolyte, and nutritional management of the extremely preterm infant
RENAL IMMATURITY

- Decreased GFR/body wt or surface area
  - limited ability to excrete Na load: $\text{PT} \approx \text{FT} < \text{adult}$
  - limited ability to excrete water load: $\text{PT} < \text{FT} < \text{adult}$

- Decreased proximal and distal tubular capacity to conserve Na in PT
  - increased urinary Na loss
  - decreased ability to conserve Na: $\text{PT} < \text{FT} \approx \text{adult}$
  - late onset hyponatremia in the PT
RENAL IMMATUREY

- Decreased capacity of the distal tubule to secrete potassium
  - limited ability to excrete K load

- Decreased capacity of the proximal tubule to reabsorb HCO3 and decreased distal tubular capacity to secrete H⁺: PT < FT < adult
  - mild, anion gap nl metabolic acidosis in PT with usual intake
RENAL IMMATURETURITY

- Decreased urine concentrating capacity:
  500 mOsm/L in PT v 600 in FT v 1500 in adult
  limited ability to conserve free water

- Minimally decreased urine diluting capacity in PT:
  < 75 Osm/L in PT v 50 Osm/L in FT & adult
  little effect on ability of the PT to secrete a water load
Challenges of F&E Management of the Extremely Preterm infant

• Insensible water loss (IWL)
• Postnatal changes in body water and electrolytes
• Phases of postnatal F&E adaptation
Insensible Water Loss

- The major route of water loss in the early life in the extremely preterm infant
- Not under feed back control
- Largely a function of environmental humidity, gestational & postnatal age, antenatal steroid exposure (ANS)
- Highly variable
- Very little data < 26 weeks GA; none < 24 weeks
19 healthy, AGA term infants within the first 30 h of life

Environment: Incubator
- $T_{\text{amb}}$ were maintained “within narrow limits” to maintain $T_R$ 36-37 °C.
- Relative humidity varied

TEWL measured from the intrascapular skin surface using the water vapor pressure gradient method

TEWL v Relative Humidity

43 healthy, AGA infants 25-41 wk GA (n = 1-11 at each wk of gestation) within the first 24 h of life

None exposed to ANS

Environment: Incubator w/
- $T_{amb}$ were maintained “within narrow limits” to maintain $T_R$ 36-37 °C.
- Relative humidity 50%

TEWL calculated from measurement of water vapor pressure gradient at three skin surface sites using an equation derived from the evaporation rate at 19 sites weighted for proportion of body surface area represented by each site

Hammarlund K et al. Acta Paediatr Scand 1983
TEWL v Gestational Age

Data from Hammarlund et al. Acta Paediatr Scand 1983

+ 5-15 ml/kg/day respiratory IWL depending on inspired humidity and RR

n = 9
TEWL at 25-27 wk v Postnatal Age

Data from Hammarlund et al. Acta Paediatr Scand 1983
Calculated IWL & Antenatal Steroids

- Retrospective review of 30 AGA neonates < 1000g
- 16 received prenatal steroids and 14 did not at the discretion of OB (before 1994 NIH Consensus Statement)
- Fluid intake managed to allow ≤ 4% wt loss/day with a maximum loss of 15-20% in the first week
- Groups similar except for prenatal steroid exposure
- IWL calculated =
  
  total fluid intake – fluid output + change in wt (g)

Omar SA et al. Pediatr 1999
Calculated IWL & Antenatal Steroids

Omar SA et al. Pediatr 1999
TEWL at 24-25 wk with ANS Exposure

- 13 AGA infants 24 (n=3) and 25 (n=10) wk GA on IMV
- 11 exposed to ANS
- Environment: Incubator
  - $T_{\text{amb}}$ were maintained “within narrow limits” to maintain $T_R 36-37 \, ^\circ C$.
  - Relative humidity 50%
- TEWL calculated from measurement of water vapor pressure gradient at three skin surface sites

<table>
<thead>
<tr>
<th>age</th>
<th>n</th>
<th>mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-22 hr</td>
<td>13</td>
<td>164 ± 46</td>
</tr>
<tr>
<td>25-47 hr</td>
<td>9</td>
<td>169 ± 59</td>
</tr>
<tr>
<td>3 days</td>
<td>10</td>
<td>123 ± 59</td>
</tr>
<tr>
<td>7 days</td>
<td>10</td>
<td>100 ± 38</td>
</tr>
<tr>
<td>28 days</td>
<td>8</td>
<td>66 ± 22</td>
</tr>
</tbody>
</table>

Challenges in F&E Management of the Extremely Preterm infant

- Insensible water loss (IWL)
- Postnatal changes in body water and electrolytes
- Phases of postnatal F&E adaptation
Early Postnatal Changes in F & E Balance: WATER & SODIUM

- Decrease in Extracellular volume:
  - Negative water balance: Loss of 10 - 20% of birth weight
  - Sodium balance proportionate to water balance: Maintain serum $[\text{Na}^+]$ 135-145 mmol/L
Postnatal Weight Loss and Change in ECW Volume

- 13 PT infants
  - median birth wt 1170 g; range 810–1455 g
  - median GA 28 wk; range 26-32 wk
- Fluid therapy managed to allow postnatal wt loss of as much as 10% of birth wt
- ECW volume (sucrose space) measured at < 12 hr of life & when > 5% of birth wt had been lost.

Postnatal Weight Loss and Change in ECW Volume

Postnatal Decrease in ECW Volume is Physiologic

- It occurs even if caloric intake mitigates postnatal wt loss (Heimler R et al. J Pediatr 1993)
- When postnatal wt loss is regained, ECW volume per kg body wt remains stable at the new lower level (Singhi S et al. Indian J Med Res 1995)
- Attenuation of this decrease may be associated with increased morbidity (Bell & Acarregui. Cochrane Database of Sys Rev 2008; Costarino AT et al. J Pediatr 1992)
Take home messages

- Contraction of the extracellular water space is physiologic

- "Liberal" v "restricted" fluid administration
  - liberal fluid administration *may* allow higher caloric intake
  - restricted fluid administration
    - *may* decrease prevalence of co-morbidities
    - requires vigilance for hypernatremia
Early Postnatal Changes in F&E Balance: POTASSIUM

- **Internal balance:** intracellular $\Rightarrow$ extracellular potassium shift in extremely preterm infants in the first 12-48 hr of life

- **External balance:** negative during diuresis/natriuresis with contraction of the ECW space
External K Balance in the 1st 72 hr of life

- 24 AGA male infants < 37 weeks GA w/urine output > 1ml/kg/hr x 24 hr:
  - group 1  24-28 wk (n = 9)
  - group 2  29-32 wk (n = 9)
  - group 3  33-36 wk (n = 6)

- Serum [K] via radial arterial catheter on DOL 1-3

Sato K et al. J Pediatr 1995;126:109
Magnitude of ICW $\Rightarrow$ ECW K SHIFT v GA during the first 24 hours of life

ICF $\Rightarrow$ ECF shift = 

\[
(\text{ECV}^{\text{birth}} - \text{wt lost}^{24\text{h}}) \times \text{serum [K]}^{24\text{h}} \]

\[
+ \ (\text{ECV}^{\text{birth}} \times \text{Serum [K]}^{\text{birth}}) - (\text{urine output/24 hr} \times \text{urine [K]})
\]

Sato K et al. J Pediatr 1995;126:109
Serum [K] v Age in Very Preterm AGA Neonates

- 31 AGA ELBW infants 539 to 1000g (GAs 23-29 weeks)
- No antenatal steroid exposure
- No exogenous potassium administered until serum [K] was normal & not rising and urine output was > 1 ml/kg/hr

Lorenz et al J Pediatr 1997
Serum [K] v Age in 23-30 wk GA Neonates

<table>
<thead>
<tr>
<th>Effect</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>group</td>
<td>20.4</td>
<td>0.001</td>
</tr>
<tr>
<td>age</td>
<td>24.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>interaction</td>
<td>2.3</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Mean +/- SEM

Effect of Antenatal Steroids on ICW ⇒ ECW K shift in extremely preterm infants

- Retrospective review of 30 AGA neonates < 1000g
- 16 received prenatal steroids and 14 did not at the discretion of OB (before 1994 NIH Consensus Statement)
- Fluid intake managed to allow ≤ 4% wt loss/day with a maximum loss of 15-20% in the first week
- Groups similar except for prenatal steroid exposure
- K intake withheld until serum [K] normal and urine output > 1 ml/kg/hr

Omar SA et al. Pediatr 2002; 106:561
Effect of Antenatal Steroids Potassium Balance

Omar SA et al. Pediatr 2002; 106:561
Effect of Antenatal Steroids on ICW $\Rightarrow$ ECW potassium shift in extremely preterm infants

Omar SA et al. Pediatr 2002; 106:561
Take home messages

- Although the pathophysiology of ICW $\Rightarrow$ ECW potassium shift in extremely preterm infants in the first 12-48 hr of life is poorly understood, it is very likely maladaptive.

- ANS decreases the risk of non-oliguric hyperkalemia.

- Exogenous potassium should be withheld until serum [K] is normal and not rising and urine output is > 1 ml/kg/hr.

- A decrease in serum [K] can be anticipated with the onset of postnatal diuresis/natriuresis.
Challenges in F&E Management of the Extremely Preterm infant

- Insensible water loss (IWL)
- Postnatal changes in body water and electrolytes
- Phases of postnatal F&E adaptation
<table>
<thead>
<tr>
<th>Phase</th>
<th>Antediuretic</th>
<th>Diuretic/ Natriuretic</th>
<th>Homeostatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Birth - 2 days</td>
<td>1 - 5 days</td>
<td>After 2 - 5 days</td>
</tr>
<tr>
<td>Urine Output</td>
<td>Low</td>
<td>Abrupt ↑↑</td>
<td>↓ then α intake</td>
</tr>
<tr>
<td>Na⁺ Excretion</td>
<td>Minimal</td>
<td>Abrupt ↑↑</td>
<td>↓ then α intake</td>
</tr>
<tr>
<td>K⁺ Excretion</td>
<td>Minimal</td>
<td>Abrupt ↑↑</td>
<td>↓ then α intake</td>
</tr>
<tr>
<td>H₂O balance</td>
<td>&lt;Intake - IWL</td>
<td>Markedly Neg</td>
<td>~ α Na⁺ balance</td>
</tr>
<tr>
<td>Na⁺ balance</td>
<td>~ Neg</td>
<td>Markedly Neg</td>
<td>0, then + w/ growth</td>
</tr>
<tr>
<td>K⁺ balance</td>
<td>~ Neg</td>
<td>Markedly Neg</td>
<td>0, then + w/ growth</td>
</tr>
<tr>
<td>ECV (ml)</td>
<td>Stable or ~↓</td>
<td>Abrupt ↓↓</td>
<td>1. α Na⁺ balance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. ↑ w/ growth</td>
</tr>
<tr>
<td>Phase</td>
<td>Antediuretic</td>
<td>Diuretic/ Natriuretic</td>
<td>Homeostatic</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Water intake</td>
<td>≈ IWL</td>
<td>↑ to allow 2- 5 % wt loss per day up to total of 8 - 15 %</td>
<td>Volume to optimize caloric intake without fluid retention</td>
</tr>
<tr>
<td>Sodium intake</td>
<td>None</td>
<td>Begin when serum [Na$^+$] is stable with weight loss or ↓ing; ↑ as necessary to maintain serum [Na$^+$] wnl</td>
<td>Approximate Na$^+$ loss ± growth allowance. Na$^+$ requirement will be inversely proportional to gestational age</td>
</tr>
<tr>
<td>Potassium intake</td>
<td>None</td>
<td>1- 3 mmol/kg/d if serum [K$^+$] &lt; 5 - 6 mmol/L &amp; not ↑ing</td>
<td>≥ 2 – 3 mmol/kg/d to maintain serum [K$^+$] wnl</td>
</tr>
</tbody>
</table>
### Postnatal Renal, F & E Adaptation: Common Problems

<table>
<thead>
<tr>
<th>Antediuretic</th>
<th>Diuretic/Natriuretic</th>
<th>Homeostatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water intoxication with unexpectedly low IWL</td>
<td>Hypernatremia with an excessive rate of weight loss</td>
<td>Water and sodium retention with PDA or CLD</td>
</tr>
<tr>
<td>Hypernatremia with unexpectedly high IWL</td>
<td>Hyperkalemia</td>
<td>Water and sodium depletion with or without hyponatremia</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Hyperglycemia</td>
<td>Hypokalemia</td>
</tr>
</tbody>
</table>
A System for Managing F&E Rx

- Estimate what changes in balances are appropriate
- Monitor parameters q 8-12 hr to estimate actual balances which result
- Estimate the intakes to the necessary to achieve these balances based on the range of outputs anticipated
- Administer these intakes
Early Nutritional Care of the Extremely Preterm infant

- Glucose
- Amino acids
- Intralipids
- Enteral feeding
Why Early Nutrition for Extremely Preterm Infant?

- Poor postnatal growth is common among extreme preterm infants.
- Poor postnatal growth may have long-term consequences, e.g. short stature, impaired neurodevelopment.
- Poor postnatal growth has been attributed to protein & energy deficits that accrue in the 1st weeks of life.
- It was hypothesized that early protein intake may improve growth.
Glucose Requirement/Tolerance

Target glucose administration rate

- minimum necessary to prevent hypoglycemia
- maximum tolerated w/o hyperglycemia to conserve limited energy stores and minimize catabolism

<table>
<thead>
<tr>
<th>Glucose Utilization Rate</th>
<th>4 - 7 mg/kg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal Metabolic Rate During the First Week of Life</td>
<td>35 - 50 kcal/kg/24 hr</td>
</tr>
<tr>
<td>60 ml D$_{10}$W/kg/24 hr provides</td>
<td>3.5 mg glucose/kg/min 20 kcal/kg/day</td>
</tr>
<tr>
<td>120 ml D$_{10}$W/kg/24 hr provides</td>
<td>7.1 glucose/kg/min 41 kcal/kg/24 hr</td>
</tr>
</tbody>
</table>
Importance of AA Administration

26 weeks:

protein balance = + 2.0 g /kg/day

protein balance = - 1.2 g /kg/day

Denne SC & Poindexter BB Semin Perinatol 2007
Early Amino Acid Administration

- Observational studies suggest preserving protein stores and promoting protein accretion are critical to improved growth outcomes in extremely preterm infants.

- Providing amino acids, even with a low energy intake, increases endogenous protein by increasing protein synthesis, thus increasing protein balance.

- Even 1.0 to 1.5 g/kg/day of parenteral amino acids and 30 to 45 kcal/kg/day can change protein balance from negative to zero or somewhat positive. (Van Doudoever JB et al. J Pediatr 1995; Rivera A et al. Pediatr Res 1993)

- Greater calorie intake reduces proteolysis and a larger intake of both protein and calories leads to anabolism. (Thureen PJ. Pediatr Res 2003)
Protein Balance with Early AA Administration in ELBW infants

Van Douover 1993
Rivera 1995
Thureen 2003

From Deene SC & Boindexter BB Semin Perinatol 2007
Early Amino Acid Administration

- Prompt provision of parenteral amino acids is recommended for ELBW infants (AAP Nutrition Handbook, 2009):
  - Initiate 1.5-2 g/kg/d within hours of birth
  - Advance to 4.0 g/kg/d by 0.5-1.0 g/kg/d steps [approx. 4.0 g/kg/day is required to match fetal protein accretion]

- However, randomized controlled trials have been too small to confirm long-term safety of early protein intake at this level, especially for extremely preterm infants.

- Over an more extended period, adequate provision of energy (1 g N:100 Kcal) is probably necessary to avoid toxicity.

- Provision of energy and protein intakes that promote anabolism require increased phosphate and protein intake to prevent hypophosphatemia, hypokalemia, and hypercalcemia (Molto SJ. Clin Nutr 2013).

- ? Optimal amino acid fluid composition
Take home messages

- A minimum glucose administration rate of 6 mg/kg/min is recommended

- Initiation of parenteral AA shortly after birth is recommended - data are insufficient to specify an optimal, safe rate of administration
  - 1.0 to 1.5 g/kg/day of parenteral amino acids and 30 kcal/kg/day can change protein balance from negative to zero or somewhat positive
  - Approximately 4.0 g/kg/day is required to match fetal protein accretion