The Piranha Effect: Managing Energy Expenditures and Caloric Loss to Promote Optimal Growth in the NICU

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Disclosure Statement

- I am an employee of Prolacta Bioscience
- I currently present/receive financial reimbursement
  - Prolacta Bioscience
  - Abbott Nutrition Health Institute (ANHI)
- I personally developed this deck for strictly educational purposes/audiences
  - Images & photographs used in the presentation are from publicly accessed sources
  - It without bias, branding or commercial influence; it is evidenced-based
- I will make no recommendation for the off-label use of any drug, nutritional, or medical device
- I am not a Registered Dietitian

Objectives

- At the conclusion of this presentation, the participant will be able to:
  - List three conditions in the neonate that can “cannibalize” the nutrient intake.
  - Discuss the impact of inflammation on growth of the preterm infant.
  - Describe the benefits associated with bolus feedings in the preterm infant.
  - Identify three interventions to maximize fat delivery when an infant is receiving continuous feedings.

“So why isn’t he growing?”

Conditions that “Cannibalize” Nutrition

- Being Small for Gestational Age (SGA)
- Higher basal metabolic rate than an AGA preterm
- Simultaneous loss of maternal nutritional support
- Thermoregulatory demands
- Limited ability for energy storage
- Prone to energy deficiency and catabolism
- Undergo multiple tissue damaging procedures (TDPs) for clinical care or diagnostic purposes
- Significant stress and pain responses
- Prone to inflammatory cascades

John, M; Tan, B; Boskovic DS, Angeles DM. The Energy Costs of Prematurity and the Neonatal Intensive Care Unit (NICU) Experience. *Antioxidants* 2018, 7, 37

“The Piranha Effect”

The Misappropriation of Energy “Shunting” Nutritional Intake
The Energy Costs of Prematurity and the Neonatal Intensive Care Unit (NICU) Experience.

Antioxidants 2018, 7, 37

**Conditions that “Cannibalize” Nutrition**

- **Temperature Dysregulation: Hypothermia**
  - Fetal temperature is \(-0.5^\circ C\) < than maternal
  - Evaporative losses through the skin
  - 2.5 times increase in heat production
  - Non-shivering thermogenesis of brown fat
  - Compensates with ↑ HR/CO = ↑ energy needs
  - Further increases metabolic rate (expenditures)
  - Release of adrenal corticosteroids

- **Temperature Dysregulation: Hyperthermia**
  - ↑ HR, RR and metabolic rate (expenditures)
  - ↑ Release of adrenal corticosteroids

**Conditions that “Cannibalize” Nutrition**

- **Environmental Stress**
  - Sound/light/activity
  - Hypothalamus triggered
  - ↑ SNS activated
  - ↑ Limbic system engaged
  - ↑ Energy Expenditures
  - Shunted away from growth

- **Pain**
  - Multiple tissue damaging procedures (TDP)
  - ↑ Activity, crying
  - ↑ Tachycardia, tachypnea
  - ↑ ATP degradation
  - ↑ Uric acid release
  - ↑ Corticosteroids activated
  - ↑ Ensuing inflammation
  - ↑ oxidative stress

- **Sleep Deprivation**
  - Preterm infants have shorter sleep cycles of 30-40 minutes with 80% of sleep being active/REM sleep
  - 75% of Human growth hormone (HGH) is released during sleep
  - Absence of screening tools for sleep in the NICU

- **Separation from Mother**
  - Induces stress response
  - ↑ Activity level, energy expenditures
  - ↑ Crying
  - Loss of sleep

- **Inflammation**
  - Hypothalamic-pituitary-adrenal axis (HPA) is a major part of the neuro-endocrine system
  - Controls reactions to stress, regulates many body processes, functions, especially around substrate utilization/metabolism
  - Stressors or inflammation during gestation/faction may result in HPA endocrine immune dysfunction
  - Permanently altering the release/function of adrenocorticotropic and glucocorticoid hormones

**Inflammation is a Hypermetabolic State**

Ng PC. Dis Child Fetal Neonatal Ed 2000;82:F250-F254 doi:10.1136/fn.82.3.F250


**The Piranha Effect**

- Conditions that "Cannibalize" Nutrition
- Environmental Stress
- Pain
- Sleep Deprivation
- Separation from Mother
- Inflammation
The brain is the most highly metabolic organ in the preterm neonate and consumes the greatest amount of nutrient resources for its function and growth.


The Piranha Effect

The Neonatal Brain

• The human infant brain is comparatively underdeveloped to that of other mammals

“A human fetus would have to undergo a gestational period of 18 to 21 months to be born at a neurological and cognitive development stage comparable to that of a chimpanzee newborn.”

Myelination and Gestational Age

- Lipid/protein sheath surrounding neurons
- Provide protection and speed of transmission
- Enables brain signals to travel 100 times faster
- Significant in developing more elaborate and faster neuron transmissions

“The First 1000 Days of Life”
Trends in Neurodevelopmental Outcomes

Study Design
- Retrospective multicenter cohort study
- 30,793 preterm infants
- Born at GA ≤32 weeks, between 2003 and 2012
- Part of the Neonatal Research Network, Japan
- N=13,661 infants followed up until 3 years of age
- Evaluated for neurodevelopmental outcomes
  - Cerebral palsy (CP)
  - Home oxygen therapy
  - Visual, hearing, cognitive impairments


Outcome Discussion
- Nutritional support remained correlated with long-term neurodevelopmental outcomes
- "The time to establishment of enteral feeding (with 5-day increments) for all disabilities suggested that the shorter the time to the establishment of full enteral feeding, the lower the prevalence of abnormal long-term neurodevelopmental outcomes..."


The Gut Brain Axis (GBA) and ND

Nutritional Goals for Preterm Infants
- For infants weighing 501 to 1500 g at birth, average growth velocity (GV) increased and the percentage with postnatal growth failure decreased from 2000 to 2013.
- "However...in 2013, half these infants still demonstrated postnatal growth failure and one-quarter demonstrated severe postnatal growth failure."


Improving Utilization of Enteral Nutrition
- "Establish consistent, comprehensive, multidisciplinary nutrition care standards of practice based on evidence, or expert opinion if evidence is lacking."

Small Bowel Size and Function In Preterms

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>Average Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 weeks</td>
<td>125 cm</td>
</tr>
<tr>
<td>30 weeks</td>
<td>200 cm</td>
</tr>
<tr>
<td>Term</td>
<td>275 cm</td>
</tr>
<tr>
<td>1 year</td>
<td>380 cm</td>
</tr>
</tbody>
</table>

Preterms ~ 5 times crown-rump length

Migratory motor complexes (MMC)
- Phase 1 - quiescence
- Phase 2 - irregular contractions
- Phase 3 - regular phasic contractions
- Recycle over a 60-90 minute period
- Mediated predominantly by motilin

Intestinal Motility
- Term infants
  - Motor activity with feeding
- Preterm infants
  - Motor activity with feeding
  - Immaturity of intestinal musculature
  - Poor coordination of peristaltic waves
  - Tendency for segmentation of peristalsis
  - 29-32 wks short bursts of activity → "clusters"
  - 32 wks ↑ organization, cycling, ↓ clustering
  - ? Antenatal steroids enhancing motor activity

Variation in Gavage Feeding Practices

“Maturity of enteric neuro-regulation is the key factor affecting gastric emptying and intestinal motility.”

Variations in Feeding Practices

- **Hypothesis**
  - VLBW infants fed by continuous nasogastric gavage (CNG) would achieve full enteral feedings (100 kcal/kg/d) at an earlier postnatal age and have less feeding intolerance (FI) than infants fed by intermittent bolus gavage (iBG)
- **Methods**
  - 80 infants
  - Stratified by BW (700 to 1000 g and 1001 to 1250 g)
  - Randomized into CNG or iBG feeding groups

Variation in Gavage Feeding Practices

<table>
<thead>
<tr>
<th>Clinical Site</th>
<th>Continuous Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scandinavia</td>
<td>50%</td>
</tr>
<tr>
<td>England/Ireland</td>
<td>20%</td>
</tr>
<tr>
<td>Australia/New Zealand</td>
<td>10%</td>
</tr>
</tbody>
</table>

67% of the respondents infused feeds intermittently through a pump over a specified time.

Variations of Gavage Feeding Practices

- **IBF - Intermittent bolus feeding**
  - Push, via gravity, or pump over 10-20 minutes every 2-3 hrs
  - Significantly prolonged gastric emptying
  - Associated with birth weight ≤1000 g

- **Continuous feeding**
  - Associated with birth weight ≤1000 g
  - Reduced days to regain BW
  - Improved intestinal growth
  - Enhanced protein synthesis
  - Spontaneous activity of preterm GI tract and its response to feeds is significantly different from that of term infants
  - Healthy preterm infants can develop similar spatial and temporal patterns of postprandial antrpyloryc motility as early as 30 weeks of PMA

- **Bolus feeding**
  - Improved intestinal growth
  - Continuous feeding associated with significant loss of key nutrients

- **Methods of Feeding**
  - Infants comparable between CF and iBF groups
  - In BW, GA, sex, race, day of onset of feeding
  - Feedings: Unidated Similac Special Care formula
  - Protocol designed for each 50 to 100 g BW category
  - Feedings ↑ by a max of 25 mL/kg/d until an endpoint of 100/kcal/kg/d for at least 48 hours
  - Any infant whose feedings withheld for >12 hours based on predetermined criteria was considered to have an episode of FI (feeding intolerance)

- **Maturity of Enteric Neuro-Regulation**
  - Key factor affecting gastric emptying and intestinal motility
  - Spontaneous activity of preterm GI tract and its response to feeds is significantly different from that of term infants
  - Rhythmic electrical activity increases with gestational maturity
  - Healthy preterm infants can develop similar spatial and temporal patterns of postprandial antrpyloryc motility as early as 30 weeks of PMA
Intestinal Motor Activity During Fasting/Feeding

Term infants characterized by:

- Periods of quiescence (phase 1)
- Irregular activity (phase 2)
- Regular phasic propagating activity (phase 3)

Preterm infants characterized by:

- Clusters of low-amplitude non-propagating pressure waves in phase 3

The characteristics of fasting motor activity mature within 10 days to resemble that of term infants if enteral feeding is commenced, irrespective of the gestational age at birth.


Two patterns of feeding response in neonates after bolus feeding:

- Mature feeding response ranges from 30% to 40% in preterms but ↑ to 90% among term infants
- Antral contractions ↓ by more than 30 peaks per 30 minutes in response to both iBF and slow infusion feeds. Both persist for 55 to 60 minutes but not continuous.
- ↓ as GA advances as feeding is continued for more than 1 week.

On the contrary, duodenal activity ↓ to 68 peaks per 30 minutes after iBF but ↑ to 180 peaks per 30 minutes after slow infusion feeds were started.

Duodenal motor quiescence after iBF is a neural feedback from sudden fundal dilation, preventing faster gastric emptying – HM vs. Formula.

Feeding Response By Gestational Age
**Interventions**

- **Protein synthesis**
- **Fat utilization**
- Maturation of enzyme activity
- Nutrient losses, especially protein accretion
- **Cyclical insulin surges**
- Nutrient losses
- Mature duodenal contractions
- Less infant stress
- Energy efficiency
- **SMA blood flow**
- **CA/P from fortifier**

**Effect:**

- **The Misappropriation of Energy**
- "Shunting" Nutritional Intake

**Summary: Intermittent Vs. Continuous Feeds**

- **Controversial Subject/Limited Data**
  - No Significant Difference
    - Time to full feedings
    - Necrotizing Enterocolitis (NEC)
    - Growth velocity
    - Regain birth weight
    - Gastroesophageal reflux (GER)
  - Controversial Subject/Limited Data
    - No difference in nutrient losses
    - Controversial Subject/Limited Data
  - Estimated Loss of Nutrients with CF vs. IBF
    - Mean difference in protein loss was 2.77 kcal/oz
    - Lipid loss is 2.7% and 11% for IBF and TF, respectively
  - Mean difference in protein or lipid loss

**Table:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Method of Qualitative Analysis</th>
<th>Estimated Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alshaikh</td>
<td>1981</td>
<td>Cartilage homogenate</td>
<td></td>
</tr>
<tr>
<td>Spencer et al</td>
<td>1987</td>
<td>Fat concentration measured by respirometry technique</td>
<td></td>
</tr>
<tr>
<td>Martinez et al</td>
<td>1981</td>
<td>Protein loss measured by Bioxytric</td>
<td></td>
</tr>
<tr>
<td>Brennan et al</td>
<td>1984</td>
<td>Protein loss measured by Bioxytric</td>
<td></td>
</tr>
<tr>
<td>Alshaikh et al</td>
<td>1994</td>
<td>Protein loss measured by Bioxytric</td>
<td></td>
</tr>
</tbody>
</table>

**Resources:**

- Stocks et al, 2017
- Greer et al, 1984
- Goswami, 1985
- Woods et al, 1978
- Alshaikh et al, 1994
- Martinez et al, 1981
- Brennan et al, 1984
- Brooke et al, 1978
- Spencer et al, 2000

**References:**

**Estimated Loss of Nutrients with CF vs. IBF**

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<th>Estimated Loss</th>
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</thead>
<tbody>
<tr>
<td>Chan et al</td>
<td>2003</td>
<td>Fat estimation by crematocrit method</td>
<td>Average fat loss from milk samples with added lecithin was 55% compared with 58% for control. Of all fat lost, 70% occurred during the first 4 hours of infusation. Lecithin improves milk fat, preventing its adherence to tubing.</td>
</tr>
<tr>
<td>Rogers et al</td>
<td>2010</td>
<td>Fat estimation by midrange infrared analysis</td>
<td>Mean calcium, phosphate, and fat loss with bolus feed is 9%, 7%, and 6%, respectively; with slow infusion (30 min) intermittent feed is 14%, 14%, and 13%; and with continuous feed is 33%, 20%, and 40%, respectively. No protein loss was noted.</td>
</tr>
</tbody>
</table>

**MOM and Donor Milk Variability**

- **DM as “Bridge to Mom” (AAP, 2017)**
- Establish and adhere to a feeding policy
- Fortify early and advance appropriately
- Bolus feedings whenever possible
- Remember human milk variability (MOM, DM)

**Donor Milk Variability**

- It should be nutritionally standardized
  - Analysis of Donor Milk: N=415 samples/273 donors

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Reported</th>
<th>Donor Milk</th>
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<tbody>
<tr>
<td>Protein</td>
<td>1.0% to 1.2%</td>
<td>1.16% ± 0.25%</td>
</tr>
<tr>
<td>Fat</td>
<td>3.9% to 4.2%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Lactose</td>
<td>7.2% to 7.3%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Energy</td>
<td>20 kcal/oz</td>
<td>19 kcal/oz</td>
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| 25% of samples had less than 17 kcal/oz |
| 30% of the samples were above 20 kcal/oz |

**Donor Milk Variability**

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Donor Milk Variability</th>
<th>Cal/Oz</th>
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<tbody>
<tr>
<td>Texas Children's</td>
<td>20.6 ± 1.15 Cal/Oz</td>
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<tr>
<td>UTHSC-San Antonio</td>
<td>21.8 ± 1.15 Cal/Oz</td>
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As measured by near IR spectroscopes calibrated specifically for human milk.

*The 2 units are approximately 125 miles apart.*
"The Piranha Effect" 

- Milk "Traffic" Chain (modified from Dr. Jack Kim, MD's work)
  - Milk in Begins
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- Applications
  - Position syringe to maximize fat delivery
  - Use shorter tubing lengths
  - Consider flushing tubing at end of feeding
  - Air, water, milk, cream
  - Evaluate expiration times/dates on tubes/tubing

"The Piranha Effect"

"Further improvements in growth for VLBW infants will require NICU teams to accept that postnatal growth failure is a serious morbidity amenable to prevention and to engage in quality improvement initiatives designed to implement nutritional practices supported by currently available evidence".

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Reference: