The Use of Human Milk for Premature Infants

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Disclosure

Dr. Rhine has served as an advisory consultant to Prolacta Biosciences
Talk Objectives

- Review the benefits of human milk for term and premature infants
- Describe the role of human milk in meeting the unique physiological and nutritional needs of premature infants
- Share strategies for optimizing the use of human milk for premature infants
Benefits of Human Milk

- Numerous studies and reviews have described multiple beneficial effects of human milk for premature and term infants, as well as mothers.

- Excellent summary found in AAP Statement “Breastfeeding and the Use of Human Milk”

  *Pediatrics* 2012; 129:e827-841
Clinical Impact of Human Milk for Term Infants – Short-term

◆ Respiratory – URI (60% reduction), LRI (72 - 77% reduction), RSV bronchiolitis (74% reduction), [all bronchiolitis (36% reduction)]

◆ SIDS – 36% reduction

◆ Otitis media – 23* - 50% reduction (77% reduction in recurrent OM)

◆ Allergies – atopic dermatitis (27 - 42% less)

◆ GI – gastroenteritis (64% reduction)*

Clinical Impact of Human Milk for Term Infants – Long-term

- GI – celiac disease (52% reduction); inflammatory bowel disease (31% reduction)
- Allergy – asthma (26 - 40% reduction)
- Obesity – 24% reduction*
- Diabetes – Type 1 (30% reduction); Type 2 (40% reduction)*
Clinical Impact of Human Milk for Term Infants – Long-term

- Cancer – leukemia (15% reduction AML, 20% reduction ALL)
- Cardiovascular – reduced BP by 3.2 mmHg - more than weight loss (2.8 mmHg), alcohol reduction (2.1 mmHg), salt restriction (1.3 mmHg), exercise (0.2 mmHg)
- Neurodevelopmental outcomes – improved IQ scores and teacher ratings
- Maternal benefits include reduction in diabetes, HTN, breast and ovarian cancer
Clinical Impact of Human Milk for Preterm Infants – ROP

- Multicenter study of 500 VLBW infants across 11 Italian NICUs over 4 years
- ROP decreased from 15.8% to 3.4% (p=.004)
- Threshold ROP decreased from 12.3% to 1.3 % (p=.01)

Manzoni, et al. Early Hum Dev 2013;89 S1:54-8

- Human milk an also be used for pain relief during eye exam. Ribeiro LM, Rev Esc Enferm USP 2013
Unique Nutritional Aspects of the Premature Infant

- Higher organ: muscle mass ratio
- Higher rate of protein synthesis and turnover
- Greater oxygen consumption during growth
- Higher energy cost due to transepidermal water loss
- Higher rate of fat deposition
- Prone to hyperglycemia
- Higher total body water content
Unique Nutritional Aspects of Premature Infants - Brain Growth

Brain growth over 8 weeks:
- At 28 wks 100% Increase
- At term 40% Increase
- At 3 mo 25% Increase
Preventing Feeding-Related Morbidities in Premature Infants

- Necrotizing enterocolitis
- Osteopenia/rickets of prematurity
- Vitamin and mineral deficiencies
- Feeding intolerance
- Prolonged TPN and related cholestasis
- Nosocomial infections
- Prolonged hospitalization
Optimal Growth of Premature Infants Influences Long-term Health and Disease

Premature infants receiving breastmilk are less likely to have excessive growth.

Adverse effects of excessive growth acceleration:

- Obesity
- Elevated blood pressure
- Insulin resistance and diabetes
- Cardiovascular mortality
Clinical Benefits of Human Milk for Preterm Infants

- Improve Host Defense – reduced infections
- Promote Gastrointestinal Development
- Provide Special Nutritional Needs
- Improve Neurodevelopmental Outcome
- Support Physically & Psychologically Healthier Mother
Human Milk Provides Protection from Infection in Premature Infants

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>Fortified BM</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen Rx (days)</td>
<td>19</td>
<td>33</td>
</tr>
<tr>
<td>NEC</td>
<td>1.6%</td>
<td>13%</td>
</tr>
<tr>
<td>Late-onset sepsis</td>
<td>31%</td>
<td>48%</td>
</tr>
<tr>
<td>NEC or sepsis</td>
<td>31%</td>
<td>54%</td>
</tr>
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</table>

Human Milk Provides Protection from Infection in Premature Infants


- Prospective cohort study of 275 VLBW infants
- Every 10 ml/kg/day of human milk in average daily dose of human milk in first 28 days of life reduced sepsis by 19% (p=.008)


> 50 ml/kg mother’s milk through week 4 reduced sepsis by 27%
Effects of Colostrum Administration in Premature Infants

- Buccal administration (NOT FEEDING) of colostrum advocated soon after birth
- Immunoglobulin elevation – trend seen in increased urine lactoferrin and secretory IGA
- Increased tolerance of feeds – treatment group reached full volume of feeds 10 days sooner (p=.032)

GI Benefits of Human Milk for the Premature Infant

- Gastrointestinal development
  - Reduces intestinal permeability faster
  - Induces lactase activity
  - Multiple factors to stimulate growth, motility and maturation of the intestine
  - Human milk empties from the stomach faster than artificial milks
  - Less residuals and faster realization of full enteral feedings
Many studies have evaluated impact of receiving breastmilk (especially fortified) on cognitive development, specifically higher IQ, Bayley (MDI improved 0.53 per 10ml/kg/day of breastmilk) Vohr, et al. *Pediatrics* 2006;118:e115-23

Benefits strongest for premature infants and males

Improvement in developmental achievements associated with breastmilk persisted at least through adolescence

Postnatal growth lag and suboptimal HC associated with neurological and sensory handicaps and poor school performance
Human Milk for Premature Infants: Cognitive Development

- Isaacs et al. measured developmental testing and brain MRI results in 50 adolescents who were formerly premature infants, and studied relationship with dietary % expressed breast milk.

- %EBM correlated significantly with verbal intelligence quotient (VIQ); in boys, with all IQ scores, total brain volume and white matter volume.

Human Milk Fortification

- Expressed human milk has variable nutritional content, and does not provide adequate nutrition for premature infants.

- Must fortify human milk to provide adequate energy, protein, minerals and vitamins for the growing premature infant.

- Starting fortifier before being on full feeds (40-100 ml/kg/day total fluids) will allow for transition from parenteral to enteral nutrition without accumulating deficits.
## Human Milk Fortification

<table>
<thead>
<tr>
<th></th>
<th>HM</th>
<th>Pro</th>
<th>Sim</th>
<th>Enf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (kcal)</td>
<td>67</td>
<td>83</td>
<td>79</td>
<td>81</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>1.4</td>
<td>2.3</td>
<td>2.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Carbohydrate (g)</td>
<td>6.6</td>
<td>7.3</td>
<td>8.2</td>
<td>7.0</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>3.9</td>
<td>4.9</td>
<td>4.1</td>
<td>4.9</td>
</tr>
<tr>
<td>Calcium (mg)</td>
<td>25</td>
<td>110</td>
<td>138</td>
<td>115</td>
</tr>
<tr>
<td>Phosphorus (mg)</td>
<td>13</td>
<td>59</td>
<td>78</td>
<td>63</td>
</tr>
<tr>
<td>Osmolality§</td>
<td>290</td>
<td>&lt;360*</td>
<td>385</td>
<td>325</td>
</tr>
</tbody>
</table>

* HM = Human Milk  Pro = Prolacta  Sim = Similac  Enf = Enfamil
* * estimated Sullivan et al., *J Pediatr* 2010; 156:562-7
Human Milk Fortification

- Babies randomized to receive human milk-based fortifier had 50% reduction in medical NEC (p < .03), 86% reduction in surgical NEC (p < .007) compared to bovine-based.

- No difference in feeding intolerance, NEC in those infants receiving human milk-based fortifier starting at 40 mL/kg/day of feeds vs. 100 mL/kg/day.

Sullivan et al., *J Pediatr* 2010; 156:562-7
Reduced NEC with HM-Based Fortifier

Sullivan et al., *J Pediatr* 2010; 156:562-7
Benefits of Exclusive Human Milk Diet in Premature Infants

Study of 260 infants < 1250 gm.

<table>
<thead>
<tr>
<th></th>
<th>Human Milk</th>
<th>Cow’s Milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>2%</td>
<td>8%</td>
</tr>
<tr>
<td>NEC</td>
<td>5%</td>
<td>17%</td>
</tr>
<tr>
<td>Every 10 % increase in diet having cow’s milk protein increased sepsis risk by 18%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPN days</td>
<td>8 days less if &lt;10% days CM</td>
<td></td>
</tr>
</tbody>
</table>

Benefits of Exclusive Human Milk Diet in Premature Infants

Prospective RCT of 53 infants 500-1250 gm.

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</thead>
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<tr>
<td>TPN days</td>
<td>27</td>
<td>36 (p=.04)</td>
</tr>
<tr>
<td>NEC</td>
<td>3%</td>
<td>21% (p=.08)</td>
</tr>
<tr>
<td>Surgical NEC</td>
<td>0</td>
<td>17% (p=.04)</td>
</tr>
</tbody>
</table>

Benefits of Exclusive Human Milk Diet in Premature Infants

- Over 600 babies < 33 weeks gestation studied either before or after nutrition policy of exclusive human milk diet
- Control cohort 36% had only HM before 33 weeks gestation, vs. EHM cohort 91%
- NEC after 7 days reduced from 3.4% in control cohort to 1% in EHM cohort (p=.009)

Benefits of Exclusive Human Milk Diet in Premature Infants

- Standardized human milk based fortification strategy implemented at large Texas NICU
- 104 infants with B.W. < 1250 gram enrolled
- NEC after 7 days reduced from 3.4% in control cohort to 1% in EHM cohort (p=.009)
- Average weight gain was 24.8 ± 5.4 g/kg/day
- Length 0.99 ± 0.23 cm/week and head circumference 0.72 ± 0.14 cm/week
- 3 medical NEC cases, 1 surgical NEC

Use of Human Milk for Premature Infants—Optimizing Commitment

- Need to start education around human milk and pumping before delivery – by Obstetrical Services and during Neonatology consultations
- Hospital policy support of WHO/UNICEF Ten Steps to Successful Breastfeeding (<5% of hospitals support 9-10 steps) for all babies
- Resource allocation includes facilitating breast pump availability, appropriate milk storage
- Post partum and NICU staff education and support of breastfeeding and pumping, as directed by adequate lactation consulting services
Human Milk Availability – Recent Studies

- Best way of optimizing milk production is a combination of hand expression and breast pump (Morton J, et al. J Perinatol 2009; 29:757-64)

- This combination also increases the caloric content of human milk available to premature infants (Morton, J. et al. J Perinatol 2012; 31:791-6)

- Mothers who deliver < 32 week by C/S have OR 4.3 of milk volume < median; MV< median has OR 7.1 of formula feeding at D/C (Murase M, et al. J Hum Lactation 2014)
Human Milk Availability – Importance of Parents’ Views

- Alves, et al., systematic review of parents views on factors that help or hinder breast milk supply (Arch Dis Child Fetal Neonatal Ed 2013; 98:F511-7)

- Successful breast milk supply depends on knowledge, reinforcement of mothers’ motivation and alignment between NICU’s routines and parents’ needs; independent of socioeconomic factors, previous expectations, public health info.

- Results highlight the need to invest in qualitative and quantitative research regarding parents’ views on breast milk supply during hospitalization in NICU.
Use of Human Milk for Premature Infants—Donor Milk Policy

- There is concern than donor milk policy might undermine maternal commitment to providing milk

- Marinelli, et al. (form Connecticut Children’s) reported on impact of implementing donor milk program on VLBW infants (J Human Lact 2014)

- Formula exposure decreased (any: 56 -> 19%)

- Human milk exposure increased – proportion of human milk diet and proportion of infants fed exclusive human milk increased; infants fed earlier

- Exposure to and proportion of MOM unchanged
Human Milk Use for Premature Infants: QI Efforts Can Make a Difference

- 11 California NICUs implemented a self-selected combination of multiple interventions (that can be found at cpqcc.org)
- Breastfeeding at D/C increased from 55% pre-intervention to 64% post-intervention (p= .003)
- NEC rates fell from 7% to 2.4% (p< .0001)

Human Milk Use for Premature Infants: QI Efforts Can Make a Difference

- QI Project to Improve the Rate of Early Breast Milk Expression in Mothers of Preterm Infants: actions included increased lactation consultant workforce, early lactation consultation, tracking of MBM supply, and physician education.

- First milk expression decreased from 9 to 6 hours (p = 0.06)

- Exclusive BM at D/C increased from 37 to 59% (p < 0.05)

Challenges to the Use of Mother’s Breastmilk for Premature Infants

- Neonatal transports
- Maternal diseases/colonization
- Maternal medications
- Concerns about CMV
- Safety of transport and storage of maternal milk
Nutritional Practices Supporting Breastmilk – Individual Patient Level

◆ Careful monitoring of nutrition
  ▪ Intake – fluid volume, calories, protein
  ▪ Growth – measuring weight, length (using board), head circumference

◆ Adjust intake volume to anticipate growth instead of reacting to decreases in growth rate

◆ Track breastmilk production – use pumping log

◆ No definitive evidence about selection and benefits of nutrition lab monitoring, e.g. alkaline phosphatase
Nutritional Practices Supporting Breastmilk – Individual Patient Level

- Should aim for weight gain of 15 – 18+ gm/kg/day during growth phase after weight nadir
- Premature infants being discharged home should have careful follow-up of their nutrition and growth
- Nutritional supplementation for premature infants should be continued for 3 - 6 months to optimize growth and development
Nutritional Practices Supporting Breastmilk – NICU Level

- Average weight gain for VLBW infants*
- NEC rate for VLBW infants*
- Track and benchmark percentage of babies starting on human milk (mom’s or banked)
- Track and benchmark percentage of babies discharged on human milk*
- Other nutritionally-related measures includes day of first feed; TPN days; length of stay*

* Data available on VON, Pediatrix NICU databases
Alternatives to Mother’s Breastmilk

- Banked breastmilk – usually in conjunction with HMBANA milk bank
  - Usually selected population for use, e.g. VLBW infants
  - Informed assent/consent should be obtained describing pros and cons of donated milk compared to formulas

- Special premature formulas – superior to term formulas as far as growth; nutritional content better meets the needs of premature infants
Cost analysis predicts savings of 3.9 NICU days and $8,167 per patient, based on cost estimates of medical and surgical NEC within California 2007 dataset.

Factors that influence costs: patient selection (gestation age), quantity and duration of fortifier use.

Factors that influence savings: patient selection, baseline NEC rate.

Can create spreadsheet estimate NICU specific

Human Milk Use for Premature Infants: Financial Analysis

- Costs of exclusive human milk diet includes labor and facilities charges for provision and feeding, such as breast pump rental, lactation care providers and milk storage.

- Reduction in costs can accrue from fewer labs, medications, less TPN

- LOS reduction may lead to decreased revenue, or to savings under ACO reimbursement models
Prospective cohort study of 175 VLBW infants

The adjusted hospital costs for infants who received the lowest dose (< 25 mL/kg/day) of human milk were significantly greater ($31,513 more expensive) than for those receiving at least 50 mL/kg/day, and significantly greater ($20,384 more expensive) than for those receiving 25 to 49.99 mL/kg/day (P< .001).

Savings accrued from reduced sepsis, decreased LOS

SUMMARY

◆ Nutrition is critically important for the growth and development of premature babies.

◆ Ideal food for premature infants is mother’s breast milk that should be fortified, or donated breast milk (fortified prn), or else premature specialty formula.

◆ Use of breastmilk depends on institutional promotion and support and maximizing availability.

◆ Should have standardized approach to provide optimal nutrition for premature infants, associated with improved growth velocity, reduced NEC, reduced LOS.