Decrease in Rates of Necrotizing Enterocolitis After Implementing a Probiotic Protocol

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Disclosure Statement
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Speaker: Mehtab Sekhon, MD
Dr. Sekhon has no personal conflicts of interest or financial relationships to report.

Background
- Probiotics in infants at risk for necrotizing enterocolitis (NEC) can reduce NEC risk
- In the University of Utah Medical Center (UUMC) NICU, rates of NEC Bell Stage ≥ 2 in infants born at <30 weeks gestation increased from 2014–2015

Intervention
- Provision of probiotics to neonates at risk for NEC
- Start date: Oct 3, 2016
- Ultimate Flora: multi-organism probiotic
  - 4 Bifidobacteria (B.breve, B.bifidum, B.infantis, & B.longum) & Lactobacillus rhamnosus

• Eligibility criteria:
  1. Gestational age at birth <33 weeks OR birth weight <1500 grams
  2. Post-menstrual age ≥ 240/7 weeks
  3. 72 hours of age
Eligibility criteria (continued):
4. Tolerating $\geq 6$ ml/day enteral feedings x 24 hrs
5. No lethal anomalies/conditions or significant gastrointestinal anomalies

Probiotics are discontinued at $36^{6/7}$ weeks CGA

Purpose
- Compare the effect of Ultimate Flora (UF) use on NEC rates in infants $\leq 29^{6/7}$ weeks gestational age in the UF period to a historical cohort from the pre-UF period
- Hypothesis: UF use will be associated with decreased rates of NEC

Methods
- Retrospective review of a prospective database of infants $\leq 29^{6/7}$ weeks gestation

Inclusion criteria:
1. Born at $\leq 29^{6/7}$ weeks gestational age
2. Inpatient in the UUMC NICU from Jun 6, 2015 to Jan 30, 2018
   - 15 months pre/post UF start date

Exclusion criteria:
1. Presence of major congenital anomalies

NEC was prospectively monitored until discharge

Classified per the modified Bell’s staging criteria

Results
- Compared incidence of NEC $\geq$ Bell 2 & surgical NEC between the pre-UF and UF periods
- Pre-UF period: June 6, 2015 to Oct 2, 2016 $\rightarrow$ Epoch 1
- UF period: Oct 3, 2016 to Jan 30, 2018 $\rightarrow$ Epoch 2

241 infants

Congenital anomalies:
- Epoch 1: n=2
- Epoch 2: n=5

234 infants

Epoch 1 (n=124)
- Received UF (n=89)
- No UF (n=35)

Epoch 2 (n=110)
- Received UF (n=40)
- No UF (n=70)
### Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Epoch 1 (n=124)</th>
<th>Epoch 2 (n=110)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (mean, SD)</td>
<td>27.1 (1.9)</td>
<td>26.7 (2.0)</td>
<td>0.120</td>
</tr>
<tr>
<td>Birth weight (mean, SD)</td>
<td>987 (304)</td>
<td>902 (307)</td>
<td>0.034</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>15 (12%)</td>
<td>18 (16%)</td>
<td>0.349</td>
</tr>
<tr>
<td>Sex - Male (n,%)</td>
<td>62 (50%)</td>
<td>64 (58%)</td>
<td>0.210</td>
</tr>
<tr>
<td>Apgar Median (25-75%) 1 min</td>
<td>4 (2-7)</td>
<td>5 (2-7)</td>
<td>0.908</td>
</tr>
<tr>
<td></td>
<td>7 (5-8)</td>
<td>7 (6-8)</td>
<td>0.886</td>
</tr>
</tbody>
</table>

### Comorbid conditions

<table>
<thead>
<tr>
<th></th>
<th>Epoch 1 (n=124)</th>
<th>Epoch 2 (n=110)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDA diagnosed</td>
<td>66 (53%)</td>
<td>66 (60%)</td>
<td>0.297</td>
</tr>
<tr>
<td>PDA treated (n,%)</td>
<td>29 (44%)</td>
<td>21 (32%)</td>
<td>0.424</td>
</tr>
<tr>
<td>SIP</td>
<td>3 (2%)</td>
<td>5 (5%)</td>
<td>0.372</td>
</tr>
<tr>
<td>CLABSI</td>
<td>8 (6%)</td>
<td>9 (8%)</td>
<td>0.278</td>
</tr>
<tr>
<td>Late onset sepsis</td>
<td>8 (6%)</td>
<td>17 (16%)</td>
<td>0.026</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>90 (73%)</td>
<td>81 (74%)</td>
<td>0.856</td>
</tr>
<tr>
<td>Death</td>
<td>12 (10%)</td>
<td>18 (16%)</td>
<td>0.127</td>
</tr>
</tbody>
</table>

### Decrease in NEC ≥ Bell 2 from Epoch 1 to 2

- Number needed to treat = 17

### NEC cases in Epoch 2

<table>
<thead>
<tr>
<th>NEC ≥ Bell 2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical</td>
<td>3</td>
</tr>
<tr>
<td>≥ Bell 2 on probiotic</td>
<td>2</td>
</tr>
</tbody>
</table>

### Conclusion

- Preliminary data shows that use of the probiotic, Ultimate Flora, was associated with a significant decrease in rates of NEC ≥ Bell 2.

- Ongoing analysis is required to assess the full effect of probiotic use on rates of NEC and other outcomes.
Acknowledgements

- Dr. Bradley A. Yoder
- University of Utah Division of Neonatology
- Care providers (nurses, pharmacists, NNP's, physicians) at the UUMC NICU

Ultimate Flora eligibility criteria:

a) Post-menstrual age ≥ 240/7 weeks
b) Gestational age at birth <33 weeks OR
c) Birth weight < 1500 grams
d) At least 72 hours of age and tolerating ≥ 6 ml/day enteral feedings for 24 hours
e) No lethal anomalies/conditions or significant GI anomalies

Criteria to discontinue Ultimate Flora:

a) Infant has reached a corrected gestational age of 360/7 weeks.
b) Infant is made NPO.
c) Infant requires surgical resection of bowel
d) If NEC is diagnosed.
e) If ordered by a medical provider.

Criteria to restart Ultimate Flora:

a) NPO due to NEC, sepsis, or clinical instability
b) NPO for procedure (e.g., MRI, PDA ligation)

Ultimate Flora administration protocol:

a) Wear gloves while handling Ultimate Flora suspension.
b) For infants on NG/OG feeds:
   i. Administer Ultimate Flora suspension first.
   ii. Flush tube with 1ml of air.
   iii. Administer feed.
c) For infants on oral feeds:
   i. Administer Ultimate Flora with 5ml of feed by mouth.
   ii. Administer remainder of feed.

Is the patient receiving Ultimate Flora?

Does the patient meet eligibility criteria for Ultimate Flora?

Can Ultimate Flora be discontinued?

Can Ultimate Flora be restarted?

Does the patient meet criteria to discontinue Ultimate Flora?

Administer Ultimate Flora at 1100/1200 ml per nursing protocol.

Does the patient meet criteria to restart Ultimate Flora?