Probiotics in the NICU: Considerations Before Routine Use
Disclaimer

This an educational webinar series.

The NEC Society and invited speakers are not marketing any probiotic products, which are not currently FDA approved for the prevention of necrotizing enterocolitis or other neonatal diseases.
JUNE 2–5
ANN ARBOR MI
NEC SYMPOSIUM 2019
NURSE PRACTITIONERS  PED. SURGEONS
NEONATOLOGISTS  INDUSTRY SCIENTISTS
NON-PROFITS  NURSES  PATIENT-FAMILIES

HIGHLIGHTS:
Prevention and early detection of NEC
Human milk and NEC
Patient-family centered care in NEC prevention
Animal models of NEC
Probiotics and NEC
NEC registry and biorepository
Treatment and neurodevelopmental outcomes

TO REGISTER
& FOR THE FULL AGENDA:
https://necsymposium.eventbrite.com

NEC SOCIETY
M.D. MEGH CHILDSREN’S HOSPITAL

THIS EVENT IS PARTIALLY FUNDED THROUGH A
PEDIATRIC RESEARCH INSTITUTE (PdRI) EVIDENCE-BASED PEDiatrics ENGAGEMENT
AWARD, CONTRACT Y1HD15-13-0033
NEC AWARENESS DAY  MAY 17

#NECday  #ThisIsNEC
Webinar Faculty

Jennifer Canvasser, MSW
Founder, Director
NEC Society

Mark Underwood, MD, MAS
Professor of Pediatrics
UC Davis, CA
Scientific Advisor, NEC Society

Ravi Patel, MD, MSc
Associate Professor of Pediatrics
Emory University, Atlanta, GA
Scientific Advisor, NEC Society
Today’s Guest Faculty Speakers

Adam M. Masin is a Partner at Shipman & Goodwin LLP. Adam represents leading health care institutions, pharmaceutical companies, and medical device manufactures in litigation involving the alleged health risks of medical products. Adam recently represented Yale-New Haven Hospital in a lawsuit involving the use of probiotics with neonates.

Dr. Jae Kim is a neonatologist and gastroenterologist at Rady Children's Hospital and Professor at UC San Diego in both the Neonatology and Pediatric Gastroenterology Departments. Dr. Kim's interests include neonatal nutrition, neonatal bowel injury, and bedside ultrasound. He co-authored the book Best Medicine: Human Milk in the NICU.
Overview of today’s webinar

- Are we moving too fast on probiotics? Efficacy, safety, and other considerations
  - Jae Kim, MD, PhD, UC San Diego

- Regulation of probiotics: dietary supplement or live biotherapeutic product?
  - Ravi Patel, MD, MSc, Emory University

- Probiotics: Is consent necessary?
  - Adam Masin, Esq., Shipman & Goodwin LLP

- How can we empower and inform families on probiotics?
  - Jennifer Canvasser, MSW, NEC Society

- Opportunities for shared learning about probiotics with the NEC Society
  - Mark Underwood, MD, UC Davis

Q&A with speakers
Are we moving too fast on probiotics? Efficacy, safety, and other considerations

Jae Kim, MD, PhD
Professor of Clinical Pediatrics
Department of Pediatrics
Division of Neonatal-Perinatal Medicine
Division of Pediatric Gastroenterology, Hepatology and Nutrition

NEC Society Probiotics Webinar 2019
## Disclosures

| Grant/Research Support       | Mallinckrodt (Infacare study)  
|                             | Fresenius-Kabi (SMOF study)    |
| Scientific Advisory Boards  | Alcresta                       |
| Consultant                  | Medela                         
|                             | Ferring                        
|                             | Astarte                        
|                             | Evivo                          |
| Speaker                     | Abbott Nutrition, Mead Johnson (ended 2018) |
| Stock Shareholder           | Nicolette                      
|                             | Astarte                        |
Can we learn from the past in neonatology?

• **Corticosteroids for BPD**
  - Use of early, high dose, version of steroids became widespread (high dose dexamethasone started in first week of life)
  - The immediate satisfaction of weaning ventilation and oxygen overshadowed the long term detrimental effects on neurodevelopment

• **PDA management**
  - Multiple studies looking for efficacy to medically close the PDA with little long term outcomes
  - Numerous adverse effects were tolerated due to our desire to close the ductus

Looking back, what cumulative harm did we cause?
If we were given a second chance, how would we have done it?
What are the gaps with probiotics?

• What is the correct and best probiotic?
• Single vs multiple treatment?
• What is the best dose?
• How early should we give this? How long should we give it?
• What is the potentiating effect of mother’s milk or donor milk?
• Why are probiotics less effective for those less than 1000 grams birth weight?
• Are we missing any risks?
Gastric acidity is an important control element to the intestinal microbiome.
Risk of the preterm infant

- Most are not delivered from birth canal
- Frequent use of early broad spectrum antibiotics
- Delay in enteral feedings
- Use of sterile infant formulas with no probiotics or prebiotics
- Nosocomial bacterial colonization
Dysbiosis

- Sick ecosystem
- Low diversity of species
- Imbalance
- Lack of functional redundancy
- Susceptibility to disease
- Measured by Microbial Dysbiosis Index

Dysbiosis ↔ Infection/Inflammation
Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer

• A single swabbing of vaginal secretions can partially restore the flora of an infant born by C-section
• The limitations include the antibiotics used by those delivered by C-section and the single application

Role of human milk?

• A combination of probiotic strains (Lactobacillus acidophilus and Bifidobacterium bifidum) was effective on NEC only in VLBW infants who were exclusively breastfed, but not in those receiving formula.
• Two meta-analyses of RCTs documented a reduction in the incidence of LOS and in the time to achieve full feeds only in HM-fed preterm infants.
• The effect of probiotics on NEC was found to be more pronounced in cohorts where higher proportions of neonates were exclusively breastfed.
ELBW INFANTS ONLY

A NEC stage ≥ 2

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Probiotic Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
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<td>239</td>
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<td>7</td>
<td>79</td>
<td>6.1%</td>
<td>0.44 [0.13, 1.46]</td>
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<td>93</td>
<td>9</td>
<td>103</td>
<td>7.8%</td>
<td>0.62 [0.21, 1.77]</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>797</strong></td>
<td><strong>799</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>0.86 [0.64, 1.16]</strong></td>
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</tbody>
</table>

Total events 71 85

Heterogeneity: Tau² = 0.00; Chi² = 2.26, df = 4 (P = 0.69); I² = 0%
Test for overall effect: Z = 1.00 (P = 0.32)

B All-cause deaths

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Probiotic Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
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<tr>
<td>Al–Hosni 2012</td>
<td>3</td>
<td>50</td>
<td>4</td>
<td>50</td>
<td>8.4%</td>
<td>0.75 [0.18, 3.18]</td>
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<tr>
<td>Costeloe 2016</td>
<td>46</td>
<td>317</td>
<td>53</td>
<td>327</td>
<td>61.2%</td>
<td>0.90 [0.62, 1.29]</td>
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<td>Lin 2008</td>
<td>0</td>
<td>102</td>
<td>6</td>
<td>79</td>
<td>2.3%</td>
<td>0.06 [0.00, 1.04]</td>
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<td>Oncel 2014</td>
<td>11</td>
<td>93</td>
<td>17</td>
<td>103</td>
<td>28.1%</td>
<td>0.72 [0.35, 1.45]</td>
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<td><strong>562</strong></td>
<td><strong>559</strong></td>
<td><strong>100.0%</strong></td>
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<td><strong>0.78 [0.50, 1.20]</strong></td>
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</table>

Total events 60 80

Heterogeneity: Tau² = 0.05; Chi² = 3.74, df = 3 (P = 0.29); I² = 20%
Test for overall effect: Z = 1.12 (P = 0.26)
Safety of Probiotics

- Recipient
- Other Patients
- NICU Environment
- Staff

Is the label accurate?
Cross contamination of probiotics

- ProPrems study tested
  - 5 who received probiotics (B infantis, B lactis, S. thermophilus) were colonized
  - 3 of 38 (8%) who were not treated were also colonized

- RCT with Bifidobacterium breve detected the probiotic in the feces of 44% of the control infants at six weeks of age

- RCT with B. breve found 35% of controls to be positive for probiotics at 28 days
  - Costeloe et al. abstract at Neonatal Society 2004 Spring Meeting in the UK
Development of gut microbiome

Weaning

Bifidobacteria

Anaerobes

Establishment of anaerobic environment

Facultative anaerobes

Relative numbers

Age

Genetics
Mode of delivery

Feeding type
Environmental exposure

PLASTIC

RESTRICTIVE

The metabolic role of the microbiome

• Fecal transplant from obese mice into germ free mice fed varying diets
• Increased total fat and lean body mass and obesity related metabolic consequences were transferable

Adult gut microbiome

• What do we know about the long term impact of altering the gut microbiome at a critical stage in time? Unlike other stages in life the changes in the microbiome may be more longlasting.

• What impact do probiotics have in altering the metabolic machinery in the commensal microbiome that may alter favorably or not the metabolism of the host?
Options are not mutually exclusive
Option 1: High quality probiotics

Benefits:
• Immediate access to high quality manufactured probiotics
• Cheaper than FDA drug approved product
• More rapid adoption as NICUs can start using these now
• Canada is a good example of Option 1

Risks:
• Questions will remain that may be harder to answer later: which is the best product, optimal dose, duration and co-factors
• Measurement of adverse effects—who is measuring?
Option 2: FDA approved probiotics

Benefits:
• Safety will be much better regulated and monitored
• IND application by industry required with conduct of large scale RCT design
• Greater likelihood of adoption if approved in this manner
• Capacity to answer some of the other gaps (ELBW, cross contamination)

Risks:
• Final product cost will be much higher than Option 1
• Time to implementation will be much longer (5+ years)-cost of not accessing this sooner
Option 3: The rise of prebiotics and postbiotics

• Several prebiotics have been brought out for term infant feeding (not preterm, yet)
• Prebiotics or combination of prebiotics can be chemically synthesized or isolated from donor human milk

Benefits:
• Not live product, lower biologic risk of probiotics
• Prebiotics have similar mechanisms to probiotics
• Synbiotic treatment may also be studied

Risks:
• Time for clinical efficacy and safety studies needed

**Human milk is an ideal synbiotic**
Human milk oligosaccharide composition predicts risk of necrotizing enterocolitis in preterm infants

- multicenter clinical cohort study
- recruited 200 mothers and their VLBW infants that were exclusively human milk-fed
- HMO composition analysis in breast milk fed to infants over the first 28 days post partum
- matched each NEC case with five controls

Human milk oligosaccharide composition predicts risk of necrotizing enterocolitis in preterm infants

DSLNT content in breast milk is a potential non-invasive marker to identify infants at risk of developing NEC and screen high-risk donor milk.

DSLNT could serve as a natural template to develop novel therapeutics against this devastating disorder.
## Spectrum of Implementation

<table>
<thead>
<tr>
<th>Conservative</th>
<th>Liberal</th>
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<tbody>
<tr>
<td>Need FDA approved product</td>
<td>Safe if use high quality manufactured probiotics</td>
</tr>
<tr>
<td>Not enough data</td>
<td>Enough evidence to start use</td>
</tr>
<tr>
<td>Long term safety</td>
<td>Waiting is unethical</td>
</tr>
<tr>
<td>Contamination or misidentity</td>
<td>More data can be acquired after implementation</td>
</tr>
<tr>
<td>Lack of efficacy in smallest subgroup</td>
<td></td>
</tr>
<tr>
<td>Confounding factors need to better understood</td>
<td></td>
</tr>
<tr>
<td>Willing to wait for more data</td>
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</tbody>
</table>
Regulation of probiotics: Dietary supplement vs. live biotherapeutic product

Ravi Mangal Patel, MD, MSc
Associate Professor of Pediatrics
Emory University and
Children’s Healthcare of Atlanta

rmpatel@emory.edu
@ravimpatelmd

Disclosure: Probiotics are not approved by the US Food and Drug Administration for the prevention of NEC or other diseases in preterm infants.

This webinar is intended to be educational in nature only and does not intend to provide regulatory guidance.
Overview

- The regulation of probiotics is complex
Since 2016, the US Food and Drug Administration’s regulatory oversight over probiotics falls into two separate categories:

1. Dietary supplement
2. Live biotherapeutic product
Probiotic as a dietary supplement

• Product taken by mouth that contains a "dietary ingredient" intended to supplement the diet
  – Probiotics currently sold as dietary supplements

• FDA provides good manufacturing practice guidance

• Dietary supplement labels may make claims about how the product affects the structure or function of the body without FDA approval

• However, cannot make claims that the product reduces the risk of a disease without FDA consent.
Probiotic as a live biotherapeutic product (LBP)

• If a probiotic is *marketed* as a drug for prevention of a disease (e.g. NEC), more stringent requirements.
• It must be proven safe and effective for its intended use through clinical trials and be approved by the FDA before it can be sold.
• FDA guidance requires sufficient information to assure the proper identification, quality, purity, consistency and strength of the investigational drug.
• Currently, there is no approved LBP.
Probiotic regulation outside US

• **Canada**: Probiotic as licensed health product
  – Products with a license have been assessed by Health Canada and found to be safe, effective and of high quality under their recommended conditions of use.

• **European Union**: The term “Probiotic” is considered a health claim in some countries

• In several other countries, probiotics are considered functional foods
Conclusion

• The regulation of probiotics is complex

• The regulatory environment for probiotics continues to evolve around the world

• Currently, there are no regulations that prevent clinicians from supplementing probiotics to infants
Additional resources

https://www.fda.gov


www.inspection.gc.ca/

https://www.asa.org.uk/advice-online/food-probiotic-claims.html
Probiotics and NEC: Is Informed Consent Legally Necessary?

Probiotics in the NICU: Considerations Before Routine Use, a NEC Society webinar

May 6, 2019

Adam M. Masin
amasin@Goodwin.com
(860) 251-5154
@AdamMasinEsq
Disclaimers:

• Not intended to provide legal advice

• Opinions are my own, and do not necessarily reflect those of my firm or any clients

• I will not be discussing non-public information for purposes of this presentation

• I cannot discuss information specific to Yale-New Haven Hospital or Yale University
INFORMED CONSENT

• Is it ethical?
• Is it medically required or necessary?
• Is it medically acceptable/appropriate?
• Does your institution have a policy?
• Is it practical?
• Is it legal?
• Is it legally required?
“Every human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient's consent commits an assault for which he is liable in damages.”

-- Schloendorff v. Society of New York Hospital, 105 N.E. 92 (N.Y. 1914) (Cardozo, J.)
INFORMED CONSENT: CIVIL LAW

“[W]e must be mindful not to expand unduly the contours of the informed consent doctrine such that physicians would lack a clear understanding of the scope of the disclosure that they must make, and patients thereby would be burdened with immaterial information that many might find confusing”.

-- Supreme Court of Connecticut, *Duff v. Flagg*. 
Not Informed Consent As A Legal Matter

• Telling patients you are doing something
• Extolling benefits
• Providing information sheet

BUT...
• Providing information might be ethical, medically appropriate, policy, easy, and a nice thing to do.
A “FAILURE TO PROVIDE INFORMED CONSENT” CLAIM

1. Is there a legal **duty** to provide informed consent?

2. Did the provider **breach** the duty to obtain a valid/adequate informed consent?

3. Was a failure to obtain informed consent a **cause** of the injury?

4. What **damages** did the breach cause?
A “FAILURE TO PROVIDE INFORMED CONSENT” CLAIM

1. Is there a legal duty to provide informed consent?

2. Did the provider breach the duty to obtain a valid/adequate informed consent?

3. Was a failure to obtain informed consent a cause of the injury?

4. What damages did the breach cause?
IS THERE A LEGAL DUTY TO OBTAIN INFORMED CONSENT WITH PROBIOTICS?

• SURGERY
• BLOOD TRANSFUSIONS
• PHARMACEUTICALS
• NUTRITIONAL SUPPLEMENTS
  ◆ Probiotics
IS THERE A LEGAL DUTY TO OBTAIN INFORMED CONSENT WITH PROBIOTICS?:

• Complaint *alleges* a viable claim because probiotics part of a “medical protocol”

  BUT...

• “Whether or not the claim survives in the long run will depend upon the facts.”

IS THERE A LEGAL DUTY TO OBTAIN INFORMED CONSENT WITH PROBIOTICS?

“it may be necessary to require a plaintiff to show that the risk of harm at issue was created or heightened by the patient's medical needs or condition, as opposed to being a mere background risk unrelated to and unaffected by the medical context.”

A “FAILURE TO PROVIDE INFORMED CONSENT” CLAIM

1. Is there a legal duty to provide informed consent?

2. Did the provider breach the duty to obtain a valid/adequate informed consent?

3. Was a failure to obtain informed consent a cause of the injury?

4. What damages did the breach cause?
**Hanes v. Solgar: Lack of Informed Consent Allegations**

- Not FDA approved
- “Unregulated”
- Not sterile
- Label: “not intended...to prevent a disease”
- “Sepsis” risk in immunocompromised neonates
- “Uncertainty” around using probiotics
- Potential inconsistency between stated/actual content
- Long term effects not defined
A “FAILURE TO PROVIDE INFORMED CONSENT” CLAIM

Two key aspects to providing a valid/adequate informed consent:

• Accurate medical information
  ◆ Medical expert

• Material to a patient’s decision-making
  ◆ Who decides what is material?
A “FAILURE TO PROVIDE INFORMED CONSENT” CLAIM

Accurate medical information:

• the nature of the procedure;
• the hazards and risks of the procedure;
• the alternatives to the procedure; and
• the anticipated benefits of the procedure.
A “FAILURE TO PROVIDE INFORMED CONSENT” CLAIM

What is a valid/adequate informed consent?

• the nature of the procedure;
• the hazards and risks of the procedure;
• the alternatives to the procedure; and
• the anticipated benefits of the procedure.
A “FAILURE TO PROVIDE INFORMED CONSENT” CLAIM:

Key Medical Question:

Are there any *known, material, risks* of using probiotics to prevent NEC?
A “FAILURE TO PROVIDE INFORMED CONSENT” CLAIM:

Key Legal Question:

What standard is used to decide if a known risk is material?

- A reasonable medical provider?
- The actual medical provider (e.g., learned intermediary)?
- A reasonable patient/parent?
- The actual patient/parent?
A “FAILURE TO PROVIDE INFORMED CONSENT” CLAIM:

Key Legal Question:
What standard is used to decide?

- The reasonable medical provider?
- The actual medical provider (e.g., learned intermediary)?
- The reasonable patient/parent.
- The actual patient/parent.
Suggested questions:

• Do you believe that providing medically accurate information to parents could cause a reasonable parent to reject probiotics based on a reasonable view of that information?

• Do you believe that providing medically accurate information to parents about probiotics could cause parents to unreasonably reject probiotics?
A “FAILURE TO PROVIDE INFORMED CONSENT” CLAIM

1. Is there a legal duty to provide informed consent?

2. Did the provider obtain a valid/adequate informed consent?

3. Was a failure to obtain informed consent a cause of the injury?
Different approaches

• Nothing – considered routine treatment
• Information sheet part of larger hospital NICU package
• Information sheet given only if parents ask questions
• Information sheet only given to parents of candidates
• Verbal discussion extolling benefits of probiotics
• Verbal discussion only if parents ask questions
• Verbal assent
• Verbal consent implied from silence after discussion
• Verbal consent initially, then abandoned
• Written consent as part of research
INFORMED CONSENT

• Should you talk to parents about probiotics at all?

• Do you believe that there is a known medical risk associated with giving probiotics for NEC prevention?

• Would a reasonable parent want to know about such risk(s), if any? Is it material to a decision?

• What is the right way to talk about benefits/risks based on the known science?
INFORMED CONSENT

• Is it ethical?
• Is it medically required or necessary?
• Is it medically acceptable/appropriate?
• Does your institution have a policy?
• Is it practical?
• Is it legal? -- YES
• Is it legally required? -- ???
FDA does regulate probiotics

- Strong benefit evidence
- No meta-analyses or RCTs showing risk
- No cohort studies showing risk
- Case reports of bacteremia
  - no serious adverse events
- One serious contamination incident
  - Lot recalled
  - Product off market

Alternatives to probiotics?
- Benefit to your NICU microbiome?
- Scare parents unnecessarily?

INFORMED CONSENT: Is it legally required?
Questions?

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Strategies to Empower and Inform Families on Probiotics
Micah before he developed NEC
Micah after he developed NEC
Parents as Partners in Care

- Build trust and rapport

- Most engaged and committed member of your patient’s care team

- Listen and be responsive

- Build a culture in your NICU that values parents
Provide Parents with Information

- Information does not further overwhelm families
- Information prepares them to better advocate and care for their baby
- Delivered by different providers in different ways
- Mentor parents’ skills and knowledge base
What do NICU parents want to know?

- We want to know that our baby is at risk of NEC
- We want to know that probiotics may help to reduce the risks of NEC
- We want to know the potential associated risks and protective factors of both NEC and probiotics

We want to be part of our baby’s care team and help to make decisions about our baby’s care.
How can we empower & inform families about probiotics?

- Talk *with* parents about NEC, breast milk, and probiotics
- Use the NEC Society’s resources
- Listen authentically & be responsive
Information for Parents
Probiotics, Breast Milk, and Necrotizing Enterocolitis

What is necrotizing enterocolitis (NEC)?
Necrotizing enterocolitis (NEC) is a common and devastating intestinal condition that mostly occurs in premature infants, usually between 2 and 8 weeks of age. NEC can be life-threatening. NEC is caused from inflammation of the intestine. Some babies need surgery because of NEC.

How can we prevent NEC?
Breast milk from the baby’s mother offers the most protection against NEC for very premature and medically fragile infants. When mothers are unable to provide their own milk, pasteurized donor milk provides more protection than formula against NEC. There is also good evidence that giving premature babies probiotics reduces their risk of NEC and increases their chance of survival. Neither human milk nor probiotics can eliminate the risks of NEC.

What are probiotics?
Probiotics are healthy, live bacteria that have benefits in the intestine and on the immune system. Probiotics are like bacteria found in yogurt. Probiotics are more effective when premature babies also receive breast milk.

Are there any risks of getting probiotics?
There are risks and benefits to every treatment. The benefits of probiotics include maintenance of healthy bacteria in the intestine. This is believed to help prevent NEC. In rare situations, probiotic bacteria can get into the blood and cause infections. If babies develop an infection in the blood with the probiotic bacteria, they are given an antibiotic to kill the probiotic bacteria. When this has happened, the infections have been responsive to treatment. Based on the literature, it appears that the benefits of probiotic administration outweigh the potential risks.

If you have questions about breast milk, probiotics, or your baby’s health status, please ask your baby’s healthcare provider.

Probiotics are not currently approved by the U.S. Food and Drug Administration (FDA) nor recommended by the American Academy of Pediatrics (AAP) for the prevention of necrotizing enterocolitis or other neonatal diseases. This educational resource aims to share information and empower NICU parents.
How can we empower & inform families about probiotics?

- Engage your NICU’s patient-family advisory committee
- Engage post-NICU families in patient-centered research
- Engage your multidisciplinary team
NEC Society Probiotic Quality Improvement Project

Mark A. Underwood
Background

- Why have large clinical trials of probiotics in premature infants not been performed in the U.S.?
  - RCTs with >1000 preemies: UK and Australia/NZ
  - Cohort studies with > 1000 preemies: Germany, Switzerland, Finland, France, Australia, Canada

- Key knowledge gap: comparisons of different probiotics and doses
Quality Improvement Project

- Eligible NICUs and infants
- Epoch 1 = 18 months prior to routine probiotic administration
- Epoch 2 = 18 months after initiation of routine probiotic admin
- Primary exposure = probiotic strain, dose and duration
- Secondary exposures = feeding type, antibiotic days
- Primary outcome = weight gain
- Secondary outcomes = NEC, death, sepsis (including sepsis related to the probiotic product), days to full enteral nutrition, TPN days, and length of hospital stay
Goals and Alternatives

100 NICUs
10,000 premature infants

Alternative strategies for data collection: existing infrastructure
US RCT: Infant Bacterial Therapeutics trial of *L. reuteri*
Evaluation, Feedback, Thoughts ...