Probiotics in the NICU: Considerations Before Routine Use

NEC SOCIETY
Building a World Without NEC

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.

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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

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NEC AWARENESS DAY MAY 17
#NECday #ThisIsNEC
SIGNEC
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NEC SOCIETY

Webinar Faculty

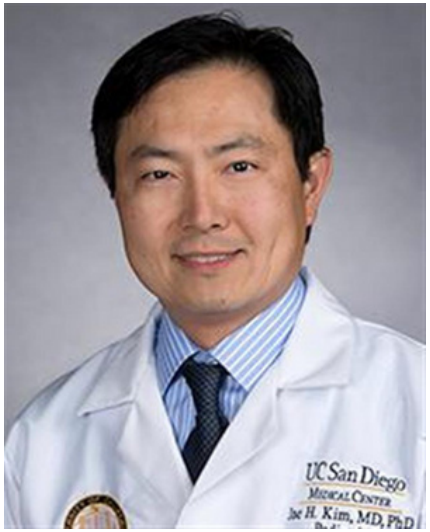
Jennifer Canvasser, MSW
Founder, Director
NEC Society

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

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spin SUPPORTING PREMATURE INFANT NUTRITION

SAN DIEGO MOTHERS' MILK BANK
UC San Diego Health

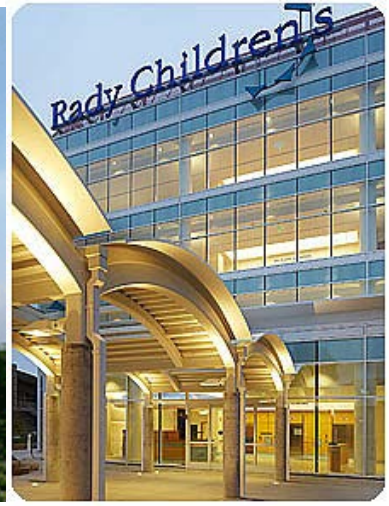
Mommy's Milk
HUMAN MILK RESEARCH BIOREPOSITORY

Larsson-Rosenquist Foundation
Mother-Milk-Infant
Center of Research Excellence
LRF MoMI CoRE
Unraveling the Complexity of Human Milk

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



UC San Diego Health

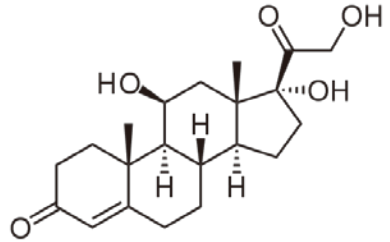
Rady Children's Hospital San Diego

Disclosures

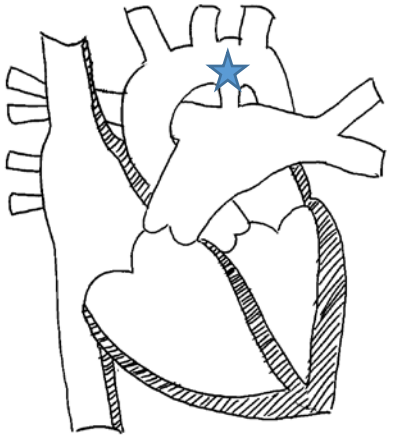
Grant/Research Support	Mallinckrodt (Infacare study) Fresenius-Kabi (SMOF study)
Scientific Advisory Boards	Alcresta
Consultant	Medela Ferring Astarte Evivo
Speaker	Abbott Nutrition, Mead Johnson (ended 2018)
Stock Shareholder	Nicolette Astarte

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



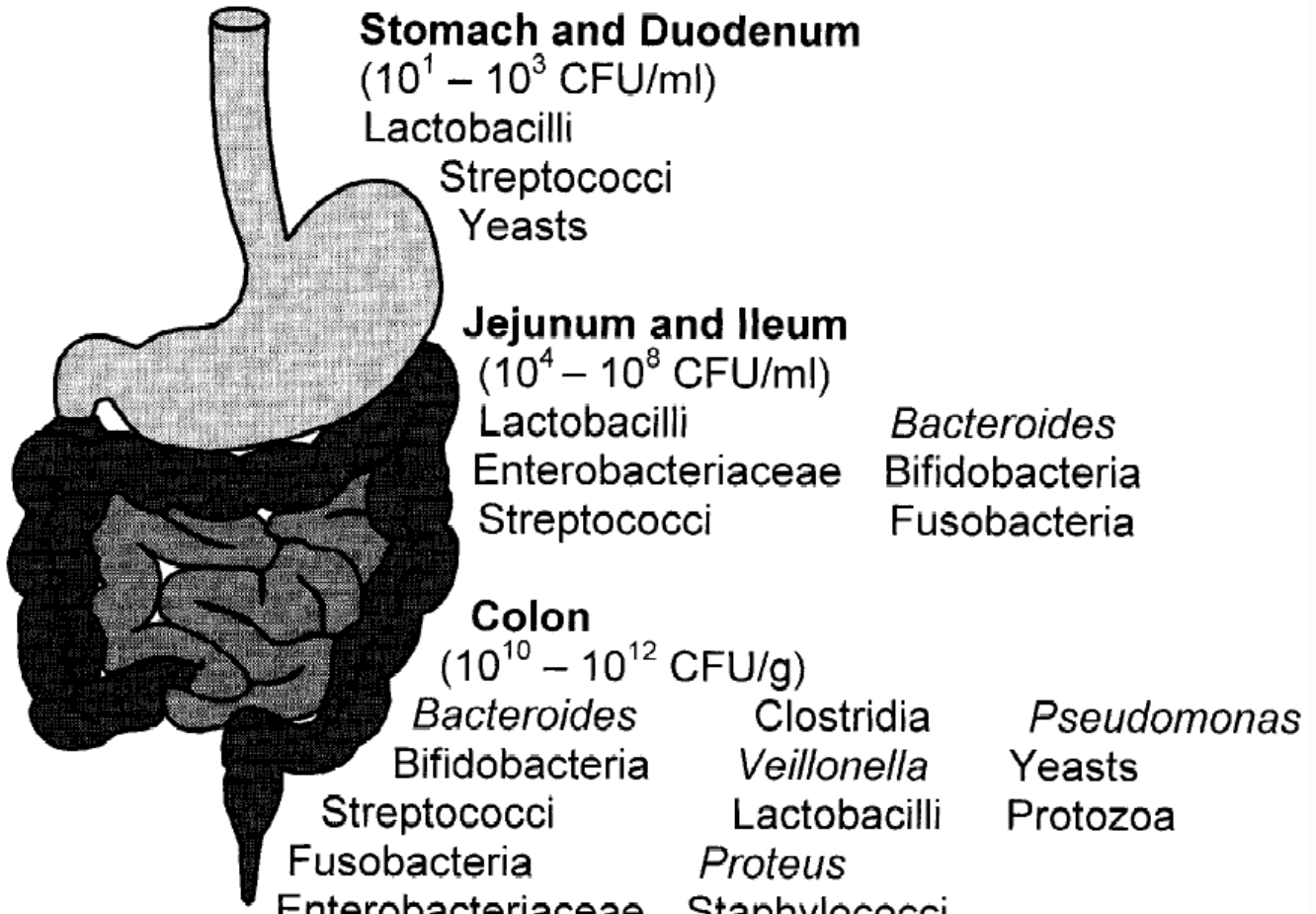
Looking back, what cumulative harm did we cause?
If we were given a second chance, how would we have done it?

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?

Microbes in the GI Tract

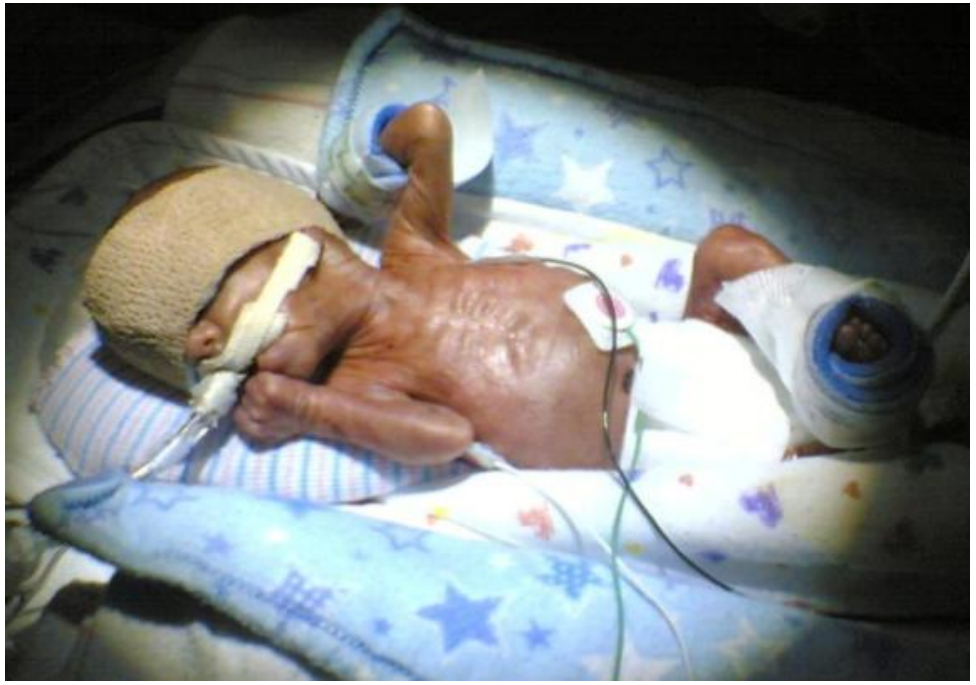
Gastric acidity is an important control element to the intestinal microbiome



Holzapfel et al. (1998) Int J Food Microbiol 41:85-101

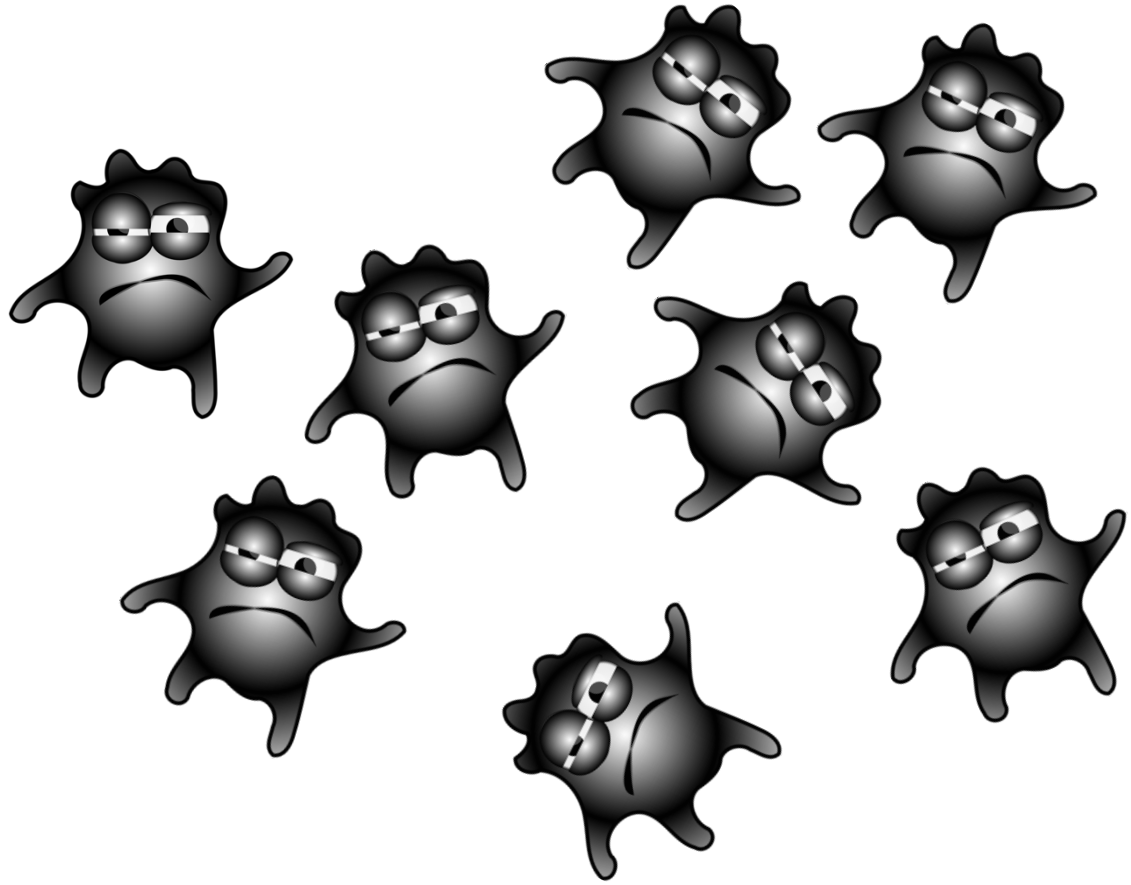
Risk of the preterm infant

- 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

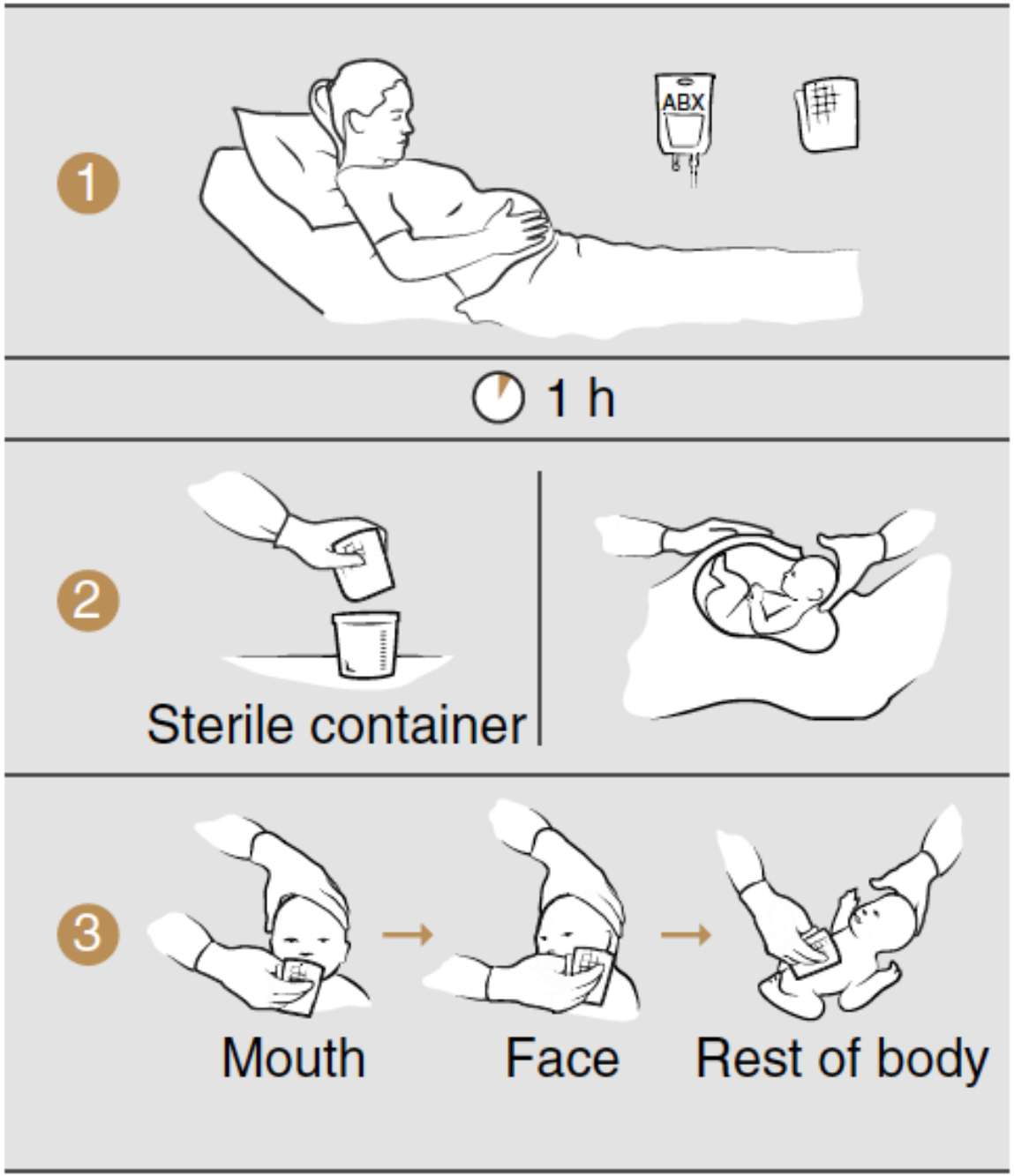


Image: M.J. Schoen

Dominguez-Bello et al Nat Med. 2016 Mar;22(3):250-3.

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

Aceti A et al. Nutrients. 2018 Review. PubMed PMID: 30308999

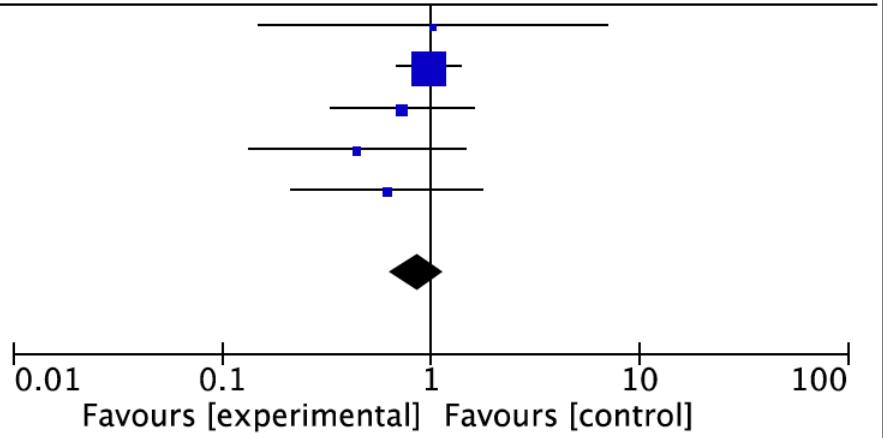
ELBW INFANTS ONLY

A NEC stage ≥ 2

Study or Subgroup	Probiotic Events	Probiotic Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Al-Hosni 2012	2	50	2	51	2.4%	1.02 [0.15, 6.96]
Costeloe 2016	50	317	53	327	69.7%	0.97 [0.68, 1.39]
Jacobs 2013	10	235	14	239	14.0%	0.73 [0.33, 1.60]
Lin 2008	4	102	7	79	6.1%	0.44 [0.13, 1.46]
Oncel 2014	5	93	9	103	7.8%	0.62 [0.21, 1.77]
Total (95% CI)		**797**		**799**	**100.0%**	**0.86 [0.64, 1.16]**
Total events	71		85			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.26$, df = 4 (P = 0.69); $I^2 = 0\%$

Test for overall effect: Z = 1.00 (P = 0.32)

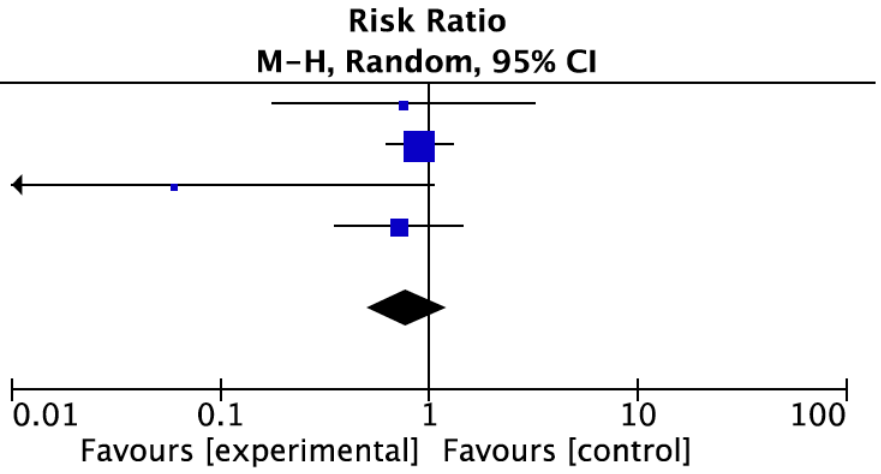


B All-cause deaths

Study or Subgroup	Probiotic Events	Probiotic Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Al-Hosni 2012	3	50	4	50	8.4%	0.75 [0.18, 3.18]
Costeloe 2016	46	317	53	327	61.2%	0.90 [0.62, 1.29]
Lin 2008	0	102	6	79	2.3%	0.06 [0.00, 1.04]
Oncel 2014	11	93	17	103	28.1%	0.72 [0.35, 1.45]
Total (95% CI)		**562**		**559**	**100.0%**	**0.78 [0.50, 1.20]**
Total events	60		80			

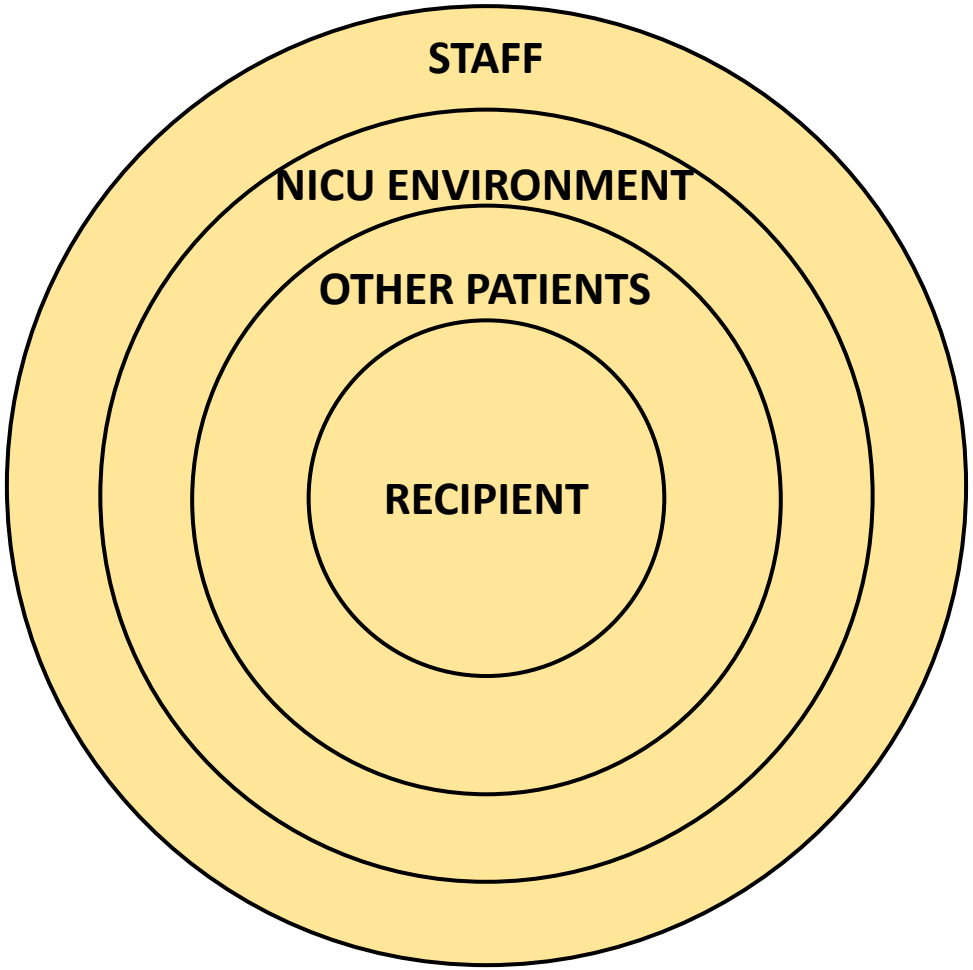
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 3.74$, df = 3 (P = 0.29); $I^2 = 20\%$

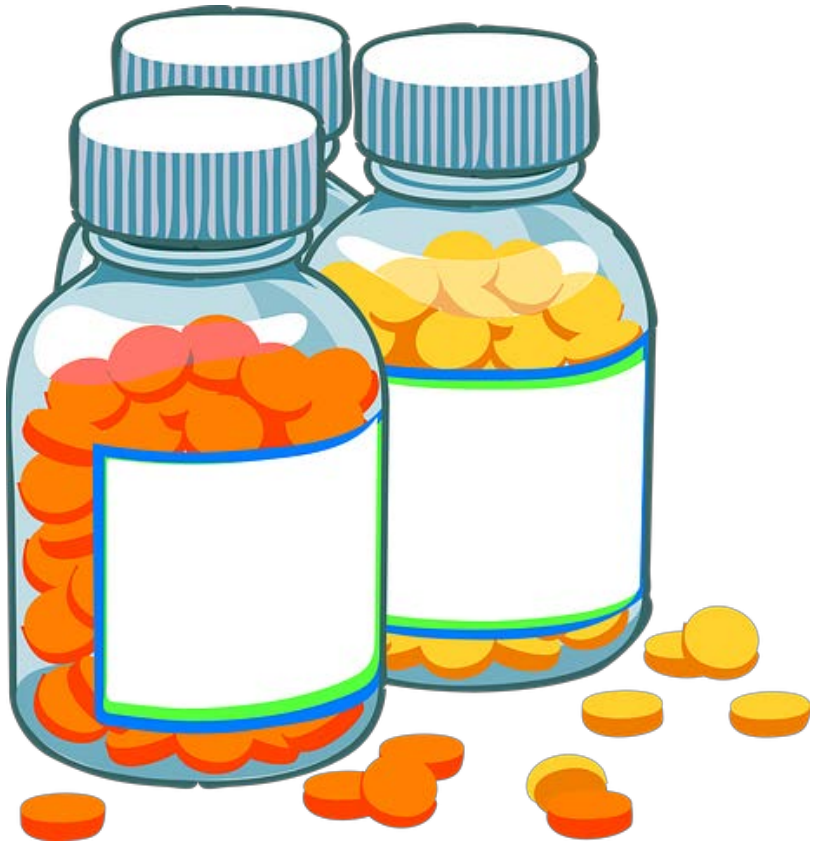
Test for overall effect: Z = 1.12 (P = 0.26)



Thomas JP et al. Acta Paediatr. 2017 Nov;106(11):1729-1741.
Chang HY et al. PLoS One. 2017 Feb 9;12(2):e0171579.

Safety of Probiotics



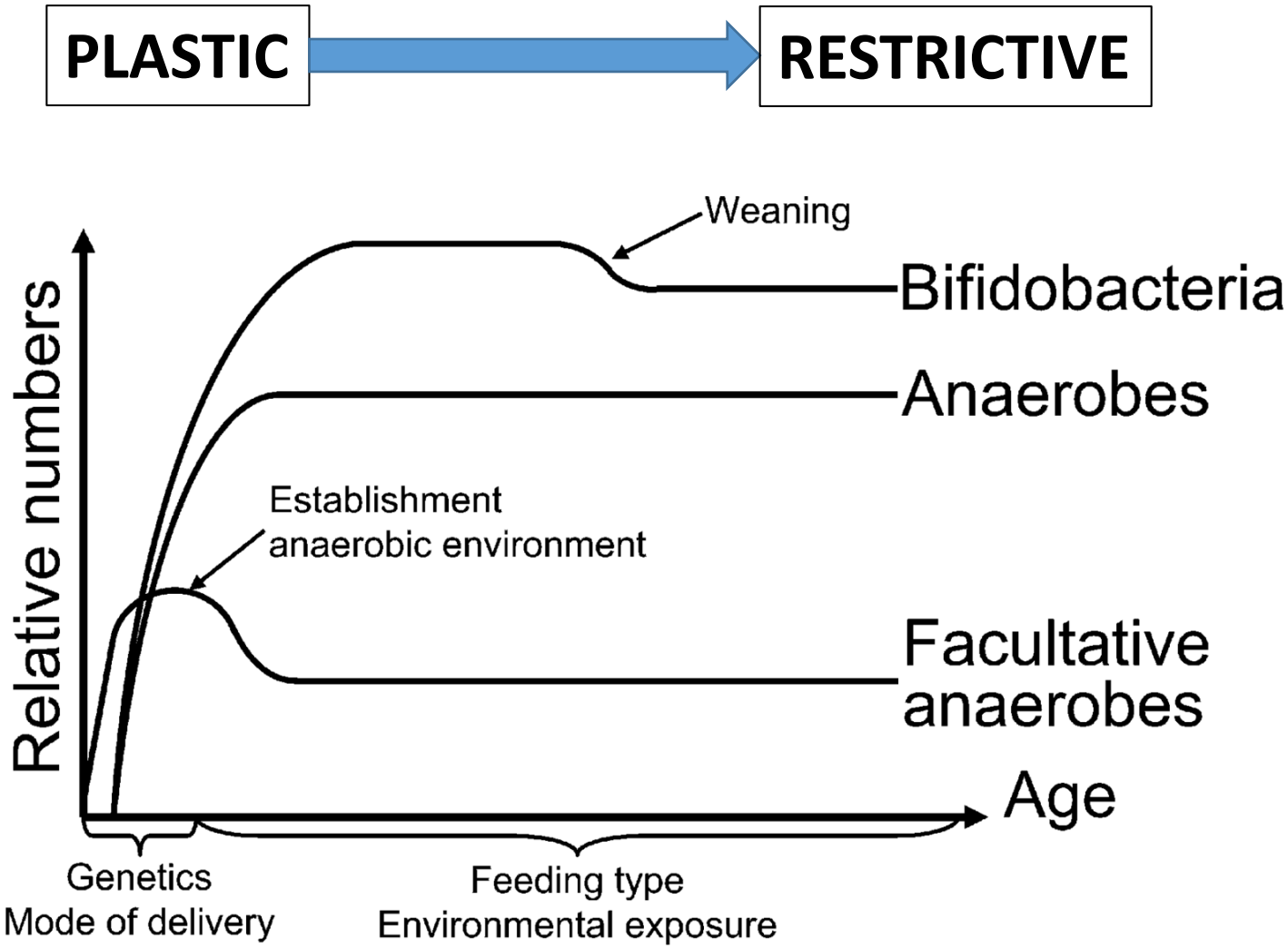


IS THE LABEL ACCURATE?

Cross contamination of probiotics

- ProPrems study tested
  - Hickey et al J Hosp Infect. 2014 Dec;88(4):226-9. (PROPREM trial)
  - 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
  - Kitajima et al. Archs Dis Child Fetal Neonatal Ed, 76 (1997), pp. F101–F107
- 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

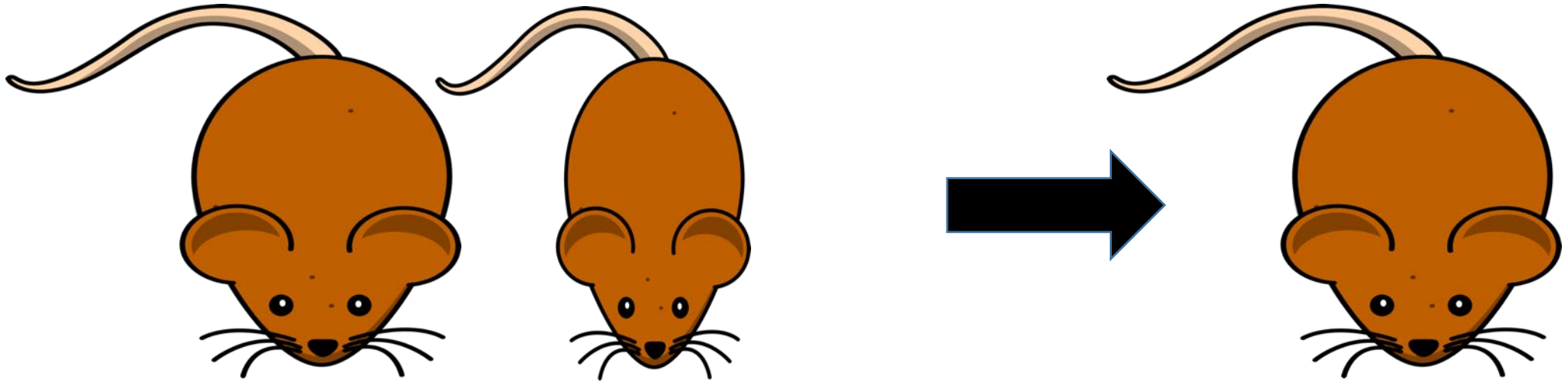
Development of gut microbiome



Rautava et al. J Pediatr Gastroenterol Nutr. 2004 Apr;38(4):378-88.

The metabolic role of the microbiome

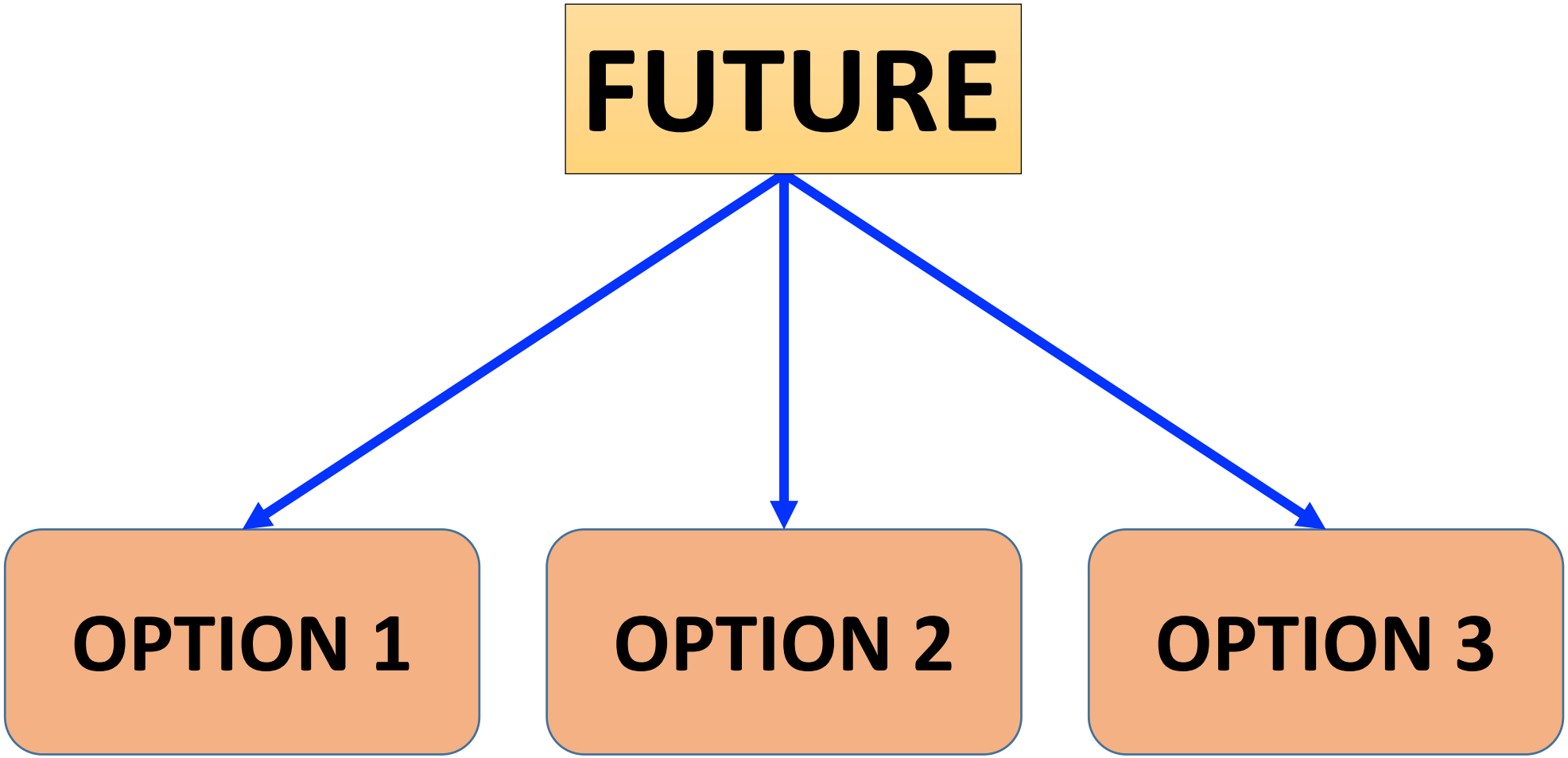
- Fecal transplant from obese mice into germ free mice fed varying diets
- Increased total fat and lean body mass and obesity related metabolic consequences were transferable



Ridaura et al. Science. 2013 Sep 6;341(6150):1241214.

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

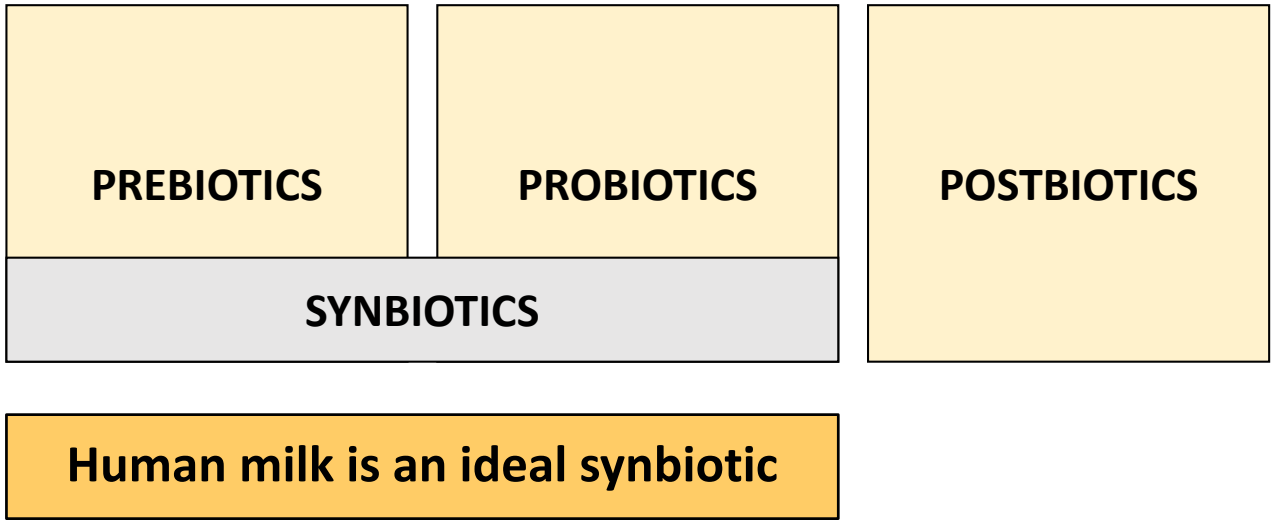
- Several prebiotics have been brought out for term infant feeding (not preterm, yet)
- Prebiotics or combination of prebiotics can be chemically synthesized or isolated from donor human milk

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

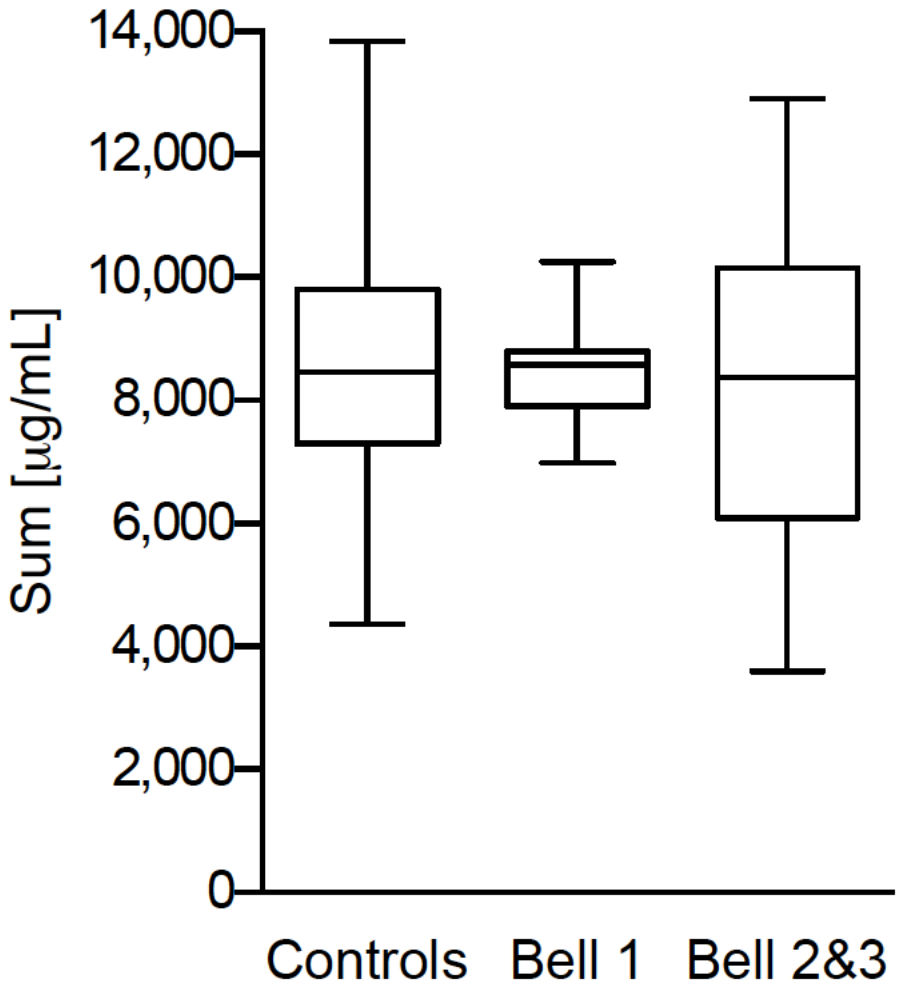


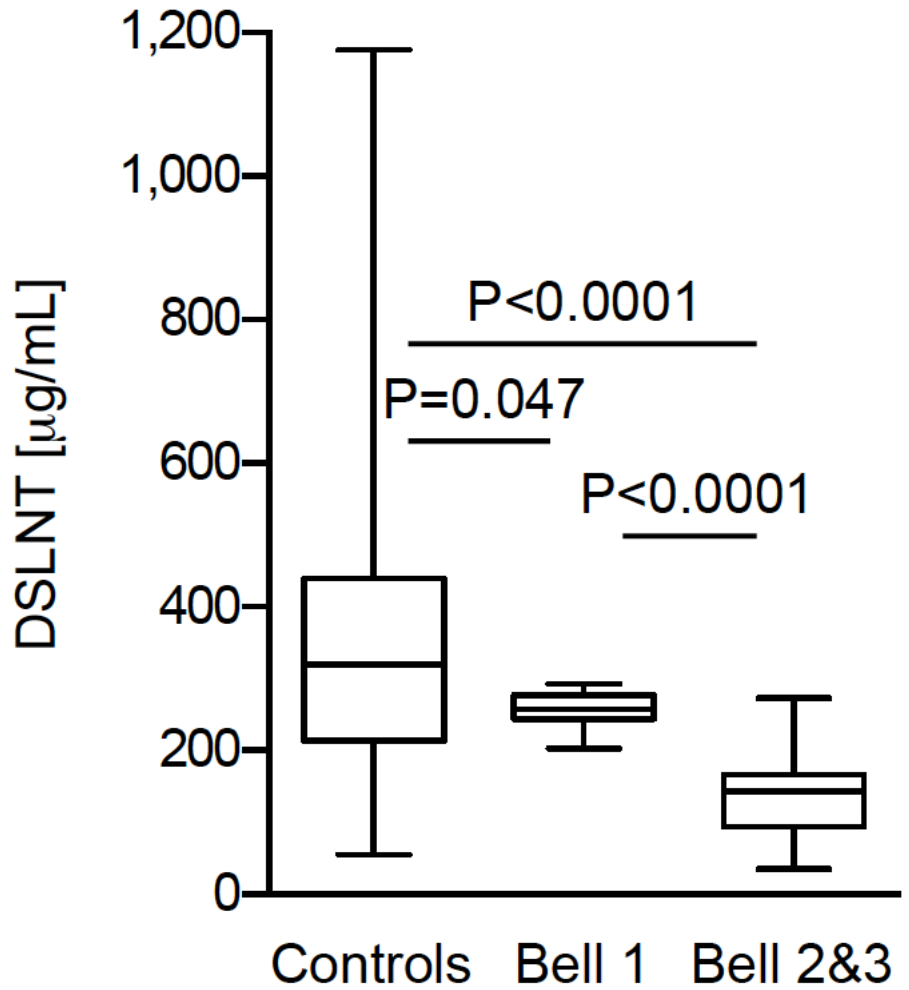
Human milk oligosaccharide composition predicts risk of necrotizing enterocolitis in preterm infants

- 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

Autran et al. Gut. 2018 Jun;67(6):1064-1070. PMID: 28381523.

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





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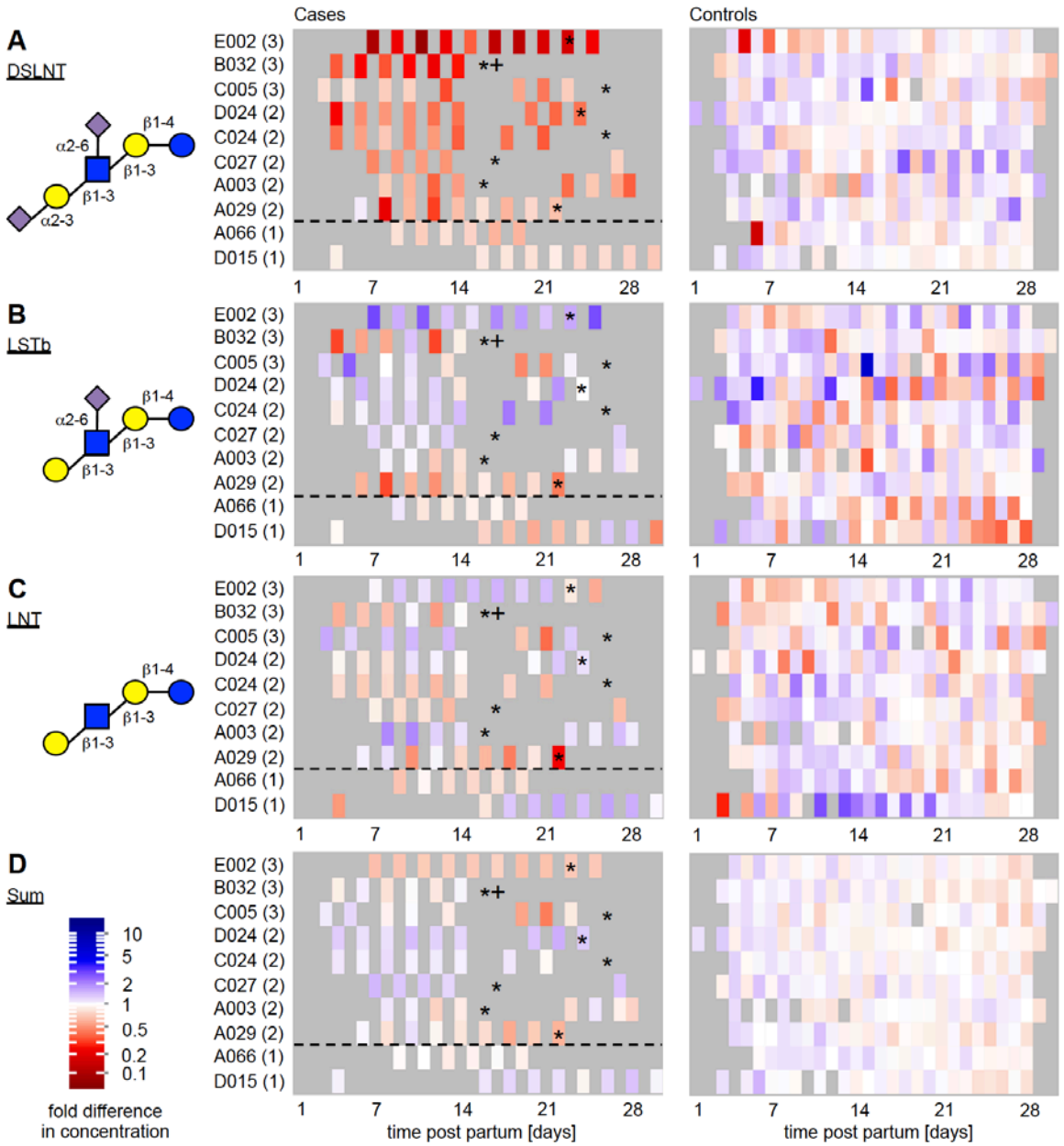

DSLNT content in breast milk is a potential non-invasive marker to identify infants at risk of developing NEC and screen high-risk donor milk.

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

Autran et al. Gut. 2018 Jun;67(6):1064-1070. PMID: 28381523.

SPECTRUM OF IMPLEMENTATION

CONSERVATIVE	LIBERAL
Need FDA approved product	Safe if use high quality manufactured probiotics
Not enough data	Enough evidence to start use
Long term safety	Waiting is unethical
Contamination or misidentity	More data can be acquired after implementation
Lack of efficacy in smallest subgroup	
Confounding factors need to better understood	
Willing to wait for more data	

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

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

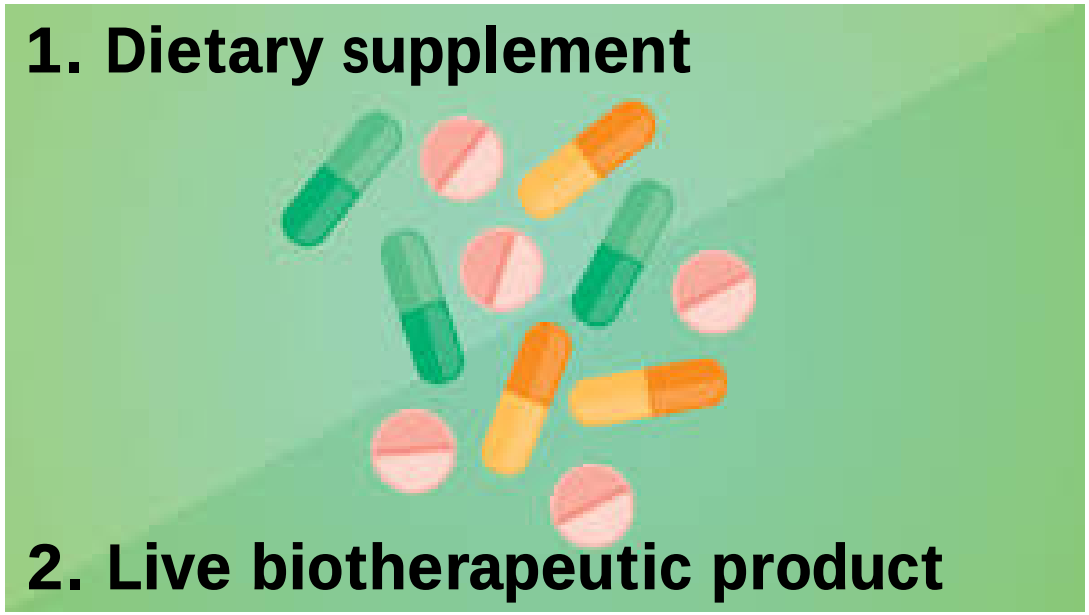
This webinar is intended to be educational in nature only and does not intend to provide regulatory guidance.

Overview

- The regulation of probiotics is complex

Overview

- Since 2016, the US Food and Drug Administration's regulatory oversight over probiotics falls into two separate categories:



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.

www.fda.gov (2016, 2018)

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

https://nccih.nih.gov/health/probiotics/introduction.htm

www.inspection.gc.ca/

https://www.asa.org.uk/advice-online/food-probiotic-claims.html

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Probiotics and NEC:
Is Informed Consent Legally Necessary?

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

May 6, 2019

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

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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?

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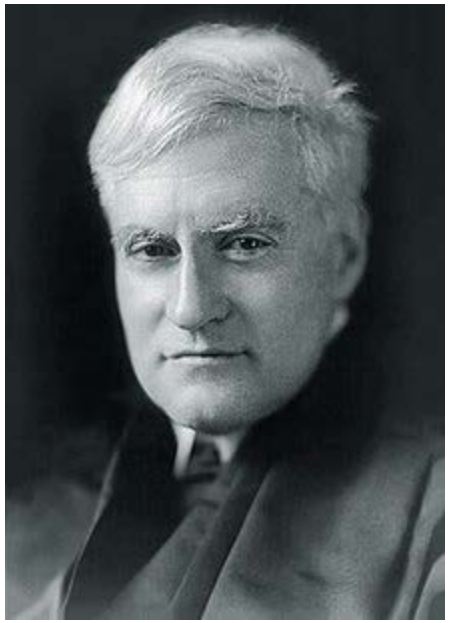
INFORMED CONSENT: CIVIL LAW



"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.)

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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.*

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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.

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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?

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

- SURGERY
- BLOOD TRANSFUSIONS
- PHARMACEUTICALS
- *NUTRIONAL SUPPLEMENTS*
  - *Probiotics*

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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."

-- *Hanes v. Solgar, Inc.,* 2017 WL 1238417, at *8 (Conn.Super., 2017)

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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."

-- *Hanes v. Solgar, Inc.,* 2017 WL 1238417, at *8 (Conn.Super., 2017)

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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?

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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

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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?

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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.

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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.

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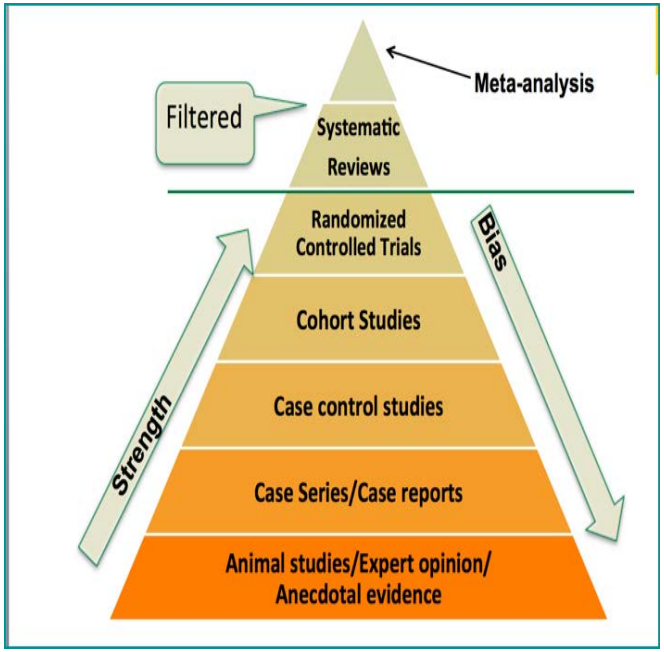
A "FAILURE TO PROVIDE INFORMED CONSENT" CLAIM:

Key *Medical* Question:

Are there any known, material, risks of using probiotics to prevent NEC?



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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?

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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.

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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?

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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?

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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

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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?

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INFORMED CONSENT

- Is it ethical?
- Is it medically required or necessary?
- Is it medically acceptable/appropriate?
- Does you institution have a policy?
- Is it practical?
- Is it legal? -- *YES*
- Is it legally required? -- ???

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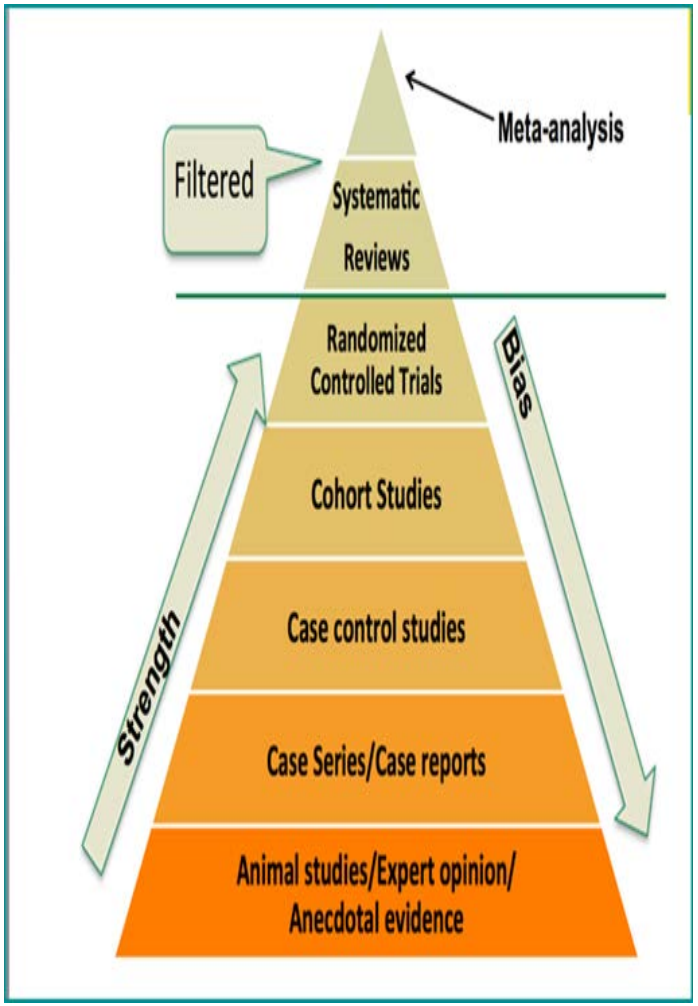
INFORMED CONSENT: Is it legally required?



- 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?

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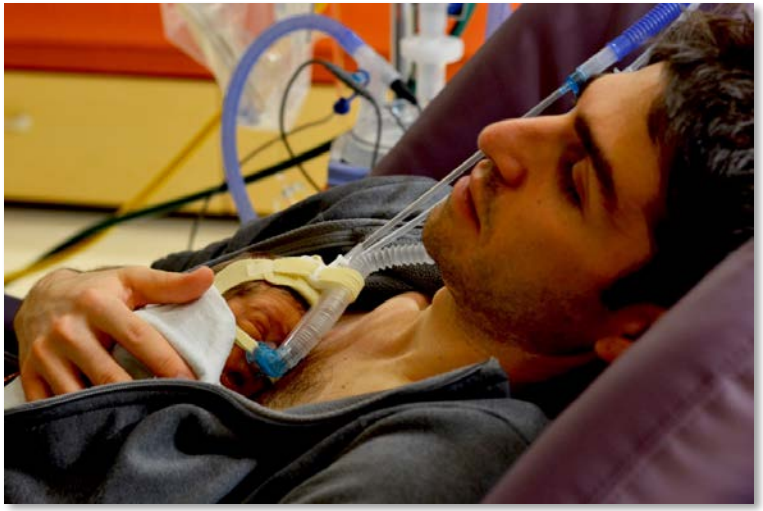
Questions?

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

May 6, 2019

Strategies to Empower and Inform Families on Probiotics



NEC SOCIETY
Building a World Without NEC

NEC SOCIETY

Micah before he developed NEC

NEC SOCIETY

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

NEC SOCIETY

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

NEC SOCIETY

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.

NEC SOCIETY

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

NEC SOCIETY

NEC SOCIETY

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


NEC SOCIETY

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 …

http://bit.ly/2019probioticwebinareval