The Identification and Prevention of Necrotizing Enterocolitis

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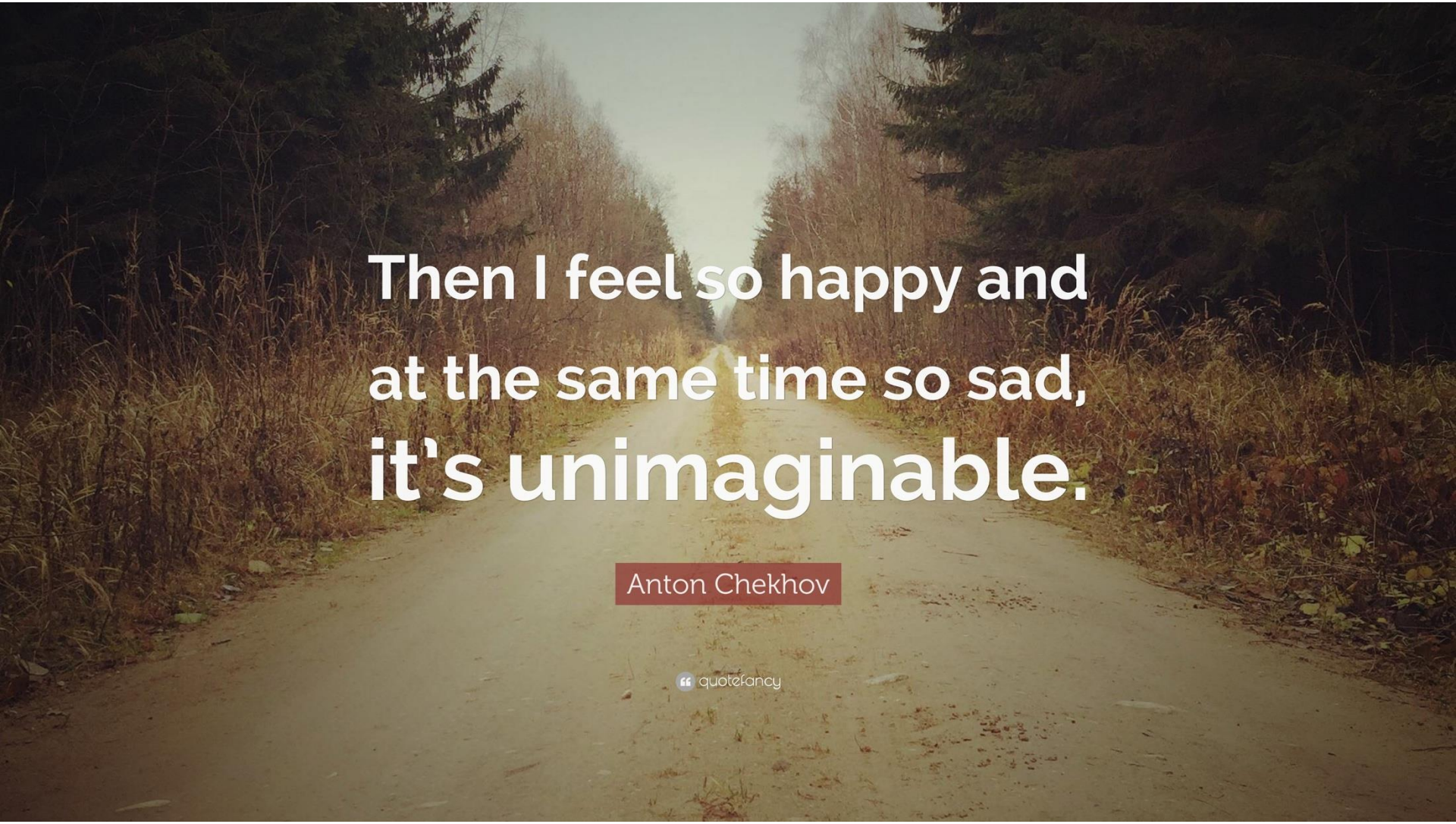
NEO THE CONFERENCE FOR NEONATOLOGY
pediatrix

Disclosure

Dr. Neu has disclosed the following financial relationships. Any real or apparent conflicts of interest related to the content of this presentation have been resolved.

Affiliation / Financial Interest	Organization
Global Scientific Council	Nestle Nutrition Institute
Scientific Advisory Board	Astarte
Scientific Advisory Board	Medela
Research Grant	Infant Bacterial Therapeutics
Speakers Bureau	Mead Johnson
Expert Witness	Abbott Laboratories
Expert Witness	Winston & Strawn LLP

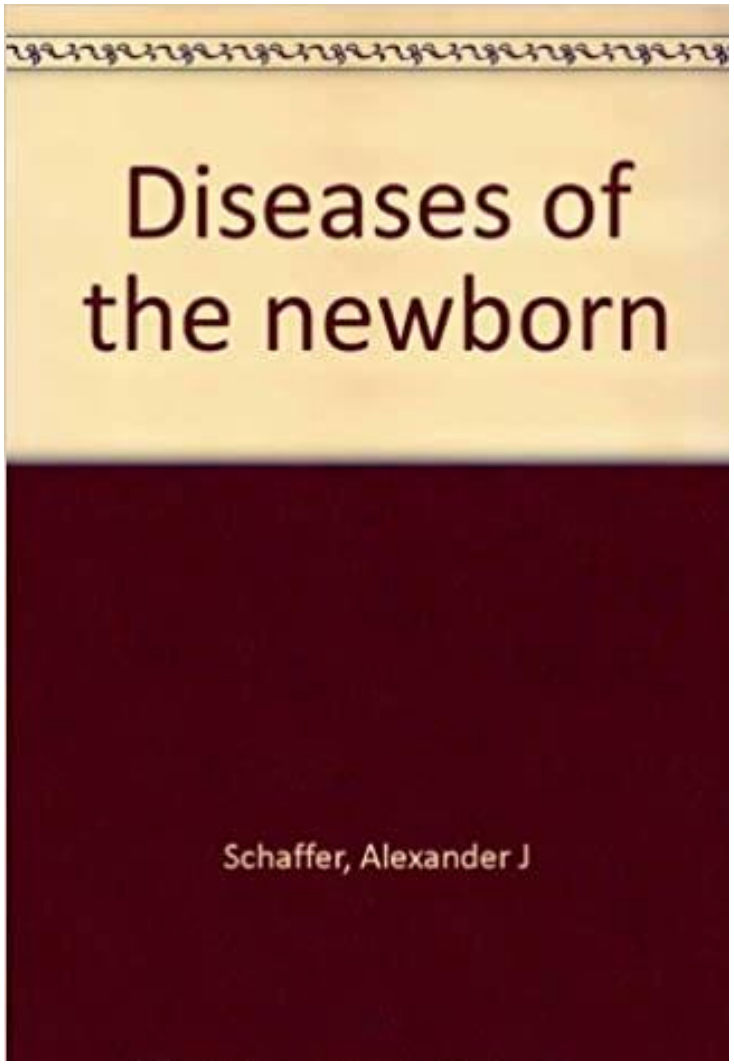

Then I feel so happy and
at the same time so sad,
it's unimaginable.
Anton Chekhov
quotefancy

NIH report recommends strategies for advancing research on necrotizing enterocolitis

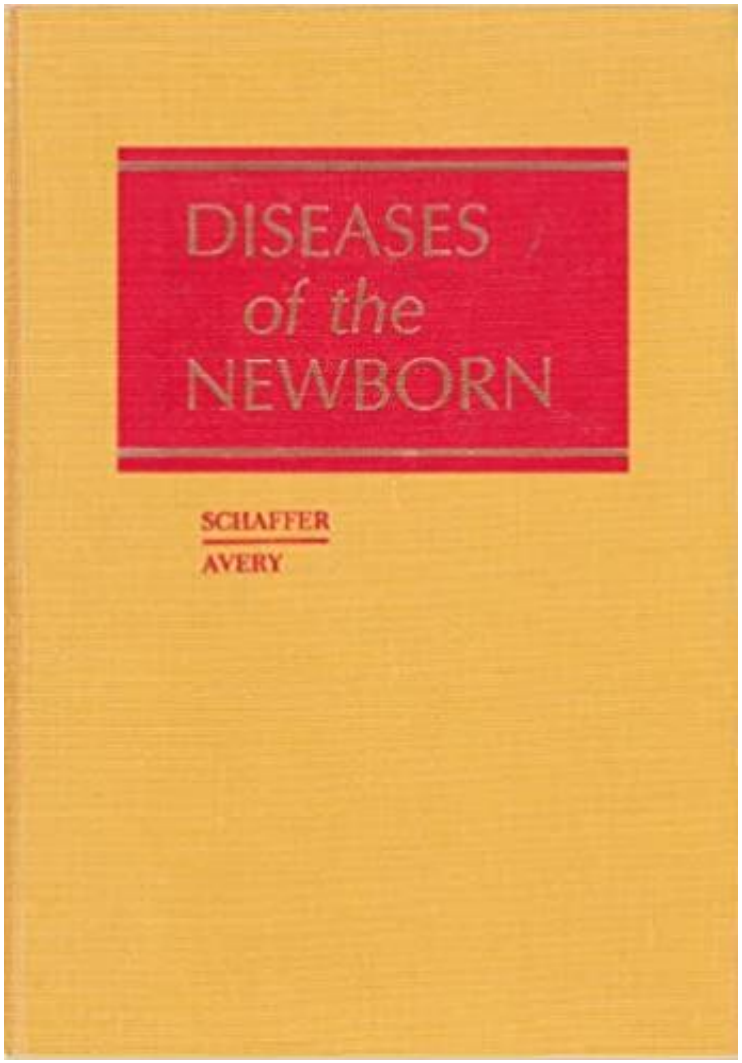
Thursday, September 19, 2024

Quiz

1. Please define neonatal necrotizing enterocolitis.
2. Is necrotizing enterocolitis a distinct disease?
3. Do babies with Bell's Stage 1 or 2 "NEC" have intestinal necrosis?
4. Do we have a clear understanding of the pathophysiology of "NEC"?
5. Do we have accurate biomarkers for NEC?
6. Are there clearly effective preventative strategies?
7. Should we start over again and redefine intestinal injuries and feeding dysfunctions we are calling "NEC"?

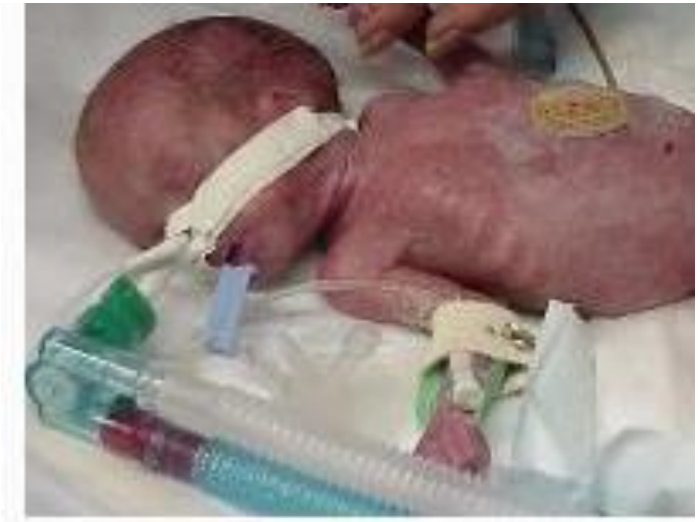

Diseases of the newborn
Schaffer, Alexander J

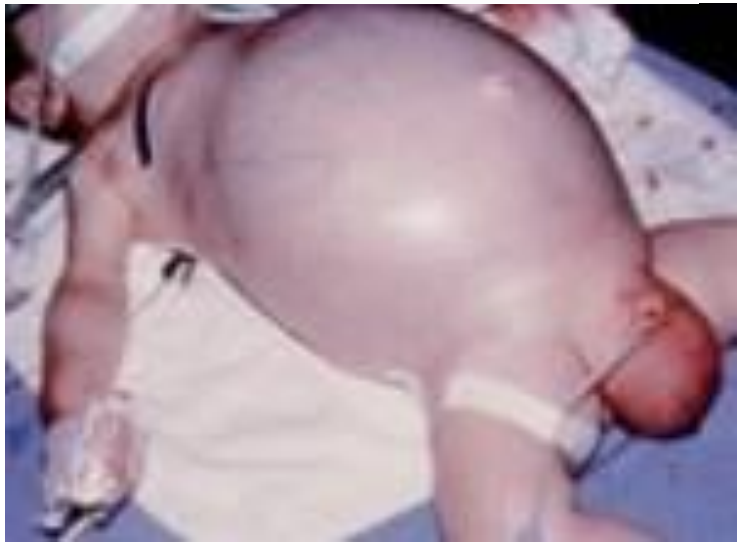
1965


DISEASES of the NEWBORN
SCHAFFER
AVERY

1971

Historical Perspective: Being led astray: 60 years---not much progress





- Lumping of several diseases called "NEC" into the same data set.
- Animal models do not correctly represent what we see in human preterms.
- Narrow focus on individual pathways rather than systems.

“NEC”

Pediatr Res. 2020 August ; 88(Suppl 1): 10–15. doi:10.1038/s41390-020-1074-4.

Defining Necrotizing Enterocolitis: Current Difficulties and Future Opportunities

Ravi Mangal Patel, MD, MSc[1], Joanne Ferguson, BSc[2], Steven J. McElroy, MD[3], Minesh Khashu, MBBS, FRCPCH, MD[4,5], Michael S. Caplan, MD[6]

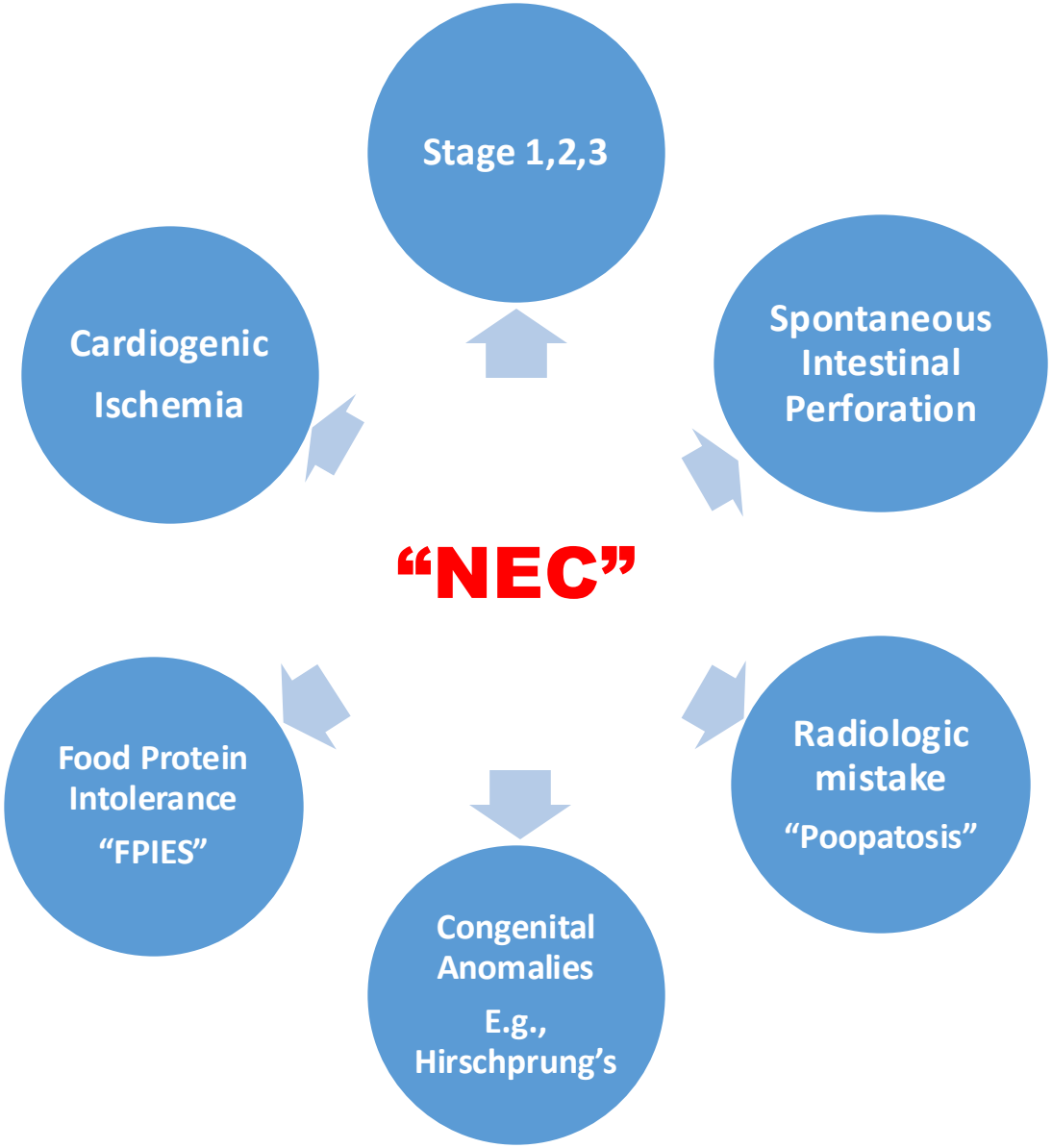
[1]Department of Pediatrics, Emory University School of Medicine and Children's Healthcare of Atlanta, Atlanta, GA, USA. [2]Special Interest Group in Necrotizing Enterocolitis (SIGNEC), Belfast, Northern Ireland. [3]Stead Family Department of Pediatrics, Department of Microbiology and Immunology, University of Iowa, Iowa City, IA, USA [4]Poole Hospital NHS Foundation Trust, Poole, Dorset, U.K. [5]SIGNEC, Poole, Dorset, U.K. [6]Department of Pediatrics, NorthShore University Health System, Evanston, IL, USA

Abstract

Necrotizing enterocolitis (NEC) is a leading cause of morbidity and mortality in hospitalized infants. First classified through Bell staging in 1978, a number of additional definitions of NEC have been proposed in the subsequent decades. In this review, we summarize 8 current definitions of NEC, and explore similarities and differences in clinical signs and radiographic features included within these definitions, as well as their limitations. We highlight the importance of a global consensus on defining NEC to improve NEC research and outcomes, incorporating input from participants at an international NEC conference. We also highlight the important role of patient-families in helping to redefine NEC.

Defining a disease or condition has important implications. Meeting a set of criteria for a

What do we call "NEC"



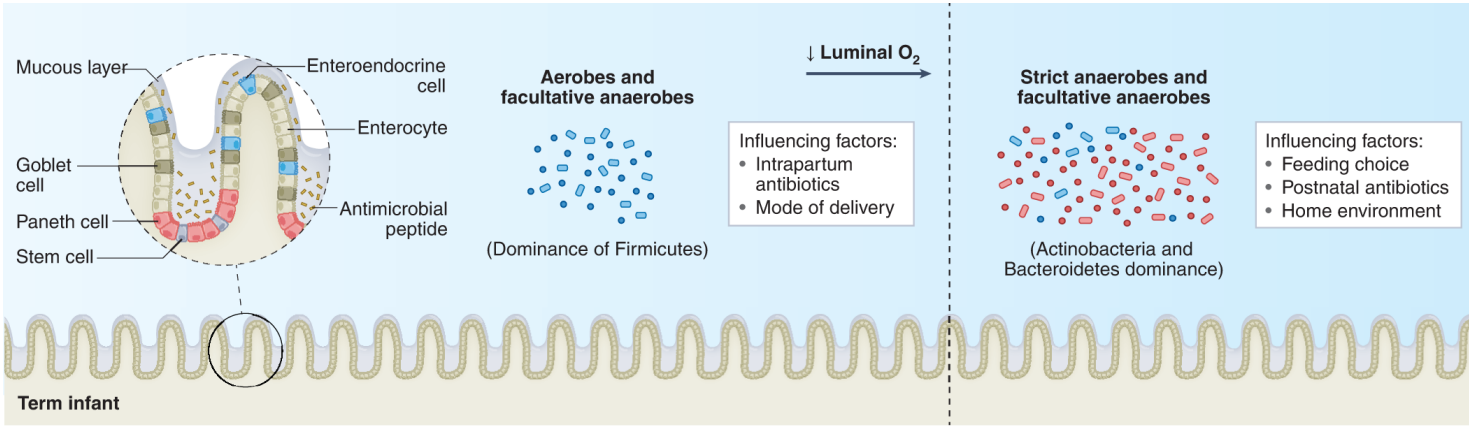
NEC Pathophysiology

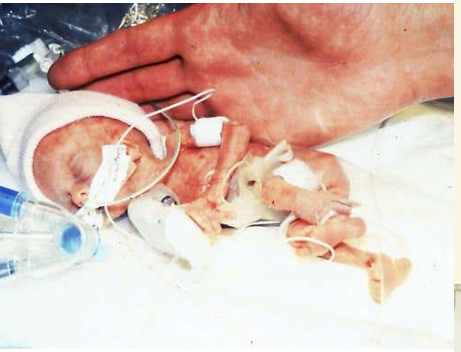
Warning: We are talking about current concepts of pathophysiology, diagnosis and treatment. If we don't have a good definition and if what we are calling "NEC" is several different entities, then how can we trust our current data sets, basic and clinical studies?

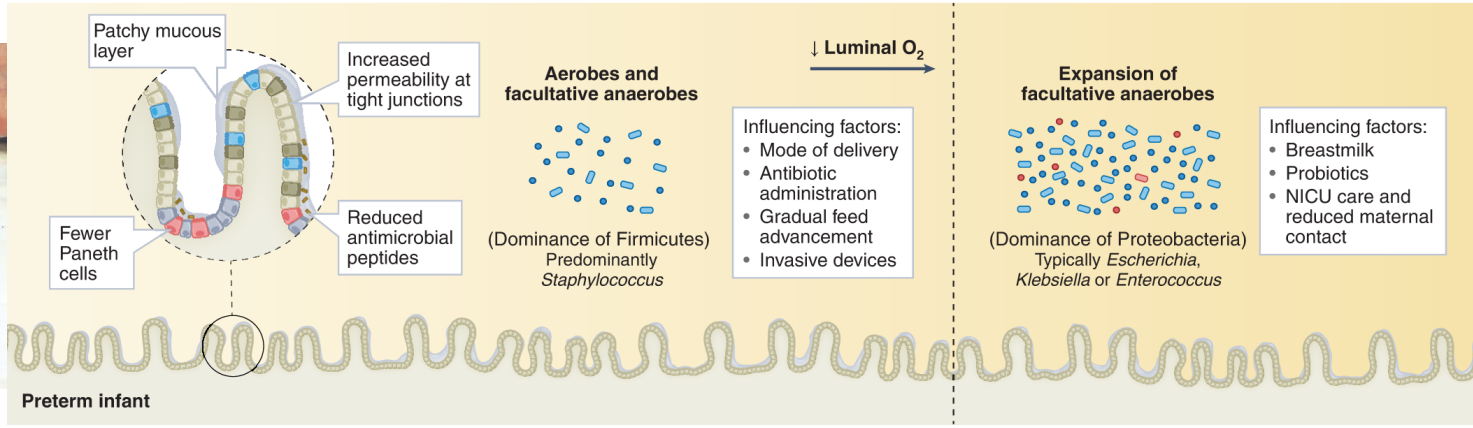
Disclaimer: The following part of this presentation about pathophysiology will discuss our current understanding and will hopefully be refined soon.

Rat model of "NEC".

Preterm vs. Term Intestine

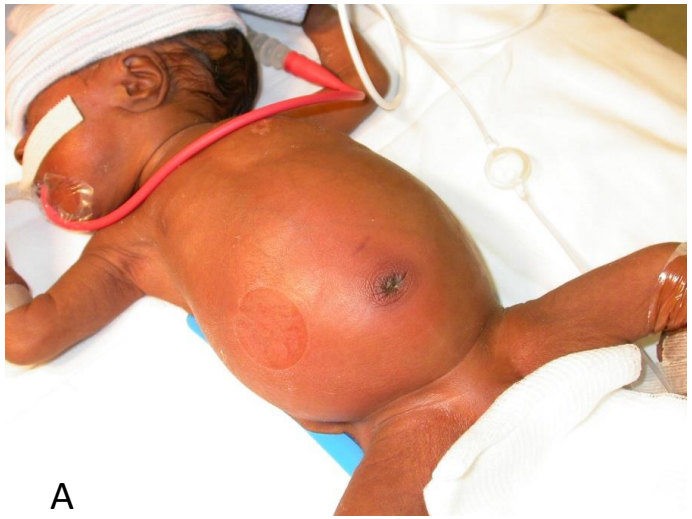


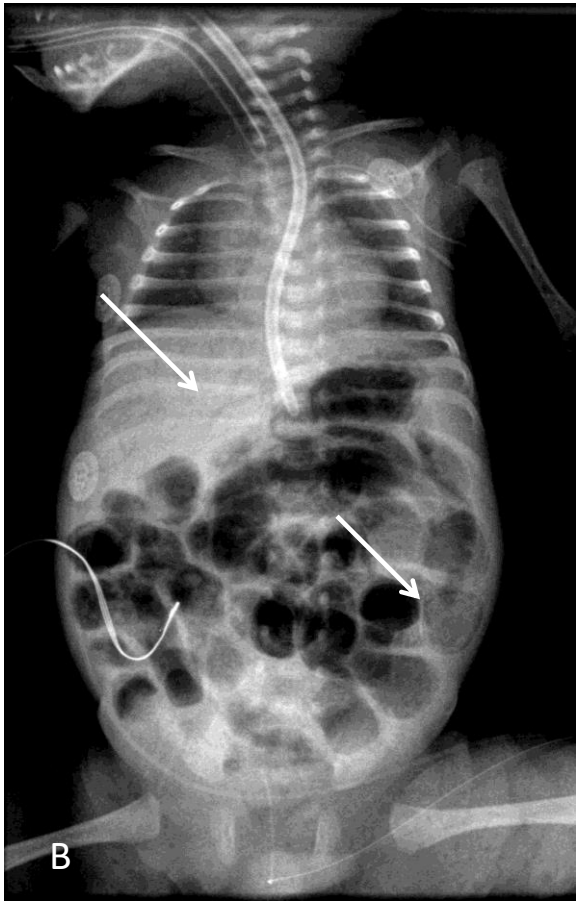


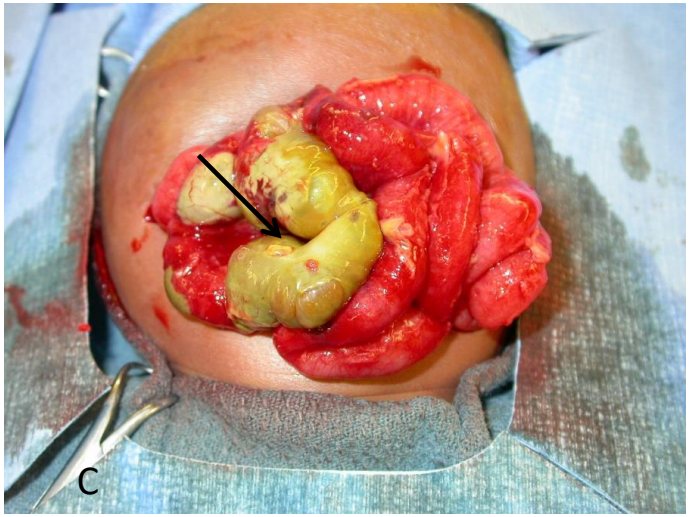


Healy, DB. Et al, Nature Microbiology, 2022

“Classic” NEC

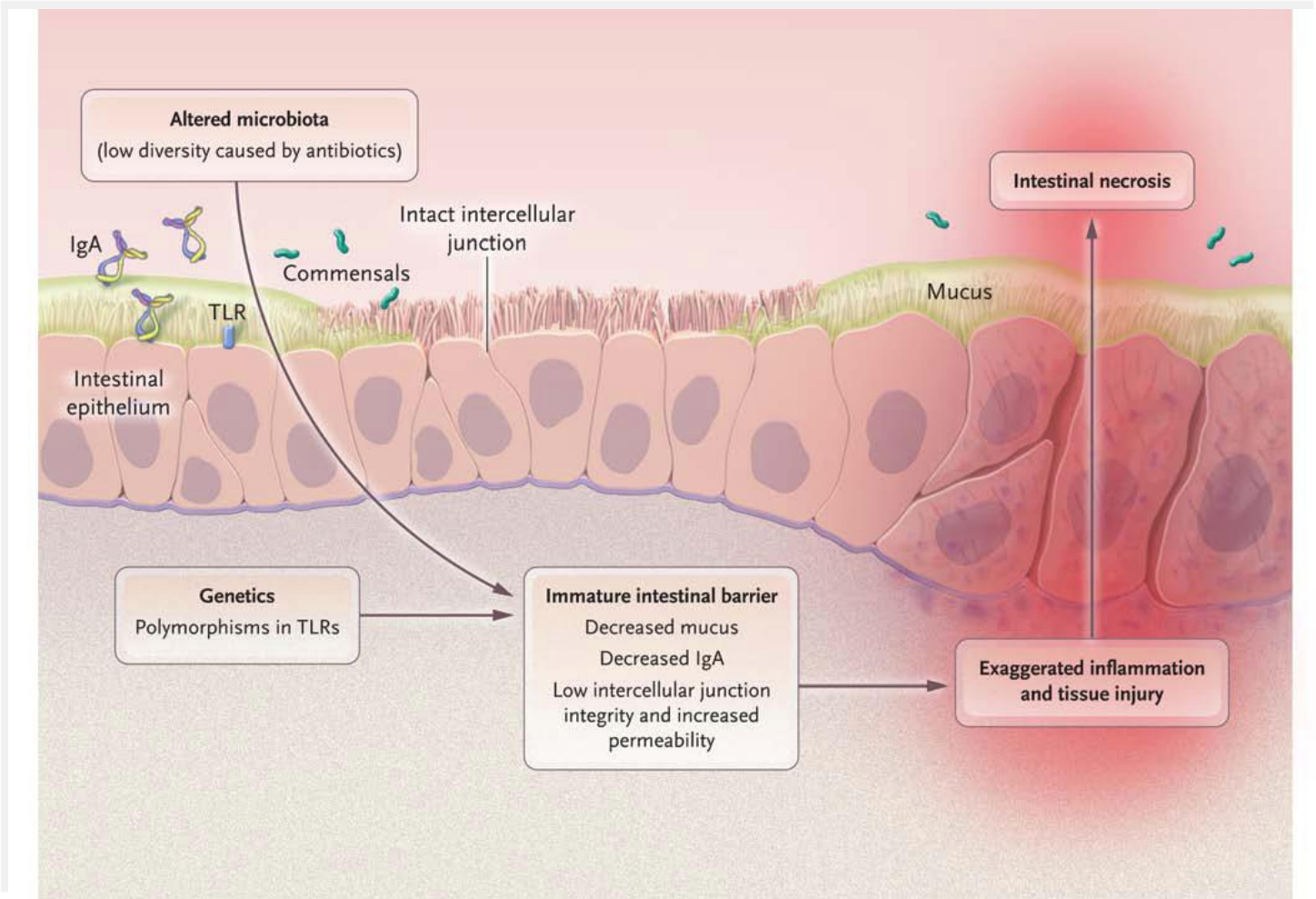






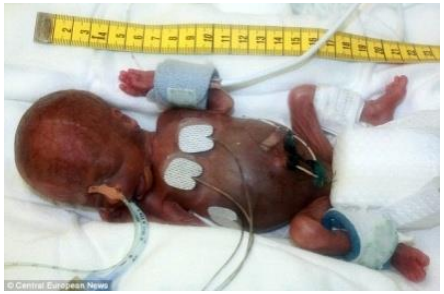
Neu, J. and Walker , W. A. New England Journal of Medicine, Jan. 2011

Pathophysiologic Overview at the Barrier: A Perfect Storm



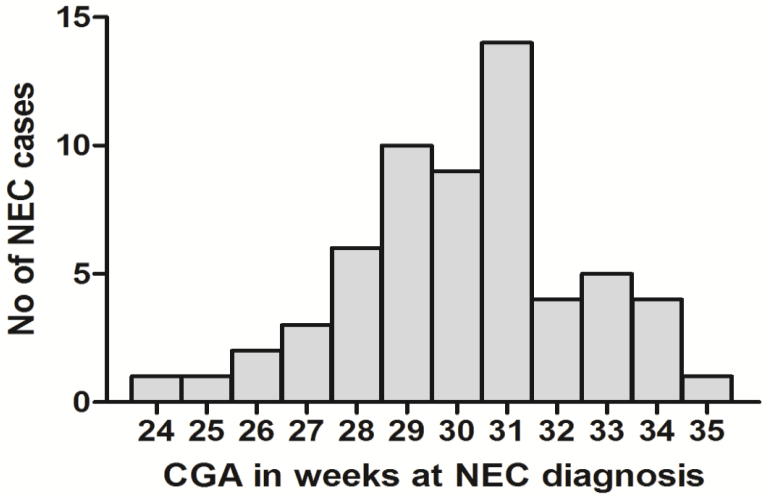
Neu, J. , Walker, WA. NEJM, 2011

Mean Corrected Gestational Age at NEC Diagnosis



23 week preterm

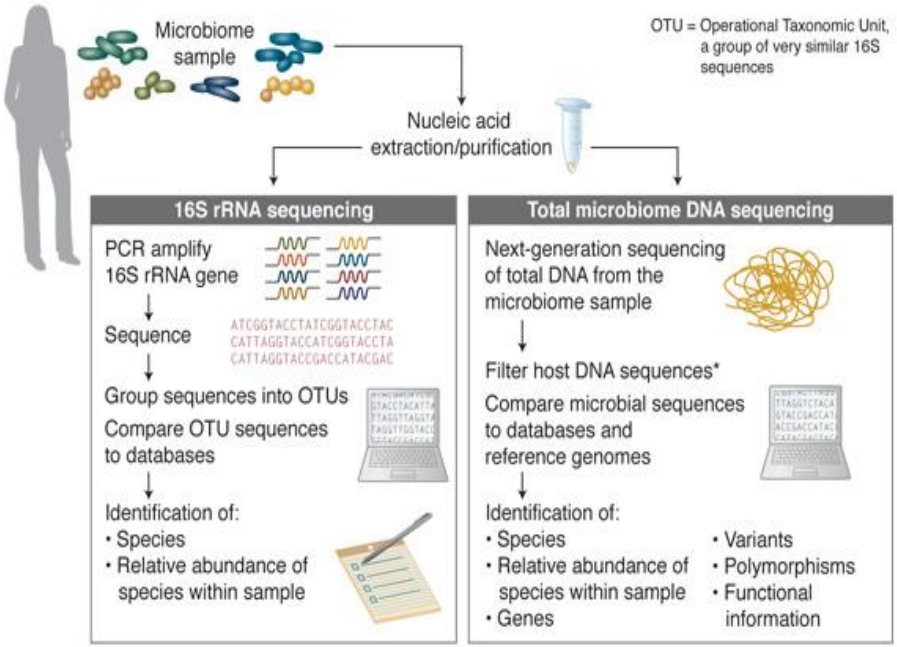
29 week preterm



Pammi, M. et al. Microbiome, 2017

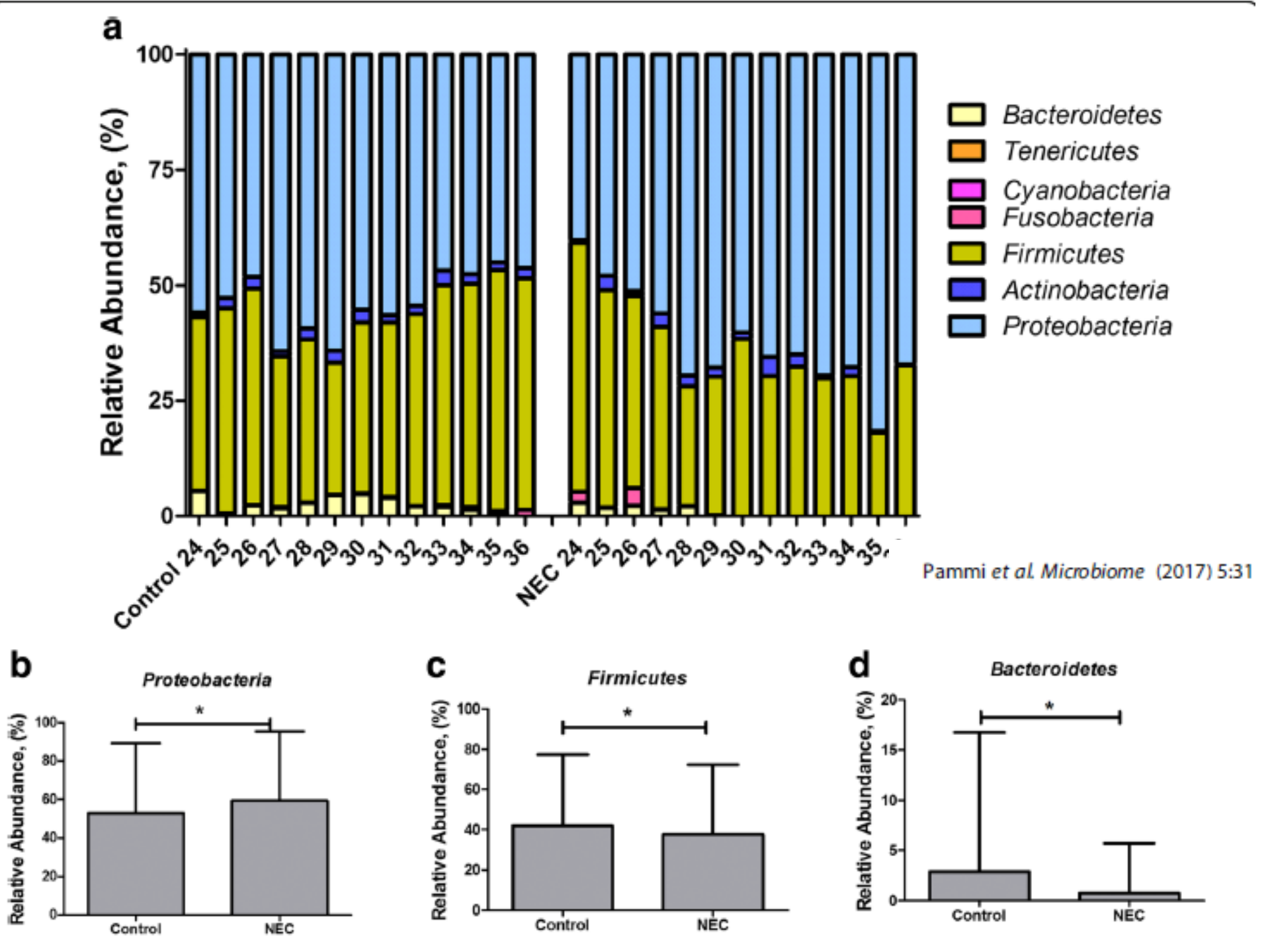
Major Microbiome Sequencing Technologies

Who's There?



What are they doing?

Adapted from : https://www.neb.com/tools-and-resources/feature-articles/addressing-challenges-in-microbiome-dna-analysis


a
Relative Abundance, (%)
100
75
50
25
0
Control 24 25 26 27 28 29 30 31 32 33 34 35 36
NEC 24 25 26 27 28 29 30 31 32 33 34 35
Bacteroidetes
Tenericutes
Cyanobacteria
Fusobacteria
Firmicutes
Actinobacteria
Proteobacteria
Pammi et al. Microbiome (2017) 5:31
b
Proteobacteria
Relative Abundance, (%)
Control
NEC
c
Firmicutes
Relative Abundance, (%)
Control
NEC
d
Bacteroidetes
Relative Abundance, (%)
Control
NEC

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journal homepage: www.elsevier.com/locate/siny

Necrotizing enterocolitis comes in different forms: Historical perspectives and defining the disease

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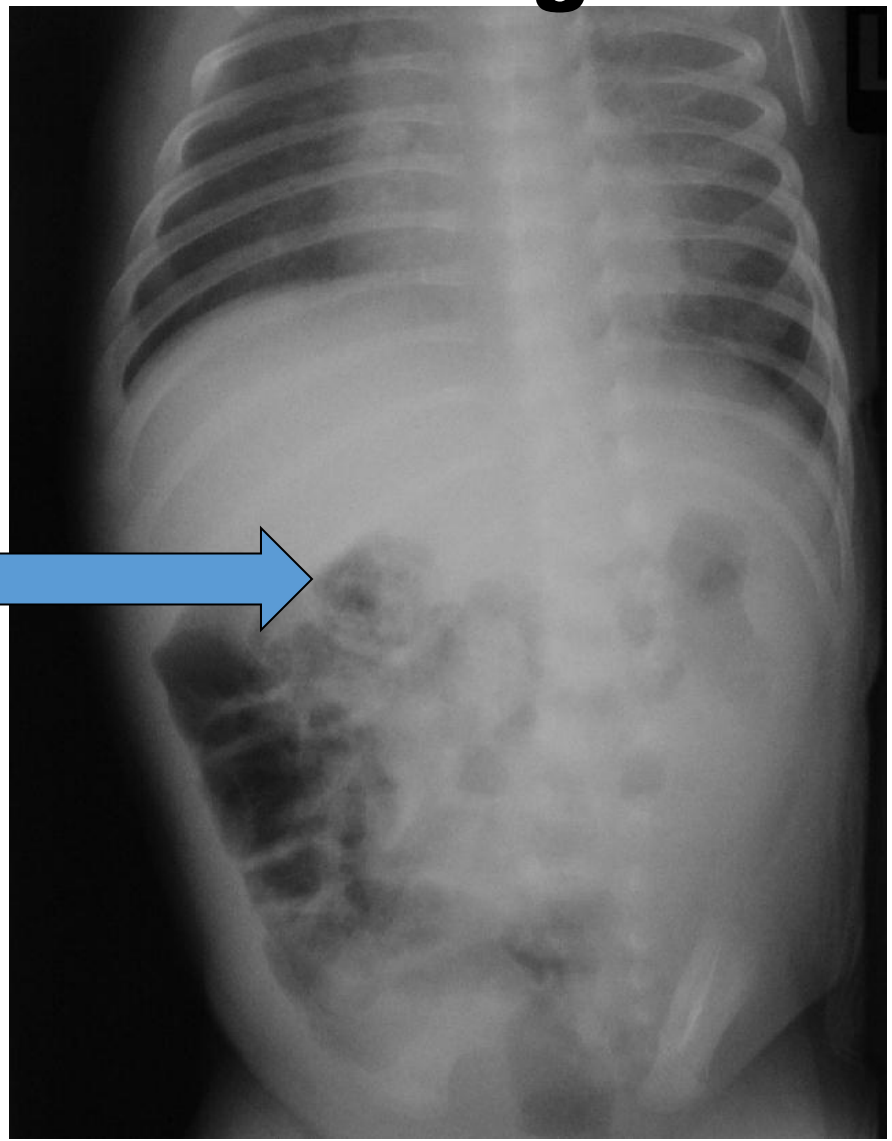
ABSTRACT

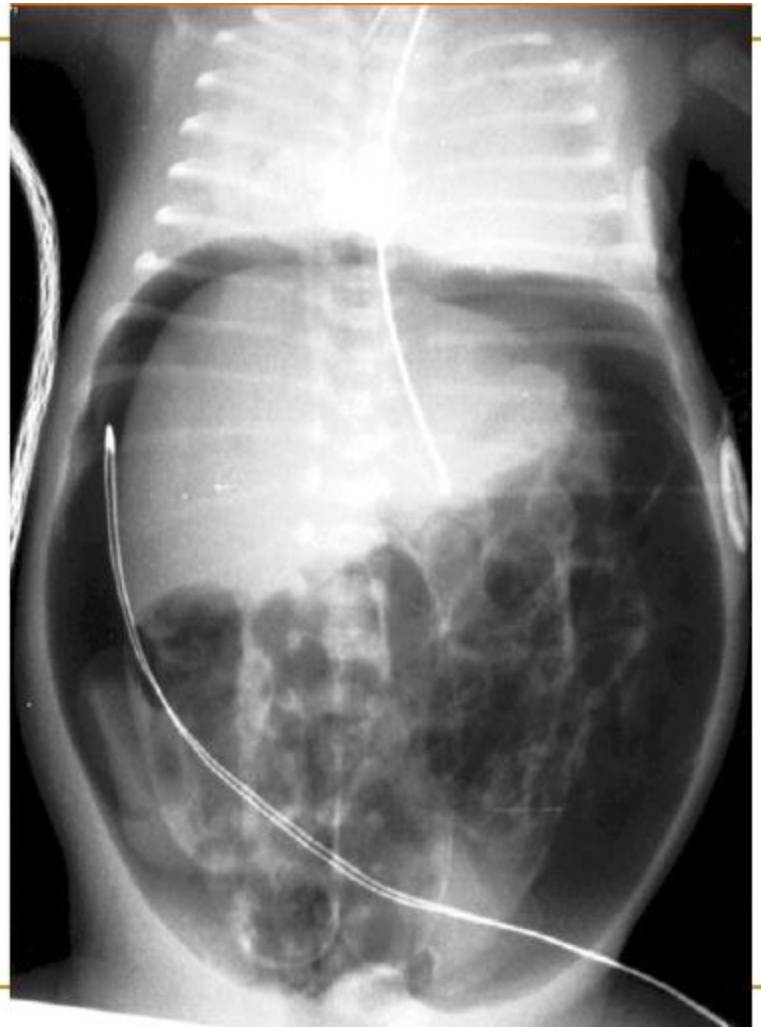
The specific cause of what is commonly referred to as necrotizing enterocolitis (NEC) disease has been elusive largely because it is becoming clear that this entity represents more than one disease with multifactorial pathogenic mechanisms. Furthermore, finding clear and consistent diagnostic biomarkers will be difficult until the different subsets of what we are calling this disease are better delineated. In this introductory chapter, we discuss different disease entities that are frequently termed "NEC" in the newborn infant. We hope this will set the stage for more focused research and development of preventative measures for at least the most common forms of this disease.

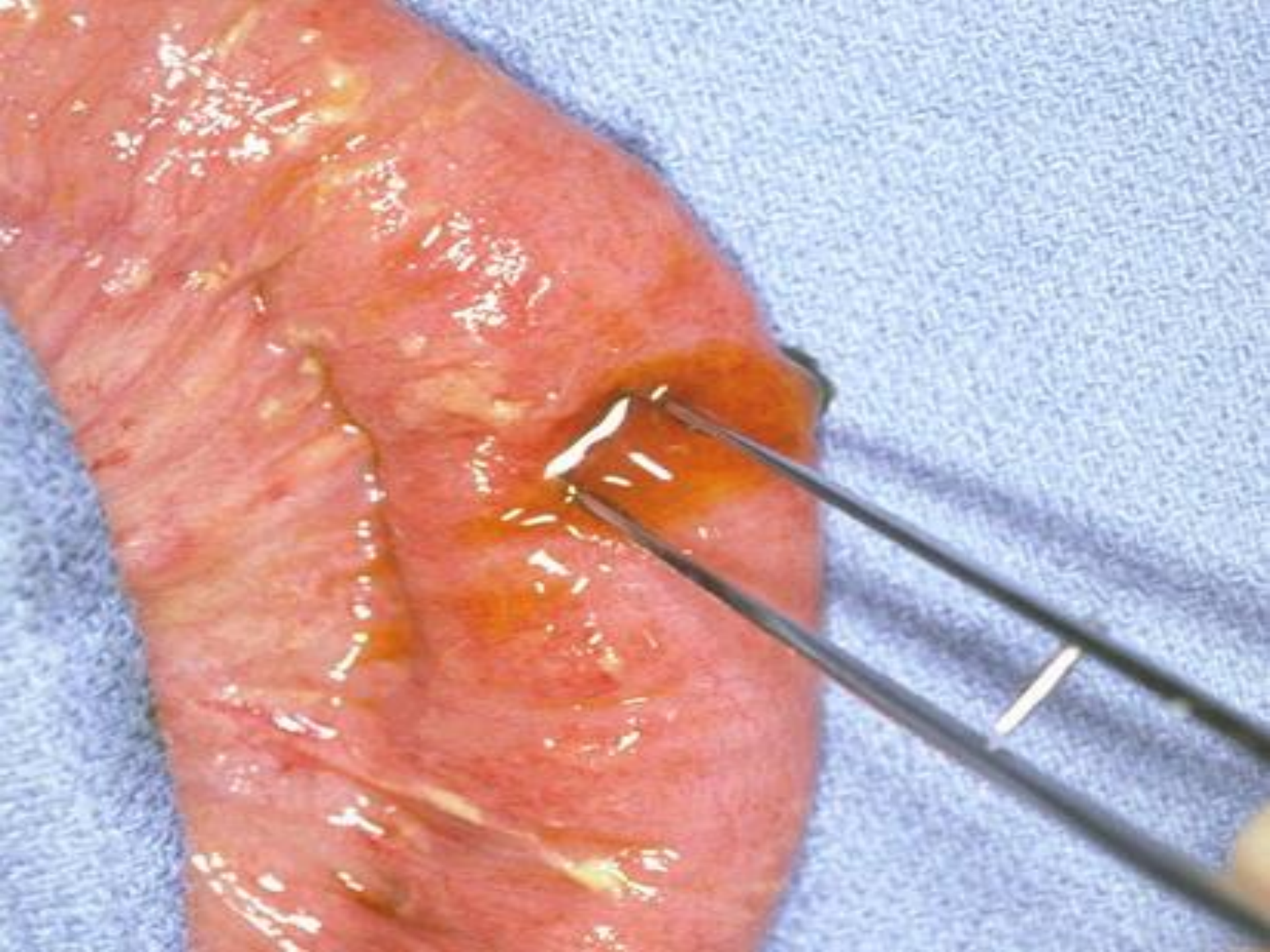
Diagnostic Challenges: Status of Data Bases

29-week Gestation Preterm: Abdomen Soft, baby taking NG feeds well but Incidental Finding on Radiograph



25 week Preterm, 5 days old, breast milk, on hydrocortisone for “hypotension”---distended abdomen.





Is there a Clear Definition of NEC? Bells is Broken

- Stage 1-Too non-specific and the term should not be used.
- Stage 2-Radiographic signs can be “fuzzy”.
- Stage 3- Free air on radiograph could signify intestinal necrosis or Spontaneous Intestinal Perforation (SIP)


When studies find an
ASSOCIATION
between two things
≠
it does not mean one thing
CAUSED
the other one to happen.

VIEWPOINT

When Biological Causality Is Determined in a Court of Law

Josef Neu, MD; Neena Modi, MD

There are currently thousands of lawsuits being litigated in the US against physicians, nurses, hospitals, and industry related to 2 recent court rulings that formula causes necrotizing enterocolitis (NEC) in preterm infants. These are symptomatic of a much larger issue that involves courts conflating association with causation, other examples of which are lawsuits relating to claims that agents such as talc cause certain cancers and acetaminophen taken during pregnancy causes autism in offspring. The legal process also places enormous value on the views of individuals, although medicine has long eschewed this in favor of systematic reviews of peer-reviewed evidence and statistical analyses that incorporate formal measures of probability. A current cause célèbre is the growing tide of criticism against legal acceptance of "expert" opinion, and flawed interpretation of data, that was instrumental in the conviction of a neonatal nurse, Lucy Letby, for the murder of 7 infants.[1] Targets for litigation are easy to find as associations abound. NEC litigation has been encouraged through advertising by solicitors to distraught parents, persuading them that a specific action, the feeding of formula, was the cause of their infant's intestinal problems. Medicine and the law preside over life-changing decisions: surely an understanding of scientific method for determining causality, and ethical standards of behavior, should be an essential requirement for both?

In this Viewpoint, we discuss the (1) lack of a clear definition and human donor milk is also protective. However, a whole-population 2-year surveillance study in England and Wales showed that 50% of infants developing NEC resulting in surgery and/or death had received only human milk feeds before onset.[3]

Clinical trial evidence to date is inconclusive. A Cochrane Library systematic review identified 9 small randomized clinical trials (RCTs) that compared donor milk and formula as either sole diet or supplement to an infant's own mother's milk and included NEC as an outcome.[4] Meta-analysis in which the comparison combined trials of sole and supplementary diets shows higher risk with formula (relative risk, 1.87; 95% CI, 1.23-2.85). However, the Cochrane reviewers sound several notes of caution. The majority of the RCTs took place in the 1970s and 1980s, when the patient population differed substantially from that of today; sample sizes were inadequate, methodological quality was poor, and no differences were shown in key outcomes such as mortality and sepsis that would be important corroboration of benefit.

Patient Safely Considerations

Infants are harmed when their own mother's milk is unavailable. Mothers of very preterm infants who want to breastfeed must express milk for many weeks because the developmental maturity to suckle is only reached at around 32 to 34 weeks' gestation. This

Neu, J. Modi N., JAMA Pediatrics Dec. 2024

The term “NEC” has been misused for decades!!

Why should we say “necrosis” when the evidence in most cases is lacking?

Preventative Strategies

Routine Use of Probiotics for Prevention of “NEC”

Meta-Analysis -NEC

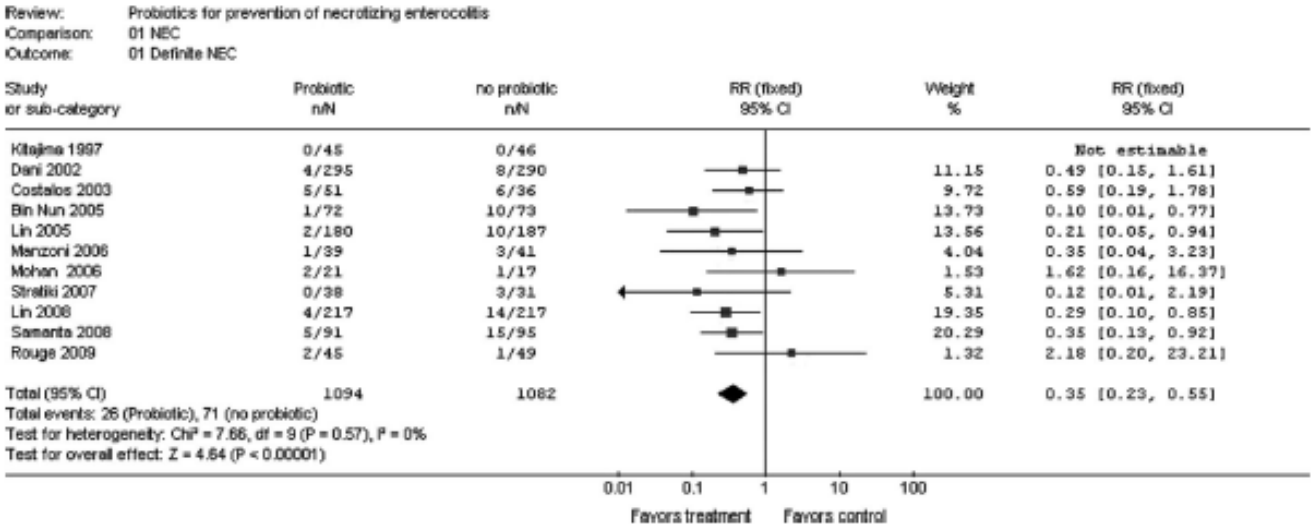


FIGURE 2
Effect of probiotics on NEC.

Deshpande, G. Pediatrics, 2010

Cochrane Review of 60 trials with 11,156 infants: July 26, 2023

Authors' conclusions:
Given the low to moderate certainty of evidence for the effects of probiotic supplements on the risk of NEC and associated morbidity and mortality for very preterm or VLBW infants, and particularly for extremely preterm or ELBW infants, there is a need for further large, high-quality trials to provide evidence of sufficient validity and applicability to inform policy and practice.

CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

Use of Probiotics in Preterm Infants

Brenda Poindexter, MD, MS, FAAP; COMMITTEE ON FETUS AND NEWBORN

Probiotic products in the United States are available for use in the general category of dietary supplements, bypassing the rigor of the US Food and Drug Administration (FDA) approval process in safety, efficacy, and manufacturing standards. As a result, currently available probiotics lack FDA-approved drug labeling and cannot be marketed to treat or prevent disease in preterm infants, including necrotizing enterocolitis and late-onset sepsis. Despite lack of availability of a pharmaceutical-grade product, the number of preterm infants receiving probiotics in the United States and Canada is steadily increasing. According to recent reports from large collaborative databases in the United States, approximately 10% of extremely low gestational age neonates receive a probiotic preparation during their stay in the NICU, with wide variation in practice among units. In sum, more than 10 000 preterm infants have been enrolled in randomized clinical trials of probiotic supplementation worldwide. Methodologic differences among study protocols included different strains and combinations of therapy, masking of trials, and a priori definitions of the primary outcome measure. Large meta-analyses of these trials have demonstrated the efficacy of multiple-strain probiotics in reducing necrotizing enterocolitis and all-cause mortality, whereas the efficacy of single-strain probiotic preparations is less certain. In the absence of an appropriate medical-grade product in the United States, dietary supplement–grade probiotics, some of which have been the subject of recent recalls for contamination, are being prescribed. Given the lack of FDA-regulated pharmaceutical-grade products in the United States, conflicting data on safety and efficacy, and potential for harm in a highly vulnerable population, current evidence does not support the routine, universal administration of probiotics to preterm infants, particularly those with a birth weight of <1000 g.

abstract

Children's Healthcare of Atlanta and School of Medicine, Emory University, Atlanta, Georgia

Clinical reports from the American Academy of Pediatrics benefit from expertise and resources of liaisons and internal (AAP) and external reviewers. However, clinical reports from the American Academy of Pediatrics may not reflect the views of the liaisons or the organizations or government agencies that they represent.

Dr Poindexter was responsible for conceptualizing, writing, and revising the manuscript and considering input from all reviewers and the board of directors; the author approved of the final manuscript as submitted.

The guidance in this clinical report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

All clinical reports from the American Academy of Pediatrics automatically expire 5 years after publication unless reaffirmed, revised, or retired at or before that time.

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

DOI: https://doi.org/10.1542/peds.2007-0243

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

"Given the lack of FDA-regulated pharmaceutical Grade products in the United States, conflicting data on safety and efficacy,, and potential for harm in a highly vulnerable population, current evidence does not support the routine universal administration of probiotics to preterm infants, particularly with a birthweight of <1000 grams."

What is the difference between a probiotic and a Live Biotherapeutic Product?

Connection Study: Historical Perspective

2012 - Work initiated by IBT (Infant Bacterial Therapeutics). Existing data was unclear with several small trials, meta-analyses.

2013 - Discussions commenced with FDA and European Agency.

2016 - Initiation of Phase 2 trial under IND.

2016- ongoing - Safety concerns about probiotic agents (mucormycosis, sepsis, most recent FDA warning after sepsis and death).

2024 - Enrollment of Phase 3 Connection study completed in summer.

Objectives

Evaluate the first live biotherapeutic product, IBP-9414 vs. sterile water placebo in very low birthweight infants in terms of:

- Safety
- Prevention of NEC (primary endpoint)
- Improved sustained feeding tolerance (primary endpoint)
- Reduction of deaths due to any causes (secondary endpoint)
- Decrease in severity of NEC
- Other prespecified outcomes such as length of hospitalization, growth, other morbidities

2117 Treated Infants

Birth weight 500-1,500 grams (overall median 850 grams)

- 551 infants (26%) with 500-749 grams
- 1351 infants (64%) with 750-1,000 grams
- 215 infants (10%) with 1,001-1,500 grams

Females (50%), Caucasian (58%), Black/African American (27%), cesarean section (77%)

Well balanced groups treated with IBP-9414 and placebo with respect to birth weight, age, sex, geographic region, race, ethnicity, method of delivery etc

Necrotizing Enterocolitis (NEC)

NEC	IBP-9414	Placebo	RR (95% CI)	P
NEC, all mITT	93 (8.7%)	107 (10.2%)	0.86 (0.66 - 1.11)	0.248

1. (mITT) population (defined as infants receiving at least one dose of IBP-9414)

Necrotizing Enterocolitis (NEC)

NEC	IBP-9414	Placebo	RR (95% CI)	P
NEC, all mITT	93 (8.7%)	107 (10.2%)	0.86 (0.66 - 1.11)	0.248
NEC beyond day 14d	59 (5.7%)	79 (7.7%)	0.74 (0.53-1.02)	0.067

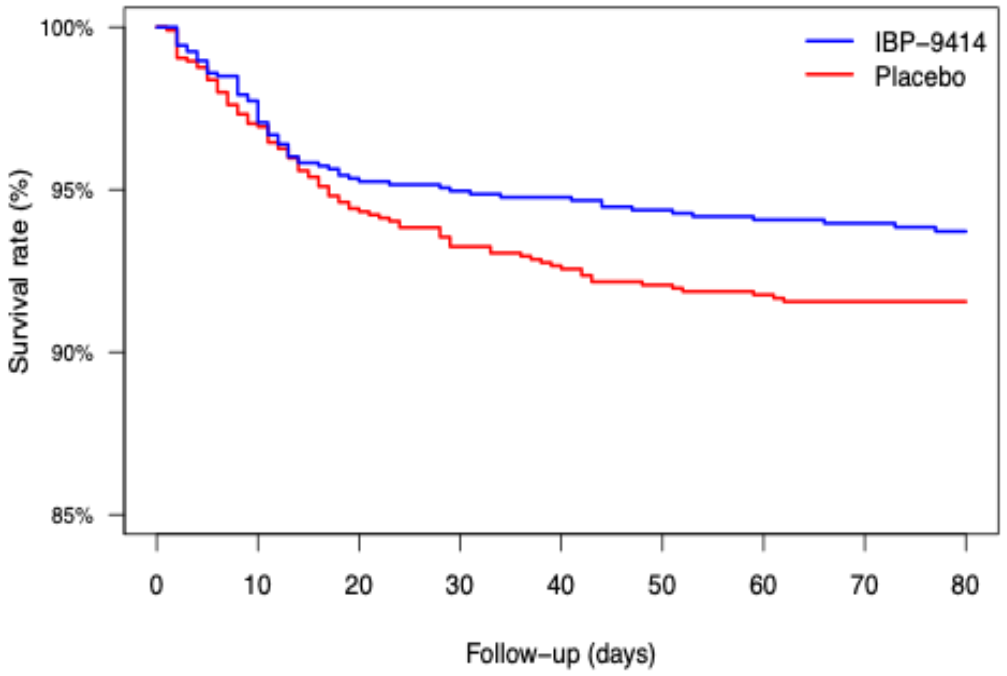
Taking the heterogeneity of the disease, the difficulty in x-ray analysis and time required for the pharmacodynamic effect

NEC by surgery beyond day 14d	3 (0.3%)	10 (1.0%)	0.29 (0.08-1.06)	0.046

1. (mITT) population (defined as infants receiving at least one dose of IBP-9414)

IBP-9414 - Reduction of Mortality

All-cause deaths	IBP-9414	Placebo	RR (95% CI)	p
Deaths mITT	66 (6.2%)	89 (8.5%)	0.73 (0.54 - 0.98)	0.036
Deaths, beyond 14d	22 (2.2%)	40 (4.0%)	0.54 (0.33-0.89)	0.014



- Pharmacodynamic effect of IBP-9414 observed after 14 days of treatment
- Preventive effects on mortality coincides with when NEC and BPD occur in preterm infants

1. (mITT) population (defined as infants receiving at least one dose of IBP-9414)

Conclusions

Largest study ever of a live biotherapeutic product in premature infants

- Numerical benefit of IBP-9414 treatment on NEC and SFT
  - NEC ambiguous clinical diagnosis unless laparotomy or autopsy are performed
  - SFT hampered by variable adherence to advocated enteral feeding protocol
- Significant reduction of the risk of death from any cause
- No concerns as to safety
- *Lactobacillus reuteri* never found in blood cultures taken for clinical suspicion of sepsis

Positive benefit-risk of IBP-9414 in premature infants born at very low birth weight

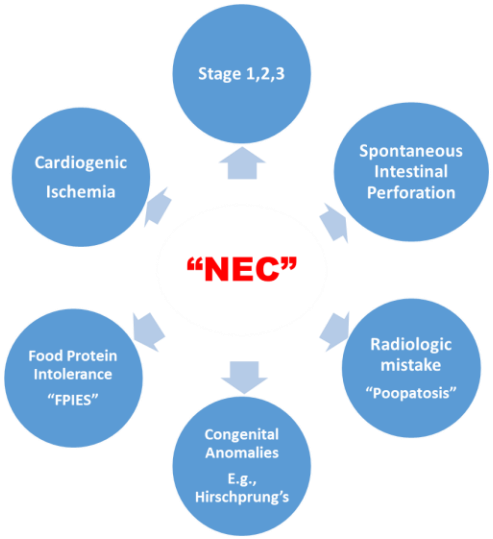
Canadian Study: "Effectiveness and Risks of Probiotics in Preterm Infants" :

Alshaikh BN, Ting J, Lee S, et al. Effectiveness and Risks of Probiotics in Preterm Infants. Pediatrics. 2025;155 (3):e2024069102

- Review of 32,667 infants born before 34 weeks gestation in Canadian Neonatal Network. Probiotics vs. no probiotics.
- No difference in NEC or sepsis between the groups.
- Decreased mortality rate (aOR 0.62, CI 0.53-0.73).
- Probiotic sepsis seen in 31 infants, 3 died.

Studies on “NEC” are problematic: WHY?

“NEC”



www.nature.com/pr

COMMENT

INVITED COMMENTARY

Definitions of necrotizing enterocolitis: What are we defining and is machine learning the answer?

Camilia R. Martin[1,2]✉

Pediatric Research (2022) 91:488–489; https://doi.org/10.1038/s41390-021-01687-0

The quest to adequately define, diagnose, and manage human disease is recorded as early as 2600 BC as evidenced by the Egyptian Edwin Smith Papyrus.[1] This process continues to be iteratively explored and updated as new approaches (e.g., the scientific method and evidence-based medicine) and new information become available with advancing technologies. Disease classifications can serve many purposes. It can be used to diagnose, predict disease risk, optimize therapeutics, assess morbidity and/or mortality, determine quality of life and health care utilization, and predict long-term medical needs. At the same time, ideally, disease classification should not overdiagnose or overtreat. All these elements are important when considering necrotizing enterocolitis (NEC), the infants it afflicts, and the families it impacts.

It is often discussed that Dr. Martin Bell proposed the first "definition" of NEC in 1978.[2] However, this is not a definition of the

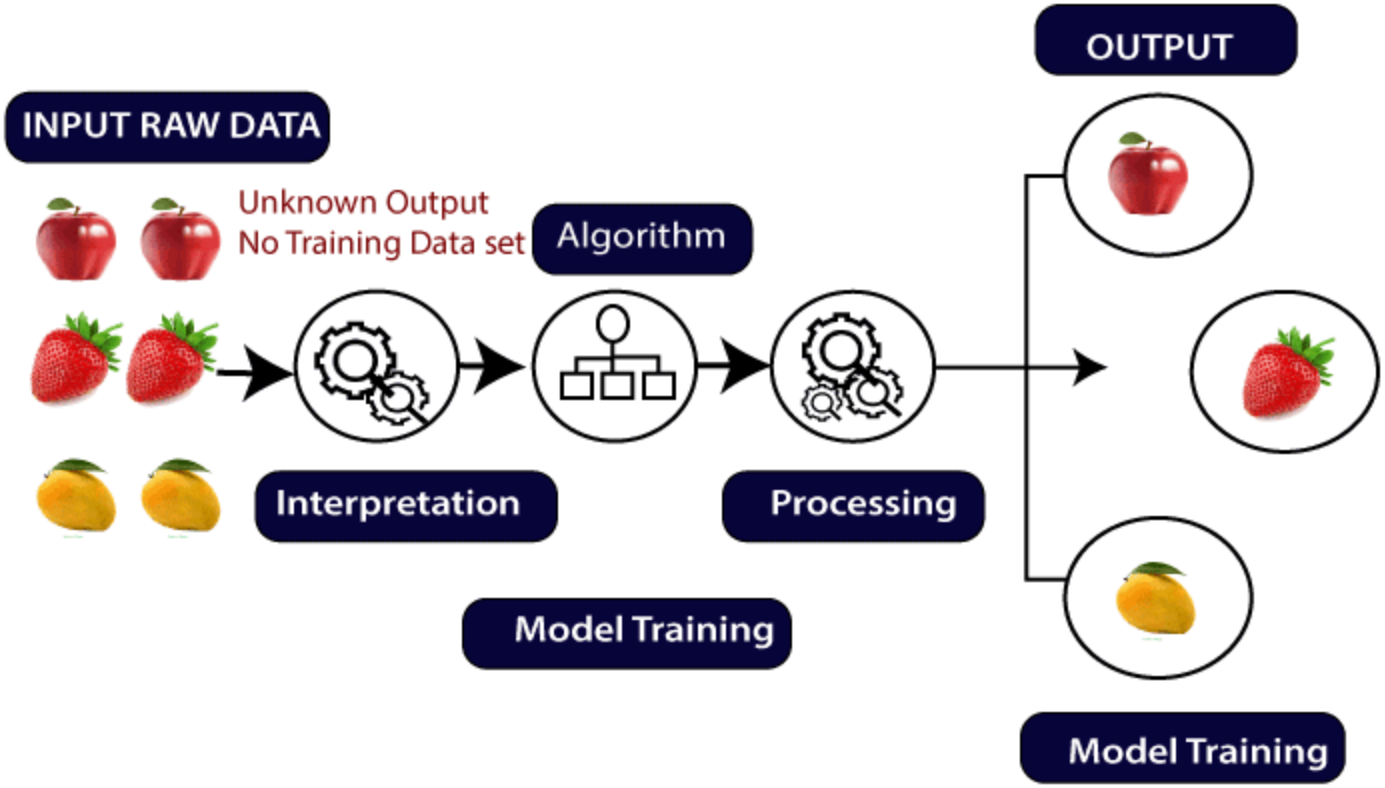
get NEC? What is a reliable set of risk factors that are modifiable and are subject to practice change and early therapies to minimize the risk of disease? To resolve these issues, it rests on us to determine a robust definition of disease presence and here we enter a continuous imperfect circular argument.

Six definitions have since been proposed in the literature to chip away at our clinical uncertainties and were recently analyzed in a thorough review by Patel et al.[8] The more contemporary definitions include the Vermont Oxford Network definition, the Centers for Disease Control and Prevention definition, the gestational age-specific case definition of NEC (UK), the two out of three rule, the Stanford NEC score, and the International Neonatal Consortium NEC workgroup definition. With now a handful of models to potentially use for clinical and research purposes, should the dominant position of the modified Bell's criteria be replaced?

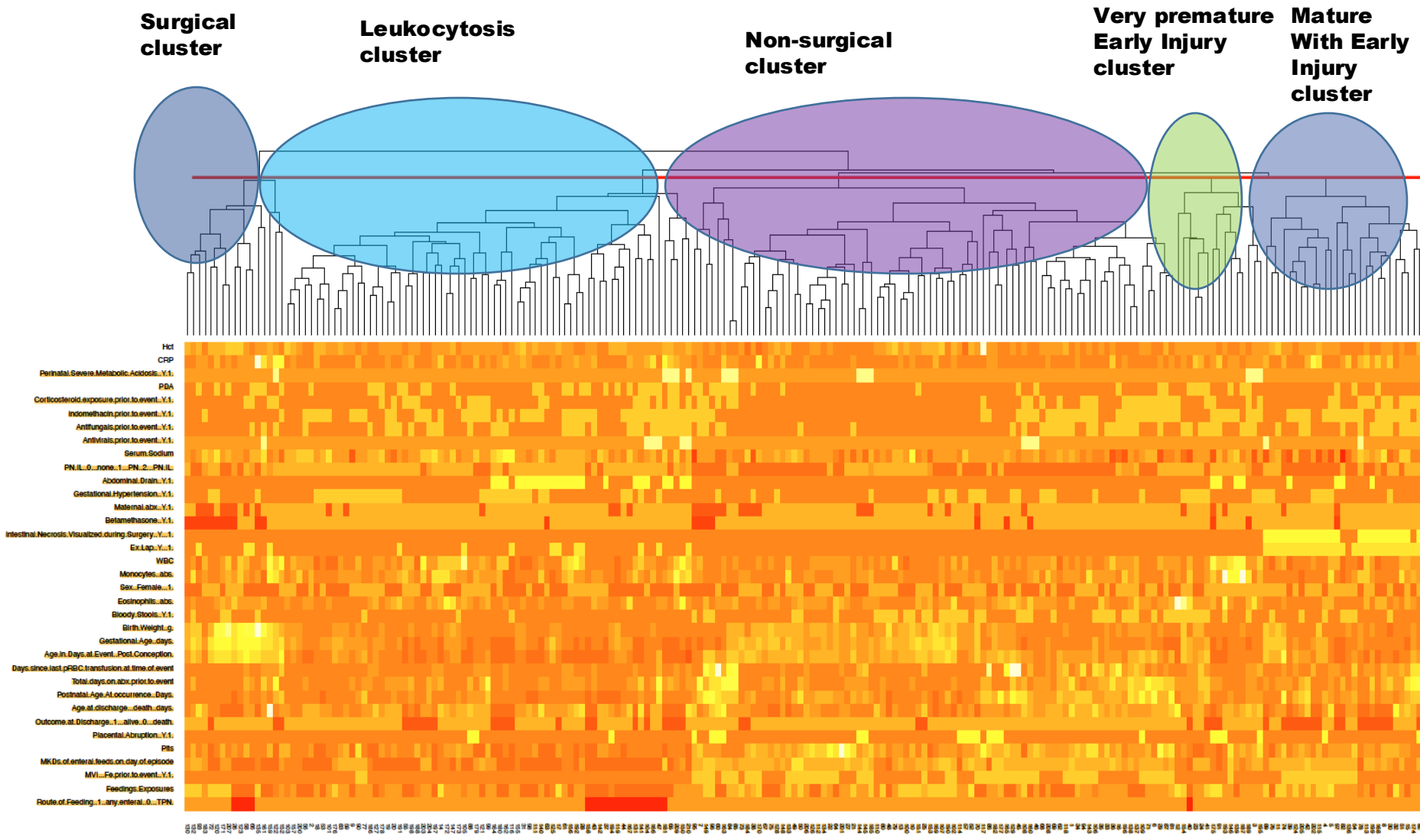
The Future:

How can we mesh AI with multiomics and diagnostics and therapeutics in neonatology?

Unsupervised Machine Learning



Unsupervised machine learning: Starting all over again



Gipson, et al. Pediatric Research, 2024

APS European Society for Pediatric Research SPR Society for Pediatric Research

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COMMENT

Check for updates

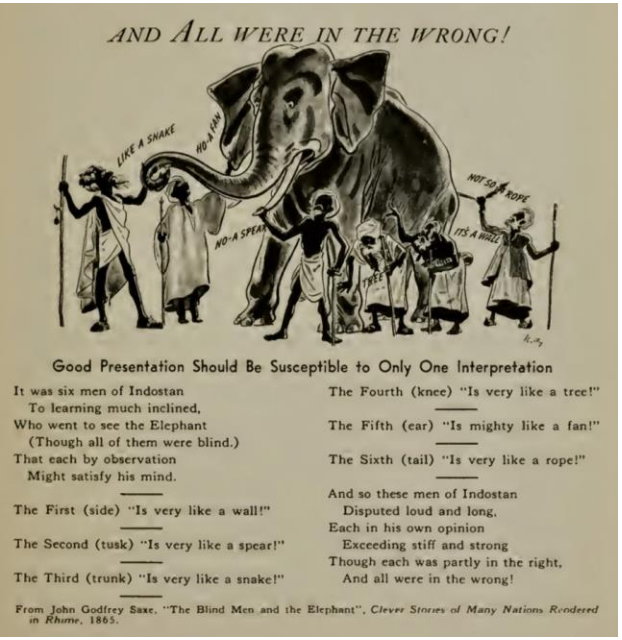
Artificial intelligence to classify acquired intestinal injury in preterm neonates—a new perspective

Alain Cuna[1,2,4], Muralidhar H. Premkumar[3,4] and Venkatesh Sampath[1,2]✉

Pediatric Research; https://doi.org/10.1038/s41390-024-03148-w

In conclusion, this study represents a promising and novel approach to redefining acquired neonatal intestinal diseases, including NEC and SIP, using unsupervised machine learning. This predominantly phenomics' approach can be substantially improved upon in future studies by incorporating large datasets from multiple centers and by including more learning features combining clinical, laboratory, radiographic, genomic, metabolomic, and microbiota data.[1–4] In the quest for better classification of acquired neonatal intestinal diseases, the intent to develop tools that can be applied in the clinical and research setting should be paramount. Ideally, such endeavors would redefine disease according to pathophysiologic mechanisms, which in turn could provide new paths to prevention and therapy. Any new re-classification schemes based on machine learning should undergo prospective evaluation to ascertain their performance and real-world impact in the clinical setting.

Developing an Improved Taxonomy: Why Multiomics



Good Presentation Should Be Susceptible to Only One Interpretation

It was six men of Indostan
To learning much inclined,
Who went to see the Elephant
(Though all of them were blind.)
That each by observation
Might satisfy his mind.

The First (side) "Is very like a wall!"

The Second (tusk) "Is very like a spear!"

The Third (trunk) "Is very like a snake!"

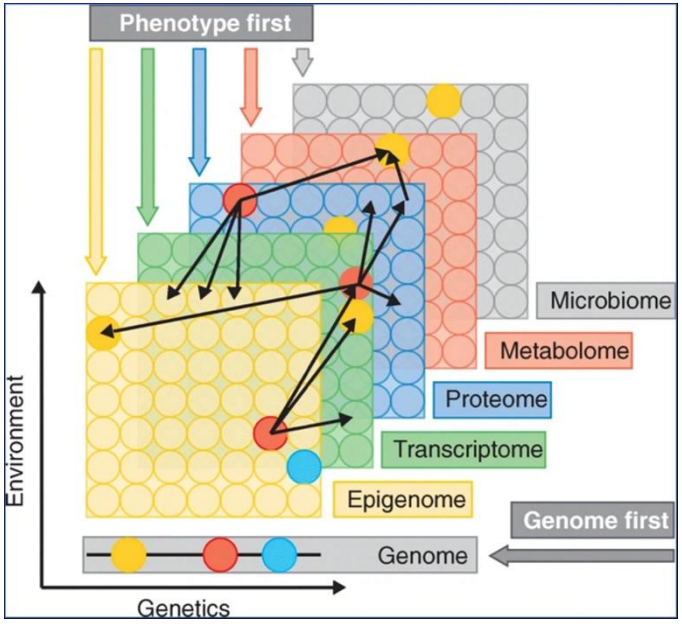
The Fourth (knee) "Is very like a tree!"

The Fifth (ear) "Is mighty like a fan!"

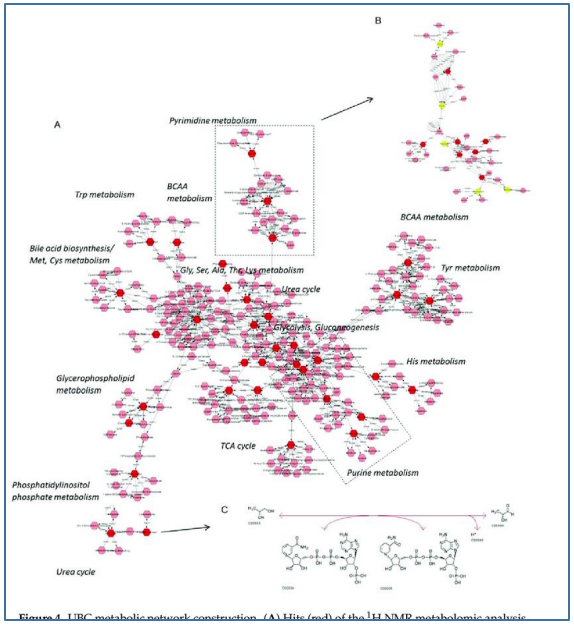
The Sixth (tail) "Is very like a rope!"

And so these men of Indostan
Disputed loud and long,
Each in his own opinion
Exceeding stiff and strong
Though each was partly in the right,
And all were in the wrong!

From John Godfrey Saxe, "The Blind Men and the Elephant", *Clever Stories of Many Nations Rendered in Rhyme*, 1865.



Multiomic Integration



Systems Biology Mechanism

Strategy for the Future (one possible approach)

1. Make believe the term necrotizing enterocolitis never existed for neonates.
2. Evaluate large datasets of preterm infants with various forms of feeding intolerance, putative intestinal problems, defined intestinal problems and perform unsupervised clustering.
3. Prospectively cluster infants using unsupervised AI, collect samples and utilize integrated multiomics to interrogate mechanisms.
4. Delineate clinical features and biomarkers that can be used for early detection for each cluster.
5. Develop preventative and therapeutic measures based on pathophysiologic mechanism.