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Necrotizing Enterocolitis

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Learning objectives

- Understand the epidemiology, pathophysiology, clinical features, investigations, staging, and management of necrotizing enterocolitis (NEC)
- Be aware of the evidence for and against the use of probiotics to prevent NEC
- Understand how next-generation sequencing can be used to understand the pathophysiology of NEC

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Overview

- The unwell baby
- What's so different about premature babies?
- Necrotizing enterocolitis
- Probiotics – Evidence based medicine
- Latest research

The unwell baby
Clinical features

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The unwell baby
Clinical features

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Observations
- Brady/tachycardia
- ↑RR
- Desats
- Hypotension
- Temperature instability

Cardio-respiratory
- Apnoeas
- Respiratory distress
- Collapse/shock

Gastrointestinal
- Poor feeding
- Vomiting
- Abdominal distension

Musculoskeletal
- Reduced limb movement

Skin changes
- Jaundice
- Petechiae/bruising

Neurology/behaviour
- Moaning cry
- Irritability
- Lethargy
- Seizures
- Tense/bulging fontanelle

The unwell baby
Investigations

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- Blood tests
  - Haemoglobin
  - White cells
    - Neutrophils
    - Lymphocytes
  - Platelets
  - Blood film
  - CRP
  - Blood cultures
  - Also... glucose, blood gas, coagulation screen etc.
  - And... Urine culture, LP, CXR etc.

Premature babies
Why are they at risk?

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•Immature immune system
•Reduced IgG antibody levels

•Thin skin and mucosae
•Lots of electrodes/tape etc.

Ventilated

Invasive lines, TPN (total parenteral nutrition)

ENVIRONMENT!

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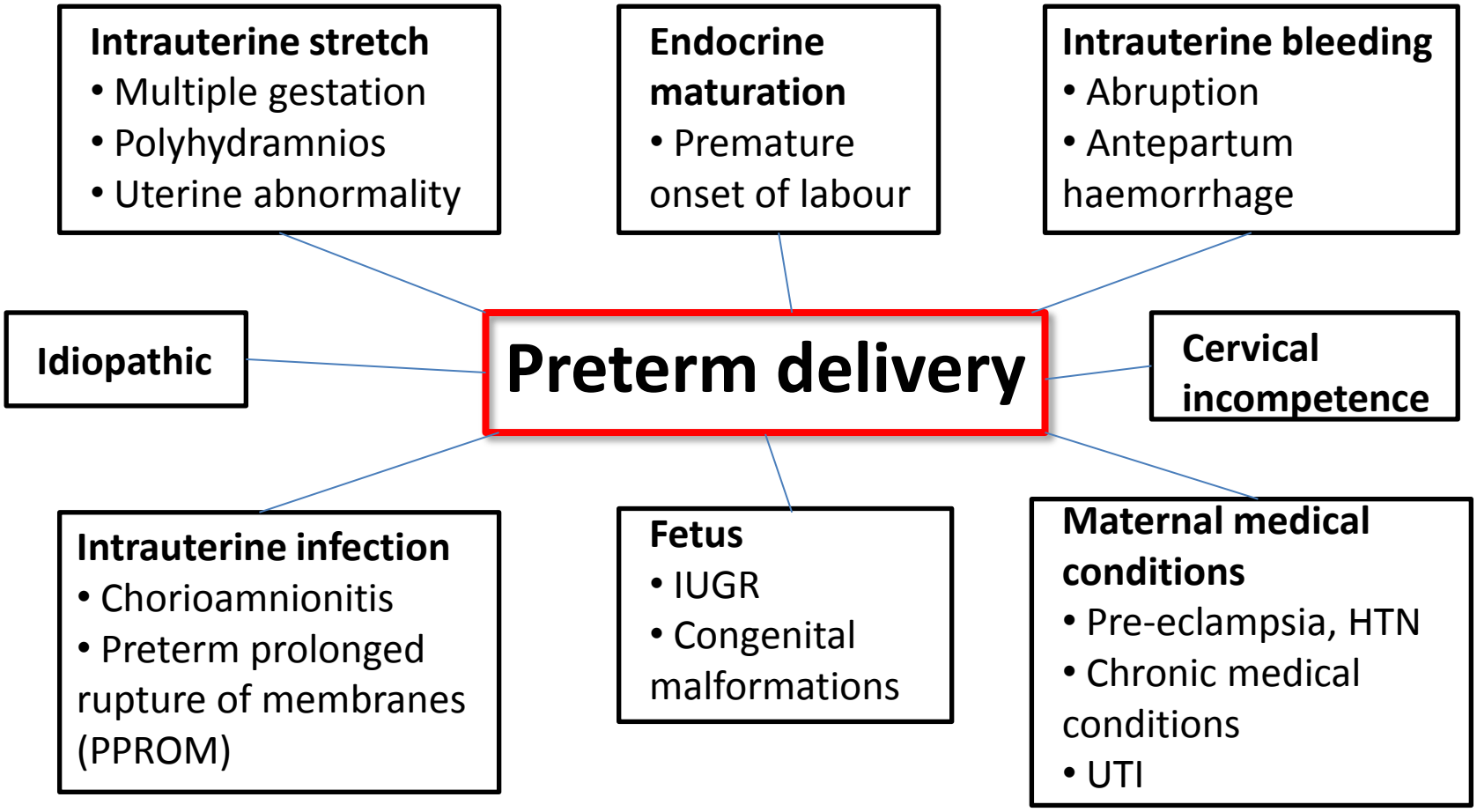
Why are babies born prematurely?



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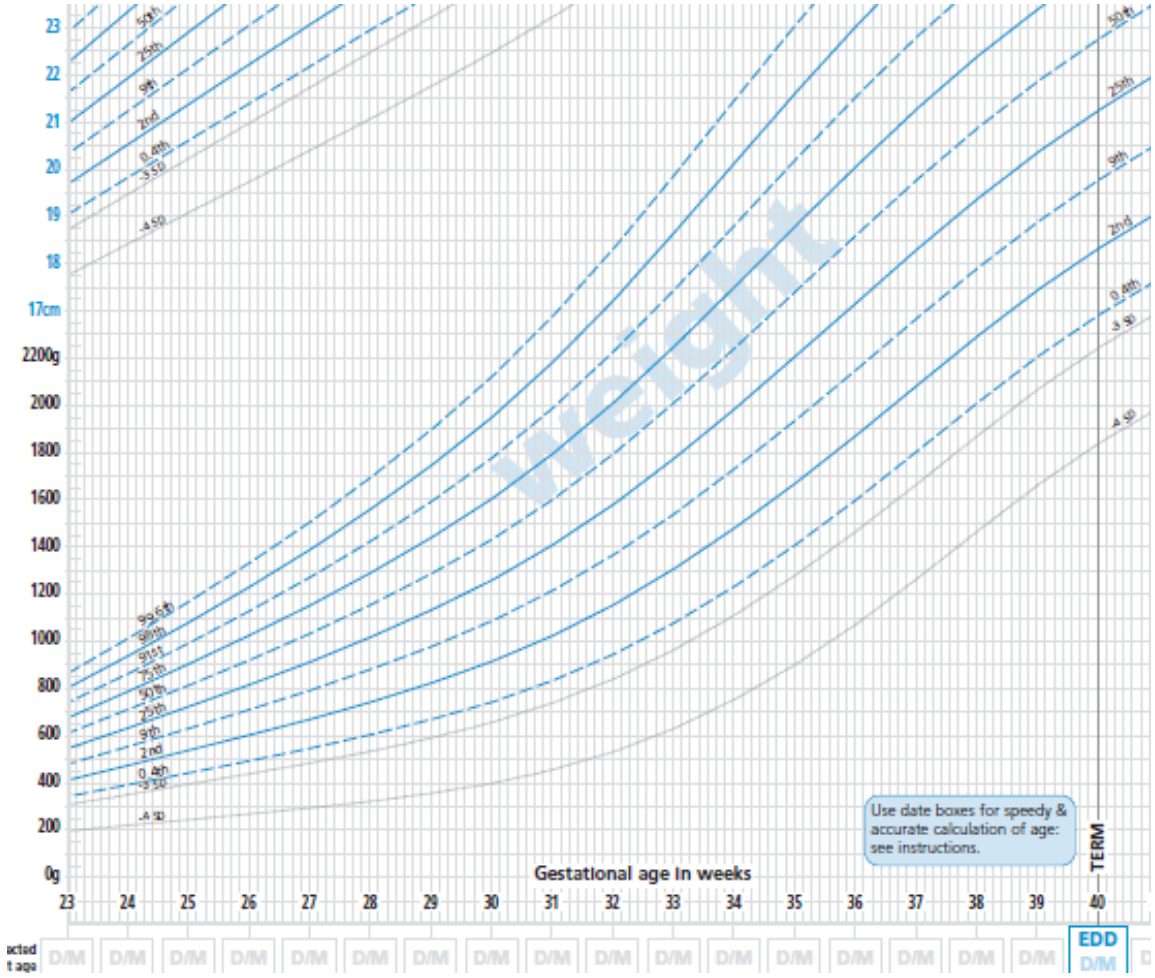
Some definitions

- Preterm: <37 completed weeks of gestation
- Term: 37-41 completed weeks of gestation
- Post-term: >/= 42 completed weeks of gestation
- Low birthweight (LBW): <2500g
- Very low birthweight (VLBW): <1500g
- Extremely low birthweight (ELBW): <1000g



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Necrotizing enterocolitis - NEC

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Necrotizing enterocolitis - NEC

- Inflammatory bowel disease
- Inflammatory process leading to tissue death
- Onset is at 1-2 weeks but may be up to several weeks of age (inversely proportional to gestational age)

Necrotizing enterocolitis Epidemiology

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- Mainly affects premature infants
  - >90% affected are less than 36 weeks gestation
- Incidence
  - 3-7% preterm infants
  - Inversely proportional to birth weight
    - 401-750g – 11.5%
    - 751-1000g – 9%
    - 1001-1250g – 6%
  - 0.005% term infants
- Gender and ethnicity
  - Slightly higher incidence in black infants
  - Male = Female, BUT, males are at greater risk of death if do develop NEC
- Approximately 1/3rd require surgery

Necrotizing enterocolitis Pathophysiology

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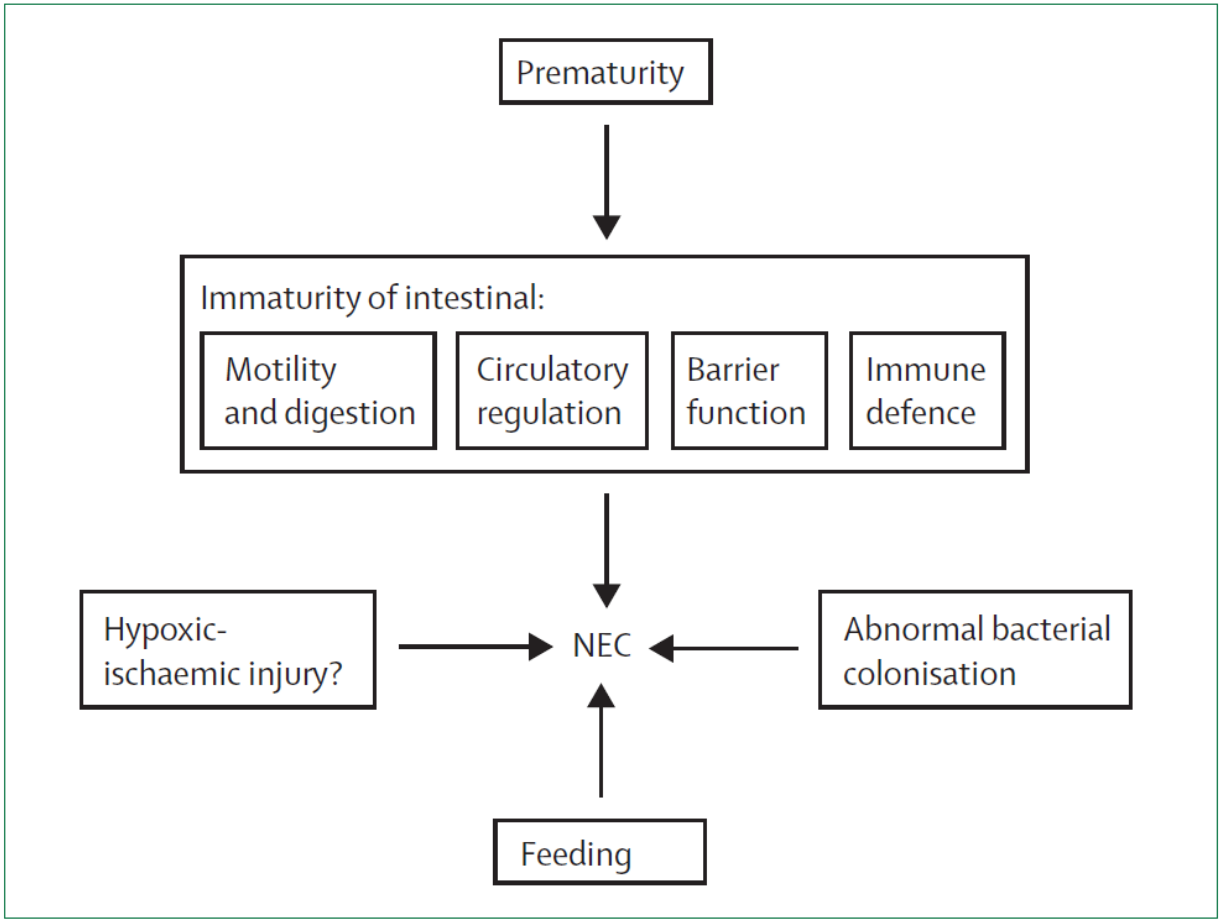

Lin, P et al. Necrotizing enterocolitis. *The Lancet.* 2006;**368**:1271-1283

Necrotizing enterocolitis Pathophysiology – the gut

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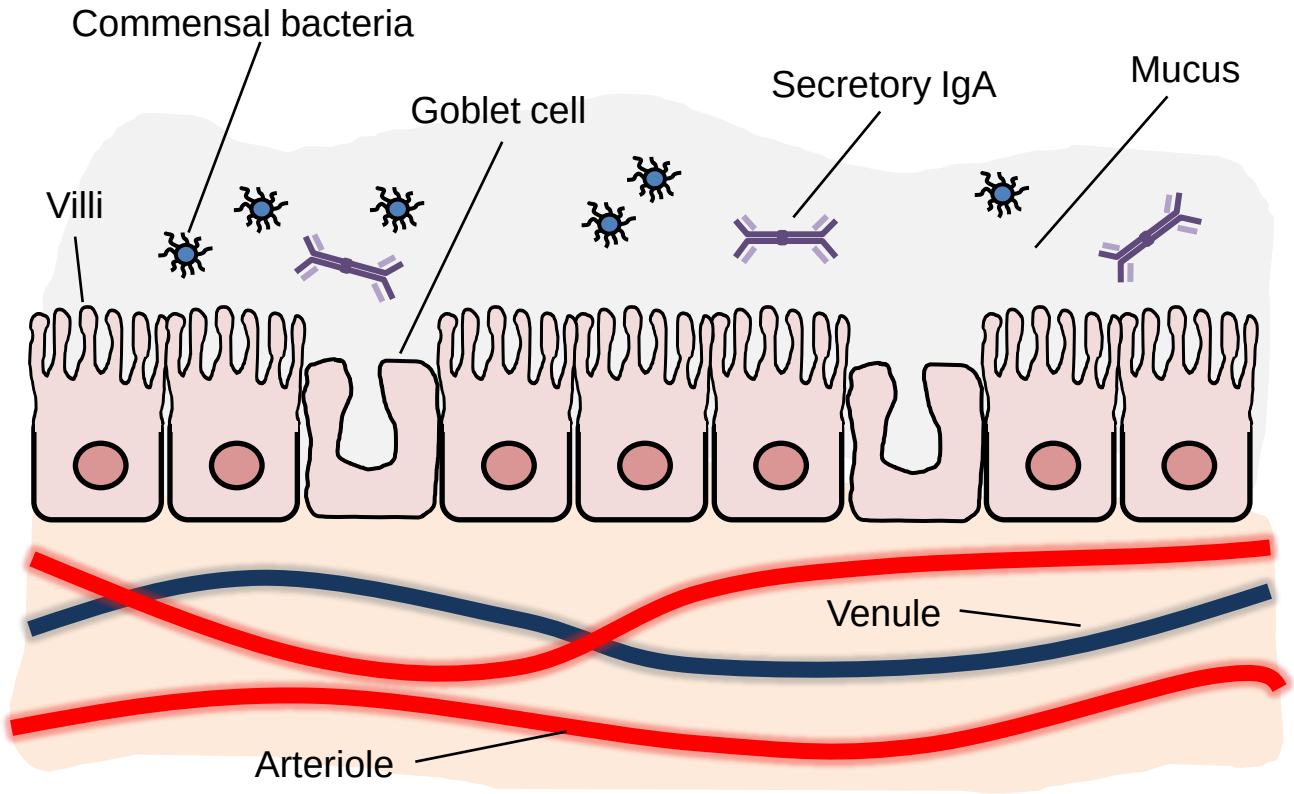

- Abnormal bacteria colonisation

- Increased fragility and permeability of gut epithelia
- Reduced amounts of protective mucus and secretory IgA
- Poor gut motility leading to gut stasis and bacterial overgrowth

- Unstable premature neonatal circulation – e.g. intermittently patent ductus arteriosus
- Poorly regulated oxygenation
- Osmotic and nutrient fluctuation from parentaral feeding

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Necrotizing enterocolitis Colonisation

- Gastrointestinal tract of the newborn thought to be sterile
- Colonised by microbes from the mother and the environment
- Premature infants
  - Delayed colonisation, limited number of bacterial species
- Commensal organisms reduce adherence of pathogenic bacteria to the intestinal mucosa

Claud, E et al. Hypothesis: inappropriate colonization of the premature intestine can cause neonatal necrotizing enterocolitis. *The FASEB Journal.* 2001;**15**:1398-1403

Schwiertz, A et al. Development of the intestinal bacterial composition in hospitalized preterm infants in comparison with breast-fed, full-term infants. *Pediatric Research.* 2003;**54**:393-399

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Necrotizing enterocolitis
Role of microbes

- Outbreaks are well documented
- No single infectious agent consistently implicated
- Common infectious agents have been isolated from blood, stool and peritoneal fluid during outbreaks.

Bacteria	Viruses
Clostridium perfringens	Coronavirus
Clostridium butyricum	Coxsackie B2 virus
Clostridium neonatale	Rotavirus
Clostridium difficile	Adenovirus
Klebsiella pneumoniae	Torovirus
Escherichia coli	Astrovirus
Cronobacter sakazakii	Echovirus 22
Staphylococcus epidermidis	
Pseudomonas aeruginosa	

- Mice in a germ-free environment do not develop NEC
- Does not occur in utero

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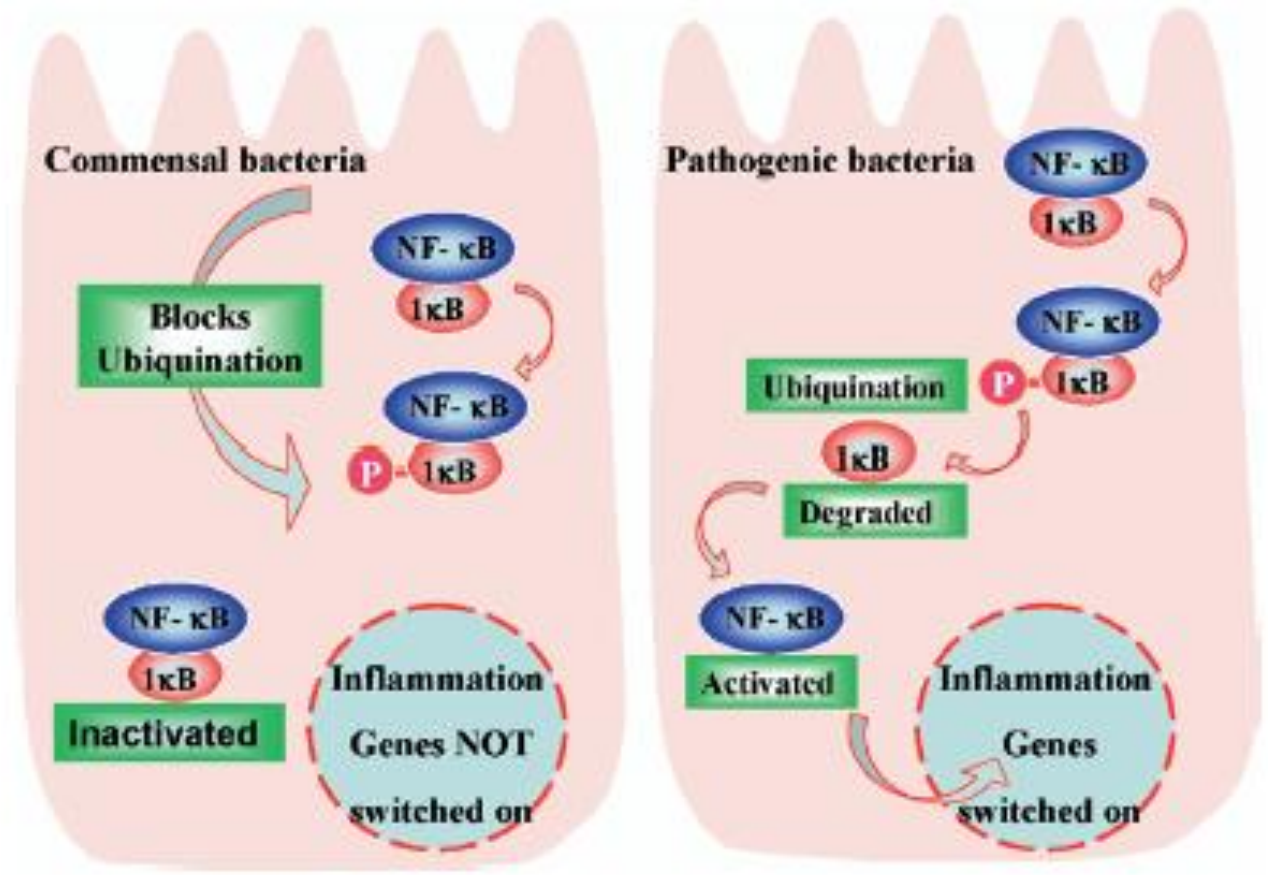
Necrotizing enterocolitis
Role of microbes



Necrotizing enterocolitis
Enteral feeds

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- NEC is rarely seen in infants who have never been fed
- Type of milk
  - Human milk – estimated 3-10x risk reduction vs. formula milk
  - Bank milk
- Volume of feeds – rate of increment
- Method of feeding – NG, bolus, continuous, trophic feeds

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Necrotizing enterocolitis
Platelet Activating Factor (PAF)

- Thought to be a primary mediator in the pathogenesis of NEC
- Intra-aortic infection of PAF in rats → experimental bowel necrosis similar to NEC
- In a rat model of NEC, PAF antagonism prevented necrotic changes in the small intestine induced by hypoxia challenge
- Human patients with NEC have high levels of PAF
- PAF levels correlated with severity of NEC

Necrotizing enterocolitis
Clinical features

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- Systemic
  - Respiratory distress, apnoeas
  - Poor perfusion, circulatory collapse
  - Temperature instability
- Gastrointestinal
  - Feed intolerance
  - Occult or gross blood in the stool
  - Abdominal distension, discolouration, tenderness

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Necrotizing enterocolitis
Clinical features

Necrotizing enterocolitis Investigations

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- **Support the diagnosis, determine severity, consider differential diagnosis**
- Blood tests
  - FBC
  - CRP
  - Coagulation
  - Blood cultures
  - Blood gas
  - U&E, LFTs
- Faecal samples, etc
- Imaging
  - AXR

Necrotizing enterocolitis Radiology

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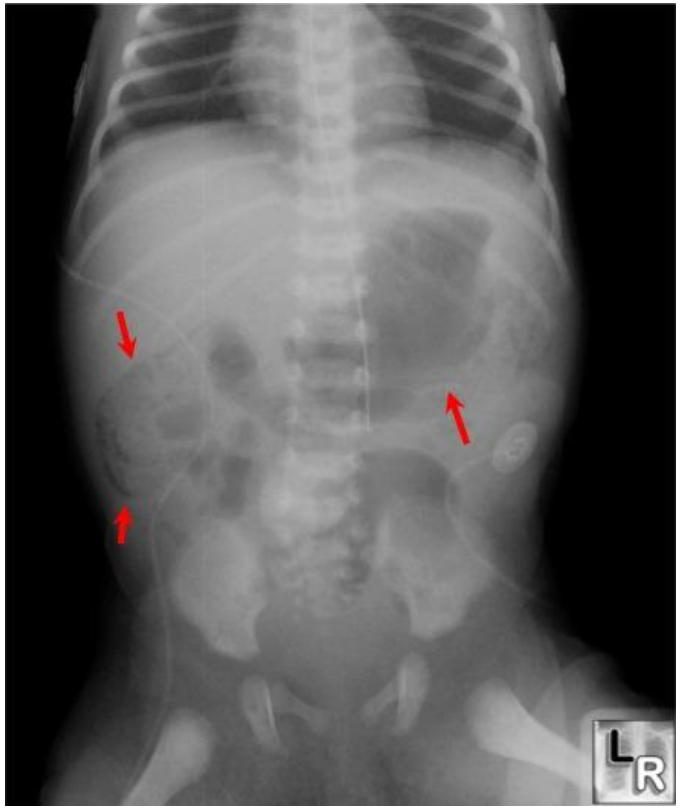

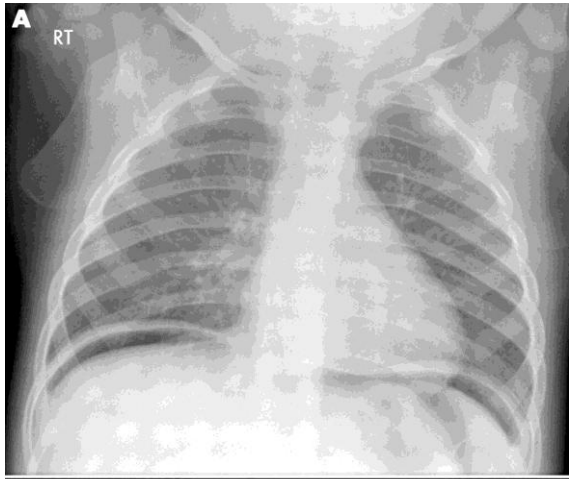

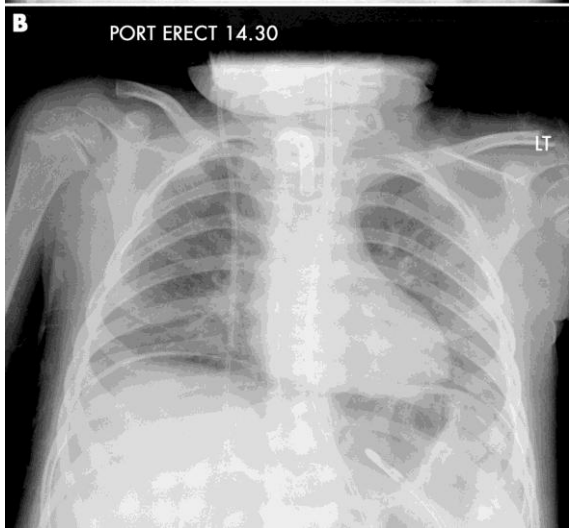

Necrotizing enterocolitis
Staging – Modified Bell's Criteria

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Stage	Systemic criteria	Abdominal criteria	Radiographic criteria
Stage 1a = suspected NEC	Temperature instability, apnoea, bradycardia	Increased gastric aspirates, mild abdominal distension, occult blood in stool	Normal or intestinal dilatation, mild ileus
Stage 1b = suspected NEC	Same as above	Grossly bloody stool	Same as above
Stage 2a = definite NEC; mildly ill	Same as above	Same as stage 1 plus lack of bowel sounds, possible abdominal tenderness	Ileus, pneumatosis intestinalis
Stage 2b = definite NEC; moderately ill	Same as stage 1 plus mild metabolic acidosis, mild thrombocytopenia	Same as above plus peritonitis, definite abdominal tenderness, possible abdominal cellulitis, right lower quadrant mass	Same as above plus possible portal venous gas
Stage 3a = advanced NEC; severely ill, intact bowel	Same as stage 2b plus hypotension, bradycardia, severe apnoea, combined respiratory and metabolic acidosis, DIC, neutropenia	Same as above, with marked tenderness and abdominal distension	Same as above plus ascites
Stage 3b = advanced NEC; severely ill, perforated bowel	Same as stage 3a	Same as stage 3a	pneumoperitoneum

Necrotizing enterocolitis Differential diagnosis

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- Systemic and intestinal infections
- Congenital intestinal obstruction
  - Volvulus
  - Ileal atresia
  - Hirschsprung's disease
- Spontaneous intestinal perforation (SIP)
- Pseudomembranous colitis

Necrotizing enterocolitis Treatment

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- 'ABC'
- NBM – start TPN
- IV antibiotics
- Supportive care
- Surgery
  - Peritoneal drainage
  - Laparotomy → resection of non-viable bowel (anastomosis or ileostomy + resection)

Necrotizing enterocolitis
Prognosis & long term outcome

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- Mortality
  - 10 – 25%
  - Case fatality rate with surgical interventional- up to 50%
- Morbidity
- Short gut syndrome
  - Diarrhoea (due to loss of bowel mucosa and rapid GI transit)
  - Failure to thrive
  - Vit B_{12} deficiency if terminal ileum resected
  - Stricture formation → intestinal obstruction
- Adverse neurodevelopmental outcome

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Probiotics

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Probiotics… What are they?

- WHO definition:
  - "live microorganisms which when administered in adequate amounts confer a health benefit on the host."

A probiotic should:
• Be of human origin • Be non-pathogenic in nature • Be resistant to destruction by technical processing • Be resistant to destruction by gastric acid and bile • Adhere to intestinal epithelial tissue • Be able to colonize the gastrointestinal tract, if even a short time • Produce antimicrobial substances • Modulate immune responses • Influence human metabolic activities (i.e, cholesterol, assimilation, vitamin production, etc.)

Probiotics to prevent NEC? You decide!

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Study	Birth weight/GA	Numbers	Feeds	Organisms, dose, duration	Primary Outcome	Conclusion 👍/👎
Dani et al 2002	<33 wk, or <1500g	585 (295 study group, 290 control)	MM, DM or FM	LB-GG, $6x10^9$ CFU od from 1st feed → d/c	UTI, sepsis, NEC	👎
Bin Nun et al 2005	<1500g	145 (72 study group, 73 control)	MM, or FM	BI $0.35x10^9$ CFU, ST $0.35x10^9$ CFU, BBB $0.35x10^9$ CFU od from 1st feed to 36wk	NEC	👍
Lin et al 2005	<1500g	367 (180 study group, 187 control)	MM or DM	LB-A 1004356 and BI 1015697 organisms bd from day7 → d/c	NEC or death	👍
Lin et al 2008	<34 wk and <1500g	434 (217 study group, 217 control)	MM or FM	BBB, LB-A $2x10^9$ CFU/d for 6 wk	NEC or death	👍
Samanta et al 2009	<34 wk and <1500g	186 (91 study group, 95 control)	MM or FM	BBB, BB-L, BI, LB-A $2.5x10^9$ CFU/d until d/c	NEC, TFF, sepsis, death, hospital stay	👍

BB = *Bifidobacterium breve*, LB GG = *Lactobacillus* GG, SB = *Saccharomyces boulardii*, BI = *Bifidobacteria infantis*, ST = *Streptococcus thermophilus*, BBB = *Bifidobacterium bifidus*, LB-A = *Lactobacillus acidophilus*, LB-C = *Lactobacillus casei*, BB-L = *Bifidobacterium lactis*, BB-LG = *Bifidobacterium longum*, MM = mother's milk, DM = donor milk, FM = formula milk, CFU = colony forming unit, d/c = discharge, TFF = time to full feeds

Probiotics to prevent NEC? You decide!

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- Organisms
  - Different!
  - Single vs. multiple
  - Dose
  - First dose
  - Duration
- Feeds
  - Maternal vs. donor vs. formula
- Outcomes
- Also...
  - Some trials excluded all babies in the first 1 to 2 weeks of life - including babies who developed NEC.
  - Confirmation of colonisation
  - Cross contamination
  - Numbers

Probiotics Meta-analysis

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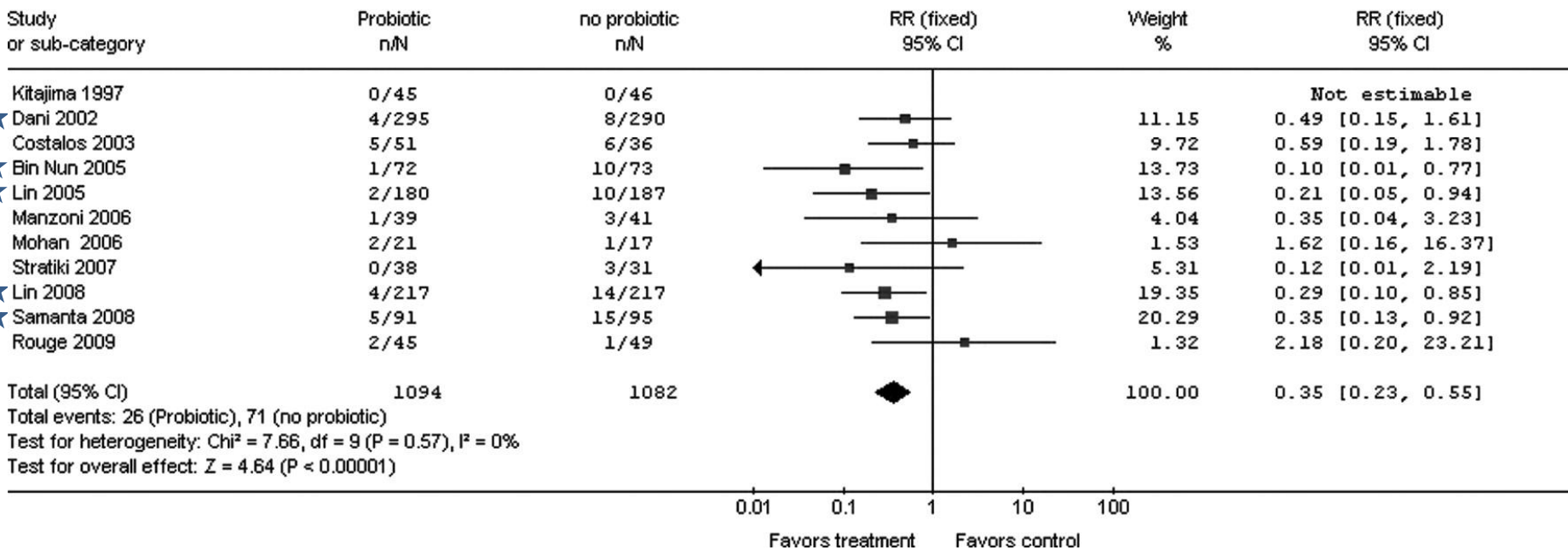
Updated Meta-analysis of Probiotics for Preventing Necrotizing Enterocolitis in Preterm Neonates

Girish Deshpande, Shripada Rao, Sanjay Patole and Max Bulsara

Pediatrics 2010;125;921-930; originally published online Apr 19, 2010;
DOI: 10.1542/peds.2009-1301

Review: Probiotics for prevention of necrotizing enterocolitis
Comparison: 01 NEC
Outcome: 01 Definite NEC



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Probiotics Meta-analysis

Estimated sample sizes for various primary outcomes in ELBW neonates

Primary Outcome	Incidence in Control Group (%)	Incidence in Probiotic Group (%)	% Reduction	Power	α	Sample Size
Definite NEC	6.0[a]	4.2	30	0.8	.05	4908
	10.7[b]	7.5	30	0.8	.05	2658
Death or definite NEC	30.0[b]	21.0	30	0.8	.05	740
	30.0[b]	25.5	15	0.8	.05	2520

[a] Figures based on Luig et al.

[b] Figures based on Hintz et al.

Probiotics: Are We Ready for Routine Use?

Roger F. Soll

Pediatrics 2010;125;1071-1072; originally published online Apr 26, 2010;

DOI: 10.1542/peds.2010-0643

Probiotics
PiPS Study

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PiPS Study

A multi-centre, double blind, placebo-controlled randomised trial of probiotic administration in preterm infants

The latest baby was recruited at **Homerton University Hospital NHS Foundation Trust** on **7 January 2011**. Congratulations!

PiPS has recruited **53** infants.

- This randomised placebo-controlled trial studies the effect of early administration of a single probiotic strain *Bifidobacterium breve* strain BBG given to an unselected group of babies at high risk of NEC and sepsis.

Probiotics
The risks

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Lactobacillus Sepsis Associated With Probiotic Therapy

Michael H. Land, Kelly Rouster-Stevens, Charles R. Woods, Michael L. Cannon, James Cnota and Avinash K. Shetty

Pediatrics 2005;115;178-181
DOI: 10.1542/peds.2004-2137

- Septicaemia
- Meningitis

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Next-generation sequencing & NEC

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NeoM - The Neonatal Microbiota Study

PI: Prof Simon Kroll

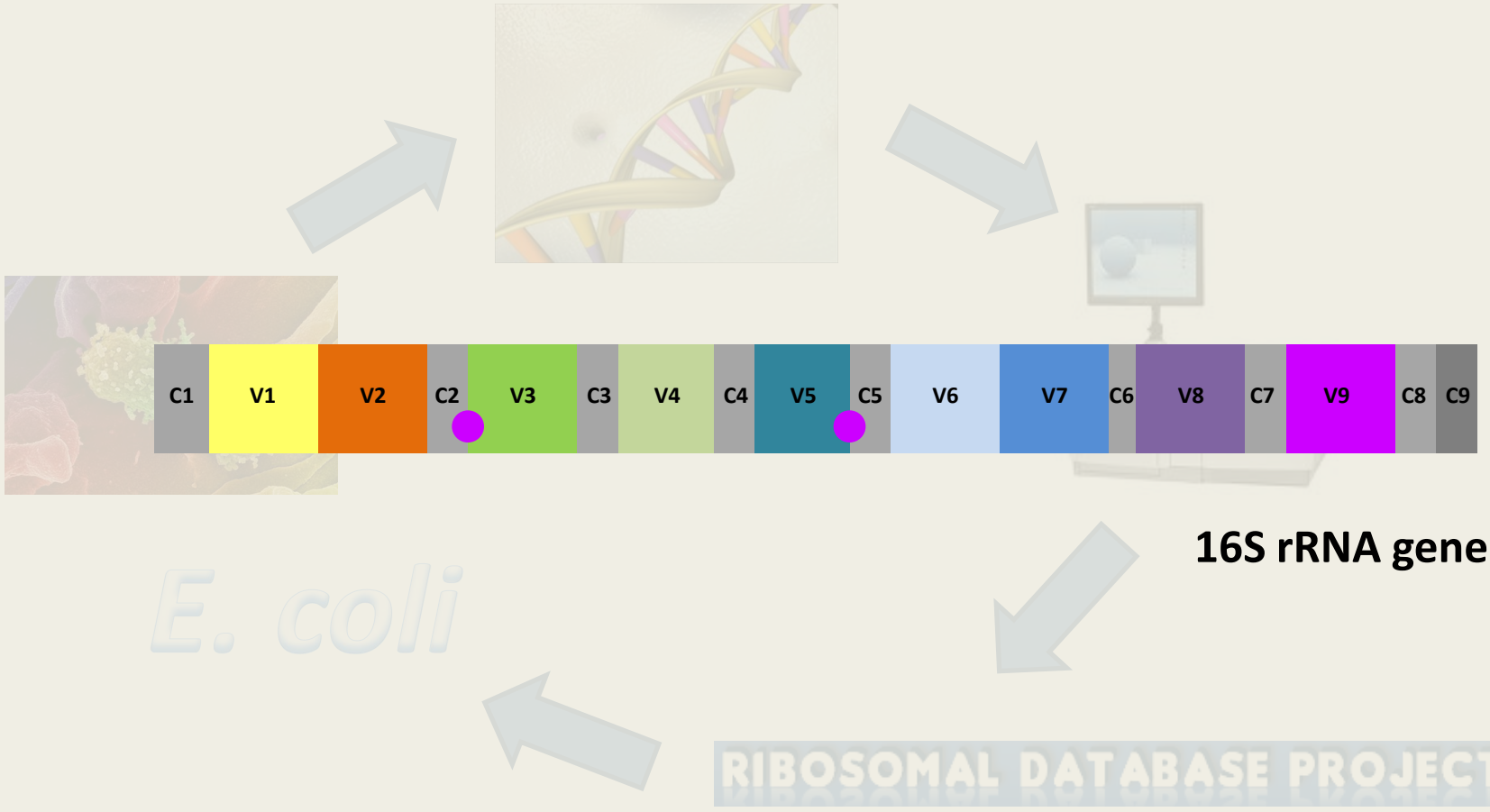
1. To chart the **development of the intestinal microbiota** in premature infants (<32 weeks), in health and in association with major diseases – NEC and late-onset bloodstream infection.

2. Through defining associated (***in particular, pre-morbid***) intestinal microbiota in these sick infants, to inform **rational preventive and treatment strategies** through:
   - judicious use – or the withholding – of antibiotics
   - improved feeding regimes, ± probiotics, ± prebiotics

Bacterial culture

- 60-80% of bacteria are missed using routine culture

Outline of sample analysis



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Take home messages

- Overview of the unwell neonate – non-specific presentation
- Differences in premature babies – high risk
- Necrotizing enterocolits – multifactorial
- Probiotics – the verdict is out there...
- Latest research – next-generation sequencing

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Questions?

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