The impact of antibiotics and other medications in the NICU on the microbiome and infection outcomes

Gergely Toldi
Liggins Institute, University of Auckland, NZ
@ToldiGergely

Objectives

- Microbiome and the neonatal immune system
- Dysbiosis
- Antibiotics
- Mechanisms: short chain fatty acids
- The airway microbiome
- PPIs and H2RAs
- Other medications
- What can we do?

- No conflicts of interest

Microbiome

Article | Published: 31 July 2019

Human placenta has no microbiome but can contain potential pathogens

Marcus C. de Goffau, Susanne Lager, Ulla Sovio, Francesca Gaccioli, Emma Cook, Sharon J. Peacock, Julian Parkhill, D. Stephen Charnock-Jones & Gordon C. S. Smith

Nature **572**, 329–334 (2019) | Cite this article

- Intrauterine environment is physiologically sterile
- Evolving microbiome after birth
- First 100 days: **the window of opportunity** for the microbiome to influence immune development

Microbiome & the immune system

- Alpha diversity: the observed richness (number of taxa), or evenness (the relative abundance of those taxa) in a single sample

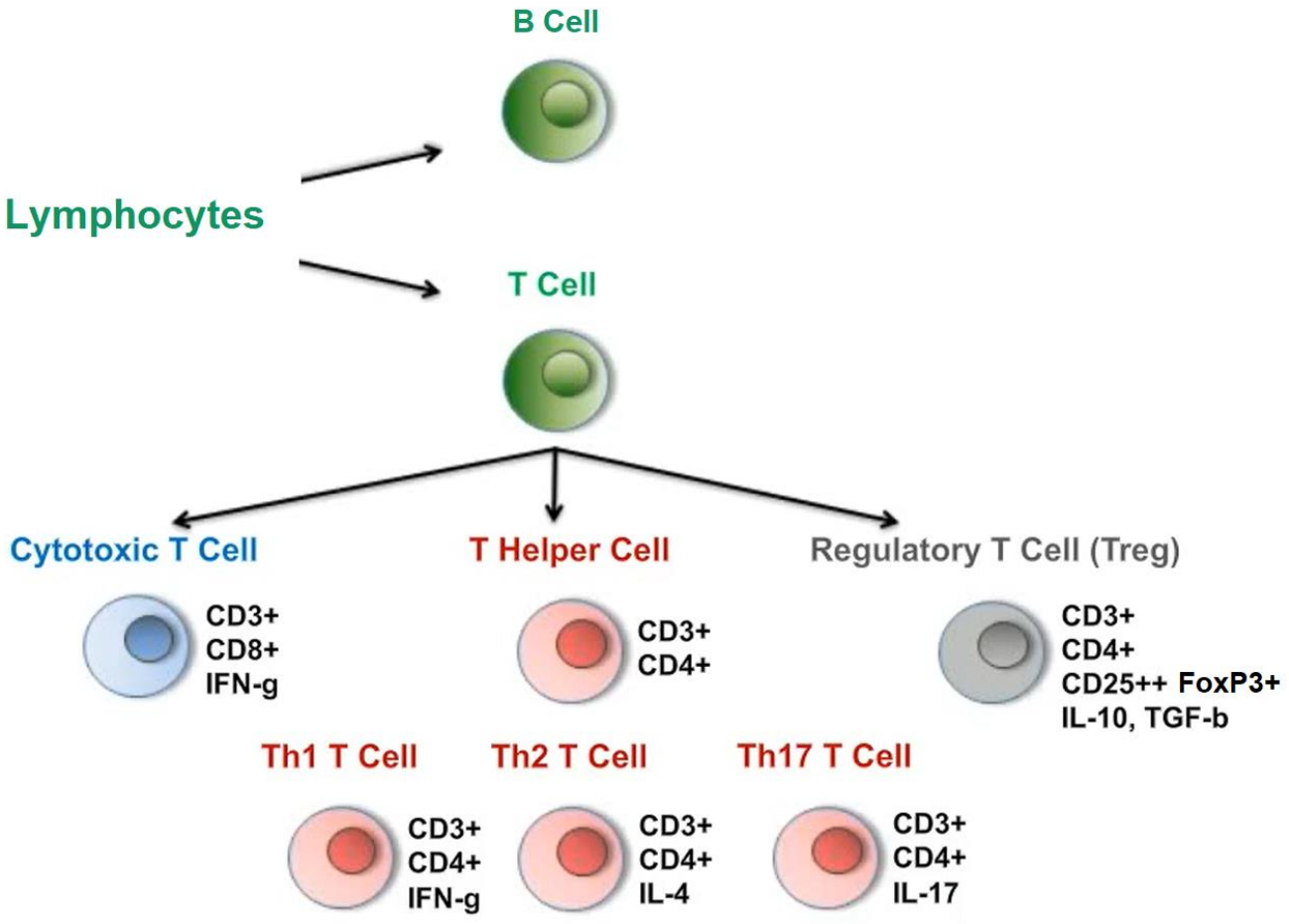
- During early life, it is favorable if alpha diversity rapidly increases in the gut, encompassing greater phylogenetic diversity from the environment

- Acquired intestinal bacteria train the immune system

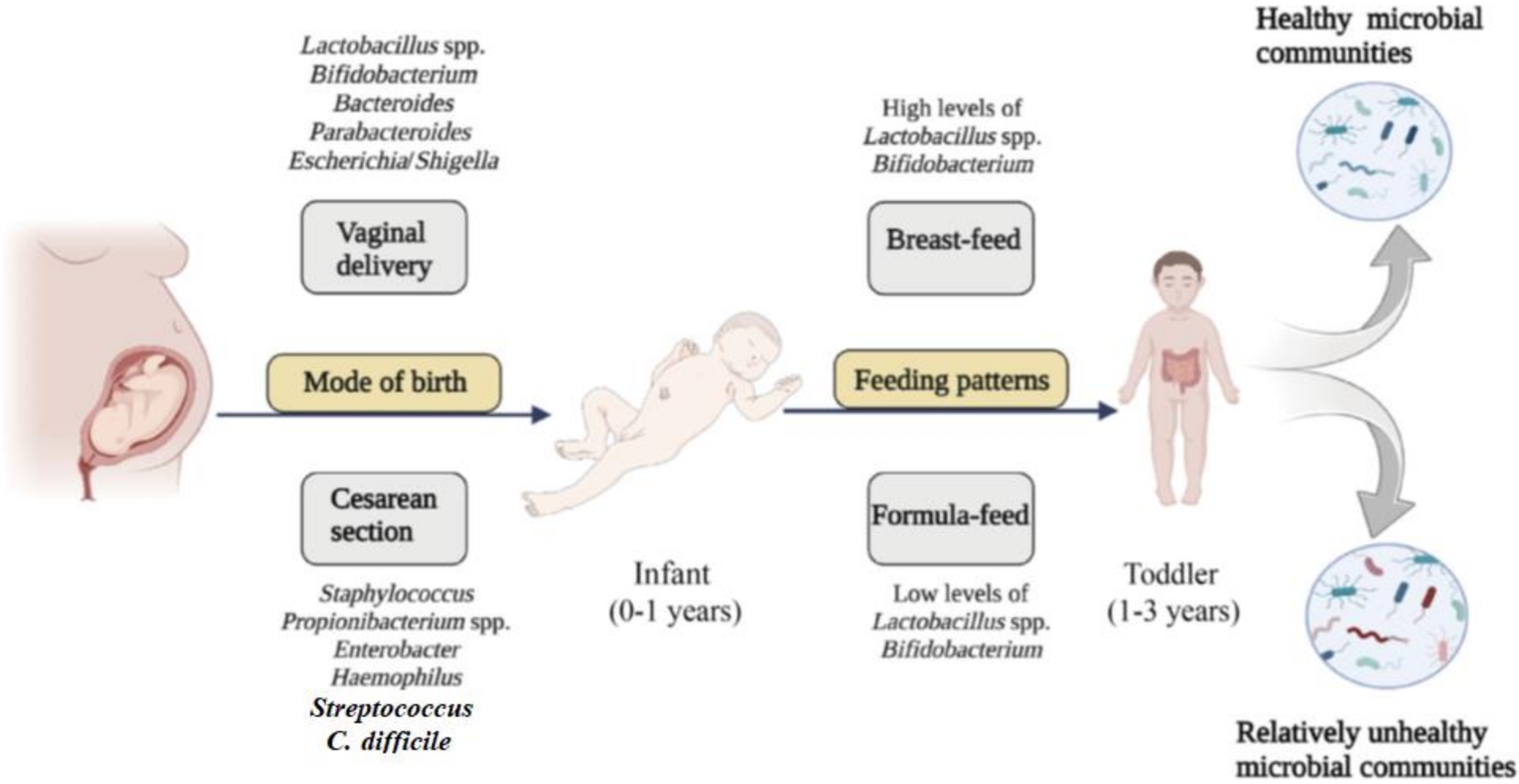
- B cell and Ig repertoire established during the window of opportunity

- Weaning and solids

The adaptive immune system

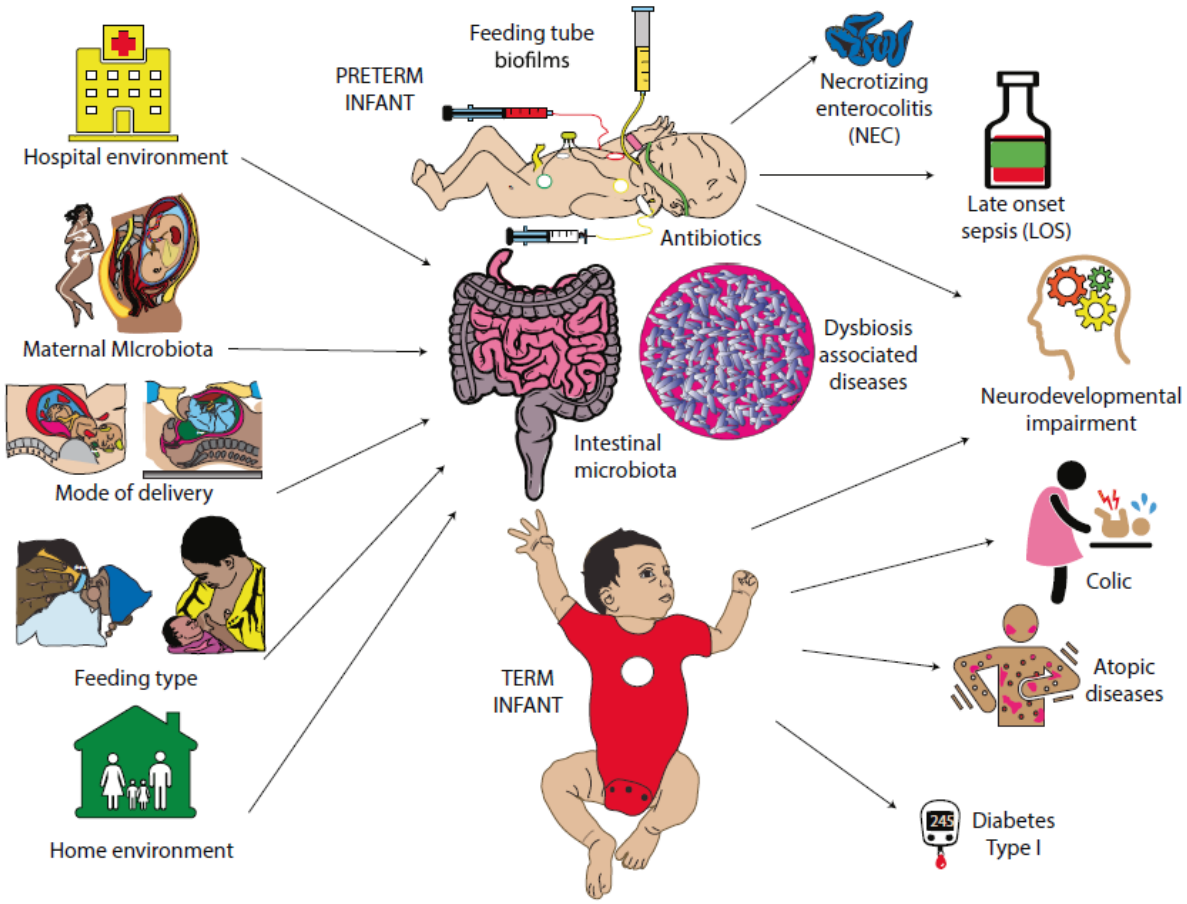


Establishment of the gut microbiome



eClinicalMedicine 2024;68:102428

Contributors to dysbiosis



J Perinatol 2020;40:1597-608

Antibiotics – it starts before birth

- Antibiotics are the most prescribed medications in NICU
- Immediate benefit vs health consequences in later life
- The use of intrapartum antibiotics is steadily increasing worldwide (approx. 1/3 of all deliveries)
- The average US child receives 3 antibiotic courses by the age of 2, and 10 courses by the age of 10

Antibiotics in preterm babies

- 98% of ELBW neonates received antibiotic treatment in the first three postnatal days, while <2% of them had positive blood cultures and clinical symptoms of EOS

- Each additional day of empiric treatment was associated with a 4% increase in the odds of NEC and a 16% increase in the odds of death

- Prolonged administration of empirical antibiotics was associated with increased incidence of LOS and the composite outcome of LOS, NEC, or death

- Increased incidence of invasive candidiasis

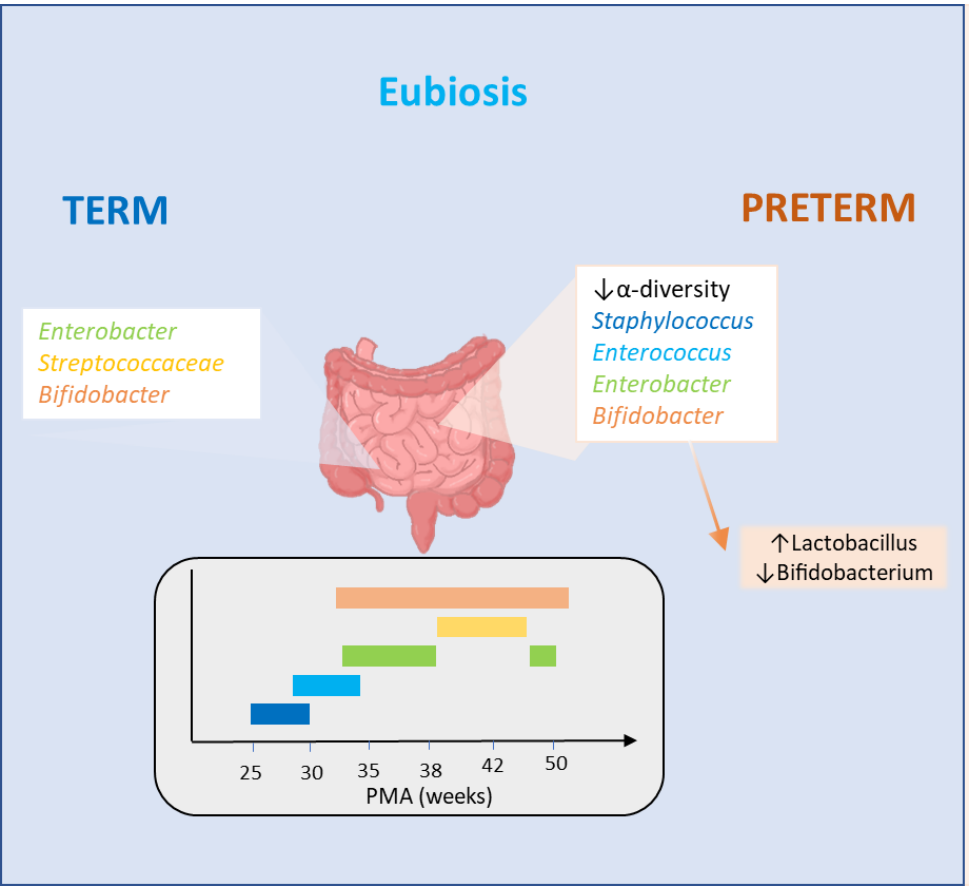
Antibiotics in preterm babies

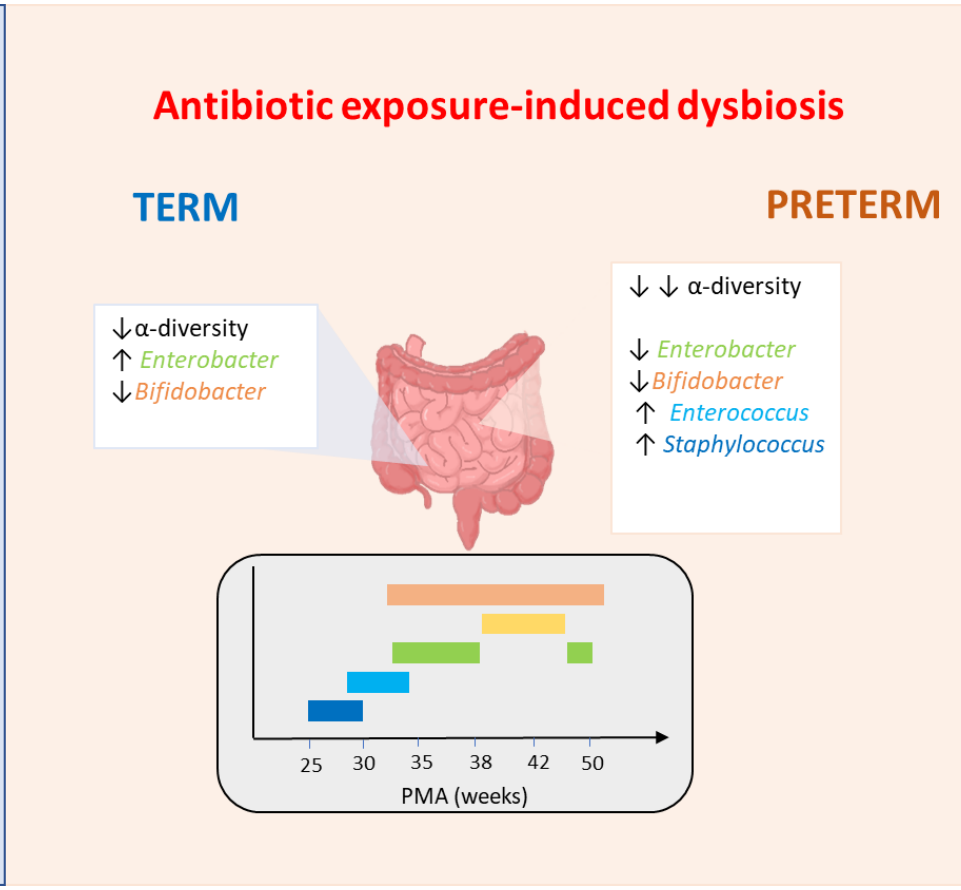
- Preterm infants had:
  - a reduced bacterial diversity
  - an increased relative abundance of pathogenic bacteria such as Enterobacteriaceae
  - a decrease or absence of symbiotic bacteria such as Bifidobacterium spp.
- Antibiotic discontinuation restored diversity, with variances linked to the antibiotic spectrum and treatment duration in some but not all cases.
- Long-term health consequences: decreased absorption of nutrients and vitamin production, increased risk of infections, asthma, diabetes, and obesity.
- Breastfeeding confounded the association between antibiotic use and dysbiosis

Antibiotics – which combination?

- RCT from the Netherlands, 2022 (Reyman et al.)
- 147 term infants treated for suspected EOS:
  - penicillin + gentamicin
  - co-amoxiclav + gentamicin
  - amoxicillin + cefotaxime
- Control group of 80 infants
- Stool: after treatment and at 1, 4 and 12 months
- Average exposure 48 hrs
- Antibiotic treatment associated with decreased abundance of Bifidobacterium spp. and increased abundance of Klebsiella and Enterococcus spp. **directly** following exposure
- Normalisation takes 12 months
- Penicillin + gentamicin exhibits the least effects

Term vs preterm





Antibiotics 2023;12:258

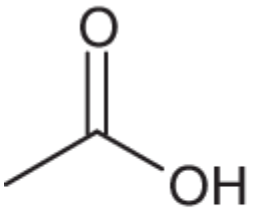
UNIVERSITY OF AUCKLAND Waipapa Taumata Rau NEW ZEALAND | LIGGINS INSTITUTE

Neonatal dysbiosis

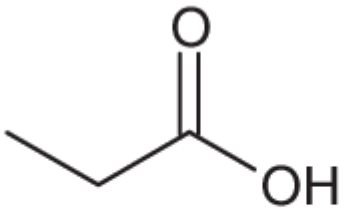
Intrapartum antibiotics	↓ Bacteroides and Bacteroidetes
	↓ Parabacteroides
	↓ Bifidobacterium and Actinobacteria
	↑ Proteobacteria
	↑ Veillonella, Enterococcus and Firmicutes
	↑ Clostridia
	↓ Alpha diversity
	↓ Fecal acetate
	↑ Antibiotic resistance genes
Postnatal antibiotics (term infant)	↓ Bacteroidetes
Postnatal antibiotics (preterm)	↓ Alpha diversity
	↑ Antibiotic resistance genes
Cesarean delivery	↓ Actinobacteria
	↓ Bacteroidetes
	↑ Firmicutes
Home birth	↑ Bifidobacterium
	↑ Bacteroides
	↑ Streptococcus
	↑ Lactobacillus
	↓ Clostridium
	↓ Enterobacteriaceae
Very preterm birth	↑ Proteobacteria
	↓ Firmicutes
	↓ Bifidobacterium
	↓ Short chain fatty acids
Mother's own milk	↑ Bifidobacteriaceae
	↓ Staphylococcaceae
	↓ Clostridiaceae
	↓ Pasteurellaceae

J Perinatol 2020;40:1597-608

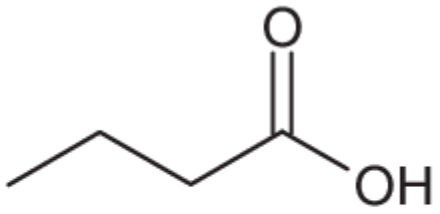
Short chain fatty acids



Acetate



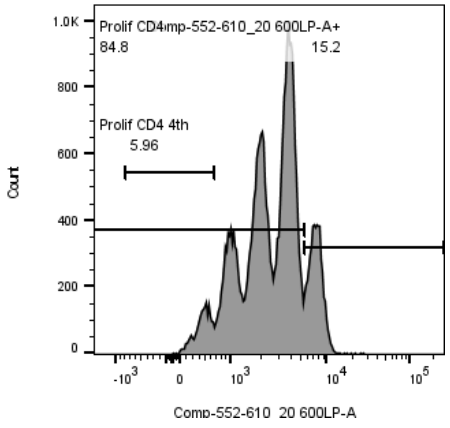
Propionate



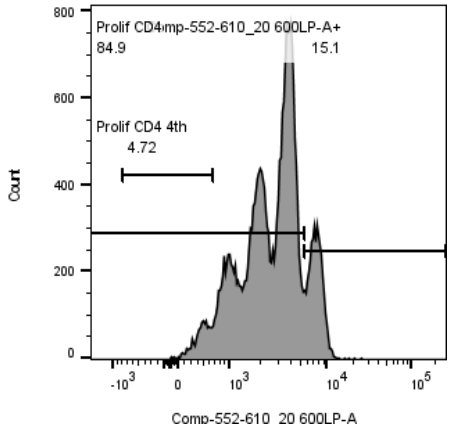
Butyrate

- Products of fermentation of dietary fibre or HMOs
- Metabolic effects: glucose and lipid homeostasis
- Improved insulin sensitivity
- Differentiation of neural, intestinal, and pancreatic cells
- Regulatory T cells: enhanced gene transcription by increasing histone acetylation → downregulation of inflammatory responses

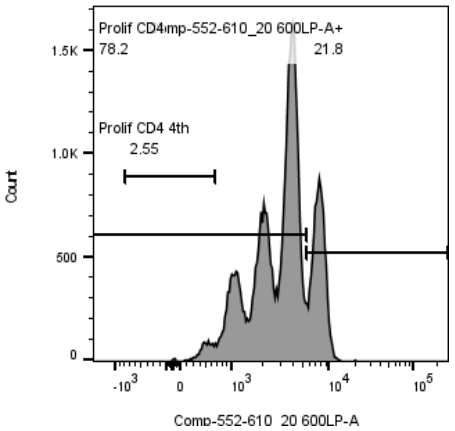
T cell proliferation



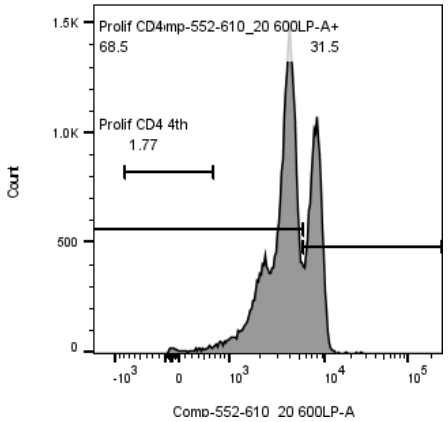
Acetate 1mM



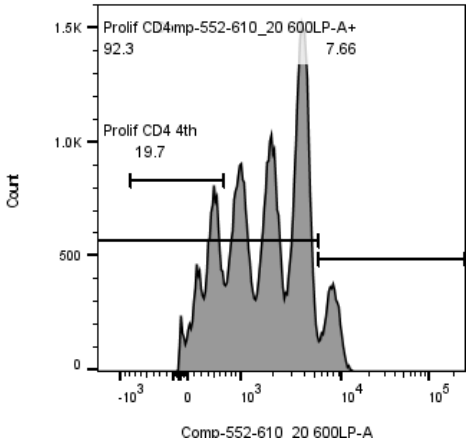
Acetate 5mM



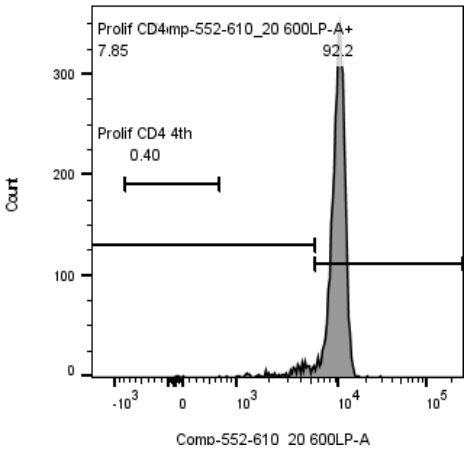
Acetate 10mM



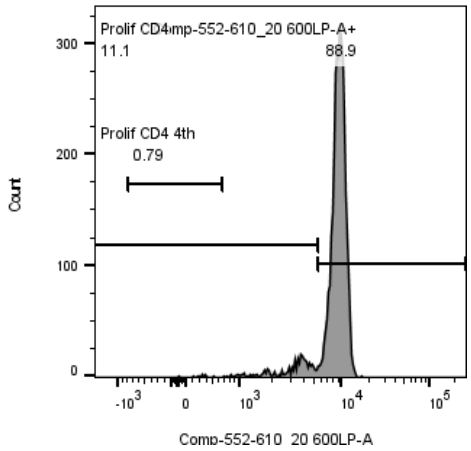
Acetate 20mM



No SCFA positive



No SCFA negative



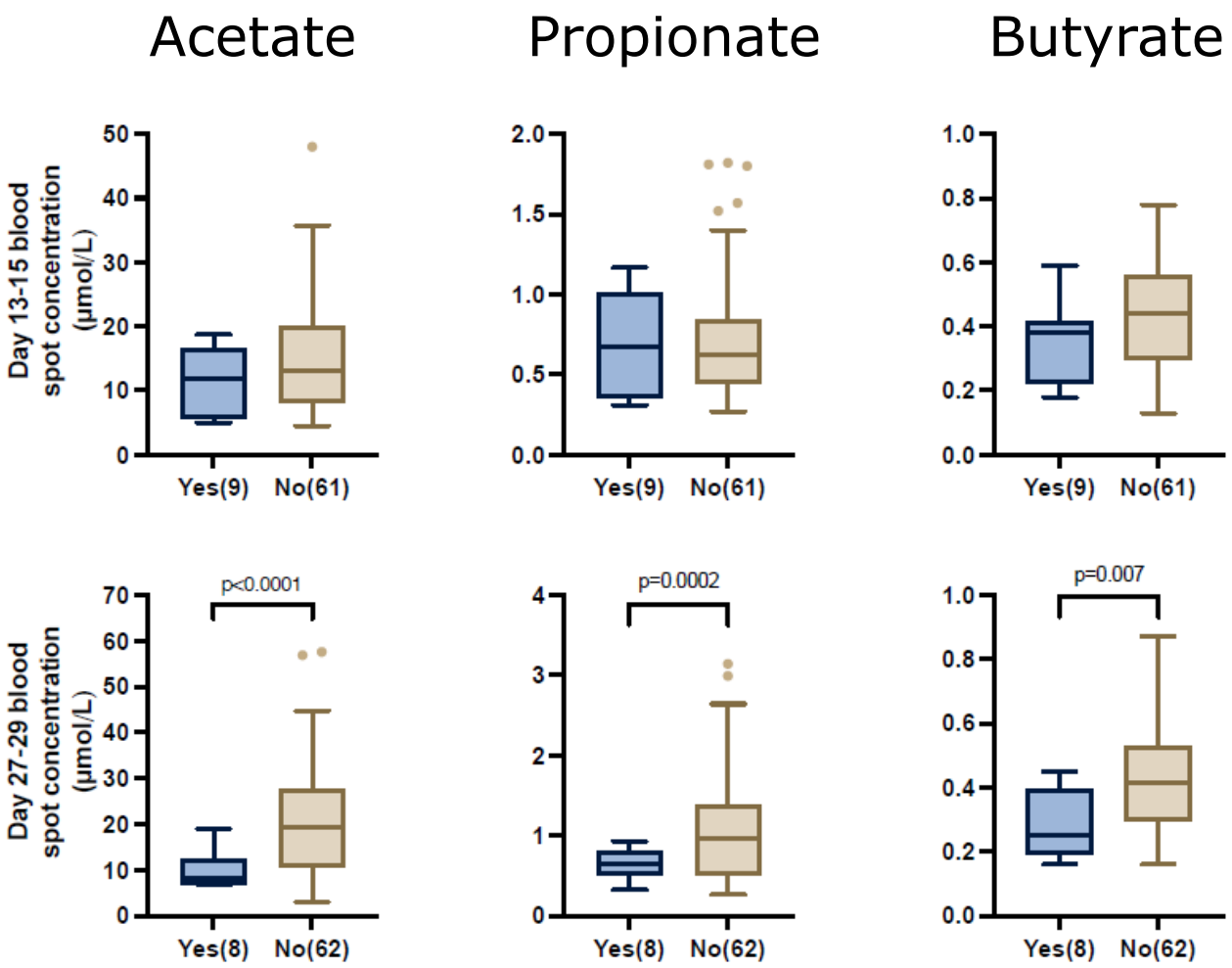
Acetate 20mM negative

unpublished

UNIVERSITY OF AUCKLAND Waipapa Taumata Rau NEW ZEALAND

LIGGINS INSTITUTE

Short chain fatty acids and NEC



unpublished

UNIVERSITY OF AUCKLAND Waipapa Taumata Rau NEW ZEALAND

LIGGINS INSTITUTE

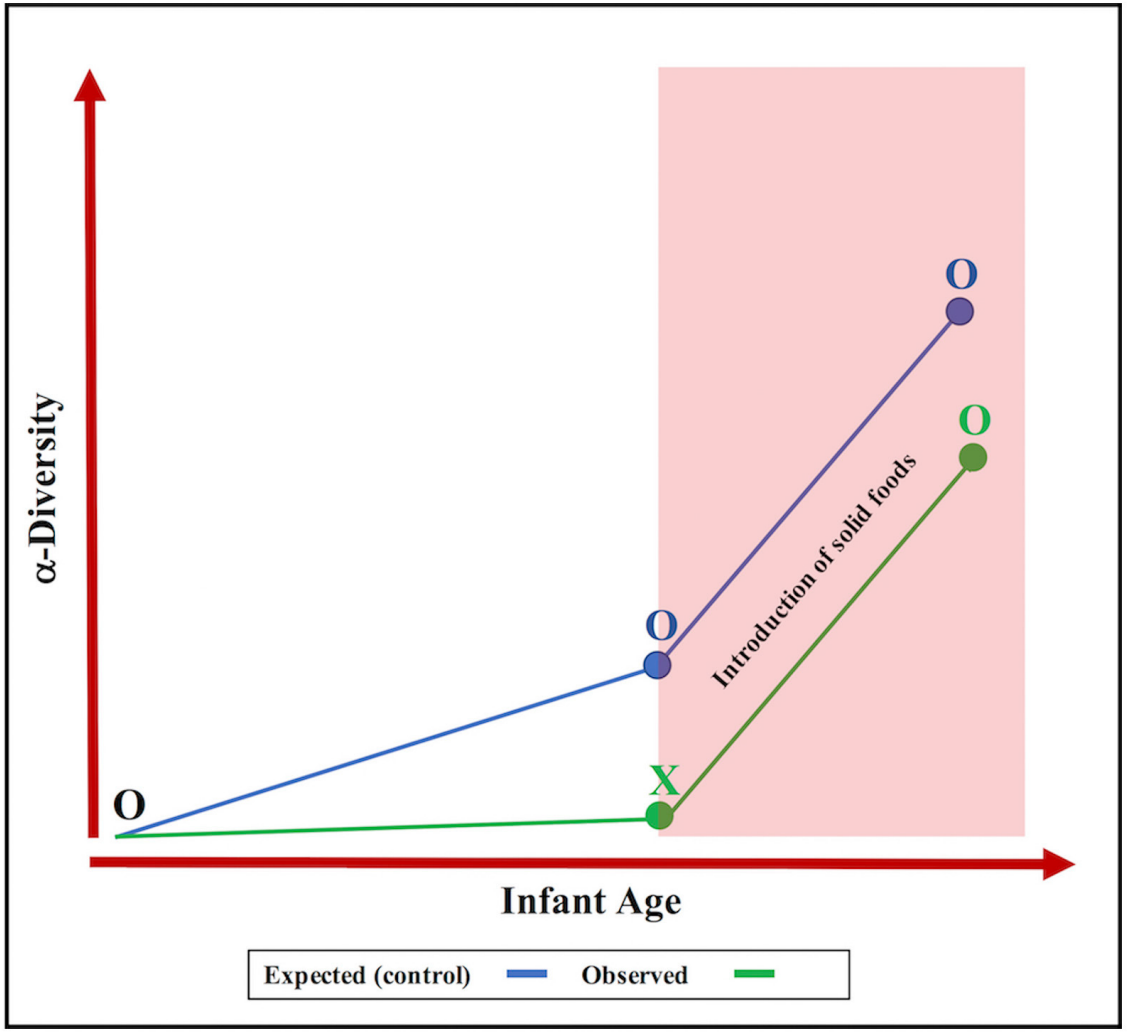
Airway microbiome

- Sampling and methodological problems
- Abundance of Proteobacteria and Firmicutes (Ureaplasma), and decreased Lactobacilli were reported with the progression of BPD
- Azithromycin: highly effective against Ureaplasma
- Azithromycin: anti-inflammatory effect via increasing the levels of tryptophan catabolites
- RCT in preterm infants (GA 24-29 wks), 2020 (Viscardi et al.): n=60 azithromycin, n=61 placebo
- A three-day course of azithromycin improved Ureaplasma-free survival and showed a promising trend towards a shorter exposure to invasive ventilation and supplemental oxygen and a shorter duration of hospitalization
- AZTEC trial – results awaited

PPIs and H2RAs

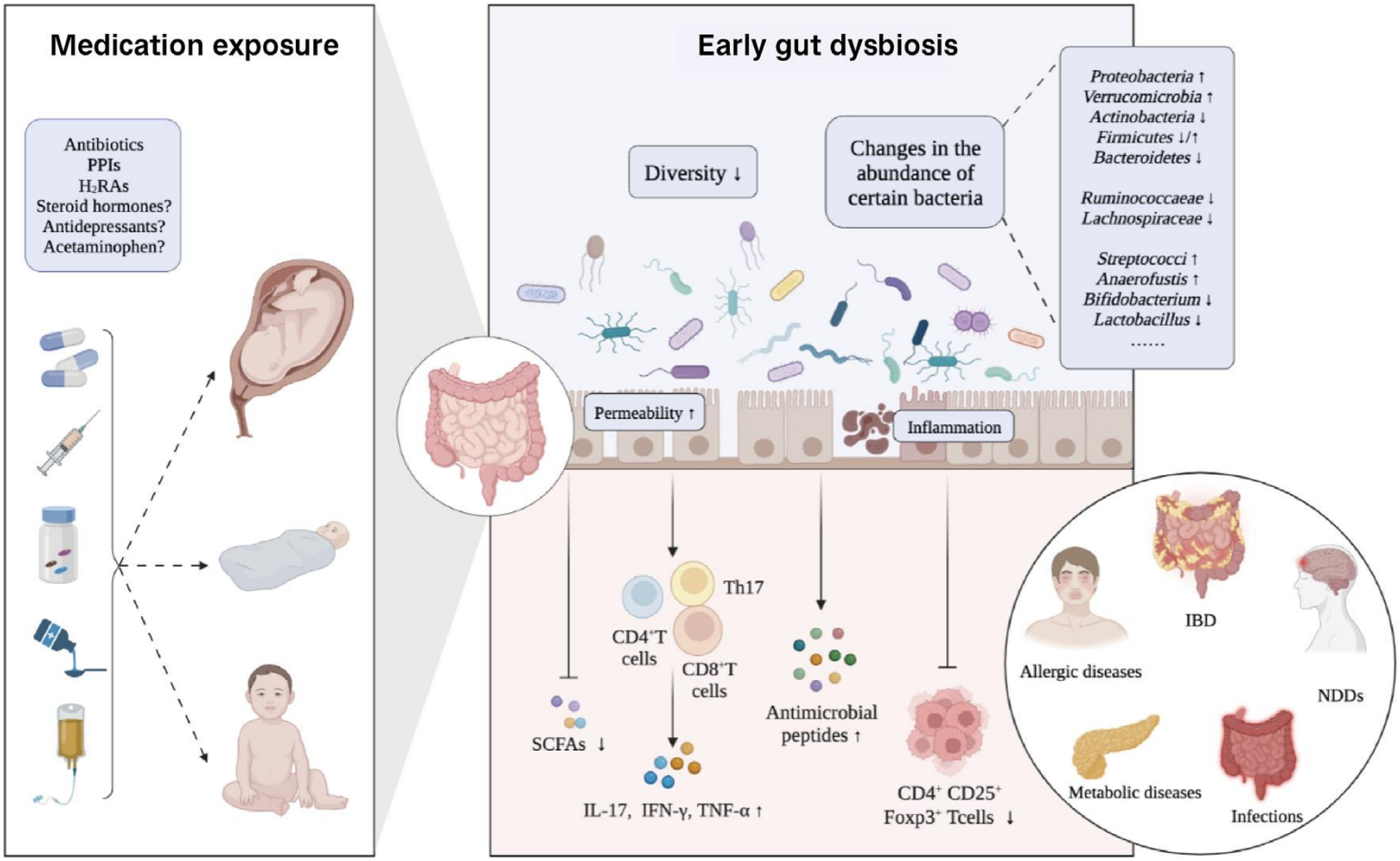
- Alter the microbiome of the mouth, gut and lungs
- Decrease in diversity
- Depletion of bacteria from the Ruminococcaceae and Lachnospiraceae families (crucial SCFA-producers)
- Increased relative abundance of Proteobacteria (mainly Enterobacteriaceae) and Haemophilus
- Decreased relative abundance of Lactobacillus and Firmicutes
- Increased risk of C. difficile
- Increased risk of NEC and LOS in premature infants
- Increased risk of asthma, obesity and small intestine bacterial overgrowth in young children

PPIs and H2RAs



Front Cell Infect Microbiol 2019;8:430

Medications and the microbiome



eClinicalMedicine 2024;68:102428

What can be done?

- Antibiotic stewardship
- Vaccine development
- Pre- and probiotics
- Breastfeeding support
- Faecal microbiota transplantation

Summary

- First 100 days: the window of opportunity for the microbiome to influence immune development
- Dysbiosis sometimes leads to severe disease in the neonatal period, but can often have subtle lifelong consequences
- Dysbiosis is almost universal in preterm infants in the NICU
- Immediate benefit vs health consequences in later life
- Use strategies to counterbalance negative effects as much as possible