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Probiotics for newborn infants

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- Probiotics

Definition

- Live microorganisms that when administered in adequate amounts confer a health benefit to the host

- Prebiotics
  - A substrate that is selectively utilized by host microorganisms conferring a health benefit
- Synbiotics
  - Dietary food supplements combining probiotics with prebiotics that support the chosen probiotics

Probiotics

- A micro-organism of human origin
- Non-pathogenic
- Resistant to destruction by technical processing & GIT secretions
- Able to colonise the GIT
- Capable of producing antimicrobial substances

- Modulating immune responses
- Influencing human metabolic activities
- Unlikely to develop resistance to commonly used antibiotics

The human intestinal microbiome

At birth, the infant's gastrointestinal tract (GI tract) is essentially "**sterile**".

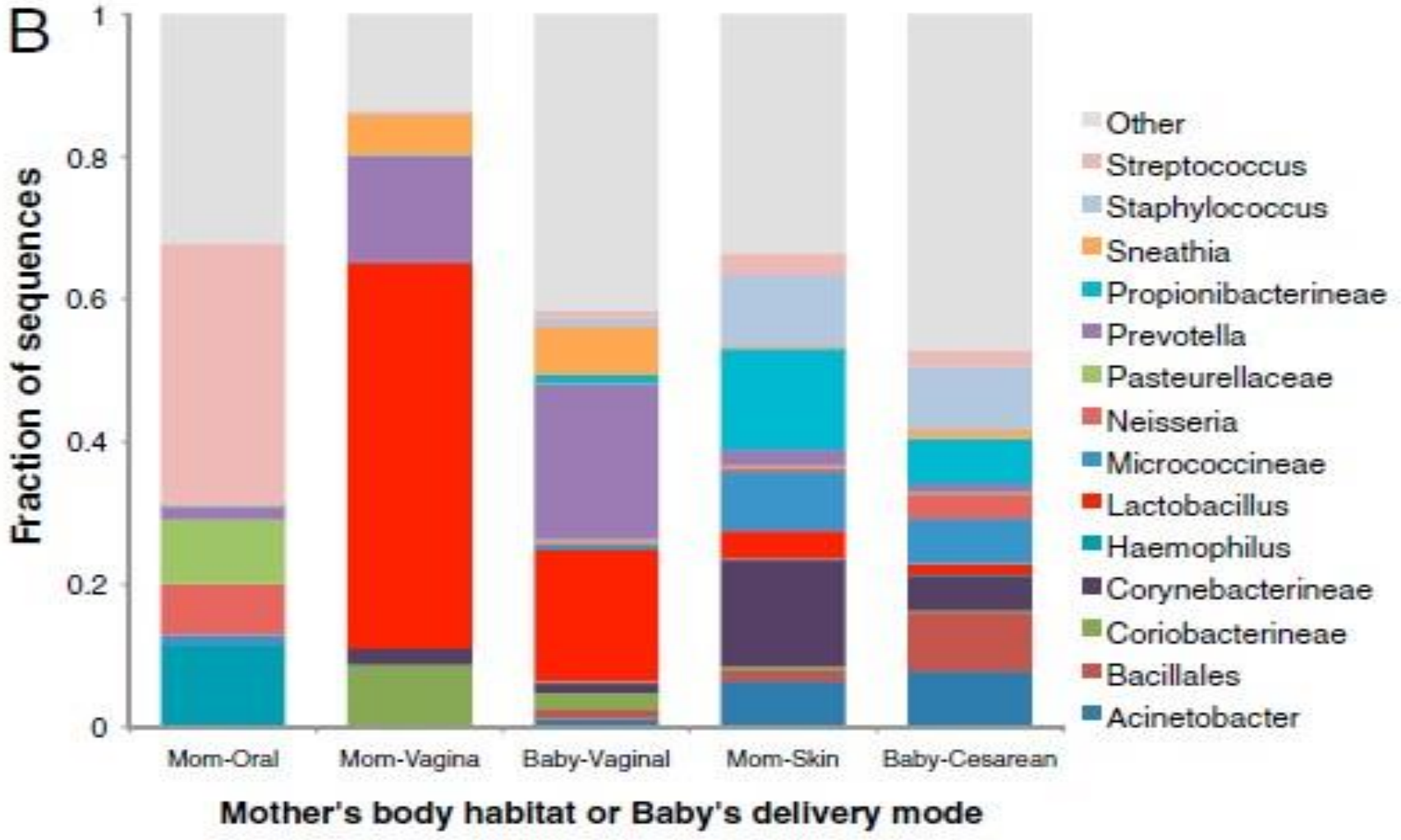
Colonization of the GI tract starts immediately after birth with the initiation of **enteral feeding**, and is well established within the first few days of life.

Intestinal flora varies widely from person to person. In adults, normal intestinal microflora consists of more than **100,000 billion** bacterial cells comprising more than **400 different species.**

- Digestion the nutrient
- Regulation of fat storage

- Metabolism of endogenous & exogenous compounds
- Immuno-regulation
- Limiting the colonisation with pathogenic microbes

Development of the infant microbiome



Dominguez-Bello et al, PNAS 2010.

The human intestinal microbiome

In **formula-fed** infants, coliforms, enterococci, and bacteroides predominantly colonize the intestinal tract. Bifidobacterium and Lactobacillus are present occasionally.

However, in **breastfed infants**, Bifidobacterium and Lactobacillus predominate with other enteric organisms being present less frequently.

The human intestinal microbiome

This pattern of bowel colonization is different in **preterm infant** in an intensive care setting.

- Antibiotic use
- infection control procedures

- and delayed initiation of enteral feeding may influence the type and amount of micro-organisms colonizing the GI tract.

The human intestinal microbiome

The GI tract of **ELBW** infants are colonized by fewer than **three** bacterial species by the **10th day** of life

Species of Bifidobacterium and Lactobacillus are found in the stool of **less than 5%** of patients studied within the 1st month of life

By **day 30 of life**, predominant organisms were enterobacteriaceae and coagulase-negative staphylococci, which are the most frequent pathogens responsible for nosocomial infection in the NICU.

Gewolb and colleagues. Arch Dis Child Fetal and Neonatal Ed. 1999

Probiotics

- Current evidence indicates that probiotic supplementation significantly reduces allcause mortality and definite necrotising enterocolitis without significant adverse effects in preterm neonates

- clinician-friendly guidelines are urgently needed to optimise use of probiotics in preterm neonates

Probiotics for preterm infants

Probiotic bacteria are defined as live nonpathogenic bacteria species that normally reside in the GI tract of healthy term infants.

It has been postulated that introducing probiotics to preterm infants might be beneficial in order to **avoid overgrowth** of pathogenic organisms.

Probiotics supplementation has been proposed to enhance **enteral feeding** and prevent **NEC** and nosocomial **infections** in preterm infants.

NEC

- Despite the advances in neonatal intensive care over past 20 years, the incidence of NEC

in preterm neonates has not changed significantly

- The mortality 20 to 25%
- morbidity
- prolonged hospitalization
- survival with short-bowel syndrome
- long-term neurodevelopmental impairment

- Previous systematic reviews of RCTs showed

– probiotic supplementation significantly reduces

  - the risk of definite NEC
  - all-cause mortality
  - the time to reach full enteral feeds (~120 to 150 ml/kg/day of milk) in preterm neonates
  - updated systematic review and meta-analysis confirmed previous results

– at least 30% reduction in the incidence of NEC

Reasons for opposing routine use of probiotics in preterm neonates

- problems in pooling data in the presence of clinical heterogeneity
- reproducibility of the results in different studies
- role of breast milk
- lack of availability of safe and effective products
- development of antibiotic resistance
- cross-contamination

- long-term adverse effects
- Many level III neonatal units in Japan, Italy, Finland and Columbia have been using probiotics routinely for over a decade, and have not reported any significant adverse effects
- Offering probiotics routinely, but still within a framework of research other than placebocontrolled trials, is the way forward

to deal with the as yet unanswered questions

Cochrane Neonatal

Probiotics for preterm infants

A variety of probiotic agents may be available for study. Lactobacillus and Bifidobacterium species are available commercially in different forms and concentrations.

Selection of strains

- Bifidobacteria and lactobacilli are the species of choice in probiotics, given the evolution of the gut flora in preterm neonates
- Bifidobacteria are the dominant strains in infancy
- the combination of lactobacilli and bifidobacteria is known to promote the growth of indigenous lactic-acid bacteria (bifidogenic effect) by

formation of short-chain fatty acids as a product of the fermentation process

- Strains isolated from humans are preferable because of their natural occurrence, long-term record of safety in infants, and adaptability to both mucosal and dairy ecosystems
- bovine strains may also be used if they have a good record of safety and efficacy

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- the specificity of the action rather than the source of the microorganism is important Evidence indicates that the functionality of a multistrain or multispecies probiotic could be more effective and more consistent than that of a monostrain probiotic

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- It was unclear whether this was due to synergistic interactions between strains or to the higher probiotic dose used

  systematic review of RCTs indicates that the trials reporting a significant decline in NEC used multistrain products

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- It is better to avoid untested combinations, because strain combinations can be antagonistic, compatible or synergistic

Dose

- An optimal mass or dose is essential for any probiotic strain to survive and colonise the gut
- Evidence indicates that to be functional, probiotics have to be viable and in sufficient dosage levels, typically 10^6 to 10^7 colonyforming units (cfu)/g of product
- There is no data on the toxic or lethal dose of probiotics for preterm neonates

- a daily dose of 3×10^9 cfu/day may be appropriate for neonates of less than 32 weeks gestation
- starting dose should be 1.5×10^9 cfu/day for ELBW neonates until they reach enteral feeds of 50 to 60 ml/kg/day
- preferably be given as a single rather than divided dose, in view of the rapid decline of the strain mass in vivo

- The osmotic load, pH and volume of a single dose are crucial in ELBW neonates

When to start

- Because of the importance of early establishment of commensal flora in preterm neonates , the probiotic supplementation should be started as early as possible before pathogens colonise
- The earliest reported age at start of supplementation was 4 hours of life

- when the neonates were ready for enteral feeds
- Clinical stability (for example, no sepsis, patent ductus arteriosus, inotropes or ileus) is desirable
- to ensure that the gut function has recovered
- with minimal risk of intolerance or translocation
- The optimal protocol for probiotic administration in ELBW neonates with intrauterine growth restriction needs to be confirmed

When to stop

- shedding of probiotic organisms in the stool commonly stops about 2 to 3 weeks after the probiotic supplement is stopped
- Hence continued administration is necessary to promote sustained colonisation in preterm neonates until evidence is available for this high-risk population

- supplementation could be stopped after reaching the corrected gestational age of 36 to 37 weeks
- The risk of probiotic translocation and sepsis is higher in critically ill and/or extremely preterm neonates with potentially compromised gut integrity

Clinical monitoring during supplementation

- Intolerance (higher osmotic load causing abdominal distension, diarrhea or vomiting)
- probiotic sepsis
- AEs (flatulence, loose stools) of additives such as prebiotic oligosaccharides need to be monitored

Dose probiotic supplementation improve growth and feeding tolerance?

- Improved GIT motility
- Improved feeding tolerance
- Reduction in days of hospitalisation
- Improved weight gain
- Intestinal colonisation with probiotic organisms

- Favorably altered immune responses
- Decreased fungal colonisation in preterm

Effects of probiotic supplementation On

- Late onset sepsis
- Weight gain
- Neurodevelopmental outcome

In preterm infants is not supportive for routine use

Studies focused on

- Allergic diseases
  - Which result from dysfunction of immune regulation
- The Cochrane review reported an inconsistent effect of probiotics in atopic eczema

Allergic diseases

- Insufficient evidence to recommend for prevention of allergic disease or food hypersensitivity
- Most beneficial if commenced ante-natally and continued post-natally

Probiotics for term infants

- Other reported benefits
  - Enhanced vaccine effects
  - Increased feeding tolerance with less colic
  - Decreased antibiotic use

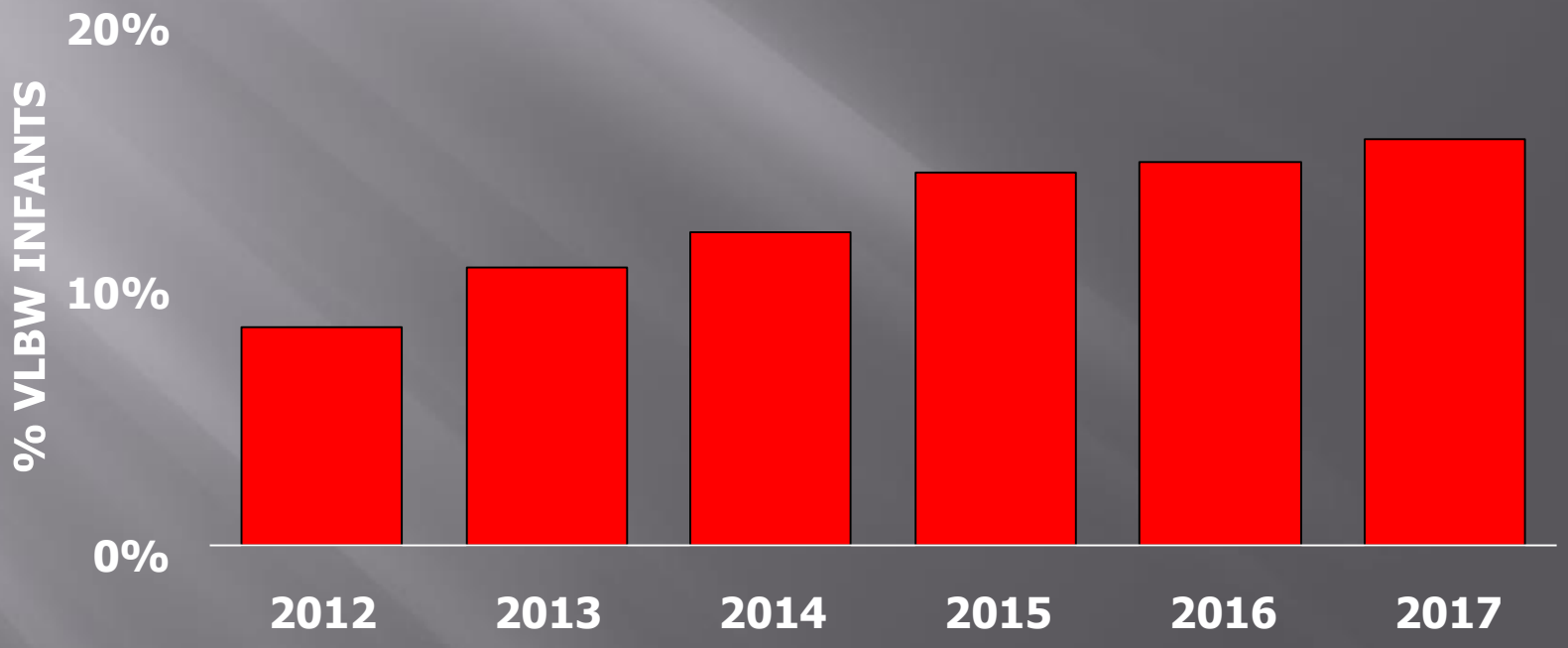
Caution

- Caution is still advised as rare adverse outcomes
  - Sepsis
  - Meningitis
  - Death

- With probiotic administration in immunocompromised patients
- Neonates have an immature immune system

Probiotics in VLBW Infants

VERMONT OXFORD NETWORK ANNUAL REPORTS 2012-2017



THANK YOU