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ROLE OF GUT MICROBIOME IN THE DEVELOPMENT OF MALNUTRITION

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ABSTRACT:
Malnutrition remains the leading cause of death worldwide in children under five, and India carries one of the highest burdens of childhood under-nutrition and, increasingly, over-nutrition. Beyond poverty, poor feeding practices, infection and socio-cultural factors, a growing body of evidence points to the gut microbiome as an additional, modifiable determinant of nutritional status. This review outlines how malnutrition is classified and identified, and traces the assembly of the infant gut microbiome from birth through breastfeeding, describing the maternal, dietary, genetic and immune factors that shape its composition. It then examines the functional roles the gut microbiome plays in host physiology, including nutrient absorption, vitamin synthesis, maturation of the intestinal barrier and regulation of the mucosal immune system, and considers how disruption of these functions through altered intestinal permeability contributes to the vicious cycle linking infection, impaired immunity and worsening malnutrition. Evidence from clinical and experimental studies, including a placebo-controlled trial of symbiotic supplementation in children with failure to thrive, is discussed to illustrate the therapeutic potential of microbiome-targeted interventions. Taken together, the findings support a view of malnutrition not simply as a lack of food, but as a condition shaped by the composition and function of the gut microbiota, with implications for how it is prevented and managed.

KEYWORDS: Gut microbiome; Malnutrition; Under-nutrition; Intestinal permeability; Infant microbiota; Symbiotic

MALNUTRITION

Malnutrition is the leading cause of death worldwide in children under the age of five, and accounts for the deaths of between one and six million children every year. It is also the focus of the first Millennium Development Goal. Malnutrition can be defined as inadequate nutrition, ranging from under-to over-nutrition. Under nutrition includes deficiency in macronutrients (protein, global energy) or micronutrients (metals such as zinc, selenium or vitamins). Although stunting rates are dropping, 159 million children around the world continue to be affected by it, and wasting still threatens the lives of 50 million children across the globe.

Under nutrition

According to the World Food Program and the M.S. Swaminathan Research Foundation (MSSRF), over the past decade there has been a decrease in stunting among children in rural India, but inadequate calorie intake and chronic energy deficiency levels remain steady. Today child malnutrition is prevalent in 7 percent of children under the age of 5 in China and 28 percent in sub-Saharan African compared to a prevalence of 43 percent in India. Under nutrition is found mostly in rural areas and is concentrated in a relatively small number of districts and villages with 10 percent of villages and districts accounting for 27-28 percent of all underweight children.
Under nutrition includes both protein-energy malnutrition and micronutrient deficiencies. Undernourishment not only affects physical appearance and energy levels, but also directly affects many aspects of the children's mental functions, growth and development which have adverse effects on children's ability to learn and process information and grow into adults that are able to be productive and contributing members of society. Undernourishment also impairs immune function leaving them more susceptible to infection. Child malnutrition is responsible for 22 percent of India's burden of disease.
Micronutrient deficiencies are also a widespread problem in India. The prevalence of micronutrient deficiencies varies in different states, More than 75 percent of preschool children suffer from iron deficiency anemia (IDA) and 57 percent of preschool children have sub-clinical Vitamin A deficiency (VAD). Iodine deficiency is endemic

in 85 percent of districts, mostly due to the lack of iodized salt that is common in the developed world. Progress in reducing the prevalence of micronutrient deficiencies in India has been slow. The prevalence of different micronutrient deficiencies varies widely across states. Most growth retardation occurs by the age of two, and most damage is irreversible. The prevalence of underweight in rural areas 50 percent versus 38 percent in urban areas and higher among girls (48.9 percent) than among boys (45.5 percent).

Over nutrition

At the same time as a large number of population suffers from malnutrition, more than 100 million people (11% of Indian population) in India are over-nourished. Over-nutrition can be defined as consuming either too much calories or the wrong types of calories such as saturated fat, Tran's fat or highly refined sugar which leads to obesity and many other chronic diseases.

The World Bank estimates that India is ranked 2nd in the world of the number of children suffering from malnutrition, after Bangladesh (in 1998), where 47% of the children exhibit a degree of malnutrition. The prevalence of underweight children in India is among the highest in the world, and is nearly double that of Sub-Saharan Africa with dire consequences for mobility, mortality, productivity and economic growth. The UN estimates that 2.1 million Indian children die before reaching the age of 5 every year – four every minute - mostly from preventable illnesses such as diarrhea, typhoid, malaria, measles and pneumonia. Every day, 1,000 Indian children die because of diarrhea alone. According to the 1991 census of India, it has around 150 million children, constituting 17.5% of India's population, who are below the age of 6 years. India is one of the fastest growing countries in terms of population and economics, sitting at a population of 1,139.96 million (2011) and growing at 10-14% annually (from 2001–2010).

The combination of people living in poverty and the recent economic growth of India has led to the co-emergence of two types of malnutrition: under nutrition and over nutrition. The implications of both over nutrition and under nutrition indicate that a country can exert rates of infectious diseases and chronic diseases simultaneously: A situation that has not been observed before in history. This new phenomenon of the rising incidence of chronic diseases such as heart disease, cancer and type II diabetes along with the presence of infectious diseases such as pneumonia, and tuberculosis is mainly attributed to rapid population growth and the increase in the country's economy.

Anthropometric definition

Childhood under-nutrition encompasses several clinical forms, including stunting (low height-for-age <-2 Standard deviation(SD), wasting (low weight-for-age <-2 SD) and underweight (low weight-for-height <-2 SD). Each of these terms can be considered as moderate (between -2 and -3 SD) and severe (under -3SD). While acute malnutrition corresponds to wasting (thinness), or nutritional edema, chronic malnutrition is associated with stunting (shortness/poor cognitive development), and acute and/or chronic malnutrition is associated with underweight. While stunting is considered to be more common, wasting is associated with a higher mortality.

Identifying malnutrition: Malnutrition can be identified into two constituents, protein-energy malnutrition and micronutrient deficiencies, where protein-energy malnutrition is clearly observed in India and other developing countries. There are different methods of identifying malnutrition; physical findings generally help in the diagnosis of advanced malnutrition. In identifying it early in the development malnutrition, it is of advantage to allowing early rehabilitation. One of the classifications of protein-energy malnutrition is done by Gomez, which uses anthropometric indices.

Degrees of malnutrition

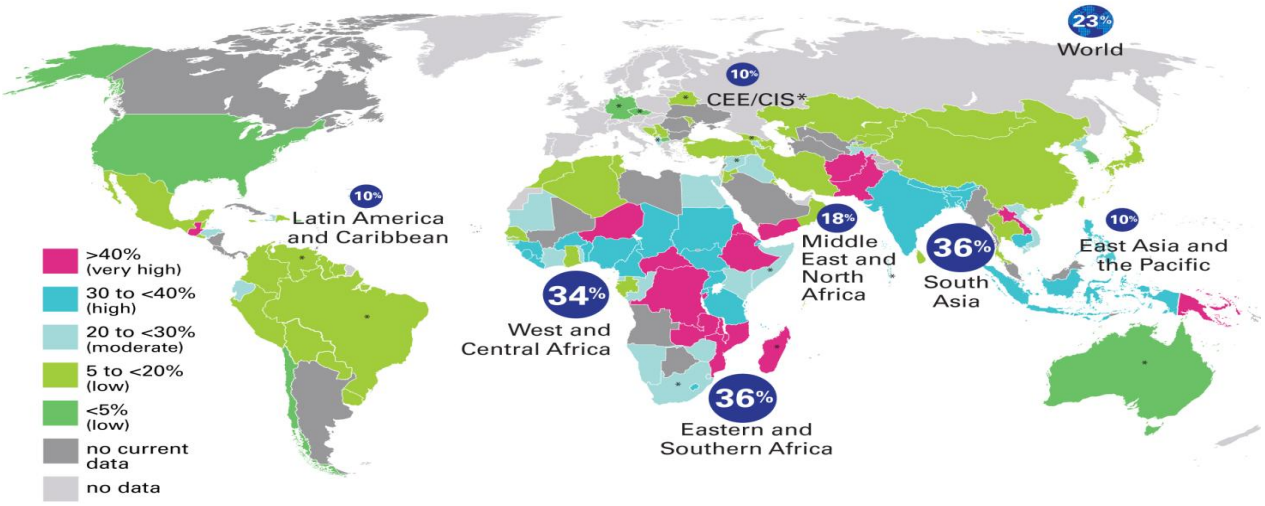
Gomez classification of PEM:

Degree of PEM % of desired body wt. for age and sex

- Grade I. Severe Malnutrition
- 90%-100%
- Grade II. Moderate Malnutrition
- 75%-89%
- Grade III. Mild Malnutrition
- <60%

Protein-energy malnutrition can also be classified as marasmus, kwashiorkor or a combination of both. In marasmus conditions are characterized by extreme wasting of the muscles and a daunt expression; where kwashiorkor is identified as swelling of the extremities and belly, which is deceiving to their actual nutritional status (Black, et al., 2006).

Prevalence of malnutrition



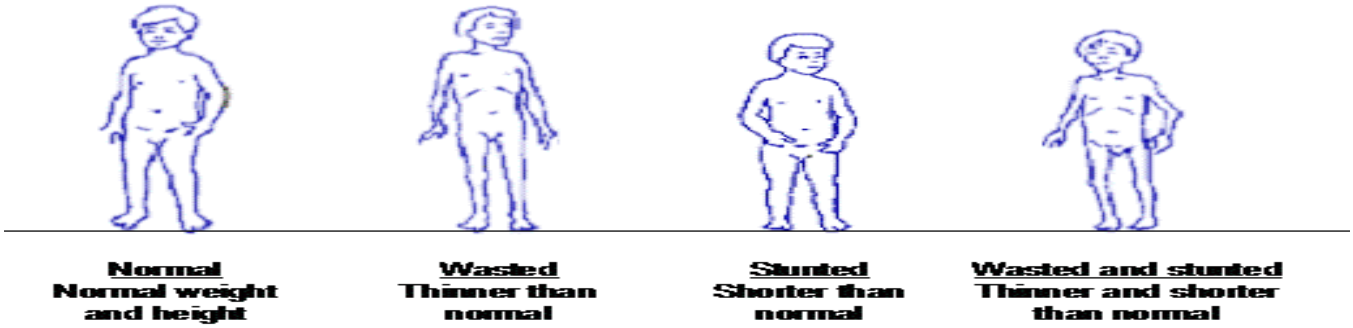
Nearly half of all deaths in children under 5 are attributable to under nutrition. This translates into the unnecessary loss of about 3 million young lives a year. Under nutrition puts children at greater risk of dying from common infections, increases the frequency and severity of such infections, and contributes to delayed recovery. In addition, the interaction between under nutrition and infection can create a potentially lethal cycle of worsening illness and deteriorating nutritional status. Poor nutrition in the first 1,000 days of a child's life can also lead to stunted growth, which is irreversible and associated with impaired cognitive ability and reduced school and work performance (UNICEF, 2016).

Protein-energy malnutrition

There are three types of protein-energy malnutrition in children:

Type	Appearance	Cause
Acute malnutrition	Wasting or thinness	Acute inadequate nutrition leading to rapid weight loss or failure to gain weight normally
Chronic malnutrition	Stunting or shortness	Inadequate nutrition over long period of time leading to failure of linear growth
Acute and chronic malnutrition	Underweight	A combination measure, therefore, it could occur as a result of wasting, stunting, or both

These forms of protein-energy malnutrition in children can be pictured like this:



The two clinical forms of PEM:

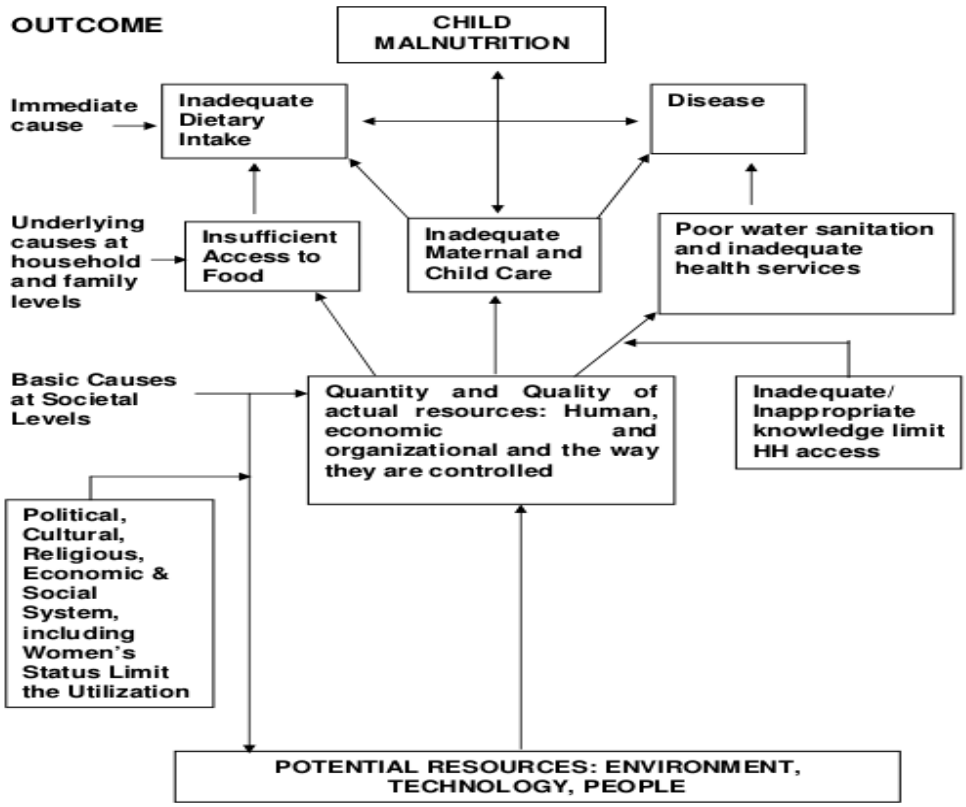
- Marasmus : Deficiency of energy, Marasmus severe loss of body weight or wasting
- Kwashiorkor: deficiency of protein, Kwashiorkor nutritional bilateral oedema.

Clinical Signs of Marasmus

- A thin 'old man' face
- 'Baggy pants' loose skin around the buttocks
- No nutritional oedema
- Prominent ribs
- The children are usually active and may appear to be alert in their condition

Clinical Signs of Kwashiorkor

- Nutritional oedema
- Loss of appetite
- Hair changes
- Skin lesions and de-pigmentation
- Children are usually apathetic, miserable and irritable.
- Moon Face



Causes of malnutrition

Gut Microbiomes

Poverty

Poor socioeconomic position was associated with chronic malnutrition since it inhibits purchase of nutritious foods such as milk, meat, poultry, and fruits. Low purchasing power, poor cannot afford to buy desired amount and desired quality of food for the family. This adversely affects their capacity for physical work and they earn less. Thus starts a vicious cycle of poverty, under nutrition, diminished work capacity, low earning and poverty.

Feeding habits

Lack of awareness of nutritional qualities of food, irrational beliefs about food, inappropriate child rearing and feeding habits all lead to under nutrition in the family.

Infections

Infections like malaria and measles or recurrent attacks of diarrhoea may precipitate acute malnutrition and aggravate the existing nutritional deficit. Metabolic demands for protein are higher during infections and the child may take in less food either due to reduced appetite or due to food restrictions by the mother. Thus leading to malnutrition

Socio-cultural factors

- Inequitable distribution of food in the family. In most of the poor households, women and preschool children especially girls receive less food than the economically active male members
- Large families Rapid succession of pregnancies adversely affects the nutritional status of the mother. As she tries to manage the big family she may neglect her own health and antenatal checkups during pregnancy. Under nutrition may lead to low birth weight baby. In large families per capita availability of food is also less.

- Poor quality of housing, sanitation and water supply. These contribute to ill health and infections thus contributing to malnutrition.
- Inadequate maternal and child care- Improving the primary health centers and other health care services in the rural areas will definitely improve the nutrition profile of women and children (Gragnolat, et al., 2012).

Other this factors microbiome is also one of the casual factors of affecting the malnutrition:

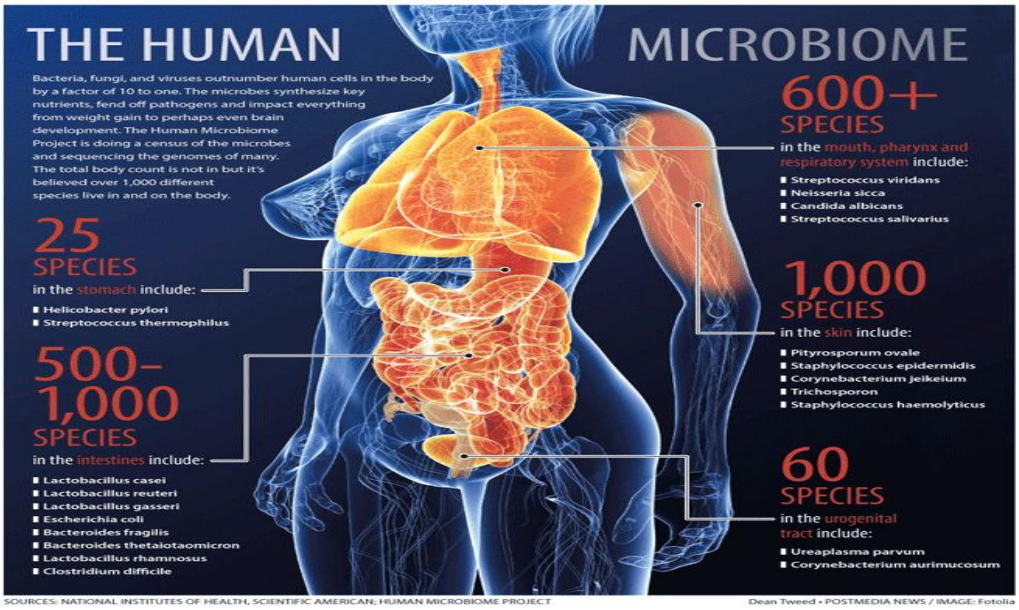
Microbiome

Microbe : Tiny living organism, such as bacterium, fungus, protozoan, or virus
Microbiome : Collectively all the microbes in the human body; a community of microbes

What is the microbiome

Microbes are extremely small living organisms that include bacteria and fungi. Viruses, while technically not living organisms (they require a living host to reproduce), are also considered microbes. Individual microbes cannot usually be seen with the naked eye; however, large collections of microbial cells can sometimes be seen. For example, bacteria can form visible colonies or 'streaks' when spread on gels containing nutrients for them. Additionally, mushrooms are reproductive structures made by some fungi, and we can certainly see the mold colonies that grow on old food. These visible structures are made up of millions of cells.

- We humans are mostly microbes, over 100 trillion of them. Microbes outnumber our human cells ten to one. The majority live in our gut, particularly in the large intestine.
- The microbiome is the genetic material of all the microbes - bacteria, fungi, protozoa and viruses - that live on and inside the human body.
- The number of genes in all the microbes in one person's microbiome is 200 times the number of genes in the human genome. The microbiome may weigh as much as five pounds.
- The bacteria in the microbiome help digest our food, regulate our immune system, protect against other bacteria that cause disease, and produce vitamins including B vitamins B12, thiamine and riboflavin, and Vitamin K, which is needed for blood coagulation.



HIM comprises of over 100 trillion distinct organisms with more than 1,000 distinct species and approx. 5 million microbial genes.

- 100 trillion microbes in human intestine
- 3 million genes
- 2 kg weight
- 300-1000 species of bacteria
- Control almost all body function
- There are over 40,000 species identified to date.

The bacteria in the microbiome

Bacteria present in the gut microbiome play an essential role in human health by aiding in the digestion of food, regulating the immune system, and protecting the host against pathogenic bacteria. In addition, these bacteria contribute to the synthesis of essential vitamins, including B-group vitamins such as vitamin B1 (thiamine), vitamin B2 (riboflavin), and vitamin B12, as well as vitamin K, which is important for normal blood coagulation.

Human Gut Micro biome

The human intestinal micro biota (HIM) is one of the richest bacterial environments within the human body. Gut colonization begins at birth and stabilizes by approximately 3–4 years of age. The predominant microbial communities in the human gut belong to the phyla Bacteroidetes, Firmicutes, Actinobacteria and Proteobacteria. These microorganisms play an important role in maintaining human health and contribute to almost all major physiological functions of the body, including digestion, metabolism, immune regulation, and protection against pathogenic microorganisms.

What does the microbiome have to do with health?

The microbiome is essential for human development, immunity and nutrition. The bacteria living in and on us are not invaders but beneficial colonizers. Autoimmune diseases such as diabetes, rheumatoid arthritis, muscular dystrophy, multiple sclerosis, and fibromyalgia are associated with dysfunction in the microbiome. Disease-causing microbes accumulate over time, changing gene activity and metabolic processes and resulting in an abnormal immune response against substances and tissues normally present in the body. Autoimmune diseases appear to be passed in families not by

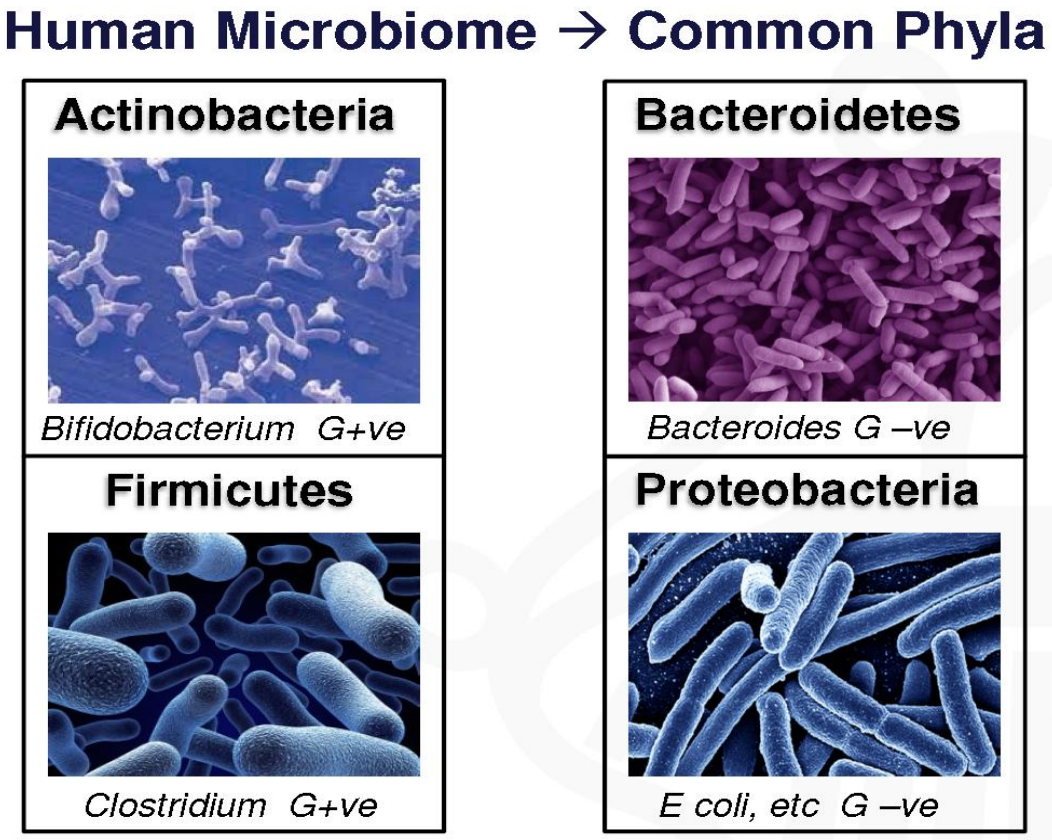
DNA inheritance but by inheriting the family's microbiome.

The human gastrointestinal tract harbors a diverse microbial community throughout its extent, which supports their hosts mostly for healthy living. It has been estimated that the adult human colonic bacteria reaches approximately 10^{14} organisms throughout the GI tract, which is 10 times the total number of somatic and germ cells within the body. The colon of a healthy human adult harbors around 400–500 different species of bacteria belonging to 190 different genera, although a few genera together comprise the major cultivable flora of the feces (Ramakrishna, 2007). These bacteria have important metabolic roles, e.g., production of short-chain fatty acids and vitamins such as vitamin K and biotin, structural functions like immune system development and protective functions, e.g., pathogen displacement by colonization competition (Annand et al., 2006). Colonization of commensal bacteria in the gut of newborns has profound implications in weaning period.

Indigenous microbiota play an important role in developing homeostatic immunity by suppressive mechanisms to avoid local and peripheral hypersensitivity to innocuous antigens particularly food proteins and components of commensal bacteria by dendritic cells (DCs) and regulatory T cells in mesenteric lymph nodes. Pathogenic bacteria can alter the gut microbiota proportions significantly. Namely, colonization of Vibrio cholerae in the gut epithelial cells causes profuse loss of water and electrolytes which results in expulsion of Bifidobacteria and invites increasing proportion of Enterobacteriaceae (Monira et al., 2010).

Role of gut microbiota in immune diseases has been demonstrated and bacterial imbalance has been associated with pathologies such as inflammatory bowel disease and obesity. Microbial ecology of the gastrointestinal tract also plays a key role in nutrition research into the relation between colonic microbiota signatures and age, diet, dietary allergies, or diseases. These observations have stimulated renewed interests in research on the GI tract microbiota (biomarkers) of healthy and diseased individuals. Diet and nutritional status are specifically most important factors which are known as the modifiable determinants of human health. As gut microbiota play an important role in nutrient extraction from food in the lower part of GI tract, then the nutritional value of food is influenced partially by a person's gut microbial community (microbiota) and its component genes. Malnutrition continues to remain a persistent problem for children under 5 years of age in developing countries.

The concept of malnutrition is changing rapidly and it is not always related to lack of food, but can also be related to the set of gut flora that can play both positively and negatively by influencing the intestinal absorption of nutrients. It has been hypothesized that changes in intestinal microbial ecology and the microbiome because of pathogenic infection or treatment by antibiotics can also disrupt the intricate balance between the gut flora and thus affect the harvest of nutrients from the diet. Additionally, human genetic polymorphisms that alter host genes can also have impact on nutrient absorption and metabolism.



Actinobacteria

- Actinobacteria is a phylum of gram-positive bacteria with high G+C content.
- The Health Benefits of Bifidobacterium Lactis. Even though there are over a dozen probiotic strains, Bifidobacterium lactis is one of the most versatile and hardest working for the human body. Similarly to other strains, these lactic acid bacteria can help fight lactose intolerance and boost the immune system.

Bacteroidetes

- The phylum Bacteroidetes is composed of three large classes of Gram-negative, non spore forming, anaerobic or aerobic, and rod-shaped bacteria that are widely distributed in the guts and also present in the skin. Porphyromonas, a group of organisms inhabiting the human oral cavity.

Firmicutes

- The Firmicutes (Latin: firmus, strong, and cutis, skin, referring to the cell wall) are aphylum of bacteria, most of which have Gram-positive cell wall structure.
- Ex: ,Clostridium, Megasphaera, Pectinatus, Selenomonas and Zymophilus

Health implications

- Firmicutes make up the largest portion of the human gut microbiome.
- The division Firmicutes as part of the gut flora has been shown to be involved in energy resorption,
- Gut microbiota influence the growth and differentiation of gut epithelial cells and play pivotal nutritive, metabolic, immunological and protective functions.

Proteobacteria

- The "Proteobacteria" are a major phylum of Gram-negative bacteria. The name of the phylum has never been validly published as no type genus has been proposed, thus it must be styled in quotation marks as the name has no standing in nomenclature.
- They include a wide variety of pathogens, such as *Escherichia, Salmonella*, *Vibrio, Helicobacter, Yersinia* and many other notable genera. Others are free-living (nonparasitic) and include many of the bacteria responsible for nitrogen fixation.

Genomic approaches to characterize skin bacteria have revealed a much greater diversity of organisms than that revealed by culture-based methods, predominantly from four different phyla: Actinobacteria, Firmicutes, Bacteroidetes and Proteobacteria. Our group and others have demonstrated that the proportion of these bacterial phyla is dependent on the physiology of the skin site, with specific bacteria being associated with moist, dry and sebaceous micro environments (Costello et al., 2009). Propioni bacterium spp. are the dominant organisms in sebaceous areas, which confirms classical microbiological studies. Staphylococcus and Corynebacterium spp. are the most abundant organisms colonizing moist areas. The most diverse skin sites are the dry areas, with mixed representation from all four phyla. A surprising feature of the microbiota of dry sites, as captured by molecular analysis, is the abundance of gram-negative organisms, which were previously thought to colonize the skin only rarely, as contaminants from the gastrointestinal tract. As shown in Figure 1, the microbiome of the antecubital fossa, back, nare and plantar heel are more similar to the same site on another individual than to a different site on the same individual. In this sense, the ecological niche, or skin site, is a greater determinant of the microbiota composition than the individual genetic variation among healthy volunteers. Some sites on an individual are similar, such as different sebaceous regions that share common ecological features. Molecular analysis of skin micro biota has also revealed that the temporal variability of the skin microbiome is dependent on the site sampled. In healthy adults, skin niches including the nares, glabella, and external auditory canal demonstrate relative stability as compared to dry regions such as the inner forearm and the heel. In general, contralateral sites on the same individual are more similar to each other than to a corresponding site on another individual.

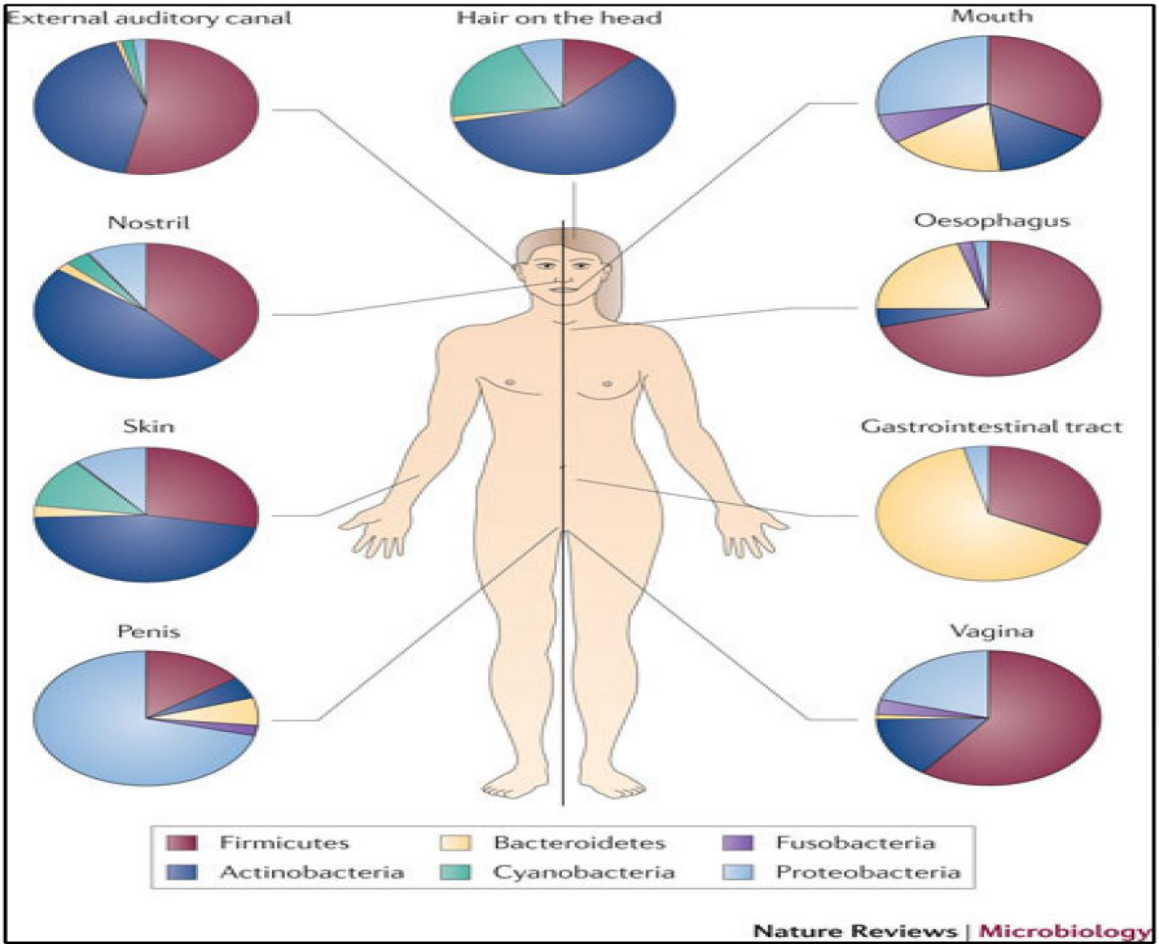
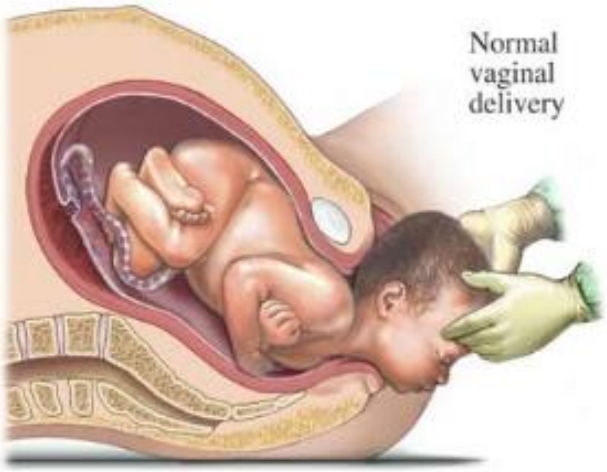


Figure 1: Human micro biome- common& Rare Phyla

Initial colonization stages of development of microbiome

1. Birth canal

- Previously, we thought that babies were sterile in their mother's womb, and they were first exposed to micro biome in the birth canal.
- However, we now know that the placenta has its own micro biome, and that our life long micro biome balance is started at the moment of conception.
- The placenta micro biome is based on our mothers. This is why it is really important to plan pregnancy, and to ensure that the mother is in a good state of health.



2. Birth

- The next stage of micro biome conditioning is birth.
- As the baby passes down the birth canal, its face, eyes, ears and mouth are covered in secretions from the birth canal, which give the baby a heavy dose of his lifelong micro biome.
- 3 weeks before the birth, (if the birth is at the expected time) the mother's body will populate the birth canal with billions of beneficial bacteria and yeasts, in preparation for the baby to swallow and set the standard for health.

Problems occur when:

- The baby is premature and the appropriate micro biome has not been place in the birth canal
- The mother is on antibiotic before or during the birth
- The baby is born by caesarean

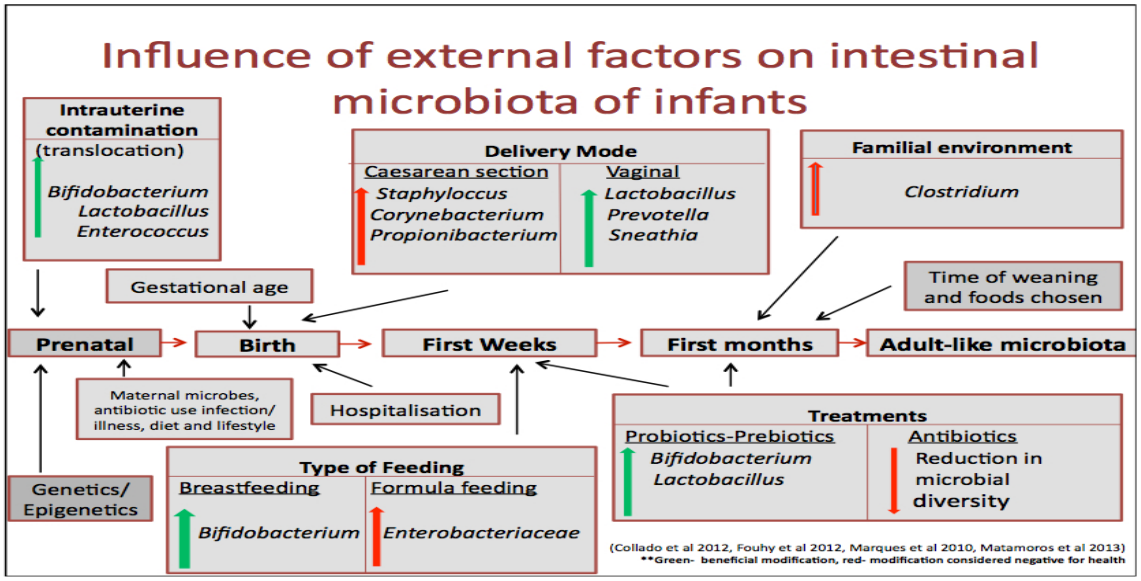
3. Skin to skin transfers of micro biome

- The third stage of micro biome transmission is skin to skin contact.
- Skin to skin transfers the micro biome of the skin from the mother to the babies skin.
- This is why imitate skin to skin contact is so important.
- If we miss out this vital stage, then the baby will pick up the microbiome from the environment around him. This can be a problem if it is a hospital birth or if the mother is too unwell to care for her child.

4. Breast milk

The fourth stage of micro biome transmission is through breast milk.

Breast milk is a power house of bacteria! The bacteria line the digestive tract of the baby and prepare the baby's gut for foods later on. (Olesen et al., 2016).



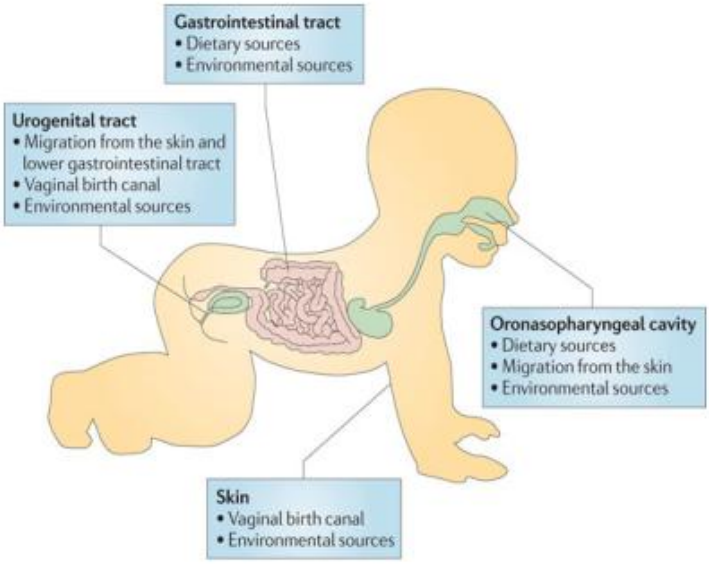


Figure 2: Influence of external factors on intestinal microbiota of infants

Pre-conception and Pregnancy

The commonly accepted belief that the the baby inside the uterus is sterile (whilst membranes are intact) is being challenged. It seems that maternal gut micro biota may be able to translocate to the baby/placenta via the blood stream. Women's gut microbiota change during pregnancy and this impact on metabolism. So ideally, women need to head into pregnancy with a healthy micro biome and then maintain it. Unfortunately our modern lifestyle is not very micro biome friendly and many of us have dysbiosis (an imbalance in gut bacteria). Dysbiosis and too much of the 'wrong' bacteria has been linked to premature rupture of membranes and premature birth (Figure 2).

Birth

There is a difference between the microbiome of a baby born vaginally compared to a baby born by c-section. During a vaginal birth the baby is colonized by maternal vaginal and faecal bacteria. Initial human bacterial colonies resemble the maternal vaginal microbiota – predominately Lactobacillus, Prevotella and Sneathia. A baby born by c-section is colonised by the bacteria in the hospital environment and maternal skin – predominately Staphylocciand C difficile. They also have significantly lower levels of Bifidobacterium and lower bacterial diversity than vaginally born babies. These differences in the microbiome 'seeding' may be the reason for the long-term increased risk of particular diseases for babies born by c-section.

The environment in which the baby is born also influences their initial colonization. A study by found that term infants born vaginally at home and then breastfed exclusively had the most 'beneficial' gut microbiota. It is likely that these babies only came into contact with the microbiota of their family during the key period for 'seeding' the microbiome. The chance of colonisation and infection with group B streptococcus (GBS) is reduced with water birth. This may be due to dilution of the GBS or additional colonization of the baby with beneficial bacteria.

Postnatal

After birth, colonization of the baby by microbiota continues through contact with the environment and breastfeeding. There are significant differences in the microbiota of breastfed babies compared to formula fed babies. Beneficial bacteria are directly transported to the baby's gut by breastmilk and the oligosaccarides in breastmilk support the growth of these bacteria. The difference in the gut microbiome of a formula fed baby may underpin the health risks associated with formula feeding. In the short term, infant colic may be associated with high levels of proteobacteria in the baby's gut Figure 2 (Annand, et al., 2011).

Impacting factors on Gut Microbiome

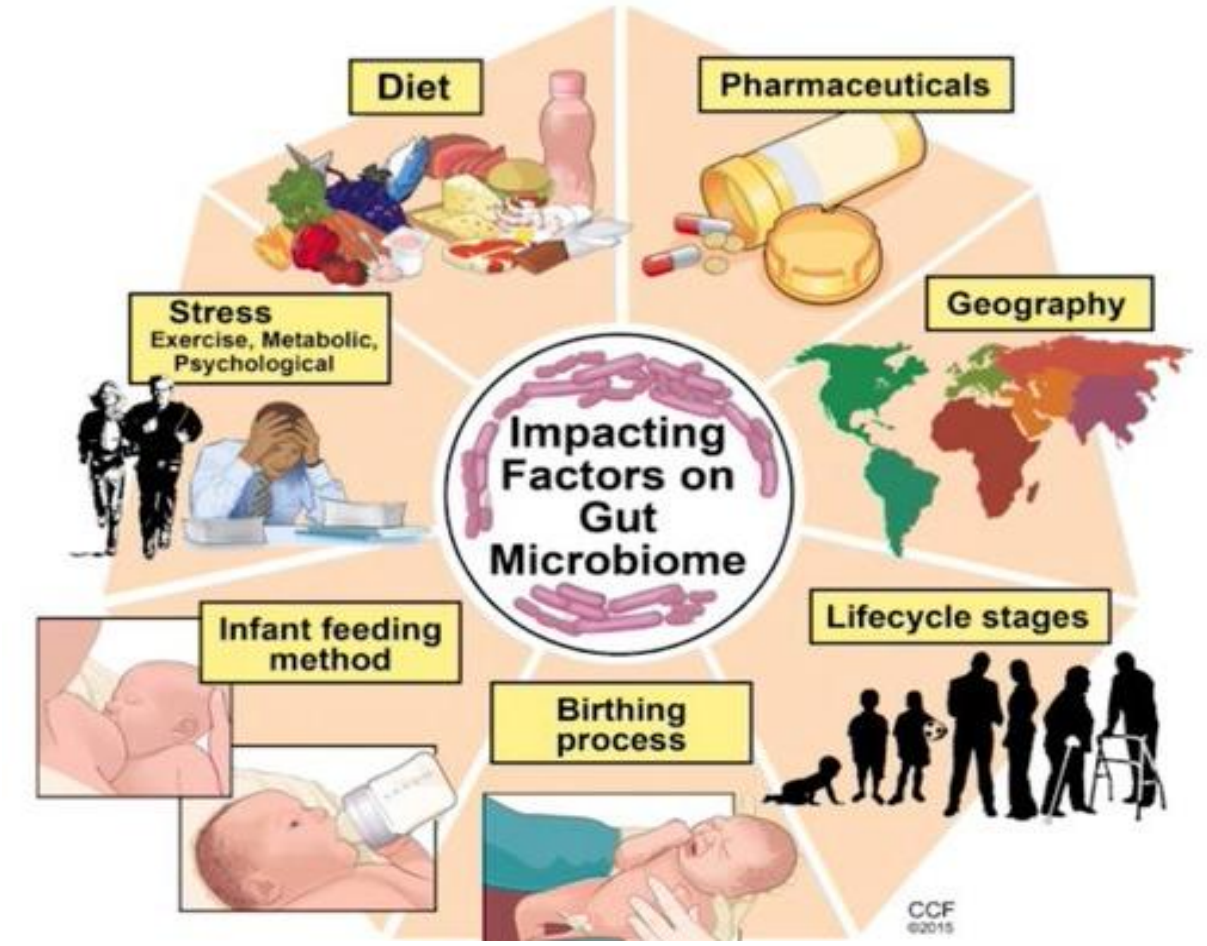


Figure 3: Factors influencing gut microbiota

Maternal Gut Microbiota

Many recent studies suggest a mother-to-infant vertical transmission of gut microbes, and particularly bifidobacteria and lactobacilli. While the mother's microbiota is altered during pregnancy, Bifidobacterium and, specifically, B. longum are enriched in the mother's gut microbiota at delivery. B. longum is also the predominant bifidobacterial species in the gut of infants from Italy, Spain and Ireland. Several pieces of data suggest that the mother's gut microbes can reach the infant's gut via one or multiple routes, including in utero colonization and breastfeeding, but also vaginal delivery. Each route may, however, transmit specific microbes, with the mother's milk being particularly associated with bifido bacteria. This vertical transmission suggests a transgenerational alteration of gut microbiota.

Breastfeeding

Maternal milk, the first natural symbiotic breastfeeding, induces gut microbiota rich in Bifidobacterium and depleted in E. coli, Clostridium difficile, Bacteroides, and lactobacilli. The mother's milk is critical shaping the baby's gut microbiota as it is a synbiotic food that supplies B. longum and its prebiotics (galactooligosaccharides) to the baby's gut, promoting its very-broad-spectrum lantibiotic. This prevents the over-growth of Enterobacteriaceae, linked to malnutrition-associated enteropathy. Secretory IgA class (SIgA) antibodies in breastmilk also promote long-term intestinal homeostasis by regulating gut microbiota. Infant formula more closely resembling human milk (with the addition of B. longum) was found to be more bifidogenic than the control formula without probiotic and led to a microbiota profile similar to that for breastfed infants (decreased Enterobacteria and Clostridia). In developed countries most, if not all, infant formulae are supplemented with lactic acid bacteria probiotics, previously shown to be associated with better growth (Figure 3).

Diet

For a long time, it has been demonstrated that food with or without probiotics is able to shape the gut microbiota. In obese people, a restricted diet correlated with a global change in the Bacteroidetes/Firmicutes ratio. Haro recently showed that a long-term consumption of a Mediterranean diet or a low-fat, high-complex carbohydrate diet has a protective effect on the development of Type 2 diabetes by introducing different specific changes to the gut microbiota, increasing the abundance of the Roseburia genus and Faecalibacterium prausnitzii, respectively.

The diets of undernourished children are commonly depleted in iron, zinc and meat. Krebs et al. studied the effects of three different complementary feeding diets (commercially available pureed meats, iron- and zinc-fortified infant cereals, iron-only fortified infant cereals) upon enteric microbiota in exclusively breastfed infants. The most significant difference between the diets was the butyrate-producing clostridia group XIVa increase in the meat group. This cluster is of foremost importance, since it included several bacteria previously associated with gut microbiota maturation, notably in the Lachnospiraceae family, accounting for almost 60% of the mucin-adhered microbiota. Of the many acetate and/or lactate-converting butyrate producers within this cluster, Roseburia intestinalis and Eubacterium rectale most specifically colonized mucins, and are two major representatives of gut microbiota maturation. In African children, iron fortification produced a potentially more pathogenic gut microbiota profile, with increased Enterobacteria and Clostridium and decreased lactobacilli, and this profile was associated with increased gut inflammation (Figure 3).

Host Genetics

Genome-wide associations have recently been reported, linking, for example, Akkermansia and a variant near PLD1, a gene previously associated with body mass index. This confirmed previous culture studies linking the genetic constitution of animals with the composition of flora characteristic of the mouse colony.

Host Immunity: Immunoglobulin A

Immunoglobulin A represents a carefully regulated link between host immunity and a fraction of the gut microbiota (the IgA+ fraction). IgA-deficient mice have dramatically altered gut microbiota and maturation of gut microbiota was shown to be, in part, regulated by induction of a Proteobacteria-specific IgA response.

Infections

Enteric infections are undoubtedly a critical factor in disrupting the overall gut microbiota, and this has been well described with C. difficile. In addition, a global depletion of digestive bacteria has been described in enteric salmonellosis (Figure 3) (Kerac et al., 2009).

Figure 4: Factors Affecting Infant Microbiome Development

A fecal sample analysis of 98 Swedish infants over the first year of life found a connection between the development of a child's gut microbiome and the way he or she is delivered. Babies born via C-section had gut bacteria that showed significantly less resemblance to their mothers compared to those that were delivered vaginally.

The study, which appears May 11 in Cell Host & Microbe's special issue on "The Host-Microbiota Balance," also found nutrition to be a main driver of infant gut microbiome development--specifically the decision to breast-feed or bottle-feed. "The study findings surprisingly demonstrated that cessation of breastfeeding, rather than introduction of solid foods, is the major driver in the development of an adult-like microbiota," says lead study author (Backhed et al., 2015) of The University of Gothenburg, Sweden. "However, the effect of an altered microbiome early in life on health and disease in adolescence and adulthood remains to be demonstrated."

Gut bacteria are suspected to be a source of nutrients and vitamins for a growing infant. Our intestinal tenants are able to interact with normal cellular processes to, for example, produce essential amino acids. Understanding the role individual gut microbes play in metabolism, immunity, and even behavior is an active area of investigation

once bacteria take hold in an infant's gut, their populations shift depending on what a child eats. The researchers believe that the cessation of breast-feeding is such a significant moment in microbiome development because certain types of bacteria thrive on the nutrients breast milk provides. Once these nutrients are no longer available, other bacteria emerge that are more commonly seen in adults.

"The results underscore the role of breast-feeding in the shaping and succession of gut microbial communities during the first year of life," the authors write. "The gut microbiota of children no longer breast-fed was enriched in species belonging to Clostridia that are prevalent in adults, such as Roseburia, Clostrium, and Anaerostipes.

In contrast, *Bifidobacterium* and *Lactobacillus* still dominated the gut microbiota of breast-fed infants at 12 months"(Figure 4).

Microbiome function

- Preserve barrier function of gut mucosa
- Absorption of minerals
- Maturation of the gastrointestinal tract.
- Protects from the intestinal infections
- Interact with CNS
- Role in immunity

Intestinal Permeability - Path physiology

The important role of the intestinal barrier and intestinal permeability for health and disease. However, these terms are poorly defined, their assessment is a matter of debate, and their clinical significance is not clearly established. In the present review, current knowledge on mucosal barrier and its role in disease prevention and therapy is summarized. First, the relevant terms 'intestinal barrier' and 'intestinal permeability' are defined. Secondly, the key elements of the intestinal barrier affecting permeability are described. This barrier represents a huge mucosal surface, where billions of bacteria face the largest immune system of our body. On the one hand, an intact intestinal barrier protects the human organism against invasion of microorganisms and toxins, on the other hand, this barrier must be open to absorb essential fluids and nutrients. Such opposing goals are achieved by a complex anatomical and functional structure the intestinal barrier consists of, the functional status of which is described by 'intestinal permeability'. Third, the regulation of intestinal permeability by diet and bacteria is depicted. In particular, potential barrier disruptors such as hypo perfusion of the gut, infections and toxins, but also selected over-dosed nutrients, drugs, and other lifestyle factors have to be considered. In the fourth part, the means to assess intestinal permeability are presented and critically discussed. The means vary enormously and probably assess different functional components of the barrier. The barrier assessments are further hindered by the natural variability of this functional entity depending on species and genes as well as on diet and other environmental factors. In the final part, we discuss

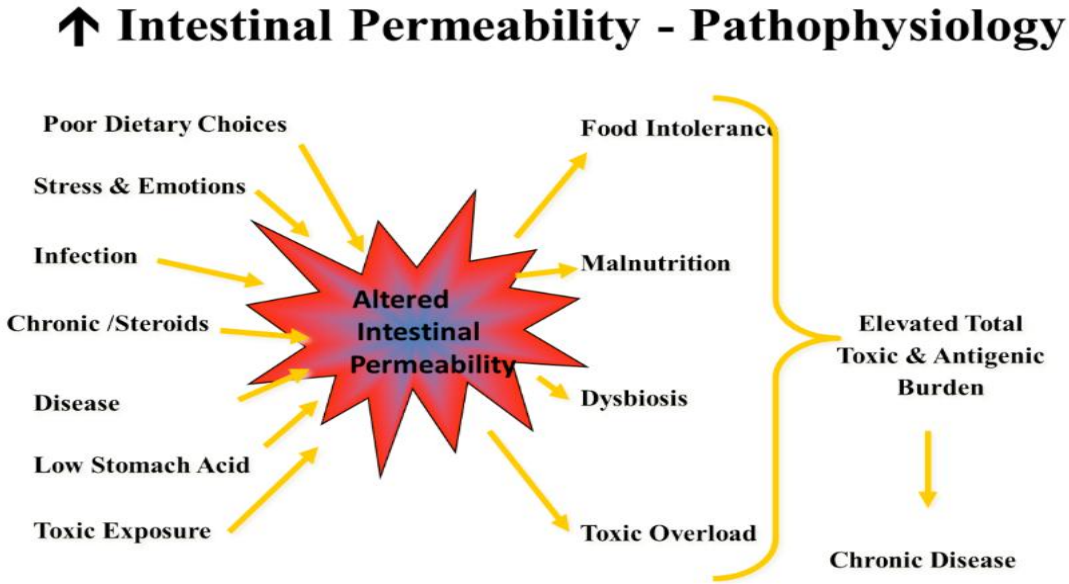


Figure 5: Intestinal Permeability - Path physiology

selected diseases associated with increased intestinal permeability such as critically illness, inflammatory bowel diseases, celiac disease, food allergy, irritable bowel syndrome, and – more recently recognized – obesity and metabolic diseases. All these diseases are characterized by inflammation that might be triggered by the translocation of luminal components into the host. In summary, intestinal permeability, which is a feature of intestinal barrier function, is increasingly recognized as being of relevance for health and disease.

Intestinal permeability is a barrier feature closely linked to the intestinal commensal micro biota as well as to the elements of the mucosal immune system (Figure 5). Many factors can alter intestinal permeability such as gut

micro biota modifications, mucus layer alterations, and epithelial damage, resulting in translocation of luminal content to the inner layers of the intestinal wall. Moreover, lifestyle and dietetic factors like alcohol and energy-dense food can increase intestinal permeability such as alcohol and energy-dense Western style diet (Genton, et al., 2015).

Famouri et al. (2014) conducted a triple-blind, placebo-controlled trial to evaluate the effects of symbiotic supplementation on children with failure to thrive. As shown in Fig 1. results indicated that the mean height in the intervention group increased from 87.77 cm at baseline to 89.40 cm after 3 months and 91.40 cm after 6 months. In the control group, mean height increased from 88.86 cm to 90.42 cm and 92.15 cm, respectively. The increase in height was observed in both groups, but the difference between the groups was not statistically significant. Symbiotic supplementation did not produce a significant additional improvement in height compared with the control group. The findings suggest that the beneficial effects of symbiotic on growth may be more evident in weight gain than in linear growth.

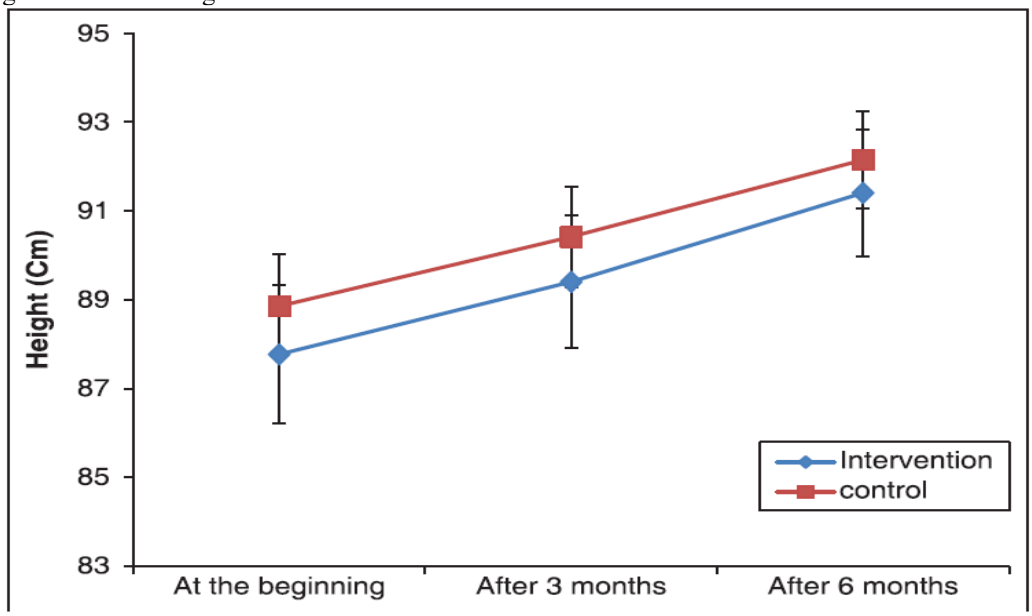


Figure 1: The mean of height at the beginning after 3 and 6 months

Management of Malnutrition

- Targeting the effect of gut microbiota or microbial composition represents a novel approach to reducing malnutrition rates.
- Probiotics are an attractive alternative to chronic antimicrobial therapy in modifying microbiota composition.
- Changes of gut flora composition with microbial faecal transplantation.
- Eat fermented foods
- Sauerkraut contains Bacillus clausii.
- Nato contains Bacillus Subtillus.
- Saccharomyces boulardii is a beneficial yeast and is related to bakers yeast.
- It produces lactic acid and supports GALT, modulates immunoglobulins (Ren, et al.,2011).

CONCLUSION

The evidence reviewed here shows that childhood malnutrition cannot be fully explained by food availability alone. Under-nutrition and over-nutrition can coexist in the same population, and both are shaped by a gut microbiome that begins assembling at birth and continues to mature through breastfeeding, diet, host genetics and immune signaling in early life. When this process is disrupted, whether by infection, a restricted diet or loss of microbial diversity, the resulting dysbiosis compromises the intestinal barrier, increases permeability, and weakens the host's ability to absorb nutrients and resist infection. This creates the self-reinforcing cycle of infection, impaired immunity and worsening nutritional status that underlies much of persistent childhood malnutrition. Interventions that act on the microbiome directly, such as the synbiotic supplementation trial discussed above, show that this cycle can be influenced, even where their effects on outcomes such as linear growth remain modest compared with their effects on weight gain. This points to the gut microbiome as a legitimate target for future malnutrition management strategies, alongside conventional nutritional rehabilitation. A clearer understanding of how specific microbial communities support nutrient harvest and gut barrier integrity will be needed before microbiome-based interventions can be reliably translated into clinical practice, but the findings summarized in this review make a strong case that the composition of the gut microbiota should be considered a core part of how malnutrition is understood, prevented and treated.

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