



## **FACTORS INFLUENCING THE COMPOSITION AND ACTIVITY OF HUMAN COLOSTRUM BACTERIA**

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### **ABSTRACT**

Human colostrum is the basic requirement for the nourishment of neonatals. Apart from its nutritional aspects, human colostrum contains several bioactive compounds, such as oligosaccharides proteins, vitamins and even microbes. This bioactive compounds are involved in host-microbe interactions and have a vital role in infants immune system. New techniques have improved our understandings of human colostrum composition, but very little information of bioactive compounds such as microbes and their role on infants is available up to date. Several factors may be influencing the human colostrum microbiome such as - nutrition, breastfeeding, stage of lactation, geographical locations, genetics and many more. But the impact of these factors on infant microbiome are not yet clearly known. This review will give an overview of colostrum microbiota composition and it's activity and will also highlight the factors influencing microbial composition and their potential biological relevance on infants immune system.

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### **INTRODUCTION**

Recent studies demonstrated the importance of our gut microbiome for optimal health. They highlighted the potential role of microorganisms in various activities such as metabolic, immunological and microbial programming (Rautava S, *et. al*, 2012). Microbes are considered to be the key environmental factors for providing specific signals to guide immune system development and also its maturation (Bendiks M & Kopp MV, 2013). The microflora of maternal environment directly have its impact on neonatal's immune system and consequently the health in early and late life. The microbiota of maternal environment is identified as a significant determinant of the maternally transferred factors which impacts the neonatal's health (Dunlop AL, *et. al*, 2015). Outcomes may be affected by specific perinatal factors that alters the neonatal's microbiome development. For example, unbalanced diet, increasing incidences of cesarean section deliveries, excess usage of antibiotics during pregnancy and at the period of lactation, continuous stress and unnecessarily stringent hygiene are the factors that influences maternal microbiome. Disturbances in formation of maternal microbiome along with reduction of microbial diversity or richness of microbiome will describe a strong risk factors such as allergies, diabetes, obesity, irritable bowel syndrome, metabolic syndrome and other inflammatory-related problems (Rodriguez JM, *et. al*, 2015).

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The maternal microbiome and infant's diet play a crucial role in infant's immune system maturation, adequate microbial colonization, metabolic development and overall infant's growth. This microbial colonization process will have an impact on immunological response and will result in programming of health in later life (Hooper LV & Littman DR, 2012). The present review aims to describe the impact of maternal microbiome on neonatal's health through breastfeeding and will provide an overview of colostrum microbiota activity and its composition, along with factors that influences microbial composition and their biological potentials.

#### **Human Colostrum - A Boon to Infant Food**

Human milk is the complete sources of nutrition for infant development. Energy of human milk, its nutrients and bioactive components have great importance and influence on infants. Among all the bioactive compounds, colostrum contains many immune substances, such as cytokines and chemokines, growth factors, hormones, antibodies and immunoglobulin's. There are also several non-specific compounds such as lactoferrin, peptides, whey proteins and large number of bacteria (Walker A, 2010). All these essential components are transferred to infant through breastfeeding.

Human colostrum is one of the most relevant postnatal element for metabolic and immunological programming of infant's health (Aaltonen J, *et. al*, 2011). Breastfeed is the most basic requirement for infant immune system, adequate gut function and immune meostasis maintenance (Turfkruyer M &

Verhasselt V, 2015). Infants taking nutrition through breastfeed are shown to have a reduced risk of necrotizing enterocolitis, diarrhea, diabetes, obesity, allergy and asthma and other inflammatory diseases (Guaraldi F & Salvatori G, 2012).

Colostrum is a postnatal microbial link as it contains high diversity of microbes that drives the infants microbial colonization (Martin R, *et. al*, 2003). Researchers have also reported that specific bacteria belonging to *Staphylococcus* and *Bifidobacterium spp* are directly transmitted to infants (Benito D, *et. al*, 2015). This reports gives us an idea about unique link between family members as specific straws that are present in each of the mother-infant pair. These reports also suggested that transfer of aberrant microbes from mother is possible. Though, it is important to define the factors and composition of milk microbiota that may be transferred as commensal bacteria in infant gut. For example, *Bifidobacterium* and Lactic acid bacteria transmitted to infant gut through breastfeeding may form a natural protective mechanisms that helps in developing infants gut microbiota for later resilience and reduction of risk of diarrhea and other inflammatory problems. Improved knowledge of this field may suggest the novel means of modulating infant and maternal microbiota in order to reduce specific disease that are associated to microbiota.

#### Microbiota of Human Colostrum

Traditionally, human colostrum has been considered as almost sterile fluid. But recent studies, revised this dogma. The first study reported that Rhesus monkey (*Macaca mulatta*) milk contains about 19 species of culturable bacteria belonging to five different genera (Jin L & Hinde K, 2011). Same results have also been reported in other mammals (Quingley L, *et.al*, 2013). The presence of microbes in human colostrum were detected and confirmed by culture-dependent techniques for a long period of time. Most of the bacteria in colostrum such as *Lactobacillus*, *Staphylococcus*, *Streptococcus*, *Bifidobacterium spp*. have a crucial role of probiotics to infants. (Mc Guire MK & Mc Guire MA, 2015). Studies have reported that "colostrum is the main source of bacteria to infant gut as infant consumes about 800 ml/day and it would ingest about  $10^5$  to  $10^7$  bacteria daily" (Fernandez L, *et.al*, 2013). But the biological role of these bacteria on infants health at short and long- term has yet not been identified.

The origin of bacteria in colostrum is yet not known, but their presence in colostrum corresponds to perinatal period which starts during third trimester of pregnancy and continues through lactation (Jost T, *et.al*, 2015). Hypothesis from several researches were made that bacteria in colostrum would have derived from infant's oral cavity during sucking, mothers gut via the entero-mammary pathways or from the colonization of mothers skin (Fernandez L, *et.al*, 2013). However, commensal microbiota has been reported in the tissue of breast, giving an idea about specific bacteria that inhabit the breast tissue and colonize the milk ducts. With the benefits and development of culture-independent techniques (e.g.-PCR & Next Generation Sequencing) the presence of microbial DNA has been confirmed. Such techniques have confirmed the rich existence of milk microbial community (Cabrera-Rubio R, *et.al.*, 2016).

The milk microbiota has been evaluated by many researchers (Mc Guire MK & Mc Guire MA, 2015). Their reports showed that *Streptococcus*, *Staphylococcus* and *Lactobacillus spp*. are the most common bacteria. The milk bacterial communities are

generally complex was demonstrated in the first study of milk microbiome using pyrosequencing (Hunt KM, *et.al*, 2011). A large inter-individual variation was reported through various studies regarding abundance and number of different species of bacteria in human milk. However, researchers have found out a common core of nine different bacterial groups present in milk samples. (*Streptococcus*, *Pseudomonas*, *Corneybacterium*, *Ralstonia*, *Serratia*, *Bradyrhziobaceae*, *Staphylococcus*, *Propionibacterium* and *Sphingomonas spp.*) (Hunt KM, *et.al*, 2011). Variations in results between studies may be due difference in protocols of varied DNA extraction selection of primer with higher bacterial coverage including bacteria with more G+C contents such as *Bifidobacterium spp*. Thus, an more approach needs to be developed in future. (Sim K, *et.al*, 2012).

The isolation and identification of live bacteria and presence of anaerobes, such as *Bacteroides*, *Bifidobacterium* and *Clostridium spp*. which are usually associated with gut environments are not able to survive in aerobic location, have resulted in scientific debate on origin of bacteria associated with human colostrum. Through recent reports and studies, high throughput sequencing has indicated the presence of gut associated, strictly anaerobic microorganisms belonging to Clostridiaceae (*Clostridium*, *Blautia*, *Collinsella* and *Veillonella spp.*) in breast milk. Studies have also reported the presence of specific microbes shared between the maternal microbiota, intestinal microbiota and breast milk (Jost T, *et.al*, 2014). Researchers has also confirmed and showed the presence of Butyrate producing bacteria, including *Roseburia*, *Coprococcus* and *Faecalibacterium spp*. in both maternal feces and human milk.

Using Illumina next-generation sequencing technology of total DNA sequencing, the shotgun metagenomics analysis was carried out using 10 different pooled colostrum samples (Ward TL, *et.al*, 2013). The same study also reported that human colostrum contains more than 360 prokaryotic genera, with 34% of Firmicutes and 65% of Proteobacteria as a predominant phyla and with *Staphylococcus spp.* (33.41%), *Pseudomonas spp.* (61.1%), *Streptococcus spp.* (0.5%) as a predominant genera. (Ward TL, *et.al*, 2013). This study also concluded that most abundant open reading frame within human colostrum encoded proteins for basic cellular functions such as cell signaling; respiration; DNA, RNA and amino acid metabolism.

A recent research also reported the metagenome and microbiome of healthy human milk (n=10 mothers) and compared it with the milk of females suffering from mastitis. A healthy core of microbiome included *Staphylococcus*, *Streptococcus*, *Bacteriodes* and *Lactobacillus spp.*, as well as fungal, viral and protozoan - related sequences, whereas milk microbiota of female with mastitis was dominated by *Staphylococcus aureus* (Jimenez E, *et.al*, 2015).

All the molecular techniques have some or the other limitations. For example, in DNA extraction methods, the number of 16s gene copies which may lead to under or over-estimation of bacterial counts; the viability of colostrum microbes cannot be analyzed and the total number of bacterial counts may be under or overestimated because of cell-wall composition. Researchers have also reported the DNA contamination in extraction kits and reagents (Mc Guire MK & Mc Guire MA, 2015). Other factors influencing colostrum

microbiota composition includes sampling methods (e.g.-time of day, breast cleaning method, breast pump extraction or manual extraction), DNA extraction methods (eg.- use of commercial kits, bead-beating step, enzymatic lysis), sequencing platforms (e.g.-Ion Torrent, 454 Roche, Illumina and Solid), 16s bacterial gene region studies (e.g.- V<sub>1</sub>-V<sub>3</sub>, V<sub>3</sub>-V<sub>4</sub>, etc.) and the 16s database and bioinformatics pipelined used. Therefore, protocols and methods are needed to be standardized.

### **Potential Factors Influencing the Human Colostrum Microbiota**

It is known that mode of delivery, maternal nutrition, genetic factors, geographical location, time of day are some factors that are reported for having influences on human colostrum (Quinn EA, *et. al.*, 2012). In the same way, all factors that could modulate the microbiota of mother's oral cavity, intestine, vagina and especially skin and the microbiome of infant are potentially able to modulate the microbiota of human colostrum. Thus, maternal dietary habits, nutritional status, lactation period, mode of delivery, gestational age, use of antibiotics and other medicines during lactation can have great influence on microbiota associated with human colostrum. Reports have stated that microbial diversity of colostrum samples is higher than mature milk. Lactation stage has been also described as factor that influences the microbiota of colostrum (Cabrera-Rubio R, *et. al.*, 2012). Initially microbiota is dominated by *Leuconostoc*, *Staphylococcus*, *Streptococcus* and *Lactococcus spp.* (Khodayar-Pardo P, *et. al.*, 2016).

Human microbiota composition is also influenced by gestational stage, with significant differences among preterm-delivery and term-delivery of mothers. *Enterococcus spp.* are noted to be lower in colostrum and the counts of *Bifidobacterium spp.* are higher in mature milk which has been detected in the samples collected from females with term deliveries (Khodayar-Pardo P, *et. al.*, 2016). In addition, changes in colostrum microbiota composition are associated with maternal physiological status, including, celiac diseases, obesity, human immunodeficiency virus (HIV) positive status (Collado MC, *et. al.*, 2012). Mothers with celiac disease have lower levels of *Bifidobacterium* in their colostrum (Olivares M, 2015). Analysis of human colostrum microbiota showed that *Staphylococcus* and *Streptococcus spp.* as well as Lactic acid bacteria strains are present in colostrum (Cabrera-Rubio R, *et. al.*, 2016) but the presence of other bacterial species may be dependent on geographical locations (Urbaniak C, *et. al.*, 2014). However, there is a need of large scale studies from different locations on human breast colostrum microbiota.

Studies have also proved that use of antibiotics have direct impact on maternal microbiota, affecting prevalence of *Lactobacillus*, *Bifidobacterium* and *Staphylococcus spp.* (Panagos PG, *et. al.*, 2016) decreasing the abundance of *Bifidobacterium*, *Staphylococcus* and *Eubacterium spp.* in the colostrum samples (Urbaniak C, *et. al.*, 2017). Chemotherapy is also directly associated with microbiota of colostrum and with reduction of bacterial diversity (Urbaniak C, *et. al.*, 2014). Very less studies are carried out on the impact of maternal diet on colostrum bacteria. It is likely that nutritional diet, which are able to modulate intestinal microbiota and human milk nutritional composition may exert changes in colostrum microbiota.

Moreover, nutritional habits clearly influences the lipid profile of human milk, modulating the concentration of long-chain polyunsaturated fatty acids and the ratio of  $\omega$ -3 to  $\omega$ -6 (Nishimura RY, *et. al.*, 2014). The fatty acids have immunomodulatory properties in nursing infants, and through studies it has also been demonstrated that they are able to modulate gut microbiota composition in early life (Pusceddu MM, *et. al.*, 2015). The composition of both prebiotics and probiotics during pregnancy could influence the colostrum microbiota, but still more studies are required to document the potential transfer of gut bacteria to mammary glands and impact the specific strains of bacteria (Dotterud CK, *et. al.*, 2015). On the other hand, some reports showed that non-nutrition sweeteners, such as saccharin, sucralose, and acesulfame potassium were present in 65% of human milk samples that were analyzed (Sylvetsky AC, *et. al.*, 2015). Those report suggest that maternal diet can modulate the microbiota of human colostrum. Therefore, an urgent study is required to investigate the interactions among nutrients in maternal diet and colostrum microbiota and their effects on infant health.

### **Strategies with Potentials to Modulate Colostrum Microbiota**

As described earlier, diet is likely a powerful tool to alter gut microbiota. Dietary strategies, could be devised to modulate composition of microbes in order to affect human physiology and reduce the risk of various diseases that are related to composition of microbiota. A recent study with *Macaca fuscata* (Japanese macaques) in animal model, explained the impact of maternal diet on neonatal microbiota composition (Ma L, *et. al.*, 2014). This study also showed the effects of high fat diet on infant's microbiome composition and also effect of metabolic health. Thus, deciphering the contribution of gut microbiota and promoting nutrition and lifestyle may reduce the risks of various diseases associated with microbial composition shifts. The evidence shows that early dietary interventions would support health related issues on adult health (metabolic, immunological and microbial effect).

It has been showed that specific probiotic strains are very effective in prevention and treatment of various diseases in early life (Taipale TJ, *et. al.*, 2017) and they may reduce the risk of eczema in infants at risk populations (Rautava S, *et. al.*, 2012). In a placebo-controlled study, ingestion of probiotics during breastfeeding period and even at pregnancy has been describe to modulate in infant *Bifidobacterium* colonization and also to modulate colostrum microbiota (Gronlund MM, *et. al.*, 2007). Recently reports have also stated that perinatal probiotic supplementation also affects the composition of colostrum bacteria; including *Lactobacillus spp.* and *Bifidobacterium spp.* also affects other bioactive compounds like oligosaccharides and lactoferrin (Mastroimarino P, *et. al.*, 2018). Moreover, same study reported the beneficial effects of probiotic supplementation in vaginal birth, while no significant difference were found from the milk from C-section deliveries, suggesting probiotic-specific dependent modulation on the basis of mode of delivery. A recent report stated that on use of probiotics in first 1500 days of life, it supports healthy perinatal life with reduced risk of autoimmune problems and infections in later life (Reid G, *et. al.*, 2016).

## **CONCLUSIONS**

Several factors are responsible for the transfer of microbial population from mother to infant gut. The lactation period may

provide new target for designing a unique dietary chart and nutritional tools to modulate the colostrum microbiota and thereby reduce the chances of non-communicable diseases (NCDs), while at same time promoting breastfeeding. To get more knowledge and information on colostrum microbiota, further studies are required to be carried out using different geographical locations and among varying population groups with different genetic background and different nutrition are required to completely understand the impact of microbiome and its potentials in human health promotion.

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