

# Applied Ayurvedic Approach to prevent Necrotizing Enterocolitis in Preemies

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## ABSTRACT

Necrotizing enterocolitis (NEC) is the most common life-threatening emergency of the gastrointestinal tract in the early neonatal period. The greatest risk of NEC is prematurity. The exact cause of NEC remains unclear, but most likely is multifactorial. In the 1970s, the relationship between NEC and feeding was identified. Various research studies have suggested that early feeding, especially other than human milk may predispose to the development of NEC as the intestinal microflora is different for breastfeeding and formula feeding for infants. Human milk contains various enzymes, which reduce the incidences of ischemic injury as well as other pathogenesis of NEC. Food is life giving and life-saving. *Acharya Kashyapa* rightly says that there is no medicine like food and food alone can make people healthy without disease. In *Ayurveda*, *Basti* therapy is stated as (*Ardhchikitsa*) comprising 50% of the treatment to cure any disease. This article briefly reviews the pathogenesis of NEC, importance of breast milk in preterm babies as well as relationship between aggressive enteral feeding and development of NEC. It also highlights the benefits of breast milk enema in NEC prevention. *Bastikarma*, i.e., therapeutic enemata uses the medicine (breast milk) through the rectal route.

**Keywords:** Basti, Breast milk, Necrotizing enterocolitis, Preprobiotics, Preterm.

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## INTRODUCTION

At birth, there is a significant and immediate demand on the gastrointestinal tract to digest and absorb nutrients efficiently to maintain the high rate of growth in the neonate. The demands on the gastrointestinal tract of full-term neonates are remarkable, but the challenge for a preterm neonatal's immature gut to develop and maintain gastrointestinal homeostasis is immense.<sup>1</sup> The preterm

infant has mechanical problems including suck–swallow incoordination, which necessitates tube feeding; poor esophageal sphincter tone, which increases reflux; delayed gastric emptying and disorganized intestinal motility, which lead to feeding intolerance and intestinal stasis. The mucosal breakdown is linked to the lack of enteral nutrients and intestinal immaturity.<sup>2</sup> Mortality ranges from 20 to 50% and morbidity includes, but it is not limited to strictures, adhesions, and short bowel syndrome. The primary risk factor for NEC is prematurity, because the incidence varies inversely with gestational age.

## MATERIALS AND METHODS

- Charak Samhita, Kashyap Samhita, Sushruta Samhita
- Theory and Practical Books on Kaumarbhritya
- Research Articles

## Methods

The most common life-threatening emergency of the gastrointestinal tract in newborns is NEC. There is a high risk of NEC in infant prematurity when compared with term infants or postmaturity.<sup>3</sup> The small intestine is the major site of nutrient and water absorption. The term infant is born with adequate absorptive surface area to support its postnatal nutritional needs.<sup>4</sup> Incidence of NEC is commonly seen in preemies and formula-fed babies. The cause of NEC is multifactorial and is primarily associated with intestinal immaturity, intestinal mucosal ischemia, inflammation, and superimposed infections of gram-negative bacteria like *Escherichia coli*, *Klebsiella*, *Clostridium pathogens*, *Staphylococcus epidermidis*, and *Rotavirus* that are considered important in the pathogenesis. Another contributory consideration is reversed end diastolic flow of blood in umbilical artery prior to delivery. The distal part of the ileum and the proximal segments of the colon are involved most frequently in fetus, and gangrene may extend from the stomach to the rectum.<sup>5</sup> There is abdominal distension and tenderness with bloody stools. There is feeding intolerance with vomiting and gastric or bilious residuals. Sometimes, only bowel wall edema, apnea, lethargy, septic shock, disseminated intravascular coagulation, and death may occur.<sup>6</sup>

The immune-boosting properties of breast milk have long been known. Epidermal growth factors found in human and animal milk help to block activation

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of a protein responsible for unlocking the damaging immune cascade that culminates in NEC. The NEC is a condition that causes irreversible death of intestinal tissues. Nowadays, surgical management is the treatment employed in which there is removal of the dying or necrotizing portions of the infant's intestine. Surgical treatment can save a life, but due to insufficient intestine, the infant may suffer from complications, such as short bowel syndrome as well as may have decreased ability to absorb enough nutrients. Toll-like receptor 4 (TLR4) protein is a key instigator of the intestinal damage seen in NEC in normal babies shortly after the intestine becomes colonized with bacteria. In premature babies, TLR4 protein in the gut is also immature, which decreases or turns off oxygen supply to the intestines causing NEC.<sup>7</sup>

At birth, the gastrointestinal tract is sterile. After birth, it is subsequently colonized by microbes acquired from the mother and the surrounding environment.<sup>8</sup> It is estimated that the human colon contains as many as 400 different species, with more than  $10^{11}$  bacterial cells/gm of mucosa.<sup>9</sup>

In the human body, the vital role of gastrointestinal microbiota and its profound influence on nutritional, physiological, immunologic as well as protective processes allow some to consider it the largest metabolically adaptable and rapidly renewing organ.<sup>10</sup> There are so many factors, such as ethnicity, sanitation, hygiene, geography, and climate in shaping the gut microbiota, but diet has a dominant role over the other possible variables.<sup>11</sup> The microbes present in vaginal secretions provide the child with a starter pack of microbes. Her breast milk contains sugar that seems to selectively nourish the gut microbiota, which is the infant's need.

The breast milk contains immunoglobulin A (IgA or sIgA). It is an antibody found in our bodily secretions. Humans eventually make sIgA for themselves, but in our earliest days of life, mother's milk is the only source of the antibody. Specific bioactive factors in human milk, such as sIgA, lysozyme, cytokines, enzymes, and nucleotides have specific antigen-targeted, anti-infective action, bacterial lysis, anti-inflammatory epithelial barrier function, enhancement of antibody responses, and immunomodulation respectively.<sup>12,13</sup>

Breast milk is truly a miracle, which contains various vitamins, minerals, probiotics, prebiotics, antibodies, growth factors, and different unique sugars that selectively feed your baby's good bacteria. A healthy microflora in babies helps to absorb nutrients, produce antibacterials, and stimulate the immune system. Researchers tested bacterial growth in breast milk, cow's milk, and in formula feed and found that in the breast milk, bacteria grew together into layers that protected the gut as well as sealed the openings.<sup>14,15</sup>

In the first week of life, giving formula feed can delay the development of a healthy gut flora by 2 to 6 weeks, which is a critical time of development. Therefore, breast feeding has a very important role for the baby.<sup>16</sup> The intestinal microflora differs between breast-fed and formula-fed infants, with the predominant species in the breast-fed infants being *Lactobacillus* species and *Bifidobacterium* species, whereas formula-fed infants have a large proportion of *Bifidobacterium* species and *Enterobacter* species.<sup>17</sup>

Prenatally, during the last trimester of pregnancy, the small intestine doubling its length is observed.<sup>3</sup> Gastric emptying is faster for an infant fed with human milk compared with commercial formula feed or cow's milk. Large gastric residual volumes are reported less frequently in the preterm infants fed with human milk. Enzymes, such as acetyl hydrolase, which blocks the ischemic injury produced by platelet activating factor in the pathogenesis of NEC, may lower the risk of this condition.<sup>18</sup>

It has been suggested that immunologic and antimicrobial components of human milk reduce the incidence of NEC.<sup>19</sup> Human milk for preterm infants is well tolerated and promote the earlier achievement of full enteral feeding compared with infant formula feed. In addition to its nutritional value, human milk provides immunologic and antimicrobial components, hormone, and enzymes that may contribute positively to the infant's health and development.<sup>20</sup> Although the intrauterine growth restriction and extremely low birth weight experience during NICU stay largely a result of the management of acute neonatal illness and gradual advancement of feeding to minimize the risk of feeding-related complications, such as NEC.<sup>21</sup> Milk from the mothers of preterm infants, especially during the first 2 weeks after delivery, contains higher amounts of energy and higher concentrations of fat, protein, sodium, but slightly lower concentrations of lactose, calcium, and phosphorus compared with milk from mothers of term infants.<sup>22</sup> Human milk contains more than 130 different oligosaccharides that are fermented in part of the infant's colon. The concentration changes with the duration of lactation, being highest in the colostrum at 20 to 23 gm/L, about 20 gm/L on day 4 of lactation, and 9 gm/L on 20 day of lactation.<sup>23</sup> The content of lactose and oligosaccharides along with the microbes in human milk contributing to a healthy microbial ecosystem is an area of recent interest.<sup>24</sup> Preterm infant shows some absorption of intact human milk oligosaccharides, but most are resisted digestion in the small intestine and undergo fermentation in the colon.<sup>25</sup>

*Enterobacteria* and *Streptococci* are first groups to colonize the intestines, and all infants are colonized with *Escherichia coli* within a few days.<sup>26</sup> Prebiotics have been shown to increase fecal *Bifidobacteria* counts, reduce stool

pH, reduce viscosity, and accelerate gastrointestinal transport.<sup>27</sup> It has been hypothesized that GosFos (prebiotics) reduce the incidence of gastrointestinal complications, such as NEC, improve immunological functions, improve long-term outcomes, but there are no data available from preterm studies to support these assumptions.<sup>28</sup> A recent systematic review showed a significant decrease in NEC after the introduction of different strains and dosages of probiotics. In addition, the time taken to feed the baby satisfactorily was significantly shorter.<sup>29</sup>

*Acharya Kashyapa* rightly says that there is no medicine like food and food alone can make people healthy without disease<sup>R</sup>. In *Ayurveda Basti* therapy is stated as (*Ardhchikitsa*) and comprises 50% of the treatment to cure any disease<sup>R</sup>. Type of *Basti* differs according to route administration. The mode of action of *Basti* is more complicated and very difficult to explain with the available modern technologies. However, our classics explained it in a simplified language with certain beautiful similes. Although the rectum is not a usual site for absorption of ingested nutrients, drugs introduced in the rectum may be absorbed here. Thus, drugs introduced by this route may have a systemic effect as well as a local effect. The water-soluble substances may be easily absorbed as the water moves in both the directions across the mucus membrane of the small and large intestines. Short-chain fatty acids are also absorbed from the colon. Colon mucosa under the effect of medication can be made to absorb unusual substances also. As all organs related to *Basti Karma* are *Marmas*, it can be inferred as one of the reasons for the mode of action of *Basti Karma*. *Nabhi* and its relevance in *Ayurveda* may be another reason for the systemic action of *Bastikarma*. We can only postulate certain hypothesis about the mode of action of *Basti*. It may be some absorptive mechanism, neural stimulation, or chemical or mechanical stimulation.<sup>30</sup>

### *Pakvashyasth Basti*

Here, the drug is administered through the rectal route. The drug administered through this route reaches the *Pakvashaya*, i.e., large intestine. The *pakvashyagatabasti* is frequently used in clinical practice. This is found to be very beneficial in both diseases of *pakvashaya* as well as many other systemic diseases. The therapeutic effect of the drug is not restricted to the large intestine, as the drug absorbed from this site causes systemic effect and, hence, useful in many other systemic disorders.<sup>31</sup>

### *Brihan Basti*

The *Basti* therapy is administered with the purpose of nourishing the body, i.e., by improving the physical appearance is known by the name *Brihan Basti*.

### *Rasayana Basti*

The *Basti* therapy producing the *rasayana* effect, i.e., the *basti* that improves the longevity of an individual by delaying the aging process is referred to by the name *rasayana basti*.

### PROBABLE MODE OF ACTION OF *BASTI*

*Acharya Sushruta* has told that the *virya* of *basti* drug reaches everywhere in the body through the *srotas* in the same way as the water poured at the root of the plant reaches up to the leaves. He has further explained that even though *basti* drugs quickly come out with mala, their *virya* acts all over the body by the action of *apanavayu* and other *vayu*. The action takes place just like as the sun draws moisture from the earth. *Parashara* had highlighted the importance of *guda*, by saying that *guda* is *mula* for all the *siras* in the body; hence, the medicine administered through the *guda* reaches up to the head and nourishes the body. The given medicine (through *Basti*) will flush off in the feces and come out in quick time along with the excreta by the action of *Apana Vayu* (the subtype of *vayu* which governs the functions of the lower parts of the body). But, the *Basti* acts on the virtue of its *Veerya* (as already said). By the virtue of its *Veerya*, the *Basti* reaches every corner of the body from the toes to head, drags the morbid *doshas* from every part of the body, and expels them from the body. Just as the Sun being located lakhs of miles away is capable of sapping off the fluids of living beings on earth by the virtue of the effect (*virya, prabhava*) of its heat and intensity, the *Basti* medicine administered into the *Pakvashaya* by the virtue of its *veerya* will dissolve in it all the impurities and morbidities located in all the parts of the body and expel them from the system.<sup>32</sup> *Charaka* enumerates the below-mentioned *gunas* (qualities) and *karmas* (functions) of *Basti*.

- *Vayasthapana*: Stabilizes, fortifies, and strengthens the tissues of the body and, hence, enhances the lifespan of an individual by postponing or delaying the process of aging
- *Ayushya*: Enhances the lifespan (quality and quantity of life)
- *Sukha*: Provides comfort and happiness by establishing good health
- *Balakrit*: Provides strength, endurance, and immunity
- *Agni krit*: Stabilizes the digestion and metabolism
- *Medhakrit*: Enhances the intelligence
- *Svarakrit*: Provides good voice
- *Varna krit*: Enhances color
- *Sarvarthakari*: Can be readily administered at all ages
- *Sarvagadaapaha*: Remedy for all the diseases
- *Vitshleshma, pitta, anilamootrakarshi*: Eliminates stools, morbid kapha, pitta and vata, and urine

- *Dhaardyakrit*: Makes the body strong and stable
- *Shukrabalaprada*: Strengthens the shukra (semen, reproductive fluid)
- *Vishvaksthitamdoshaschanirasya*: Eliminates all the morbid doshas accumulated in the body.<sup>32</sup>

*Kashyapa* tells that Vasti is equal to the amrita (nectar of life) to the children and also to the old-aged people.

## DISCUSSION

### Discussion on Maturity of Gut in Preterm Review

Loss of an appreciable of the small intestine in the preterm infant will have a major impact on the absorptive capacity of the new born because did not undergone the late gestational acceleration in intestinal growth.<sup>33</sup> Currently, we have a poor understanding of the development of neurological and endocrine factors that control intestinal motility.<sup>38</sup>

### Discussion on Drug Review

#### Breast Milk

Human milk presents a complex and dynamic composition influenced by gestational age at parturition and lactation period, which differs from the formula feed in nutrient concentration and composition. This is so more importantly for the presence of immunoglobulins, growth factors, and different enzymes helpful for digestion. Each mother's milk is unique, changes depending on the gestational age and health of the infant, and is modified to meet the need of the infant. All 10 amino acids present in human colostrum have properties of low renal solute load for infant's immature kidneys. The growth factors in colostrum help the gut to mature. Physicochemical properties, amino acid concentration, and bioactive peptides affect mechanical, hormonal, and neuroendocrine functions of the gastrointestinal tract.<sup>34,35</sup> Colostrum is often called the first immunization because it is high in immunoglobulins, especially IgA. Lactose in colostrum prevents hypoglycemia. Breastfeeding started earlier in infancy can boost the immune system of the baby. Gestational age affects human milk and preterm milk is higher in protein and anti-infective properties. In breast milk, secretory immunoglobulins are IgA, which fights against infections. The SIgA coats the gut like a white paint and protects the GI tract where most infections start in early infancy. Exclusive breastfeed is important because some infants are sensitive to cow's milk. Human insulin content in breast milk is significantly higher than in formula feed (low or absent). Insulin supports the maturation of the infant gut. Formula feed may increase the risk of diabetes, and the developing bacterial flora in the infant's gut may change the bacterial profiles in the

first week of life. *Bifidobacteria* are dominant in breast-fed infants compared with those that are formula fed. Human milk is easy to digest compared with formula feed or cow's milk. Pre- and probiotics are helpful for colonizing microbes in the sterile gastrointestinal tract of the infant. Necrotizing enterocolitis probably develops in preterm babies due to immaturity of gut. Breast milk of preterm babies has higher protein content; TLR4 protein has an important role in oxygen supply to the intestine decreasing the incidence of necrotizing colitis. Exposure of the neonatal small intestine to enteral feed is followed by changes in mucosal structure and function, an acceleration of epithelial cell turnover, activation of absorptive processes, and decline in passive permeability.<sup>36,37</sup> Certain nutrients, such as n-3 fatty acids and amino acids, such as glutamine, have been found to play a potential role in immunity and the downregulation of intestinal inflammation.

#### Uses of Pre- and Probiotics

The recent reports showed that preterm human infants are randomly assigned to receive daily feeding supplements of a probiotic mixture (*Bifidobacteria bifidus*, *Streptococcus thermophiles*, and *Bifidobacteria infantis* in one study and *Lactobacillus acidophilus*, *Bifidobacteria infantis* in the another) had a relatively lower risk for NEC and death also appeared to have decreased due to late onset sepsis.<sup>38-40</sup>

### Discussion on Bastikarma

*Bastichikitisa* is *ardhchikitsa* because of the action on all systems. *Basti* according to disease, person, time, and with proper medicine can treat any disease and will make a person healthy.

Drugs can be absorbed well from the intestine than from the stomach because of the large surface area. Increased vascularity can increase absorption. Absorption of drugs from gut occurs by passive diffusion. Passive diffusion is a movement of ions and other atomic or molecular substances across cell membrane without the need of energy input unlike active transport.<sup>41</sup>

Action of *Basti* can be postulated by certain hypothesis based on the mode of action.

- Absorption mechanism
- Neural stimulation
- Chemical stimulation
- Mechanical stimulation

The gastrointestinal tract is lined with epithelial cells. Drugs must pass or permeate through these cells in order to be absorbed into the circulatory system. One particular cellular barrier that may prevent absorption of a given drug is the cell membrane. The concentration of drug reaching

the colon depends on formulation factors, the extent of retrograde spreading, and the retention time. There is close resemblance in the functioning of *Vata Dosha* and nervous system and *Basti* is prescribed as the best remedy for *Vata*. It again validates the efficacy of *Bastikarma* on the nervous system.<sup>42</sup> Certain mechanical or chemical stimulation is responsible for the action of *Basti*. Both of them cause nervous stimulation and thus, produce the effect.<sup>42</sup>

## CONCLUSION

Colostrum is like a thick latex paint. It decreases the permeability and prevents the passage of large particles and pathogens. The growth factors in colostrum help the gut to mature. The breast milk of preterm infants has immunoglobulins as well as other anti-infective properties. A randomized controlled trial has demonstrated that early aggressive enteral and parental nutrition in sick infants with very low birth weight can improve growth outcomes without increasing the risk of all measured clinical and metabolic sequelae. The implication of enema (*basti*) with mother's milk for preterm infants and certain drugs (pre- and probiotics) may be helpful to prevent life-threatening gastrointestinal diseases that cause rapid intestinal diseases like NEC. Further research on *Matrukshir Basti* could help it to serve as a direct therapy for diseases due to immaturity of the gastrointestinal tract in infants, similar to those that practices that have been accomplished with the immature lung e.g. surfactant therapy.

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