



## The Impact of Oral Maternal Colostrum Administration on the Immune System of Premature Babies

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### Abstract

*In children under five years of age, premature complications are now the second leading cause of death. Colostrum has important benefits in promoting the maturity of premature infants' organ functions and preventing infections. Preterm infants are recommended to be given colostrum orally and pharyngeally as early as possible after birth to provide immune protective effects for their bodies. However, the sucking and swallowing functions of preterm infants are often not optimal, partly due to comorbidities, which poses a significant challenge. As a result, the immune system of preterm infants is often low. This literature review aimed to evaluate the effect of oropharyngeal colostrum feeding through subgroup analysis based on complications. Descriptive research was conducted in April-June 2024 using the literature review method with PRISMA guidelines for RCTs. Literature sources were obtained from Pubmed (MEDLINE), Science Direct, Google Scholar, and Cochrane with a publication limit of the last ten years (2014-2023). Of the 1,657 results, 13 articles met the criteria. A total of 1,451 preterm infants were included in the 13 RCT studies. Results showed a lower incidence of late-onset sepsis and Necrotizing Enterocolitis (NEC) in the group that received oropharyngeal colostrum. The administration of oropharyngeal colostrum was shown to have a positive impact on the development and defense of the immune system of preterm infants, reduce health problems such as sepsis and NEC, accelerate the recovery of birth weight, and reduce the incidence of mortality.*

### Introduction

Based on WHO data, it is reported that there are around 15 million cases of premature babies born every year around the world, in developed countries the number is quite large, namely at 5% - 13% (Taha et al., 2020; Pinto et al., 2019). Because their organs and body systems are not yet fully developed, babies born prematurely often face various complications that occur after birth, such as sepsis and Necrotizing Enterocolitis (NEC). According to Blencowe's research, it is said that complications that occur in premature babies are currently the second leading cause of death in children under the age of five (Blencowe et al., 2012). The breast milk produced by the mother, especially colostrum, can act as the first best immune stimulator that the baby has. Colostrum has a concentration of immunoglobulin A (sIg A), cytokines, and other bioactive substances with a higher immunoregulatory effect compared to mature breast milk (Sriraman, 2017). Immunoglobulin A (IgA) prevents pathogens from attaching to the epithelium of the intestinal mucosa and respiratory tract, in other words Immunoglobulin A (IgA) acts as a barrier (Pietrzak et al., 2020; Turula & Wobus, 2018). The content of Immunoglobulins (Igs) in colostrum on days 1-3 consists of IgG: 80-50mg, IgM: 120-40mg,

IgA: 11,000-2,000mg, while in mature breast milk ranges from 1-3g. This can be interpreted that a newborn who is breastfed will receive passive immunity to bacterial and viral infections (Wilson & Ogra, 2011).

The survival of premature babies with very low birth weight has increased significantly. However, this increase is also associated with an increase in cases of late onset sepsis (LOS) and Necrotizing Enterocolitis (NEC). Breastfeeding has been shown to be effective in protecting premature infants from the incidence of late-onset sepsis (LOS) and Necrotizing Enterocolitis (NEC). Then, organs and systems that are not yet fully developed often cause delays in enteral feeding in premature infants, sometimes taking several weeks before the oropharynx receives immunological protection and trophic factors when oral feeding is introduced. In addition, this also causes premature babies to not be able to receive maternal colostrum which can consequently increase the vulnerability of premature babies to various viral and bacterial infections as well as inflammation. Cytokines contained in colostrum and breast milk can activate the immune cascade in the lymphoid tissue connected to the oropharyngeal mucosa and can provide antibacterial, immunomodulator, antiviral, and anti-inflammatory effects against an infection (Abd-Elgawad et al., 2020). Giving colostrum and breast milk (OMOM) orally or oropharyngeal has become an emerging option to overcome the delay in enteral feeding in premature babies (Lee et al., 2015).

Some researchers have proposed the application of oral immunotherapy to regulate the immune system function of premature babies and improve outcomes. Rodriguez became the first person in his research to propose the concept of giving oropharyngeal colostrum to premature babies with very low birth weight (da Cruz Martins et al., 2020). There are several previous studies that have shown how anti-inflammatory, immunoprotective effects, and intestinal maturity in premature babies who are given maternal colostrum early through oropharynx have an impact on the incidence of enterocolitis and late onset sepsis. However, there are still some theoretical debates and inconsistent research results. Therefore, this study aims to analyze the impact of limited maternal colostrum administration in this study, namely oropharyngeal colostrum to improve the development and defense of the immune system, in addition to exploring whether oropharyngeal colostrum administration can safely reduce the incidence of late onset sepsis (LOS) and Necrotizing Enterocolitis (NEC) in premature infants with a gestational age of < 34 weeks.

## Methods

In the design and implementation of this study, the researcher adheres to the guidelines detailed in the Optional Reporting Items for Systematic Review and Meta Analysis for Randomized Controlled Trials (RCTs). All full-text RCTs published and analysing the development and defence of the immune system in premature infants were included in this review. However, conference abstracts, unpublished RCTs, questionnaires, randomized trials, and observational studies were issued. Babies born prematurely aged 0-12 months, regardless of their health status were included in this review with a gestational age of <34 weeks. The study analyzed the administration of maternal colostrum oropharyngeal to improve the development and defense of the immune system of premature infants in this limited study associated with sepsis and *necrotizing enterocolitis* (NEC) in premature infants was considered for inclusion. Studies that reported outcomes related to the development and defense of the immune system in premature infants including those associated with sepsis and *necrotizing enterocolitis* (NEC). PubMed (MEDLINE) databases, Science Direct, Google Scholar, and Cochrane searched between 2014 and 2023. In addition, researchers conducted a direct search on selected study references to find other potentially eligible studies. Some of the MeSH terms used in this literature review are "Colostrum" AND "Oropharyngeal" AND "Immune System" AND "Premature Birth" OR "Preterm Infants" AND "Randomized Controlled Trial". The data collection and analysis procedures used refer to the guidelines outlined in the Cochrane

Handbook for the Review of Systematic Interventions. In the initial stage, researchers refine the research title and abstract to identify potentially eligible studies. The same authors independently assessed the full text of studies that met the inclusion criteria to determine their eligibility.

The retrieved documents are imported into literature management software (Mendeley) to eliminate duplicates. Then literature related to titles and abstracts of literature is strictly checked in accordance with inclusion and exclusion criteria, and publications that do not meet the requirements are eliminated. Document re-screening is done to get a complete test of the remaining documents after the initial screening is checked to determine the final documents entered.

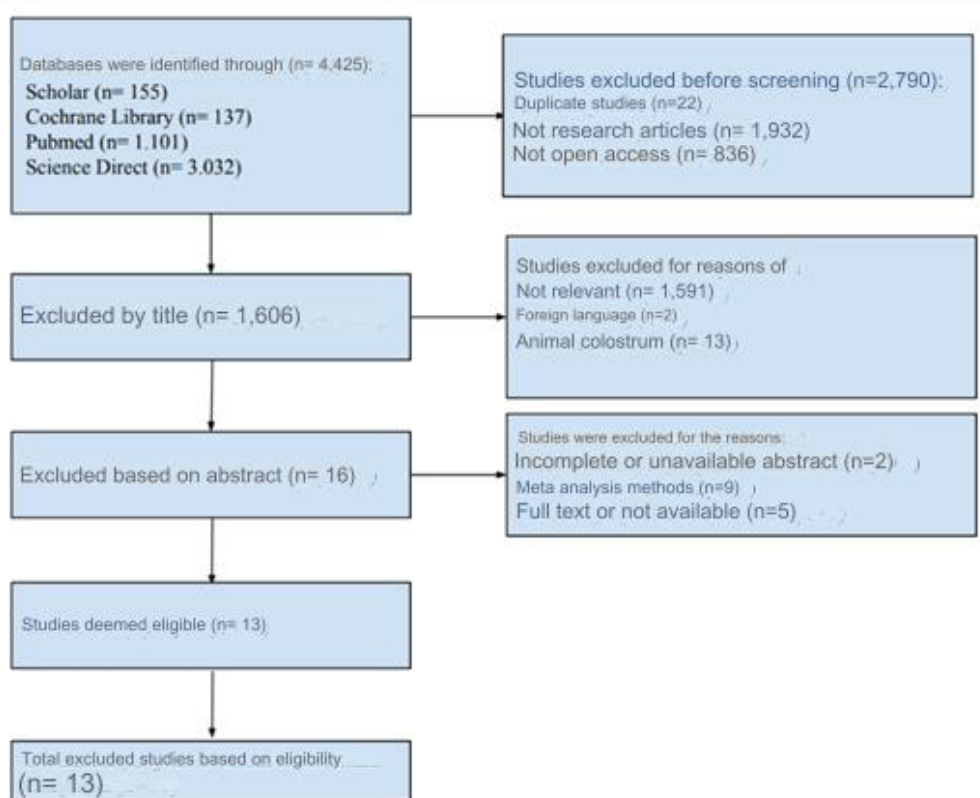


Figure 1. Preferred Publication Search Flowchart

Data analysis was conducted using various analysis techniques, such as thematic, content, and statistics, to assess and synthesize the findings of the thirteen selected articles thoroughly. In addition, during the design and implementation of this study, the researcher adhered to the guidelines outlined in the Preferred Reporting Item for Systematic Review and Meta-Analysis (PRISMA) for Randomized Controlled Trials (RCTs).

## Result and Discussion

The study for colostrum administration was conducted with a randomized controlled trial (RCT) to assess the immune system of premature babies, including those related to clinical namely sepsis and *necrotizing enterocolitis* (NEC). Relevant papers are identified with their titles. Non human studies, non interventional studies, and review articles were not included. Furthermore, the title of the article is used to identify irrelevant research and exclude it. The abstracts from the remaining articles are then analyzed to determine their suitability. In the end, thirteen articles were included in this review.

Characteristics of the included studies

Table 1 summarizes the characteristics of the thirteen included trials. These studies used a rigorous research design, namely Randomized Controlled Trials (RCTs), focusing on premature babies with a gestational age of < 34 weeks and systematically observing and analyzing the effects of oral maternal colostrum administration on various health outcomes, including in cases of sepsis and Necrotizing Enterocolitis (NEC).

The incorporation of RCTs allows for the allocation of controlled and randomized participants into test and controlled groups, reduces bias and confounding variables and provides a more optimal assessment of the effects of oropharyngeal maternal colostrum.

Table 1. Included trial characteristics

Heading	Writer	Place	Gestational Age/ Birth Weight	Sample	Administration of oropharyngeal colostrum				Control	Result
				Intervention/ control	Start Time	Freq	Dose	Duration	Placebo/ Regular care	
Oropharyngeal Administration of Mother's Milk Prior to Gavage Feeding in Preterm Infants: A Pilot Randomized Control Trial	Abd_Elgawad et al., 2020	Egypt	< 32 weeks/1500 g	100/100	When colostrum is available	2-4 hours	0.2 ml	During the initial period of feeding	Regular maintenance	Oropharyngeal administration of colostrum has an impact on the incidence of necrotizing enterocolitis, slow-onset sepsis, bronchopulmonary dysplasia, ventilator-associated pneumonia, time to full enteral feeding, and death.
Does oropharyngeal administration of colostrum reduce morbidity and mortality in very preterm infants? A randomised parallel-group controlled trial	Aggarwal et al., 2021	India	26-31 weeks/ Not mentioned	117/115	24 hours after life	Every 3 hours	0.2 ml	During the start of oral feeding	Sterile water	Oropharyngeal administration of colostrum has an impact on the incidence of necrotizing enterocolitis, slow-onset sepsis, bronchopulmonary dysplasia, retinopathy of prematurity, intraventricular bleeding, ventilator-associated pneumonia, time to full enteral feeding, days of birth weight recovery, and death.
Oropharyngeal administration of mother's own milk influences levels of salivary sIgA in preterm infants fed by gastric tube	Chen et al., 2022	China	< 32 weeks/< 1500 g	56/55	After receiving breast milk for the first time	Every 3 hours	0.3 ml	On the 14th day	0.9% normal salt	Oropharyngeal administration of colostrum has an impact on the incidence of necrotic enterocolitis, slow-onset sepsis, intraventricular hemorrhage, ventilator-associated pneumonia, time to full enteral feeding, food intolerance.
Randomized controlled trial of oropharyngeal colostrum administration in very-low-birth-weight preterm infants	Ferreira et al., 2019	Brazil	< 34 weeks / < 1500 grams	47/66	The first 48-72 hours after life	Every 2 hours	0.2 ml	48 hours	Sterile water	Oropharyngeal administration of colostrum has an impact on the incidence of necrotic enterocolitis, late-onset sepsis, bronchopulmonary dysplasia, retinopathy of prematurity,

											intraventricular bleeding, time to full enteral feeding, and death.
Oropharyngeal Colostrum Administration and Anti-inflammatory Effects in Very Low Birth Weight Preterm Neonates	Ferreira et al., 2021	Brazil	< 34 weeks/ < 1500 grams	29/26	The first 48 hours after life	every 2 hours	0.2 ml	48 hours	Distilled water		Oropharyngeal administration of colostrum has an impact on reducing the level of urinary proinflammatory cytokines which can contribute to a decrease in the incidence of neonatal sepsis.
Oropharyngeal Administration of Colostrum Increases Salivary Secretory IgA Levels in Very Low-Birth-Weight Infants	Glass et al., 2017	United States	23 – 32 weeks/ < 1500 grams	17/13	Days 2-7 of early life	Every 3 hours	0.2 ml	6 days	Sterile water		Oropharyngeal administration of colostrum has an impact on the incidence of necrotic enterocolitis, slow-onset sepsis, and time to full enteral feeding.
Oropharyngeal colostrum administration in extremely premature infants: an RCT	Lee et al., 2015	Korean	< 28 weeks/ Not mentioned	24/24	First 48-96 hours after life	Every 3 hours	0.2 ml	72 hours	Sterile Water		Oropharyngeal administration of colostrum has an impact on the incidence of necrotizing enterocolitis, slow-onset sepsis, bronchopulmonary dysplasia, retinopathy of prematurity, intraventricular hemorrhage, ventilator-associated pneumonia, time to full enteral feeding, and death.
Oral application of mother's own milk for prevention of late onset sepsis in preterm very low birth weight neonates: a randomized controlled trial	Jain et al., 2022	India	Not mentioned/ < 1500 grams	55/55	Found on average at 7.91 – 3.03 days	Every 8 hours	0.1 ml	Until the baby starts drinking his mother's breast milk	Empty syringe		Oropharyngeal administration of colostrum has an impact on the incidence of necrotizing enterocolitis, slow-onset sepsis, time to full enteral feeding, and death.
Oropharyngeal administration of colostrum for preventing necrotizing enterocolitis and late-onset sepsis in preterm infants with gestational age ≤ 32 weeks: a pilot	OuYang et al., 2021	China	< 32 weeks/ Not mentioned	127/125	The first 48 hours after life	Every 3 hours	0.4 ml	10 days	Regular brine		Oropharyngeal administration of colostrum has an impact on the incidence of necrotizing enterocolitis, slow-onset sepsis, bronchopulmonary dysplasia, retinopathy of prematurity, intraventricular bleeding, and time to full enteral feeding.
Effect of Oropharyngeal Administration of Colostrum in Premature Newborns ≤ 32 Weeks of Gestation on the Immune Response	Romero Maldonado, 2022	India	< 32 weeks/ Not mentioned	46/50	Within 24 hours of life	Every 4 hours	0.3 ml	4 days	Water that has been double-distilled		Oropharyngeal administration of colostrum has an impact on the incidence of necrotizing enterocolitis, late-onset sepsis, bronchopulmonary

and Neonatal Morbidity: A Double-Blind Randomized Clinical Trial										dysplasia, retinopathy of prematurity, intraventricular bleeding, time for full enteral feeding, days of birth weight recovery, and death.
Role of Oropharyngeal Administration of Colostrum in Very Low Birth Weight Infants for Reducing Necrotizing Enterocolitis: A Randomized Controlled Trial	Sharma et al., 2020	India	< 30 weeks / < 1250 grams	59/58	After 24 hours after birth	Every 2 hours	0.2 ml	72 hours	Regular maintenance	Oropharyngeal administration of colostrum has an impact on the incidence of necrotizing enterocolitis, slow-onset sepsis, bronchopulmonary dysplasia, retinopathy of prematurity, ventilator-associated pneumonia, time to full enteral feeding, and death
Oral Application of Colostrum and Mother's Own Milk in Preterm Infants—A Randomized, Controlled Trial	Sudeep et al., 2022	India	26 – 30 weeks	66/67	Early 24-72 hours of life	Every 3 hours	0.2 ml	Until the baby reaches 32 weeks of age	Sterile water	Oropharyngeal administration of colostrum has an impact on the incidence of necrotizing enterocolitis, late-onset sepsis, bronchopulmonary dysplasia, retinopathy of prematurity, intraventricular bleeding, ventilator-associated pneumonia, time to full enteral feeding, and death
Oropharyngeal colostrum administration in very low birth weight infants: a randomized controlled trial	Zhang et al., 2017	China	32+2–33+4 weeks/ < 1500 grams	32/32	67.3 hours after birth	Every 4 hours	0.2 ml	7 days	Regular brine	Oropharyngeal administration of colostrum has an impact on the incidence of necrotic enterocolitis, slow-onset sepsis, and time to full enteral feeding.

Colostrum is the first breast milk that comes out of the breast before breast milk (breast milk) which has a use as the first food for newborns. From the gestation period, precisely in the 7th month to the 2nd-4th day after giving birth, it is the time when colostrum begins to be produced (Aziz et al., 2016). Colostrum has a slightly different color appearance from breast milk, namely colostrum is generally dark yellow or golden yellow, the high fat content in it causes the intense yellow color. In addition, the texture of colostrum is also different from breast milk where colostrum has a thicker concentration of liquid than breast milk. There are many contents in colostrum that are very beneficial for the baby's immune system, including colostrum containing high immune substances and immunoglobulins that can be used to fight infection with a disease. Due to the lack of knowledge that mothers have regarding the benefits of colostrum, most mothers often do not give colostrum to their babies. In addition, the hereditary understanding related to colostrum is "stale milk" where this is an assumption or cultural belief is also one of the reasons why mothers do not give colostrum to their babies (Suyanti, 2018). When compared to cooked milk, colostrum has a 10-17 times higher content of immune substances (Mose et al., 2021). According to Aziz et al. (2016) research, mothers who have given birth within 48-72 hours after that generally produce or produce as much as 50 ml of colostrum. It is also stated that colostrum contains immune-forming substances, namely

immunoglobulins and white blood cells that can play a role in supporting the baby's body against various microorganisms that cause infection (Aziz et al., 2016).

Garg in his research stated that slow onset sepsis and Necrotizing Enterocolitis (NEC) is a severe complication disease with a high incidence and mortality rate that occurs in premature babies (Garg et al., 2018). Colostrum is considered the best starting food for premature babies because it contains various ingredients that have bioactive effects on living organisms. Colostrum can also help support the maturation process of the immune system in premature babies, including their digestive tract (Gila-Diaz et al., 2019). Generally, babies who are born normally will suck and swallow colostrum through their mouths independently, this will later cause the immune-active components in colostrum to be absorbed by the oropharyngeal lymphoid tissue. However, in premature babies this (oral administration of colostrum) is generally rare to be done, therefore in order for premature babies to still receive the same immune protection as other normal babies, the administration of colostrum can be done oropharyngeal (Panchal et al., 2019), this is in line with Zhen Yan Fu's research which stated that babies who received oral colostrum administration had higher levels of anti-inflammatory factors high and lower levels of proinflammatory factors (Fu et al., 2023). Colostrum administration has been shown to reduce the incidence of slow onset sepsis and Necrotizing Enterocolitis (NEC) effectively in premature babies, based on the results of the meta-analysis that has been carried out, this is also directly proportional to several studies that mention that the administration of colostrum oropharyngeal can also reduce the mortality rate of premature infants, which in the Masi & Stewart (2019) study it was stated that slow onset sepsis and Necrotizing Enterocolitis (NEC) is one of the causes of mortality in premature infants. Colostrum acts as the first immunological protective agent for premature babies because it is proven to contain immunomodulating biofactors, one of which is lactoferrin. The lactoferrin content in colostrum is quite high and one of the advantages of this is that lactoferrin can help protect the intestines both from inflammation and injury due to oxidative stress (Superti, 2020; Gomes et al., 2021). Lactoferrin also functions to reduce the risk of systemic bacteria by inhibiting the growth of pathogenic bacteria in the intestines where this can be the main factor in the development of the event Necrotizing Enterocolitis (NEC), therefore lactoferrin contained in colostrum can also prevent and reduce the risk of late onset sepsis and Necrotizing Enterocolitis (NEC). The results of the analysis in Zhen Yan Fu's study stated that the frequency of giving oropharyngeal colostrum is high but in a short time will only affect the short time of getting enteral food in premature babies. To prevent the incidence of slow-onset sepsis and Necrotizing Enterocolitis (NEC) is therefore recommended to administer oropharyngeal colostrum every 4 hours for 8-10 days. Oropharyngeal administration of colostrum also has an impact on the feeding time of premature babies. Zhen Yan Fu in his study explained that in the intervention group (oropharyngeal colostrum) the enteral feeding time only ranged from 1-3 days, while in the control group the enteral feeding time ranged from 4-7 days (Fu et al., 2023).

## **Conclusion**

Oral administration of colostrum to premature babies has consistently been proven to have an impact and influence on the development and defense of the immune system of premature babies. This is evidenced by the declining incidence of health disorders including those associated with sepsis and necrotizing enterocolitis (NEC) in infants fed oropharyngeal colostrum, shortening the time to achieve full enteral feeding, accelerating birth weight recovery in premature infants, and a lower incidence of mortality. The proper frequency of administration of oropharyngeal colostrum is every 4 hours, and the optimal duration is 8-10 days. Therefore, it is recommended that medical staff or medical personnel continue to give oropharyngeal colostrum according to the recommended frequency and duration.

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