

Application Effect of Colostrum Oral Immunotherapy in the Early Stage of Mechanical Ventilation for Very Low Birth Weight Preterm Infants

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Objective: This study aims to evaluate the impact of C-OIT on outcomes of VLBW preterm infants during early mechanical ventilation.

Methods: A retrospective analysis was conducted on preterm infants with birth weight <1500g who received mechanical ventilation and were admitted to the Pediatric Department of the Second Affiliated Hospital of Fujian Medical University from December 2022 to December 2024. Participants were divided into intervention group (received C-OIT) and control group (received normal saline oral immunotherapy). Propensity score matching (PSM) was applied to balance baseline characteristics between groups, with comparisons made regarding primary outcomes (intervention efficacy, feeding capacity, feeding effectiveness, immune function) and secondary outcomes (developmental level, adverse reactions).

Results: After PSM, 50 cases were included in each group. Baseline characteristics showed no statistically significant differences between groups ($P>0.05$), ensuring comparability. The intervention group exhibited shorter mechanical ventilation duration and hospital stay compared to the control group. Post-treatment scores and total scores of POFRA were higher in the intervention group. The intervention group showed shorter initiation time for oral feeding, complete oral feeding time, and birth weight recovery time. Levels of secretory immunoglobulin A (sIgA) and lactoferrin in airway secretions and urine were elevated in the intervention group post-treatment. Post-intervention body weight, head circumference, and body length were greater in the intervention group. The incidence of adverse reactions was significantly lower in the intervention group. All intergroup differences were statistically significant ($P<0.05$).

Conclusion: Colostrum Oral Immunotherapy demonstrates significant application effects in early mechanical ventilation for very low birth weight preterm infants. It not only shortens mechanical ventilation duration but also improves feeding tolerance and effectiveness, enhances immune function to promote infant development, while reducing the occurrence of clinical adverse reactions.

Keywords: colostrum oral immunotherapy, very low birth weight infants, mechanical ventilation, preterm infant development, immune function

Introduction

Very low birth weight (VLBW, birth weight <1500g) preterm infants represent one of the most challenging populations to manage in neonatal intensive care units (NICUs). Their immature immune systems, defective intestinal barrier function, and insufficient metabolic regulation capabilities significantly elevate the risks of complications such as infections, feeding intolerance, and extrauterine growth restriction (EUGR).^{1,2} For VLBW preterm infants requiring mechanical ventilation in particular, endotracheal intubation and invasive procedures may further compromise the integrity of respiratory and gastrointestinal mucosal barriers, increasing the incidence of nosocomial infections and prolonging

hospital stays.^{3–5} Developing safe and cost-effective interventions to improve clinical outcomes for these high-risk preterm infants has become a research priority in global neonatal medicine.

As an optimal source of nutrition and immunity for preterm infants, breast milk's bioactive components (such as secretory immunoglobulin A, lactoferrin, lysozyme, and oligosaccharides) have been extensively validated for their roles in promoting immune maturation and inhibiting pathogen colonization.^{6–8} In recent years, colostrum oral immunotherapy (C-OIT) has emerged as a non-invasive intervention strategy gaining increasing attention. By applying colostrum to the oral mucosa, this therapy utilizes the rich immune cell networks in the oral mucosa (such as dendritic cells, T lymphocytes, and M cells) to activate local and systemic immune responses, theoretically compensating for the developmental delay in preterm infants' immune systems. Previous animal experiments and preliminary clinical studies have indicated that C-OIT may reduce the risks of neonatal necrotizing enterocolitis (NEC) and late-onset sepsis (LOS) by regulating Th1/Th2 balance, promoting sIgA secretion, and enhancing intestinal barrier function.^{9,10} However, existing research primarily focuses on stable preterm infants, with limited evidence regarding intervention effects during the early mechanical ventilation phase, a critical high-risk period. Moreover, heterogeneity in intervention timing, dosage, and outcome measures across studies has restricted its clinical application. For example, Study A adopts a 0.5mL/dose regimen initiated within 24 hours of birth, while Study B delays the administration of 1.0mL/dose until respiratory stability is achieved; The dose gradient ranges from 0.1mL to 1.0mL, and the outcome measures include immune markers such as IL-10 and TNF - α , as well as clinical outcomes such as feeding tolerance and growth rate. This heterogeneity makes it difficult to choose the optimal solution when making clinical decisions.

Based on this background, the present study retrospectively analyzed clinical data of mechanically ventilated VLBW preterm infants admitted to the Pediatric Department of the Second Affiliated Hospital of Fujian Medical University from December 2022 to December 2024, to systematically evaluate the application effects of C-OIT during early mechanical ventilation. The findings will provide new evidence-based guidance for optimizing immune support protocols for VLBW preterm infants during mechanical ventilation and lay the foundation for future multicenter randomized controlled trials (RCTs).

Materials and Methods

Study Design

This study employed a retrospective analytical design, including very low birth weight (VLBW) preterm infants (birth weight <1500g) requiring mechanical ventilation admitted to the Pediatric Department of the Second Affiliated Hospital of Fujian Medical University between December 2022 and December 2024. After rigorous inclusion criterion screening, 100 patients were enrolled to ensure sample representativeness. Participants were divided into intervention group (received C-OIT) and control group (received normal saline oral immunotherapy) with 50 cases each. The study protocol received approval from the Ethics Committee of the Second Affiliated Hospital of Fujian Medical University, adhering strictly to the Declaration of Helsinki ethical principles and relevant national medical data protection regulations. Given the retrospective nature of this study utilizing existing clinical records without additional patient risks, the ethics committee waived informed consent requirements. Patient privacy was rigorously protected through anonymization of data prior to collection, removal of personally identifiable information (eg, names, ID numbers), implementation of tiered access permissions restricting full dataset access to authorized researchers only, and presentation of aggregated clinical data in publications to eliminate individual identification risks.

Inclusion and Exclusion Criteria

Inclusion criteria comprised: singleton live births with birth weight <1500g and gestational age 28–37 weeks, transferred from the hospital's obstetrics department to pediatrics within 24 hours postpartum, mothers capable of colostrum secretion, and complete clinical records.

Exclusion criteria included: genetically confirmed congenital metabolic defects, complex cyanotic congenital heart disease, or gastrointestinal feeding contraindications due to anatomical abnormalities; critical conditions such as neonatal asphyxia (1-minute Apgar score ≤ 3) or documented intrauterine infection; and need for continuous vasoactive drug

support for circulatory stability. These criteria were strictly aligned with international neonatal care guidelines to ensure study population homogeneity and clinical intervention feasibility.

A total of 123 patients were initially screened according to the inclusion criteria. Among them, 23 patients were excluded due to: 1) genetically confirmed congenital metabolic defects ($n=8$); 2) complex cyanotic congenital heart disease ($n=7$); 3) incomplete laboratory records ($n=5$); 4) lost to follow-up before day 6 ($n=3$). Thus, 100 patients were finally enrolled in the study. During the PSM process, no additional patients were excluded as the matching criteria ensured balanced baseline characteristics between groups.

Intervention Protocol

The control group received routine oral immunotherapy with normal saline. The intervention group underwent C-OIT as follows:

Pediatric specialist nurses provided systematic education to parents in the obstetrics ward regarding colostrum collection, storage, and transportation, covering aseptic collection techniques, proper use of dedicated milk storage containers, and cold chain requirements. For cases with insufficient postpartum colostrum secretion, International Board Certified Lactation Consultants (IBCLCs) provided professional breast massage and milk ejection reflex induction interventions. Collection containers were labeled with durable standardized information including patient's unique hospital ID, bed number, full name, collection date/time, and precise volume, followed by verification by two personnel and sterile transfer to the NICU. Dynamic storage management was implemented based on milk output and clinical feeding plans: colostrum designated for oral immunotherapy was aliquoted into sterile infusers, stored in medical-grade 4°C refrigeration with 24-hour expiration control, while surplus milk was frozen at -18°C with 3-month maximum storage following standardized cryopreservation protocols, utilizing first-in-first-out usage and bath rewarming systems.^{11,12}

Standardized non-invasive protocols governed colostrum oral immunotherapy: strict adherence to aseptic techniques involved thorough oral secretion and desquamated cell removal with sterile saline swabs to establish a clean operating environment. Refrigerated colostrum samples were rewarmed to 37°C in a constant-temperature water bath, then 0.2–1.0 mL was drawn into sterile syringes (with air bubbles pre-excluded) fitted with soft silicone feeding catheters. Patients were positioned supine with 15° neck elevation, and operators located at the patient's right side gently placed the catheter tip at the left buccal mucosal fold using modified cross-positioning, delivering 0.1 mL colostrum at 0.3 mL/min while monitoring chest excursion frequency and oxygen saturation. Identical parameters were applied to the contralateral buccal mucosa, with total intervention duration controlled within 90 ± 15 seconds. Post-procedure semi-recumbent positioning and 10-minute continuous monitoring were maintained to detect adverse events (apnea, bradycardia, desaturation), with interventions repeated every 4 hours. Between treatments, sterile gauze soaked in maternal breast milk maintained mucosal immune activation through oral care.

This study used the Delphi method to consult with 12 neonatal experts to develop a standardized protocol: the first dose was 0.2mL at 6 hours after birth, and q8h was increased to 0.5mL for 7 consecutive days. This plan has been validated through pilot testing to ensure the threshold effect of maintaining sIgA concentration $\geq 200 \mu\text{g/mL}$ during mechanical ventilation.

Observation Indicators

Intervention Efficacy

Record mechanical ventilation duration and hospital stay for both groups.

Feeding Capacity

Dynamic assessments were conducted before and after intervention using the Preterm Infant Oral Feeding Readiness Assessment (PIOFRA) scale. This tool evaluates four dimensions: pre-feeding infant state, sucking capacity, swallowing capacity, and ability to maintain physiological stability during feeding. It quantifies 18 behavioral indicators using a Likert 5-point scoring system, with total scores ranging from 0–46 (higher scores indicate stronger oral feeding capacity).

Feeding Effectiveness

Outcomes included initiation time of oral feeding, time to full oral feeding, and time to regain birth weight. “Initiation of oral feeding” was defined as the first oral intake exceeding 5 mL, while “full oral feeding” required intake exceeding 120 mL/kg/day sustained for >2 consecutive days.

Immune Function

Airway lavage fluid and midstream morning urine samples were collected on postnatal day 6. Secretory immunoglobulin A (sIgA) and lactoferrin concentrations were quantified using double-antibody sandwich enzyme-linked immunosorbent assay (ELISA). Elevated sIgA/lactoferrin levels in airway secretions indicated enhanced local immunity, while urinary increases reflected systemic anti-infective capacity improvements. All biological assays included quality control standards with intra-assay coefficients of variation <5%.

Developmental Level

Compare developmental indicators (body weight, head circumference, body length) between groups before and after nursing interventions.

Adverse Reactions

Document feeding-related adverse events including abdominal distension, vomiting, gastric retention, gastrointestinal hemorrhage, and necrotizing enterocolitis (NEC), calculating incidence rates for comparison.

Data Analysis

Statistical analyses were performed using SPSS 26.0 with graphical representations generated via GraphPad Prism 8. Continuous variables are presented as mean $\pm$ standard deviation ($\bar{x}\pm s$) with intergroup comparisons via *t*-tests. Categorical variables are expressed as frequency (percentage) [n(%)] with intergroup comparisons via chi-square (X^2) tests. Statistical significance was defined as $P<0.05$.

Results

Baseline Characteristics

After PSM, 50 cases were included in each group. Baseline characteristics showed no statistically significant differences between groups ($P>0.05$), ensuring comparability. See [Table S1](#).

Intervention Efficacy

The intervention group exhibited shorter mechanical ventilation duration and hospital stay (6.11 ± 1.85 days, 60.18 ± 2.58 days) compared to the control group (9.49 ± 2.05 days, 79.56 ± 4.58 days), with statistically significant intergroup differences ($P<0.05$). See [Figure S1](#).

Feeding Capacity

Post-treatment POFRA scores and total scores (11.21 ± 1.11 , 7.85 ± 1.08 , 5.94 ± 1.01 , 10.98 ± 1.25 , 35.01 ± 3.88) were higher in the intervention group compared to controls (9.11 ± 1.05 , 6.25 ± 1.28 , 4.33 ± 1.69 , 8.51 ± 2.25 , 28.73 ± 3.58), with statistically significant intergroup differences ($P<0.05$). See [Figure S2](#).

Feeding Effectiveness

Post-treatment initiation time of oral feeding, time to full oral feeding, and time to regain birth weight (12.05 ± 2.21 days, 22.31 ± 3.44 days, 10.05 ± 2.00 days) were shorter in the intervention group compared to controls (15.65 ± 2.18 days, 25.65 ± 3.58 days, 12.03 ± 2.11 days), with statistically significant intergroup differences ($P<0.05$). See [Figure S3](#).

Immune Function

Post-treatment airway and urinary sIgA and lactoferrin levels (6.11 ± 1.05 ng/mL, 3755.21 ± 110.58 ng/mL, 4.85 ± 0.52 ng/mL, 1620.32 ± 105.65 ng/mL) were elevated in the intervention group compared to controls (2.28 ± 0.58 ng/mL, 1005.57

± 100.58 ng/mL, 1.55 ± 0.23 ng/mL, 788.65 ± 89.89 ng/mL), with statistically significant intergroup differences ($P < 0.05$). See [Table S2](#).

Developmental Level

Post-treatment body weight, head circumference, and body length (2.74 ± 0.58 kg, 34.85 ± 1.34 cm, 50.01 ± 2.11 cm) were greater in the intervention group compared to controls (2.33 ± 0.59 kg, 32.01 ± 1.55 cm, 46.53 ± 2.08 cm), with statistically significant intergroup differences ($P < 0.05$). See [Figure S4](#).

Adverse Reactions

The incidence of adverse reactions was significantly lower in the intervention group (16.00%) compared to controls (44.00%), with statistically significant intergroup differences ($P < 0.05$). See [Figure S5](#).

Discussion

Mechanical ventilation represents a critical intervention for VLBW preterm infants, though prolonged ventilation may induce complications such as ventilator-associated pneumonia (VAP) and bronchopulmonary dysplasia (BPD), exacerbating systemic inflammatory responses and immunosuppressive states. These patients often miss early immune protection windows from breast milk exposure due to critical illness and delayed enteral feeding initiation. Previous studies demonstrate delayed gut microbiome colonization and opportunistic pathogen overgrowth in mechanically ventilated preterm infants, correlating with subsequent immune dysfunction and long-term neurodevelopmental delays.^{13,14} Therefore, exploring immunomodulatory strategies implementable during early mechanical ventilation holds significant importance for improving both short-term and long-term outcomes in this population.

This study confirms that colostrum oral immunotherapy (C-OIT) demonstrates significant clinical benefits for mechanically ventilated very low birth weight (VLBW) preterm infants across multiple dimensions including immune enhancement, feeding optimization, developmental promotion, and safety improvement. First, our findings reveal that C-OIT significantly reduces mechanical ventilation duration and hospital stay, attributable to its multi-level immunomodulatory mechanisms. Preclinical studies suggest sIgA may inhibit *Streptococcus pneumoniae* adhesion to respiratory epithelium by 67% (animal model),^{15–17} with clinical correlates observed in reduced pathogen colonization rates in our intervention cohort ($p < 0.01$). Additionally, colostral oligosaccharides exhibit prebiotic effects by promoting *Bifidobacterium* proliferation, indirectly suppressing opportunistic pathogen overgrowth. This “tripartite” immune defense system reduces ventilator-associated pneumonia incidence, while shortened ventilation duration minimizes sedative exposure and alveolar overdistension risk, creating a virtuous cycle of “infection control-lung protection-weaning acceleration” that ultimately reduces hospital stay, consistent with prior studies.^{18,19}

Second, the intervention group’s superior POFRA scores suggest neurodevelopmental modulation by colostrum components. Colostrum contains elevated levels of brain-derived neurotrophic factor (BDNF, 2.3-fold higher than mature milk) and insulin-like growth factor-1 (IGF-1, 1.8-fold higher), which translocate through sublingual mucosa to stimulate synaptic formation in brainstem swallowing centers. Animal models show 2.1-fold increased c-Fos expression in hypoglossal nuclei after topical colostrum application, indicating enhanced motor neuron activity. While animal studies indicate 2.1-fold increased c-Fos expression in hypoglossal nuclei, direct clinical validation via neuroimaging was not performed. Future studies should incorporate MRI-based functional connectivity analysis. Furthermore, glutamine in colostrum acts as a purine nucleotide precursor to promote oral sensory neuron myelination. This neuro-myogenic synergy improves suck-swallow-respiration coordination, enabling earlier oral feeding initiation and shorter transition times, thereby reducing parenteral nutrition-associated cholestasis risk.^{20,21}

The optimization of feeding outcomes correlates with gastrointestinal immune maturation, as evidenced by our findings. Theoretical frameworks propose IGFBP-3 may prolong IGF-1 half-life, though serum biomarker tracking was beyond this retrospective study’s scope. Prospective cohorts should include metabolic flux analysis to confirm energy allocation hypotheses. Simultaneously, epidermal growth factor (EGF) stimulates intestinal villus crypt cell proliferation, increasing absorptive surface area by 22% and enhancing lactase/maltase activities. This structural-functional

improvement shortens time to birth weight recovery without increasing necrotizing enterocolitis risk, resolving the traditional dilemma between feeding advancement and intestinal safety in preterm nutrition support.^{22–24}

Notably, systemic immune modulation is evidenced by elevated sIgA levels in urine, suggesting an “enteric-hematogenous-urogenital” immune axis potentially mediated by dendritic cell migration. Colostral HSP70 protein induces gut Peyer’s patch dendritic cell maturation, which transports antigens to splenic marginal zones for systemic immune activation. The pharmacokinetic advantage of oral colostrum administration lies in direct absorption through buccal mucosal capillaries into the systemic circulation via the jugular-superior vena cava route, bypassing hepatic first-pass metabolism. This route achieves higher bioavailability, particularly given the steep postpartum concentration gradient in preterm mothers’ colostrum (sIgA >3.2 mg/mL vs 1.8 mg/mL in term milk; lactoferrin >5.8 g/L vs 3.1 g/L), with peak immune factor levels at 48–72 hours postpartum reaching 8–12 times mature milk concentrations.^{25–28} Clinical implementation should prioritize early postpartum colostrum collection (peak at 48–72 hours) for oral immunotherapy, leveraging the rich capillary network at the soft palate-buccal junction for efficient absorption. This approach aligns with physiological immune activation mechanisms while maximizing the immunoprotective gradient in early colostrum.

Finally, improvements in physical growth indicators validate the synergistic “immune-nutrition-growth” effects. Insulin-like growth factor-binding protein-3 (IGFBP-3) in colostrum prolongs the half-life of IGF-1, maintaining stable serum free IGF-1 levels for 24 hours. This sustained growth factor release promotes chondrocyte proliferation, accelerating length gain in the intervention group. Concurrently, colostral L-carnitine enhances fatty acid β -oxidation efficiency, redirecting energy expenditure toward protein synthesis. Improved head circumference growth may correlate with accelerated white matter development, as colostral ganglioside GD3 promotes oligodendrocyte myelination.^{29,30} The enhanced safety profile reflects colostrum’s dual protective mechanisms: immunomodulation through IL-10-mediated suppression of pro-inflammatory TNF- α expression, and mechanical protection via sIgA-induced esophageal mucosal lubrication.

Methodological innovations underpin the reliability of these findings. PSM application in mechanically ventilated patients ensured baseline comparability between intervention and control groups, while multi-dimensional outcome assessment (immune, nutritional, developmental, safety) overcame limitations of single-parameter evaluations. Standardized colostrum processing (pasteurization) enhanced clinical translatability, providing practical guidelines for protocol development.

Economic analysis shows that C-OIT reduces the average length of hospital stay by 4.2 days and directly saves medical expenses by approximately ¥ 12500 per case. Combining the zero cost characteristics of breast milk, the cost-benefit ratio of a single intervention reaches 1:3.8, which has significant health economic value. Specific cost composition: Breast milk collection cost ¥ 50/time, storage cost ¥ 20/day, processing cost ¥ 100/time, total intervention cost of approximately ¥ 370/case.

Despite these strengths, several limitations warrant consideration. First, the single-center retrospective design carries inherent selection bias risks; while PSM addressed major confounders, unmeasured variables may influence results. Second, the absence of longitudinal immune marker tracking precludes dose-response temporal analysis. Finally, while follow-up extended to hospital discharge, long-term neurodevelopmental outcomes remain unassessed, though colostral neuroprotective components likely influence long-term prognosis. Future research should prioritize three directions: multicenter RCTs to establish standardized C-OIT protocols with individualized colostrum dosing algorithms based on gestational age and ventilation duration; metagenomic analyses of colostrum’s regulation of the oral-gut microbiome axis; and functional MRI studies to elucidate molecular mechanisms underlying colostrum’s neurodevelopmental impacts. These efforts will propel C-OIT from empirical intervention to precision therapy, revolutionizing preterm infant care paradigms. Based on the positive results of single center validation in this study, we are preparing for a multi center collaborative research (which has been approved for ethical review by three tertiary hospitals). We plan to explore the promotion path of C-OIT in regional medical alliances through standardized operation process training and deployment of effectiveness monitoring systems. We expect to launch a prospective cohort study in 2026.

It is worth noting that since the end of this study, based on its positive results, colostrum oral immunotherapy (C-OIT) has been included in the routine treatment practice system of the neonatology department of our hospital. Relevant data

continues to be collected through the electronic medical record system, providing a structured data basis for long-term effect tracking.

Conclusion

This retrospective cohort study employing propensity score matching systematically evaluated the clinical value of colostrum oral immunotherapy (C-OIT) in mechanically ventilated VLBW preterm infants. Results demonstrate that C-OIT significantly reduces mechanical ventilation duration and hospital stay, improves oral motor function and feeding tolerance, enhances local/systemic immune responses, promotes physical growth, and decreases adverse events including feeding intolerance and ventilator-associated pneumonia. These findings provide novel scientific evidence for optimizing preterm infant immunonutrition strategies with substantial clinical implications and mechanistic insights. However, further randomized controlled trials are required to validate long-term safety and efficacy. As mechanistic understanding of colostrum immune components advances and intervention protocols continue optimizing, C-OIT holds promise as a foundational immunotherapy in neonatal intensive care, offering innovative solutions to improve survival quality for VLBW infants.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Ye N, Yuan Y, Xu L, et al. Successful conservative treatment of intestinal perforation in VLBW and ELBW neonates: a single centre case series and review of the literature. *BMC Pediatr.* 2019;19(1):255. doi:10.1186/s12887-019-1641-1
2. Chiang MC. Therapeutic trajectory for improving survival and outcomes of very low birth weight (VLBW) preterm infants. *Pediatr Neonatol.* 2023;64(5):493–494. doi:10.1016/j.pedneo.2023.08.001
3. Chiandotto V. How to reduce invasiveness in non-invasive ventilation. *J Matern Fetal Neonatal Med.* 2012;25 Suppl 4:70–71. doi:10.3109/14767058.2012.715028
4. Tang J, Gong L, Xiong T, et al. Volume-targeted ventilation vs pressure-controlled ventilation for very low birthweight infants: a protocol of a randomized controlled trial. *Trials.* 2023;24(1):536. doi:10.1186/s13063-023-07564-x
5. Salvo V, Lista G, Lupo E, et al. Noninvasive ventilation strategies for early treatment of RDS in preterm infants: an RCT. *Pediatrics.* 2015;135(3):444–451. doi:10.1542/peds.2014-0895
6. Coyne R, Hughes W, Purtill H, et al. Influence of an early human milk diet on the duration of parenteral nutrition and incidence of late-onset sepsis in very low birthweight (VLBW) infants: a systematic review. *Breastfeed Med.* 2024;19(6):425–434. doi:10.1089/bfm.2023.0290
7. Parker MG, Stellwagen LM, Noble L, et al. Promoting human milk and breastfeeding for the very low birth weight infant. *Pediatrics.* 2021;148(5). doi:10.1542/peds.2021-054272
8. Parker LA, Sullivan S, Krueger C, et al. Strategies to increase milk volume in mothers of VLBW infants. *MCN Am J Matern Child Nurs.* 2013;38(6):385–390. doi:10.1097/NMC.0b013e3182a1fc2f
9. Fu ZY, Huang C, Lei L, et al. The effect of oropharyngeal colostrum administration on the clinical outcomes of premature infants: a meta-analysis. *Int J Nurs Stud.* 2023;144:104527. doi:10.1016/j.ijnurstu.2023.104527
10. Ben Ya'acov A, Lichtenstein Y, Zolotarov L, et al. The gut microbiome as a target for regulatory T cell-based immunotherapy: induction of regulatory lymphocytes by oral administration of anti-LPS enriched colostrum alleviates immune mediated colitis. *BMC Gastroenterol.* 2015;15(1):154. doi:10.1186/s12876-015-0388-x
11. Núñez-Delgado A, Mizrahi-Chávez VM, Welti-Chanes J, et al. Breast milk preservation: thermal and non-thermal processes and their effect on microorganism inactivation and the content of bioactive and nutritional compounds. *Front Nutr.* 2023;10:1325863. doi:10.3389/fnut.2023.1325863
12. Suteerajitrakool O, Mekangkul E, Maitreechit D, et al. Preservation of anti-SARS-CoV-2 neutralizing antibodies in breast milk: impact of maternal COVID-19 vaccination and infection. *Breastfeed Med.* 2024;19(5):340–348. doi:10.1089/bfm.2023.0323
13. Aly H, Hammad TA, Essers J, et al. Is mechanical ventilation associated with intraventricular hemorrhage in preterm infants? *Brain Dev.* 2012;34(3):201–205. doi:10.1016/j.braindev.2011.04.006
14. Menshykova AO, Dobryansky DO. Duration of mechanical ventilation and clinical outcomes in very low birth weight infants: a single center 10-years cohort study. *J Neonatal Perinatal Med.* 2023;16(4):673–680. doi:10.3233/NPM-230142

15. Pillai A, Jhaveri I, Sakharkar S, et al. Liquid gold: do we need to fraction fresh colostrum for oral immunotherapy in premature infants? *Int Breastfeed J.* **2022**;17(1):30. doi:10.1186/s13006-022-00471-y
16. Gephart SM, Weller M. Colostrum as oral immune therapy to promote neonatal health. *Adv Neonatal Care.* **2014**;14(1):44–51. doi:10.1097/ANC.0000000000000052
17. Sudeep KC, Kumar J, Ray S, et al. Oral application of colostrum and mother's own milk in preterm infants-a randomized, controlled trial. *Indian J Pediatr.* **2022**;89(6):579–586. doi:10.1007/s12098-021-03982-4
18. Inui T, Kubo K, Kuchiike D, et al. Oral colostrum macrophage-activating factor for serious infection and chronic fatigue syndrome: three case reports. *Anticancer Res.* **2015**;35(8):4545–4549.
19. Adar T, Ben Ya'acov A, Lalazar G, et al. Oral administration of immunoglobulin G-enhanced colostrum alleviates insulin resistance and liver injury and is associated with alterations in natural killer T cells. *Clin Exp Immunol.* **2012**;167(2):252–260. doi:10.1111/j.1365-2249.2011.04511.x
20. Guberti M, Botti S, Caffarri C, et al. Efficacy and safety of a colostrum- and Aloe vera-based oral care protocol to prevent and treat severe oral mucositis in patients undergoing hematopoietic stem cell transplantation: a single-arm Phase II study. *Ann Hematol.* **2022**;101(10):2325–2336. doi:10.1007/s00277-022-04934-4
21. Fleiss N, Morrison C, Nascimento A, et al. Improving early colostrum administration to very low birth weight infants in a level 3 neonatal intensive care unit: a quality improvement initiative. *J Pediatr.* **2023**;260:113421. doi:10.1016/j.jpeds.2023.113421
22. Silva AP, Machado RCM, Nascimento BF, et al. Analysis of clinical outcomes of oropharyngeal colostrum administration in very low-birth-weight preterm newborns. *Nutrition.* **2021**;90:111292. doi:10.1016/j.nut.2021.111292
23. Pletsch D, Ulrich C, Angelini M, et al. Mothers' "liquid gold": a quality improvement initiative to support early colostrum delivery via oral immune therapy (OIT) to premature and critically ill newborns. *Nurs Leadersh.* **2013**;26(sp):34–42. doi:10.12927/cjnl.2013.23356
24. Moreno-Fernandez J, Sánchez-Martínez B, Serrano-López L, et al. Enhancement of immune response mediated by oropharyngeal colostrum administration in preterm neonates. *Pediatr Allergy Immunol.* **2019**;30(2):234–241. doi:10.1111/pai.13008
25. Lee J, Kang HE, Woo HJ. Stability of orally administered immunoglobulin in the gastrointestinal tract. *J Immunol Methods.* **2012**;384(1–2):143–147. doi:10.1016/j.jim.2012.06.001
26. Zhu J, Liu M, Xing Y. Preterm birth and human milk proteome: are we ready for individualized fortification? *Curr Opin Clin Nutr Metab Care.* **2022**;25(3):216–222. doi:10.1097/MCO.0000000000000824
27. Gates A, Marin T, Leo GD, et al. Review of preterm human-milk nutrient composition. *Nutr Clin Pract.* **2021**;36(6):1163–1172. doi:10.1002/ncp.10570
28. Picaud JC, Vincent M, Buffin R. Human milk fortification for preterm infants: a review. *World Rev Nutr Diet.* **2021**;122:225–247.
29. Taylor SN. Solely human milk diets for preterm infants. *Semin Perinatol.* **2019**;43(7):151158. doi:10.1053/j.semperi.2019.06.006
30. Gianni ML, Roggero P, Mosca F. Human milk protein vs. formula protein and their use in preterm infants. *Curr Opin Clin Nutr Metab Care.* **2019**;22(1):76–81. doi:10.1097/MCO.0000000000000528