

Emerging Developments in Human Milk Fortification: Problem Solving for Clinical Practice

- Agha L, Staiger D, Brown C, Soll RF, Horbar JD, Edwards EM. Association of hospital adoption of probiotics with outcomes among neonates with very low birth weight. *JAMA Health Forum*. 2023;4(5):e230960. doi:10.1001/jamahealthforum.2023.0960
- Ahnfeldt AM, Aunsholt L, Hansen BM, et al. Bovine colostrum as a fortifier to human milk in very preterm infants - A randomized controlled trial (FortiColos). *Clin Nutr*. 2023;42(5):773-783. doi:10.1016/j.clnu.2023.03.008
- Almeida CC, Mendonça Pereira BF, Leandro KC, Costa MP, Spisso BF, Conte-Junior CA. Bioactive Compounds in Infant Formula and Their Effects on Infant Nutrition and Health: A Systematic Literature Review. *Int J Food Sci*. 2021;2021:8850080. doi:10.1155/2021/8850080
- Alshaikh B, Abo Zeed M, Yusuf K, Guin M, Fenton T. Effect of enteral zinc supplementation on growth and neurodevelopment of preterm infants: a systematic review and meta-analysis. *J Perinatol*. 2022;42(4):430-439. doi:10.1038/s41372-021-01094-7
- Asbury MR, Shama S, Sa JY, et al. Human milk nutrient fortifiers alter the developing gastrointestinal microbiota of very-low-birth-weight infants. *Cell Host Microbe*. 2022;30(9):1328-1339.e5. doi:10.1016/j.chom.2022.07.011
- Athalye-Jape G, Esvaran M, Patole S, et al. Effect of single versus multistrain probiotic in extremely preterm infants: a randomised trial. *BMJ Open Gastroenterol*. 2022;9(1):e000811. doi:10.1136/bmjgast-2021-000811
- Bagga N, Panigrahi N, Germain A, et al. Extrauterine growth restriction: Need for an accurate definition. *Newborn (Clarksville)*. 2023;2(3):198-202. doi:10.5005/jp-journals-11002-0072
- Ballard O, Morrow AL. Human milk composition: nutrients and bioactive factors. *Pediatr Clin North Am*. 2013;60(1):49-74. doi:10.1016/j.pcl.2012.10.002
- Beck LC, Masi AC, Young GR, et al. Strain-specific impacts of probiotics are a significant driver of gut microbiome development in very preterm infants. *Nat Microbiol*. 2022;7(10):1525-1535. doi:10.1038/s41564-022-01213-w
- Biesalski HK, Dragsted LO, Elmadfa I, et al. Bioactive compounds: definition and assessment of activity. *Nutrition*. 2009;25(11-12):1202-1205. doi:10.1016/j.nut.2009.04.023
- Bingham R, Pineda D, Gates A, Thompson AB, Stansfield BK. Displacement of human milk during fortification: An experimental study. *JPEN J Parenter Enteral Nutr*. 2023;47(8):1062-1066. doi:10.1002/jpen.2553
- Bode L. Human milk oligosaccharides: every baby needs a sugar mama. *Glycobiology*. 2012;22(9):1147-1162. doi:10.1093/glycob/cws074
- Bresemi I, Salvatore S, Valetti G, Baj A, Giaroni C, Agosti M. The microbiota-gut axis in premature infants: Physio-pathological implications. *Cells*. 2022;11(3):379. doi:10.3390/cells11030379
- Castanet M, Costalos C, Haiden N, et al. Early effect of supplemented infant formulae on intestinal biomarkers and microbiota: A randomized clinical trial. *Nutrients*. 2020;12(5):1481. doi:10.3390/nu12051481
- Colaizy TT, Poindexter BB, McDonald SA, et al. Neurodevelopmental outcomes of extremely preterm infants fed donor milk or preterm infant formula: A randomized clinical trial. *JAMA*. 2024;331(7):582-591. doi:10.1001/jama.2023.27693
- Colombo J, Harris CL, Wampler JL, et al. Improved neurodevelopmental outcomes at 5.5 years of age in children who received bovine milk fat globule membrane and lactoferrin in infant formula through 12 months: A randomized controlled trial. *J Pediatr*. 2023;261:113483. doi:10.1016/j.jpeds.2023.113483
- Embleton ND, Moltu SJ, Lapillonne A, et al. Enteral Nutrition in Preterm Infants (2022): A Position Paper From the ESPGHAN Committee on Nutrition and Invited Experts. *J Pediatr Gastroenterol Nutr*. 2023;76(2):248-268. doi:10.1097/MPG.0000000000003642
- Embleton ND, Sproat T, Uthaya S, et al. Effect of an exclusive human milk diet on the gut microbiome in preterm infants: A randomized clinical trial. *JAMA Netw Open*. 2023;6(3):e231165. Published 2023 Mar 1. doi:10.1001/jamanetworkopen.2023.1165

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- Fujishiro S, Tsuji S, Akagawa S, et al. Dysbiosis in gut microbiota in children born preterm who developed autism spectrum disorder: A pilot study. *J Autism Dev Disord.* 2023;53(10):4012-4020. doi:10.1007/s10803-022-05682-0
- Gates A, Hair AB, Salas AA, Thompson AB, Stansfield BK. Nutrient composition of donor human milk and comparisons to preterm human milk. *J Nutr.* 2023;153(9):2622-2630. doi:10.1016/j.tjnut.2023.07.012
- Gialeli G, Kapetanaki A, Panagopoulou O, et al. Supplementation of mother's own milk with preterm donor human milk: Impact on protein intake and growth in very low birth weight infants-A randomized controlled study. *Nutrients.* 2023;15(3):566. doi:10.3390/nu15030566
- Gounaris AK, Sokou R, Gounari EA, Panagiotounakou P, Grivea IN. Extrauterine growth restriction and optimal growth of very preterm neonates: State of the art. *Nutrients.* 2023;15(14):3231. doi:10.3390/nu15143231
- Guellec I, Lapillonne A, Marret S, et al. Effect of intra- and extrauterine growth on long-term neurologic outcomes of very preterm infants. *J Pediatr.* 2016;175:93-99.e1. doi:10.1016/j.jpeds.2016.05.027
- Hair AB, Blanco CL, Moreira AG, et al. Randomized trial of human milk cream as a supplement to standard fortification of an exclusive human milk-based diet in infants 750-1250 g birth weight. *J Pediatr.* 2014;165(5):915-920. doi:10.1016/j.jpeds.2014.07.005
- Hascoët JM, Chevallier M, Gire C, et al. Use of a liquid supplement containing 2 human milk oligosaccharides: The first double-blind, randomized, controlled trial in pre-term infants. *Front Pediatr.* 2022;10:858380. doi:10.3389/fped.2022.858380
- Hellström A, Ley D, Hansen-Pupp I, et al. New insights into the development of retinopathy of prematurity--importance of early weight gain. *Acta Paediatr.* 2010;99(4):502-508. doi:10.1111/j.1651-2227.2009.01568.x
- Hennet T, Weiss A, Borsig L. Decoding breast milk oligosaccharides. *Swiss Med Wkly.* 2014;144:w13927. doi:10.4414/smw.2014.13927
- Hopperton KE, O'Connor DL, Bando N, et al. Nutrient enrichment of human milk with human and bovine milk-based fortifiers for infants born <1250 g: 18-month neurodevelopment follow-up of a randomized clinical trial. *Curr Dev Nutr.* 2019;3(12):nzz129. doi:10.1093/cdn/nzz129
- Isaacs EB, Morley R, Lucas A. Early diet and general cognitive outcome at adolescence in children born at or below 30 weeks gestation. *J Pediatr.* 2009;155(2):229-234. doi:10.1016/j.jpeds.2009.02.030
- Jantscher-Krenn E, Zhrebtsov M, Nissan C, et al. The human milk oligosaccharide disialyllacto-N-tetraose prevents necrotising enterocolitis in neonatal rats. *Gut.* 2012;61(10):1417-1425. doi:10.1136/gutjnl-2011-301404
- Jensen GB, Domellöf M, Ahlsson F, Elfvin A, Navér L, Abrahamsson T. Effect of human milk-based fortification in extremely preterm infants fed exclusively with breast milk: a randomised controlled trial. *EClinicalMedicine.* 2024;68:102375. doi:10.1016/j.eclinm.2023.102375
- Kappel SS, Sangild PT, Ahnfeldt AM, et al. A randomized, controlled study to investigate how bovine colostrum fortification of human milk affects bowel habits in preterm infants (FortiColos Study). *Nutrients.* 2022;14(22):4756. doi:10.3390/nu14224756
- Klamer A, Toftlund LH, Grimsson K, Halken S, Zachariassen G. IQ was not improved by post-discharge fortification of breastmilk in very preterm infants. *Nutrients.* 2022;14(13):2709. doi:10.3390/nu14132709
- Kleinman RE, Greer FR, eds. *Pediatric Nutrition, 8th ed.* American Academy of Pediatrics; 2020.
- Kumbhare SV, Jones WD, Fast S, et al. Source of human milk (mother or donor) is more important than fortifier type (human or bovine) in shaping the preterm infant microbiome. *Cell Rep Med.* 2022;3(9):100712. doi:10.1016/j.xcrm.2022.100712
- Lasekan J, Choe Y, Dvoretzkiy S, et al. Growth and gastrointestinal tolerance in healthy term infants fed milk-based infant formula supplemented with five human milk oligosaccharides (HMOs): A randomized multicenter trial. *Nutrients.* 2022;14(13):2625. doi:10.3390/nu14132625
- Li F, Wu SS, Berseth CL, et al. Improved neurodevelopmental outcomes associated with bovine milk fat globule membrane and lactoferrin in infant formula: A randomized, controlled trial. *J Pediatr.* 2019;215:24-31.e8. doi:10.1016/j.jpeds.2019.08.030

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- Liang N, Koh J, Kim BJ, Ozturk G, Barile D, Dallas DC. Structural and functional changes of bioactive proteins in donor human milk treated by vat-pasteurization, retort sterilization, ultra-high-temperature sterilization, freeze-thawing and homogenization. *Front Nutr*. 2022;9:926814. doi:10.3389/fnut.2022.926814
- Lönnerdal B. Bioactive proteins in breast milk. *J Paediatr Child Health*. 2013;49 Suppl 1:1-7. doi:10.1111/jpc.12104
- Masi AC, Embleton ND, Lamb CA, et al. Human milk oligosaccharide DSLNT and gut microbiome in preterm infants predicts necrotising enterocolitis. *Gut*. 2021;70(12):2273-2282. doi:10.1136/gutjnl-2020-322771
- Mercer EM, Arrieta MC. Probiotics to improve the gut microbiome in premature infants: are we there yet? *Gut Microbes*. 2023;15(1):2201160. doi:10.1080/19490976.2023.2201160
- Moltu SJ, Bronsky J, Embleton N, et al. Nutritional Management of the Critically Ill Neonate: A Position Paper of the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr*. 2021;73(2):274-289. doi:10.1097/MPG.0000000000003076
- Morgan RL, Preidis GA, Kashyap PC, Weizman AV, Sadeghirad B; McMaster Probiotic, Prebiotic, and Synbiotic Work Group. Probiotics reduce mortality and morbidity in preterm, low-birth-weight infants: A systematic review and network meta-analysis of randomized trials. *Gastroenterology*. 2020;159(2):467-480. doi:10.1053/j.gastro.2020.05.096
- O'Connor DL, Kiss A, Tomlinson C, et al. Nutrient enrichment of human milk with human and bovine milk-based fortifiers for infants born weighing <1250 g: a randomized clinical trial. *Am J Clin Nutr*. 2018;108(1):108-116. doi:10.1093/ajcn/nqy067
- Ochoa TJ, Zegarra J, Bellomo S, et al. Randomized controlled trial of bovine lactoferrin for prevention of sepsis and neurodevelopment impairment in infants weighing less than 2000 grams. *J Pediatr*. 2020;219:118-125.e5. doi:10.1016/j.jpeds.2019.12.038
- Pammi M, Cope J, Tarr PI, et al. Intestinal dysbiosis in preterm infants preceding necrotizing enterocolitis: a systematic review and meta-analysis. *Microbiome*. 2017;5(1):31. doi:10.1186/s40168-017-0248-8
- Philip RK, Romeih E, Bailie E, et al. Exclusive human milk diet for extremely premature infants: A novel fortification strategy that enhances the bioactive properties of fresh, frozen, and pasteurized milk specimens. *Breastfeed Med*. 2023;18(4):279-290. doi:10.1089/bfm.2022.0254
- Pineda D, Bingham R, Gates A, Thompson AB, Stansfield BK. Acid/base balance in fortified donor human milk: An experimental study. *JPEN J Parenter Enteral Nutr*. 2023;47(7):904-910. doi:10.1002/jpen.2537
- Pineda D, Bingham R, Gates A, Thompson AB, Stansfield BK. Osmolality of fortified donor human milk: An experimental study. *JPEN J Parenter Enteral Nutr*. 2024;48(1):57-63. doi:10.1002/jpen.2558
- Poindexter B; COMMITTEE ON FETUS AND NEWBORN. Use of probiotics in preterm infants. *Pediatrics*. 2021;147(6):e2021051485. doi:10.1542/peds.2021-051485
- Puccio G, Alliet P, Cajozzo C, et al. Effects of infant formula with human milk oligosaccharides on growth and morbidity: A randomized multicenter trial. *J Pediatr Gastroenterol Nutr*. 2017;64(4):624-631. doi:10.1097/MPG.0000000000001520
- Ramel SE, Gray HL, Christiansen E, Boys C, Georgieff MK, Demerath EW. Greater early gains in fat-free mass, but not fat mass, are associated with improved neurodevelopment at 1 year corrected age for prematurity in very low birth weight preterm infants. *J Pediatr*. 2016;173:108-115. doi:10.1016/j.jpeds.2016.03.003
- Razzaghy J, Shukla VV, Gunawan E, Reeves A, Nguyen K, Salas AA. Early and exclusive enteral nutrition in infants born very preterm. *Arch Dis Child Fetal Neonatal Ed*. Published online December 22, 2023. doi:10.1136/archdischild-2023-325969
- Reis JD, Heyne R, Rosenfeld CR, et al. Follow-up of a randomized trial optimizing neonatal nutrition in preterm very low birthweight infants: growth, serum adipokines, renal function and blood pressure. *J Perinatol*. 2024;44(1):78-86. doi:10.1038/s41372-023-01821-2
- Reis JD, Tolentino-Plata K, Caraig M, et al. Double-blinded randomized controlled trial of optimizing nutrition in preterm very low birth weight infants: Bayley scores at 18-38 months of age. *J Perinatol*. 2023;43(1):81-85. doi:10.1038/s41372-022-01572-6

Emerging Developments in Human Milk Fortification: Problem Solving for Clinical Practice

- Rossholt ME, Bratlie M, Wendel K, et al. A standardized feeding protocol ensured recommended nutrient intakes and prevented growth faltering in preterm infants <29 weeks gestation. *Clin Nutr ESPEN*. 2023;53:251-259. doi:10.1016/j.clnesp.2022.12.024
- Salas A et al. Early, exclusive, enteral nutrition followed by early or delayed human milk fortification in very preterm infants: a randomized clinical trial. Presented at: Pediatric Academic Societies Meeting. Abstract 0313. Toronto, CA: May 2-6, 2024.
- Salas AA, Gunawan E, Nguyen K, et al. Early human milk fortification in infants born extremely preterm: A randomized trial. *Pediatrics*. 2023;152(3):e2023061603. doi:10.1542/peds.2023-061603
- Salas AA, Jerome M, Finck A, Razzaghy J, Chandler-Laney P, Carlo WA. Body composition of extremely preterm infants fed protein-enriched, fortified milk: a randomized trial. *Pediatr Res*. 2022;91(5):1231-1237. doi:10.1038/s41390-021-01628-x
- Sammallahti S, Pyhälä R, Lahti M, et al. Infant growth after preterm birth and neurocognitive abilities in young adulthood. *J Pediatr*. 2014;165(6):1109-1115.e3. doi:10.1016/j.jpeds.2014.08.028
- Sánchez C, Franco L, Regal P, Lamas A, Cepeda A, Fente C. Breast Milk: A source of functional compounds with potential application in nutrition and therapy. *Nutrients*. 2021;13(3):1026. doi:10.3390/nu13031026
- Singh P, Al Mohannadi N, Murugesan S, et al. Unveiling the dynamics of the breast milk microbiome: impact of lactation stage and gestational age. *J Transl Med*. 2023;21(1):784. doi:10.1186/s12967-023-04656-9
- Staub E, Evers K, Askie LM. Enteral zinc supplementation for prevention of morbidity and mortality in preterm neonates. *Cochrane Database Syst Rev*. 2021;3(3):CD012797. doi:10.1002/14651858.CD012797.pub2
- Tanaka M, Nakayama J. Development of the gut microbiota in infancy and its impact on health in later life. *Allergol Int*. 2017;66(4):515-522. doi:10.1016/j.alit.2017.07.010
- Tarnow-Mordi WO, Abdel-Latif ME, Martin A, et al. The effect of lactoferrin supplementation on death or major morbidity in very low birthweight infants (LIFT): a multicentre, double-blind, randomised controlled trial. *Lancet Child Adolesc Health*. 2020;4(6):444-454. doi:10.1016/S2352-4642(20)30093-6
- FDA raises concerns about probiotic products sold for use in hospitalized preterm infants [press release]. US Food & Drug Administration (FDA). October 26, 2023. Accessed April 29, 2024. <https://www.fda.gov/news-events/press-announcements/fda-raises-concerns-about-probiotic-products-sold-use-hospitalized-preterm-infants>. <https://www.fda.gov/news-events/press-announcements/fda-raises-concerns-about-probiotic-products-sold-use-hospitalized-preterm-infants>
- Uthaya S, Jeffries S, Andrzejewska I, Vasu V, Embleton ND, Modi N. Randomised controlled trial of human derived breast milk fortifier versus bovine milk fortifier on body composition in very preterm babies. *Early Hum Dev*. 2022;171:105619. doi:10.1016/j.earlhumdev.2022.105619
- van den Akker CHP, Embleton ND, Lapillonne A, et al. Reevaluating the FDA's warning against the use of probiotics in preterm neonates: A societal statement by ESPGHAN and EFCNI. *J Pediatr Gastroenterol Nutr*. Published online April 4, 2024. doi:10.1002/jpn3.12204
- van den Akker CHP, van Goudoever JB, Shamir R, et al. Probiotics and Preterm Infants: A Position Paper by the European Society for Paediatric Gastroenterology Hepatology and Nutrition Committee on Nutrition and the European Society for Paediatric Gastroenterology Hepatology and Nutrition Working Group for Probiotics and Prebiotics. *J Pediatr Gastroenterol Nutr*. 2020;70(5):664-680. doi:10.1097/MPG.0000000000002655
- Wang Y, Florez ID, Morgan RL, et al. Probiotics, Prebiotics, Lactoferrin, and Combination Products for Prevention of Mortality and Morbidity in Preterm Infants: A Systematic Review and Network Meta-Analysis. *JAMA Pediatr*. 2023;177(11):1158-1167. doi:10.1001/jamapediatrics.2023.3849
- Wejryd E, Martí M, Marchini G, et al. Low diversity of human milk oligosaccharides is associated with necrotising enterocolitis in extremely low birth weight infants. *Nutrients*. 2018;10(10):1556. doi:10.3390/nu10101556
- Westaway JAF, Huerlimann R, Kandasamy Y, et al. The bacterial gut microbiome of probiotic-treated very-preterm infants: changes from admission to discharge. *Pediatr Res*. 2022;92(1):142-150. doi:10.1038/s41390-021-01738-6
- Winter Z, Stansfield B. Manuscript accepted by *J Perinatol*. 2024.

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Yan X, Pan X, Ding L, et al. Bovine colostrum to supplement the first feeding of very preterm infants: The PreColos randomized controlled trial. *Clin Nutr.* 2023;42(8):1408-1417. doi:10.1016/j.clnu.2023.06.024

Yee WH, Soraisham AS, Shah VS, et al. Incidence and timing of presentation of necrotizing enterocolitis in preterm infants. *Pediatrics.* 2012;129(2):e298-e304. doi:10.1542/peds.2011-2022

Zeng S, Ying J, Li S, Qu Y, Mu D, Wang S. First 1000 days and beyond after birth: Gut microbiota and necrotizing enterocolitis in preterm infants. *Front Microbiol.* 2022;13:905380. doi:10.3389/fmicb.2022.905380



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