International Journal of Contemporary Pediatrics
Balla KC et al. Int J Contemp Pediatr. 2025 Dec;12(12):2036-2038
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20253790

Case Report

Cow's milk protein intolerance unmasked by bovine-derived human milk fortifier and successfully rescued by human milk-based fortifier in a preterm infant

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Received: 05 October 2025
Accepted: 14 November 2025

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ABSTRACT

Preterm infants require human milk fortification to achieve adequate growth. Most fortifiers are bovine-derived and may trigger feeding intolerance or immunological reactions. We describe a 25+5 week, 720 g male infant who developed recurrent apnea, reflux, and dependence on respiratory support soon after initiation of bovine-based human milk fortifier (HMF). Investigations excluded sepsis and necrotizing enterocolitis. Stool calprotectin was markedly elevated, and eosinophilia was noted. Symptoms resolved rapidly after discontinuation of bovine HMF and initiation of a human milk-derived fortifier, with dramatic improvements in weight gain and respiratory stability. This case highlights cow's milk protein intolerance (CMPI) precipitated by bovine fortifier and the therapeutic benefit of human milk-based HMF.

Keywords: Human milk fortifier, Cow's milk protein intolerance, Preterm infant, Feeding intolerance, Exclusive human milk diet

INTRODUCTION

Preterm infants <32 weeks require additional protein, calcium, phosphorus, and micronutrients beyond what mother's milk alone can provide.[1] Bovine-derived fortifiers are widely used but are associated with adverse outcomes including feeding intolerance, reflux, necrotizing enterocolitis (NEC), late-onset sepsis, bronchopulmonary dysplasia, retinopathy, and impaired growth.[2,3]

Cow's milk protein intolerance (CMPI) may be unmasked when bovine-derived human milk fortifier (HMF) is introduced, even in infants exclusively receiving mother's own milk.[4,5]

Human milk-derived fortifiers allow an exclusive human milk diet and have been used successfully as rescue therapy in such infants.[4,5]

CASE REPORT

A male infant was delivered at 25+5 weeks' gestation via lower segment caesarean section to a primigravida mother with placental abruption. Antenatal steroids were incomplete. Birth weight was 720 g. Apgar scores were 4 and 7 at 1 and 5 minutes. He was intubated at birth, given surfactant, and ventilated for 6 days, followed by NIV (2 days) and CPAP (4 days). Patent ductus arteriosus closed after a course of paracetamol.

Feeds with mother's expressed breast milk were initiated on day 2 and advanced to full enteral feeds by day 14.

On day 13, bovine-derived HMF was introduced. Within 24 hours, the infant developed recurrent apnea, vomiting, and reflux requiring escalation from room air to high-flow nasal cannula and subsequently NIV. Sepsis evaluation was negative. CBC revealed eosinophilia, and stool calprotectin was elevated (>1000 U). X-rays, abdominal

ultrasound, stool occult blood, and stool analysis were unremarkable, excluding NEC.

Investigations

Investigations included - CBC: eosinophilia (day 15), stool calprotectin: >1000 U (during bovine HMF) → decreased to 24 U after switch to human HMF, abdominal X-ray and ultrasound: normal, stool occult blood and microscopy: negative, and sepsis screen: negative.

Differential diagnosis

Differential diagnosis included: cow's milk protein intolerance (CMPI) precipitated by bovine-derived HMF – most consistent (supported by eosinophilia, high calprotectin, symptom resolution after switch), NEC – excluded by normal imaging, no blood in stools, stable abdominal examination, and sepsis – excluded by negative cultures and sepsis screen.

Treatment

Treatment included: bovine HMF discontinued on day 15, escalated back to full feeds with unfortified human milk, initiated human milk-derived fortifier after stabilization, continued over 2 weeks with excellent tolerance, supportive therapy: respiratory support de-escalated to room air within 5 days of discontinuation of bovine HMF, and supplements: vitamin D and iron.

Outcome and follow-up

Outcome and follow-up included: Weight gain improved from 8 g/kg/day (bovine HMF) to 24 g/kg/day (human HMF), respiratory support discontinued permanently after 5 days on human HMF, eosinophil counts normalized, stool calprotectin decreased to 24 U, discharged at 35 weeks corrected age, weight 2140 g, on 180–200 ml/kg/day unfortified human milk, and planned neurodevelopmental follow-up at 3 months corrected age.

DISCUSSION

Preterm infants, particularly those <28 weeks and <1000 g, require fortification of breast milk to achieve optimal growth and neurodevelopmental outcomes.[1] While bovine-derived HMFs are widely available, their safety profile in extremely preterm infants is increasingly questioned.

Evidence indicates that exposure to cow's milk proteins in this vulnerable period may lead to gastrointestinal intolerance, reflux, systemic inflammatory responses, and higher risks of NEC and mortality.[2,3] In a multicenter analysis, cow's milk-derived fortifiers were associated with a fourfold increase in NEC and a fivefold increase in NEC surgery or death compared to human milk-derived fortifiers.[2]

Our case highlights CMPI unmasked by bovine-derived HMF, manifesting with apnea, reflux, and eosinophilic intestinal inflammation (elevated calprotectin). These symptoms were reversible upon discontinuation of bovine HMF and initiation of human HMF, which aligns with prior reports of HMDF as effective rescue therapy.[4,5] Notably, weight gain improved from 8 g/kg/day to 24 g/kg/day, underscoring the nutritional adequacy of human HMF.

CMPI in preterm infants is often under-recognized, and presentations may be misattributed to sepsis or early NEC. In our case, normal imaging and negative sepsis workup helped rule out these conditions. Elevated stool calprotectin, a biomarker of intestinal inflammation, proved useful in supporting the diagnosis of CMPI.

This case contributes to the growing body of evidence that an exclusive human milk diet, including human milk-derived fortifiers, may improve tolerance and outcomes in preterm infants. While randomized controlled trial data remain limited, observational studies and case series consistently suggest reduced morbidity and better growth with HMDF.[1,4,5] Cost and accessibility remain challenges, but selective or rescue use of HMDF in suspected intolerance is a pragmatic approach.

CONCLUSION

This case demonstrates that bovine-derived human milk fortifier can unmask cow's milk protein intolerance in extremely preterm infants, even when exclusively fed mother's milk. Recognition of early red flags such as reflux, apnea, eosinophilia, and elevated stool calprotectin is essential to avoid misdiagnosis as sepsis or NEC. Prompt discontinuation of bovine fortifier and initiation of a human milk-derived fortifier resulted in rapid clinical stabilization and significantly improved growth. These findings support the selective use of human milk-derived fortifiers as effective rescue therapy in suspected intolerance. Increased awareness of CMPI in preterm infants may improve feeding tolerance and reduce morbidity. Further studies are needed to optimize fortifier selection in high-risk neonatal populations.

Recommendations

Preterm infants require fortification of human milk to achieve adequate growth. Bovine-derived fortifiers can unmask cow's milk protein intolerance, even in exclusively breastfed preterm infants. Clinical manifestations may include reflux, apnea, eosinophilia, and elevated stool calprotectin, often mimicking sepsis or NEC. Switching to human milk-derived fortifier can dramatically improve tolerance, growth, and respiratory stability. Clinicians should maintain a high index of suspicion for CMPI when intolerance develops soon after bovine HMF introduction.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Balla KC, Sudarsanam S, Paramashivaiah G. Cow's milk protein intolerance unmasked by bovine-derived human milk fortifier and successfully rescued by human milk-based fortifier in a preterm infant. Int J Contemp Pediatr 2025;12:2036-8.