Human and Bovine Colostrum for Prevention of Necrotizing Enterocolitis: A Meta-analysis

Behnam Sadeghirad, PharmD, MPH,[a,b,c] Rebecca L. Morgan, MPH, PhD,[a] Dena Zeraatkar, MSc,[a] Adriana M. Zea, RD,[d] Rachel Couban, MSc,[b] Bradley C. Johnston, PhD,[a,e] Ivan D. Florez, MD, MSc[a,f]

abstract

CONTEXT: Human and bovine colostrum (HBC) administration has been linked to beneficial effects on morbidity and mortality associated with necrotizing enterocolitis (NEC).

OBJECTIVES: To determine the effectiveness and safety of HBC for reducing NEC, mortality, sepsis, time to full-feed and feeding intolerance in preterm infants.

DATA SOURCES: We conducted searches through Medline, Embase, Cumulative Index of Nursing and Allied Health Literature, Cochrane Central Register of Controlled Trials, and gray literature.

STUDY SELECTION: Randomized controlled trials comparing human or bovine colostrum to placebo.

DATA EXTRACTION: Two reviewers independently did screening, review, and extraction.

RESULTS: Eight studies (385 infants) proved eligible. In comparison with placebo, HBC revealed no effect on the incidence of severe NEC (relative risk [RR]: 0.99; 95% confidence interval [CI] 0.48 to 2.02, I^2 = 2.2%; moderate certainty of evidence), all-cause mortality (RR: 0.88; 95% CI 0.39 to 1.82, I^2 = 0%; moderate certainty), culture-proven sepsis (RR: 0.78; 95% CI 0.53 to 1.14, I^2 = 0%; moderate certainty), and feed intolerance (RR: 0.97; 95% CI 0.37 to 2.56, I^2 = 55%; low certainty). HBC revealed a significant effect on reducing the mean days to reach full enteral feed (mean difference: −3.55; 95% CI 0.33 to 6.77, I^2 = 41.1%; moderate certainty). The indirect comparison of bovine versus human colostrum revealed no difference in any outcome.

LIMITATIONS: The number of patients was modest, whereas the number of NEC-related events was low.

CONCLUSIONS: Bovine or human colostrum has no effect on severe NEC, mortality, culture-proven sepsis, feed intolerance, or length of stay. Additional research focused on the impact on enteral feeding may be needed to confirm the findings on this outcome.

[a]Department of Health Research Methods, Evidence, and Impact and [b]The Michael G. DeGroote Institute for Pain Research and Care, McMaster University, Hamilton, Canada; [c]HIV/STI Surveillance Research Center, World Health Organization Collaborating Center for HIV Surveillance, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran; [f]Department of Pediatrics and [d]School of Nutrition and Dietetics, University of Antioquia, Medellin, Colombia; and [e]Department of Community Health and Epidemiology, Medicine, Dalhousie University, Halifax, Canada

Dr Sadeghirad conceptualized and designed the study, coordinated and supervised the systematic review, designed the search strategy, selected the articles, extracted the data, assessed the quality of the evidence, performed the data analysis, interpreted the data, and drafted the initial manuscript; Dr Morgan coordinated and supervised the systematic review, selected the articles, extracted the data, assessed the certainty on the evidence, and interpreted the data analysis; Ms Zaraatkar and Ms Zea selected the articles, extracted the data, assessed the quality of the evidence, and interpreted the data analysis; Ms Couban

To cite: Sadeghirad B, Morgan RL, Zeraatkar D, et al. Human and Bovine Colostrum for Prevention of Necrotizing Enterocolitis: A Meta-analysis. *Pediatrics*. 2018;142(2):e20180767

Preterm birth is defined by the World Health Organization (WHO) as live births before 37 weeks of pregnancy. Preterm birth complications are the leading cause of death among children <5 years of age and were responsible for ~1 million deaths in 2015.[1] Extremely premature (birth weight <1250 g) newborns have substantial mortality and morbidity, often resulting from infectious morbidities including late-onset sepsis and necrotizing enterocolitis (NEC).[2]

NEC is a multifactorial and life-threatening inflammation of the gastrointestinal tract and the most frequent surgical emergency in neonates. The mechanism of NEC is poorly understood, but researchers suggest that factors such as bowel hypoperfusion, use of antibiotics, and the delay to start enteral feeding seem to promote intestinal atrophy and abnormal bacterial intestinal colonization, which are crucial features of the disease.[3] Despite the significant advances in neonatal care, morbidity and mortality related to NEC have remained unchanged for decades. The rate of NEC-related mortality is reported to be 20% to 30%, whereas in infants in need of surgery, the rate could be up to 50%.[4–6] Furthermore, infants recovering from NEC are at increased risk for microcephaly, short-bowel syndrome, serious neurodevelopmental delays, and functional disabilities.[7,8]

Mother's milk has many immune and trophic factors (such as growth factors, cytokines, lactoferrin, lysozymes, and immunoglobulins)[9,10] that may protect newborns from infection and might have an effect on the gastrointestinal tract maturation. Mother's milk feedings have been linked with a reduced incidence of several prematurity-specific morbidities including NEC, bacteremia, and enteral feed intolerance for premature infants.[11] Colostrum is the first milk produced by the mammary when the tight junctions in the mammary epithelium are open.[12] It has been found that the immune protective factors are more highly concentrated in the colostrum of mothers delivering premature infants than in those who give birth at term.[13,14] This, in turn, suggests that immune components in colostrum may provide infants with protection against infection.[15]

The method of colostrum administration has been studied in 2 different ways: oropharyngeal and enteral. Human colostrum has been administered in small volumes directly into the buccal cavity of intubated premature infants.[16] Likewise, commercially available bovine colostrum has been administered via enteral along with the enteral feeding. Bovine colostrum also contains protective factors, which have substantial homology to their human counterparts.[17]

Randomized trials of both bovine and human colostrum in comparison with placebo have been performed in preterm infants to assess their potentially protective effects. To date, this evidence has not been systematically summarized. We have therefore conducted a systematic review to determine the effectiveness and safety of human and bovine colostrum in preterm infants for decreasing NEC-related outcomes, including mortality and morbidities.

METHODS

Protocol Registration

The protocol for this systematic review is registered with PROSPERO: CRD42018085566.

Data Sources

We searched Medline, Embase, the Cumulative Index to Nursing and Allied Health Literature, and the Cochrane Central Register of Controlled Trials for relevant published randomized controlled trials (RCTs) (search strategy is provided in the Supplemental Information). We did not apply language or publication status restrictions. We reviewed reference lists from eligible trials and related reviews for additional eligible RCTs and searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform for ongoing or unpublished trials.

Study Selection

Reviewers (B.S., I.D.F., and R.L.M.) independently screened the titles and abstracts of all identified studies by using a priori selection criteria. Subsequently, reviewers independently assessed eligibility of the full texts of potentially eligible studies. Reviewers resolved discrepancies through discussion.

We included RCTs in which researchers compared oropharyngeal or enteral administration of human or bovine colostrum to preterm infants (gestational age <37 weeks) within the first week of life irrespective of when enteral feeding was initiated, the type of milk used for enteral feeding or the feed advancement regimen with placebo, standard clinical care, or standard clinical care plus placebo. Standard clinical care typically includes parenteral nutrition or feeding of the infant's own mother's milk, donor's milk, or preterm formula milk.

Our outcomes of interest were as follows: (1) NEC: stage II or more based on Bell's criteria[18,19]; (2) NEC-related mortality; (3) all-cause mortality; (4) culture-proven sepsis; (5) patent ductus arteriosus; (6) intraventricular hemorrhage; (7) duration of hospitalization; (8) weight gain; and (9) incidence of adverse events (as reported by authors).

Data Abstraction and Risk of Bias Assessment

Reviewers (B.S., I.D.F., R.L.M., A.M.Z., and D.Z.) extracted the following

data, independently and in duplicate: (1) general study information (author's name, publication year, study design, and number of arms), (2) population-related information (birth weight, gestational age, Apgar score at 1 and 5 minutes, percentage of cesarean deliveries, and percentage of infants small for gestational age), (3) feeding details (feeding protocol and percentage of infants receiving mother's milk or formula milk), (4) details on the intervention and comparison (type of colostrum, time of initiation, dose, duration of therapy, and type of control group), and (5) outcomes as listed above.

Two reviewers independently assessed risk of bias by using a modified Cochrane risk of bias instrument for RCTs[20,21] that addresses the following issues: random sequence generation, allocation concealment, blinding of study participants, health care providers, and outcome assessors and/or adjudicators, incomplete outcome data, and other potential sources of bias.

To assess the certainty of evidence (CoE), we used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach for evidence assessment that classifies evidence as high, moderate, low, or very low quality on the basis of considerations of risk of bias, inconsistency, indirectness, imprecision, and publication bias.[22] We resolved disagreements between reviewers in data extraction, and assessments of risk of bias or CoE by discussion and, if needed, by third party adjudication. We used the GRADE profiler (GRADEpro GDT; https://gradepro.org/) to generate the GRADE summary of findings table.

Data Synthesis and Statistical Methods

For dichotomous outcomes, we calculated the relative risk (RR) and its corresponding 95% confidence interval (CI) and calculated the absolute effect by multiplying the RR and its CI with the estimated baseline risk. The median of the placebo group of included RCTs provided the baseline risk. For continuous outcomes, we calculated the mean difference and its corresponding 95% CI.

Statistical heterogeneity was determined by using the Q statistic and I^2. We used the DerSimonian–Laird random-effects model for the meta-analysis of all outcomes. Regardless of the observed statistical heterogeneity, we conducted the following prespecified subgroup analyses: birth weight, assuming larger effects for infants with larger birth weights; gestational age, assuming larger effects for infants with higher gestational age; type of colostrum, assuming a larger effect for infants receiving human colostrum; and risk of bias, assuming larger effects for studies at high risk of bias. For subgroup analysis, we tested for interaction by using a χ^2 significance test, when each subgroup was represented by at least 2 studies.[23] We performed univariate and multivariate metaregression to assess the effects of birth weight, gestational age, duration of therapy, Apgar score at 1 and 5 minutes, percentages of cesarean deliveries, and publication year on the treatment effect. We planned to examine publication bias by using funnel plots for outcomes in which 10 or more studies were available.[24] We performed indirect meta-analysis using the frequentist approach to compare the effect of human versus bovine colostrum. A conventional meta-analysis combines effect estimates from direct comparisons of interventions (ie, evidence from trials with head-to-head comparison of interventions). Indirect comparisons are made by looking at the impact of the interventions of interest versus a third intervention, a common comparator (in this case, inferring the effect of bovine versus human colostrum through trials of bovine colostrum versus placebo, and human colostrum versus placebo). Indirect meta-analysis is a relatively new technique and is intended for situations in which there is no direct evidence and comparisons are made pairwise. More details on the statistical methods can be found in Miladinovic et al.[25] Data were analyzed by using Stata software version 14.2 (Stata Corp, College Station, TX).

RESULTS

Description of Included Studies

We identified 1075 titles and abstracts through our literature search, of which 26 proved potentially eligible for full-text evaluations, and 18 were excluded for the following reasons: (1) not randomized trials (n = 8), (2) colostrum was not used as the intervention (n = 5), (3) not preterm infants (n = 2), and no relevant outcome was reported (n = 3). Figure 1 provides the details of the study selection process.

We included 8 RCTs that proved eligible, enrolling 394 individuals. The intervention in 6 studies[13,14,16,26–28] was human colostrum, and in 2 studies the intervention was bovine colostrum.[29,30] In 2 studies, researchers enrolled preterm infants with a birth weight of ≤1.0 kg or gestational age <28 weeks.[13,14] In 5 studies, researchers enrolled preterm infants with a birth weight of ≤1.5 kg or gestational age <32 weeks.[16,26–29] In 1 study, researchers enrolled infants with a birth weight between 1.0 to 1.8 kg and gestational age ≥28 weeks.[30] Table 1 presents details of included trials.

Among the included studies, 5 out of 8 RCTs demonstrated concerns for high risk of bias due to allocation concealment, blinding, and outcome

TABLE 1 Characteristics of Studies Included in the Systematic Review

Study	Mean BW, g	Mean GA, wk	No. Randomized (Intervention, Control)	Type of Colostrum	Duration of Therapy or Dose	Time of Initiation	Method of Colostrum Administration
Rodriguez et al[13]	842.0	26.3	9, 6	Human	0.2 mL every 2 h for 2 d	Within 48 h of life	Oropharyngeal
Lee et al[14]	815.0	26.8	24, 24	Human	0.2 mL every 3 h for 3 d	48–96 h after birth	Oropharyngeal
Sohn et al[16]	1053.5	27.0	6, 6	Human	0.2 mL every 2 h for 46 h	Median age of 39 h (range 32–87)	Oropharyngeal
Balachandran et al[29]	1202.9	29.9	43, 43	Bovine	1.2–2.0 g 4 times per d until discharge or death or d 21 of life	In the first 96 h of life	Orogastric tube
Romano-Keeler et al[27]	1219.5	25.5	48, 51	Human	0.2 mL every 6 h for 5 d	In the first 48 h of life	Oropharyngeal
Glass et al[26]	1109.0	28.4	17, 13	Human	0.2 mL every 3 h for 7 d	In the first 48 h of life	Oropharyngeal
Zhang et al[28]	1244.5	30.2	32, 32	Human	0.2 mL every 4 h for 7 d	Between d 2–4 of life	Oropharyngeal
Juhl et al[30]	1487.5	30.5	21, 19	Bovine	Volume limited by a pre-set total protein intake of 4.5 g/kg per d for 10–14 d	In the first 48 h of life	Enteral

BW, birth wt; GA, gestational age; NR, not reported.

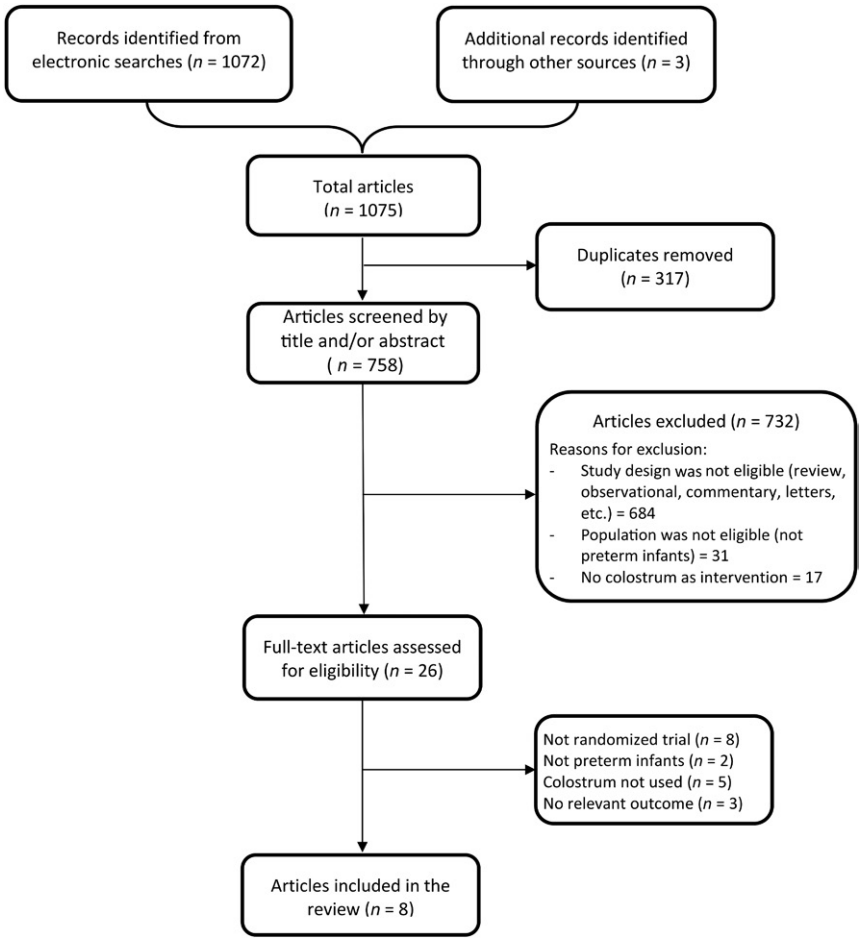

FIGURE 1
Study selection flowchart.

reporting.[16,26–28,30] One study had issues in incomplete outcome reporting,[28] 4 studies had issues in blinding of participants and/or outcome assessors,[16,26,27,30] and 2 studies had issues in concealing the treatment allocation (the risk of bias assessment is described in Supplemental Figs 6 and 7).[27,28]

NEC and NEC-Related Mortality

The meta-analysis from 7 studies in which researchers reported the incidence of NEC stage II or more[13,14,16,26–29] revealed no difference among infants who received colostrum versus those who received a placebo or usual care group (RR 0.99, 95% CI: 0.48 to 2.02; I^2 = 2.2%; moderate CoE; Fig 2, Table 2). In 1 study, researchers reporting this outcome used bovine colostrum. Tests of interaction revealed no evidence of any subgroup effect (Table 3). The univariate metaregression confirmed the results of subgroup analysis (Supplemental Tables 4 through 6). The indirect comparison of human and bovine colostrum revealed no difference (Supplemental Table 7).

In the 4 RCTs in which researchers reported NEC-related mortality,[13,14,16,26] no infant died as a result of developing NEC in colostrum or placebo or usual care group (moderate CoE; Table 2).

All-Cause Mortality

All-cause mortality was reported in 7 RCTs,[13,14,16,26,27,29,30] and the results

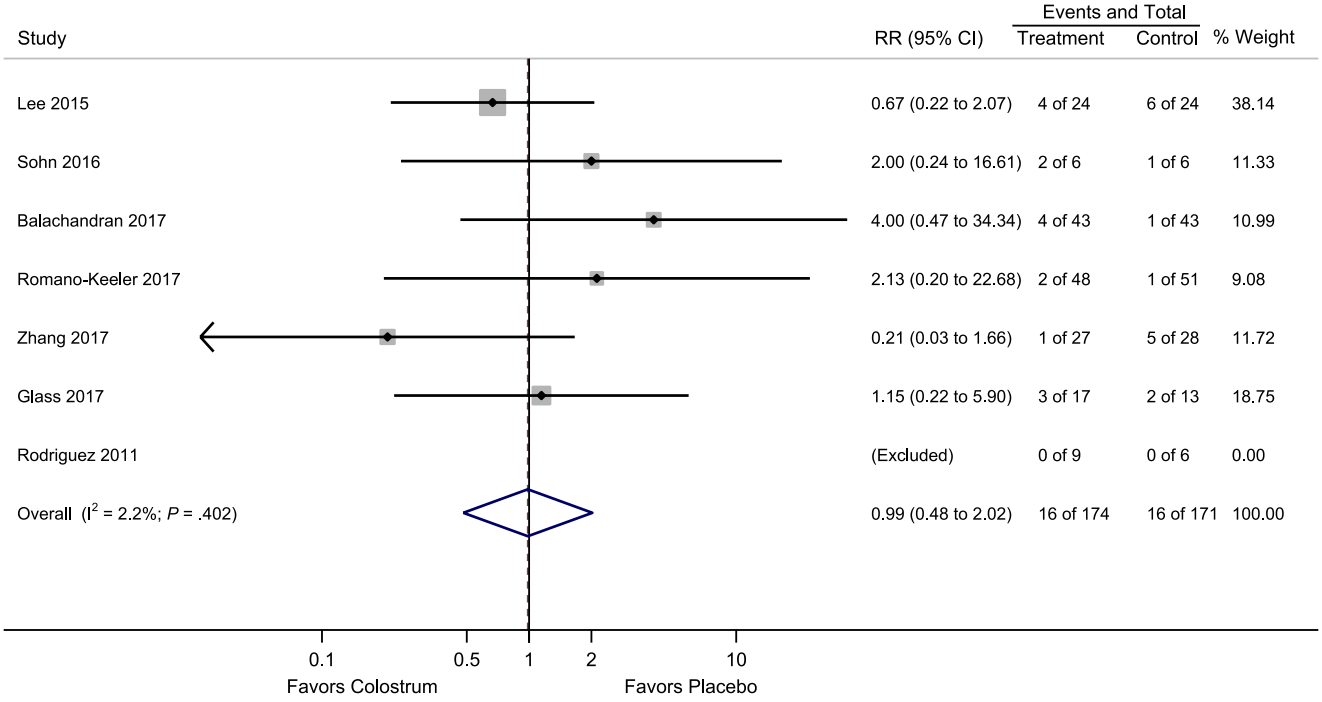

FIGURE 2

Forest plot revealing RR for NEC stage II or more (based on Bell's criteria) for colostrum versus placebo groups. Horizontal bars denote 95% CIs. Studies are represented as squares centered on the point estimate of the result of each study. The area of the square represents the weight given to the study in the meta-analysis. The pooled RR was calculated by DerSimonian-Laird random-effects model. The diamond represents the overall estimated effect and its 95% CI in total (center line of diamond, dashed line). The solid vertical line is the line of no effect. Weights are from random effects analysis.

of meta-analysis revealed no effect for colostrum compared with placebo or usual care (RR 0.84, 95% CI: 0.39 to 1.82; I^2 = 0%; moderate CoE; Fig 3, Table 2). There was no evidence of any subgroup effect (Table 3, Supplemental Table 6). In 2 studies, researchers reporting this outcome used bovine colostrum. The indirect comparison of human and bovine colostrum revealed no difference (Supplemental Table 7).

Culture-Proven Sepsis

In the 8 studies in which researchers reported on culture-proven sepsis,[13,14,16,26–30] the risk of developing sepsis for infants who received colostrum was 22% less than those who received a placebo or usual care (RR 0.78, 95% CI: 0.53 to 1.14; I^2 = 0.0%; moderate CoE, Fig 4, Table 2). We found no evidence of subgroup effect for this outcome (Table 3, Supplemental Table 6). In 2 studies, researchers reporting this outcome used bovine colostrum. The indirect comparison of human and bovine colostrum revealed no difference (Supplemental Table 7).

Feed Intolerance and Time to Reach Full Feed

Of the 2 studies in which feeding intolerance was reported, researchers for 1 study used human colostrum[26] and the other researchers used bovine colostrum.[30] None of these researchers reported a benefit for using colostrum, and the pooled estimate was not significant (RR 0.97, 95% CI: 0.37 to 2.56; I^2 = 55.5%; low CoE; Supplemental Fig 8, Table 2).

Time to reach full enteral feeding was reported in 6 studies.[13,14,26–28,30] On average, infants receiving colostrum reached full feed 3.5 days earlier (95% CI: −0.33 to −6.77; I^2 = 38.3%; moderate CoE; Fig 5, Table 2). We found no evidence of subgroup effect for this outcome (Table 3, Supplemental Table 6). The results of indirect meta-analysis revealed larger effect for human colostrum, but the difference was not statistically significant (mean difference −7.1 days, 95% CI: −18.2 to 3.9; Table 3).

Other Outcomes

In 3 studies, researchers reported on duration of hospital stay.[13,14,27] The results of meta-analysis didn't reveal any significant difference between the duration of hospitalization between the infants who received colostrum and those who received a placebo or usual care (mean difference 1.3 days, 95% CI: −13.7 to 16.3; I^2 = 41.1%; low CoE; Supplemental Fig 9 and Table 2). Juhl et al[30] reported 4 cases of intraventricular hemorrhage (3 grade I and 1 grade II) in the placebo or usual care group (21.1%), whereas no infants in the bovine colostrum group were reported to develop intraventricular hemorrhage. None of the 5 studies in which researchers assessed the occurrence of adverse

TABLE 2 Summary of Findings

Outcome (Studies), No. Participants	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty
		Risk With No Colostrum	Risk With Colostrum	Difference	
NEC stage II or more (7 RCTs) No. participants: 345	Risk ratio: 0.99 (0.48 to 2.02)	9.4%	9.3% (4.5% to 18.9%)	0.1% fewer (4.9 fewer to 9.5 more)	⨁⨁⨁◯ Moderate[a,b]
Culture-proven sepsis (8 RCTs) No. participants: 385	Risk ratio: 0.78 (0.53 to 1.14)	21.1%	16.4% (11.2% to 24.0%)	4.6% fewer (9.9 fewer to 2.9 more)	⨁⨁⨁◯ Moderate[a,b]
All-cause mortality (7 RCTs) No. participants: 330	Risk ratio: 0.88 (0.39 to 1.82)	7.4%	6.5% (2.9% to 13.5%)	0.9% fewer (4.5 fewer to 6.1 more)	⨁⨁⨁◯ Moderate[a,b]
Feed intolerance (2 RCTs) No. participants: 70	Risk ratio: 0.97 (0.37 to 2.56)	43.8%	42.4% (16.2% to 100.0%)	1.3% fewer (27.6 fewer to 68.3 more)	⨁⨁◯◯ Low[a,b,c]
NEC-related mortality (4 RCTs) No. participants: 105	Not estimable	0.0%	0.0% (0.0% to 0.0%)	0.0% fewer (0 fewer to 0 fewer)	⨁⨁⨁◯ Moderate[a,d]
Duration of hospital stay (3 RCTs) No. participants: 160	—	The mean duration of hospital stay was 79.0 d	—	MD 1.26 d more (13.73 fewer to 16.26 more)	⨁⨁◯◯ Low[a,b,e]
Time to reach full enteral feed (6 RCTs) No. participants: 285	—	The mean time to reach full enteral feed was 22.1 d	—	MD 3.55 d fewer (0.33 fewer to 6.77 fewer)	⨁⨁⨁◯ Moderate[a,f]

The table contains human or bovine colostrum compared with placebo or usual care for prevention of morbidity and mortality in preterm infants. Population: preterm infants (gestational age <37 wk); intervention: colostrum (human or bovine); comparator: no colostrum. GRADE Working Group grades of evidence. High certainty: we are highly confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect. Very low certainty: We have little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect. The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). MD, mean difference; —, not applicable.

[a] Although some studies were at risk for bias because of allocation concealment and blinding, subgroup analyses did not suggest that any heterogeneity due to risk of bias was introduced.

[b] The 95% CI includes values suggesting substantial benefit and values suggesting substantial harm.

[c] I^2 value is 56%, suggesting some heterogeneity; however, exploratory analyses did not highlight the source.

[d] No events were reported for either arm.

[e] I^2 value is 41%, demonstrating potential heterogeneity.

[f] I^2 value is 38%, potential heterogeneity; however, it is unlikely related to bias.

events contained reports of any serious adverse events associated with the intervention.[13,14,26,27,30]

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis of human and bovine colostrum administration in preterm infants for NEC, mortality, and related health outcomes. In our review, we synthesized the evidence from 8 RCTs, including 394 infants, to describe the effect of bovine and human colostrum administration in preterm infants. On the basis of low to moderate CoE, we found that colostrum has no effect on mortality or morbidities in preterm infants. Nonetheless, colostrum administration resulted in less time to get full enteral feeding (moderate CoE). We explored and found no evidence of subgroup effect for any of the outcomes, and our univariate metaregression was not significant for any of the covariates (birth weight, gestational age, Apgar score at 1 and 5 minutes, proportion of infants delivered in a cesarean delivery procedure, and duration of treatment). These findings reveal that there is no effect of colostrum on NEC-related outcomes.

Although we did not find differences in culture-proven sepsis, there was a trend toward a positive effect. This effect, if present, may be related to the immune effects of colostrum. The lack of effect may be related to the lack of power given the relative low number of subjects studied. Additional clinical trials will increase the number of patients and may change the results for this outcome.

Colostrum contains numerous protective immune and trophic factors that seem to play an important role in the first days of extrauterine life.[9,11] Mother's milk provides the ideal form of administration of colostrum. However, considering that the content of bovine colostrum has been described as similar in many components to the human colostrum,[31] when the latter is not available, bovine colostrum might be considered a good alternative.

Both types of colostrum have been used in different ways. Human colostrum has been administered by using an oropharyngeal method, whereas the bovine colostrum administration has been administered enterally. The rationale behind the oropharyngeal administration is that, because of the gastric tube feeding, preterm infants are not being exposed to the effect of protective bio-factors on the oropharyngeal associated

TABLE 3 Results of the Meta-analysis and Subgroup Analysis of RCTs Assessing the Effects of Colostrum

Outcome and Subgroups[a]	No. Trials	ES	95% CI		No. Participants		I^2	*P* for Interaction
			Lower	Upper	Intervention	Control		
NEC (stage ≥II)								
Human	5	0.83	0.39	1.75	131	128	0.0	—[b]
Bovine	1	4.00	0.47	34.34	43	43	—	
BW <1000 g	2	0.67	0.22	2.07	33	30	—	.488
BW ≥1000 g	5	1.26	0.49	3.27	141	141	9.4	
Low risk of bias	5	1.13	0.51	2.49	99	92	0.0	.752
High (due to allocation concealment)	2	0.62	0.06	6.06	75	79	52.5	
Low risk of bias	3	1.29	0.23	7.30	76	73	54.0	.871
High (due to blinding)	4	0.98	0.35	2.70	98	98	3.6	
Total	7	0.99	0.48	2.02	174	141	2.2	—
Mortality								
Human	5	0.74	0.27	2.06	104	100	0.0	.765
Bovine	2	1.00	0.31	3.21	64	62	—	
BW <1000 g	2	0.86	0.15	4.80	33	30	33.7	.922
BW ≥1000 g	5	0.99	0.36	2.78	135	132	0.0	
Low risk of bias	6	0.78	0.35	1.72	120	111	0.0	—[b]
High (due to allocation concealment)	1	3.18	0.13	76.31	48	51	—	
Low risk of bias	3	0.83	0.36	1.88	76	73	0.0	.947
High (due to blinding)	4	0.98	0.11	8.91	92	89	1.9	
Total	7	0.84	0.39	1.82	168	162	0.0	—
Culture-proven sepsis								
Human	6	0.79	0.51	1.23	131	128	0.0	.873
Bovine	2	0.73	0.33	1.61	64	62	0.0	
BW <1000 g	2	1.22	0.24	6.20	33	30	43.8	.744
BW ≥1000 g	6	0.72	0.41	1.24	162	160	0.0	
Low risk of bias	6	0.83	0.55	1.25	120	111	0.0	.331
High (due to allocation concealment)	2	0.47	0.16	1.43	75	79	0.0	
Low risk of bias	3	0.80	0.50	1.26	76	73	0.0	.839
High (due to blinding)	5	0.73	0.36	1.48	119	117	0.0	
Total	8	0.78	0.53	1.14	195	190	0.0	—
Time to reach full feed, d								
Human	5	−2.87	−6.02	0.28	123	122	34.3	—[b]
Bovine	1	−9.60	−19.46	0.26	21	19	—	
BW <1000 g	2	−4.55	−14.33	5.23	31	30	72.5	.794
BW ≥1000 g	4	−3.17	−6.65	0.31	113	111	29.8	
Low risk of bias	4	−4.19	−9.40	1.03	69	62	48.8	.854
High (due to allocation concealment)	2	−3.47	−9.06	2.13	75	79	48.1	
Low risk of bias	2	−4.55	−14.33	5.23	31	30	72.5	.794
High (due to blinding)	4	−3.17	−6.65	0.31	113	111	29.8	
Total	6	−3.55	−6.77	−0.33	144	141	38.3	—

BW, birth weight (mean, as reported in RCTs); ES, effect estimate (weighted mean difference for time to reach full enteral feed, and RR for the remaining outcomes); —, not applicable.
[a] We did not perform any subgroup analysis for duration of hospital stay and incidence of feeding intolerance because there were ≤3 studies containing reports of those outcomes.
[b] Because of the small number of trials, we did not perform a statistical test of interaction between the 2 groups.

lymphoid tissue to obtain an effect on their immune system.[13] Thus, the administration of small amounts of colostrum in the oral mucosa aims to provide that exposure and to produce a positive impact on the immune system and therefore on the incidence of NEC-related health outcomes. Although this rationale has not been specifically described for bovine colostrum, it may be possible that this type of colostrum may also have an effect on the lymphoid tissue if administered via oropharyngeal.

In contrast, the bovine colostrum has been administered via an enteral route.[17,29] For example, Juhl et al[30] administered colostrum as a reconstituted colostrum powder to reach the required energy density, whereas Balachandran et al[29] used small amounts of a different product powder that was mixed with expressed human milk and given 4 times per day. In this case, the aim was to produce an effect on the maturation of the gut as has been described on infant piglets.[32,33]

Although they have been administered through different routes, in our review, we considered both types of colostrum. We hypothesized that the beneficial effects from colostrum contents could be similar; however, acknowledging the potential differences among both interventions, we conducted a between-study subgroup analysis and an indirect comparison to determine potential differences on the basis of colostrum type. In the direct comparisons of bovine and

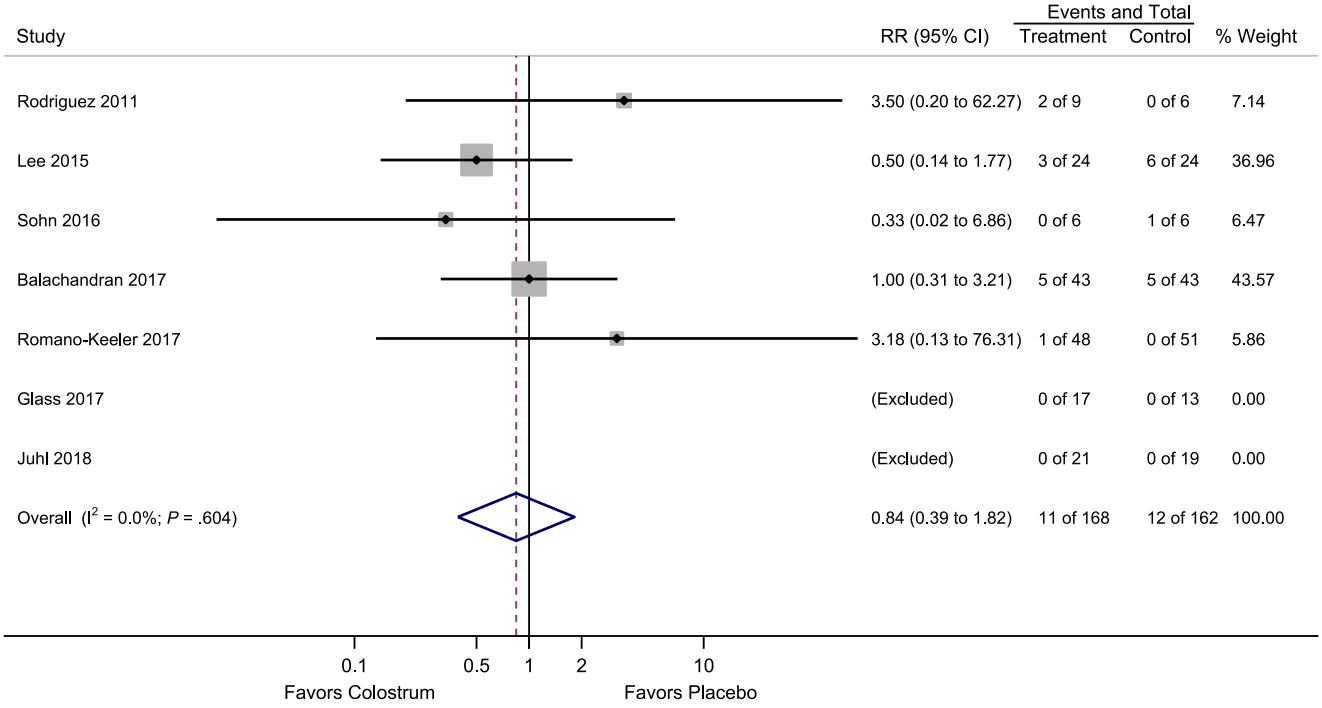

FIGURE 3

Forest plot revealing RR for mortality for colostrum versus placebo groups. Horizontal bars denote 95% CIs. Studies are represented as squares centered on the point estimate of the result of each study. The area of the square represents the weight given to the study in the meta-analysis. The pooled RR was calculated by DerSimonian-Laird random-effects model. The diamond represents the overall estimated effect and its 95% CI in total (center line of diamond, dashed line). The solid vertical line is the line of no effect. Weights are from random effects analysis.

human colostrum, we did not find any difference.

The only outcome in which we found differences was the time to achieve full-enteral feeding and the CoE was judged as moderate. Colostrum administration reduced the time to achieve the enteral feeding by ~3.5 days. Although the definition of full-enteral feeding provided by authors varied, ranging from 100 to 150 mL/kg per day, these results may be clinically relevant. The exact cause of this effect is not clear, but 1 potential explanation could be the presence of trophic factors on colostrum that may enhance intestinal maturation.[9,33,34]

Achieving full-enteral feeding in a shorter period of time is with no doubt an important effect because it will relate to an earlier removal of central lines and, perhaps, to less associated infections. We identified fewer cases of culture-proven sepsis in colostrum groups but without statistically significant differences, which, as we described above, could be caused by a lack of power. In the subgroup analysis, we did not find differences by type of colostrum. However, the results, based on this limited number of trials, trended toward a treatment effect but were nonsignificant. We await published data from ongoing trials to further assess the potential of colostrum for time to achieve full-enteral feeding.

The certainty across the body of evidence was judged to be moderate or low. The reasons for rating down the CoE were due to heterogeneity and imprecision. Potential reasons for heterogeneity were explored by using both metaregression and subgroup analyses, and all analyses were nonsignificant. Imprecision was the reason for rating down because of the lack of significant effects (CIs ranged from values suggesting a substantial benefit to values suggesting substantial harm) and the modest sample size.[35] Additional RCTs with more participants and more events will likely have an impact on the precision of estimates, which in turn will improve our certainty in evidence.

To date, there are at least 4 ongoing RCTs in which researchers are comparing colostrum to placebo that are registered in clinical trials register platforms (WHO and clinicaltrials.gov). In 3 trials, researchers are currently comparing oropharyngeal administration of human colostrum with placebo,[2,36,37] and in 1 trial, researchers are comparing bovine colostrum with infant formula.[38] In total, these researchers will analyze >1300 patients. Certainly, incorporating the results of these trials will add precision to the estimates, which in turn will provide higher certainty in our estimates of effect.

The strengths of this review include explicit eligibility criteria; a comprehensive search developed

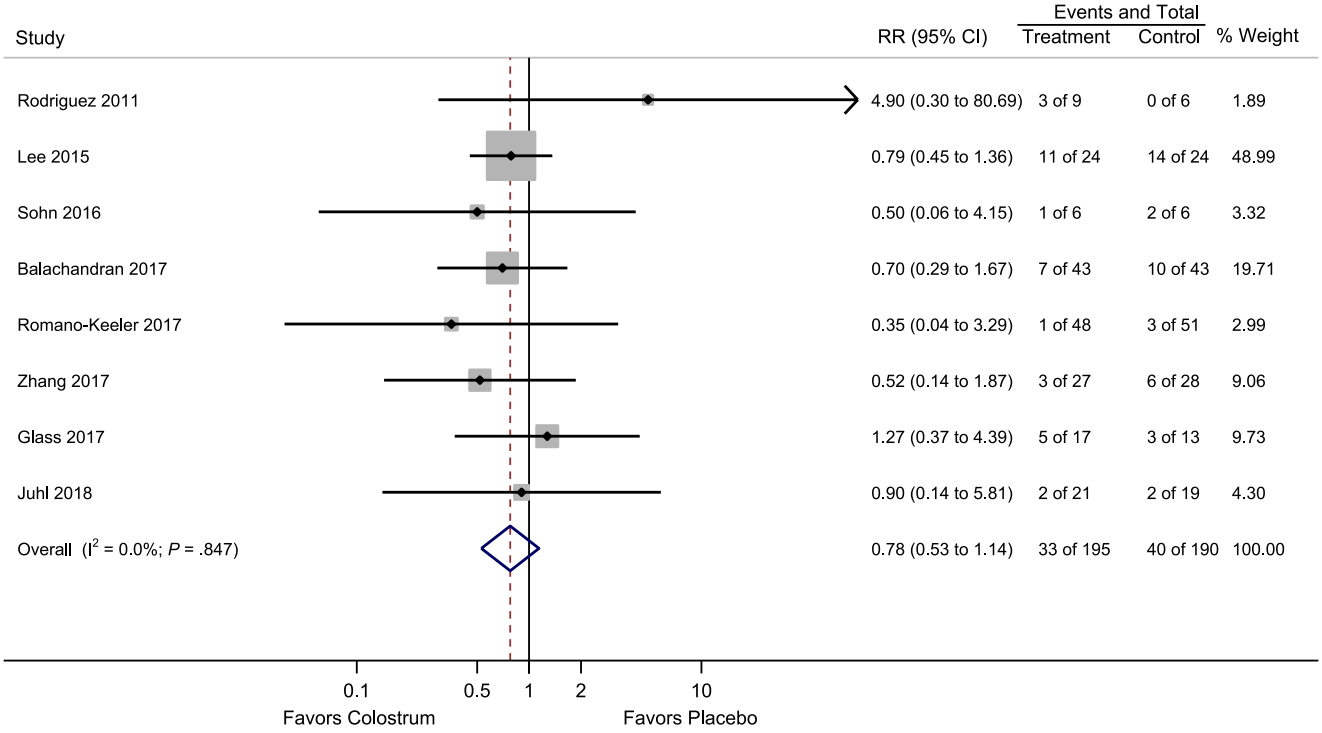

FIGURE 4

Forest plot revealing RR for culture-proven sepsis for colostrum versus placebo groups. Horizontal bars denote 95% CIs. Studies are represented as squares centered on the point estimate of the result of each study. The area of the square represents the weight given to the study in the meta-analysis. The pooled RR was calculated by DerSimonian-Laird random-effects model. The diamond represents the overall estimated effect and its 95% CI in total (center line of diamond, dashed line). The solid vertical line is the line of no effect. Weights are from random effects analysis.

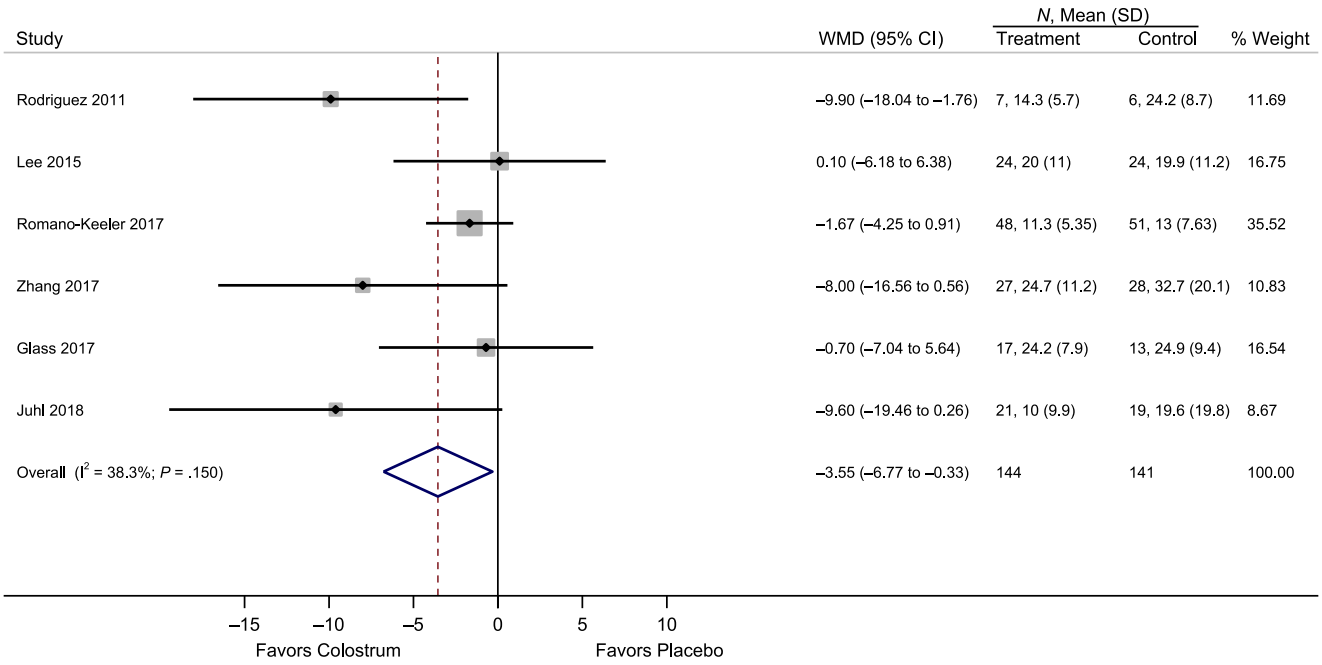

FIGURE 5

Forest plot revealing the weighted mean difference in mean time to reach full enteral feed for colostrum versus placebo groups. Horizontal bars denote 95% CIs. Studies are represented as squares centered on the point estimate of the result of each study. The area of the square represents the weight given to the study in the meta-analysis. The pooled mean difference was calculated by DerSimonian-Laird random-effects model. The diamond represents the overall estimated effect and its 95% CI in total (center line of diamond, dashed line). The solid vertical line is the line of no effect. Weights are from random effects analysis. WMD, weighted mean difference.

with a research librarian, with no language or publication status restriction; duplicate assessment of eligibility and independent data abstraction, risk of bias, and CoE assessment by using the GRADE approach; summarizing evidence for both human and bovine colostrum; and consideration of possible subgroup effects. Currently, there is a protocol for a Cochrane review that is designed to summarize the evidence of the administration of oropharyngeal human colostrum on morbidity and mortality in preterm infants[39]; however, this review is not considering bovine colostrum. To our knowledge, this is the first review that synthesizes the evidence from bovine colostrum.

The limitations of our review have to do with the underlying evidence. The total number of patients was modest, whereas the number of NEC-related events was low, which along with the heterogeneity led to low CoE. The inclusion of future ongoing trials will likely lead to more precise estimates and more confidence in the results. We pooled the evidence for both types of colostrum, although they are different interventions administered through different routes. To explore the potential heterogeneity related to type and administration route of colostrum, we performed subgroup analysis and indirect comparisons to evaluate the differences between both interventions, and our results demonstrated nonsignificant differences.

CONCLUSIONS

Moderate to low CoE suggests that human and bovine colostrum have no effect on NEC incidence, mortality, length of stay, and culture-proven infections among preterm infants. Colostrum may reduce the time for achieving full-enteral feeding. Future researchers need to confirm whether the effect on this outcome is similar between both types of colostrum or is limited only to human colostrum. Data from at least 4 ongoing trials will be useful in providing more patients to improve the precision of estimates for each of our outcomes. Given the interest in this topic, readers should look for review updates.

ABBREVIATIONS

CI: confidence interval
CoE: certainty of evidence
GRADE: Grading of Recommendations, Assessment, Development, and Evaluation
NEC: necrotizing enterocolitis
RCT: randomized controlled trial
RR: relative risk
WHO: World Health Organization

designed the search strategy and interpreted the data analysis; Dr Johnston assessed the certainty of evidence and interpreted the data analysis; Dr Florez conceptualized and designed the study, coordinated and supervised the systematic review, selected the articles, extracted the data, assessed the certainty on the evidence, interpreted the data analysis, and drafted the initial manuscript; and all authors reviewed and revised the manuscript, approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

This protocol has been registered with the PROSPERO International prospective register of systematic reviews (registration CRD42018085566).

DOI: https://doi.org/10.1542/peds.2018-0767

Accepted for publication May 23, 2018

Address correspondence to Ivan D. Florez, MD, MSc, Department of Pediatrics of University of Antioquia. Hospital Universitario San Vicente Fundación, Pabellón Infantil, Calle 64 N°51 D - 154. Medellin, Colombia. E-mail: ivan.florez@udea.edu.co

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. World Health Organization. Preterm birth. 2017. Available at: www.who.int/mediacentre/factsheets/fs363/en/. Accessed April 20, 2018
2. Rodriguez NA, Vento M, Claud EC, Wang CE, Caplan MS. Oropharyngeal administration of mother's colostrum, health outcomes of premature infants: study protocol for a randomized controlled trial. *Trials*. 2015;16:453
3. Westerbeek EA, van den Berg A, Lafeber HN, Knol J, Fetter WP, van Elburg RM. The intestinal bacterial colonisation in preterm infants: a review of the literature. *Clin Nutr*. 2006;25(3):361–368
4. Thyoka M, de Coppi P, Eaton S, et al. Advanced necrotizing enterocolitis part 1: mortality. *Eur J Pediatr Surg*. 2012;22(1):8–12
5. Neu J, Walker WA. Necrotizing enterocolitis. *N Engl J Med*. 2011;364(3):255–264
6. Raval MV, Hall NJ, Pierro A, Moss RL. Evidence-based prevention and surgical treatment of necrotizing enterocolitis-a review of randomized controlled trials. *Semin Pediatr Surg*. 2013;22(2):117–121

7. Lin PW, Stoll BJ. Necrotising enterocolitis. *Lancet*. 2006;368(9543):1271–1283
8. Christensen RD, Gordon PV, Besner GE. Can we cut the incidence of necrotizing enterocolitis in half–today? *Fetal Pediatr Pathol*. 2010;29(4):185–198
9. Radillo O, Norcio A, Addobbati R, Zauli G. Presence of CTAK/CCL27, MCP-3/CCL7 and LIF in human colostrum and breast milk. *Cytokine*. 2013;61(1):26–28
10. Hettinga K, van Valenberg H, de Vries S, et al. The host defense proteome of human and bovine milk. *PLoS One*. 2011;6(4):e19433
11. Rodriguez NA, Caplan MS. Oropharyngeal administration of mother's milk to prevent necrotizing enterocolitis in extremely low-birth-weight infants: theoretical perspectives. *J Perinat Neonatal Nurs*. 2015;29(1):81–90
12. Zhang Y, Ji F, Hu X, Cao Y, Latour JM. Oropharyngeal colostrum administration in very low birth weight infants: a randomized controlled trial. *Pediatr Crit Care Med*. 2017;18(9):869–875
13. Rodriguez NA, Groer MW, Zeller JM, et al. A randomized controlled trial of the oropharyngeal administration of mother's colostrum to extremely low birth weight infants in the first days of life. *Neonatal Intensive Care*. 2011;24(4):31–35
14. Lee J, Kim H-S, Jung YH, et al. Oropharyngeal colostrum administration in extremely premature infants: an RCT. *Pediatrics*. 2015;135(2). Available at: www.pediatrics.org/cgi/content/full/135/2/e357
15. Ronayne de Ferrer PA, Baroni A, Sambucetti ME, López NE, Ceriani Cernadas JM. Lactoferrin levels in term and preterm milk. *J Am Coll Nutr*. 2000;19(3):370–373
16. Sohn K, Kalanetra KM, Mills DA, Underwood MA. Buccal administration of human colostrum: impact on the oral microbiota of premature infants. *J Perinatol*. 2016;36(2):106–111
17. Schams D. Growth factors in milk. *Endocr Regul*. 1994;28(1):3–8
18. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Ann Surg*. 1978;187(1):1–7
19. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. *Pediatr Clin North Am*. 1986;33(1):179–201
20. Higgins JPT, Altman DG, Gøtzsche PC, et al; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928
21. Akl EA, Sun X, Busse JW, et al. Specific instructions for estimating unclearly reported blinding status in randomized trials were reliable and valid. *J Clin Epidemiol*. 2012;65(3):262–267
22. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924–926
23. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ*. 2003;326(7382):219
24. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*. 2011;343:d4002
25. Miladinovic B, Hozo I, Chaimani A, Djulbegovic B. Indirect treatment comparison. *Stata J*. 2014;14(1):76–86
26. Glass KM, Greecher CP, Doheny KK. Oropharyngeal administration of colostrum increases salivary secretory IgA levels in very low-birth-weight infants. *Am J Perinatol*. 2017;34(14):1389–1395
27. Romano-Keeler J, Azcarate-Peril MA, Weitkamp JH, et al. Oral colostrum priming shortens hospitalization without changing the immunomicrobial milieu. *J Perinatol*. 2017;37(1):36–41
28. Zhang Y, Ji F, Hu X, Cao Y, Latour JM. Oropharyngeal colostrum administration in very low birth weight infants: a randomized controlled trial. *Pediatr Crit Care Med*. 2017;18(9):869–875
29. Balachandran B, Dutta S, Singh R, Prasad R, Kumar P. Bovine colostrum in prevention of necrotizing enterocolitis and sepsis in very low birth weight neonates: a randomized, double-blind, placebo-controlled pilot trial. *J Trop Pediatr*. 2017;63(1):10–17
30. Juhl SM, Ye X, Zhou P, et al. Bovine colostrum for preterm infants in the first days of life: a randomized controlled pilot trial. *J Pediatr Gastroenterol Nutr*. 2018;66(3):471–478
31. Davis TA, Nguyen HV, Garcia-Bravo R, Fiorotto ML, Jackson EM, Reeds PJ. Amino acid composition of the milk of some mammalian species changes with stage of lactation. *Br J Nutr*. 1994;72(6):845–853
32. Jensen ML, Sangild PT, Lykke M, et al. Similar efficacy of human banked milk and bovine colostrum to decrease incidence of necrotizing enterocolitis in preterm piglets. *Am J Physiol Regul Integr Comp Physiol*. 2013;305(1):R4–R12
33. Rasmussen SO, Martin L, Østergaard MV, et al. Bovine colostrum improves neonatal growth, digestive function, and gut immunity relative to donor human milk and infant formula in preterm pigs. *Am J Physiol Gastrointest Liver Physiol*. 2016;311(3):G480–G491
34. Sisk PM, Lovelady CA, Gruber KJ, Dillard RG, O'Shea TM. Human milk consumption and full enteral feeding among infants who weigh </= 1250 grams. *Pediatrics*. 2008;121(6). Available at: www.pediatrics.org/cgi/content/full/121/6/e1528
35. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence–imprecision. *J Clin Epidemiol*. 2011;64(12):1283–1293
36. US National Library of Medicine. Bovine colostrum for preterm newborns (PreColos-RCT). 2018. Available at: https://clinicaltrials.gov/ct2/show/NCT03085277?term=colostrum&age=0&rank=6. Accessed April 20, 2018
37. World Health Organization. Oral immunotherapy in very low birth weight preterm infants - randomized double-blind, placebo-controlled clinical trial. 2018. Available at: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=RBR-83dk7z. Accessed March 15, 2018

38. World Health Organization. Efficacy of oropharyngeal administration of colostrum in reducing morbidity and mortality in very preterm infants: a randomized controlled trial - colostrum. 2018. Available at: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2017/11/010396. Accessed April 20, 2018

39. Nasuf AW, Ojha S, Dorling J. Oropharyngeal colostrum in preventing mortality and morbidity in preterm infants. *Cochrane Database Syst Rev*. 2015;(10):CD011921

Human and Bovine Colostrum for Prevention of Necrotizing Enterocolitis: A Meta-analysis

Behnam Sadeghirad, Rebecca L. Morgan, Dena Zeraatkar, Adriana M. Zea, Rachel Couban, Bradley C. Johnston and Ivan D. Florez

Pediatrics 2018;142;
DOI: 10.1542/peds.2018-0767 originally published online July 10, 2018;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Human and Bovine Colostrum for Prevention of Necrotizing Enterocolitis: A Meta-analysis

Behnam Sadeghirad, Rebecca L. Morgan, Dena Zeraatkar, Adriana M. Zea, Rachel Couban, Bradley C. Johnston and Ivan D. Florez

Pediatrics 2018;142;
DOI: 10.1542/peds.2018-0767 originally published online July 10, 2018;