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Acidified Feedings in Preterm Infants: A Historical and Physiological Perspective

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Abstract

The use of acidified milk for feeding infants has a long, interesting history that appears to have developed from the use of buttermilk in Holland as early as the late 19th century for feeding infants with diarrhea. Physicians in the early 20th century assumed that the observed benefits were from buttermilk's acidity leading to the practice of acidifying infant formula. The historical and physiological perspective on the use of acidified infant formula is now especially relevant with the emergence of an acidified liquid human milk fortifier for preterm infants. Here, we review that history, with a deeper dive into the contemporary research on the use of acidified human milk fortifiers, the consequences for preterm infants, and the underlying physiological mechanisms.

Keywords

- acidified feedings
- human milk fortifier
- infant formula
- premature infant

Key Points

- In the late 19th and early 20th century acidified feedings were in common use for sick infants.
- By the mid-20th century, acidified feedings tested in preterm infants resulted in acidic physiology and poor growth.
- The current practice of acidifying feedings in preterm infants has been associated with metabolic acidosis, poor tolerance, and delayed growth.

In this study, we intend to review the history of the use of acidified feedings as an alternative to breastfeeding. Of particular interest is what is known about the physiological responses of both term and premature infants. Although clinical data are somewhat sparse until the latter half of the 20th century, the physiology of premature infants given acidified feedings more recently is especially illuminating.

The belief in the early 20th century as to why acidified milk would be beneficial was based on the concept that infants cannot produce sufficient hydrochloric acid to overcome the buffering capacity of cow's milk and have, therefore, poor digestion.[1] It was also recognized to be pathogen free and thought to have other advantages such as "denaturization of the protein, stimulation of bile flow, pancreatic

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and intestinal secretions, favorable effect on the absorption of fat, protein, and mineral matter, and stimulation of the muscular construction in the gastrointestinal tract."[2]

Marriott developed lactic acid milk made from undiluted bacterially soured whole cow's milk, enriched with corn syrup for failure to thrive infants.[3] By the early 1920s, he had extended its use to all formula-fed infants, and approximately 90% of the infants in the St. Louis Children's Hospital were fed on lactic acid milk and corn syrup formulas.[4] The formulation called for either souring milk with lactic acid organisms or by adding lactic acid to sterilized milk.[4] In addition to lactic acid, Marriot et al suggested vinegar and others suggested citric acid[5] and even hydrochloric acid.[6] Clearly, the focus was on acidification rather than fermentation for its probiotic effect.

By the 1930s, the use of evaporated cow's milk-based infant formulas had become the most widely used feeding for formula-fed infants.[7] Evaporated milk formulas were not acidified, and interest in acidified formulas dissipated. In three reviews of the history of infant feeding,[7–9] not even one mentioned acidified formula. Although interest in acidified formulas for term infants did not disappear, they have not necessarily been widely accepted as beneficial. In an ESPGHAN Medical Position Paper[10] that evaluated the efficacy of formulas acidified by fermentation before processing, they concluded "The available data do not allow general conclusions to be drawn on the use and effects of fermented formulae for infants." Nevertheless, acidified term infant formulas are still available and generally promoted for inhibition of the growth of harmful bacteria in the prepared feeding[11,12] and for the prevention of gastroenteritis.[12]

Acidified Feedings for Premature Infants

In the late 1950s, Karelitz et al thought that it was important to determine if lactic-acid milk might be beneficial for preterm infants.[13] Infants with birth weights of around 1,600 g were fed lactic-acid evaporated milk, evaporated milk, or half-skimmed milk formulas, and their respective average weight gains were 11.8, 16.6, and 15.2 g/kg/d.[13] That study led Goldman et al[4] to investigate whether the difference in the rate of weight gain might be associated with an acidosis produced by the lactic acid.

Goldman et al's study is the first to closely examine the metabolic effects of an acidified feeding for premature infants.[14] There were significant effects not only on weight gain but also on the indicators of acidosis-blood pH and CO_2 that were measured in the study. Urine sodium, ammonia, and lactate were measured in a subset of infants while being fed a half-skimmed formula followed by an acidified half-skimmed formula. Sodium excretion increased from 0.6 to 1.5 mEq/d, ammonia from 1.7 to 2.8 mEq/d, and lactate from 0.2 to 1.1 mEq/d as often observed in acidosis. There were several reports in the 1970s that described the effects of acidified feedings on infants, which add to the historical perspective of understanding the consequences of the pH of infant feedings. These reports were not about the addition of acid to formula but rather about the existing acid load from different feedings.

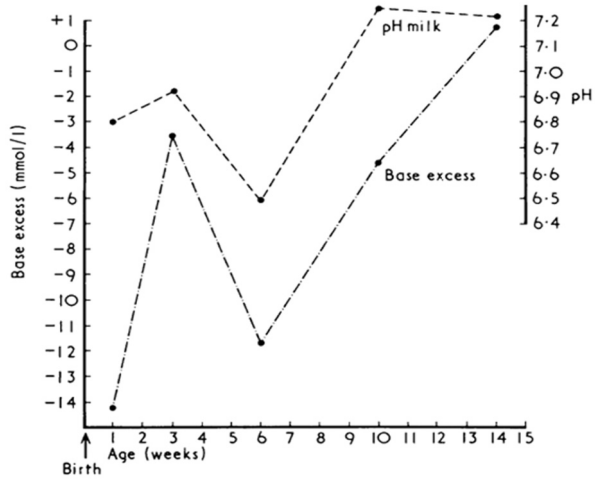

Fig. 1 Variations in pH of breast milk reflected by variations in pH and base excess of one infant over 3 months. (Adapted from Moore et al[19]).

Harrison and Peat determined that the pH of cow's milk was more acidic than breast milk and tested whether adding sodium bicarbonate or trometamol (Tris, an organic amine proton acceptor) to infant formula would affect outcomes in newborn infants.[15] Doing so had a bacteriostatic effect on *Escherichia coli* in vitro, and infants produced stools with a preponderance of *Lactobacilli* over *E. coli*. Furthermore, when alkali was removed, it led to a decreased weight gain.

Moore et al examined the relationship between the acid load of infant feeding and the occurrence of metabolic acidosis (MA).[16] They reported "significant correlation between the pH of the feed and the degree of acidosis in the infant as measured by the base deficit." The graphics of a single infant are particularly instructive as shown above (►Fig. 1.). Base excess (BE) clearly follows milk pH, dropping simultaneously with a drop in milk pH.

Interestingly, in their introduction, they describe the previous history of acidifying milk feedings to sick infants to promote digestibility and reduce the risk of bacterial infection, citing a report in the Proceedings of Pediatric Societies at the European Society for Pediatric Gastroenterology, but that report noted "Acidified milks fell into disfavor when it was realized that some of the infants became severely acidotic."[17]

From the work of Karelitz et al and Goldman et al through the reports in the 1970s, it should have been quite clear that acidification of infant feedings and particularly feedings for premature infants would dramatically increase the risk of MA and its accompanying consequences.[13–17]

Recent Use of Acidified Feedings in the NICU

The recent marketing of an acidified liquid human milk fortifier [(ALHMF)] by one of the leading infant formula manufacturer's in the United States has led to a resurgence of acidified preterm infant feedings. What led to the

transition from acidifying preterm formula to an acidified HMF? Feeding options, especially HMFs, for the preterm infant have greatly expanded over the recent past, with multiple concentrations of energy and protein, added bioactive nutrients, and nutrient-dense postdischarge feedings. These advances have been critically important for the growth and long-term development of the preterm infant because regardless of their gestational age (GA) at birth, premature infants generally fall behind in growth and development from where they would have been if born at term,[18–20] and poor growth in the neonatal intensive care unit (NICU) markedly increases the risk of developmental delay.[21–26] Also, of importance is that current recommendations in the NICU are to use commercially sterile liquid nutrition products rather than powder nutrition products because of the potential for contamination.[27–29]

The now widely accepted first choice for preterm infant feeding is human milk (HM). The benefits of HM in reducing morbidity and mortality are well established.[30] However, because HM is not sufficiently nutrient rich to adequately support the growth and development requirements of the preterm infant,[31,32] human milk fortifiers have been developed to provide macronutrients and micronutrients such as protein, calcium, phosphorus, and electrolytes to meet the rapidly growing preterm infants' needs. In recent years, highly concentrated HMFs have been developed to provide commercial sterility and sufficient fortification without diluting HM.

The development of commercially sterile, concentrated liquid HMFs, has presented significant challenges. Infant formula companies have taken different approaches to processing and manufacturing the latest generation of HMFs. One method is aseptic filling, the process by which a product is heat sterilized and then filled into a previously sterilized package under aseptic conditions.[28] Although this approach minimizes processing effects on the product, there are manufacturing challenges that add considerably to the production timeline. "Aseptic systems are quite complex and require sophisticated instrumentation to ensure that an adequate process is delivered and that sterility is maintained. These systems require highly trained personnel."[28]

Another method that significantly reduces the production timeline is simply to acidify the liquid HMF. The use of fermentation with lactic acid-producing bacteria to preserve food by reducing pH to prevent the growth of undesirable species of bacteria is a preservation technique that dates from antiquity to the present.[33–35] As demonstrated by the work of Marriott et al that can also be accomplished by the direct addition of an acid. ALHMF is acidified by the addition of citric acid and has a pH of 4.0 to 4.6.[2,36]

Although aseptic filling and acidification both effectively produce commercially sterile products, since the marketing of ALHMF, there have been at least nine published reports in[37–45] the literature indicating that its use echoes the research of Goldman[14] that using an acidified feeding for preterm infants significantly increases biochemical markers of acidic physiology and further, significantly increases the incidence of frank MA.

In these nine studies of preterm infants fed ALHMF (Mead Johnson),[37–45] comparator HMFs included powder HMFs and nonacidified concentrated liquid HMF (Abbott Nutrition).[39,41–44] Regardless of the comparator HMF, there are striking parallels across these studies. This category of HMFs will be referred to as nonacidified human milk fortifiers (NAHMFs). To our knowledge, all studies of acidified HMFs are included in ►Table 1. Using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) guideline to evaluate the quality of evidence from these studies, the three randomized controlled trials were rated "moderate" and the remaining observational studies as "low."[46]

Much of the recent focus in preterm nutrition has been on achieving sufficient protein intake to support catchup growth, and several have shown a direct correlation between protein intake and growth in the NICU.[47–51] As seen in ►Table 1, in all of the aforementioned studies, infants in the ALHMF group consumed significantly more protein but showed no improved growth[37,42] or significantly decreased growth.[38–41,43,44] Cordova et al[45] adjusted protein intake to be equivalent. Perhaps even more striking is that in seven of the nine studies,[38–45,52] infants fed ALHMF had significantly more MA (►Table 1). In general, these studies defined MA as a significant base deficit, generally defined as a BE < -4 to -6 mmol/L. The relationship between unexpectedly poor growth despite significantly increased protein intake and the occurrence of MA can be explained by examining the mechanisms by which infants respond to acidotic physiology. In these studies, there were no differences between the groups in baseline characteristics such as GA (range: 27–31 weeks) or birthweight.

Three of the major physiological controls of acid-base balance are renal regulation, ventilatory response, and bone metabolism. These physiological mechanisms tightly maintain blood pH, i.e., $[H^+]$ (hydrogen ion concentration), within a very narrow range. In pure chemical terms, to reverse acidotic pressure, an infant must be able to eliminate H^+ ions.

The bicarbonate buffering system is a series of reactions that lead to the production of carbon dioxide $[H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2\uparrow]$. Venting CO_2 from the lungs effectively decreases $[H^+]$.[53] This response leads to the hyperventilation typically seen with MA and contributes to the significant decreases in $[HCO_3^-]$ and/or $[CO_2]$ as seen in several of these studies (►Table 2).[37–41,43–45]

Another major buffering system that eliminates $[H^+]$ is through the excretion of urea following a series of transamination and deamination reactions in the kidneys between amino acids and α-ketogluterate.[53] The source of the amino acids required for this latter process comes from protein catabolism as shown in studies where acidosis is induced experimentally. These studies show decreased fractional protein synthesis rates in rats[54] and in humans increased amino acid oxidation[55] and decreased albumin synthesis while increasing N excretion sufficient to create a negative N balance.[56]

Falling blood urea nitrogen (BUN) values are another indicator that protein metabolism is disturbed by the

Table 1 Protein in study HMFs, protein intake, growth, and incidence of metabolic acidosis in studies where infants were fed acidified HMF

	Moya et al[37]		Thoene et al[38]		Thoene et al[39]		Cibulskis and Armbrecht[40]		Kumar et al[41]		Lainwala et al[42]		Schanler et al[43]		Darrow et al[44]		Cordova[45]	
	AL	EP	AL	SP	AL	CL	AL	SP	AL	HPCL	AL	HPCL	AL	HPCL	AL	CL	AL[d]	NALHMF[d]
Protein content (g/100 mL fortified PTHM)	3.2	2.6	3.2	2.35	3.2	2.4	3.2	2.4	3.2	2.84	3.2	2.84	3.2	2.84	3.82	3.02	ADJ	ADJ
Protein intake (g/kg/d)	NR	NR	4.3[h]	3.9[h]	NR	NR	3.97[h]	3.62[h]	4.2	3.7[g]	NR[a]	NR[a]	4.17	4.03[i]	NR	NR	NR	NR
Wt gain (g/kg/d)	15.8	15.7	10.6[f]	15.4[f]	NR	NR	13.7	14.7	13[i]	16.5[i]	17.8	19.1	16.4	16.9	14.0[h]	15.4[h]	13.4	13.8
Metabolic acidosis (% of infants)	1.4	1.4	NR[c]	NR[c]	NR	NR	54[g]	10[g]	56.2[h]	6.6[h]	33[g]	3[g]	27[g]	5[g]	70.5[g]	11.8[g]	42.4[g]	19.6[e,g]
GRADE rating	Moderate		Low		Low		Low		Moderate		Low		Moderate		Low		Low	

Abbreviations: ADJ, both groups adjusted to receive 4 g/kg/d; AL, Enfamil acidified liquid HMF; CL, Similac concentrated liquid HMF; EP, Enfamil powder HMF; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; HPCL, Similac hydrolyzed protein concentrated liquid HMF; NALHMF, nonacidified liquid human milk fortifier; NR, not reported; PTHM, preterm human milk; SP, Similac powder HMF; Wt, weight.

Notes: Superscripts on values of formulas in the same study column are significantly different [f]$p \leq 0.0001$; [g]$p \leq 0.001$; [h]$p \leq 0.01$; [i]$p \leq 0.05$.

[a]Noted to be higher in AL than HPCL.

[b]Noted to be significantly different; CL > AL.

[c]Noted to be significantly different; AL > SP.

[d]Fortifier not identified.

[e]Significant difference in bicarbonate treatment; 33 vs. 1.1% AL > NALHMF, $p < 0.001$.

acidotic conditions associated with ALHMF. In Moya et al, BUNs in the ALHMF fell from 11.0 mg/dL at week 1 to 8.0 mg/dL at 4 weeks.[37] At 4 weeks in Schanler et al, BUN in the ALHMF group was 9.0 versus 13.0 mg/dL in the hydrolyzed protein concentrated liquid HMF group ($p < 0.001$).[43] Many NICUs opt to increase protein intake when BUNs fall below 10 mg/dL.

Bone metabolism also plays a key role in maintaining acid-base balance. MA may impair bone mineralization even in its early stages.[57,58] Due to its large stores of calcium, an alkaline metal, the skeleton serves as a reservoir of base [OH^-] that is utilized to buffer acidosis through the degradation of hydroxyapatite [$Ca_5(PO_4)_3OH \rightarrow 5Ca^{2+} + 3\ PO_4^{3-} + OH^-$].[45] Hydrogen ions directly stimulate osteoclast activity with a simultaneous reduction in alkaline phosphatase.[59] The significantly decreased alkaline phosphatase associated with ALHMF in Schanler et al is consistent with this response.[43] This particular mechanism would also account for the effect of an HMF-induced MA on decreasing bone mineralization in preterm infants as reported by Rochow et al.[58]

As illustrated in many of these studies, acidotic conditions associated with the feeding ALHMF lead to tolerance-related issues as well. Schanler et al noted significant increases in gastric residuals, abdominal distension, vomiting, diaper dermatitis, and nonserious adverse events.[43] Cibulskis and Armbrecht[40] in comparing ALHMF to NAHMF reported a significant increase in the stoppage of fortifiers for feeding intolerance (31 vs. 66% of infants, $p = 0.005$; ALHMF > NAHMF), and Kumar et al[41] reported that more infants fed ALHMF had feeding stopped for abdominal distension (25 vs 0% of infants; ALHMF > NAHMF, $p = 0.04$). In Darrow et al, more infants fed ALHMF had their fortifier changed (41.0%) than infants fed NAHMF (7.4%, $p < 0.001$).[44]

Although bicarbonate therapy is commonly used to correct the clinical disturbances associated with MA, this practice is somewhat controversial.[60] A disequilibrium across cellular membranes may occur between carbon dioxide and bicarbonate ions, leading to intracellular acidosis in the face of seemingly resolving the acidic pH.[60,61] In that regard, a recently published study[45] that compared infants fed ALHMF versus NALHMF reported that infants who received the ALHMF had significantly more MA than infants receiving NALHMF (42% vs. 20%; $p = 0.001$.), and not surprisingly almost all infants who received sodium bicarbonate treatment were in the ALHMF group compared with the NALHMF group (34 vs. 1.0%; $p = 0.001$; ►Table 1).

Also, of importance, the difference in sterilization, acidification versus aseptic filling, has an immediate effect on the physical properties of HM. The addition of ALHMF to HM reduces the pH from 7.4 to 4.7.[61] This has raised questions regarding the effects of HM fortified with ALHMF on the bioactive properties of HM.

The effects on the bioactive properties of HM are described in Erickson et al where they acidified human milk with citric acid to a pH of 4.5, similar to the pH of human milk after the addition of ALHMF.[61] They report about a 75%

Table 2 Plasma bicarbonate and carbon dioxide in studies where infants were fed acidified HMF (superscript by name is reference number).

Source of data	Moya et al[37] (mEq/L)		Thoene et al [38] (mmol/L)		Cibulskis and Armbrecht [40] (Δ mmol/L)		Lainwala et al[42] (mmol/L)		Schanler et al[43] (mEq/L)		Darrow et al[44] (mmol/L)		Cordova[45]	
Type of HMF	AL	EP	AL	SP	AL	SP	AL	HPCL	AL	HPCL	AL	CL	AL[d]	NALHMF[d]
HCO_3^-	22.6[a]	26.6[a]	NR	NR	−2.7[a]	+0.47[a]	24.4[b]	28.4[b]	25[a]	27[a]	17.9[a]	22.5[a]	16[a]	17[a]
CO_2	25[c]	26[c]	20[b]	25[b]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: AL, Enfamil acidified liquid HMF; CL, Similac concentrated liquid HMF; EP, Enfamil powder HMF; HPCL, Similac hydrolyzed protein concentrated liquid HMF; NALHMF, nonacidified liquid human milk fortifier; NR, not reported; SP, Similac powder HMF.
Notes: Superscripts on values of formulas in the same study column are significantly different.
[a]$p \leq 0.001$; [b]$p \leq 0.01$; [c]$p = 0.021$; [d]fortifier not identified.

reduction of lymphocytes (3.6 vs. 14.5×10^3 cells/mL; $p < 0.001$), not surprising as these are living cells not designed to survive under acidic conditions. There was also a 61% decrease in lipase activity (86 vs. 222 U/mL; $p < 0.01$), which has implications beyond the loss of this important enzymatic property. HM has two key lipases, lipoprotein lipase and bile-salt stimulated lipase (activated in the presence of bile salts in the small intestine). Both are important in helping breast-fed infants digest HM fat. Beyond this, lipases are enzymes and enzymes are proteins. Protein function is based on its three-dimensional structure, which is held together by hydrogen and disulfide bonds.[62] These bonds may be broken under acidic conditions (thus, the loss of lipase activity). Many of the bioactive components of HM are proteins (including hormones, enzymes, and growth factors such as insulin, epidermal growth factor, nerve growth factor, and insulin-like growth factors). Which of these may also be denatured by acidity is unknown.

Premature infants fed ALHMF compared with liquid or powder nonacidified HMFs get more protein (►Fig. 2)[37–44] but have no improved weight gain (►Fig. 3)[37,41] or significantly lower weight gain[38–41,43,44] and significantly more MA.[38–45] Combining the evidence in a meta-analysis, infants fed NAHMF showed greater weight velocity than infants fed ALHMF (Mean difference (95% confidence interval): 0.18 (0.04, 0.33) g/kg/d (►Fig. 3). In addition, infants fed ALHMF were 3.58 times relative risk (95% confidence interval): 3.58 (2.61, 4.89) as likely to develop MA than infants fed NAHMF (►Fig. 4).

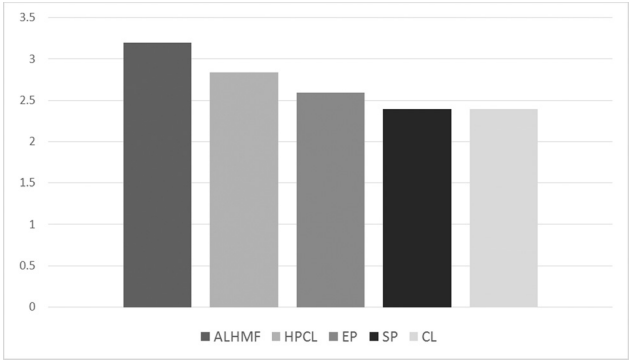

Fig. 2 Protein content of human milk fortifiers (g protein/100 mL fortified HM). ALHMF, Enfamil acidified liquid HMF; CL, Similac concentrated liquid HMF; EP, Enfamil powder HMF; HPCL, Similac hydrolyzed protein concentrated liquid HMF; SP, Similac powder HMF.

The excess energy required to increase CO_2 expiration, and protein catabolism, both involved in combating acidotic pressure, explain, at least in part, the lack of expected growth with higher protein. The stoppage of feeding due to intolerance[40,41] also interrupts the growth curve recovery that is sought in the NICU. Furthermore, there may well be an economic cost. Premature infants with MA in the Schanler et al study had an approximately 8.5 day longer stay in the NICU (66 ± 4.1 vs. 57 ± 1.8 days, with MA > no MA, $p = 0.028$).[43,63] A similar finding was also reported in another study that showed that infants fed ALHMF vs. NAHMF had approximately 9 day longer stay in the NICU.[44] The incidence of MA in the ALHMF group was 70.5%.[44]

Conclusion

It is clear from studies dating from the late 50s through today[13,15,37–45] that the practice of acidifying feedings for preterm infants leads these infants down a path of acidic physiology and often, frank MA, poor protein utilization and growth interference.

Eight of the nine published studies in which premature infants were fed ALHMF[37–45] reported a significantly higher incidence of MA with ALHMF. The likelihood that eight independent studies would have the same outcome by chance is a statistically rare event occurring only approximately 1.8% of the time. Hence, the evidence indicates that the association of MA with feeding AL is not a chance finding as it has been replicated in several studies.

It is important to recognize that the laboratory values in these studies are not static measurements. They are a snapshot of an extremely dynamic physiologic process, the primary function of which is maintaining homeostasis. Small but consistently significant perturbations in HCO_3^-, CO_2, BE, Cl^-, and/or pH in the face of a high incidence of MA paint a picture of infants being fed ALHMF struggling to find ways to

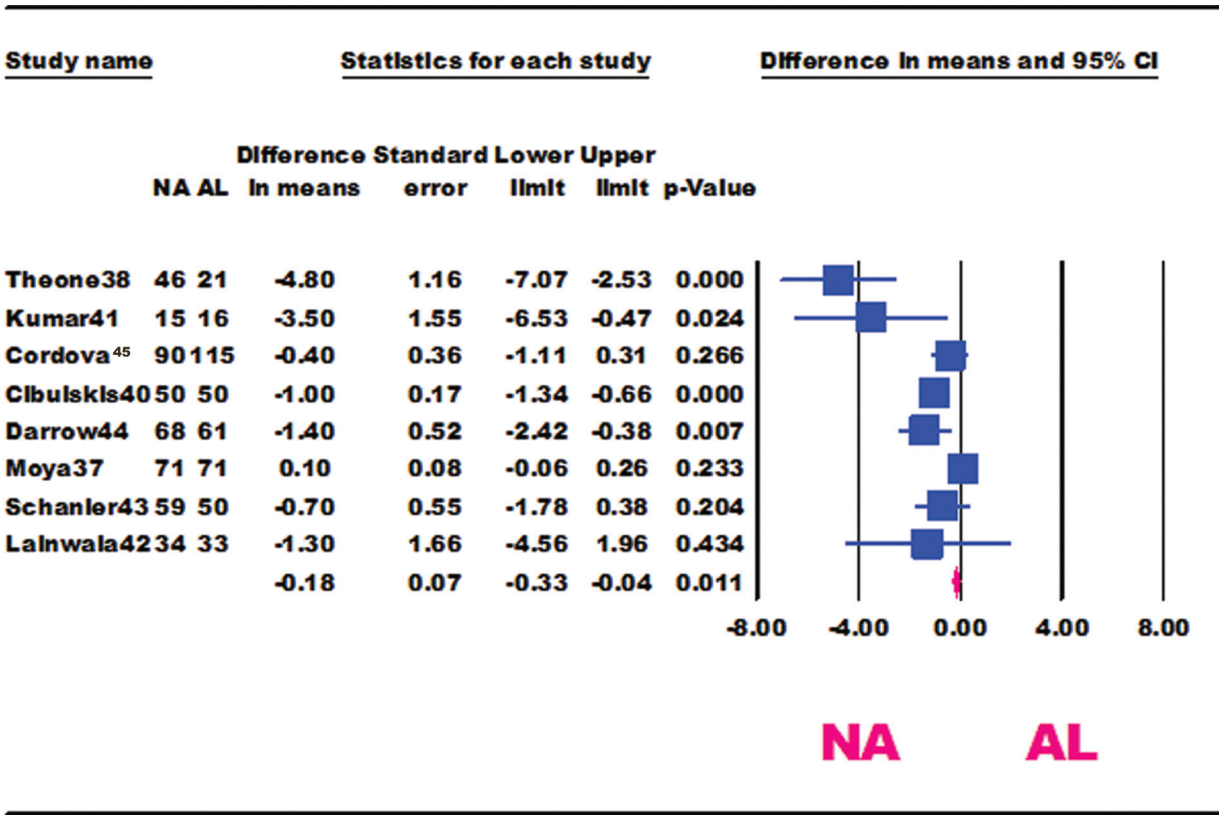

Fig. 3 Meta-analysis of weight gain (g/kg/d). Negative weight gain difference favors NA. AL, acidified HMF; NA, nonacidified HMF.

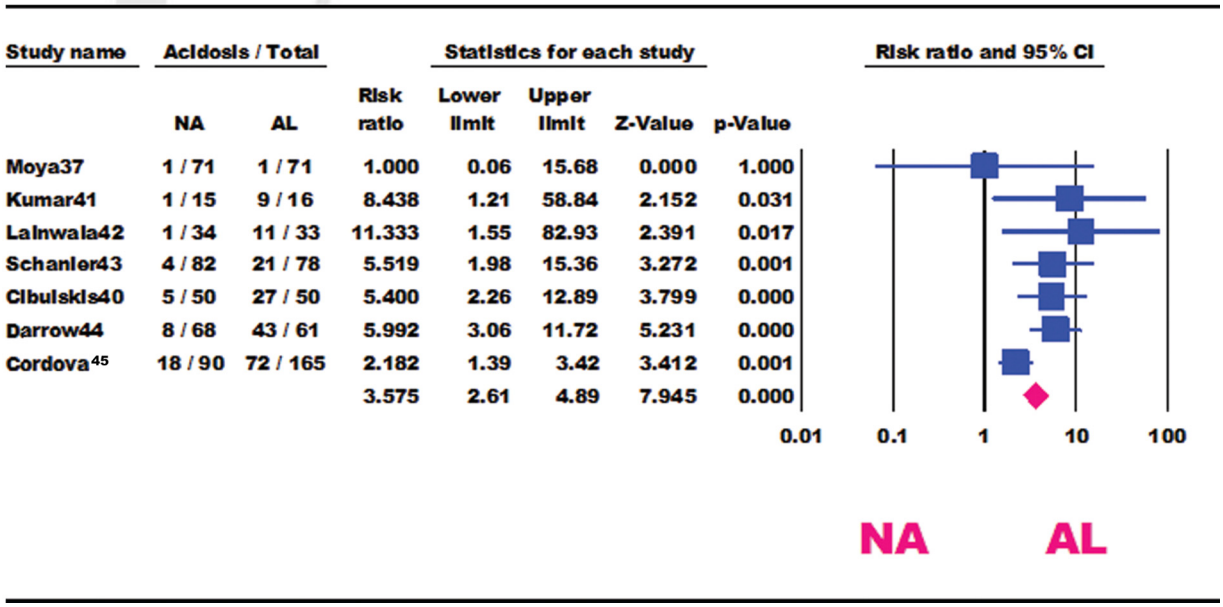

Fig. 4 Meta-analysis of metabolic acidosis incidence. AL, acidified HMF; NA, nonacidified HMF.

remove acid [H^+] to maintain blood pH in the normal range. That struggle appears to impair the growth rate, and the consequences of poor growth in the NICU on cognitive development are well established. Given that the use of ALHMF has also been associated with poor tolerance[40,41,43,44] and that nonacidified liquid HMFs are available, one must ask what role there is for an acidified HMF in the contemporary NICU.

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