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Necrotizing Enterocolitis and the Use of Thickened Liquids for Infants With Dysphagia

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Abstract

Necrotizing enterocolotis (NEC) is a common cause of morbidity and mortality in infants that are born prematurely. The exact cause of NEC is not known. Clinical correlations between the use of thickened fluids and the development of NEC have been established. Thickened fluids are commonly used for the treatment of symptoms from both dysphagia and gastroesophageal reflux disease (GERD) in fragile infant populations. Despite its frequent recommendation, there is little empirical evidence to support the use of thickened fluids in pediatric populations for the treatment of dysphagia or GERD. There is emerging evidence to support the use of slower flowing bottle/nipple systems and side lying feeding position to support safe oral intake in infant populations. Speech-language pathologists who work in neonatal intensive care units and who work with other fragile infant populations must be aware of the risks associated with the use of thickened fluids in these populations and be prepared to provide alternative treatment options as appropriate.

Necrotizing enterocolotis (NEC) is a condition seen almost exclusively in infants born prematurely and it is the second most common cause of morbidity in this population (Berman & Moss, 2011). Portions of the gut experience tissue death in NEC and treatment can vary from implementing bowel rest with frequent monitoring to surgical resection if there is bowel perforation (Panigrahi, 2006). While the exact cause of NEC is not yet established, there is a correlation between the age at which infants born prematurely begin enteral feedings and the type of enteral feed provided (Yee et al., 2012). Typically, NEC develops after enteral feedings are started in the second week of life. Infants born prematurely are also reported to have significant challenges learning to coordinate sucking, swallowing, and breathing for the safe intake of oral feedings (Dodrill, Donovan, Cleghorn, McMahon, & Davies, 2008).

A popular intervention for infants experiencing dysphagia and/or reflux symptoms, including aspiration, involves the use of thickened fluids. While there have been clinical questions regarding the safety of thickened fluid use in fragile populations, such as those with a history of prematurity, there is no documented, empirical evidence illustrating a clear causative relationship between the use of thickened feeds and the development of secondary sequelae, such as diarrhea, dehydration, or NEC in pediatric populations (Drenckpohl et al., 2010; Gosa, Schooling, &

Coleman, 2011). However, there have been multiple clinical concerns raised involving the use of thickened fluids and the onset of NEC in infants.

Clarke and Robinson (2004) reported on the unusual late development of NEC in two infants with a history of prematurity who were discharged from the hospital utilizing thickened fluids. In 2011, the U.S. Food and Drug Administration (FDA) issued a consumer advisory warning against using SimplyThick® in infants born prematurely due to a potential association with NEC (U.S. Food and Drug Administration, 2012). The consumer advisory warning prompted a case series investigation by Beal, Silverman, Bellant, Young, and Klontz (2012) into the occurrence of late onset NEC in infants consuming xanthan gum based thickening agents. Beal et al. (2012) concluded that there was sufficient evidence to propose that the use of SimplyThick® in preterm populations may increase the risk of developing NEC. The clinical concerns raised in the literature have prompted additional scrutiny to the practice of using thickened fluids for infants with dysphagia. This article will provide the reader with the background information necessary to understand why the use of thickened fluids may be harmful to the developing gut of infants and explore alternative interventions to thickened fluids that may facilitate safe oral feeding without introducing risk to the developing gut.

Embryonic and Neonatal Development of the Gut

The embryo begins with the egg and the sperm and, through mitosis, one cell quickly becomes a sphere of cells. The sphere flattens into the embryonic disk with three layers: the ectoderm, endoderm, and in between the mesoderm. The disc folds in with the endoderm in the middle to form the first organ, the "tube gut" at 2–3 weeks gestation. With time, this elongates and becomes the actual gastrointestinal (GI) tract. The upper portion of this develops a "bud" at 3.5–4 weeks gestation that leads the mesoderm cells it contacts to become lung cells. This "bud" should completely separate from the upper part of the GI tract over time. An error in any of the developmental steps can lead to the variety of anomalies possible in the esophagus and airway. The most common congenital anomaly is a tracheoesophageal fistula (1:3000 births; Kovesi & Rubin, 2004).

An important consideration about the blood supply of the gut is that there is a transition in the blood supply at the area of the ileum and cecum. The primary blood supply in this area transitions from the superior mesenteric artery to the inferior mesenteric artery. This area of transition is called the watershed area and is the most common area for necrotizing enterocolotis to develop (Lin, Nasr, & Stoll, 2008). The pervading theory proposes that this transitional area offers decreased perfusion and oxygen as compared to other areas of the gut, and that is what makes this area more susceptible to necrotizing enterocolotis.

Neonatal Gastro-Intestinal Differences

The first and most obvious difference between the neonate and adult bowel is length. With the shorter gut, the transit time should be shorter in an infant. If an infant is born prematurely, the nervous system that controls many aspects of gut functioning, including motility is immature. The immature nervous system results in prolonged transit times through the GI tract. The infant GI tract also plays an important role in the infant's immune system. Premature infants have less of the protective secretory immunoglobulin A (IgA) produced in the GI tract as compared to term infants (Berman & Moss, 2011). This difference puts the premature infant at greater risk for infection as compared to the term infant.

At birth, all human beings transition from a sterile gut to a colonized gut, with the introduction of GI flora from the environment and enteral feeding. The flora that an infant's gut are colonized with varies by their method of birth and by what they are fed. The neonatal gut lining is also more permeable, and does not repair as quickly as that of the older infant (Neu & Walker, 2011).

The actual cause of NEC is not known, but the differences between the gut of the infant born prematurely and the gut of the infant that is born at term make evident why the gut of the infant born prematurely is more susceptible to injury. The leading hypothesis concerning NEC is that it results due to an excessive response to an insult in the gut, with the gut flora being one of the possible potential stimulants (Berman & Moss, 2011). However, there is an association with increased osmolarity (a measure of solute concentration per unit volume of solvent) and NEC (Pearson et al., 2013). The American Academy of Pediatrics (AAP, 1976) recommends keeping osmolarity below 400 mOsm/L. Any nutritional additive to breast milk or formula increases the osmolarity, even the human milk fortifier (Kreissl et al., 2013).

Use of Thickened Fluids in Infants

Thickened fluids are frequently recommended for use in infants to treat either dysphagia (thicker fluids are less likely to be aspirated) or reflux (thicker fluids are less likely to be regurgitated; Gosa et al., 2011; Vandenplas et al., 2009). Horvath, Dziechciarz, and Szajewska (2008) presented a review article on the effect of thickened fluid intervention on reflux in infants and they found from their systematic review of randomized, controlled trials that thickened fluids are only moderately effective in remediating the symptoms of reflux in healthy infants. In their analysis, they included 14 randomized controlled trials that compared the use of regular (thin) formula with the use of thickened formula and showed that with the use of thickened formula there was an increase in the number of infants with no regurgitation, slight reductions in the number of episodes of vomiting per day, and an increase in the infant's overall weight gain. Their analysis also revealed no definitive information that there were any life-threatening adverse effects associated with thickened formula use and that no one thickening agent was more effective than another (Horvath et al., 2008).

Similarly, Gosa et al. (2011) completed a systematic review of the published empirical literature on the reported benefits of thickened fluids as a treatment for pediatric patients (including infants) with dysphagia and any possible adverse effects. They found six published studies that met their inclusion criteria and reported on the effect of thickened fluid use on swallowing physiology and dysphagia signs and symptoms. All of the studies reported improvement in swallowing function with the use of thickened fluids by elimination of laryngeal or tracheal penetration (75% of participants, n=27 out of 36), elimination of aspiration (50% of participants, n=60 out of 121), and elimination of nasopharyngeal reflux (100% of participants, n=2 out of 2) with the use of thickened fluids as compared to standard (thin) fluids. A total of 16 studies were included that reported on the presence of potential adverse effects such as weight loss, cough, aspiration, constipation, and diarrhea as a result of using thickened fluids. None of the participants reported on in the 16 studies experienced any adverse complication during the study period with the use of thickened fluid as compared to standard (thin) fluid (Gosa et al., 2011).

Despite two systematic reviews that found no empirical reports of thickened fluid use resulting in undesirable GI effects in pediatric patients, there continues to be clinical concern regarding thickened fluid use in developing populations for the treatment of both reflux and dysphagia. It has been hypothesized that the development of NEC may be related to the general use of thickening agents by patients with still developing GI systems. Particular risk was hypothesized with the use of thickening agents made with Xanthan gum (Abrams, 2011). The specific factors contributing to the increased risk of developing NEC with use of thickening agents made with Xanthan gum is not clear. The increased risk may be due to the common use of Xanthan gum as a thickening agent in the United States, the product itself, or bacterial contamination in the production line of thickening agents made with Xanthan gum.

Understanding the pulmonary damage that can come from recurrent aspiration that results from dysphagia in this population, the need for extreme caution when prescribing thickened fluid use can leave many clinicians feeling like they are stuck square between two undesirable outcomes

(Tutor & Gosa, 2012). Fortunately, there has been promising clinical research into alternative interventions to thickened fluids to help infants produce a safe swallow.

Alternatives to Thickened Fluids for Infants

While clinicians acknowledge that thickened fluids are a popular recommendation for infants experiencing feeding difficulties due to either dysphagia or reflux, we do not know the exact physiologic change that results in improved feeding performance (Gosa et al., 2011). The current hypothesis regarding improved feeding performance with thickened fluid use centers around the slowed oral transit and the increased cohesiveness of the bolus during the pharyngeal phase that are present when swallowing thickened fluids (Steele et al., 2014). Considering the potential for harm to the developing gut, it would be beneficial for clinicians to determine alternative means to achieve the same, desirable improvements in oral feeding performance without the use of thickened fluids. Side lying positioning for bottle-feeding and the use of slower flowing bottle-nipple systems have garnered recent attention in the literature as viable alternatives to thickened fluids for improving oral feeding performance.

In recent investigations, there have been reports of improved feeding outcomes with the use of a side lying feeding position as opposed to the traditional cradle hold that is typically employed for bottle-feeding. Most of the literature reports improved oxygen saturations during feeding when in the side lying position. Clark, Kennedy, Pring, and Hird (2007) found that a semi-upright elevated side-lying bottle feeding position provided greater physiological stability for their small number of preterm participants (n=6). Thoyre, Holditch-Davis, Schwartz, Roman, and Nix (2012) reported on a coregulated approach, that included side lying as a component of the total program, to feeding preterm infants and found that the coregulated approach resulted in less oxygen saturation variability, less heart rate fluctuation, better fluid management, and reduced work of breathing during the feeding as compared to a standard feeding approach for preterm infants. Park, Thoyre, Knafl, Hodges, and Nix (2014) also reported a trend for better regulation of breathing during feeding when in a side lying position. In contrast, Dawson and colleagues (2013) reported little difference in infants' physiologic stability compared during cradle hold and side lying bottle-feeding positions.

Slowing the flow of fluid boluses is another alternative to thickened fluids to improve oral feeding performance in infants with difficulty coordinating sucking, swallowing, and breathing. Unfortunately, there is not a current, standard definition of what constitutes a "slow" or a "fast" flow rate in an artificial nipple. Jackman (2013) investigated a number of different disposable (hospital) and commercially available bottle and nipple systems to determine their objective flow rate. She tested all of the bottle and nipple combinations with a Medela classic hospital grade pump that provided only suction, no compression. The suction was set to 150 mm Hg and each bottle was held at a 20-degree angle. The volume of liquid (water) in milliliters transferred from each nipple tested to the collection unit within one minute was recorded and each bottle nipple system was tested three times with resulting average milliliters per minute calculations. The results of her study provided us with the following information:

1. Disposable (hospital) nipples have greater variability in flow rate measurements due to the imprecise nature with which they are constructed.
2. Several commercially available nipples have slower flow rates than disposable (hospital) nipples.
3. First Years Breast Flow bottle and nipple system appears to have the slowest flow rate of all the systems tested.

The results of the Jackman (2013) study further illustrate for clinicians the lack of standardization among descriptors (such as slow-flowing) among different bottle and nipple systems. Speech-language pathologists must be aware of the need for close follow-up for at-risk

infants when they are discharged from the hospital and transitioned to a commercially available bottle-nipple system (Dodrill, 2011).

Conclusions

The neonatal gut has underdeveloped mucosa, vascular supply, and immunologic functioning. These neonatal gut characteristics put infant patients, particularly those born prematurely, at risk for developing NEC from a variety of causes. Clinically, an increased risk for developing NEC has been established for neonates that have a thickening agent added to their nutritional fluid intake. While a definitive relationship between thickening agents and NEC has not been established, the potential risk is sufficient to influence clinical practice. Clinicians need to consider the use of side lying positioning for bottle feeding and slower flowing bottle-nipple systems to encourage safe oral feeding when effective at compensating for dysphagia in young patients.

References

Abrams, S. A. (2011). Be cautious in using thickening agents for preemies. *AAP News, 32*(7), 23–23.

Beal, J., Silverman, B., Bellant, J., Young, T. E., & Klontz, K. (2012). Late onset necrotizing enterocolotis in infants following use of a xanthan gum-containing thickening agent. *The Journal of Pediatrics, 161,* 354–356.

Berman, L., & Moss, R. L. (2011). Necrotizing enterocolitis: An update. *Seminars in Fetal & Neonatal Medicine, 16,* 145–150.

Clark, L., Kennedy, G., Pring, T., & Hird, M. (2007). Improving bottle feeding in preterm infants: Investigating the elevated side-lying position. *Infant, 3*(4), 354–358.

Clarke, P., & Robinson, M. (2004). Thickening milk feeds may cause necrotizing enterocolitis. *Archives of Disease in Childhood Fetal and Neonatal Edition, 89*(3), F280.

Dawson, J. A., Myers, L. R., Moorhead, A., Jacobs, S. E., Ong, K., Salo, F., . . . Davis, P. G. (2013). A randomised trial of two techniques for bottle feeding preterm infants. *Journal of paediatrics and child health, 49*(6), 462–466.

Dodrill, P., Donovan, T., Cleghorn, G., McMahon, S., & Davies, P. S. W. (2008). Attainment of early feeding milestones in preterm neonates. *Journal of Perinatology, 28*(8), 549–555.

Dodrill, P. (2011). Feeding difficulties in preterm infants. *ICAN: Infant, Child, & Adolescent Nutrition, 3*(6), 324–331.

Drenckpohl, D., Knaub, L., Schneider, C., McConell, C., Wang, H., & Macwan, K. (2010). Risk factors that may predispose premature infants to increased incidence of necrotizing enterocolotis. *ICAN: Infant Child and Adolescent Nutrition, 2,* 37–44.

Gosa, M., Schooling, T., & Coleman, J. (2011). Thickened liquids as a treatment for children with dysphagia and associated adverse effects: A systematic review. *ICAN: Infant, Child, & Adolescent Nutrition, 3*(6), 344–350.

Horvath, A., Dziechciarz, P., & Szajewska, H. (2008). The effect of thickened-feed interventions on gastroesophageal reflux in infants: systematic review and meta analysis of randomized, controlled trials. *Pediatrics, 122*(6), e1268–e1277.

Jackman, K. T. (2013). Go with the flow: Choosing a feeding system for infants in the neonatal intensive care unit and beyond based on flow performance. *Newborn and Infant Nursing Reviews, 13*(1), 31–34.

Kovesi, T., & Rubin, S. (2004). Long-term complications of congenital esophageal atresia and/or tracheoesophageal fistula. *Chest, 126,* 915–925.

Kreissl, A., Zwiauer, V., Repa, A., Binder, C., Haninger, N., Jilma, B., . . . Haiden, N. (2013). Effect of Fortifiers and Additional Protein on the Osmolarity of Human Milk: Is it Still Safe for the Premature Infant? *Journal of Pediatric Gastroenterology and Nutrition, 57*(4), 432–437.

Lin, P. W., Nasr, T. R., & Stoll, B. J. (2008, April). Necrotizing enterocolitis: recent scientific advances in pathophysiology and prevention. In *Seminars in Perinatology, 32*(2), 70–82. WB Saunders.

Neu, J., & Walker, W. A. (2011). Necrotizing Enterocolitis. *New England Journal of Medicine, 363,* 255–264.

Panigrahi, P. (2006). Necrotizing Enterocolitis. *Pediatric Drugs, 8*(3), 151–165.

Park, J., Thoyre, S., Knafl, G. J., Hodges, E. A., & Nix, W. B. (2014). Efficacy of Semielevated Side-Lying Positioning During Bottle-Feeding of Very Preterm Infants: A Pilot Study. *The journal of perinatal & neonatal nursing, 28*(1), 69–79.

Pearson, F., Johnson, M. J., & Leaf, A. A. (2013). Milk osmolality: Does it matter? *Arch Dis Child Fetal Neonatal Ed, 98,* F166–F169.

Steele, C. M., Alsanei, W. A., Ayanikalath, S., Barbon, C. E., Chen, J., Cichero, J. A., . . . Wang, H. (2014). The influence of food texture and liquid consistency modification on swallowing physiology and function: A systematic review. *Dysphagia, 30*(1), 1–25.

Thoyre, S. M., Holditch-Davis, D., Schwartz, T. A., Roman, C. R. M., & Nix, W. (2012). Coregulated approach to feeding preterm infants with lung disease: effects during feeding. *Nursing research, 61*(4), 242–251.

Tutor, J. D., & Gosa, M. M. (2012). Dysphagia and aspiration in children. *Pediatric pulmonology, 47*(4), 321–337.

U.S. Food and Drug Administration. (2012). *Consumer updates: FDA expands caution about SimplyThick*. Retrieved from http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm256250.htm

Vandenplas, Y., Rudolph, C. D., Di Lorenzo, C., Hassall, E., Liptak, G., Mazur, L., . . . Wenzl, T. G. (2009). Pediatric gastroesophageal reflux clinical practice guidelines: Joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *Journal of pediatric gastroenterology and nutrition, 49*(4), 498–547.

Yee, W. H., Soraisham, A. S., Shah, V. S., Aziz, K., Yoon, W., & Lee, S. K. (2012). Incidence and timing of presentation of necrotizing enterocolitis in preterm infants. *Pediatrics, 129*(2), e298–e304.

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