

Academy of Breastfeeding Medicine Annotated Bibliography

“ALLERGIC COLITIS IN THE EXCLUSIVELY BREASTFED INFANT”

INTRODUCTION

This scientific literature review encompasses articles written in English and published between 1980 and 2010 relevant to the scientific basis, pathologic aspects, and clinical management of allergic proctocolitis in the breastfed infant. Articles investigating the influence of breastfeeding on maternal transmission of allergic susceptibility to children, or later development of the range of allergic conditions, were not reviewed here. Efforts were made to review studies with primary focus on intestinal allergy in breastfed infants. In some instances, separation for mode of feeding was not performed and studies listed include data on non-breastfed infants. A total of 54 peer-reviewed scientific papers were identified as being relevant to this subject matter and are included in this document.

Citation	Comment	**Level of Evidence
Studies characterizing the clinical course, laboratory and pathologic findings, and response to treatment of infants with allergic proctocolitis		
Szajewska H, Gawronska A, Banaszkiwicz A, Grzybowska-Chlebowczyk U. Lack of effect of Lactobacillus GG (LGG) in breast-fed infants with rectal bleeding: a pilot double-blind randomized controlled trial. <i>J Pediatr Gastroenterol Nutr</i> 2007;45:247-251.	Prospective double-blind study of 26 breastfeeding infants, <6 months of age, with rectal bleeding randomized to receive twice daily LGG or placebo as an adjunct to cow's milk restriction in the mother's diet. No differences in: mean duration of rectal bleeding; resolution of bleeding within 72 hours with no relapse afterwards; or resolution of bleeding within 72 hours followed by relapse of symptoms. Breastfeeding cessation was not needed in any infant. Results do not support use of LGG as adjunct to maternal cow's milk restriction in breastfed infants with rectal bleeding.	I

<p>Arvola T, Ruuska T, Keranen J, et al. Rectal bleeding in infancy: clinical, allergological, and microbiological examination. <i>Pediatrics</i> 2006;117:e760-e768.</p>	<p>Prospective randomized study evaluating the clinical course, response to cow's milk- elimination diet, and the presence of GI pathogens in 40 infants with rectal bleeding. Most of the infants (68%) were fully breastfed. 64 healthy infants served as controls. Infants with rectal bleeding were randomized to receive cow's milk elimination diet or continue previous diet for one month. 32 (80%) infants manifested bloody stools during follow-up and a cow's milk-elimination diet did not affect the duration of rectal bleeding. Cow's milk allergy was diagnosed in 7 (18%) patients. Virus particles were present in feces in only a minority of the patients and all fecal cultures were negative for Salmonella, Shigella, and Yersinia. These findings suggest that in the majority of infants with rectal bleeding the cause of the condition remains unknown. Authors suggest that dietary challenge is essential to reduce the number of false-positive cow's milk-allergy diagnoses.</p>	I
<p>Xanthakos SA, Schwimmer JB, Melin-Aldana H, et al. Prevalence and outcome of allergic colitis in healthy infants with rectal bleeding: a prospective cohort study. <i>J Pediatr Gastroenterol Nutr.</i> 2005;41:16-22.</p>	<p>The hypothesis that allergic colitis is over-diagnosed in healthy infants with rectal bleeding was tested. The authors also investigated whether rectal bleeding in infants without allergic colitis would resolve without diet change. 22 infants with rectal bleeding underwent flexible sigmoidoscopy and allergic colitis defined by histological criteria. Formula or maternal diet was changed only for those meeting histologic criteria of allergic colitis. 14 of 22 (64%) infants with rectal bleeding had allergic colitis. Five (23%) had normal biopsies and three (14%) had nonspecific colitis. Rectal bleeding in most infants with normal biopsies or nonspecific colitis resolved without diet change. Authors concluded that a significant proportion of infants with rectal bleeding may not have allergic colitis and may undergo unnecessary, expensive formula or maternal diet changes that may discourage breastfeeding</p>	II-2
<p>Maayan-Metzger A, Ghanem N, Mazkereth R, Kuint J. Characteristics of neonates with isolated rectal bleeding. <i>Arch Dis Child Fetal Neonatal Ed</i> 2004;89:F68-F70.</p>	<p>A retrospective study of 147 cases (83 full term and near term infants and 64 preterm infants) and 147 controls to determine the characteristics of neonates with isolated rectal bleeding (IRB). A feeding regimen that did not include breastmilk was the only variable found to predict IRB. In full term and near term babies (GA \geq 35 weeks), 52.6% of the study group were breastfed compared with 83.1% of the controls ($p < 0.0001$). In preterm babies (GA \leq 34 weeks), 45.9% of the study group were breastfed compared with 74.2% of the controls ($p = 0.0014$). No obvious systemic infection cause was detected. This study emphasizes that isolated rectal bleeding can occur in formula-fed infants, and breastfeeding, even if only partial, should be encouraged.</p>	II-2

<p>Chang JW, Wu TC, Wang KS, Huang IF, Huang B, Yu IT. Colon mucosal pathology in infants under three months of age with diarrhea disorders. <i>J Pediatr Gastroenterol Nutr.</i> 2002;35:387-390.</p>	<p>Retrospective analysis of 64 infants initially diagnosed with unknown diarrheal disorder that had undergone fiber optic sigmoidoscopy with mucosal biopsy. Pathologic findings were analyzed. 40 (62.5%) had eosinophilic colitis (EC), 19 (29.7%) had nonspecific colitis, and biopsies were normal in 5 cases. Patients were then divided into 2 groups based on the presence or lack of eosinophilic colitis and laboratory markers were studied. Patients with EC were more likely to have elevated total eosinophil counts and eosinophils in their stool smear.</p>	<p>II-2</p>
<p>Kumagai H, Masuda T, Maisawa S, Chida S. Apoptotic epithelial cells in biopsy specimens from infants with streaked rectal bleeding. <i>J.Pediatr.Gastroenterol.Nutr.</i> 2001;32:428-433.</p>	<p>19 infants with isolated rectal bleeding were compared to 6 age-matched control infants. Rectosigmoidal mucosal biopsies were performed and examined by immunohistochemistry. Infants with rectal bleeding showed nodular lymphoid hyperplasia (n = 16), abundant eosinophils (>20/high power field, n = 14) in the mucosa, and a significantly high number of apoptotic epithelial cells relative to the control group. Rectal bleeding stopped in 14/18 infants who were fed a different milk formula or breastfed (their mothers were restricted from having cow's milk or eggs). The authors suggest the higher number of apoptotic epithelial cells in infants with streaked rectal bleeding is probably caused by accelerated epithelial cell turnover.</p>	<p>II-2</p>
<p>D'Netto MA, Herson VC, Hussain N, et al. Allergic gastroenteropathy in preterm infants. <i>J Pediatr</i> 2000;137:480-486.</p>	<p>25 preterm infants with biopsy evidence of allergic gastroenteropathy (AGE) were identified (12 retrospective review/13 prospective). 13 of 25 patients initially received human milk and 2 patients were exclusively fed human milk. Clinical patterns of presentation were gastroesophageal reflux disease (group 1, n = 5); non-specific feeding intolerance (group 2, n = 8); and lower gastrointestinal bleeding (group3, n = 12). 10 patients with clinical features indistinguishable from those of groups 1 and 2 had negative biopsies, while all with lower GI bleeding had positive biopsies (12 of 12). This study demonstrated that preterm infants may develop a variety of symptoms associated with AGE however lower GI bleeding in an otherwise well appearing infant was highly predictive for the condition.</p>	<p>II-2</p>

<p>Lake AM. Food-induced eosinophilic proctocolitis. <i>J Pediatr Gastroenterol Nutr.</i> 2000;30 Suppl:S58-S60.</p>	<p>Personal experience/review of 95 exclusively breastfed infants with food-induced eosinophilic proctitis. Typically presents at 2 to 8 weeks of age with blood-tinged stools (age range 2 days to 3 months). The infant is generally well appearing and most are exclusively breastfed. Elimination of the offending protein through use of an extensively hydrolyzed casein-based formula or the elimination of the protein from the diet of the breastfeeding mother, leads to clinical resolution of the bleeding within 72 to 96 hours. It is rare that more than one protein is implicated. 10 infants in whom no specific dietary protein could be identified continued to breastfeed and 11 infants whose mothers could not maintain a restricted diet were followed for intermittent bleeding. 6 infants became mildly anemic yet were not reported as requiring intervention. All infants tolerated an unrestricted diet at one year of age. Of 35 infants observed for more than 10 years, none have developed chronic inflammatory bowel disease.</p>	<p>II-2/III</p>
<p>Lake AM. Dietary protein enterocolitis. <i>Immunol and Allergy Clinics of North America.</i> 1999;19:553-561.</p>	<p>By process of elimination and re-challenge with maternal dietary proteins cow's milk is the offending antigen in more than 50% of cases. In a 16-year experience in 95 breastfed infants with proctitis, the implicated protein was cow's milk in 62 infants, egg in 18, corn in 6, and soy in 3, with multiple antigens in only 5.</p>	<p>II-2/III</p>
<p>Machida HM, Catto Smith AG, Gall DG. Allergic colitis in infancy: clinical and pathologic aspects. <i>J Pediatr Gastroenterol Nutr.</i> 1994;19:22-26.</p>	<p>Prospective study evaluating 35 infants with fresh blood mixed with stools. All infants were otherwise well appearing. Limited colonoscopy and biopsy was performed in 34 infants. 31 were found to have histopathologic colitis and results were compared to biopsies of 19 controls. Of the 31 infants with colitis, 10 were receiving solely breastmilk and 2 breastmilk with cow's milk supplementation. The mean number of eosinophils per high-power field was greater in the patients with colitis than controls. Eosinophil counts of >20/HPF were seen in all infants with colitis but none of controls. Patients with colitis also had lower mean hemoglobin levels and elevated mean peripheral eosinophil counts; however this was poorly predictive in the individual patient. A low serum albumin was found to predict histologic colitis in 81% of patients. Infants with low serum albumin or hemoglobin had formula change recommended. 19 infants had rapid resolution of frank bleeding and gradual correction of serum albumin with dietary change. The mothers of 7 breastfed infants with normal hemoglobin levels restricted milk products from their diet and all had either immediate or gradual resolution of bleeding.</p>	<p>II-2</p>

<p>Odze RD, Bines J, Leichtner AM et al. Allergic proctocolitis in infants: a prospective clinicopathologic biopsy study. <i>Hum Pathol</i> 1993;24:668-674.</p>	<p>Colonic biopsy specimens from the same sites (4, 8, and 12 cm from the anal verge) in 20 infants with clinically confirmed allergic proctocolitis were examined. 10 out of 20 patients were receiving exclusive breastmilk or combination with formula. The major histologic finding was a focal increase in the number of eosinophils, however eosinophilic infiltration varied at different sites and within individual biopsy specimens. 12 of 20 patients had all three of their biopsy specimens categorized as abnormal, 4 patients had two abnormal biopsy specimens, and 4 had one abnormal biopsy specimen. Given the focal distribution of the eosinophils, multiple mucosal biopsy specimens should be obtained at several levels.</p>	<p>II-2</p>
<p>Glassman MS, Newman LJ, Berezin S, Gryboski D. Cow's milk protein sensitivity during infancy in patients with inflammatory bowel disease. <i>Am J Gastroenterol</i> 1990;85:838-840.</p>	<p>Seventy-eight patients with inflammatory bowel disease (35 with Crohn's disease and 43 with UC) and a control population of 36 children were surveyed to determine the frequency of symptoms compatible with cow's milk-protein sensitivity. The incidence of a history compatible with cow's milk sensitivity was 8.5% (3/35) in patients with Crohn's disease and 2.8% (1/36) in controls. Patients with ulcerative colitis had a significantly greater prevalence of symptoms, compared with the other patient groups (20.9%, 9/43; $p < 0.03$). In addition, patients with a history of cow's milk allergy, who subsequently developed ulcerative colitis, did so at an earlier age (6.68 +/- 2.05 yr vs. 10.62 +/- 0.74 yr: $p < 0.02$) than those without a history of cow's milk sensitivity. There was no significant difference among patient groups in respect to the number of exclusively breastfed infants and separation of allergic symptoms while breastfeeding was not occurring.</p>	<p>II-2</p>
<p>Host A, Halken S. A prospective study of cow milk allergy in Danish infants during the first 3 years of life. Clinical course in relation to clinical and immunological type of hypersensitivity reaction. <i>Allergy</i> 1990;45:587-596.</p>	<p>This study followed 1749 newborns to describe the clinical course of infants with cow's milk allergy (CMA). Reported infants included those receiving cow's milk based formula and/or breast milk. From this study population, the incidence of CMA in exclusively breastfed infants was previously reported (Host A et al. 1988. <i>Acta Paediatr Scand</i> 77:663-670). Overall incidence 2.2%. Of these, symptoms included cutaneous, gastrointestinal (colic, vomiting, diarrhea, failure to thrive) or respiratory symptoms. 21/39 were classified as IgE-mediated and 87% tolerated food challenge by 3 years of age. Given the lack of separation for infants receiving only breast milk and the absence of bloody diarrhea as presenting symptom, the findings of this study may not be applicable to the exclusively breastfed infant with practicalities.</p>	<p>II-2</p>

<p>Winter HS, Antonioli DA, Fukagawa N et al. Allergy-related proctocolitis in infants: diagnostic usefulness of rectal biopsy. <i>Mod. Pathol.</i> 1990;3:5-10.</p>	<p>The diagnostic usefulness of rectal biopsy was evaluated in infants with allergic proctocolitis. Histologic features and clinical information were compared between an allergy group (N=36), non-allergic inflammatory group (N=8), and controls (N=12). Infants in the allergic group were noted to have significantly higher peripheral eosinophil counts. Rectal biopsies in the allergic group more often had >60 eosinophils/10 HPF, eosinophils in crypt abscesses, and eosinophils in the muscularis mucosae. Peripheral eosinophil counts did not directly correlate with histologic findings. Thus, rectal biopsy in tandem with available clinical information may be helpful to diagnose allergic proctocolitis.</p>	<p>II-2</p>
<p>Host A, Husby S, Osterballe O. A prospective study of cow's milk allergy in exclusively breastfed infants. Incidence, pathogenetic role of early inadvertent exposure to cow's milk formula, and characterization of bovine milk protein in human milk. <i>Acta Paediatr Scand</i> 1988;77:663-670.</p>	<p>Cohort study following 1749 newborns prospectively for the development of cow's milk allergy (CMA) during 1st year of life. 39 (2.2%) fulfilled criteria for CMA. 17 out of 39 developed symptoms while breastfeeding and 9 of these were solely breastfed at time of diagnosis giving one year incidence of CMA in exclusively breastfed infants of 0.5%. All cases occurred prior to 3 months. Review of records indicated that all 9 infants (solely breastfed) were exposed to cow's milk formula during the first 3 days of life. B-lactoglobulin was detectable in the milk from 3 of these 9 cases. This study demonstrated the overall incidence of CMA in breastfed infants, however is complicated by the fact that all infants were exposed to varying amounts of cow's milk formula during infancy. In addition varying symptoms of allergy were recorded but did not specify bloody diarrhea or colitis.</p>	<p>II-2</p>
<p>Bock SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. <i>Pediatrics</i> 1987;79:683-688.</p>	<p>Prospective study examining the natural history of adverse reactions to food in 480 children from birth to their third birthdays. Number of infants receiving exclusive breast milk was not specified and gastrointestinal symptoms did not include bloody diarrhea. Therefore, findings may not be applicable to breastfeeding infants with proctocolitis. Nonetheless, the natural course of allergic responses to foods during early childhood is well described. The initial complaints occurred during the first year of life in 80%. The majority of foods were tolerated within 9 months of their incrimination. This study showed that most food reactions occur during the first year of life, but rechallenge at regular intervals has shown that the food can be reintroduced into the diet by the third year without risk. Almost all reactions that were reproduced were non-IgE mediated.</p>	<p>II-2</p>

<p>Dupont C, Badoual J, Le Luyer B, et al. Rectosigmoidoscopic findings during isolated rectal bleeding in the neonate. <i>J Pediatr Gastroenterol Nutr.</i> 1987;6:257-264.</p>	<p>This study describes a group of 34 infants under 1 1/2 months of age presenting with unexplained isolated rectal bleeding. 11 (32%) were reported as breastfeeding and 12 (35%) receiving pooled human bank milk. Rectosigmoidoscopy findings are reported. Biopsies were performed in only eight patients. Tissue eosinophilia was not reported as a common finding. In most cases, stool samples were negative for pathogens. Clinical analysis revealed that breastfed infants who continued to breastfeed on an unrestricted maternal diet had the longest duration of rectal bleeding. Authors conclude that hemorrhagic colitis of infancy is a heterogeneous group with dietary protein accounting for some cases.</p>	<p>II-2</p>
<p>Goldman H, Proujansky R. Allergic proctitis and gastroenteritis in children. Clinical and mucosal biopsy features in 53 cases. <i>Am J Surg Pathol</i> 1986;10:75-86.</p>	<p>53 cases of allergic disorders of the gastrointestinal tract in children were reviewed, including 15 with principal effects in the rectum (allergic proctitis) and 38 with dominant involvement of the upper and mid portions of the gut (allergic gastroenteritis). Mode of feeding (breast vs. formula) was not specified. Most cases of allergic proctitis had their onset at less than 6 months of age, and all were under 2 years old when they presented with rectal bleeding alone or in combination with diarrhea. Peripheral eosinophilia occurred in 50% and 43% had elevated serum IgE levels. Rectal mucosal biopsy revealed in most cases a diffuse increase of eosinophils in the lamina propria together with a focal infiltration of the epithelium by eosinophils. All cases of proctitis responded to a dietary change by cessation of symptoms without recurrences. Probable antigens were cow's milk protein in 9, soy in 5, and unknown in the remaining. Cases of allergic gastroenteritis affected more varied age groups and had a lower frequency of overt rectal bleeding. More common were other symptoms (vomiting, pain, and weight loss), an allergic history, anemia, blood eosinophilia, and increased serum IgE.</p>	<p>II-2</p>
<p>Boyce JA, Assa'ad A, Burks AW et al. Guidelines for the Diagnosis and Management of Food Allergy in the United States: Summary of the NIAID-Sponsored Expert Panel Report. <i>Nutr Res</i> 2011 January;31(1):61-75.</p>	<p>The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, working with more than 30 professional organizations, federal agencies, and patient advocacy groups, led the development of "best practice" clinical guidelines for the diagnosis and management of FA. Based on a comprehensive review and objective evaluation of the recent scientific and clinical literature on FA, the Guidelines focus on diseases that are defined as FA and include both immunoglobulin E (IgE)-mediated reactions to food and some non-IgE-mediated reactions to food.</p>	<p>III</p>

<p>Yasunori K, Takahashi N, Yada Y, et al. Selectively high level of serum interleukin 5 in a newborn infant with cow's milk allergy. <i>Pediatrics</i> 2011;127(1):e231-e234.</p>	<p>This is a case report of a term newborn with hematochezia 36 hours after first feeding with cow's milk formula. Serum IgE was not elevated although eosinophils were detected in stool. Elimination of cow's milk formula resolved symptoms, and baby was diagnosed with cow's milk allergy. The baby's serum interleukin 5 (IL-5) was selectively elevated while other proinflammatory cytokines were within normal limits. IL-5 is thought to play a role in recruiting eosinophils from the bone marrow to sites of inflammation. The role of IL-5 in allergic proctocolitis of the exclusively breastfed infant has not been studied.</p>	<p>III</p>
<p>Lake AM. Food protein-induced proctitis, enteropathy and enterocolitis of infancy. In: <i>UpToDate</i>, Basow, DS (Ed), Waltham, MA, March 2010.</p>	<p>This paper is a topic review of the clinical manifestations and diagnosis of food protein-induced proctitis/colitis, enteropathy and enterocolitis. Results of a number of different studies are presented which show that in symptomatic breastfed infants, 65% due to maternal ingestion of cow's milk; 19% egg; 6% corn; 3% soy; remaining 12% only improved after weaning to extensively hydrolyzed or amino acid-based formula. Clinically babies generally well-appearing, "except for the bloody diarrhea". Diagnosis generally made by withdrawal of the protein. Continued breastfeeding with successful elimination is recommended. Food protein-induced enterocolitis syndrome is significantly more serious, with the baby sicker, with bloody diarrhea. Other proteins may be triggers. In the acute phase the baby may present as if with sepsis, metabolic disorder, surgical abdomen or anaphylaxis. It is extremely rare in breastfed infants and if mother chooses to continue breastfeeding, she must be able to comply with a diet strictly eliminating the causal proteins. A lapse could cause severe recurrence in the child. Amino acid formulas are used. Challenges must be very carefully monitored, but most children are able to tolerate the casual protein by 1-2 years.</p>	<p>III</p>
<p>Brill H. Approach to milk protein allergy in infants. <i>Can Fam Physician</i> 2008;54:1258-64</p>	<p>This paper provides a practical, evidence-based approach to the diagnosis and management of milk protein allergy in infants. MEDLINE was searched from 1950 to March 2008 using the heading <i>milk hypersensitivity</i>. Evidence was designated as levels I, II, and III. Milk protein allergy is a recognized problem in the first year of life; cow's milk protein allergy is the most common such allergy. Diagnosis is suspected on history alone, with laboratory evaluations playing a supporting role. Confirmation requires elimination and reintroduction of the suspected allergen. Management includes diet modification for nursing mothers and hydrolyzed formulas for formula-fed infants. Assessing the underlying immunopathology can aid in determining prognosis. The therapeutic model presented allows rapid assessment of the presence of allergy, timely management, and surveillance for recurrence of symptoms. Breastfeeding can be continued with attentive diet modification by motivated mothers.</p>	<p>III</p>

<p>Kondo M, Fuko T, OmoyaK, et al. Protein-losing enteropathy associated with egg allergy in a 5-month-old boy. <i>J Investig Allergol Clin Immunol</i> 2008; Vol. 18(1): 63-66</p>	<p>A 5-month-old breastfed boy presented severe PLE with hypogammaglobulinemia, hypocalcemia, and hypomagnesemia induced by an egg allergy. He developed hypocalcemic convulsions. The diagnosis of PLE was confirmed by elevated fecal α1-antitrypsin clearance and a positive finding on a protein-losing scintigram. His allergy to egg delivered through maternal milk was confirmed as the cause of PLE, since the mother's elimination of egg from her diet improved his condition and maternal egg challenge provoked symptoms of diarrhea, occult bleeding, vomiting, and elevated α1-antitrypsin clearance. At the time of writing, he is 22 months old and has experienced no further episodes after the elimination of egg-containing food.</p>	<p>III</p>
<p>Hwang J, Park MH, Kang YN, et al. Advanced criteria for clinicopathological diagnosis of food protein-induced proctocolitis. <i>J Korean Med Sci</i> 2007;22:213-217.</p>	<p>38 babies with a diagnosis of food protein-induced proctocolitis (FPIPC) (95% exclusively breastfed) who underwent sigmoidoscopy and biopsy, were studied. Diagnosis of FPIPC made clinically: red rectal bleeding; no other cause for bleeding; disappearance of bleeding with change of (mothers') diet. Endoscopic abnormalities seen in all patients. Nodular hyperplasia with circumscribed and/or central pit-like erosions in 94.7% (this may be specific endoscopic findings in these patients); lymphoid aggregates in 94.7%; eosinophils in lamina propria of ≥ 60 cells/10 HPF in 97.4% and epithelial or muscularis mucosa eosinophilic infiltration in 97.4% of patients</p>	<p>III</p>
<p>Vandenplas Y, Brueton M, Dupont C, et al. Guidelines for the diagnosis and management of cow's milk protein allergy in infants. <i>Arch Dis Child</i> 2007;92:902-908</p>	<p>This paper reviews known information (expert discussion, clinical experience and evidence from the literature with national standards and recommendations from Germany, the Netherlands and Finland) on cow's milk protein allergy in infants, and develops guidelines for the diagnosis and management of CMPA with separate algorithms for exclusively breastfed infants, and formula fed infants. Recommendations include importance of history and physical exam, referral of patients with severe symptoms to a specialist, elimination of CMP from mother's and/or infant's diet.</p>	<p>III</p>
<p>Sierra S, Alonso CB, Sanchez JO, et al. Allergic colitis in exclusively breast-fed infants. <i>Anales de Pediatría</i> 2006;64(2):158-161.</p>	<p>Retrospective study of 13 exclusively breastfed infants diagnosed with allergic colitis. All presented with GI symptoms (12 with mucous and bloody stools); onset at 1-3 months in 77%; biopsies showed acute inflammation with an increase in eosinophils. Initial treatment was exclusion of cow's milk protein in maternal diet; 10/13 showed no improvement, requiring exclusive protein-free hydrolyzate.</p>	<p>III</p>

<p>Muraro A, Dreborg S, Halcken S et al. Dietary prevention of allergic diseases in infants and small children. Part III: Critical review of published peer-reviewed observational and interventional studies and final recommendations. <i>Pediatr Allergy Immunol</i> 2004 August;15(4):291-307.</p>	<p>An analysis of published peer-reviewed observational and interventional studies was performed following the statements of evidence as defined by WHO. The results of the analysis indicate that breastfeeding is highly recommended for all infants irrespective of atopic heredity. A dietary regimen is unequivocally effective in the prevention of allergic diseases in high-risk children. In these patients breastfeeding combined with avoidance of solid food and cow's milk for at least 4-6 months is the most effective preventive regimen. In the absence of breast milk, formulas with documented reduced allergenicity for at least 4-6 months should be used.</p>	<p>III</p>
<p>Sampson HA. Update on food allergy. <i>J Allergy Clin Immunol</i> 2004;113:805-819.</p>	<p>Food protein-induced proctocolitis is another of the eosinophilic gastrointestinal disorders but appears to involve a non-IgE mediated mechanism. Infants typically appear healthy and grow well but are identified because of gross or microscopic blood in the stool.</p>	<p>III</p>
<p>Walker WA. The dynamic effects of breastfeeding on intestinal development and host defense. <i>Adv Exp Med Biol.</i> 2004;554:155-70</p>	<p>Evidence is provided to support the hypothesis that human milk provides a link between the mother and her newborn infant in the extrauterine environment in a manner similar to the placental link between mother and fetus in utero. In addition, breastfeeding helps prevent age-related diseases affecting the gastrointestinal tract during the newborn period. Anecdotal clinical studies are cited to suggest that human milk contains factors that may be missing in inherited diseases of inborn errors in metabolism and provide passive protective factors that lessen the expression of neonatal allergic and infectious diseases. In some instances, by providing the missing factor in an inherited disease, the newborn may be protected from serious damage to its developing brain. A second line of evidence to support this hypothesis is the observation that the composition of human milk varies with the infant's needs. Using observations from the laboratory that define the immaturities in neonatal and premature human intestinal defenses as the neonate's host defense deficiency, the specific effect that anti-inflammatory and maturational factors in human milk has on these immaturities is discussed. The active stimulus of maternal milk on the rapid development of host defenses is underscored.</p>	<p>III</p>
<p>Sampson HA. Food allergy. <i>J Allergy Clin Immuno.</i> 2003;111:S540-S547.</p>	<p>Food protein-induced proctocolitis: cell mediated, gross or occult blood in stool, typically thriving, usually seen in first few months. Skin prick test results negative, elimination of food protein leads to clearing of most bleeding in 72h, positive or negative results of endoscopy and biopsy, challenge induces bleeding within 72h.</p>	<p>III</p>

Schach B, Haight M. Colic and food allergy in the breastfed infant: Is it possible for an exclusively breastfed infant to suffer from food allergy? <i>J Hum Lact</i> 2002;18(1):50-52.	A brief discussion of etiologies of "colic" in newborns/infants with conclusion that sometimes this complex can be caused by allergy to protein in mother's milk. Common allergens that produce colicky behavior in infants include proteins from cow's milk, peanuts, eggs, soy, wheat, tree nuts, and strawberries. In many infants, symptoms of colic will resolve within 48 to 72 hours of the start of a maternal elimination diet, however blood in the stool may continue. In this study, 16 breastfeeding mothers were treated with Pancrease® in addition to elimination diets, the theory that the pancreatic enzyme would further break down the proteins before they pass from the mother's digestive system and blood to the milk. 13 mothers were able to continue breastfeeding, with resolution of bloody stool and a decrease in symptoms of colic.	III
Pumberger W, Pomberger G, Geissler W. Proctocolitis in breast fed infants: a contribution to differential diagnosis of haematochezia in early childhood. <i>Postgrad Med J</i> 2001;77:252-254.	11 exclusively breastfed infants with rectal bleeding or blood streaked stool were presented. Colonoscopy was performed in 5, revealing benign eosinophilic proctocolitis. Standard treatment was exclusion of cows' milk from the mother's diet, but none replaced breastfeeding with formula. Resolution of visible rectal bleeding took place within 72 to 96 hours. Reintroduction of cows' milk in 8 children after one year did not result in recurrence.	III
Kumar D, Repucci A, Wyatt-Ashmead J, Chelimsky G. Allergic colitis presenting in the first day of life: report of three cases. <i>J Pediatr Gastroenterol Nutr.</i> 2000;31:195-197.	3 full-term infants with allergic colitis presenting within the first 28 hours of life are described. All 3 had histopathologic findings consistent with allergic colitis. The early development of rectal bleeding in these infants suggests in utero sensitization against food antigens.	III
Patenaude Y, Bernard C, Schreiber R, Sinsky AB. Cow's-milk-induced allergic colitis in an exclusively breastfed infant: diagnosed with ultrasound. <i>Pediatr Radiol</i> 2000;30:379-382.	Case report of an exclusively breastfed-8-week-old boy with history of colicky pain and bloody stools. A diagnosis of colitis was strongly suggested by findings on abdominal ultrasound. An infectious colitis was subsequently excluded and rectal biopsy supported the diagnosis of allergic proctocolitis. This study suggests potential role for diagnosing allergic proctocolitis by ultrasound however its efficacy has not yet been evaluated in a controlled trial.	III
Sampson H. Summary of recommendations: classification of GI manifestations due to immunologic reactions to foods in infants and young children <i>J Pediatr Gastro Nutr</i> 2000;30:S87-94.	Dietary protein proctitis: typically occurs in first few months of life, with blood streaked stools in an otherwise healthy-looking infant. Up to 60% seen in breastfed infants. Occasionally produces anemia. Mild hypoalbuminemia and peripheral eosinophilia rarely occur. Bowel lesions confined to distal large bowel. Biopsy reveals infiltration of eosinophils (>20/hpf), lymphoid nodular hyperplasia, and in approximately 20% PMN's also prominent. Elimination of responsible food allergen usually results in resolution of gross bleeding within 72hrs. Some children are sensitive to extensively hydrolyzed infant formulas and require amino acid-derived formulas. Most outgrow their hypersensitivity by 1 year.	III

Bloom DA, Carlo B, Fishman SJ, Furuta G, Nurko S. Allergic colitis: a mimic of Hirschsprung disease. <i>Pediatr Radiol</i> 1999;29:37-41.	Retrospective study describing 4 patients initially suspected for Hirschsprung's disease, however were diagnosed with allergic colitis after undergoing rectosigmoid biopsy. All had ganglion cells and 3/4 had eosinophils infiltrating the lamina propria. This study demonstrated that allergic colitis may at times mimic Hirschsprung's disease.	III
Repucci, A. Resolution of stool blood in breast-fed infants with maternal ingestion of pancreatic enzymes. <i>J Pediatr Gastroent Nutr</i> 1999; 29(4):500A.	The protease component of pancreatic enzyme is postulated to break down offending proteins rendering them less antigenic. Four term EBF infants (ages 1.5-3 mos.) were evaluated for visible/occult stool blood despite maternal dietary restriction of cow-milk/soy protein. Mothers were then prescribed pancreatic enzymes (Pancrease MT 4®, USP Units: 4,000 lipase/12,000 amylase, 12,000 protease) two capsules with meals/one with snacks. In ¾ infants, stool blood resolved within a few days of therapy. One mother required three capsules with meals/two with snacks before stool blood resolved. No side-effects occurred due to therapy	III
Sampson HA. Food allergy. Part 1: immunopathogenesis and clinical disorders. <i>J Allergy Clin Immunol</i> 1999;103:717-728.	Part 1: Review of food allergy: Up to 8% of children less than 3 years of age experience food-induced allergic disorders. Dietary protein proctitis is a non-IgE mediated disorder typically seen in the first few months of life as blood-streaked stools in otherwise healthy looking infants. About 60% of cases are seen in breastfed babies with the remainder largely in infants fed cow's milk or soy protein based formula.	III
Sampson HA. Food allergy. Part 2: diagnosis and management. <i>J Allergy Clin Immunol</i> . 1999;103:981-989.	Part 2: Review of food allergy: When evaluating possible food-induced allergic disorders, it is often useful to categorize disorders into IgE- and non-IgE-mediated syndromes. Once properly diagnosed, strict avoidance of the implicated food or foods is the only proven form of treatment. Clinical tolerance to food allergens will develop in many patients over time, and therefore follow-up food challenges are often indicated.	III
Feiterna-Sperling C, Rammes S, Kewitz G et al. A case for cow's milk allergy in the neonatal period—evidence for intrauterine sensitization? <i>Pediatr Allergy Immunol</i> 1997;8:153-155.	Case report of male term infant with no family history of allergic diseases. Noted bloody meconium at delivery, followed by bloody diarrhea. Mother ingested 1-2 glasses of milk daily during pregnancy. Initial blood tests only revealed eosinophilia; radiologic studies of the abdomen were normal as were all stool cultures. Cow's milk challenge led to more bloody diarrhea. Allergy suspected due to markedly increased total IgE and specific IgE antibodies to cow's milk protein. Infant thrived on breastmilk (mother on minimal dairy intake) and hydrolyzed casein formula. Strongly suggestive of in utero sensitization.	III

<p>Anveden-Hertzberg L, Finkel Y, Sandstedt B, Karpe B. Proctocolitis in exclusively breastfed infants. <i>Eur J Pediatr</i> 1996;155:464-467</p>	<p>Case series of nine exclusively breastfed, full-term infants with mild rectal bleeding due to proctocolitis. The mean age at the onset of symptoms was 5 weeks (range 1-8 weeks). Rectal mucosal biopsy specimens were obtained in eight cases and revealed intra-epithelial eosinophilic granulocytes in seven and a diffuse increase of eosinophils in the lamina propria in six. Allergy to cow's milk protein transferred to the infants via the breast milk was believed to be the cause of the inflammation. The intake of cow's milk protein was then restricted in seven mothers. Following this regimen, symptoms were relieved within 4 weeks in the six infants who were seen at follow up.</p>	<p>III</p>
<p>Odze RD, Wershil BK, Leichtner AM, Antonioli DA. Allergic colitis in infants. <i>J Pediatr</i> 1995;126:163-170.</p>	<p>Comprehensive review of allergic colitis in infants. Authors suggest most practical approach at diagnosis is a positive response to an elimination diet alone. Sigmoidoscopy in conjunction with the evaluation of multiple biopsy specimens may be helpful in confirming the diagnosis, particularly in severe cases and in patients whose condition does not improve after elimination diet.</p>	<p>III</p>
<p>Wilson NW, Self TW, Hamburger RN. Severe cow's milk induced colitis in an exclusively breastfed neonate. Case report and clinical review of cow's milk allergy. <i>Clin Pediatr (Phila)</i> 1990;29:77-80.</p>	<p>A 4-day-old female infant is presented with profuse rectal bleeding resulting in a hematocrit fall from 38% to 30% within 8 hr after hospital admission. Sigmoidoscopy revealed colonic mucosa that was red, edematous, and friable, with punctate hemorrhages. Rectal biopsy showed marked eosinophilic infiltration with multifocal hemorrhage. Further history indicated that while the infant had been exclusively breastfed since birth, the nursing mother had been drinking 4-5 glasses of cow's milk per day since delivery. Prick puncture skin testing of the infant was positive for cow's milk protein. A serum radioallergosorbent test (RAST) for cow's milk protein was positive in the infant but negative in the mother. The infant's serum IgE was also elevated. Rectal bleeding resolved when the patient was given a casein hydrolysate formula. Authors concluded that cow's milk protein passed into breast milk antigenically intact and prenatal sensitization occurred.</p>	<p>III</p>
<p>Lake AM, Whittington PF, Hamilton SR. Dietary protein-induced colitis in breastfed infants. <i>J Pediatr</i> 1982;101:906-910.</p>	<p>Six infants are reported who developed an inflammatory proctocolitis in the first month of life while being exclusively breastfed. All has been born at term and had normal perinatal courses. None had growth failure or constitutional symptoms other than bloody diarrhea. No toxic, bacterial, viral, or parasitic cause was established. Rectal biopsies demonstrated a wide spectrum of acute and chronic inflammatory changes with eosinophilic infiltration being common. All infants responded clinically to initiation of feeding with either hydrolyzed casein or a soy protein-based formula. Breastfeeding was subsequently resumed in five of the six infants; all experienced immediate recurrence of symptoms. Elimination of cow milk protein from the maternal diet led to tolerance of breastfeeding in two infants but there was no change in the other three.</p>	<p>III</p>

Studies looking at maternal factors (pre- or post-natal) that may contribute to the pathogenesis of allergic proctocolitis		
Laitinen K, Arvola T, Moilanen E, et al. Characterization of breast milk received by infants with gross blood in stools. <i>Biol Neonate</i> 2005;87:66-72.	Breast milk samples were collected from mothers of infants with gross blood in stools (n = 23) and from mothers of healthy age-matched infants (n = 71). Samples were analyzed for concentrations of transforming growth factor-beta2, tumor necrosis factor-alpha, interleukin (IL)-4, IL-10, prostaglandin (PG-E2), cysteinyl leukotrienes (Cys-LTs) and fatty acid composition. History of maternal allergy was also included in the analysis to control for its possible confounding effect. Increased concentrations of PGE2 and Cys-LTs in the breast milk together with mother's allergic disease were found to reduce the likelihood of gross blood in stools in the breastfed infant.	II-2
Jarvinen KM, Suomalainen H. Leucocytes in human milk and lymphocyte subsets in cow's milk-allergic infants. <i>Pediatric Allergy and Immunology</i> 2002;13:243-254.	The cellular composition of human milk was evaluated in mothers of 39 infants with diagnosis of cow's milk allergy (CMA), 10 infants with atopic dermatitis without CMA, and 12 healthy infants. The milk of mothers of infants with CMA contained significantly smaller proportions of macrophages and higher proportions of neutrophils than from the mothers of infants without CMA. Eosinophils comprising >1% of milk cells were only detected in the mothers who had infants with CMA. Leukocyte subsets from the peripheral blood of infants were also correlated to populations of breast milk cells from their mothers. The proportions of total B cells and those expressing CD23, (low-affinity immunoglobulin E receptor) were positively correlated with the proportions of neutrophils and eosinophils in mother's milk and negatively with the percentage of milk macrophages. These results suggest deviations in the cellular composition of breast milk may modulate postnatal immune responses and contribute to allergic responses towards dietary antigens, potentially contributing to the development of CMA in breastfed infants.	II-2
Jarvinen KM, Laine ST, Jarvenpaa AL, Suomalainen HK. Does low IgA in human milk predispose the infant to development of cow's milk allergy? <i>Pediatric Research</i> 2000;48:457-462.	This study investigated the relationship between total and cow's milk-specific IgA levels in colostrum and human milk and subsequent development of cow's milk allergy (CMA) in the breastfed infant. Nursing mothers and their infants (age, 2 d to 7 mos) were selected based on genetic risk or by initial symptoms suggestive of CMA. 48 mothers had an infant with CMA, verified by clinical cow's milk challenge, 8 had a baby who had had protracted infantile colic but no CMA and 31 had healthy infants. The levels of total and cow's milk-specific IgA antibodies in colostrum and human milk were significantly lower in the mothers whose baby later developed CMA than in the ones whose infant remained healthy or had had infantile colic but not CMA, suggesting a role in the development of CMA in breastfed infants.	II-2

<p>Szefalusi Z, Loibichler C, Pichler J et al. Direct evidence for transplacental allergen transfer. <i>Pediatr Res</i> 2000;48:404-407.</p>	<p>In this study authors used a double-sided ex vivo placental perfusion model to demonstrate transplacental antigen transfer. Using this model, birch pollen major allergen Bet v1 and the milk allergen beta-lactoglobulin, were shown to cross the placenta. The kinetics of uptake suggested an active transfer mechanism.</p>	<p>II-2</p>
<p>Jarvinen KM, Juntunen-Backman K, Suomalainen H. Relation between weak HLA-DR expression on human breast milk macrophages and cow milk allergy (CMA) in suckling infants. <i>Pediatric Research</i> 1999;45:76-81.</p>	<p>The cellular composition of breast milk and the activation of breast milk macrophages were compared between mothers with a cow's milk-allergic infant and in those with a healthy infant. HLA-DR expression on breast milk macrophages was significantly lower in the mothers whose infant was allergic to cow milk than in the mothers of a healthy infant. There was also a significant difference in the total number of breast milk leukocytes between the mothers with an allergic child and those with a healthy child. These results suggest alterations of breast milk leukocytes in mothers whose infants have cow's milk allergy.</p>	<p>II-2</p>
<p>Szefalusi Z, Nentwich I, Gerstmayr M. Prenatal allergen contact with milk proteins. <i>Clin Exp Allergy</i> 1997;27:28-35.</p>	<p>Cord blood mononuclear cells from 39 neonates were incubated with cow's milk proteins and proliferation and cytokine secretion were assessed. A pronounced proliferation of cells stimulated with cow's milk proteins as opposed to unstimulated cells was found. Results suggest prenatal priming of T cells by allergen contact <i>in utero</i>.</p>	<p>II-2</p>
<p>Jakobsson I. Food antigens in human milk. <i>Eur J Clin Nutr</i> 1991;45 Suppl 1:29-33</p>	<p>Review of literature documenting β-lactoglobulin within human breast milk. Some data is presented showing maximal concentration in breast milk of mothers previously on a cow's milk-free diet 8-12 hrs after ingestion of one glass of cow's milk. Also duration of β-lactoglobulin in breast milk after initiation of cow's milk-free diet.</p>	<p>II-2/III</p>
<p>Machtiger S, Moss R. Cow's milk allergy in breastfed infants: the role of allergen and maternal secretory IgA antibody. <i>J Allergy Clin Immunol</i> 1986;77:341-347.</p>	<p>57 mother-infant pairs were studied to determine correlation between breast milk IgA's, β-lactoglobulin concentration, and atopic symptoms in infants. 11 infants had symptoms suggestive of allergic disease. The breast milk from mothers of these 11 infants was found to have lower total IgA and IgA-specific antibodies to whole cow's milk and casein. β-lactoglobulin was detectable in 45% of breast-milk specimens but was unrelated to antibody levels or allergic symptom scores. Positive family history did not correlate to infant symptoms. Atopic symptoms did not include bloody diarrhea and therefore conclusions may not apply directly to allergic proctocolitis.</p>	<p>II-2</p>

<p>Repucci A. Resolution of stool blood in breast-fed infants with maternal ingestion of pancreatic enzymes. <i>J Pediatr Gastroenterol Nutr</i> 1999;29:500.</p>	<p>Four term exclusively breastfed infants continued to have blood in their stools despite dietary restriction of cow-milk/soy protein. No other source of blood was present. Further restriction of egg, wheat, fish, nuts and peanuts (≥ 2 weeks) did not eliminate stool blood. Two infants had endoscopy revealing allergic colitis. All 4 mothers were prescribed pancreatic enzymes (Pancrease MT 4®, USP units 4,000 Lipase/12,000 Amylase, 12,000 protease) two capsules with meals, 1 capsule with snacks. In $\frac{3}{4}$ infants stool guaiac blood resolved within a few days of therapy. One mother required 3 capsules with meals/2 with snacks before stool blood resolved. No side-effects occurred.</p>	<p>III</p>
<p>Kilshaw PJ, Cant AJ. The passage of maternal dietary proteins into human breast milk. <i>Int Arch Allergy Appl Immunol</i> 1984;75:8-15.</p>	<p>Samples of breast milk and serum were taken from 29 women at various stages of lactation before and after they had ingested 1 raw egg and half a pint of cow's milk. The samples were analyzed for cow's milk and egg proteins. β-Lactoglobulin, ovalbumin, and ovomucoid were detected in breast milk from 10 out of 19, 13 out of 22 and 7 out of 9 women. Maximum levels of proteins were detected in breast milk 4 - 6 h after ingestion and in serum 1-2 h earlier. Acidic treatment of breast milk fractions failed to reveal additional ovalbumin, suggesting that immune complexes were not present. There was also no correlation between the amount of specific antibody (IgG) in the serum and concentrations of antigen in milk. This study confirms that maternal dietary antigens are present within the breast milk (in their native form) and thus are delivered to the nursing infant.</p>	<p>III</p>

Suggestions for Areas of Future Research:

1. Determine the current incidence of allergic colitis in exclusively breastfed infants.

Most available epidemiologic data is from over 20 years ago and we know the incidence of other atopic diseases (e.g. asthma) has increased over the past few decades. In addition, the results of many studies on allergic colitis in breastfed infants are complicated by the inclusion of infants that received cow's milk formula in addition to breast milk.

2. Determine the influence of maternal or neonatal immunity on development of allergic proctocolitis.

It is clear that antigens ingested by the mother and transferred in breast milk to nursing infants are responsible for the clinical manifestations of allergic proctocolitis. However, it is uncertain if the fetus is sensitized to these antigens during pregnancy or as a newborn through repeated exposure within the human milk. Also the precise contribution of maternal immune factors transmitted to progeny during pre- and/or post-natal life on the development of allergic responses in the neonate is unclear. Additional investigation is needed to define the immunologic mechanisms involved in the context of specific genetic, developmental, and environmental factors in mother and infant. Further insight into these factors would allow more focused efforts at prevention.

3. Determine the safety and efficacy of maternal pancreatic enzyme use in alleviating the symptoms of allergic colitis, and if efficacious, under what circumstances they should be used.

Current data is either in a small case study or by word of mouth that maternal pancreatic enzyme use is both safe and efficacious. If this is shown in larger scale studies, one would want to determine if this adjunct to maternal elimination diet should be used only as last resort, when the elimination diet is not efficacious, or possibly as an earlier adjunct, to make the diet less onerous for the mother to follow.

4. Determine the contribution of other antigens to allergic colitis in infants.

In the majority of cases cow's milk protein has been identified as the inciting antigen. Thus, elimination of foods containing cow's milk protein from the mother's diet should be the first dietary recommendation. Additional antigens may be considered for removal based on dietary history (e.g. soy, egg, corn, wheat, peanuts etc.).

5. For breastfed infants who respond to maternal dietary restriction, how long should the mother continue avoidance before an antigen challenge is performed?

In the event that an infant responds to maternal dietary modification it is unclear how long the mother should continue avoidance of a particular food. Most infants with food allergy identified during the first 3 years of life will tolerate reintroduction of the offending antigen within 9 months. Furthermore, most infants with allergic proctocolitis tolerate an unrestricted diet by 1 year of age. It seems reasonable that inciting foods could be re-introduced into the diet at 9-12 months of age and for at least 6 months.

6. Should infants with history of allergic proctocolitis delay introduction of other major food allergens in effort to prevent development of other food allergies?

Because young children with allergic reactions to cow's milk protein have an increased risk of developing other food allergies, it was previously recommended that major food allergens such as peanuts, tree nuts, fish, and shellfish be avoided until at least 3 years of age. At present, there is no evidence to support this approach will be successful in preventing future allergy. Thus, consistent with recent published guidelines for the Diagnosis and Management of Food Allergy in the United States, breastfed infants with a history of allergic proctocolitis should not limit exposure to major food allergens after 4-6 months of age. Infants and breastfeeding mothers should only avoid the allergen identified during maternal elimination diets until 9-12 months of age and for at least 6 months. This is an active area of current research and additional studies may provide more substantial evidence to support or change these recommendations.

7. Determine the utility of additional laboratory tests for the diagnosis of allergic proctocolitis.

A recent case report demonstrated the selective elevation of serum interleukin 5 (a Th2-type cytokine), in an infant who developed hematochezia associated with the feeding of cow's milk formula (Koike et al. *Pediatrics* 2011). At present, it remains unclear if exclusively breastfed infants that develop allergic proctocolitis would have a similar elevation of allergic cytokines in their serum.

****US Preventive Services Task Force Ranking of Evidence from Scientific Studies**

- I Evidence obtained from at least one properly randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

The Academy of Breastfeeding Medicine Protocol Committee

Nancy Brent, MD

Maya Bunik, MD, MSPH, FABM

Caroline J. Chantry MD, FABM

Cynthia R. Howard MD, MPH, FABM

Ruth A. Lawrence, MD, FABM

*Kathleen A. Marinelli, MD, FABM, *Chairperson*

Larry Noble, MD, FABM, *Translations Chairperson*

Nancy G. Powers, MD, FABM

Julie Scott Taylor, MD, MSc, FABM

Contributor(s)

*Adam Matson, MD

Dept. of Pediatrics, University of Connecticut School of Medicine

Division of Neonatology, Connecticut Children's Medical Center, Hartford, CT

* Kathleen A. Marinelli MD, FABM

Dept. of Pediatrics, University of Connecticut School of Medicine

Division of Neonatology, Connecticut Children's Medical Center, Hartford, CT

*Lead Author(s)

Supported in part by a grant from the Maternal and Child Health Bureau, Department of Health and Human Services.