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Ranitidine is Associated With Infections, Necrotizing Enterocolitis, and Fatal Outcome in Newborns

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Pediatrics 2012;129;e40; originally published online December 12, 2011;
DOI: 10.1542/peds.2011-0796

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WHAT'S KNOWN ON THIS SUBJECT: Although still off-label for newborns, the use of inhibitors of gastric acid secretion continues to increase. Acid-suppressive drugs could facilitate the onset of infections in adults and children. Evidence for efficacy is weak in newborns, particularly if preterm.

WHAT THIS STUDY ADDS: This is the first prospective study demonstrating an association between the use of ranitidine and infections, necrotizing enterocolitis, and fatal outcome in very low birth weight newborns. Caution is advocated in using ranitidine in newborns.

abstract

FREE

BACKGROUND AND OBJECTIVES: Gastric acidity is a major nonimmune defense mechanism against infections. The objective of this study was to investigate whether ranitidine treatment in very low birth weight (VLBW) infants is associated with an increased risk of infections, necrotizing enterocolitis (NEC), and fatal outcome.

METHODS: Newborns with birth weight between 401 and 1500 g or gestational age between 24 and 32 weeks, consecutively observed in neonatal intensive care units, were enrolled in a multicenter prospective observational study. The rates of infectious diseases, NEC, and death in enrolled subjects exposed or not to ranitidine were recorded.

RESULTS: We evaluated 274 VLBW infants: 91 had taken ranitidine and 183 had not. The main clinical and demographic characteristics did not differ between the 2 groups. Thirty-four (37.4%) of the 91 children exposed to ranitidine and 18 (9.8%) of the 183 not exposed to ranitidine had contracted infections (odds ratio 5.5, 95% confidence interval 2.9–10.4, $P < .001$). The risk of NEC was 6.6-fold higher in ranitidine-treated VLBW infants (95% confidence interval 1.7–25.0, $P = .003$) than in control subjects. Mortality rate was significantly higher in newborns receiving ranitidine (9.9% vs 1.6%, $P = .003$).

CONCLUSIONS: Ranitidine therapy is associated with an increased risk of infections, NEC, and fatal outcome in VLBW infants. Caution is advocated in the use of this drug in neonatal age. *Pediatrics* 2012;129:e40–e45

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KEY WORDS

gastric acidity inhibitors, histamine-2 receptor antagonists, sepsis, pneumonia, urinary tract infections, microflora, very low birth weight

ABBREVIATIONS

BW—birth weight
CI—confidence interval
CRIB—Critical Risk Index for Babies
GA—gestational age
GERD—gastroesophageal reflux disease
H2R—histamine-2 receptor
IVH—intraventricular hemorrhage
NEC—necrotizing enterocolitis
OR—odds ratio
PDA—persistent ductus arteriosus
UTI—urinary tract infection
VLBW—very low birth weight

www.pediatrics.org/cgi/doi/10.1542/peds.2011-0796

doi:10.1542/peds.2011-0796

Accepted for publication Sep 9, 2011

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

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

Infections are a common cause of morbidity and mortality in premature infants.[1] Gastric juice is a major nonimmune defense mechanism against infections.[2] Treatment with inhibitors of gastric acid secretion leads to insufficient elimination of several ingested pathogens.[3–11] Many studies show that these drugs facilitate the onset of infections in adults[3–7,12] and children, as we recently demonstrated.[10] There is evidence of an increased risk of infections and necrotizing enterocolitis (NEC) related to the use of histamine-2 receptor (H2-R) blockers and proton pump inhibitors in neonates.[13–15] These medications, like many others administered in neonatology, have not been approved by the US Food and Drug Administration for use in this population and are prescribed in an off-label manner because of the perceived safety and potential benefit demonstrated for older populations. Despite these aspects, the use of these drugs has progressively increased.[12,16] In the NICU, the most common indications for the administration of inhibitors of gastric acid secretion are prophylaxis or therapy of stress ulcers and gastroesophageal reflux disease (GERD),[15–17] but their efficacy in preterm infants is still debated.[16] In this context, we conducted a safety study to determine whether there was an increased risk of infectious diseases, NEC, and mortality in preterm newborns exposed to ranitidine treatment.

METHODS

Populations

Newborns with birth weight ranging between 401 and 1500 g or gestational age between 24 and 32 weeks, consecutively observed in 4 Italian NICUs (University Federico II, Naples; Fatebenefratelli Hospital, Naples; Meyer Pediatric Hospital, Florence; V. Betania Evangelic Hospital, Naples), from January 2006 to June 2007, were considered eligible for the study. Exclusion criteria were immunodeficiency, malformations, evidence of infections or NEC before enrollment, critical conditions (blood pH $<$ 6.8, or hypoxia with persistent bradycardia for at least 1 hour), ranitidine therapy for fewer than 7 days, and hospitalization for fewer than 8 weeks. We evaluated 2 cohorts of very low birth weight (VLBW) newborns: those exposed or not exposed to ranitidine treatment. Indications, dosage, and duration of ranitidine treatment were decided by the caregivers of each NICU, who were unaware of the study aims. The study protocol was approved by the Ethics Committee of the University of Naples Federico II. Written informed consent was obtained from the parents.

Outcome Measures

The main end point of the study was the rate of infections in newborns exposed or not exposed to ranitidine treatment. Secondary outcomes were occurrence of NEC (Bell stage $>$II), mortality, and duration of hospital stay.[18] Sepsis was defined by the presence of signs suggestive of infection associated with a positive blood culture, as previously described.[19] Pneumonia was defined by the presence of clinical signs (progressive increase in oxygen requirement, bradycardia, and/or apnea, tachypnea, or dyspnea) associated with positive culture of endotracheal aspirate (when patients were intubated) and with pathologic signs at chest examination and radiograph.[20] Urinary tract infections (UTI) was diagnosed when a positive urine culture together with clinical findings, such as sign of sepsis, weight loss, or growth retardation were present.[21] Diagnosis of NEC and Bell stage were decided on the basis of standardized clinical and radiologic criteria.[22]

Data Collection

Researchers not in charge of the clinical management of the subjects enrolled, and unaware of the study aims, prospectively collected data regarding: gestational age (GA); birth weight (BW); Apgar score; Critical Risk Index for Babies (CRIB) score; occurrence of infections or NEC; antibiotic therapy; indications for and dosage of ranitidine treatment; duration of ranitidine treatment; modality and duration of mechanical ventilation; oxygen therapy; presence and duration of central vascular access; intraventricular hemorrhage (IVH); persistent ductus arteriosus (PDA); time to reach full enteral feeding; results of microbiological, radiologic, and laboratory tests; diagnosis of stress-induced peptic disease and of GERD, time to discharge, or death.

Feeding Protocol

Enteral feeding was started on the first day of life at 10 mL/kg per day, distributed in 8 to 12 feeds, using preterm formula in all stable infants. Maternal unfortified milk was administered when available. Aspirate residue from the orogastric tube and abdominal circumference were measured before each feed. The total amount of gastric residue was calculated daily. In the absence of food intolerance during the previous 24 hours, the total amount of enteral nutrition was increased by 10 to 20 mL/kg per day. Enteral nutrition was discontinued in case of erythematic abdominal wall, absence of bowel sounds, or blood in the stools or in aspirates, associated with radiologic markers of NEC-Bell stage higher than I.[23] Parenteral nutrition was administered through a central vascular access in all infants to maintain an adequate intake of fluids, electrolytes, and nutrients, until full enteral feeding (120 kcal/kg per day) was reached. Fluids were started at 70 to 100 mL/kg per day with increments of 10 to 20 mL/kg per day until 150 to 180 mL/kg per day.

Statistics

We estimated a minimum sample size of 90 patients for each group to obtain a power of the study of 90% (type 1 error = 0.05 with a 2-tailed test), considering the smallest difference in proportion of infectious diseases to be 20% (specifically, 10% vs 30%). The Kolmogorov-Smirnov test was used to determine whether variables were normally distributed. For continuous variables, groups were compared using the *t* test, and the Mann-Whitney *U* test. The χ^2 test and Fisher's exact test were used for categorical variables. For 2 related dichotomous variables, the McNemar test was used to detect differences before and after the use of ranitidine. Risks of sepsis, pneumonia, and UTI (plus 95% confidence intervals [CIs]) in patients treated with ranitidine were estimated. We performed a multivariate analysis using binary logistic regression analysis to evaluate whether GA, BW, sex, Apgar score, CRIB score, IVH, PDA, central vascular access, or mechanical ventilation affected the prescription of ranitidine. The level of significance for all statistical tests was 2-sided, $P < .05$. Statistical analysis was performed by a statistician blinded to patient group assignment, using SPSS, version 16.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

A total of 309 VLBW newborns were evaluated. Thirty-five infants were excluded because of critical clinical conditions (10 patients), malformations (8 patients), sepsis before enrollment (12 patients), and length of hospitalization fewer than 8 weeks (5 patients). Thus, we obtained data from 274 infants (120 from the University of Federico II, Naples; 45 from the Fatebenefratelli Hospital, Naples; 23 from the Meyer Pediatric Hospital, Florence; and 86 from V. Betania Evangelic Hospital, Naples). Ninety-one of these infants had received ranitidine (42 as prophylaxis of stress-induced peptic disease; 49 because of suspected GERD), and 183 represented the control cohort of newborns not exposed to ranitidine. In all cases, the diagnosis of GERD was made based on clinical criteria without pH-metry or endoscopy.

The main demographic and clinical characteristics of the 2 cohorts were similar (Table 1). These characteristics did not differ between patients receiving ranitidine for prophylaxis of stress-induced peptic disease and patients receiving ranitidine for GERD. Multivariate binary logistic regression analysis (constant B 6.334) revealed that the prescription of ranitidine by physicians was not affected by gestational age (B −0.167, odds ratio [OR] 0.846, 95% CI 0.694–1.031, $P = .098$), birth weight (B −0.001, OR 0.999, 95% CI 0.997–1.001, $P = .444$), sex (B 0.708, OR 2.031, 95% CI 0.972–4.243, $P = .060$), Apgar score (1 minute: B −0.147, OR 0.863, 95% CI 0.653–1.141, $P = .301$; 5 minute: B −0.099, OR 0.905, 95% CI 0.486–1.687, $P = .754$), CRIB score (B 0.008, OR 1.008, 95% CI 0.869–1.169, $P = .918$), IVH (B 0.755, OR 2.127, 95% CI 0.635–7.124, $P = .221$), PDA (B −0.281, OR 0.755, 95% CI 0.323–1.764, $P = .516$), central vascular access (B 0.004, OR 1.004, 95% CI 0.960–1.050, $P = .855$), or mechanical ventilation (B −0.062, OR 0.940, 95% CI 0.850–1.040, $P = .233$).

Newborns treated with ranitidine had more infections (OR 5.5, 95% CI 2.9–10.4, $P < .001$), namely sepsis, pneumonia, and UTI, than newborns not treated with ranitidine (Table 2). The pathogens responsible for infections are listed in Table 3. The mean time to infection after starting ranitidine treatment was 17.9 days (95% CI 13.0–22.8). Among infants treated with ranitidine, there was a slight but not significant increase in drug dosage in subjects presenting infections (intravenous 2.43 mg/kg per day, 95% CI 1.84–3.03 vs 1.85 mg/kg per day; 95% CI 1.55–2.16, $P = .052$; enteral route 11.44 mg/kg per day; 95% CI 8.08–14.80 vs 9.82 mg/kg per day; 95% CI 8.22–11.42, $P = .310$). The

TABLE 1 Demographic and Clinical Characteristics of the Neonates Enrolled in the Study

	Not Exposed to Ranitidine ($n = 183$)	Exposed to Ranitidine ($n = 91$)	*P*
Birth weight, g	1091 (1057–1124)	1083 (1031–1036)	.812
Gestational age, wk	29 (28.7–29.5)	29 (28.7–29.8)	.548
Male, *n* (%)	81 (44.3)	44 (48.4)	.522
Apgar score at 1 min	5.8 (5.6–6.1)	5.9 (5.6–6.3)	.879
Apgar score at 5 min	7.7 (7.6–7.9)	7.8 (7.6–7.9)	.786
CRIB score	1.3 (1.0–1.6)	1.7 (1.3–2.2)	.114
Persistent ductus arteriosus, *n* (%)	48 (26.2)	26 (28.6)	.681
Intraventricular hemorrhage stage III-IV, *n* (%)	11 (6.0)	10 (11.0)	.145
Central vascular access duration, d	16 (15–17)	15 (14–17)	.967
Duration of endotracheal intubation, d	4.4 (3.7–5.1)	4.3 (3.3–5.2)	.853

Data expressed as mean (95% CI) when not specified.

TABLE 2 Rate of Patients Presenting Infections During the Study Period

	Not exposed to Ranitidine ($n = 183$)	Exposed to Ranitidine ($n = 91$)	*P*
Overall infections, *n* (%)	18 (9.8)	34 (37.4)	<.001
Sepsis, *n* (%)	16 (8.7)	23 (25.3)	<.001
Pneumonia, *n* (%)	1 (0.5)	4 (4.4)	.043
Urinary tract infections, *n* (%)	1 (0.5)	7 (7.7)	.002

TABLE 3 Pathogens Responsible for Infectious Episodes During the Study

	Not exposed to Ranitidine (n = 18 of 183), n (%)	Exposed to Ranitidine (n = 34 of 91), n (%)	P
Escherichia coli	2 (11.1)	10 (29.4)	<.001
Klebsiella pneumoniae	1 (5.5)	8 (23.5)	.001
Pseudomonas aeruginosa	1 (5.5)	6 (17.6)	.006
Candida albicans	5 (27.7)	3 (8.8)	.794
Serratia marcescens	0 (0.0)	1 (2.9)	.332
Staphylococcus coagulase neg.	6 (33.3)	6 (17.6)	.735
Group B *Streptococcus*	1 (5.5)	0 (0.0)	.480
Other pathogens	2 (11.1)	0 (0.0)	.317

risk of infections was unrelated to the duration of ranitidine treatment. NEC was significantly (P = .003) more frequent (OR 6.6; 95% CI 1.7–25.0) in VLBW infants treated with ranitidine (9.8%) than in those not exposed to ranitidine (1.6%). The risk of NEC was unrelated to either the dosage or duration of ranitidine therapy. Twelve patients died during the study. Mortality rate was significantly higher in newborns receiving ranitidine (9.9% vs 1.6%, P = .003), and hospitalization was significantly longer in those exposed to ranitidine (median 52 days, interquartile range 43 vs 36 days, interquartile range 22, P < .001).

DISCUSSION

With the aim of increasing information about the use of drugs outside the terms of their license ("off-label") or of drugs that are not specifically licensed for use in children ("unlicensed"), the European Parliament and the European Medicines Agency made a call for safety studies on off-label and unlicensed prescription of ranitidine in newborns. Similarly, the US Food and Drug Administration advocated studies on the safety of off-label drugs in the pediatric age. Here we reported the results of the first multicenter prospective study focusing on the increased morbidity (ie, infections and NEC) and mortality associated with ranitidine use in VLBW newborns.

Previous reports have suggested similar conclusions, although all of them had some limitations that can be considered overcame by our study. Graham et al,[14] in a retrospective study of the effects of hand hygiene practices on hospital-acquired late-onset gram-negative sepsis, showed that the inhibitors of gastric acid secretion entailed an increased risk of infection in low birth weight newborns; however, the subjects receiving inhibitors of gastric acid secretion were more severely ill than those not receiving this treatment. Differently, in our study, the prescription of ranitidine was not influenced by the severity of the patient's clinical condition, as demonstrated by the multivariate analysis. Bianconi et al[24] reported an association between ranitidine use and the risk of late-onset sepsis, but they used a retrospective design and the number of newborns enrolled was very small. In a randomized controlled trial, Stoll et al[25] evaluated the relationship between postnatal steroid exposure and late-onset sepsis in VLBW infants. They observed that treatment with dexamethasone was associated with an increased risk of sepsis and meningitis. During the analysis of the factors present at randomization, the authors found an increased use of H_2R blocker therapy in patients developing infections. Unfortunately, this study did not differentiate the effect of steroids from those of the H_2R blocker on the risk of infections. In a prospective study, Beck-Sague et al[13] reported a fourfold increase in the risk of bloodstream infection in neonates who received H_2R blockers; however, also in this case, neonates who developed infection were more severely ill and were of lower gestational age on admission than infants not developing these infections. Finally, a recent study suggested an association between NEC and H_2R blockers, but study design was retrospective.[15]

Experimental and clinical evidence suggests that infections associated with the use of inhibitors of gastric acid secretion can occur via diverse mechanisms.[11,12] Gastric juice and intestinal microflora are 2 of the major defense factors against invasion of the gut by microorganisms. In particular, the lack of normal gastric destruction of pathogens could be considered the most important aspect that predispose to infections. The preservation of gastric acid secretion during phylogenesis supports the biological importance of this high-energy consuming system developed to inactivate ingested microorganisms. Gastric juice consists of HCl and pepsin, which kills bacteria within 15 minutes when the pH in the stomach is lower than 3.0. At a higher pH, a state defined as "hypochlorhydria," bacterial overgrowth and infections are more common.[26] Quantitative and qualitative changes in the composition of the intestinal microflora are associated with the development of sepsis and NEC.[12,15] Thus, it is conceivable that hypochlorhydria induced by ranitidine may significantly alter the intestinal microflora, which, in turn, could contribute to the increased susceptibility to infections and the abnormal immune activation observed during NEC. The development of NEC could be a result of the selective advantage acquired by pathogens, such as *Escherichia coli* and *Klebsiella pneumonia,* during inhibition of gastric acidity,[1–4,9,12,15,27] as confirmed by our microbiological evaluations. Furthermore, the direct effect exerted by ranitidine on the immune system could influence the risk for NEC in neonates.[28–30]

Activation of H_2R alters the production of inflammatory cytokines and disrupts the Th1–Th2 balance, thereby leading to insufficient control of infections and inflammation at the intestinal level.[31–33]

In VLBW infants, the diagnosis of gastric acid–related diseases is based on the evaluation of nonspecific symptoms, and the empirical treatment is frequently the first diagnostic test.[16,34] In addition, there is no clear evidence that H_2R blockers are beneficial in many clinical conditions typical of neonatal age, such as apnea.[15,17,35,36] The results of this study suggest that ranitidine should be administered only after a careful consideration of the risk-benefit ratio. In addition, in our study, we observed an increased mortality in newborns receiving ranitidine. Mortality in this group exposed to ranitidine was ~ 6 times higher than in newborns not exposed to ranitidine treatment. This suggests that caution should be exercised regarding the administration of ranitidine in subjects such as VLBW at high risk of death per se. Finally, the administration of ranitidine in VLBW infants increases health care costs because of prolonged hospital care. In western countries, the median cost of hospitalization is estimated to be about $1250 per day for a VLBW infant.[37] The difference in median duration of hospitalization between the 2 groups of our study was 20 days, thereby resulting in a reduction of about $25 000 per patient.

CONCLUSIONS

Ranitidine should be administered with care in preterm infants because of the risk of severe infectious disease, NEC, and fatal outcome. Further studies are necessary to investigate the pathogenesis of these effects and the possible prophylactic measures that could be taken to prevent them.

ACKNOWLEDGMENTS

The authors acknowledge with gratitude the commitment of the Mother and Child Health Association to the research efforts. The authors are grateful to Jean Ann Gilder (Scientific Communication SRL, Naples, Italy) for final editing of the text.

REFERENCES

1. Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG. Seventy-five years of neonatal sepsis at Yale: 1928–2003. *Pediatrics*. 2005;116(3):595–602
2. Martinsen TC, Bergh K, Waldum HL. Gastric juice: a barrier against infectious diseases. *Basic Clin Pharmacol Toxicol*. 2005;96(2):94–102
3. Dial MS. Proton pump inhibitor use and enteric infections. *Am J Gastroenterol*. 2009;104(Suppl 2):S10–S16
4. Leonard J, Marshall JK, Moayyedi P. Systematic review of the risk of enteric infection in patients taking acid suppression. *Am J Gastroenterol*. 2007;102(9):2047–2056, quiz 2057
5. García Rodríguez LA, Ruigómez A, Panés J. Use of acid-suppressing drugs and the risk of bacterial gastroenteritis. *Clin Gastroenterol Hepatol*. 2007;5(12):1418–1423
6. Doorduyn Y, Van Pelt W, Siezen CLE, et al. Novel insight in the association between salmonellosis or campylobacteriosis and chronic illness, and the role of host genetics in susceptibility to these diseases. *Epidemiol Infect*. 2008;136(9):1225–1234
7. Khatami SS, Mukunda B, Ravakhah K. Coinfection with *Giardia lamblia* and *Clostridium difficile* after use of ranitidine. *Am J Med Sci*. 2004;327(2):91–93
8. Cadle RM, Mansouri MD, Logan N, Kudva DR, Musher DM. Association of proton-pump inhibitors with outcomes in *Clostridium difficile* colitis. *Am J Health Syst Pharm*. 2007;64(22):2359–2363
9. Doorduyn Y, Van Den Brandhof WE, Van Duynhoven YTHP, Wannet WJB, Van Pelt W. Risk factors for Salmonella Enteritidis and Typhimurium (DT104 and non-DT104) infections in The Netherlands: predominant roles for raw eggs in Enteritidis and sandboxes in Typhimurium infections. *Epidemiol Infect*. 2006;134(3):617–626
10. Canani RB, Cirillo P, Roggero P, et al; Working Group on Intestinal Infections of the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP). Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. *Pediatrics*. 2006;117(5):e817–e820
11. Vakil N. Acid inhibition and infections outside the gastrointestinal tract. *Am J Gastroenterol*. 2009;104(Suppl 2):S17–S20
12. Canani RB, Terrin G. Gastric acidity inhibitors and the risk of intestinal infections. *Curr Opin Gastroenterol*. 2010;26(1):31–35
13. Beck-Sague CM, Azimi P, Fonseca SN, et al. Bloodstream infections in neonatal intensive care unit patients: results of a multicenter study. *Pediatr Infect Dis J*. 1994;13(12):1110–1116
14. Graham PL, III, Begg MD, Larson E, Della-Latta P, Allen A, Saiman L. Risk factors for late onset gram-negative sepsis in low birth weight infants hospitalized in the neonatal intensive care unit. *Pediatr Infect Dis J*. 2006;25(2):113–117
15. Guillet R, Stoll BJ, Cotten CM, et al. For members of the National Institute of Child Health and Human Development Neonatal Research Network. Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. *Pediatrics*. 2006;117:137–142
16. Malcolm WF, Gantz M, Martin RJ, Goldstein RF, Goldberg RN, Cotten CM; National Institute of Child Health and Human Development Neonatal Research Network. Use of medications for gastroesophageal reflux at discharge among extremely low birth weight infants. *Pediatrics*. 2008;121(1):22–27
17. Omari TI, Haslam RR, Lundborg P, Davidson GP. Effect of omeprazole on acid gastroesophageal reflux and gastric acidity in preterm infants with pathological acid reflux. *J Pediatr Gastroenterol Nutr*. 2007;44(1):41–44
18. American Academy of Pediatrics Committee on Fetus and Newborn. Hospital discharge of the high-risk neonate. *Pediatrics*. 2008;122:119–126
19. Modi N, Doré CJ, Saraswatula A, et al. A case definition for national and international neonatal bloodstream infection surveillance. *Arch Dis Child Fetal Neonatal Ed*. 2009;94(1):F8–F12

20. Nissen MD. Congenital and neonatal pneumonia. *Paediatr Respir Rev*. 2007;8(3):195–203
21. Mori R, Lakhanpaul M, Verrier-Jones K. Diagnosis and management of urinary tract infection in children: summary of NICE guidance. *BMJ*. 2007;335(7616):395–397
22. Hack M, Horbar JD, Malloy MH, Tyson JE, Wright E, Wright L. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Network. *Pediatrics*. 1991;87(5):587–597
23. Meinzen-Derr J, Morrow AL, Hornung RW, Donovan EF, Dietrich KN, Succop PA. Epidemiology of necrotizing enterocolitis temporal clustering in two neonatology practices. *J Pediatr*. 2009;154(5):656–661
24. Bianconi S, Gudavalli M, Sutija VG, Lopez AL, Barillas-Arias L, Ron N. Ranitidine and late-onset sepsis in the neonatal intensive care unit. *J Perinat Med*. 2007;35(2):147–150
25. Stoll BJ, Temprosa M, Tyson JE, et al. Dexamethasone therapy increases infection in very low birth weight infants. *Pediatrics*. 1999;104(5). Available at: www.pediatrics.org/cgi/content/full/104/5/e63
26. Winter JW, Heading RC. The nonerosive reflux disease-gastroesophageal reflux disease controversy. *Curr Opin Gastroenterol*. 2008;24(4):509–515
27. Smith A, Saiman L, Zhou J, Della-Latta P, Jia H, Graham PL III. Concordance of gastrointestinal tract colonization and subsequent bloodstream infections with gram-negative bacilli in very low birth weight infants in the neonatal intensive care unit. *Pediatr Infect Dis J*. 2010;29(9):831–835
28. Takagaki K, Osawa S, Horio Y, et al. Cytokine responses of intraepithelial lymphocytes are regulated by histamine H(2) receptor. *J Gastroenterol*. 2009;44(4):285–296
29. Xu X, Zhang D, Zhang H, et al. Neutrophil histamine contributes to inflammation in mycoplasma pneumonia. *J Exp Med*. 2006;203(13):2907–2917
30. Sun Q, Li W, She R, et al. Evidence for a role of mast cells in the mucosal injury induced by Newcastle disease virus. *Poult Sci*. 2009;88(3):554–561
31. Moharana AK, Bhattacharya SK, Mediratta PK, Sharma KK. Possible role of histamine receptors in the central regulation of immune responses. *Indian J Physiol Pharmacol*. 2000;44(2):153–160
32. van der Pouw Kraan TC, Snijders A, Boeije LC, et al. Histamine inhibits the production of interleukin-12 through interaction with H2 receptors. *J Clin Invest*. 1998;102(10):1866–1873
33. St Peter SD, Sharp SW, Ostlie DJ. Influence of histamine receptor antagonists on the outcome of perforated appicitis: analysis from a prospective trial. *Arch Surg*. 2010;145(2):143–146
34. Martin RJ, Hibbs AM. Diagnosing gastroesophageal reflux in preterm infants. *Pediatrics*. 2006;118(2):793–794
35. Wheatley E, Kennedy KA. Cross-over trial of treatment for bradycardia attributed to gastroesophageal reflux in preterm infants. *J Pediatr*. 2009;155(4):516–521
36. Clark RH, Spitzer AR. Patience is a virtue in the management of gastroesophageal reflux. *J Pediatr*. 2009;155(4):464–465
37. Rogowski J. Using economic information in a quality improvement collaborative. *Pediatrics*. 2003;111(4 pt 2):e411–e418

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Pediatrics 2012;129;e40; originally published online December 12, 2011;
DOI: 10.1542/peds.2011-0796