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eNeonatal Review
Podcast Issue

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VOLUME 10 — ISSUE 8: TRANSCRIPT

Treatment Strategies For GERD In Neonates And Infants

Our guest authors are Anna Maria Hibbs, MD, MSCE, FAAP, Associate Professor of Pediatrics, and Margaret Kuper-Sassé, MD, Neonatal-Perinatal Medicine Fellow at University Hospitals Rainbow Babies & Children's Hospital in Cleveland, Ohio.

After participating in this activity, the participant will demonstrate the ability to:

- Explain the impact that the distinction between gastroesophageal reflux and gastroesophageal reflux disease has on interpretation of study end-points.
- Describe current evidence supporting non-pharmacologic versus pharmacologic treatment options for GERD in neonates and infants.
- Summarize the role that the natural history of GERD symptoms has on symptomatic improvement in GERD treatment and GERD research.

This discussion, offered as a downloadable audio file and companion transcript, covers the important topic of treatment strategies for GERD in neonates and infants in the format of case-study scenarios for the clinical practice. This program is a follow up to the [Volume 10, Issue 7 eNeonatal Review newsletter—Treatment Strategies for GERD in Neonates and Infants](#).

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Dr. Hibbs and Dr. Kuper-Sassé have indicated that they will reference the unlabeled/unapproved uses of proton pump inhibitors and metoclopramide.

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Faculty Disclosure

Dr. Hibbs and Dr. Kuper-Sassé have indicated that they have no financial interests or relationships with any commercial entity whose products or services are relevant to the content of their presentation.

Release Date
June 25, 2015

Expiration Date
June 24, 2017

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- Physicians may not be aware of recent evidence-based recommendations on recognizing and treating GERD in neonates.
- Current neonatal nutritional management practices may be enhanced to optimize and meet the specific needs of low birth weight preterm infants.
- Current neonatal nutritional management practices may be enhanced to optimize and meet the specific needs of low birth weight preterm infants.
- Clinicians who treat neonates are uncertain of optimal strategies for prevention and early recognition and treatment of necrotizing enterocolitis.

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- Clinicians may be unfamiliar with some of the newest evidence-based approaches for treating neonatal persistent pulmonary hypertension.
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Reviewed and Approved by General Counsel, Johns Hopkins Medicine (4/1/03) (Updated 4/09 and 3/14)

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MR. BOB BUSKER: Welcome to this *eNeonatal Review*[™] podcast.

Today's program is a follow-up to our newsletter on *Treatment Strategies for GERD in Neonates and Infants*. With us today, from the University Hospitals Rainbow Babies & Children's Hospital in Cleveland, Ohio, are that issue's authors: Dr. Anna Maria Hibbs, Associate Professor of Pediatrics, and Dr. Margaret Kuper-Sassé, a Neonatal-Perinatal Medicine Fellow.

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Learning objectives for this audio program include:

- Explain the impact that the distinction between gastroesophageal reflux and gastroesophageal reflux disease has on the interpretation of study end-points.
- Evaluate the current evidence describing non-pharmacologic versus pharmacologic treatment options for GERD in neonates and infants.
- Summarize the role that the natural history of GERD symptoms has on symptomatic improvement in GERD treatment and GERD research.

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MR. BUSKER: I'm Bob Busker, managing editor of *eNeonatal Review*. Dr. Hibbs, Dr. Sassé, thank you for joining us today.

DR. HIBBS: It's a pleasure to be here.

DR. KUPER-SASSÉ: Yes, thank you very much for having me.

MR. BUSKER: In your newsletter issue, doctors, you reviewed some of recent data describing the pharmacological and non-pharmacological management of gastroesophageal reflux disease —

or GERD — in neonates and infants. Today I'd like to focus on how that information can be applied in the exam room and the NICU. So to start us off, Dr. Sassé, let me ask you to describe a patient situation, if you would please.

DR. KUPER-SASSÉ: Our first case is a 5 week old, former 37 week male infant who was transferred to our institution for a second opinion. He carries a diagnosis of resolved apnea and severe GERD with spitting, back arching and crying that is worse in the evening, as well as food refusal. He is on an extensively hydrolyzed protein formula, a PPI, metoclopramide, and has received a surgical G tube for his oral aversion. His course has been otherwise unremarkable. The infant's mother he told us that her pregnancy dating was based on a last menstrual period she was very unsure of, and with each addition of medication and feeding change she saw no benefit to her baby.

We stopped all medications and changed to a rice starch thickened formula. Within one week this infant was discharged on full oral feeding.

MR. BUSKER: So we have an infant that was in trouble, but then stopping the medication made the infant feel better. We have sort of a mystery here. What is it that improved this infant's symptoms? Dr. Hibbs? Your opinion?

DR. HIBBS: In cases like these we often don't truly know. It's tempting to think that the intervention caused the improvement, just as when we initiate therapy it's tempting to think the therapy caused the improvement. But it's very possible that this improvement was due to the normal maturational trajectory of this infant. For one thing, it's possible that his gestation was slightly younger than we thought and he was maturing rapidly, but even for term infants it's been repeatedly shown in studies of reflux interventions that the placebo group tends to improve over a matter of weeks, and this was also shown in the papers reviewed in the newsletter by Hussain of a PPI¹ and Lasekan in a study of rice thickened formula.²

MR. BUSKER: Dr. Sassé? Anything to add to that?

DR. KUPER-SASSÉ: I also wanted to mention that this patient was on a PPI treatment, and repeated studies have shown that there is very little efficacy of PPI treatments in this patient group. As we mentioned in our newsletter, in the article by the Davidson group looking at esomeprazole³ and the Hussain group also looking at rabeprazole¹, both PPIs, both showed no efficacy over placebo treatment in infants.

DR. HIBBS: Those are excellent points, Meggan. I would add that in the Hussain study of rabeprazole there was a nonsignificant trend toward worse spitting in the high dose group.¹ So in addition to having no benefit, there have been some signals in the opposite direction. Thickened feeds, on the other hand, have been shown to reduce spitting as the Lasekin article in the newsletter showed.² In addition, while oral aversion in this child was blamed on reflux, it could have been due to the unpleasant taste of the extensively hydrolyzed formula, or to unrecognized immaturity in this infant.

MR. BUSKER: Dr. Sassé, do you think this infant actually had GERD? And if so, did he require the aggressive treatment that was provided?

DR. KUPER-SASSÉ: That's an interesting and difficult question. He may have met diagnostic criteria with his back arching and crying; however, I think it's important to note that he did cry a lot in the evening, which tends to be associated with colic rather than reflux. But early when diagnosing GERD, the distinction between GERD and just plain physiologic reflux is that there are disturbing symptoms associated with it. So it's important to note that with his symptom association he possibly met the diagnostic criteria, but then in treating him, it should also have been stressed that his symptoms improved with every treatment that was added.

DR. HIBBS: I agree, Meggan, in addition, there is no history of other sequelae that we often see in the NICU — or at least are often attributed to GERD in the NICU — such as poor weight gain or aspiration pneumonia. So this was certainly a good case to consider a conservative approach.

MR. BUSKER: Is it likely, Dr. Hibbs, that this baby might have benefitted from treatment with a probiotic?

DR. HIBBS: Interesting question This baby did have some of the functional complaints that were described in the article by Indrio, et al., in the newsletter as being reduced with probiotic treatment.⁴ That study showed a reduction in crying, but it was definitely a different patient population. So it's not clear in this instance whether it was due to GERD, due to colic, or another neurological reason, but if a safe probiotic was available, this infant certainly could have benefitted from a trial.

DR. KUPER-SASSÉ: That's right, Anna Maria. I'd also like to point out, as you mentioned, about the products being safe. In the United States we don't really have stringent regulation on these kinds of medications, as they're regulated as dietary supplements rather than as drugs by the FDA. So there is very little control over what goes into the probiotics that you can buy over the counter, and we're not sure exactly how much probiotic is in them and whether there may also be something harmful in them.

Recently in the news we saw that the New York Attorney General looked at some of the over the counter products from common manufacturers and found that very few of them had what was supposed to be in them, and then had other additives that were potentially harmful. So this creates a big concern for us with neonates who have compromised immune systems and we're concerned we might be giving them something harmful and not actually the probiotic we intend to give them. So we would really like to be able to give these, but I think it's not really possible at this time.

MR. BUSKER: Now this baby, as you described him, had a G-tube placement. Should he also have had a fundoplication procedure when that tube was placed? Dr. Sassé, your thoughts on that?

DR. KUPER-SASSÉ: So one of our articles that we reviewed in our newsletter was by Barnhart, et al, and it talked about the effectiveness of fundoplication as a prophylactic procedure in neurologic impairment.⁵ This is not the exact same patient group, because this patient is not neurologically impaired and had a G tube procedure for his oral aversion, but I think that we can sort of apply the principles as just looking at prophylactic fundoplication in a patient who has not had diagnoses that are dangerous, like pneumonia or failure to thrive. And I think by that article showing

that there was really no benefit to having a prophylactic procedure, this patient likely would not have benefitted either.

DR. HIBBS: I agree, Meggan. In my own practice I would have probably waited longer before considering a permanent procedure, as his reflux is likely to resolve with physical maturation. Years ago, in 1997, Nelson showed that in healthy term infants spitting peaked at 4 months old, and this infant was only 6 weeks old. And so a more prolonged trial of conservative therapy would have been reasonable before committing to a fundoplication or other permanent surgical procedure.

MR. BUSKER: Thank you, doctors, for that case and discussion. And we'll return with Dr. Anna Maria Hibbs and Dr. Meggan Kuper-Sassé from the University Hospitals Rainbow Babies and Children's Hospital, in just a moment.

DR. MAUREEN GILMORE: Hello. I'm Maureen Gilmore, assistant professor of pediatrics and director of neonatology at Johns Hopkins Bayview Medical Center. I'm one of the program directors of eNeonatal Review.

eNeonatal Review is a combination newsletter and podcast program delivered via email to subscribers. Newsletters are published every other month. Each issue reviews the current literature in areas of importance to neonatologists, respiratory therapists, neonatal nurses and nurse practitioners, and other health care practitioners whose work/practice includes treating neonates.

Bimonthly podcasts are also available as downloadable transcripts, providing case-based scenarios to help bring that new clinical information into practice in the delivery room and at the bedside.

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MR. BUSKER: Welcome back to this eNeonatal Review podcast. I'm Bob Busker, managing editor of the program. Our guests are Dr. Anna Maria Hibbs and Dr. Margaret Kuper-Sassé from University Hospitals Rainbow Babies & Children's Hospital in Cleveland. And our topic is Treatment Strategies for GERD in Neonates and Infants.

We've been looking at how some of the new information presented in our guests' recent newsletter issue can inform practice change in the NICU and in the exam room. So let's continue with another patient situation. Dr. Hibbs? If you would, please?

DR. HIBBS: Let's consider the following case: a full-term male infant with an unremarkable perinatal course develops intractable seizures on day of life 3. Episodes are variable, described as extremity movements that are sometimes rhythmic, arching, crying, and some episodes of head deviation. On EEG the infant is noted to have seizure activity with some but not all of the episodes. The majority of the episodes occurring after feedings were not associated with seizure on EEG, and a diagnosis of GERD was made clinically.

Treatment with a PPI was started to decrease GERD symptoms and make clinical seizures more apparent.

MR. BUSKER: Dr. Sassé, the diagnosis of GERD that was made for this patient — do you think it was correct?

DR. KUPER-SASSÉ: That's a good question. The symptoms of back arching and crying are definitely consistent with what's considered neurobehavioral symptoms of GERD, but it's also consistent with other issues that this infant might have, like abnormal tone and neuroirritability. This child is certainly not neurologically normal at this point, given his repeated seizures, so it's a little hard to tease that out. It's always a problem even in infants who are neurologically normal to tell whether symptoms are related to GERD or reflux or other things, as they can't tell us and we just have to observe their behavior.

The same symptoms in different infants can have multiple causes, so it's hard to tell. But I think it is reasonable to think clinically that this probably is related to GERD in this infant.

MR. BUSKER: Dr. Hibbs, do you agree?

DR. HIBBS: Yes, I generally agree with Meggan. I will also add that although none of the articles that we reviewed in this newsletter discussed testing methodology for acutely and episodically occurring symptoms such as back arching, a test such as a pH probe or multichannel intraluminal impedance probe could be used to correlate reflux events and neurobehavioral symptoms.

MR. BUSKER: And do you agree with the decision to treat this infant with a PPI?

DR. HIBBS: In this case it is not unreasonable to try a PPI, although in an ideal world I would say they have not been shown to work and we should not use them, but we all know that in specific cases we cannot completely rule out that an individual infant will respond, and we also know that sometimes we have pressure from families or other specialists to try a therapy that has been shown to work in older children but not our population.

My recommendation when a trial of therapy is used is to think about when you are going to stop the medicine. If you do not see an acute response within a few days, then you have failed a trial and the medicine should be stopped. Similarly, if the infant improves, one should consider stopping the medication within weeks to months, because that improvement either may have been due to the underlying maturational improvement in the infant, or the infant may have initially responded to the medicine but no longer needed it down the road.

MR. BUSKER: Does the evidence support treatment with a PPI in a situation like this? Dr. Kuper-Sassé?

DR. KUPER-SASSÉ: The studies that I mentioned earlier, Davidson³ and Hussain¹, still apply in this case, that there really has been shown no effectiveness over placebo in this population of PPIs in this kind of GERD symptoms. So it probably was not the most evidence-based treatment, although as Dr. Hibbs mentioned, the treatment certainly is not contraindicated in that we can't be sure that this singular infant would not have any benefit from it. Although if we were going to pick the most evidence-based treatment it probably would not be a PPI.

MR. BUSKER: So what treatment would have a stronger evidence basis, Dr. Hibbs?

DR. HIBBS: In general, non-pharmacologic therapies have shown more efficacy than pharmacologic therapies in infants. Thickened feeds might have been an evidence-based first step, and this is supported by Lasekin², et al.

DR. KUPER-SASSÉ: That's a good point, Anna Maria, I'd also like to point out that extensively hydrolyzed formula, as shown in the Corvaglia study we reviewed⁶, which looked at extensively hydrolyzed formula for treatment for GERD, and was a very small pilot trial, but is relatively benign in a term infant and is worth trying as it did show some benefit in that patient population.

DR. HIBBS: Absolutely. Probiotics might also be of benefit in this patient to reduce reflux and crying as shown by the reviewed paper by Indrio, et al., although that study did not enroll medically complicated infants such as this one.⁴

MR. BUSKER: Dr. Sassé, would this patient likely benefit from a G tube and fundoplication procedure?

DR. KUPER-SASSÉ: This patient is medically very complicated and probably will need a G tube placement for long-term feeding because of his abnormal neurologic status and inability to safely feed by mouth. But I'd like to point out that according to the study by Barnhart we reviewed, the prophylactic fundoplication in a patient like this is unlikely to have any benefit.⁵

MR. BUSKER: The prognosis for this patient, Dr. Hibbs — is it likely his GERD would improve without any treatment?

DR. HIBBS: Yes, as I mentioned previously, the natural history of GERD is improvement over time, and this has been shown in multiple studies of reflux and in the article by Hussain, for instance, in this newsletter.¹ In many studies this improvement has occurred even over a matter of several weeks.

There seem to be indications to treat this infant at this time, but treatment should be withdrawn if there is no benefit. If a response is seen to pharmacological therapy, a trial off treatment can be considered in several weeks. In addition, non-pharmacologic

therapy should be considered before pharmacologic therapies.

MR. BUSKER: Thank you for that case and discussion, doctors. Dr. Sassé, let me ask you to bring us one more patient situation, if you would, please.

DR. KUPER-SASSÉ: Okay, our third patient situation is going to be a very typical one that we see in the NICU. It is a former 26 week gestation female infant who had a prolonged NICU course including sepsis, ventilator-associated pneumonia, and pneumothorax. She now is a corrected gestational age of 39 weeks and has spits of 5 to 15 mL per feed and poor weight gain.

MR. BUSKER: In your opinion, does she also have GERD, Dr. Hibbs?

DR. HIBBS: I think all potential causes of poor weight gain and spitting should be investigated in this infant before concluding it is due to reflux. While these can certainly be reflux symptoms, there are multiple competing reasons for infants in the NICU to experience these symptoms, as well.

MR. BUSKER: Dr. Sassé — your thoughts?

DR. KUPER-SASSÉ: To expand on that, spitting alone does not constitute a diagnosis of GERD. So if after an extensive evaluation looking into things that may be an issue in a former premature infant like this such as malabsorption and increased caloric need from chronic lung disease, if the weight gain is determined to be related to her reflux, she may meet criteria for a diagnosis of GERD.

MR. BUSKER: What about making a change in her formula? Could that reduce reflux in this patient? Dr. Hibbs, your opinion?

DR. HIBBS: In the NICU we always say breast is best, so if she is on breast milk we would certainly not recommend changing it.

DR. KUPER-SASSÉ: That's right, Anna Maria, but thickening feeds, as was shown by our reviewed article, Lasekin, et al., may be beneficial, although there is a lot of difficulty in choosing a thickener to add to breast milk.² As you mentioned we would like to keep them on breast milk, but a thickener certainly could be added if she were on a formula.

DR. HIBBS: One of the current issues with thickeners is the FDA statement that rice cereal may contain arsenic, and that has made choosing an appropriate thickener difficult, as we have found the AAP's recommendation for oatmeal at the bedside is technically challenging. In addition to thickened feeds for an infant who is already on formula, you may change to extensively hydrolyzed formula, as supported by the findings of Corvaglia, although this was a small pilot study.⁶

MR. BUSKER: Now what about the addition of a probiotic, Dr. Sassé?

DR. KUPER-SASSÉ: Probiotics, as shown by the Indrio study we reviewed, have been shown to improve regurgitation after three months of treatment,⁴ so this baby very well may have benefitted from some probiotic treatment.

DR. HIBBS: Yes, Meggan, this may benefit the patient periodically because of the likely disrupted gut flora related to prematurity and multiple antibiotic courses in the NICU. Although a sick NICU patient is different from the population studied in the Indrio paper⁴, it certainly is compelling to theoretically think that this infant may be very much in need of probiotics.

MR. BUSKER: Dr. Sassé, one final question on this patient. Do you think her reflux would likely improve without any treatment?

DR. KUPER-SASSÉ: That's a good question. I think the short answer is probably yes, it would; but I think it's important to note that this infant, while she is 3 months old, her corrected age is now only at term. So we're likely to not see her improvement until later on in her life. Usually we see improvement at about 4 months of life, and this infant being only term now may not improve until she's about 7 months old.

I'd also like to mention that the study by Hussain showed that physiologic reflux improves with physical maturation, regardless of treatment.¹ We've seen that in multiple studies; even in the placebo group the patients all tend to improve over time. So yes, I think she likely will improve over time, it just might take a little longer since she's a preemie.

MR. BUSKER: Dr. Hibbs?

DR. HIBBS: I agree that the natural history of GERD in term infants shows a peak in spitting at three to four months, and we don't really know how this translates into preemies. It may be that the peak is related more to their corrected gestational age than to their chronologic age. One of the challenges we have in our group is to try to use conservative therapy and non-pharmacologic approaches, because we feel that that's the most evidence-based approach, but there are multiple caretakers for these infants. When the infant is discharged from the NICU, she will be taken care of by a primary care pediatrician. In addition, if her lung disease has been severe enough, she may be involved with other providers such as pulmonology or maybe referred to GI for her GERD. And coordinating the approach, whether it emphasizes non-pharmacologic treatment or the duration of a trial of pharmacologic therapy is very important in these infants who need multidisciplinary care.

MR. BUSKER: I want to thank you both, doctors, for today's cases and discussion. Between the newsletter and today's podcast, you've provided a lot of information about the current state of recognizing and managing GERD in neonates and infants. But what about the future? What questions need to be answered to help ensure better care? Dr. Sassé?

DR. KUPER-SASSÉ: I think we need to see more large, randomized, double-blind, placebo-controlled trials of the non-pharmacologic treatments and their efficacy, as we've already seen that the pharmacologic treatments have been shown to be non-efficacious.

In addition, we also have a great need for safe and regulated probiotic treatment, and we should really do studies on those, as well.

DR. HIBBS: I absolutely agree, Meggan. I'd also like to see more studies specific to neonates less than 1 month old and to preterm infants to better reflect our NICU population, because even in much of the literature we're extrapolating from older infants. In addition, relatively rare patients in the NICU have high rates of reflux such as those with anatomic abnormalities, due perhaps to congenital diaphragmatic hernia, or esophageal atresia, or neurological impairment. I think that collaborative studies within a network are needed to address the treatment or reflux in these patients, because single-center studies won't have sufficient patients in their NICUs.

Even within the general NICU population that doesn't have neurologic abnormalities or anatomic abnormalities, there's a big difference between term neonates, larger late preterm or moderately preterm infants, and extremely preterm infants. Studies will have to parse these out, as their migrating motor complex development is different and their physiology may be different, and they may have different competing reasons for symptoms such as feeding intolerance.

So ideally, while we generally want studies to be brought to neonates in the NICU, a lot of subpopulations specifically need to be understood.

MR. BUSKER: Thank you for sharing your thoughts, doctors. I'd like to wrap things up now by reviewing what we talked about today in light of our learning objectives. So to begin: the distinction between reflux and GERD. Dr. Sassé?

DR. KUPER-SASSÉ: All three cases addressed whether the specific patient had merely reflux or symptomatic GERD, and that distinction is sometimes very difficult to determine. So we tried to elucidate those points with each patient.

DR. HIBBS: That's right, Meggan. The cases we reviewed showed a variety and severity of symptoms and included acute versus chronic symptoms; four symptoms that can be determined in time, such as spitting, back arching, or apnea; testing such as esophageal pH or impedance monitoring to help determine whether they correlate with the reflux event. Symptoms that we discussed such as failure to thrive or poor weight gain are much more difficult when trying to determine whether they are due to GERD or other morbidities.

DR. KUPER-SASSÉ: It's important to realize that the gold standard has to be symptom improvement when treating GERD in these infants, as that's what distinguishes GERD from just esophageal reflux.

MR. BUSKER: And our second learning objective: the evidence describing non-pharmacologic versus pharmacologic treatment options for GERD in infants and neonates. Dr. Hibbs?

DR. HIBBS: We discussed the utility of thickened feeds, hydrolyzed formulas, and probiotics for the patients. In general, the evidence for non-

pharmacologic therapy is stronger than that for pharmacologic therapy.

DR. KUPER-SASSÉ: We also discussed the data suggesting that PPI use is ineffective in these infants in almost every study that has ever looked at it.

MR. BUSKER: And our third learning objective: the role that the natural history of GERD symptoms has on symptomatic improvement in GERD treatment and GERD research.

DR. KUPER-SASSÉ: This is maybe the most important point we've made through this whole podcast. It's important to recognize that the anticipated natural history of these patients is that they will improve over time. And many studies have shown that and even some of the studies we reviewed showed that. Basically, we should always remember that any treatment we give to an infant should be removed after a period of time to see if the infant has resolved on their own.

MR. BUSKER: Dr. Hibbs?

DR. HIBBS: Several studies have shown that medications for reflux are among the most commonly used medications in the NICU and GERD is one of the most common diagnoses. And so better understanding how to diagnose and treat these infants is key to the care of our infants.

MR. BUSKER: From the University Hospitals Rainbow Babies & Children's Hospital in Cleveland — Dr. Anna Maria Hibbs, Dr. Meggan Kuper-Sassé — thank you for participating in this eNeonatal Review Podcast.

DR. HIBBS: Thank you very much. I've enjoyed the discussion.

DR. KUPER-SASSÉ: Yes, thank you very much, it's been my pleasure.

MR. BUSKER: To receive CME credit for this activity, please take the post-test at www.eneonatalreview.org/test.

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eNeonatal Review is supported by educational grants from Abbott Nutrition, Ikaria, and Mead Johnson Nutrition.

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REFERENCES

1. Hussain S, Kierkus J, Hu P, et al. Safety and efficacy of delayed release rabeprazole in 1- to 11-month-old infants with symptomatic GERD. *J Pediatr Gastroenterol Nutr.* 2014;58:226-236.
2. Lasekan JB, Linke HK, Oliver JS, et al. Milk protein-based infant formula containing rice starch and low lactose reduces common regurgitation in healthy term infants: a randomized, blinded, and prospective trial. *J Am Coll Nutr.* 2014;33(2):136-46.
3. Davidson G, Wenzl TG, Thomson M, et al. Efficacy and safety of once-daily esomeprazole for the treatment of gastroesophageal reflux disease in neonatal patients. *J Pediatr.* 2013;163:692-698.
4. Indrio F, Di Mauro A, Riezzo G, et al. Prophylactic use of a probiotic in the prevention of colic, regurgitation, and functional constipation. *JAMA Pediatr.* 2014;168(3):228-233
5. Barnhart DC, Hall M, Mahant S, et al. Effectiveness of fundoplication at the time of gastrostomy in infants with neurological impairment. *JAMA Pediatr.* 2013;167(10):911-918.
6. Corvaglia L, Mariani E, Aceti A, et al. Extensively hydrolyzed protein formula reduces acid gastro-esophageal reflux in symptomatic preterm infants. *Early Hum Dev.* 2013;89:453-455.