

## GER and GERD in Infants: What Are Your Treatment Strategies?

Editor's Note: This is a transcript of a live webcast delivered in English in October 2024. It has been edited for clarity.

### Overview of GER and GERD

**Julie Khlevner, MD:** Thank you, Jessica. My name is Julie Khlevner and it really is a privilege to be here with you. It is also my absolute privilege to copresent this with Dr. Rachel Rosen who'll follow me in a little bit. I'm a pediatric gastroenterologist and I work at Columbia University Medical Center in New York. My subspecialty is within neurogastroenterology and motility, and reflux is something that I see quite often, but particularly when it becomes refractory.

It is my pleasure to talk to you about reflux and how we can guide all clinicians to be comfortable with diagnosing and treating this really important and prevalent diagnosis.

When we think about preventative measures to help the body prevent reflux episodes, there is this antireflux barrier, which is physiologic, and it's made up of 3 things:

- One is the lower esophageal sphincter, which is a sphincter that is within the esophagus; it's made up of smooth muscle
- The other is the actual diaphragm
- And then, the phrenoesophageal ligament

All those 3 help, together, to provide the barrier to prevent things from coming back from the stomach into the esophagus.

If you notice, to the left, the scheme of something called an angle of His. That's an important angle to think about, when you think about reflux, because in infants this angle is quite obtuse. If it doesn't have a lot of pressure and capacity to withhold pressure from the stomach into the esophagus, that angle is obtuse until the infant starts to develop a little bit more of a core. You can imagine things can slosh up into the esophagus quite frequently.

There are also airway protective mechanisms that are in place that are quite intricate. But, more importantly, when the swallow is started and the upper esophageal sphincter opens, the vocal cords close to avoid spilling over into the respiratory tree. There's also coughing, which helps to clear if there's anything residual in the pharynx to avoid it spilling into the respiratory tree.

Unfortunately, there are risks for reflux within this physiology, including transient lower esophageal sphincter relaxation, that can happen routinely. It can also be induced by certain foods that we eat as adults or teenagers or adolescents, but with infants it's more related to the actual phenomenon, not necessarily induced by anything like food. And, of course, impaired esophageal clearing also propentiates the reflux

episodes and doesn't help clear. That's another reason why patients can have more frequent reflux.

When we think about reflux, there's so many terms that we use. I want to just take a moment to define some of them. Gastroesophageal reflux is really the passage of gastric contents into the esophagus with or without regurgitation, which means that the refluxate can get into your esophagus, your mouth, or pharynx, or vomiting, which is the actual expulsion of the refluxate outside of your mouth. But when you talk about GERD, which is gastroesophageal reflux disease, that D is quite important because that really talks about the troublesome symptoms that can accompany reflux and that can affect daily functioning or result in complications such as actual inflammation in the esophagus, poor growth, feeding difficulties, etc. And we'll talk a little bit more about that.

Then refractory GERD—I mentioned that in my quick introduction—but that's really when you cannot get a child or an infant to respond to optimal treatment after 8 weeks. This is a very loose term; it hasn't been really optimized. Perhaps 8 weeks is a little bit too much with too little time, but this is the best that we've got so far. And that's really what we coin as refractory GERD.

Reflux is quite prevalent. And if you look at this diagram, this sort of depicts how many infants, throughout their 12 months of life, have just episodes of regurgitation if it's more than 1, and that's that dark orange color. And as you could see, it's quite prevalent even at 1 month of age, and 3 months, and 6 months. But reflux really peaks at about 3 months of age and then usually starts to get better by 6 months of age. That's when infants get more core musculature. They're stronger; they can sit up a little bit, and that angle of His actually diminishes a little bit. It's no longer as obtuse; it's more acute. And that helps to prevent some of the reflux episodes that are happening.

As you can see, by 10 and 12 months, it's really dwindling down. And in fact, if you still continue to see reflux episodes in some patients between 12 and 15 months of age, that should strike you to really think about what else is going on—should you be thinking about something else as well? So really, most of our infants get better by 6 months and most resolved by 12 months.

There are certain risk factors that we are familiar with for reflux disease in infants. Particularly with preterm birth infants, we know that they're at risk for reflux, cystic fibrosis, and other chronic lung conditions in patients and infants; some congenital malformations, including congenital diaphragmatic hernia and esophageal atresia; cerebral palsy; and some neurological conditions can also be at risk. Obesity is also risk factor for



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reflux, but in infancy we don't necessarily need to think about that.

When we think about reflux in our infants, we're looking to understand what symptoms and signs they're presenting with. And sometimes—and oftentimes—they're quite nonspecific and can be quite variable, depending on the age. These are some of the more common symptoms and signs that we see in infants. In general, families often report some discomfort or irritability. It may be related to feedings. It may be after feeds. It may not be related to feedings. You can elicit poor growth—undernutrition or failure to thrive, as we used to call it. It can lead to feeding refusal in some infants. If they're associating food intake or formula intake or breast milk intake with symptoms, they can start to refuse. And that's something that we should be talking to families about.

They can have dystonic neck posturing or Sandifer syndrome, which I know is a term that a lot of folks are familiar with. You can have anemia, and that's mostly related to esophagitis, leading to some loss of blood in your gastrointestinal (GI) tract. You can have regurgitation, again, with or without vomiting. Some patients who actually have developed esophagitis can have hematemesis. You can have feeding difficulties, actual esophagitis and histology, which is inflammation in the esophageal mucosa lining. You can develop peptic strictures. We fortunately don't necessarily see that much in infancy, but we certainly can see that in older children that we care for. And, of course, Barrett's [esophagus] is something that we are very keen on. There are certain patient populations that are more at risk for Barrett's, particularly in the younger age group like our patients with esophageal atresia. But thankfully, we don't necessarily worry about that in infancy.

And there are airway symptoms that we also elicit: wheezing, cough, hoarseness, stridor, apnea spells. You can have recurrent pneumonia, recurrent ear infections. I would just caution to say that some of these things can be a little bit tricky because there are more common reasons for some of the airway problems than just reflux. And particularly if you see a patient with recurrent ear infections, I wouldn't think of reflux as the first thing to think about, but certainly should be on your differential.

We often get referrals from our ear/nose/throat (ENT) colleagues for patients with presumed reflux based on an airway exam. And I want to sort of caution you that there have been multiple studies to say that an airway exam by an ENT specialist cannot predict the presence of reflux. You can have red airway as pictured on the left. And that does not correlate with any reflux, whether it's objectified on impedance/pH probes or clinically relatable. And there's actual quite low

concordance between an airway exam and the presence of reflux in the gastroenterology world. A lot of these families come for treatment for reflux based on that exam. And sometimes, we almost have to take a step back and explain that this may not be the case, and start to wean off some of the medications that they often get started on.

You have heard a little bit about some of the challenges already. The symptoms and signs are quite vast, but there are significant challenges because there are no universal diagnostic criteria. We don't have any definitive diagnosis of GERD in infants at this point. We know what to look for, but we don't have anything that we can sort of fit into a box and say the patient fits this criteria. Again, and it's sometimes really hard to correlate symptoms with reflux events. A lot of infants cry, a lot of infants are irritable, and it may not be relatable to anything that is related to reflux events. And so just be cautious of that. Sometimes, families report a lot of reflux concerns, but it may just be colic and other things that are not related to that. Infants cannot verbalize their symptoms. The families are the ones coming to your office and the ones that are really reporting the concerns. And oftentimes caregivers' concerns lead to the determination of treatment options. Just be cautioned that a lot of families may have concerns, but you really need to understand whether there are concerns from medical standpoints and whether these patients need some treatment pathway that is outside of what they've been doing.

It is also important to get a thorough history and physical exam because, again, sometimes it's really difficult to decipher what you're dealing with in terms of differential diagnoses. Really important to understand the age of onset of symptoms. If symptoms started around 12 months of age, that's a little bit atypical for reflux at that point. So that should put you on an alert that maybe something else is going on. Understanding the typical age of onset is really important, which is that infancy, early infancy, peaking at 3 months of age or so.

Then, understanding whether the regurgitation happens right after a meal, within a meal, hours after a meal. Does it ever happen at night when the patient is sleeping? And whether something is digested or undigested. We'll have a little case at the end to talk about this a little bit, but sometimes patients can have an esophageal problem, and they're vomiting exactly what they're taking without any digestive process because it doesn't even reach into the stomach.

Then understanding the feeding pattern of an infant. How long is the infant feeding? Is the infant breastfeeding? Is it on formula? What type of a bottle? What type of a nipple are they using? How much are they taking? They can be overfed, and that's why they're spitting up or regurgitating. And also



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understanding how they're mixing: if they're using formulas, are they doing the right mixing instructions? Because sometimes it's really confusing to read those instructions, and so you want to make sure that they're not concentrating it too much or underconcentrating it. Are they adding anything additional to it to increase calories or thickening it? That's important for us to also understand because that can have manifestations and what the patients can come in with in terms of their symptoms. And then, how long in-between feeds the parents are giving the infant? All these things are important because this is where some of that behavioral modifications—lifestyle modifications—come into play because some of these things can be really remedied through proper feeding techniques.

Then, understanding family history. Family history of reflux disease is important because these things do run in family, so gauging that to understand the risks for that infant. And then understanding if there are any other possible triggers in the household, if there are any smokers in the household, etc, just to see and collect more data so that you're more comfortable with your diagnosis. And what the infant has been on in the past—any interventions? Has anyone done modifications, lifestyle or behavioral? Has anyone prescribed any medications, etc? That's also quite important because that can guide just how you're evaluating and treating the infant.

Growth is extremely important for all of us, particularly in the GI world. We want to understand if a patient is gaining the appropriate amount of weight and whether there's been any loss in percentiles through the infancy, and obviously red flags, which we'll talk about.

The red flags are quite important because that's where your reflux—gastroesophageal reflux—goes into that disease process or GERD. In general, any weight loss or lethargy, fever, excess irritability (which is a very poorly defined term), difficulty urinating (although a newborn may not be able to voice that). Again, regurgitation that happens a little bit later in life, more than 6 months of age, but definitely if it starts around 12 months of age, and then if the symptoms persist beyond 15 months of age, because you really want to understand whether there's other things that you should be thinking about outside of just reflux. Any persistent forceful vomiting should also be a trigger that there's something else going on. And one of the examples is pyloric stenosis, particularly if it's in the right patient population. Nocturnal vomiting is always a concern to us, particularly when the patient is sleeping, and that can signal that there's intracranial pathology. Bilious vomiting is also a concern. It can signal that there is some sort of an obstructive process, even things like malrotation, etc. Hematemesis is always a concern for a bleed, esophagitis, Mallory-Weiss tear,

multiple things can happen, so that's important to gauge. Chronic diarrhea in a setting of regurgitation is also important to elicit because that can move your diagnosis or differential towards potentially some sort of a milk protein allergy or potentially food-protein-induced enterocolitis syndrome (FPIES). Rectal bleeding, abdominal distension—so all those things are really important to understand because those are red flags that potentially can identify as GERD. But also, it could be that there are other diagnoses to consider.

This is a very busy slide, but really just to be comprehensive about what else can look like reflux in infants. And there's a lot of different things that we want to talk about. We've talked about some of them, which is, from a GI standpoint, pyloric stenosis, malrotation, Hirschsprung's disease, achalasia, which is a motor disorder of the esophagus. So again, if the patient is vomiting everything immediately after eating, it's undigested, you may start to think about an esophageal motor disorder. You may think about gastroparesis, which is delayed gastric emptying. If a patient is vomiting, for example, hours and hours after eating, there's discomfort associated with it, weight loss, it could be a little bit more than just GERD and you need to think about that. Obviously, peptic ulcers, eosinophilic esophagitis or eosinophilic GI disorders as an umbrella term, different food allergies and intolerances, inflammatory bowel disease, although we don't need to think about it too much in infancy. We do have very early-onset IBD that we take care of, and that can happen in infancy. That's also something to think about. And then pancreatitis, appendicitis, etc.

I'm not going to go through all of them, but just to point out that patients with heart disease can vomit. And sometimes, the diagnosis of heart disease comes through a gastroenterology office, and you see a patient who is vomiting and something doesn't seem right. And then potentially there is an X-ray that looks like the heart looks quite large or an electrocardiogram (EKG) that looks off. And so sometimes you can pick something up like that, but a lot of the times our patients with different congenital heart disease are vomiters, and they definitely can have reflux, but oftentimes it is related to their primary problem.

And then always think about other things, including neurological causes. That's always in the differential, specifically for nighttime vomiting. But that's something to think about and especially in a setting of a bulging fontanelle or a concerning eye exam in infants.

We don't necessarily need to do a lot more than just diagnosing reflux clinically, but sometimes, particularly in the presence of red flags or when other systems are affected and there's concern for additional feeding or growth or developmental



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problems, you may want to think about what else this could be outside of reflux. We may get something called an upper GI study, which looks at anatomy, and that is really helpful to rule out outlet obstructions, pyloric outlet obstructions, malrotation or other anatomic malformations. We sometimes do employ ultrasounds, particularly to rule out ureteropelvic junction (UPJ) obstruction or other etiologies for why the patient is having regurgitation or vomiting.

Sometimes when you, from a pediatrician standpoint, are treating patients for reflux, you recommended things, but you understand the next point in line is to refer to a gastroenterologist. And a gastroenterologist may consider doing an endoscopy. It's not always necessary, but it may be necessary if you suspect that there is actual esophagitis going on that you need to really treat aggressively or you're worried about something else like eosinophilic GI disorder because it's a histological diagnosis in addition to a clinical phenotype. You really want to make sure you get the biopsies done, or you're really not sure what is happening and you want to assess the GI tract a little bit more carefully, and you would employ an endoscopy at that point.

You can also do testing for reflux. It's a little bit more objective, called pH impedance testing. It's a probe study that you put through in there, and that gives you 24 to 48 hours' worth of information about what is happening between the stomach and the esophagus. That also helps you to correlate clinical symptoms. For example, if you have a patient who has extraintestinal manifestations and you're not even sure if they're related to the GI tract, that sometimes helps us understand whether there could be some correlative properties that are going on. And then, if you do suspect a motility disorder like achalasia, I've mentioned—that's just one—you may employ esophageal manometry. Again, all these tools are utilized by gastroenterologists.

What's important to note is, even if a gastroenterologist does an endoscopy and does biopsies and the histology is normal, it does not rule out reflux. You can have significant reflux with normal histology. And we know that, particularly in infants and young children, the mucosa—it's a good barrier mechanism—and sometimes they may not be inflamed, even with significant clinical concerns.

### GERD Management: Nonpharmacologic Treatment

**Rachel Lee Rosen, MD, MPH:** Thanks, Dr. Khlevner. When we think a lot about reflux, as you heard, Dr. Khlevner and I both are motility physicians. And when I'm on X and I'm tweeting about things, almost always I use the hashtag, #itsnotreflux because I think our understanding of reflux has really changed quite a bit over the last 10 years. And things that previously

were blamed on reflux really are not reflux. And we really see our goal as gastroenterologists to think about other differential diagnoses. And we'll talk a little bit about our concerns about why overdiagnosing GERD really has implications, going forward, for pediatrics.

We are going to talk a little bit upfront about the nonpharmacologic treatments, and I think these are really important, and our understanding of these has really evolved over time where this is now, in my practice, numbers 1, 2, 3, 4 for intervention. This is really a big part of what we do. Most patients who get to a gastroenterologist are not here to hear reassurance that things are fine, because usually at this point things have escalated to the point where the patients are having other symptoms that are severe enough to merit referral to a specialist. But I think, for most, regurgitation—or what we used to call happy spitters—those babies, for all of our purposes, have normal physiology. And as Dr. Khlevner talked about, regurgitation is really, really common. Regurgitation in itself doesn't give you the D diagnosis—doesn't give you the GERD disease. We know, as you heard, that things get better over time. Our goal is really how can we buy time to get to that 6-month mark where things start to improve at 6 months? And in addition to the changes in physiology, there's another big factor that happens at 6 months, and actually now even a bit earlier because of the changes in the American Academy of Pediatrics, but it's early solid introduction. So solid food really results in less reliance on the liquids, which are easily refluxed, and early solid food introduction, which is something we use a lot in babies with significant reflux.

As you heard about the warning signs, we really take those seriously. We look a lot for other diagnoses. Now, one of the things that comes up other than reassurance is positioning. This always is, "I have to hold my baby upright for an hour, 2 hours, 3 hours." And, oh my goodness, families are walking around the house with an upright baby for 12 hours at a time, which isn't really conducive to much of anything. Despite us recommending that, there's not a lot of data to support that. And we'll talk a little bit about the positioning data that's out there.

You already heard about how to assess for what the volume of feeds are. Trying to avoid overfeeding is really important. Knowing what nipple the patients are taking is really important. If you have a baby who is on a level 3 nipple, they may be swallowing lots of air that may be contributing to their regurgitation, or they may be aspirating because they're using such a wide-holed nipple. Again, just knowing all of the aspects of feeding, including what bottle system they're using, what nipple type they're using, are they adding anything into the bottle, is really important.





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And then there's nutritional interventions. And this is one of my most favorite topics of all times, which is thickening—because we do a lot of it—and we'll talk a lot about thickening today. But thickening has really become the mainstay of our management, and not only for infants, but for all patients, to the point where we're now thickening almost everything that goes through gastrostomy tubes at this point, as well. And we can talk a bit about that.

We're also going to talk a little bit about using hypoallergenic diets. Again, a lot of these recommendations are from our pediatric GERD guidelines that we published, but I think things have changed a lot. Whereas in the past we had a several-week trial of a hydrolyzed formula or amino acid-based formula, I think now, really thickening has taken over that. And I think I suspect in the next iteration of guidelines, this may change a little bit.

What about the data on positioning? We know from very early studies that being prone or being left-side-down are positions that reduce gastroesophageal reflux. And these are studies that were done with both pH probes but also pH impedance probes. We know those positions reduce reflux, but as we also know, sudden infant death syndrome (SIDS) is a really big problem. Babies cannot be prone or cannot be left-side-down when sleeping. These are things that if you're playing on a mat and the baby is awake, that's something to think about. Tummy time is always great when kids are awake, but obviously not when asleep. From an inclined position, while we often hear that keeping the baby upright is helpful, there's not a lot of data to support that. While we often will recommend it or families will find it helpful, the studies just haven't been done to show that there's a major benefit to reducing symptoms. And again, just a reminder that babies should always be asleep flat on their back, without the head of the crib elevated, to reduce the risk of SIDS.

What about thickening of feeds, and why am I so excited to talk about thickening today? It's because the data suggests that it really does help. We know that thickening reduces visual regurgitation in meta-analyses. This has been shown to be beneficial. We know that we reduce the number of days with any regurgitation, and we increase weight gain when babies are fed thickened formula or breast milk. Thickened feeds have not been shown to reduce these extraesophageal symptoms or these other symptoms that Dr. Khlevner talked about. And I think this is really key when we're talking about refluxes. Are these symptoms really reflux-related or is it just people automatically jump to the belly as a cause for things, but we don't really have any data to support it? And, in fact, there are studies that have been done where people have had pH-impedance probes in the esophagus, and babies were videotaped and people scored, do you think the baby's having

reflux, yes, no? And in fact, people were wrong 50% of the time when observing babies. The bottom line is, we stink at diagnosing gastroesophageal reflux. You really have to be careful in just relying on symptoms to make assumptions.

What about the stepped-care approach for nonpharmacologic interventions? These guidelines that we have talked about, we talk about reviewing the feeding history. Often we recommend smaller, more frequent meals. We know that there's an instinct to concentrate formulas, add more calories to give less volume. But what we know is, more or less, that the more calories you put in the bottle, the slower the gastric emptying. You don't want to make a patient worse by concentrating the formula to very high calories per ounce, so you do have to take that into consideration. And then lastly, a trial of thickened feeds, and I cannot stress enough how important it is if you can work with a dietitian if you have that ability in your practice to help you with these things, as well as a speech language pathologist or an occupational therapist, depending on which hospital system you're in.

What about breast milk and thickening? This is a really controversial topic. We love breastfeeding. Breastfeeding is an amazing thing to do. But for babies who have significant gastroesophageal reflux disease, sometimes we have to just change the way we give breast milk and we need to give it by bottle with thickening in the breast milk. Just as a reminder to everybody, you cannot put cereal in breast milk. It will not thicken appropriately because the amylases in the breast milk will chew up the cereal. You have to use commercial thickeners if you're going to use breast milk thickening. For infants, the only one that is approved for use is the carob bean gum thickeners. And these are for babies who are past term. And the other option is food-based thickeners, which I'm sure we'll talk about in the questions. And just a reminder that xanthan gum thickeners have been associated with necrotizing enterocolitis in babies, and so they cannot be used for infants under the age of 1. But food-based thickeners are always a possibility. Again, just keep in mind that if you need to thicken breast milk, you have to go with a commercial thickener.

Are there any contraindications to thickening? And I think this is really, really important when we think about which infants should get thickening. And here, the question has to be, can the infant get thickening? And what thickening are you thinking about? What you see on the slide are the contraindications for commercial thickeners. These are the carob bean gum contraindications, and this is the Rachel Rosen bias. This is not based on data per se, but this is who, at Boston Children's Hospital, we will not give commercial thickeners to. If the patient has a significant motility disorder, so Hirschsprung's disease, for example, or pseudo-obstruction, we will not use



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commercial thickeners. If the baby has heme-positive stools, we will not use commercial thickeners because in our head, we're worried, "Is there a mucosal breakdown that may trigger this patient to develop necrotizing enterocolitis (NEC)?" We don't use commercial thickeners in babies with poor intestinal perfusion. These are the congenital cardiac disease patients that are in poor perfusion states. And then, lastly, any baby who has a history of NEC or had a NEC watch while in the neonatal intensive care unit (NICU), we will not give commercial thickeners.

The other thing that you have to think about when you're recommending thickeners is all of the other stuff that goes with the thickening products. And I can't stress enough, as a dietician or as a speech language pathologist or as a gastroenterologist or pediatrician, you need to know about the products that you're recommending to your patients. First of all, clumping or inconsistent thickening. Often, we see clumping when we use oatmeal cereal, which can be problematic. Sometimes, before we put oatmeal in a bottle or rice cereal in a bottle, we put it in a blender, and we pulverize it before we put it in to try to make the grains as small as possible. We think about viscosity changing over time. If a family has to make thickened bottles before they send their kid to daycare and those bottles are going to sit in a refrigerator all day, they may take that bottle out at 3 PM, and it may look like liquid concrete. You have to know, is that thickener going to change over time? Because if it is, and the child's in daycare, you need to work with the daycare to mix the bottles on demand or change the thickener you're recommending.

What about nipple clogging? The worst thing that could happen is, we recommend a thickener and the baby can't get the formula or breast milk out of the bottle. We don't want the families then cutting the nipple or going to a bigger size nipple without consulting because we may take a baby with reflux and convert them to an aspirating baby because now they're getting waterboarded by a nipple that has too big of a hole. We have to think about decreased liquid intake. Although, to be honest with you, that is almost never the case in our practice. If we have decreased liquid intake, you have to stop and say, "Is that an extraction problem?" That raises the red flag, is this a neurologic condition if they can't get the thickening out? And then, stooling changes. Some kids get looser stools; some kids get firmer stools. And I think the key here is rotating thickeners whenever possible.

### GERD Management: Pharmacologic Treatment

**Rachel Lee Rosen, MD, MPH:** Let's talk about medications. And this is why the hashtag #itsnotreflux is really important. There's lots of medications out there for reflux. We have antacids and alginates, which are really given on an as-needed basis. This is

things like Maalox, Mylanta, those types of medications that neutralize on contact but do not last very long in the stomach. And we almost never will use these in infants. And I just want to highlight, as Dr. Khlevner talked about, that a lot of reflux in infants is the formula or milk that's coming back up. You may not have mucosal damage there. It may be bothersome because the esophagus gets stretched, but the majority of babies have nonacidic gastric contents. A lot of these things that we're going to talk about really don't work because acid isn't a problem in infants for the vast majority of infants.

The other acid suppression agents that we have are proton pump inhibitors, and these are your omeprazole, lansoprazole, esomeprazole, which typically are given once a day, and they impact the proton pumps in the parietal cells. You have the H<sub>2</sub>-receptor antagonists, and right now, the only one on the market for infants is famotidine. These are more mild than the proton pump inhibitors. And then lastly, just approved this past month, are the potassium competitive acid blockers (PCABs), which are not sensitive to meals to the same extent that proton pump inhibitors are. Proton pump inhibitors have to be given—or preferably given—on an empty stomach. PCABs can be given at any time during the day.

Okay, so mentioning those, but the bottom line is I don't want you guys giving those. And here's the reason, and I think our understanding has really, really changed on how these meds work. First of all, there's 2 randomized controlled trials of infants showing no benefit of these medications for infants. But perhaps more importantly, is that we have lots of risks now that we're just starting to come to understand, 1 of which is dysbiosis. We know that from studies that we did, and others, that the gastric fluid of patients on these medications, they grow staph and strep in the gastric fluid, which really worries us. We don't want overgrowth of these bacteria. We know that kids are at increased risk for infection such as *Clostridioides difficile*, related to acid suppression. We know there may be an increased risk of fracture and maybe obesity. But the 1 that I really want to highlight to you is this potential increased risk of allergic disease. We don't want kids to develop allergies as a result of these meds, and what it's looking like is early infant exposure to these meds increases your risk of asthma, food allergies and—more concerningly from the gastroenterologist's perspective—eosinophilic esophagitis, which is a lifelong allergic condition of the esophagus. We really don't want infants exposed to these drugs if we don't have to.

We already talked about the risks, and for preterm infants, I just want to mention necrotizing enterocolitis, late-onset sepsis including sepsis related to UTIs and increased risk of mortality. Currently, the North American Society for Pediatric Gastroenterology, Hepatology & Nutrition



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(NASPGHAN)/European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recommendations are really not to use acid suppression for otherwise healthy infants who have regurgitation or in patients with crying or distress who are otherwise healthy or for extraesophageal symptoms. We really do not treat cough, choking—those spells—with acid suppression anymore because we worry a lot about the respiratory infections associated with acid suppression use. It is first-line recommended, these medications, if you have proven esophagitis, as Dr. Khlevner talked to you about. And then lastly, if you cannot get to a gastroenterologist or you want to try acid suppression and you feel that the child needs it, the original guidelines recommended 4 to 8 weeks of acid suppression. My hope is that with any future guidelines we'll get down to 2 weeks at most. I think we really, really want to treat for the shortest amount of time possible, and so we would recommend that for all of you.

### Management of Uncomplicated GER in Clinical Practice: A Case Study

**Julie Khlevner, MD:** We'll start with the case and hopefully as we go through this, some of the points that we talked about will come up in your mind as something that sounds quite familiar. This is a case of a breastfed infant with regurgitation. It's a 5-week-old who is exclusively breastfed, a term infant brought in by parents with concerns about constant irritability, fussing, and regurgitation.

When you get a little bit more of a history, the infant is having regurgitation of curdled milk 4 to 5 times per day, usually in 10 to 15 minutes of feeds. They're quite frequent, and in addition, he seems to be inconsolable—crying or fussing. And these episodes can last anywhere between 30 and 60 minutes, and they occur throughout the day.

On exam, the baby looks fine, unremarkable vitals. There's been a great weight gain from the past visit, which was 3 weeks ago. The infant has gained 900 g, and on exam, the infant is fussy when laid supine, but improved when held upright. And otherwise, it's unremarkable. I'm going to just troubleshoot Dr. Rosen here just for a moment to get her opinion whether she thinks any of this is concerning for something that is a problem, or are there any red flags that we should be concerned about for this infant?

**Rachel Lee Rosen, MD, MPH:** Yeah, no, I think this is a pretty typical case that we might see or that you guys might see. And I think the key from my perspective when I'm listening to the story is that the spitting up happens right after a feed. So again, this gets to that nonacid reflux component. What's coming up is going to be milk. I don't think that this would be a case where I would take meds and put them... Take them off the table at

this point because, in my opinion, what's coming up is not going to be acidic. This would be a great case where we would talk about more of the feeding-related issues, and I would think in my head, "Oh, this might be a great case to think about some thickened bottles." And what I would say is, especially in infants that are breastfed, this might be a kid where you would say, "Okay, breastfeed throughout the day, but why don't we take 2 feeds and just put those 2 of the let's say 8 feeds, and try that in a bottle with thickening, and let's see if with the feeds that got thickened vs being fed on the breast, the kid improved in any way." And if there was improvement, then we could add some more breast milk-thickened bottles.

There's nothing in the story that would make me say I shouldn't use a commercial thickener for this baby. There was no prematurity. There's no blood in the stool. There's no history that would make me think that that wouldn't be a possibility if we needed to do that. Now, the fact that the baby was fussy when supine but improved when held upright or prone doesn't push me one way or another to say this is GERD or not. I'm happy this baby is growing well, which is amazing. I don't see any big red flags here, so this would be a kid where you could either offer reassurance or I would offer some thickening to see how things go, but I probably wouldn't do a whole lot more, but I'd love to see, Dr. Khlevner, what comes next.

**Julie Khlevner, MD:** Alright. You provide the parents with counseling as Dr. Rosen has just kindly discussed, which is that this is likely gastroesophageal reflux. It's quite common and you really just counsel the family on some of the lifestyle and behavioral modifications that we talked about. Make sure that the volume of the feed isn't insane, that the patient isn't feeding every hour of the day and that potentially the thickening could be something that could help with the episodes of reflux that are happening. And again, you stand on your stance, which is that there is no indication for acid-suppressive medications at this point, exactly to the fact that there's no evidence for it and there's actually significant risks that should be accounted for. And then you also remind the family to follow up and of course, always reach out if there are any concerning reflux that had developed or anything else that perhaps develops from the point that you saw that patient.

And to support some of the things that we just talked about—again, bringing up Dr. Rosen's guideline, which was published in 2018—and really in the absence of alarm signs, it's really behavioral and lifestyle modifications. Avoid overfeeding. You can consider thickening feeds but should continue breastfeeding as it is for this infant that I just presented. If the patient is improved, great, but if not improved, you can consider having the mother eliminate milk from the diet as a trial period, as the next step in this algorithm. Or, if the infant is



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being formula fed, you can consider extensively hydrolyzed formula in that setting. Again, it used to be that you do this forever and ever and really keep these families dairy free or an extensively hydrolyzed formula until they're 12 months of age. This has all been reneged, and we think that it should be a really small trial period where you really encourage the families to go back and see, because a lot of times when they go back to a prior formula or just breastfeeding without milk elimination, they actually are fine. But if the patient is still not doing well, then you really want to involve your subspecialist, including a gastroenterologist.

But just to put things in perspective, we know that acid suppression is not good for infants. There's no data to support its use, and yet a lot of studies are showing that we're still very prevalently prescribing it. This is a study, the first one where 7% of all infants have prescribed acid suppressive therapies, I believe this was out of Virginia where they pulled Rx for H2 blockers and proton pump inhibitors (PPIs), and 7% of healthy infants were prescribed these type of medications. It's a very crude study, so it's really hard to know exactly what the indications were, but it's quite prevalent knowing that it's not helpful. And then it's also being prescribed in the inpatient setting as well. One in 4 is a study looking at a NICU (neonatal intensive care unit), and 1 in 4 infants were prescribed a PPI or an H2 blocker. But what's worse is 56% of those infants were actually sent home on these medications without reconsidering whether they actually were needed. So again, it remains a problem. It's still quite overprescribed, and hopefully we'll change your mind about doing that in your own practice.

I think we've beaten this point, but I would want to say that the timing of reflux onset is really important. We talked about why that is, and most of the time there is no indication for any further workup in a healthy infant who's thriving, who's just regurgitating.

### Differential Diagnostic Approach to GER Red Flags: A Case Study

**Rachel Lee Rosen, MD, MPH:** This is an infant with feeding difficulties, a 7-month-old former preterm infant, now 6 months corrected, brought in with the symptoms of feeding difficulties, reflux, crying, and wheezing. The baby was born by 36 weeks' gestation by cesarean delivery and was discharged from the NICU at 40 weeks.

Going back, this child had lots of respiratory infections, infrequent otitis media, gagging and coughing during feeds, started about 2 to 3 weeks prior. A lot of regurgitation, occasional vomiting, family reports audible wheezing, and thank goodness no cyanosis or apnea. What would you be thinking at this point?

**Julie Khlevner, MD:** I think this is a little bit more of a concerning infant. There's definitely red flags involved here (feeding difficulties). I would like to understand a little bit more. There's also concern that potentially there is now extraintestinal manifestations, so the respiratory tract is now being involved as well, and the wheeze is also a concern. That there is a little bit more than just a typical reflux that potentially is happening here. At this point I would like to understand whether this is just a respiratory problem or this is a reflux that's causing or leading to respiratory difficulties and whether there is presence of oropharyngeal dysphagia or other aspirations for this infant that's presenting with such a significant history.

**Rachel Lee Rosen, MD, MPH:** Yes, great point. I'm going to give you some more history. The kid's been growing, initially 50th percentile weight-for-age, and then that dropped down to 10th percentile over time. On physical exam there were some transmitted upper airway sounds, but otherwise unremarkable. Any red flags here for you?

**Julie Khlevner, MD:** I think the poor weight gain is a significant problem. There's a downtrend in weight percentiles and that's always a red flag in all of our minds. And the transmitted upper airway sounds is very nonspecific. A lot of infants who have potentially reflux with aspiration just sound junky and congested at all times, and it's mostly just from their sort of oropharynx and not necessarily a problem, like a lung issue that you would think about in a child with asthma.

**Rachel Lee Rosen, MD, MPH:** That's great. Great. Alright, and just because we are getting short on time, and I see there are a lot of questions, I'm going to zoom forward ahead. Dr. Khlevner, what appropriate next step would you do? If you could pick 1 test, what would it be?

**Julie Khlevner, MD:** If I were to pick a test, I would probably do a speech-language pathology evaluation. I would send this child for a feeding.

**Rachel Lee Rosen, MD, MPH:** And I think that's amazing. As we say in GI, that reflux is only a problem if you can't protect your airway. You've got to rule out aspiration, and I love that suggestion to see speech-language pathology. And as you can see in this case, the infant was diagnosed with oropharyngeal dysphagia and managed with thicken formula and feeding. So just as a reminder to everybody that when you thicken, you're not just treating reflux but you're also treating oropharyngeal dysphagia and swallowing dysfunction. You're treating 2 things for the price of one, which is great.





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Just as a reminder, in the big pediatric medical centers, there's lots of multidisciplinary care. Dr. Khlevner is in an amazing multidisciplinary care program at Columbia and there's others elsewhere where you can get perspective from pulmonary ENT and GI.

### Key Takeaways

**Julie Khlevner, MD:** Hopefully from today's presentation you have taken away some key points which I'll review quickly. Because infants cannot verbalize when symptoms are troublesome, as we talked about, the extent of caregiver concerns is usually the driver for some of the things that we do on a day-to-day basis. Just be careful and try to objectify some of that with your own history and physical exam. Again, that is the only thing that is mostly needed for uncomplicated reflux. Infants should be evaluated for potential red flags at all times, including persistent forceful vomiting, if there's any issues with urinary complaints, and also take it seriously when onset of symptoms happens after 6 months of age, because that's mostly concerns for something else going on.

It's also quite important for all of us to do a good job in reassuring some of these families, particularly if there's no red flags and you really do think this is just simple reflux. Provide the right counseling on proper feeding practices. Some nutritional interventions, as discussed by Dr. Rosen, that are really the cornerstones of reflux management at this point. Perhaps head elevation in left lateral position may improve reflux symptoms, specifically in the first hours. But I think we still need a lot more evidence to routinely recommend this. And infants with persistent reflux and significant distress may benefit from thickened feeds as an intervention in your office. Pharmacological interventions like acid suppressants are really not routinely recommended, in fact are not recommended at all unless there's certain patient population, particularly if there's histological evidence of esophagitis that you're trying to treat. There's really no role for these agents. All right, well, let's get to some questions.

### Questions

**What is the earliest age you recommend thickening formula or human milk? Do you have any concerns regarding changing the macronutrient profile, since thickeners increase carbs, and thereby decrease protein and fat concentration?**

**Rachel Lee Rosen, MD, MPH:** Yeah, that's a great question. The answer for us typically is there's no age where we won't thicken. I think this is where that multidisciplinary care is really important. We're very blessed that we have speech-language pathology and nutrition in our clinics with us. We're able to talk about these issues. One of the key things I think with infants that's really important is the rotation of thickeners. It is very

rare for us to take an infant and just put them, let's say, on just a carob bean gum thickener. We would often do 2 bottles with carob bean thickener, 1 bottle with banana, and 1 bottle with cereal, just to rotate things.

We prevent the microbiome from changing significantly. We're also pretty conscious about the macronutrients, and as you appropriately mentioned, that's something that we think about a lot. Our goal for reflux thickening is to thicken to slightly thick or mildly thick on the International Dysphagia Diet Standardisation Initiative (IDDSI) testing. That's what our goal is. Sometimes we have to go to moderately thick, but again, it depends on the child. I would say there's no age that we won't thicken. We'd much rather thicken than, say, put in a feeding tube. If given the risk benefit, we will choose thickening over other interventions. But my recommendation to you guys is to rotate your thickeners as best as you can.

**What would you suggest to use to thicken regular infant formulas if specialized thickened formulas are unavailable?**

**Julie Khlevner, MD:** As Dr. Rosen has mentioned, you can actually use baby foods to thicken formula and cereal. I would just put a caution out that there are risks of toxicity, so just be careful how much you're putting in. There's a risk of toxicity for arsenic and other things that you're utilizing, even if it's jarred baby food or even baby food that you make at home. Just be careful. There are guidelines that are out there in terms of how much would be a concern per day, particularly for using things like rice cereal or something like that. Again, that is that rice or any type of cereals are not feasible for breast milk because they will chew it up. But if it's breast milk, I would probably just use baby food.

**Will thickening formula help a leaking G-tube for an older child?**

**Rachel Lee Rosen, MD, MPH:** That's a great question. When we think about G-tubes, one, the first thing we think about is, is the size right or wrong? The second thing is, is it leaking because the pressures in the stomach are too high, which is often a sign for us that there's a motility problem? But then the third option is, again, is what we're giving too thin? And so absolutely the first thing we do with a leaking G-tube, if we've looked at all of the hardware and everything looks okay, is to add thickening to the G-tube feed. A hundred percent, I think that's a great question, an absolute yes.

**When babies in the NICU have some desaturation and bradycardia events while an NG tube is infusing, suggesting the spells are attributed to reflux, are there data that show that positioning with the head of the bed up during the feeding helps decrease these spells?**



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**Julie Khlevner, MD:**

I can tackle it. I think Rachel has also mentioned this before, we have zero data on this, and I think it's really important that we practice what is feasible and best for that infant and how many of our infants can keep their head up positioned and on an incline without falling off or sliding off, so it's not always a tactic that has any evidence for it, but if you find that that is helpful in your own patient population, go for it. But again, there's really no evidence to say that it is absolutely effective in the NICU atmosphere.

**Rachel Lee Rosen, MD, MPH:** I would just put a plug in there for the babies that are on NGs, that is where the products that have the anti-reflux formulas that have the rice starch in them would be very good. And 24-calorie anti-reflux formulas are typically slightly thick, but they become much thicker in the stomach. In the baby with significant reflux in the NICU, we would often go straight to an antireflux formula.

**Is the presence of bradycardias and desaturations with feeds always associated with reflux?**


**Rachel Lee Rosen, MD, MPH:** Absolutely not. This is also another favorite question that what we know now is these apnea and bradycardia episodes often actually are a sign of oropharyngeal dysphagia. And I think this is where Dr. Khlevner's point about getting a speech-language pathology consult is critical because we really, really, really know now that this is much more an impaired airway protective mechanism than anything else. This is where a speech-language pathologist or a video fluoroscopic swallow study would be very helpful. I would say definitely not. And again, with apnea and bradycardia, also always think about the heart, as Dr. Khlevner had mentioned.

**What thickeners would you recommend for a preterm infant?**

**Julie Khlevner, MD:** I think we touched on that for preterm infant. I think you really want to make sure before you thicken that there's no concern for NEC, that there's no concern that there's any blood in a stool. Really evaluate the infant. And if you are not concerned about any of these things, then again, food-based thickeners can certainly be an option in that patient population.

**Can we expect new guidelines on the management of GERD from NASPGHAN?**

**Rachel Lee Rosen, MD, MPH:** Yes, we are absolutely working on this, Dr. Khlevner and I are deep in the weeds on getting this going because I think we really need to, so much has changed in this field and we really need to update those to really limit the role of medicine.

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