Over-Prescription of Acid-Suppressing Medications in Infants: How It Came About, Why It's Wrong, and What to Do About It

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It has been almost 20 years since proton pump inhibitors (PPIs) were initially shown to be effective, safe, and well-tolerated for the short-term treatment of gastroesophageal reflux disease (GERD) in children over 1 year of age[1]; GERD diagnosed on the basis of symptoms and hard diagnostic evidence of erosive esophagitis seen at endoscopy.[2] In these studies, mostly performed in children 2 to 17 years of age,[1-3] PPIs were shown to effectively treat symptoms and erosive esophagitis that were refractory to histamine-2-receptor antagonists (H2RA), buffering agents, prokinetics, and in some subjects, antireflux surgery. Subsequent to those studies with omeprazole, other PPIs were found to be similarly effective.[4-8] Efficacy and safety were also shown for maintenance of remission of chronic, relapsing erosive esophagitis in prospective studies as long as 2 years,[9] and retrospective studies as long as 11 years of use.[10] Approximately 80%[10] of children who require long-term treatment for GERD have underlying disorders that predispose them to GERD, such as neurologic impairment, repaired congenital esophageal anomalies (eg, esophageal atresia), chronic lung disease, hiatal hernia, a strong family history of GERD, Barrett's esophagus, or esophageal adenocarcinoma, or obesity.[11] In children without these underlying disorders, GERD is usually not chronic or severe,[12] and most commonly follows a presumed upper gastrointestinal infection with post-infectious dysmotility and delayed gastric emptying, which resolves with time. In other words, in most otherwise healthy children, GERD is not chronic. In children in whom it is, the use of PPIs has revolutionized the long-term treatment of GERD, much for the better, including allowing for significantly decreased rates of antireflux surgery in some centers.[13]

In this overall context, the topic of reflux in infants (ie, <1 year of age) deserves special and urgent attention. Recently, the use of PPIs in infants has rocketed. One large study of US healthcare databases showed that in the 6 years from 1999 to 2004, there was a >7-fold increase in PPI prescription. One of the PPIs, available in a child-friendly liquid formulation, saw a 16-fold increase in use during that 6-year period.[14] Overall, approximately 0.5% of the approximately one million infants in the study database received a PPI during their first year of life. Approximately 50% of the infants started taking a PPI before 4 months of age.[15] These data would imply that somehow the diagnosis of GERD has been missed over the past several decades or has recently become a major scourge of infants in the developed world, with acid suppressing drugs becoming a new essential food group in their own right. This change in practice has come about for several reasons, none based in medical science. There is, however, data to show that this practice does not serve our patients.

Two phenomena have long been observed in otherwise healthy, thriving infants. First, many of them spit up on a daily basis—some 40% to 70%.[16,17] The developing, rapidly-growing infant takes in feeding volumes that on a per-kg basis are huge compared with older children or adults. Infants have relatively poor gastric compliance and a short esophagus; therefore, some of the large volume intake simply overflows upward, or sometimes "spills" (lingua Australiana) out through the mouth. This has long been recognized as physiologic reflux not reflux disease [ie, not GERD]), and it is self-resolving in approximately 95% of infants by 12 to 15 months of age.[16,17]

Second, many infants are irritable or have "unexplained crying,"[18] sometimes also referred to as "infant colic," especially in the first 3 or 4 months of life. Spitting up and crying are common; in most infants, it is a case of highly prevalent symptoms or signs occurring contemporaneously, without necessarily having a cause-and-effect relationship (ie, a case of true-true-unrelated). However, increasingly, crying and spitting up have become conflated into a diagnosis of GERD. In the case of infants, most reflux is buffered by frequent feeds and seldom is of acid pH,[19] which seems to have been largely ignored by prescribers of medication. Even when crying is temporally related to reflux, the crying might be caused by distension of the stomach by meal or distension of the esophagus by meal-buffered refluxate which is non-acid (ie, "volume reflux")[19]; or the crying itself, of whatever cause, might result in gastroesophageal reflux (GER) secondary to raised intra-abdominal pressure.[19,20] The largest randomized, controlled study to date in infants showed that for symptoms purported to be those of GERD, a PPI was no better than placebo.[21] A smaller placebo-controlled, cross-over study with a different PPI showed similar findings.[22] With increasingly less time to evaluate

DTC	Direct-to-consumer
GER	Gastroesophageal reflux
GERD	Gastroesophageal reflux disease
H2RA	Histamine-2-receptor antagonist
PPI	Proton pump inhibitor

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patients, rather than take on the more time-consuming history, discussion, and approaches, including behavioral and dietary, that are required around the evaluation of unexplained crying, and not without parental pressure to "do something," doctors have taken to a quicker approach: prescribing.

The rise of prescriptions owes a lot to advertising, specifically to use of the term "acid reflux." Before the mid-1990s, this term was hardly ever used in clinical practice; the medical terms were and are "GER" and "GERD." In the mid-1990s, rules around direct-to-consumer (DTC) advertising were relaxed in the United States, and expenditures on broadcast advertising for drugs began to ramp up by multiples.[23] Around this time, marketers for pharmaceutical companies began to promote and popularize the term "acid reflux" in the increasing advertising blitz for acid-suppressing drugs, both PPIs and H2RAs. "Acid reflux" became embedded in the popular lexicon thanks to the strategy devised by those "not so Mad Men." The reasoning was simple: if reflux is possibly present—whether physiologic, acid, or non-acid—and you choose to call it *acid* reflux, it naturally follows that it requires an *acid*-reducing drug! This manages to blur the lines between normality and pathologies and, with an uncomplicated message to the marketplace, bypass the need for the subtleties of clinical diagnosis. In 2005, PPI sales grossed approximately $13 billion in the United States alone, and the drug on which the most DTC advertising was spent was a PPI.[23] A price is paid for advertising and over-prescription, and, one way or another, that price ultimately is paid by patients. The price may be more than financial.

Only in the last few years has the term "acid reflux" been used in a bona fide sense to refer to the actual acid reflux found on pH-impedance testing, which is different from reflux that is "nonacid" or "weakly acid" (ie, results of a very specific test versus a clinical condition).

Before long, infants who were spitting up (ie, physiologic reflux) or were just irritable without an immediately apparent explanation were being diagnosed by their parents or doctors as having "acid reflux." To be fair, it should be pointed out that, to date, marketing by pharmaceutical companies has not been directed at use in infants because PPIs are not US Food and Drug Administration-approved for use in infants (ie, <1 year of age). Furthermore, most of the clinical research pertaining to the use of PPIs in children in the last many years, which has yielded invaluable efficacy and safety data, has been funded by industry. This includes positive studies in older children and the study in infants that showed that drug performed no better than placebo.[21] Regardless, it is recognized that more advertising leads to more requests by patients for advertised medicines and more prescriptions.[24] The term "acid reflux" as used in the marketing of PPIs to adults has simply trickled down to children and, in more recent years, to infants.

As a result of DTC advertising, from the mid-1990s, a definite shift began to occur. Instead of patients complaining to their doctor of heartburn or describing their symptoms, their presenting complaint became the self-diagnosis or diagnosis of their child as having "acid reflux." Many children themselves come in telling their doctor they have "acid reflux"! In the absence of better information and physician guidance and fed by advertising and misinformation on the Internet, parent blogs have increasingly promoted the "my-baby-has-acid-reflux-and-needs-drugs" concept. Parents, concerned by their infant's symptoms of apparent suffering, take their concern to doctors, who very frequently comply and prescribe acid-suppressing medications for symptoms and signs that in most cases are not GERD. GERD-mania is in full cry, so to speak.

"Infant colic" is a behavioral syndrome of early infancy involving long crying bouts and hard-to-soothe behavior, often with arching of the back or turning away from the bottle or breast. There is no proof that this unexplained crying in otherwise healthy infants is caused by pain in the abdomen or any other body part. However, parents and healthcare providers often assume that the cause of excessive crying is abdominal pain of gastrointestinal origin.[25] The most common cause of unexplained crying is probably an inability to "change state" (ie, an infant who starts crying may have difficulty changing its "state" to a calmer one).[18] The difficulty for some infants to self-calm is well-recognized and is a basic tenet of developmental pediatrics. In addition, it is within the normal range of infant behavior to have a pattern of increased crying in the first 3 to 5 months of life.[26, 27] With time and maturation, this failure to self-calm or increased crying resolves in most infants. However, in some infants, irritability or crying may have an identifiable treatable cause and some of these causes are gastrointestinal. Some common causes are sensitivity to ingested antigens or other dietary components, including those that cross in breast milk, constipation, or the state of being new in the world, of being exposed to various new sensations and stimuli, including dietary components, and gas generated by maldigestion of the high lactose content of breast milk.[28]

For years, we have operated under the assumption that acid-suppressing medications are benign. After all, they appear to be well tolerated, with few immediate adverse effects. With PPIs, some patients get headache or constipation, but are usually fine when switched to another PPI. Elevation of transaminase levels has been described, but is transient in most patients.[1,3] Other concerns arose early on in the trajectory of use of PPIs, related to the reflex hypergastrinemia resulting from drug-induced hypochlorhydria. On PPI therapy, hyperplasia of the parietal cell layer develops almost routinely,[29] and gastric polyps develop in a few patients.[30] These changes are benign and resolve when patients stop taking the medication. Hyperplasia of gastric enterochromaffin-like cells also develops in adults and in as much as 61% of children treated with PPIs for as long as 11 years continuously, but carcinoid tumors do not.[31,32] These histologic changes are indicators of parietal cell secretion blocked during PPI therapy, the clinical significance being that when the drug is stopped, the swollen parietal cell mass is liberated from its suppressors, and rebound acid hypersecretion occurs.[33] This causes

symptom exacerbation[33] requiring, it would seem, further PPI therapy! This is illustrated by a study of asymptomatic adult volunteers who received a PPI for 3 months, and who developed upper gastrointestinal symptoms when the medication was stopped abruptly.[34] This situation is circumvented by tapering patients off medication—the longer they have been taking the medication, the longer the taper should be.

Gastric acid is an early line of defense against infection and important for absorption of certain nutrients. Therefore, it is not surprising that adverse effects could result from suppressing acid secretion. For example, increased prevalences of these conditions have been shown in individuals who received acid-suppressing medications: acute gastroenteritis and community-acquired pneumonia (children 4-36 months age, H2RA or PPI)[35]; necrotizing enterocolitis (preterm infants, H2RA)[36]; candidemia in neonatal intensive care units (H2RA)[37]; pneumonias (infants, PPI)[21]; bacterial overgrowth of the upper gastrointestinal tract (adults, PPI)[38]; *Clostridium difficile*-associated disease (adults, PPI)[39]; bacterial gastroenteritis (adults, PPI)[40]; community-acquired pneumonia (adults, PPI)[41]; vitamin B12 deficiency (older adults, H2RA or PPI)[42]; hip fracture (adults, PPI)[43]; decreased calcium absorption (adults, PPI)[30]; life-threatening hypomagnesemia (adults, PPI)[30]; long-term magnesium depletion[44]; and increased incidence of food allergy (animal and human data, PPI or H2RA).[45] There are conflicting data about some of these adverse effects, such as community-acquired pneumonia and hip fracture,[30] but for others the evidence appears solid. Finally, interstitial nephritis is a not-infrequent adverse effect of PPIs, unrelated to acid suppression.[30]

Because most of these risks are related to suppression of gastric acid secretion, it stands to reason that it would be prudent to use the least acid suppression required to control the patient's symptoms or condition. For most patients with GERD, giving a PPI once daily, before the first meal of the day when most acid pumps are generated and can be blocked, is what is advised and what has been demonstrated to be effective in clinical studies. A minority of patients require twice-daily treatment or treatment with doses at the high end of those shown to be effective in clinical studies. In this regard, misinformation that is in the public domain poses potential additional risk to children. For some years, a website called MarciKids (www.marci-kids.com) has published total daily doses that are far in excess of the doses published in pediatric clinical studies. The rationale given is that PPIs have a short half-life, and therefore acid breakthrough may occur and should be suppressed. Pediatric and adult clinical studies have shown that once-daily dosing resolves symptoms and heals most patients. What the website's pharmacist authors seem to have failed to grasp is that we treat patients, not pharmacokinetic graphs, and MarciKids has no published/peer-reviewed clinical studies to support their dosing regimens. Since the days of peptic ulcer clinical studies with H2RAs, it has been recognized that patients do not have to be made achlorhydric to heal; suppressing acid for only part of the day seems to work well for most patients. Furthermore, acid breakthrough is almost certainly a good thing (unless accompanied by symptoms) because it may be protective against infections. This website recommends routine 3-times daily use of PPI in children <2 years old and more frequent dosing than necessary in older children. The pharmacokinetics of PPIs show that infants <4 to 6 months of age metabolize these medications more slowly than older infants and children, meaning that more potent acid suppression results from smaller doses. Many parents use this website and arrive in doctors' offices demanding high-dose PPIs, likely not recognizing the potential downside to acid suppression, especially inappropriate and unnecessary high-doses thereof.

Because PPIs and H2RAs have very few adverse effects that are immediately apparent and young children often get coughs or pneumonias or diarrhea anyway, physicians and parents have little way of being able to ascribe these infectious "adverse events" to medication effect. Only by cohort studies have these adverse effects been determined to be of greater prevalence in acid-suppressed individuals. Even with the relatively few current adult data on the potential adverse nutritional effects of marked acid suppression (eg, calcium, magnesium, vitamin B12, and iron), it stands to reason that exposing infants and young children to medications or more medication than is necessary may start a process of nutritional deficiency, with as yet unknown, but likely not desirable consequences. This is particularly of concern for infants and children because of their rapid rates of growth and development and increased requirements for many essential nutritional components.

Before discussing management, it is worth mentioning that diagnostic testing for GERD in infants has a very limited role.[11] Only when symptoms are very severe, with anemia or failure to thrive or chronic forceful vomiting or chronic cough, is endoscopy likely to be helpful, mostly to look for erosive esophagitis or eosinophilic esophagitis, but these are very uncommon in infants <6 to 9 months old. Therefore, endoscopy is seldom warranted in this age group, unless symptoms are severe or intractable. Intraesophageal pH study is seldom going to provide helpful information in an infant who is vomiting, and the test has its own vagaries.[11] Similarly, barium study or ultrasound examination are indicated only when persistent projectile vomiting is present, to determine the presence of an anatomic obstruction.[11]

What is to be done? First, in the day-to-day care of infants, healthcare providers should stop using the term "acid reflux" unless it was shown on a pH study, because it subverts rational thinking and subliminally encourages the prescription of acid-suppressant medication even when acid or reflux is unlikely to be the problem. Second, it is key to recognize that although GERD does occur in infants, it is uncommon in otherwise healthy infants who do not have one of the main GERD-predisposing conditions. It should not be spitting up that gets treated; it is the unexplained crying that is the real issue, causing real and considerable distress and concern for parents.

The precise complaint and concern of the parents should be clarified in the history-taking. For infants who are spitting up, but only occasionally irritable or crying, and usually consolable, reassurance about the benign natural history of infant regurgitation is the desirable approach.

For infants in whom the major issue is protracted inconsolable crying, with rejection of the bottle or breast, arching or screaming, regardless of spitting up or not, in most cases non-pharmacological measures should be the first approach.

Explanation and reassurance are required—a return to the basics of behavioral pediatrics: what it means when infants cannot self-calm and how to help them do so. Non-analgesic, non-nutritive soothing maneuvers, such as rhythmic rocking and patting 2 to 3 times per second in a quiet environment, may quiet the baby who may still resume crying as soon as he or she is put down. A common maneuver that does not eliminate pain but stops the crying (eg, a car ride) has diagnostic and therapeutic value.[25] Parental anxiety may perpetuate the cycle of crying, but parents are hardly ever the primary cause and can hardly be blamed for becoming rattled and concerned about their crying infant. The ideal anxiolytic for most parents is for a cause to be identified and managed. This often cannot occur instantly, but the journey can begin. It is important to acknowledge their concern, explain the various possible mechanisms at play, including the spectrum of normal infant behavior, point out that irritability often improves with time, regardless of the intervention, including none.[21,22] But it is also important to discuss the range of possible causes and measures available, start implementation, and be available for follow-up.

Orenstein et al showed that unexplained crying resolved completely in 24% of infants and improved overall in 78% within 2 weeks with only positional and feeding changes and exclusion from exposure to tobacco smoke.[46] Hill et al showed that unexplained crying is often dramatically improved by excluding certain dietary antigens and components from the diet of breastfeeding mothers.[47] After improvement is seen, the mother can re-introduce items sequentially into her diet, to test tolerance by the infant. This approach should be accompanied by explanation that sensitivity to food antigens early in life is not a harbinger of later food allergy and that by approximately 12 months most infants are able to tolerate the major antigens. For formula-fed infants, use of a hypoallergenic formula for a period often is helpful, with later introduction of cow's milk and other antigens.[48] These measures are also temporizing and serve to assist parents getting through these difficult periods, which are transient in most healthy infants. I use both these approaches concurrently (position and diet) for 4 to 6 weeks before considering further measures. In addition, after the age of approximately 4 months, thickening of feeds or adding solids to the diet to provide satiety helps many infants settle.

There are some infants who do have GERD and who fail to respond to the aforementioned measures.

Because special testing is invasive and unlikely to contribute to the diagnosis unless symptoms or signs are severe, the more benign next approach is an empirical, 2-week trial of an acid-suppressing drug. Starting with an H2RA is prudent.[49] An infant who shows no response to 2 weeks of an H2RA in full therapeutic dose is unlikely to have GERD. When some, but incomplete, response is seen, a PPI should be tried, again time-limited to 2 weeks. Ongoing treatment needs to be earned, by repeated attempts at weaning off medication.[50] A small number of patients require longer-term treatment and later diagnostic testing.[11] Symptoms refractory to all measures, including acid-suppression therapy may require investigation, especially those persisting after 9 to 12 months of age. In this regard, it is important to note that although PPIs do not have a US Food and Drug Administration-approved indication for use in children <1 year of age, they are useful in selected patients in this age group; when acid-related disease is present, they do work.

Because the great majority infants will respond to non-pharmacological measures, tincture of time, or both, the stepwise approach buys time constructively, removing from medical attention with a no-risk approach children who respond, leaving fewer children who have earned a time-limited trial of an acid-suppressant. Of these children, only relatively few relapse when medication is weaned, and this is the group who are likely to have GERD and will require longer-term medication and later investigation. With this approach, far fewer infants are likely to be unnecessarily investigated or exposed to acid-suppressant drugs at all, especially to PPIs. Because other practitioners often take their cues from child specialists, we have an obligation to lead the way.

It is all about risk compared with benefit. Young children, especially infants, are highly vulnerable populations. In a child with likely or proven GERD, the benefits of being on an acid-suppressing medication in appropriate dose obviously outweigh the risks, and, in most cases, also far outweigh the risks of antireflux surgery, because of its morbidity and high failure rates.[13] For infants with benign, ultimately self-resolving symptoms such as physiologic reflux, "unexplained crying," or both or transient sensitivity to dietary components, the opposite is true. Because of the high prevalence of spitting up, unexplained crying, or both in otherwise healthy infants, these symptoms and signs are just "life," not a disease, and, as such, do not warrant drug therapy. There is plenty of time for that in later years. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Serum Amino Acid Nitrogen in Infancy and Childhood

Andrews BF, Bruton OC, de Barre L. J Pediatr 1962;60:201-5

Andrews et al published normal values for total amino acid nitrogen in 57 infants and children and compared these values with data from 52 children with a variety of pathological conditions, including infection, fevers, neurologic abnormalities, hepatic failure, and intoxications, but none with genetic disorders of specific amino acids.

Today, concentrations of individual amino acids are measured instead of total amino acid nitrogen. Genetic amino acid disorders are diagnosed when markedly elevated concentrations of specific amino acids are identified by newborn screening laboratories and in children with encephalopathy, metabolic acidosis, and hyperammonemia using tandem mass spectrometry and ion-exchange chromatography. Mildly elevated, nontoxic concentrations of amino acids in patients receiving intravenous (IV) nutrition reflect a balance of intake and urinary disposal of amino acids, as well as protein synthesis, breakdown, and oxidation, rather than specific pathological conditions. Such metabolic rates have been measured using stable isotopic tracers, now a fundamental approach to quantifying human metabolism.

Most recently, normal amino acid profiles in preterm and term newborns have been measured from IV amino acid solution trials in which amino acid mixtures designed for adults were modified for neonates to match serum amino acid concentrations from healthy, breast-fed, term newborns. Human cordocentesis studies determined normal fetal amino acid concentrations, guiding rates of IV amino acid infusions in preterm infants needed to achieve rates of protein accretion consistent with normal in utero growth. This revolutionized neonatal practice from seldom providing IV amino acids, often for days after birth, to starting IV amino acid infusions after birth using gestational age-specific rates ranging from 2 g/kg/day (term) to 4 g/kg/day (24-28 weeks).

The most consistent observation from such studies over the past 50 years has been that protein balance is directly related to amino acid supply and plasma amino acid concentrations. This is true under normal conditions, as well as in sick infants who experience considerable stress. Current research continues to define the comparative values of enteral and IV amino acid nutrition and to examine how amino acid metabolism is further affected by clinical disorders. Amino acid metabolism now is central to all nutritional management in preterm and term newborns, infants, and children.

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