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INVITED COMMENTARY

Infant GERD: Symptoms, Reflux Episodes & Reflux Disease, Acid & Non-acid Refflux—Implications for Treatment with PPIs

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Davidson et al. have this year put a keystone in the arc of data regarding symptoms and reflux in very young children [1]. Taken together, the cumulative data on symptoms and reflux bear consequential implications for the role of gastric acid suppression in this age group; this new work supports hypotheses outlined in this journal several years ago [2]. Here, we will reconsider this area, summarizing what we now know and filling in the newer data, with a focus on children younger than a year of age—including infants (1–12 months of age), neonates (less than 1 month), and premature infants (born at less than 38 weeks gestational age).

Attribution of symptoms as due to GER episodes or to GERD depends on the methods of detecting both the reflux and the symptoms.

Detection of Reflux

Simple Observation of Expelled Reflux

Among the earliest descriptions of symptoms of infant GERD, in 1947, frequent and voluminous regurgitation and consequent malnutrition were observed visually as the predominant symptoms due to "cardioesophageal relaxation or 'chalasia'"—a patulous gastroesophageal junction [3]. (Note that what is often inexactly termed "vomiting" in infant GER or GERD is actually regurgitation; although refluxing pressurized fluids may backflow from the stomach to the esophagus and be expelled from the mouth with such force as to appear to be "projectile vomiting," the pathophysiology of such expulsion does not include the central emetic reflex, nausea, or retrograde contractions that are physiologic hallmarks of actual vomiting, so the more correct term "regurgitation" will be used here throughout.)

Fluoroscopy

With increasing use of diagnostic fluoroscopy in the 1950s, the shortened esophagus of severe reflux esophagitis accompanied by stricture and herniation was described in children, including some infants [4]. This facet of GERD—complicated esophagitis and stricture—was also manifest by symptoms of prominent regurgitation and malnutrition despite eager feeding, but the refluxed material often contained blood, and dysphagia ensued when solids were introduced.

Endoscopy

In the 1970s, endoscopy began to be used in infants similarly to, but with greater sensitivity than, fluoroscopy—to demonstrate complications of severe acid reflux [5]. Milder degrees of esophagitis were detectable histologically [6, 7].

EpHM

While this fluoroscopically- and endoscopically-diagnosed GERD exhibited flagrant symptoms due to irreplaceable loss of calories or to severe esophagitis and consequent stricture, these methods were unable to associate discrete symptoms with reflux episodes over time. In the 1970s and 1980s, however, introduction of esophageal pH monitoring (EpHM) to measure gastric acid refluxed into the esophagus enabled radiation-free, round-the-clock detection of reflux episodes that were not expelled from the mouth, and was more widely used in less symptomatic infants than fluoroscopy [8–10].

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Various quantitative formulas using an esophageal pH cut-point of <4 (incorporating, e.g., total reflux time, total number of episodes, longest episode, and number of acid reflux episodes longer than 5 min) were tested for their ability to identify "abnormal" (either associated with complications or simply quantitatively abnormal) amounts of EpHM-detected acid reflux, particularly in infants presenting with prominent regurgitation or crying, or those with respiratory symptoms ascribed to possible GERD [8–12].

However, in infants, in contrast to older individuals, the neutralization of gastric contents that occurs for about 2 h after each of many daily milk feedings obscured post-meal reflux from EpHM detection during a large proportion of the day, even while reflux episodes are concentrated in those post-meal periods because gastric distension by the meal prompts lower esophageal sphincter relaxation. Therefore, to document post-meal reflux in infants, investigators began to acidify the feeds, often by feeding apple juice (pH ~4) instead of milk (pH ~7) during EpHM [8]. This use of acidified feedings facilitated attribution of milder symptoms to reflux and also allowed association of individual reflux episodes with individual symptoms.

MII

Development of multiple intraluminal impedance (MII) measurement for the esophagus in the early 2000s provided a way to monitor the movement of non-acid fluid and gas in the esophagus over time, and enabled detection of reflux-symptom associations in a far more physiologic context, after standard infant milk feedings [13]. Initially used predominantly for persisting respiratory symptoms [13, 14], MII alone does not distinguish acid from non-acid reflux episodes, but MII is frequently combined with EpHM to do so [15].

Detection of Symptoms

…of Individual GER Episodes

The non-physiologic acidified meals that were introduced for infant EpHM studies in the 1970s and 1980s [8] permitted temporal association of discrete behaviors with individual reflux episodes in the post-meal setting as well as during fasting. When these behaviors were carefully recorded via video monitoring electronically linked to EpHM, crying, regurgitation, stridor, and even yawning, stretching, and mouthing were "symptoms" documented to closely follow reflux episodes [16, 17]. Exquisite attention to temporal relationships can help to distinguish behaviors that result from reflux episodes from those that promote them: cough, for example, can play either role [16, 18].

However, GER episodes occur virtually universally, and, behaviors that co-occur with acid reflux episodes do not necessarily represent "disease," a negative state that may warrant therapy. Behaviors such as the surprised look and re-swallowing that manifests reflux episodes that have breached the upper esophageal sphincter in some young infants, or the occasional "wet burp" (or "spitting" or "spilling") when the contents of such reflux episodes continue their retrograde journey and are ejected from the mouth, are normal consequences of the huge volumes that infants must ingest to triple their weight in their first 12 months, combined with modern-day episodic feeding that enlarges their meals beyond the smaller, more physiologic amounts taken in during more frequent nursing. Even behaviors such as crying, that represent distress, may be "normal" (judged both quantitatively, with regard to a bell-curve, and qualitatively, as representing non-pathology) expressions of physiologic sensations and not need treatment; "normal" infant crying increases from birth to a peak during the second month, then decreases until about 4 months, and changes little thereafter [19].

…of Reflux Disease

As early as the late 1970s, the medical arrogance of defining pathology exclusively in terms of quantitative "data," without regard for the subjective components of the patient's experience, spawned a reactive focus on "quality of life" measures, and a determination to define disease with great emphasis on subjective experience (Patient Reported Outcomes, PROs), rather than on objective data. These methods of diagnosing disease were applied to adult GERD in the 1990s [20] and to pediatric GERD thereafter [21]. In reflux disease, this led to a focus on patient distress as a primary determinant of disease, and resulted, for example, in the concentration on "troublesome symptoms" as a key term in 2006 and 2009 evidence-based expert consensus documents for both adult and pediatric reflux disease—the Montreal definitions [22, 23]. Although some of us who participated in those efforts felt challenged by the vagueness, circularity, and imprecision of the concept of "troublesome symptoms," such definitions are intrinsically difficult. They are more so when the patient cannot verbally express much of anything—are infants expressing "troublesomeness" of sensations simply by crying? Should we ask their surrogates (e.g., parents) to interpret for them?

The other part of the Montreal definitions of gastroesophageal reflux *disease* (in addition to "troublesome symptoms")—"or complications"—is easier: an esophageal ulcer is a discrete, measurable, relatively objective finding. But such findings are also relatively rare in infants, because of their mitigating lack of reflux acidity and chronicity. Thus reflux *disease* defined by *complications* is rare in infants; whether reflux *disease* defined by *troublesome symptoms* exists in infants is debatable.

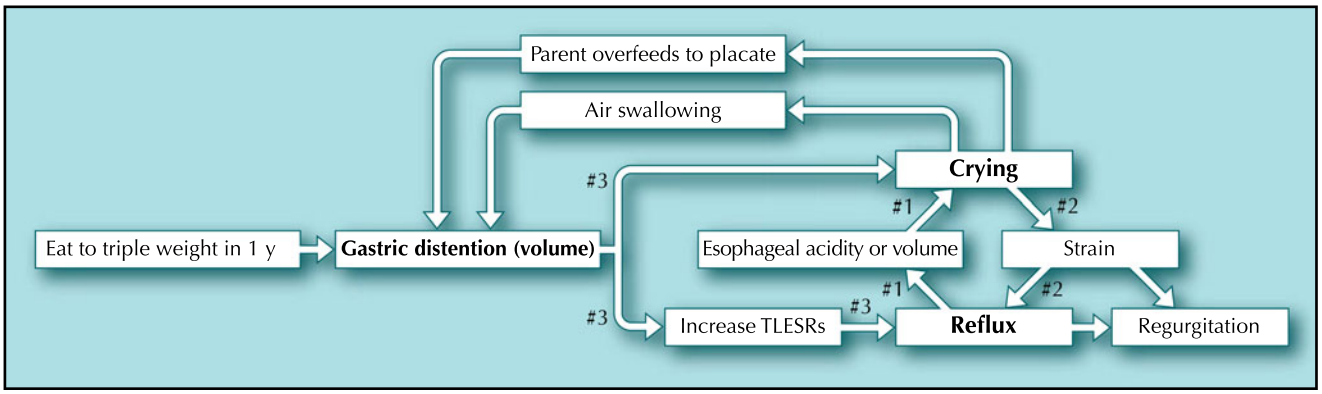

Fig. 1 Likely interactions between crying and reflux in infants. #1-traditional (acid-mediated) or functional (volume-mediated) heartburn; #2-strain-mediated reflux; #3-dyspepsia; TLESRs-transient lower esophageal sphincter relaxations. Reprinted with permission from Orenstein SR. [2]

Various ways of identifying a symptom/behavior as troublesome include: (1) using statistically "normal" cut points (e.g., crying > × h/day [19, 24], regurgitation > × amount [24]); (2) requiring a complication (e.g., regurgitation that results in a drop on the weight curve); and (3) soliciting parental/physician subjective judgment. Cumulative symptoms and patterns of symptoms may also be deemed abnormal using questionnaire instruments that have been validated diagnostically as associated with other evidence of "disease" [21, 24–29].

Treatment of Gerd

The importance of defining a cut-point on the continuum of "normal" to "disease," both in terms of reflux quantity and of symptom quantity, is that disease generally warrants assuming the costs and potential risks of treatment. Severe esophagitis pain, malnutrition, or stricture warrants pharmacotherapy, while normal infant fussiness, or mess due to regurgitation, probably does not, although they may warrant non-pharmacologic measures to reduce the fussiness or mess.

Potential treatments for GERD include acid suppression/neutralization (PPIs, H2RAs, antacids), prokinetics, and "conservative, life-style" measures (smaller but more frequent feedings, thickening of feedings, and positioning). Acid-reducing medications are compelling for acid-related symptoms; prokinetics for non-acid-reflux-related symptoms, and conservative measures [30, 31] for symptoms/behaviors in GER (as well as to provide support of pharmacotherapy in symptoms due to GERD).

Implications of the Current Study

In their well-designed, randomized, double-blind, placebo-controlled, multicenter study, Davidson et al. evaluated neonates (premature to 1 month corrected gestational age, $n = 52$) with simultaneous MII, EpHM, and video/cardiorespiratory monitoring for 8 h after up to 14 days of once-daily esomeprazole (0.5 mg/kg) or placebo [1]. Similar to an earlier study of the link between behaviors and reflux episodes [16], behaviors quantified by review of the video monitoring were crying (including fussing/irritability), regurgitation ("vomiting"), gagging, and back arching, while cardiorespiratory monitoring captured apnea, bradycardia, and oxygen desaturation. (A problematic aspect of the design is the definition of behaviors "associated with" reflux episodes as occurring up to 2 min *before* or after the reflux, and the long latency (2 min) allowed. It is difficult to conceive of a reflux episode "causing" a behavior that occurs 2 min prior to it.)

Conforming to essentially all the available literature and to its known mechanism of action, the PPI they studied significantly decreased esophageal acid exposure. However, the authors found no effect of the PPI on total (acid plus non-acid) reflux, nor on any of the symptoms/behaviors they studied. Thus, the symptoms seem to be more related to the reflux episodes than to their acidity, and the drug simply converted acid reflux episodes to non-acid ones. If our acid-suppressing treatment is designed to reduce symptoms in infants, it does not seem to work. These findings replicate those reported for other PPIs: in a larger, longer-duration study using questionnaires in older infants rather than video monitoring in neonates, lansoprazole also did not significantly affect symptoms [32]. Other PPIs have produced comparable findings [33, 34].

Conclusion

Volume, Rather Than Acid, is Often the Key Promoter of Reflux-Associated Symptoms in Infants

This review of the literature on relationships between reflux and symptoms supports the concept that, in infants, even

symptoms such as excessive crying accompanying prominent regurgitation are often caused by gastric distension ("dyspepsia," or possibly even "functional heartburn") rather than esophagitis ("heartburn") (Fig. 1). (Alternatively, in some situations, the causality may be reversed, and excessive crying may increase regurgitant reflux by its effect on intragastric pressures.) In the "dyspepsia/functional heartburn" formulation, the crying (as well as the reflux) is caused by volumetric distension, rather than being caused by acid reflux impacting the esophagus, as it does in simple heartburn. Such a formulation, supported by Davidson's recent work, should now guide our treatment recommendations for infants in the absence of demonstrated acid-mediated disease such as esophagitis, reducing the over-prescription of acid-suppressing medication and re-focusing management of infant reflux on measures that affect gastric volume and non-acid reflux [30, 31].

Compliance with Ethics Guidelines

Conflict of Interest Susan R. Orenstein declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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