Gastroesophageal reflux disease in infants

Myths and misconceptions, where is the evidence?

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ABSTRACT

يعد الجزر المعدي المريئي عند الأطفال من الأمراض الشائعة التي يمكن أن تختفي عفوياً باستخدام العلاج المناسب أو بدونه، كما أنه من الظواهر الفيسيولوجية الشائعة. يتحول الجزر المعدي المريئي إلى مرض (مرض الجزر المعدي المريئي) عندما تصبح الأعراض شديدة أو مرتبطة بالعديد من المشاكل الصحية كضعف النمو أو قيئ الدم. وبالرغم من انتشار مثل هذه الحالة عند الأطفال إلا أن هناك الكثير من اللغط والاشتباه بين الجزر المعدي المريئي عند الأطفال ومرض الجزر المعدي المريئي وذلك من ناحية التشخيص والعلاج، حيث يتم عمل العديد من الفحوصات وصرف العقاقير الغير ضرورية. يوجد هناك العديد من طرق العلاج التي يمكن استخدامها من أجل التحكم بمرض الجزر المعدي المريئي غير أن الأدلة العلمية التي تثبت التشخيص والعلاج عادة ما تكون غير كافية أو محلاً للخلاف.

Infantile gastroesophageal reflux (GER) is a common self-limited, physiological phenomenon. Infantile gastroesophageal reflux becomes pathological (gastroesophageal reflux disease [GERD]) when symptoms become more severe or are associated with complications such as failure to thrive or hematemesis. Though it is a very common condition, there are several misconceptions and myths on GER/GERD diagnosis and management. Inappropriate investigations are frequently requested and unnecessary medications are increasingly prescribed, particularly in infants with symptoms attributed to possible GER/GERD. Several therapeutic interventions are used widely in GERD management, although some evidence is either insufficient or controversial.

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Gastroesophageal reflux (GER) and gastroesophageal reflux disease (GERD) are common clinical problems seen in pediatrics. Though they are encountered daily by primary health care providers and pediatricians, there are still numerous myths and misconceptions on GER and GERD management. This may reflect ongoing unawareness of the most recent recommendations and guidelines in GER/GERD management in infants and children. This review aims to highlight some of these misconceptions often seen in pediatric gastroenterology and to summarize the current evidence and recommendations.

Misconception 1: Gastroesophageal reflux is equivalent to GERD. Gastroesophageal reflux is a common physiological phenomenon in infants. It is characterized by the retrograde movement of gastric contents into the esophagus, with or without obvious regurgitation or vomiting.[1] Regurgitation occurs in up to 50% of the infants younger than 3 months and spontaneously resolves by the age of 12-18 months.[1] Physiological GER can cause significant trouble to parents and might cause considerable anxiety for them; however, it is usually self-limited and should improve gradually as the infants grow up. A recent cohort study followed 163 healthy infants longitudinally to determine the natural history of infant regurgitation during the first year of life; regurgitation was seen in 73% during the first month of life and decreased gradually to 50% during the fifth month of life. After the age of 12 months, only 4% of the infants had daily regurgitation.[2] This improvement could be attributed to several factors, including development of the esophagus as well as increasing ability to sit upright and eat solid food.[2] Gastroesophageal reflux becomes pathological (GERD) when symptoms become more severe or are associated with sequelae such as failure to thrive (FTT), feeding refusal, or esophagitis causing hematemesis, melena or anemia. Furthermore, GERD can cause extra-esophageal complications such as Sandifer's syndrome or dental erosions and may increase the risk for recurrent

aspiration pneumonias. Regurgitation is the most common symptom of GERD; however, it is neither sensitive nor specific in terms of diagnosis (**Figure 1**). The pathophysiology of GERD is complex; multiple factors are involved including genetic, environmental (such as diet), anatomic, hormonal, and neurogenic factors.[3] Current evidence has demonstrated that frequent transient lower esophageal sphincter relaxation (TLESR) is the predominant mechanism of reflux in infants and children.[3,4] Inappropriate investigations and over-prescriptions of unnecessary medications are observed in infants with physiological GER. Khoshoo et al[5] found that among 44 infants referred to the pediatric gastroenterology service with regurgitation; only 8 had abnormal pH, while 24 out of the 44 infants who were already started on anti-reflux therapy by their primary health care providers were found to have normal pH. When treatment with anti-reflux medications was stopped, the patient's symptoms did not get worse.[5]

Bottom line: GER is a common, benign physiological phenomenon in infants. Educating, reassuring, and guiding the parents is usually enough at this stage; however, when symptoms become worse or are associated with complications, the condition becomes pathological (GERD), and further diagnostic and therapeutic interventions are indicated.

Misconception 2: GERD is the primary cause of vomiting in infants. In infants, it is crucial to make sure that other possible causes of vomiting, such as infections, gastrointestinal tract malformations, including malrotation and pyloric stenosis, or cow's milk protein intolerance, are excluded before concluding that GERD is the primary cause of an infant's symptoms. Ruling out such conditions is vital before labeling an infant as having GERD because the management of

these conditions is completely different; not diagnosing malrotation can lead to a catastrophic event in the future, if present with volvulus. Considering GERD as the initial diagnosis may be more appropriate in older children when they can articulate their complaints. This is not the case in infants, in whom more careful evaluation to rule out other possibilities should be considered before diagnosing an infant with GERD.

Bottom line: In infants, it is crucial to consider other differential diagnoses of regurgitation/vomiting before considering GERD as the primary cause of infant's symptoms.

Misconception 3: The barium swallow study is a simple, quick and accurate tool to diagnose GERD. Barium swallow is one of the most commonly utilized radiological tools in GERD diagnosis, although it has been shown that it has poor sensitivity and specificity in detecting reflux. When compared with esophageal pH monitoring, sensitivity was reported to range between 29% and 86% and the specificity between 21% and 83%.[1] The technique used in the barium swallow test, whereby an infant is usually given liquid barium orally or via a naso-gastric tube and then turned to different positions to delineate the upper gastrointestinal tract (GIT) anatomy, can artificially elicit reflux episodes.[6] Clearly, this is different from the normal feeding experience. In addition, barium study carries some radiation risk. In fact, the main utility of barium meal study in infants is primarily to delineate the anatomy of the upper GIT and to rule out anatomical malformations such as esophageal stricture, achalasia, trachea-esophageal fistula, and malrotation (**Figure 2**). When symptoms are suggestive for GER rather than
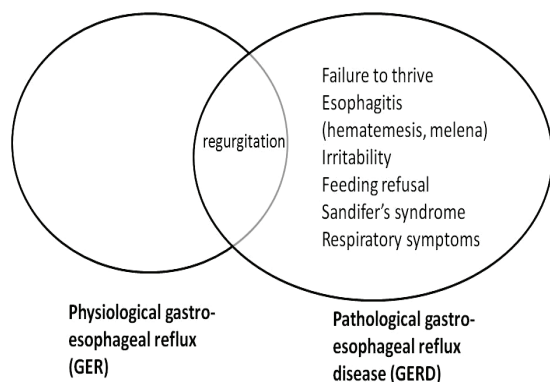
Figure 1 - Regurgitation is seen both in physiological gastroesophageal reflux (GER) and gastroesophageal reflux disease (GERD); however, it is neither sensitive nor specific for GERD diagnosis.

Venn diagram: Physiological gastro-esophageal reflux (GER); Pathological gastro-esophageal reflux disease (GERD); overlap labeled "regurgitation". GERD circle lists: Failure to thrive, Esophagitis (hematemesis, melena), Irritability, Feeding refusal, Sandifer's syndrome, Respiratory symptoms.

Figure 2 - Barium study showing signs of malrotation in an infant presenting with intermittent vomiting, note the ramification of the proximal small bowel on the right rather than the left side of the abdomen.

GERD, it is even more inappropriate to consider a barium swallow because of the low likelihood of finding anatomical abnormalities in an otherwise healthy, but vomiting infant. Simanovsky et al[7] found that of 344 infants aged less than one year, with chronic vomiting, only 2 patients had anatomical abnormalities.

Bottom line: In infants with recurrent vomiting, the barium swallow test is neither sensitive nor specific enough to diagnose GERD. The main utility of this test is rather to rule out the possibility of anatomical malformation. The routine performance of this test is not necessarily justified according to the most recent guidelines and recommendations.[1]

Misconception 4: Esophageal pH monitoring is the definitive diagnostic tool for GERD. The pH monitoring study is generally accepted as the standard test for diagnosing GERD; however, this statement should be interpreted with caution because pH monitoring has its limitations. Esophageal pH monitoring is designed to quantify the esophageal mucosa exposure to acid (pH of less than 4) and to detect if there is a correlation between the attributed symptoms and the recorded acidic reflux events. This means that pH monitoring is not designed to detect weakly acid refluxes (pH 4-7) or alkaline reflux events (pH >7), which are observed more postprandially in infants, secondary to the buffering effect of frequent infant feeding. It has been demonstrated that nearly 90% of the reflux events in infants are non-acidic in nature; therefore, pH monitoring underestimates the total number of reflux episodes[8] (**Figure 3**). Another limitation of pH monitoring is related to the poor correlation between reflux events and the proposed symptoms; however, this is not unexpected, as the technique misses weak acid and alkaline reflux events. To overcome these limitations, a recently developed diagnostic tool called multi-channel intraluminal impedance (MII) has been utilized in GERD diagnosis. This technique allows for the detection of reflux events,

their chemical compositions (acid, weakly acid, and alkaline) and their physical composition (liquid, mixed, or gas). A pH monitoring can be performed in addition to this new technique, and it has been shown that combined MII and pH monitoring is superior to pH monitoring alone and significantly increases the diagnostic yield in detecting reflux events in infants.[9-11] In a study by Pilic et al[10] a combined MII-pH study was performed in 700 children presenting with symptoms suggestive of GERD: 37% of 207 measurements were found to be abnormal with the combined MII-pH study, 18% yielded only pathological pH measurements, and almost half of the measurements (45%) yielded only abnormal MII recordings that were not detected by pH measurement.[10] Other studies found that the addition of MII to conventional pH monitoring significantly increased the yield in revealing an association between reflux events and symptoms, especially respiratory symptoms.[9,11,12] Moreover, because impedance measurements are performed along the entire length of the esophagus, rather than at one or 2 positions, as is the case in pH monitoring, it is possible to precisely determine the proximal extent of the reflux events.[4] Finally, it has been demonstrated that adding MII results to pH monitoring results change the nature of clinical decision making among treating physicians.[13]

Bottom line: pH monitoring detects only acidic reflux events. Primary health care providers should be aware of its limitations before requesting the test. Combined MII-pH study is expected to replace pH monitoring for GERD diagnosis in the near future.

Misconception 5: Irritable infants. GERD is always the culprit. Irritability is a common symptom in infants, which may impose a significant burden on the parents. It could be related to simple conditions such as hunger and pain or serious ones such as infections and hidden trauma; it also can be related to unsatisfactory parent-infant interaction. Symptoms such as regurgitation,
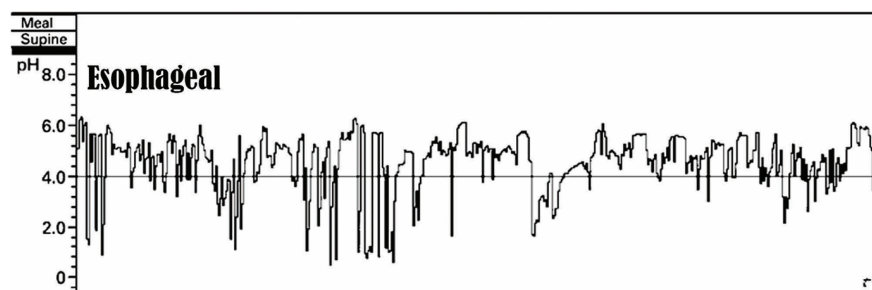

Figure 3 - A pH tracing showing intermittent drop of the pH below 4 indicating acid reflux (the horizontal line); however, this drop is not seen frequently in infants because of the buffering effect of frequent feeding.

recurrent vomiting, back arching or feeding refusal are usually attributed to GERD, though there is no strong evidence to suggest this.[1,14,15] Unfortunately, some infants experiencing such symptoms will be exposed to unnecessary anti-reflux medications, even without the appropriate workup. Jordan et al[16] conducted a controlled trial in 103 infants, <9 months of age, were randomized to receive medical anti-reflux treatment (ranitidine and cisapride), placebo or a form of a mother's counseling program, to assess their effect on persistent crying in infants, and maternal distress. The authors found that anti-reflux medications and maternal counseling were not superior to placebo in treating infants with persistent crying; in addition, the study found that maternal counseling reduced the need for subsequent admissions to a mother-infant unit.[16] Moore et al[17] conducted another randomized controlled trial (RCT) to assess the efficacy of omeprazole in treating irritable infants with GER and/or esophagitis. Among 30 infants (aged 3-12 months) included in the study, omeprazole was found to reduce esophageal acid exposure compared to placebo; however, it did not have an effect on the irritability, which was found to improve over time regardless of treatment.[17] A more recent RCT by Orenstein et al[18] was conducted to assess the efficacy and safety of a 4-week course of lansoprazole compared to placebo in treating infants with symptoms attributed to GERD. The study did not find a difference between placebo and lansoprazole in improving the symptoms attributed to GERD, such as crying, back arching or regurgitation.[18]

Bottom line: Irritability is a non-specific sign in infants. Evidence shows that acid suppression therapy is not better than placebo in controlling irritability or excessive crying in infants. Primary health care providers should provide a thorough evaluation before starting infants on unnecessary acid suppression therapy.

Misconception 6: Prokinetic agents for all. Prokinetic agents have been used for several decades in GERD management, although their efficacies are still controversial.[1,19] The most common prokinetic agents currently in use are domperidone, metoclopromide, erythromycine and, in very restricted cases, cisapride. Domperidone is a peripheral dopamine receptor antagonist. Because of its favorable safety profile, domperidone has been used frequently as an alternative to metoclopramide and cisapride, although the effect of domperidone on treating symptomatic GERD is still questionable and lacks convincing evidence. At least 2 systematic reviews did not find enough evidence from RCTs to support the use of domperidone or metoclopramide in GERD management.[19,20] While

domperisone acts peripherally, metoclopramide is a central acting dopamine antagonist found to increases gastric motility by enhancing GIT response to acetylcholine and increases lower esophageal sphincter tone.[21] It has been demonstrated that metoclopramide reduce but does not normalize the reflux index (RI) on pH monitoring.[22] A Cochrane review conducted by Craig et al identified 7 RCTs conducted in developmentally normal children between the ages of one month and 2 years, and found that metoclopromide was able to reduce the daily GER symptoms and RI; however, it was associated with several side effects including irritability and extrapyramidal reactions (dystonia and tardive dyskinesia).[23] Similar results were obtained by other systematic reviews.[24,25] Cisapride is a serotonergic agent that stimulates the release of acetylcholine from post-synaptic neurons in the enteric nervous system; this leads to increased gastric empty and improves esophageal and intestinal peristalsis.[26] It was used heavily, for some time, as an effective prokinetic agent in GERD, gastroparesis and pseudo-obstruction conditions; however, because of its association with prolonged QT interval and the risk of inducing cardiac arrhythmia and sudden death, it was withdrawn from the market in July 2000. Since then, its prescription in many countries has been limited to special access programs.

Cisapride was found to induce a significant reduction in the RI; however, as RI and clinical symptoms are poorly correlated, the clinical importance of this finding is uncertain, as demonstrated in 2 systematic reviews.[27,28] When compared to domperidone in a head-to-head trial, cisapride was as effective as domperidone in reducing regurgitation, but cisapride was found to be more effective in acid reflux, while domperidone has a better safety profile.[29] Several anecdotal studies reported a positive effect of cisapride, although this might be attributed to a substantial publication bias.[27]

Erythromycin is a commonly used macrolide antibiotic. At lower doses (1-5 mg/kg), it has been shown to have potent prokinetic properties by acting directly upon motilin receptors in GI tract. Multiple studies have shown a beneficial effect of erythromycin in promoting the tolerance of enteral feeds and enhancing gastrointestinal motility,[30-33] but its effect on improving GERD symptoms in infants was not proven.[33] It is important to recognize that the studies involving prokinetic agents have a significant heterogeneity with regard to the included population, dosing, and outcome measures; this makes it difficult to obtain a solid conclusion from these studies and clearly indicates the need for larger and properly designed trials to evaluate the efficacy of prokinetic agents in GERD management.

Bottom line: According to the most recent guidelines, there is insufficient evidence to justify the routine use of metoclopramide, domperidone or erythromycin for GERD management.[1] The adverse effects may outweigh the benefits of these medications.

Misconception 7: Proton pump inhibitors (PPIs) are the way to go. Proton pump inhibitors are the most potent inhibitors of gastric acid secretion available; they work via blocking acid production through H+/K+ ATPase inhibition, which is the final step in the acid secretion pathway. The discovery of PPIs profoundly altered GERD management and significantly reduced the need for fundoplication in both adults and children.[34]

Omeprazole, lansoprazole, and esomeprazole are the currently approved PPIs in children over one year of age; none is approved yet for infants less than one year old.[1] Initially, PPIs were used as a step-up therapy for acid suppression when H2RAs had failed; however, in the last decade, the number of PPIs prescriptions for GERD treatment in children has increased enormously to become the first-line therapy. Barron et al reported a more than 4-fold increase in insurance claims for PPIs from 1999 to 2003 and a greater than 7.5-fold increase from 1999 to 2004 in infants younger than 12 months of age. In this report, GERD was found to be the diagnostic code for 59% of the PPIs claims.[35] A recent pediatric study examined the patterns of GERD treatment in primary care practice in UK. The authors found that PPIs were prescribed as the first-line therapy in 22.9%, while 24.7% were switched from the initial therapy with H2RAs to PPIs.[36] Proton pump inhibitors are effective in healing erosive esophagitis in children.[37] They were found to have several advantages over H2RAs; they produce higher and faster rates of esophagitis healing compared to H2RA, inhibit meal-induced acid secretion and are not affected by the tolerance phenomenon that usually diminishes the effect of H2RAs over time.[38]

Although PPIs are effective in healing erosive esophagitis; however, they are not expected to change TLESRs, which are the most relevant pathophysiologic mechanism of GERD. Wenzl et al[8] demonstrated that nearly 90% of the refluxes in infants are non-acidic in nature; this may partially explain the findings from some studies that did not find a significant effect of PPIs in reducing GERD symptoms in infants.[39,40] How long PPIs need to be administered to children to treat GERD is unknown. To examine this, Boccia et al[41] conducted a RCT to evaluate the efficacy of acid-suppressive maintenance therapy for GERD in children, after the reflux esophagitis had healed. The authors found that there is a low rate of erosive esophagitis relapse and

GERD symptom recurrence up to 30 months after healing, irrespective of the type of maintenance therapy (omeprazole, ranitidine or no treatment); this study challenged the assumption that GERD in children is a life-long disease that requires long-term acid suppression therapy.[41] However, it is important to recognize that the data from this study are applicable mainly to healthy infants without chronic neurological, respiratory, or congenital esophageal abnormalities, whom are expected to require a longer term of medical therapy.

Short-term usage of PPIs is generally well tolerated; however, the safety of long-term usage was recently questioned due to increasing reports of an association between the long-term usage of PPIs and the increased risk of complications such as acute gastroenteritis, community-acquired pneumonia,[42] acquired clostridium difficile infections,[43] and the risk of atrophic gastritis, as well as an association between PPIs and bone fractures, as shown in studies of adults.[44] Other reports found that PPIs may interfere with the absorption of various minerals and vitamins.[45] Most of these complications associated with PPIs were described in small observational studies that carry a substantial risk of confounding biases; such a limitation makes it difficult to draw a definitive conclusion without validation by larger prospective studies.

Bottom line: PPIs are effective in treating erosive esophagitis in children; however, they have no effect on infants with proposed but unproven symptoms of GERD. Physicians should weigh the pros and cons of prescribing PPIs, particularly in patients on remission, as evidence suggests that the relapse of GERD symptoms or esophagitis is not common in children.

Misconception 8: Anti-reflux surgery (ARS)/ fundoplication is the ultimate solution for GERD. Pediatric gastroenterologists are frequently asked to assess infants for ARS or fundoplication to resolve their reflux symptoms. Although there are specific indications for performing ARS, it is unfortunate that it is sometimes carried out without having a confirmed diagnosis of GERD. Some patients may undergo the surgery without documented failure of maximal medical therapy. Not every patient with GERD symptoms is a good candidate for ARS. It is therefore important to carefully select ARS candidates after rigorous diagnostic workups to maximize the benefits of this surgery and minimize its risks.

Studies assessing the efficacy of ARS showed controversial results in children. This is not unexpected, considering the retrospective nature of most of these studies, their small sample size and the significant heterogeneity of the included population.[46] A recent

systematic review that included only prospective longitudinal studies, and RCTs reported a success rate (defined as complete relief of symptoms) between 57%-100% (median of 86%).[46] In general, the success rate of ARS is reported to be higher in neurologically normal infants, compared with neurologically impaired infants.[47] Anti-reflux surgery was found to be more effective in relieving the digestive symptoms of GERD and may be effective over the short term in reducing respiratory symptoms; however, no significant improvement was observed over the long-term follow-up.[48-50] Unfortunately, there are no large-scale studies comparing ARS to long-term PPI therapy with regard to long-term outcomes.

The introduction of laparoscopic ARS helped in reducing post-operative hospital stay, reducing morbidity and mortality, and achieved feeding sooner than with open surgery;[51] however, in some centers, ARS was found to lower the threshold for surgical treatment of GERD in children.[52] The ARSs are not without risks; several studies reported a high recurrence rate, surgical failure and significant mortality and morbidity such as forceful retching, vomiting, gas bloating syndrome, dumping syndrome and disabling dysphagia if wrapped tightly. Such complications were observed more in neurologically impaired infants; this could be related to poor esophageal and gastric motility in this subgroup of patients.[47,53]

Performing ARS may not represent the end of the need for acid-suppressive medications. Lee et al[54] reported that 75.6% of patients restarted anti-reflux medications within one year of Nissen fundoplication. This was observed less frequently in neurologically normal as compared to neurologically impaired patients.[54] Until more sound evidence with regard to the comparison of ARS to long-term PPI therapy has been collected, a careful assessment of each patient is required before performing the surgery to maximize its benefit and to reduce the associated risks.

Bottom line: The decision to perform ARS is a major decision; the availability of laparoscopic techniques should not be a reason to implement a less rigorous diagnostic workup or not to maximize medical therapy before considering ARS.

In conclusion, GER is a common physiological phenomenon in infants. Primary health care providers should be able to differentiate between physiological and pathological GERD. Primary health care providers and pediatricians must be aware of the current guidelines and recommendations of GERD diagnosis and management to minimize the exposure of infants and young children to unwanted investigations and medications.

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