Etiology and pathogenesis of gastroesophageal reflux.

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I. Gastroesophageal reflux disease: scientific evidence versus Delphi decisions.

Evidence is information derived from systematic observation, measurement, experimentation, or other empirical methods that can be independently verified and used to support or refute a proposition about reality. In evidence-based medicine, evidence originates from the objective investigation of nature and is evaluated according to methodological criteria such as validity, reliability, reproducibility, and susceptibility to bias.

In contrast, a **Delphi method** decision is not evidence itself but the result of a structured process for obtaining and refining expert opinions. The Delphi method seeks consensus among experts through multiple rounds of anonymous questionnaires and feedback. Its conclusions reflect collective professional judgment rather than direct empirical demonstration of a fact. Delphi doesn't create new facts. It can only interpret existing data. If the data is weak, consensus doesn't transform it into strong evidence. Therefore, evidence and Delphi consensus are epistemologically distinct. Evidence derives its authority from correspondence with observed reality, while Delphi consensus derives its authority from the expertise and agreement of participating experts. From a philosophical perspective, another question arises. If experts have financial ties to industry, this may influence not the facts themselves, but rather their interpretation and the formation of recommendations. This is why conflicts of interest are considered especially strictly for clinical guidelines and consensus documents. For example, the US Institute of Medicine (now the National Academy of Medicine) Committee recommended excluding individuals with conflicts of interest from clinical guideline development groups whenever possible, not accepting direct funding from medical device manufacturers, and only allowing experts with conflicts to participate in a limited number and with full transparency. Thus, the scientific credibility and trustworthiness of the consensus can be diminished if a significant portion of the participants have financial ties to the industry, especially if these ties are insufficiently disclosed. Evidence is assessed primarily by its methodological soundness, whereas Delphi consensus is assessed not only by the qualifications of the participants but also by the independence of their judgment. Review articles, expert consensus papers, and Delphi documents rely more heavily on the subjective judgments of authors and are therefore more sensitive to conflicts of interest.

II. On the etiology of gastroesophageal reflux disease.

Acid-related diseases are among the most common gastrointestinal disorders, but their overall prevalence as a single nosologically group has not been precisely determined. Gastroesophageal reflux disease (GERD) is diagnosed in approximately 10–20% of the population in Western countries. The incidence of GERD varies significantly across different regions of the world, from 4.16% in China to 22.40% in Turkey [1]. This suggests that a significant portion of the population has an etiologic factor that causes acid-related diseases.

Based on studies of the volume and acidity of gastric juice in normal conditions and in gastric and duodenal ulcers, scientists concluded that these conditions are caused by hypersecretion of gastric juice. The objective results are presented in Fenwick's article: -"Experiments invariably show that when a healthy stomach is carefully washed out and emptied overnight and again aspirated in the early morning, no food or drink having been taken in the interval, it is never found to contain more than a few cubic centimetres of a neutral or faintly acid fluid. When, however, a typical case of hypersecretion is examined in the same manner a very different picture is presented. Thus, if the stomach be washed out and emptied overnight, and no food or drink be taken in the interval, aspiration on the following morning will show the organ to contain from 50 c.c. to 300 c.c. of an opalescent or bile-stained fluid which gives all the reactions of an active gastric juice with a total acidity varying from forty to seventy. The mere withdrawal of its contents appears to stimulate the fasting organ to fresh secretory exertions, for if aspiration be repeated hour by hour a similar quantity may be drawn off on each occasion. It is obvious that in certain cases the stomach continues to secrete an active juice without the normal stimulus supplied by the ingestion of food. In the light of this fact the symptoms that usually accompany hypersecretion are easily explained. In mild instances, where the stomach contains only a small quantity of fluid in the early morning, very little discomfort is experienced before breakfast, but in the more severe types of the complaint, fullness, distension, nausea, giddiness, and perhaps acid eructations, ensue immediately the patient rises from bed and may even awaken him before the usual time" [2]. For most of the 20th century, the diagnosis and treatment of acid-related diseases was based on gastric intubation and determination of the volume and acidity of gastric juice [3,4,5].

Everything has changed since DeMeester et al. published the normal esophageal pH limit as <4% pH <4 over a 24-hour period. The study itself assumed the possibility of reflux in healthy individuals, which contradicts the physiology of the esophagus's defense against aggressive

gastric chyme. Secondly, exposure to acid with a pH <4 for 58 minutes a day cannot be safe for the esophagus, as it, together with pepsin, denatures dietary proteins, which are little different from esophageal mucosa. Thirdly, DeMeester selected 15 control subjects who claimed to have no symptoms typical of GERD. This violated scientific methodology, as it is known that GERD can be asymptomatic and can manifest with extraesophageal symptoms. The authors did not use any of the diagnostic methods (radiological, manometric, endoscopic) that they used in their practice. Therefore, there is no logical explanation for why they did not use these methods to exclude GERD patients from the control group. Due to methodological flaws, their proposed DeMeester score [6,7] has no scientific, and therefore, no practical, value. However, since then, using the Delphi method, pH monitoring and its advanced analogues have become considered the gold standard in diagnosing GERD.

The Lyon Consensus uses the following approach: AET <4% — usually found in healthy individuals; AET >6% - significantly more common in patients with proven GERD; 4–6% — “gray zone” [8]. From an evidence-based perspective, all patients examined in this way suffered from acid hypersecretion. If they had no symptoms, they would not have been monitored for pH. The presence of a gray zone, which supposedly reduces the sensitivity of pH monitoring, is resolved, according to the voting experts, by the use of pH-impedance monitoring, histopathology scores, dilated intercellular spaces, and motor evaluation of hypotensive lower oesophageal sphincter, hiatus hernia, and oesophageal body hypomotility on high-resolution manometry, and novel impedance metrics (baseline impedance, postreflux swallow-induced peristaltic wave index). There is no evidence in the article; there is not a single reference to known laws of physiology. The large list in the "Competing Interests" section clearly shows whose interests consensus participants voted for.

Currently, the results of the Delphi method have completely replaced evidence-based medicine.

1. Gastric hypersecretion is not considered a cause of acid-related diseases, and the term "etiology" is not mentioned anywhere in articles. All articles begin with the phrase "pathophysiology is complex and multifactorial" [9].

2. It turns out that LA-A esophagitis is found in 5–7.5% of healthy people. This is because their AET is <4%. Meanwhile, the absence of symptoms does not exclude pathological reflux, just as a normal endoscopy does not exclude GERD.

3. Instead of acknowledging the low diagnostic value of pH monitoring, functional diseases have been invented that are supposedly unrelated to hydrochloric acid hypersecretion: functional heartburn, esophageal hypersensitivity, functional dyspepsia, and irritable bowel syndrome, which are supposedly caused by impaired gut-brain interaction. As a result, patients do not receive timely pathogenetic therapy, but new interested parties are emerging who recommend medications to restore the connection between the brain and the gut [10].

4 The authors, using off-PPI impedance-pH monitoring (MII-pH), found the prevalence of pathological supragastric belching (>13 episodes/24 h). They ignored the well-known fact that healthy people do not know what belching is [11].

Rome V, "Pediatric Upper Gastrointestinal Disorders of Gut-Brain Interaction," presented all the symptoms that occur with hydrochloric acid hypersecretion as syndromes, that is, independent disorders. This view is the result of a Delphi vote and although it is not based on reliable evidence, they create the appearance of an important practical recommendation [12].

Evidence-based medicine analysis shows that all acid-related diseases, including GERD, occur in individuals with hypersecretion of gastric juice. However, the question of why hypersecretion occurs in 10–30% of people remain unclear. Since GERD is known to occur in infants, we will examine its causes at this age.

III. On the etiology of GERD in infants

The newborn receives mother's milk, which has everything necessary for its development and rapid growth. It contains protein and lactose. Lactose is a disaccharide sugar that is digested into glucose and galactose by the enzyme lactase, produced in the brush border mucosa of the small intestine. In all mammals, lactase concentrations are at their highest shortly after birth and decline rapidly after the usual age of weaning. In some children, lactase secretion remains high after weaning. In other cases, the transition to regular food, which requires processing with acid, the amount of lactase decreases to 10% of its initial level. The percentage of genetically determined primary lactase deficiency varies among different peoples. For example, among the Irish it is about 4%, among the peoples of northern Europe - 20%, among Ashkenazi Jews - 70%, and among the Chinese - 98% [1-3]. It has been shown that lactose, by acting on mast cells of the small intestine, leads to the release of histamine, which causes hypersecretion of hydrochloric acid [13, 14].

A baby is born with a small stomach, shaped like a teapot or retort, due to its narrow antrum (Figure 1ab). It sucks out milk, the volume of which exceeds the stomach's capacity. This causes the stomach walls to stretch and gradually increase in volume. The baby regurgitates the excess milk. However, this is not vomiting or reflux. It is a physiological phenomenon characteristic only of newborns.

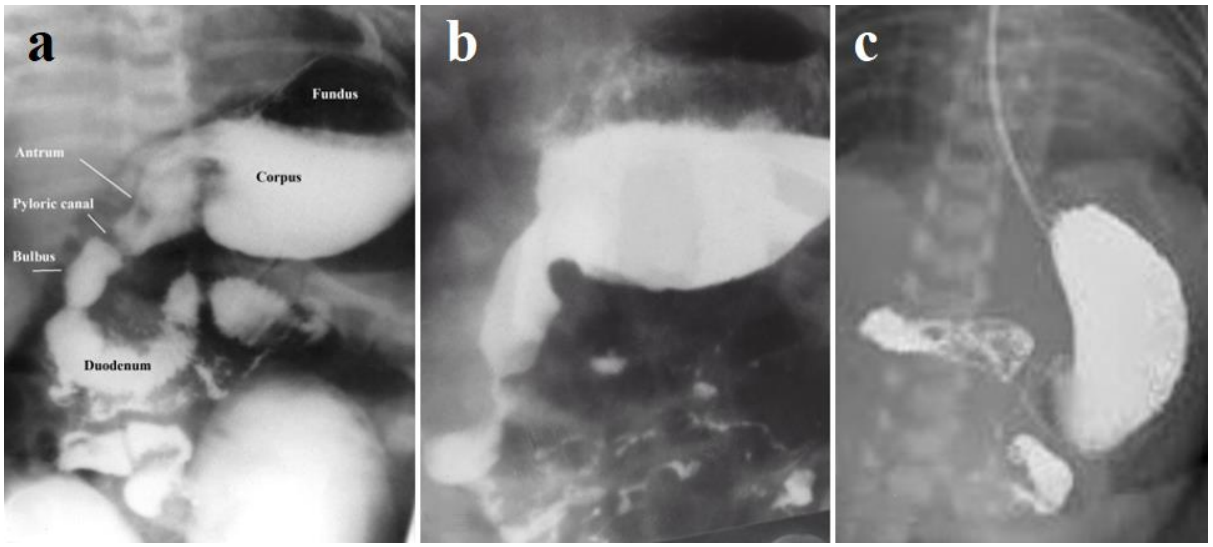

Figure 1. Radiographs of the stomach in children in the first months of life. **(a, b).** Stomach in the form of a teapot in children with good evacuation of barium from the stomach. The body of the stomach has a rounded shape and a small volume. Therefore, its lower contour is located cranial to the duodenal bulb. The narrow antrum is like the tip of a teapot. **(c).** Infant with intestinal malrotation, which is manifested by deformation of the duodenum and scanty evacuation of barium from the stomach. The stomach is represented by a single camera, which is typical of an adult. The distal contour of the stomach is located caudal to the duodenal bulb.

If a baby is exclusively sucking milk, regurgitation of milk is painless. If they are introduced to foods that require chemical processing, two scenarios may arise. In lactose-tolerant infants, the amount of lactase secreted remains unchanged. It is sufficient to break down lactose into glucose and galactose. Therefore, histamine is not released from the mast cells of the small intestine, and hydrochloric acid is not secreted by the gastric mucosa. Therefore, the baby remains calm. In infants with genetic lactose intolerance, lactase production decreases sharply. Undigested lactase leads to the release of hydrochloric acid, which passes through the esophagus during milk letdown, causing irritation and inflammation. This causes severe pain, manifested by the typical symptoms of infant colic. This is the onset of gastroesophageal reflux,

which irreversibly damages the function of the LES. By 4-6 months, the baby calms down because by this time the volume of a single feeding is less than the maximum capacity of the stomach. The reflux stops, and therefore the acid stops contacting the stomach wall.

Histological studies of Chandrasoma and DeMeester have proven: (a) The normal state where the esophageal squamous epithelium transitions at the EGJ to gastric oxyntic epithelium with no intervening cardiac epithelium; (b) cardiac metaplasia of the squamous epithelium due to exposure to gastric juice results in cephalad movement of the squamo-columnar junction (SCJ). This creates the squamo-oxyntic gap and the dilated distal esophagus, which is distal to the endoscopic EGJ. The length of the squamo-oxyntic gap in the dilated distal esophagus is concordant with the shortening of the abdominal segment of the lower esophageal sphincter (LOS); (c) in the early stages, the gap is <5 mm and the LES retains its competence. Reflux is uncommon and patients are asymptomatic; (d) The squamo-oxyntic gap increases in length, consistent with the extent of shortening of the LES, which becomes increasingly incompetent [15]. This study demonstrates that reflux occurs because of mucosal metaplasia and shortening of the LES. This excludes the possibility of physiological reflux. Secondly, shortening of the LES is an irreversible condition and therefore leads to relapse. As shown by Eckardt's study, esophageal motility does not improve after healing of esophagitis, which may contribute to the frequent occurrence of relapses in patients receiving drug treatment [16]. This means that GERD is a chronic, relapsing, and progressive disease. The earlier the diagnosis is made and treatment is initiated, the greater the chance of halting progression and controlling the clinical manifestations of the disease.

The prevailing hypothesis in the literature is that lactase is fermented in the colon by bacteria to form carbon dioxide, hydrogen, methane, propionic, and butyric acids, which cause diarrhea and abdominal pain due to colon distension. This hypothesis was confirmed by the increase in expired hydrogen and methane during the lactose breath test. This hypothesis is untrue. First, the lactose breath test is currently not used due to false positives. Second, if this were true, the colon would react similarly in lactose tolerant children. Third, in lactose-intolerant adults, a reaction to dairy products manifests as heartburn and rarely diarrhea. Fourth, in patients with radiologically confirmed GERD, avoiding dairy products typically resulted in symptom relief, even in those unaware of their lactose intolerance [17, 18].

Aguilera-Lizarraga et al showed that injection of “food antigens (gluten, wheat, soy and milk) into the rectosigmoid mucosa of patients with irritable bowel syndrome induced local oedema

and mast cell activation" [20]. It is known that mast cell activation leads to the release of histamine, and the histamine directly or through stimulation of gastrin secretion causes the release of hydrochloric acid in the stomach. Thus, both lactose and other foods can cause the release of histamine from mast cells, like what occurs in allergies. It must be considered that this variant of irritable bowel syndrome, which is stated as a functional disorder, is the result of hydrochloric acid hypersecretion.

IV. Hypothesis of the etiology of acid-related diseases

Based on scientifically proven research, I propose a hypothesis for the etiology of acid-related diseases. GERD is the tip of the iceberg of clinical manifestations of these diseases, because, unlike the stomach and duodenal bulb, the esophagus lacks protection from the destructive effects of gastric juice. A significant portion of the population (10-30%) is susceptible to this pathology because they have a hereditary intolerance to lactose. While a baby consumes breast milk, they produce sufficient lactase to break it down into glucose and galactose. Therefore, the milk they produce during the period of stomach enlargement up to 4-6 weeks does not contain hydrochloric acid, and the baby develops normally without colic. This phenomenon is well-known, as the use of wet nurses or obtaining milk in a clinic confirms the correctness of this conclusion. If, however, during this period, the infant is given food that requires hydrochloric acid treatment, lactase production decreases sharply (by a factor of 10). Undigested lactose acts on mast cells in the small intestine, causing the release of histamine, which leads to hypersecretion of hydrochloric acid. In such cases, the milk the infant expels contains hydrochloric acid, which damages the esophageal wall, causing pain. Gradually, the LES shortens due to the opening of its intra-abdominal portion, and the esophagus above the sphincter (phrenic ampulla) widens. Treatment alleviates symptoms, but the shortening of the LES and impaired esophageal motility persist, which can lead to disease progression despite the absence of symptoms. Adult patients with GERD almost always have a history of infantile colic (a restless child). I will give two typical examples.

The child was born premature and had vomiting with frequent aspiration pneumonia, for which he received streptomycin. I followed him as a teenager. He had significant hearing loss and frequent vomiting after eating. X-rays revealed complete insufficiency of the LES (chalasia). Despite the absence of other complaints, he agreed to surgery because he was embarrassed to eat outside the home. After a Nissen fundoplication, he had problems with patency. The fundoplication collapsed, and he did not want it repeated. This was an example

of LES insufficiency due to his immaturity. He did not suffer from reflux because he was lactose tolerant. Another example is published on my website [21]. You can find articles on this topic there. I would be grateful for any feedback. (http://www.anorectalmalformations.com).

P. S. Until now, articles on the role of milk in the pathogenesis of GERD and infant colic have assumed an allergic reaction to the protein. However, the proposed treatment with milk protein denaturation did not lead to significant symptom relief, which did not support this hypothesis. Barkholt et al. planned a study designed to provide evidence on the efficacy of a cow's milk protein-free diet and proton-pump inhibitor therapy for infant GERD [22]. This study will help determine whether the etiological factor of GERD is protein or lactose.

References

1. Nirwan JS, Hasan SS, Babar ZU, Conway BR, Ghori MU. Global Prevalence and Risk Factors of Gastro-oesophageal Reflux Disease (GORD): Systematic Review with Meta-analysis. Sci Rep. 2020 Apr 2;10(1):5814. doi: 10.1038/s41598-020-62795-1.
2. Fenwick WS. The Clinical Significance of Gastric Hypersecretion and its Connexion with Latent Disease of the Appendix. Proc R Soc Med. 1910;3(Surg Sect):177-86. doi: 10.1177/003591571000301617. PMID: 19974808; PMCID: PMC1961045.
3. Collen MJ, Lewis JH, Benjamin SB. Gastric acid hypersecretion in refractory gastroesophageal reflux disease. Gastroenterology. 1990 Mar;98(3):654-61. doi: 10.1016/0016-5085(90)90285-9.
4. Collen MJ, Jensen RT. Idiopathic gastric acid hypersecretion. Comparison with Zollinger-Ellison syndrome. Dig Dis Sci. 1994 Jul;39(7):1434-40. doi: 10.1007/BF02088045. PMID: 8026253.
5. Lewis JH. Idiopathic gastric acid hypersecretion: treatment implications for refractory acid/peptic disorders. Aliment Pharmacol Ther. 1991;5 Suppl 1:15-24. doi: 10.1111/j.1365-2036.1991.tb00745.x. PMID: 1888834.
6. Clark J, DeMeester TR, Johnson LF, Skinner DB. Twenty-four-hour lower esophageal pH monitoring and the lower esophageal sphincter. Surg Forum. 1975;26:362-3. PMID: 2986.
7. Demeester TR, Johnson LF, Joseph GJ, et al. Patterns of gastroesophageal reflux in health and disease. Ann Surg. 1976 Oct;184(4):459-70. doi: 10.1097/00000658-197610000-00009.

8. Gyawali CP, Kahrilas PJ, Savarino E, et al. Modern diagnosis of GERD: the Lyon Consensus. Gut. 2018 Jul;67(7):1351-1362. doi: 10.1136/gutjnl-2017-314722.
9. Bertin L, Savarino V, Marabotto E, Ghisa M, de Bortoli N, Savarino EV. Pathophysiology of Gastroesophageal Reflux Disease. Digestion. 2026;107(2):185-201. doi: 10.1159/000547023
10. Levin MD. Functional Heartburn is Gastroesophageal Reflux. (2025). Mathews Journal of Gastroent. ISSN: 2572-6471.
11. Levin MD. (2025). Belching Pathophysiology. Mathews J Gastroenterol Hepatol. 10(3):35.
12. Rosen R, Borrelli O, Faure C, et al. Rome V Pediatric Upper Gastrointestinal Disorders of Gut-Brain Interaction. Gastroenterology. 2026 May;170(6):1347-1366. doi: 10.1053/j.gastro.2026.01.039.
13. Bhatnagar S, Aggarwal R. Lactose intolerance. BMJ. 2007 Jun 30;334(7608):1331-2. doi: 10.1136/bmj.39252.524375.80.
14. Camilleri M, Park SY, Scarpato E, Staiano A. Exploring hypotheses and rationale for causes of infantile colic. Neurogastroenterol Motil. 2017 Feb;29(2):10.1111/nmo.12943. doi: 10.1111/nmo.12943.
15. Chandrasoma P, DeMeester T. A New Pathologic Assessment of Gastroesophageal Reflux Disease: The Squamo-Oxyntic Gap. Adv Exp Med Biol. 2016;908:41-78. doi: 10.1007/978-3-319-41388-4_4.
16. Eckardt VF. Does healing of esophagitis improve esophageal motor function? Dig Dis Sci. 1988 Feb;33(2):161-5. doi: 10.1007/BF01535727. PMID: 3338364.
17. Levin MD. (2025). Prevention and Treatment of Esophageal Reflux Disease: Literature Analysis. Mathews J Gastroenterol Hepatol. 10(2):33.
18. Levin MD. Hydrochloric acid hypersecretion is the cause of pathology of the upper digestive tract. Literature analysis. 8 January 2025, Preprint v1 · CC-BY 4.0. doi.org/10.32388/4QXH2Q
19. Levin MD. (2025). Pathogenesis of Infantile Colic. Hypothesis. Mathews JGastroenterol Hepatol. 10(1):29.
20. Aguilera-Lizarraga J, Florens MV, Viola MF, et al. Local immune response to food antigens drives meal-induced abdominal pain. Nature. 2021 Feb;590(7844):151-156. doi: 10.1038/s41586-020-03118-2.
21. Levin MD. An analysis of a case of severe GERD with extraesophageal symptoms

https://www.anorectalmalformations.com/_files/ugd/4d1c1d_994cada4e15a46509e9512fed6589d65.pdf?index=true

22. Barkholt NK, Dalby K, Mogensen CB, et al. Infant Reflux Trial: study protocol for a multicentre randomized controlled trial on the treatment of gastroesophageal reflux disease in infants. Trials. 2026 Jan 29;27(1):169. doi: 10.1186/s13063-026-09477-x.