Dear colleagues,

I propose to analyze the article by Chen et al, who published “Best Practice Guidelines for Gastroenterologists” [1]. How these four authors from different cities in the United States agreed on these recommendations is not entirely clear. However, neither a review of the published literature nor the expert’s opinion has anything to do with science, like all decisions made by voting. For example, if Albert Einstein's works had been discussed by professors, most of whom did not understand what they were talking about, then civilization would be on a different level.

BEST PRACTICE ADVICE 1: Gastroenterologists should be aware of potential extraesophageal manifestations of gastroesophageal reflux disease (GERD) and should inquire about such disorders including laryngitis, chronic cough, asthma, and dental erosions in GERD patients to determine whether GERD may be a contributing factor to these conditions.

I agree with the recommendation that gastroenterologists finally become aware of the potential extraesophageal manifestations of gastroesophageal reflux disease (GERD). However, it is not practitioners, but scientists who must answer the question of whether chronic cough is a consequence of GERD or whether it causes GERD because of repeated increases in intragastric pressure during the cough reflex. Given the high prevalence of GERD, it is important to determine what the cause-and-effect relationship is and what is the coincidental combination.

BEST PRACTICE ADVICE 2: Development of a multidisciplinary approach to extraesophageal (EER) manifestations is an important consideration because the conditions are often multifactorial, requiring input from non-gastroenterology (GI) specialties. Results from diagnostic testing (i.e., bronchoscopy, thoracic imaging, laryngoscopy, etc.) from non-GI disciplines should be taken into consideration when gastroesophageal reflux (GER) is considered as a cause for extraesophageal symptoms.

1. The only factor that separates the 40% of the population with GERD from the remaining 60% without GERD is hypersecretion of hydrochloric acid. All other factors are the results of pathogenesis (hiatal hernia, shortening of the LES, transient lower esophageal sphincter relaxations, etc.). They arise during the development of the disease.

2. When gastroesophageal reflux (GER) is suspected as the cause of extraesophageal symptoms, only a gastroenterologist should prescribe and evaluate the results of radiological, manometric, endoscopic, histological, and other studies.

BEST PRACTICE ADVICE 3: Currently, there is no single diagnostic tool that can conclusively identify GER as the cause of EER symptoms. Determination of the contribution of GER to EER symptoms should be based on the global clinical impression derived from patients' symptoms, response to GER therapy, and results of endoscopy and reflux testing.

These recommendations require detailed explanation.

1). GERD is a chronic, relapsing, progressive disease. Therefore, if a patient had a history of recurrent heartburn, belching and abdominal pain, then the diagnosis of GERD is certain, regardless of whether these symptoms are currently present.

2) A negative response to GER therapy has no significance since many patients with GERD are refractory to therapy.

3) As you know, current recommendations do not recommend performing histological examination if there are no suspicious areas. Therefore, in a huge percentage of patients, nonerosive esophagitis caused by reflux is not diagnosed. To increase the diagnostic accuracy of endoscopy, it is important not only to indicate the need for histological examination, but also to indicate the research method. The most accurate and simple scientifically based method for diagnosing GERD was developed by prof. Chandrasoma [2]. Unfortunately, practitioners who have not undergone scientific school do not use it, since it destroys all the false concepts of pathophysiology of GERD that were introduced by non-GI specialists.

4). The "DeMeester score", and the proposed method of pH monitoring, were developed with numerous methodological flaws. (a) It was originally based on the misconception of the possibility of physiological reflux. (b) 15 people who considered themselves healthy were selected as controls. If DeMeester were a scientist, he should have ruled out GERD in them by radiological, endoscopic, histological and manometric methods, because it was known that in many patients with GERD can be asymptomatic. After numerous articles appeared that pH monitoring did not detect GERD in more than 30% of patients, equipment manufacturers with the help of practitioners had already advertised impedance-ph monitoring, developed based on previous ideas about the pathophysiology of GERD. Thus, impedance-ph monitoring allows us to detect only severe forms of GERD. The use of pH monitoring has no advantage over clinical symptoms and should not be adopted at all, as it misleads doctors.

BEST PRACTICE ADVICE 4: Consideration should be given toward diagnostic testing for reflux before initiation of proton pump inhibitor (PPI) therapy in patients with potential

extraesophageal manifestations of GERD, but without typical GERD symptoms. Initial single-dose PPI trial, titrating up to twice daily in those with typical GERD symptoms, is reasonable.

This proposal is contrary to existing guidelines based on an understanding of the pathological physiology of GERD. In patients with typical symptoms of GERD, according to existing rules, PPI is prescribed at 20 mg 2 times a day for 4 weeks. If there is a positive effect in the next 4 weeks, PPI is prescribed at a dose of 20 mg 1 time per day, followed by a gradual reduction in the dose until complete cessation [3]. To get the effect, complex treatment is necessary. There can be no other testing. Experience has shown that PPI treatment can reduce gastric acidity and typical GERD symptoms, but often has no effect on extraesophageal symptoms. When the antireflux function of the lower esophageal sphincter (LES) is insufficient, even “normal” acidity causes wall damage with each episode of reflux, because the “normal” acid that denatures the proteins of meat foods damages the wall of the esophagus. The walls of the stomach and duodenal bulb are protected from acid, but the wall of the esophagus is not.

BEST PRACTICE ADVICE 5: Symptom improvement of EER manifestations while on PPI therapy may result from mechanisms of action other than acid suppression and should not be regarded as confirmation for GERD.

An accurate diagnosis of GERD is established based on endoscopy with histology, and/or the radiological methods described below, which allows you to accurately determine the function of the LES, its length, as well as the width and contours of the esophagus. Judging the presence of GERD by the reaction to PPI therapy is not acceptable. Because GERD is asymptomatic in almost 30% of cases, and in some patients PPI treatment is ineffective.

BEST PRACTICE ADVICE 6: In patients with suspected extraesophageal manifestation of GERD who have failed one trial (up to 12 weeks) of PPI therapy, one should consider objective testing for pathologic GER, because additional trials of different PPIs are low yield.

In medicine, there are rules that were developed by previous generations of scientists. One of them is that the disease is first diagnosed and then treatment is prescribed. This rule was violated in relation to GERD because when practitioners, not trained in scientific work, received diagnostic equipment that had not been tested by scientists, they perverted the scientific achievements of previous generations. For example, in BEST PRACTICE ADVICE 3, which states: - "Currently, there is no single diagnostic tool that can conclusively identify GER as the cause of EER symptoms." This is true because diagnostic methods were developed for profit (pH monitoring, HRM, exhaled air diagnostic devices, etc.). As shown above, they have no scientific basis and give a large percentage of false conclusions. On their basis, a perverted hypotheses of the

normal and pathological physiology of the esophagogastric junction were developed, contrary to scientific research.

BEST PRACTICE ADVICE 7: Initial testing to evaluate for reflux should be tailored to patients' clinical presentation and can include upper endoscopy and ambulatory reflux monitoring studies of acid suppressive therapy.

First, the study cannot and should not be tailored to clinical symptoms. Secondly, as was shown above, endoscopy without histology, like pH monitoring, have low sensitivity. Their use is not justified.

PRACTICE ADVICE 8: Testing can be considered for those with an established objective diagnosis of GERD who do not respond to high doses of acid suppression. Testing can include pH-impedance monitoring while on acid suppression to evaluate the role of ongoing acid or non-acid reflux.

If pH-impedance monitoring diagnoses only severe forms of GERD, its use is also pointless to determine therapeutic measures.

BEST PRACTICE ADVICE 9: Alternative treatment methods to acid suppressive therapy (eg, lifestyle modifications, alginate-containing antacids, external upper esophageal sphincter compression device, cognitive-behavioral therapy, neuromodulators) may serve a role in management of EER symptoms.

Lifestyle modifications, alginate-containing antacids, and esophageal mucosal protectors are not an alternative to acid suppressive therapy. Alternative means either one or the other. All conservative treatment methods should be included in the complex treatment of GERD from the very beginning to avoid severe complications and not always reliable surgical methods of correction.

BEST PRACTICE ADVICE 10: Shared decision-making should be performed before referral for anti-reflux surgery for EER when the patient has clear, objectively defined evidence of GERD. However, a lack of response to PPI therapy predicts lack of response to anti-reflux surgery and should be incorporated into the decision process.

If the patient has clear, objectively defined evidence of GERD, this is an indication for complex treatment of the disease, and not for surgery, especially since lack of response to PPI therapy predicts lack of response to anti-reflux surgery.

I suggest x-ray examination with maximum provocation of EGJ function.

This method can be part of an X-ray examination of the esophagus, stomach, and duodenum or as an independent study if the suspicion of GERD was not

confirmed after endoscopy. It is based on a known physiological pattern: an increase in pressure in the stomach causes a reflex contraction of the upper and lower esophageal sphincters [4,5]. Patient, lying on the X-ray table, he continuously drinks a barium suspension through a straw from a jar standing near his head. When the barium runs out (200-250 ml), he raises his straightened legs. At this moment, an x-ray is taken from the pharynx to the body of the stomach. After that, the patient rises and lies down again after 5 minutes. The second radiograph is taken at rest to determine the completeness of barium evacuation into the stomach and possible free reflux.

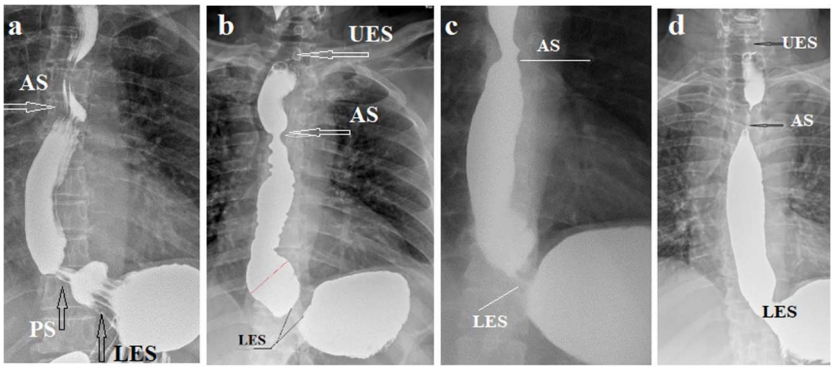

Figure 1. Radiographs of patients with GERD with non-esophageal symptoms, performed with the highest pressure in the stomach. All people have two anatomical sphincters in the esophagus: the upper esophageal sphincter (UES) and the lower esophageal sphincter (LES). In patients with GERD, physiological sphincters appear. The proximal sphincter (PS) arises over a dilated portion of the esophagus called the phrenic ampulla. It contracts to create high pressure in the ampulla for open the LES. It continues to contract until the ampulla injects its contents into the stomach. The pressure in the ampulla must be higher than the gastric pressure. If during the ampulla contraction, PS relaxes, the contents of the stomach are thrown into the esophagus. This is how transient LES relaxations occur during swallowing saliva. The PS also contracts during acid reflux to prevent the bolus from leaking into the proximal esophagus. The second barrier to the penetration of the acid bolus into the pharynx is the aortic functional sphincter (AS), which forms near the aortic narrowing of the esophagus. It occurs when PS is deficient. Dysfunction of the AS causes the reflux of acidic contents into the pharynx and the occurrence of non-esophageal symptoms. Details can be found here [6,7].

The assessment of x-ray examination is based on comparison with standards. For adults, the normal width of the esophagus is 1.5 cm, and the length of the LES is 3.2-4.2 (3.60±0.08) cm [6,8]. In healthy individuals, the contrast bolus penetrates from the esophagus into the stomach without delay, despite the increase in LES tone. Thus, if a contraction of the LES occurs, this is evidence of peristaltic weakness of the esophagus. With GERD, an increase in tone in the

UES and LES leads to contraction of these sphincters with visualization between them of the esophagus filled with a contrast agent. With GERD, the esophagus is dilated (> 1.5 cm), the LES is shortened (< 3.0 cm), and the phrenic ampulla and functional sphincters (PS and AS) are detected. Normally, the ratio of the width of the esophagus to the length of the LES is always less than 1. With GERD, this ratio is always greater than one - the larger it is, the more severe the GERD.

Complex treatment GERD. PPI monotherapy is based on the misconception of the possibility of physiological reflux.

1. Exclusion from the diet of foods containing lactose.

Many patients with GERD do not drink milk, as it causes heartburn and abdominal pain. However, even those patients who did not feel the negative effects of milk experience relief after stopping the consumption of products containing lactose. In people who are lactose intolerant, it causes the release of histamine from intestinal mast cells. Both histamine, and gastrin released under its influence stimulate hypersecretion of hydrochloric acid.

2. Acid Suppression

Proven advantage of PPI

3. Lifestyle modifications

Due to the weakness of the LES, a horizontal position, a tight belt, and a large amount of food contribute to reflux. Any amount of acid and pepsin, which aid digestion, damage the esophagus. Therefore, you need to go to bed with an empty stomach and avoid conditions for increasing pressure in the stomach.

4. Antacids and protectors of the esophageal mucosa

20-30 minutes after eating, a large volume of food and gastric juice accumulates in the stomach, after which gastric peristalsis begins. This period, accompanied by an increase in pressure in the stomach, promotes reflux in an upright position. Taking antacids and protectors of the esophageal mucosa after meals and before bed prevents damage to the esophagus.

5. Dilation of the esophagus и sphincters by swallowing of a large tablet.

According to Bayliss-Starling's low of the intestine, everything in the intestine moves along because of peristalsis, which is described as contraction of the intestine above the bolus and relaxation below it [9]. I have GERD patients swallow 1.9 and 2.3 cm barium-containing hard tablets to stretch inflammatory

rigid anatomical (UES, LES, pyloric sphincter) and functional sphincters (PS, AS, post-bulbar sphincter, Ochsner's sphincter) (**Figure 2**). A positive effect was recorded in most patients, and in all with non-esophageal symptoms [7].

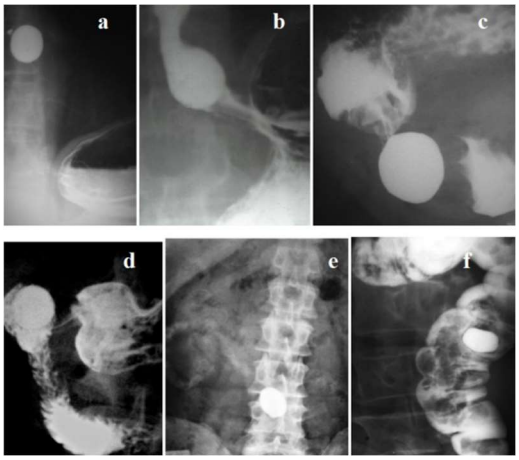

Figure 2. Radiographs of different patients who swallowed LT. (a) LT in the middle of the esophagus; (b) above the contracted lower esophageal sphincter; (c) in the antrum of the stomach during antral systole; (d) in the duodenal bulb; (e) an x-ray was taken 28 hours after swallowing the LT. A reduced tablet is visible at the level L 3-4. Traces of barium from the disintegrated surface layer of the tablet are visible in the loops of the small intestine; (f) in the descending colon.

The passage of the tablet through the sphincters improves their throughput: they accelerate the cleansing of the esophagus from food and chyme and speed up the evacuation from the stomach. This method was effective without the use of other treatments but should only be used as part of a comprehensive treatment.

Conclusion. I suggest every doctor carefully read my analysis along with the references. Science is based only on evidence (reliable facts). You decide for yourself where the truth is.

I believe that we should know the turning point in history where basic science failed to defend the truth. Thanks to financial support from equipment manufacturers, pH monitoring in the esophagus has become the “gold standard” for diagnosing GERD. This study was initially flawed and, as shown above, methodologically unscientific. All hypotheses that were based on this study turned out to be false. And now, when it has become clear that pH monitoring does not diagnose about 30% of patients with GERD, these false hypotheses are the only ones that gastroenterologists refer to.

References

1. Chen JW, Vela MF, Peterson KA, Carlson DA. AGA Clinical Practice Update on the Diagnosis and Management of Extraesophageal Gastroesophageal Reflux Disease: Expert Review. Clin Gastroenterol Hepatol. 2023 Jun;21(6):1414-1421.e3. doi: 10.1016/j.cgh.2023.01.040.
2. 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.
3. Ksiądzyna D, Szeląg A, Paradowski L. Overuse of proton pump inhibitors. Pol Arch Med Wewn. 2015;125(4):289-98. doi: 10.20452/pamw.2790.
4. Shafik A, El-Sibai O, Shafik AA, Mostafa R, Shafik I. Effect of straining on the lower esophageal sphincter: identification of the "straining-esophageal reflex" and its role in gastroesophageal competence mechanism. J Invest Surg. 2004 Jul-Aug;17(4):191-6. doi: 10.1080/08941930490471948.
5. Levin MD, Korshun Z, Mendelson G. [Pathological physiology of gastroesophageal reflux disease. Hypothesis (Literature review)]. Eksp Klin Gastroenterol. 2013;(5):72-88.PMID: 24501951 Review. Russian. . (PubMed).
6. Levin MD. X-ray imaging of lower esophageal sphincter and its role in the diagnosis of gastroesophageal reflux disease. https://www.anorectalmalformations.com/_files/ugd/4d1c1d_72d9deec832e430cbc25f2a9b7e1eef4.pdf
7. Levin MD. Gastroesophageal reflux disease with only extraesophageal symptoms. Case report. https://www.anorectalmalformations.com/_files/ugd/4d1c1d_a44a89c2f90d40f3b9665f19c126bc53.pdf
8. Levin MD. REACTION TO ARTICLES ON HIGH RESOLUTION MANOMETRY, THE LENGTH OF THE LOWER ESOPHAGEAL SPHINCTER AND THE DIAGNOSIS OF GASTROESOPHAGEAL REFLUX DISEASE. Arq Gastroenterol. 2019 Aug 13;56(2):209-210. doi: 10.1590/S0004-2803.201900000-39.
9. Alvarez WC. BAYLISS AND STARLING'S LAW OF THE INTESTINE or THE MYENTERIC REFLEX. https://journals.physiology.org/doi/epdf/10.1152/ajplegacy.1924.69.2.229

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