CORSO
INTERREGIONALE
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LA NUOVA GASTROENTEROLOGIA

EMILIA ROMAGNA
MARCHE
TOSCANA

Gli integratori ed i fitoterapici per il reflusso gastroesofageo. Principi di efficacia

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Gastroesophageal reflux disease (GERD)
Varied perspectives

Montreal definition

Condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications.

Clinical

Lyon consensus

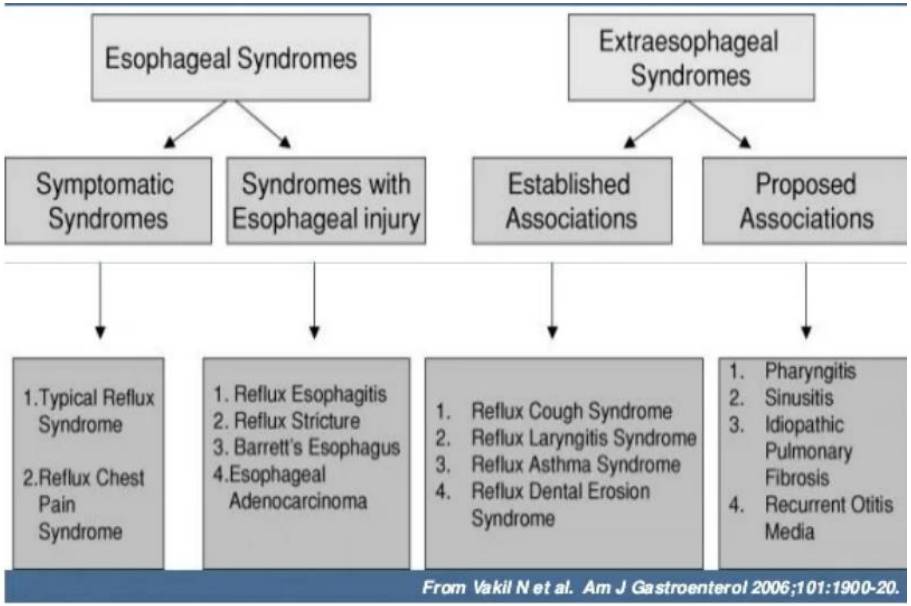
Presence of excess GE reflux, esophageal motor perturbations and increased epithelial permeability that can be associated with reflux.

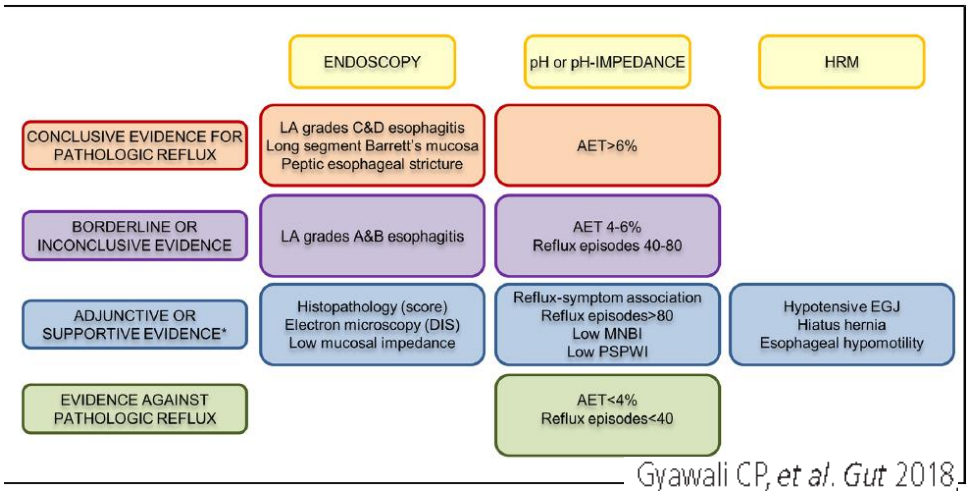
Physiomorphologic

Rome IV Criteria

Focused on defining functional syndromes with GERD characteristics. That can mimic GERD without reflux causality

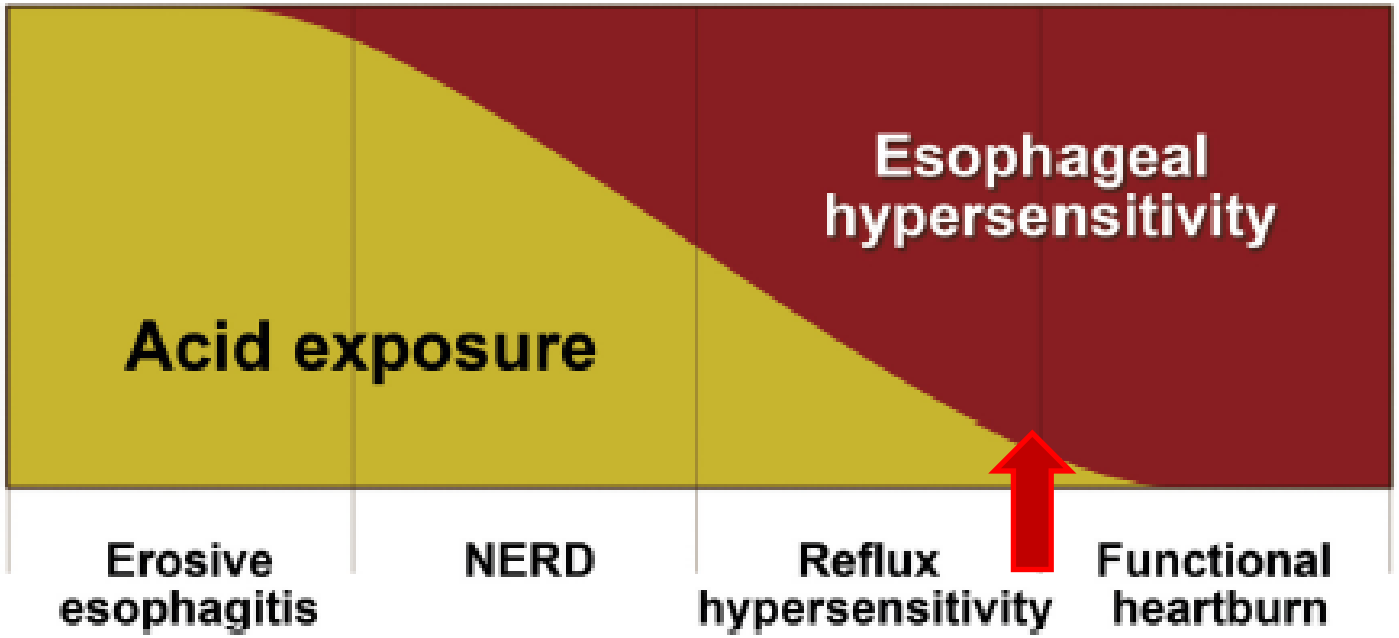
Symptom based





Katzka DA et al, Clin Gastroenterol Hepatol 2020

Restrictive definition of GERD

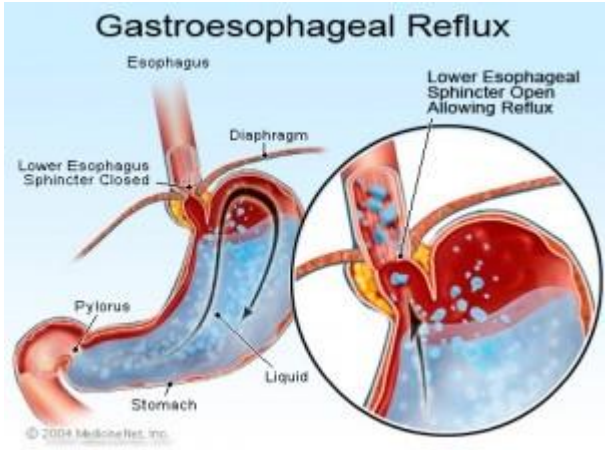


The interplay between esophageal hypersensitivity and acid exposure in the reflux symptom spectrum. Symptoms in erosive esophagitis are dominated by abnormal acid exposure whereas symptoms in functional heartburn are dominated by hypersensitivity. Symptoms in NERD and reflux hypersensitivity are related to a combination of both acid exposure and hypersensitivity, with a shift reflecting a more pronounced effect of acid exposure along the NERD diagnostic spectrum and a more pronounced effect of esophageal hypersensitivity along the reflux hypersensitivity diagnostic spectrum.

Gastroenterology 2016;150:1368–1379

GERD

Family of syndromes attributable to, or exacerbated by, gastroesophageal reflux, evident symptomatically, endoscopically, or by physiological testing, which impart morbidity through troublesome symptoms and/or risk.



The goal of medical therapy in GERD is to control heartburn, heal gastroesophageal mucosal injuries, and improve quality of life

PJ Kahrilas et al, 2020

Medical therapy

Lifestyle and dietary modifications may benefit some selected patients with GERD, but alone they are almost ineffective in relieving reflux symptoms.
GoR B; ExC 100 %, SCC 97 %

Acid suppressive drugs are safe and effective in patients with esophageal syndromes. Proton pump inhibitors (PPIs) are more powerful than H2 receptor antagonists in providing mucosal healing and symptomatic relief.
GoR A; ExC 100 %; SCC 100 %

30%-35% of the patients require additional intervention to control symptoms

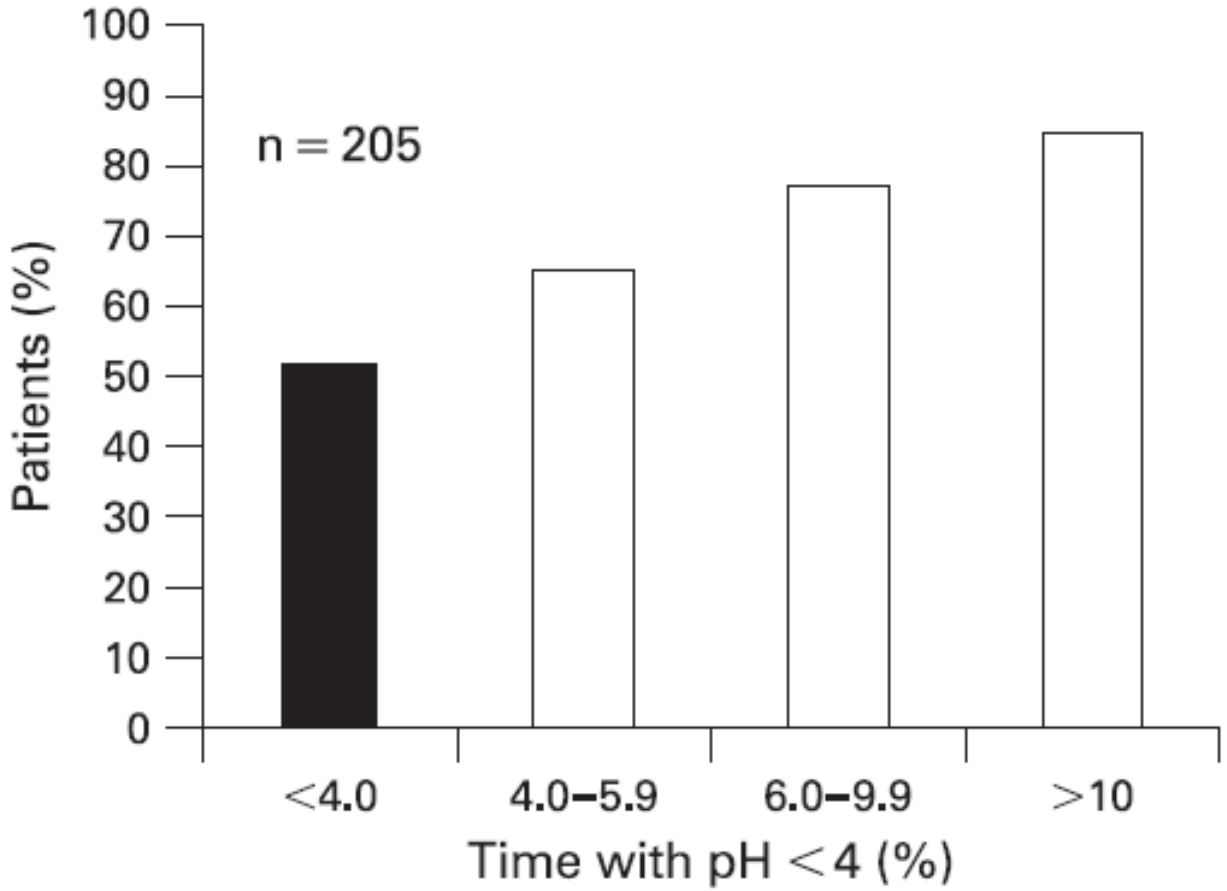
ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease

Philip O. Katz, MD, MACG[1], Kerry B. Dunbar, MD, PhD[2,3], Felice H. Schnoll-Sussman, MD, FACG[1], Katarina B. Greer, MD, MS, FACG[4], Rena Yadlapati, MD, MSHS[5] and Stuart Jon Spechler, MD, FACG[6,7]

EAES recommendations for the management of gastroesophageal reflux disease

Karl Hermann Fuchs · Benjamin Babic · Wolfram Breithaupt · Bernard Dallemagne · Abe Fingerhut · Edgar Furnee · Frank Granderath · Peter Horvath · Peter Kardos · Rudolph Pointner · Edoardo Savarino · Maud Van Herwaarden-Lindeboom · Giovanni Zaninotto

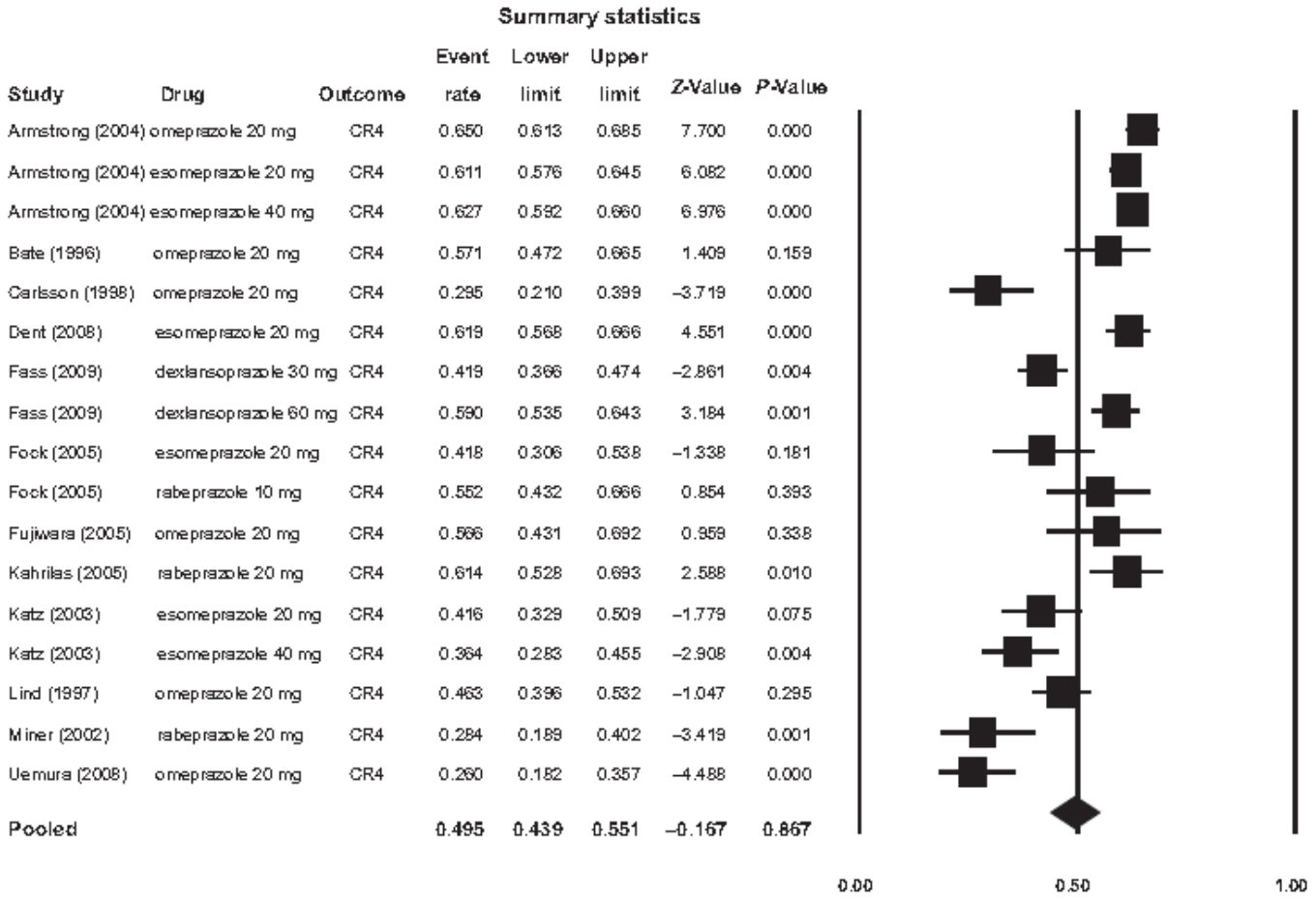
PPI refractory GERD



NERD patients with oesophageal acid exposure within the normal range (black bar) have the lowest response rate to PPIs once daily

Fass R and Sifrim D, 2009

Complete relief of heartburn after 4 weeks of proton pump inhibitor therapy in patients with non-erosive reflux disease defined by the presence of heartburn and a normal endoscopy

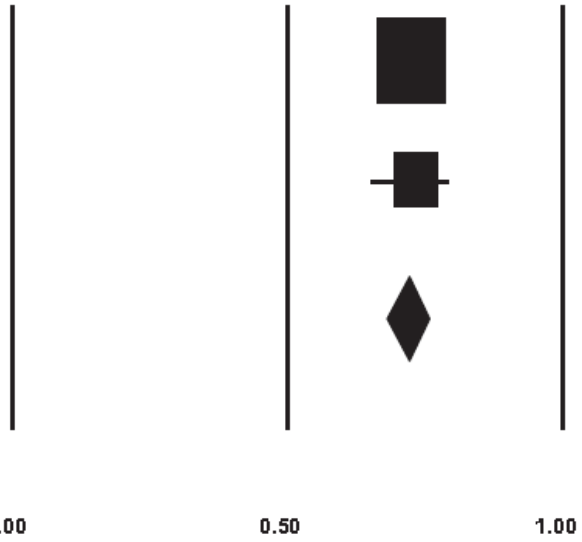


Neurogastroenterol Motil (2012) 24, 747–e350

Complete relief of heartburn after 4 weeks of proton pump inhibitor therapy in patients with non-erosive reflux disease defined by the presence of heartburn, a normal endoscopy and a positive pH measurement

Summary statistics

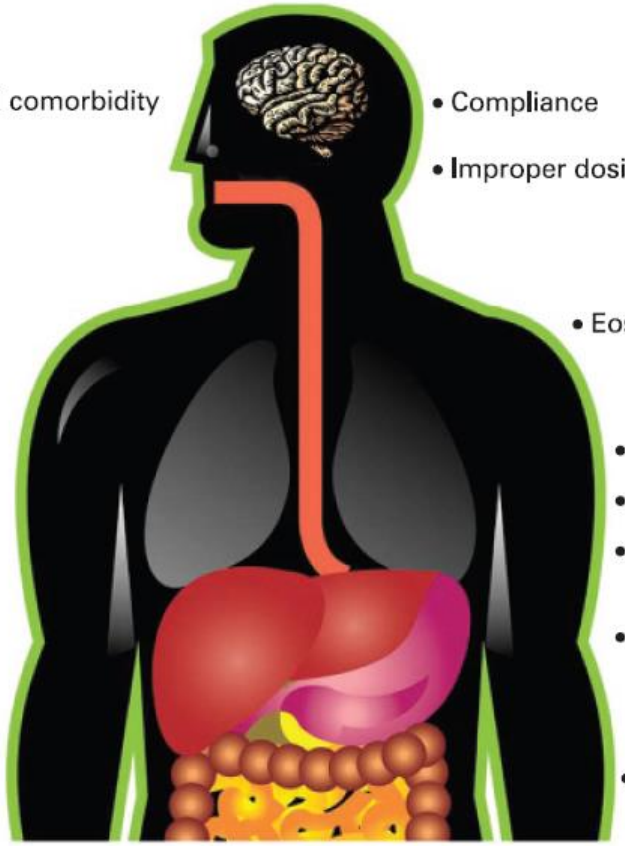
Study	Drug	Outcome	Event rate	Lower limit	Upper limit	*Z*-Value	*P*-Value
Johnson (2003*)	esomeprazole 40 mg	CR4	0.730	0.676	0.779	7.430	0.000
Richter (2000)	omeprazole 20 mg	CR4	0.737	0.651	0.809	4.933	0.000
Pooled			**0.735**	**0.691**	**0.776**	**9.145**	**0.000**



Studies reporting complete relief of heartburn after 4 weeks of proton pump inhibitor therapy in patients with non-erosive reflux disease defined by the presence of heartburn, a normal endoscopy and a positive pH measurement (group c). *Response rate at 2-weeks.

Neurogastroenterol Motil (2012) 24, 747–e350

Underlying mechanisms for persistent heartburn despite treatment with PPI

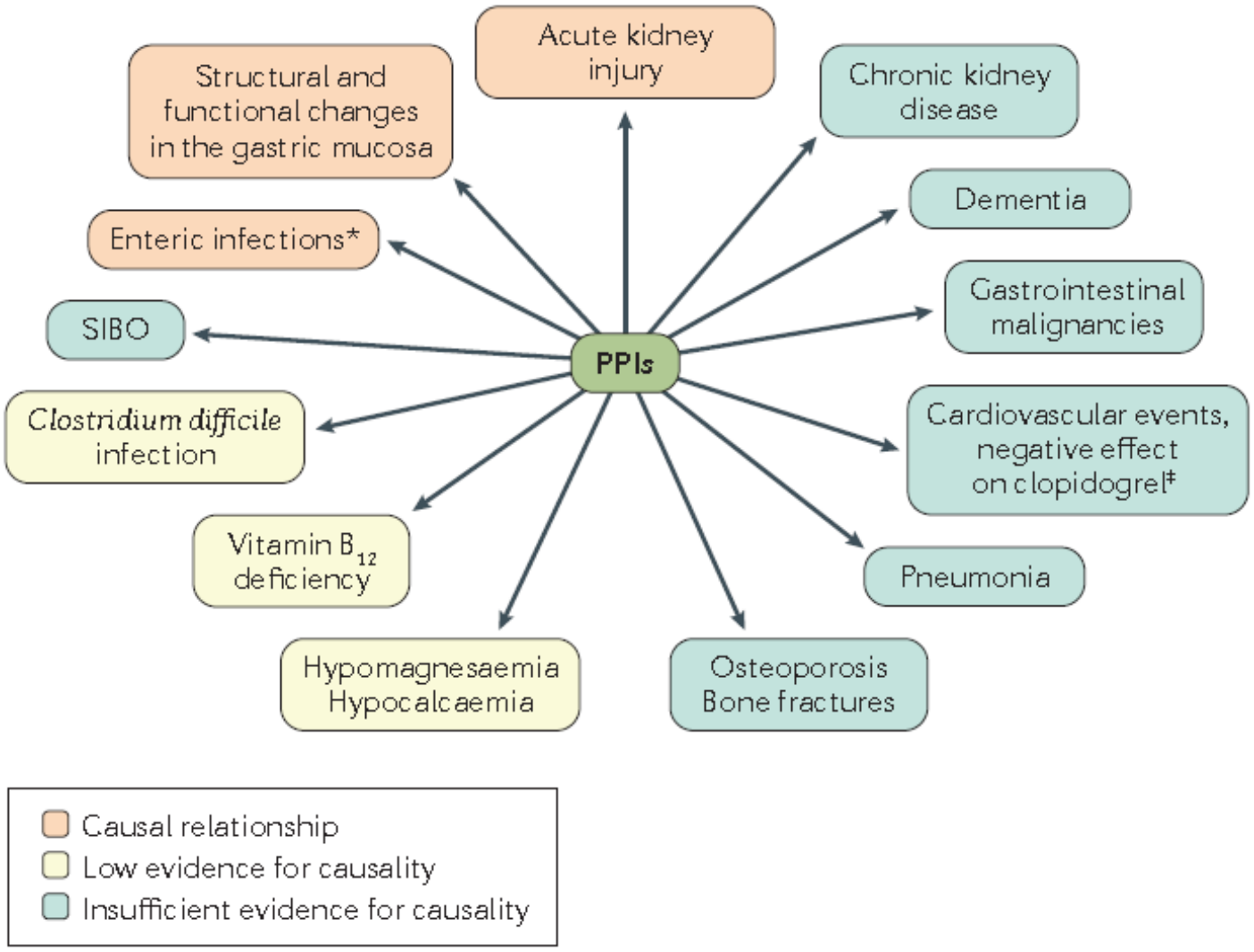


- Psychological comorbidity
- Compliance
- Improper dosing time
- Eosinophilic oesophagitis (?)
- Functional heartburn (oesophageal hypersensitivity)
- Weakly acidic reflux
- Duodenogastro-oesophageal reflux
- Residual acid reflux
- Reduced PPI bioavailability
- Rapid PPI metabolism
- PPI resistance
- Others
- Delayed gastric emptying
- Concomitant functional bowel disorder

In the area of refractory GERD focuses primarily on weakly acidic reflux, duodenogastro-oesophageal reflux, and oesophageal hypersensitivity.

Gut 2009;**58**:295–309. doi:10.1136/gut.2007.145581

PPI and adverse events



Reviews in gastroenterology, Hepatology and Nutrition, 2015

Surg Endosc
DOI 10.1007/s00464-014-3431-z

CONSENSUS STATEMENT

EAES recommendations for the management of gastroesophageal reflux disease

Karl Hermann Fuchs · Benjamin Babic · Wolfram Breithaupt · Bernard Dallemagne · Abe Fingerhut · Edgar Furnee · Frank Granderath · Peter Horvath · Peter Kardos · Rudolph Pointner · Edoardo Savarino · Maud Van Herwaarden-Lindeboom · Giovanni Zaninotto

Antacids are well tolerated, safe, and effective in reducing heartburn and controlling acid regurgitation (typical symptoms of GERD) in patients with mild reflux disease.

GoR B; ExC 100 %; SCC 96 %

However, they are less effective in controlling nonacid reflux and regurgitation

ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease

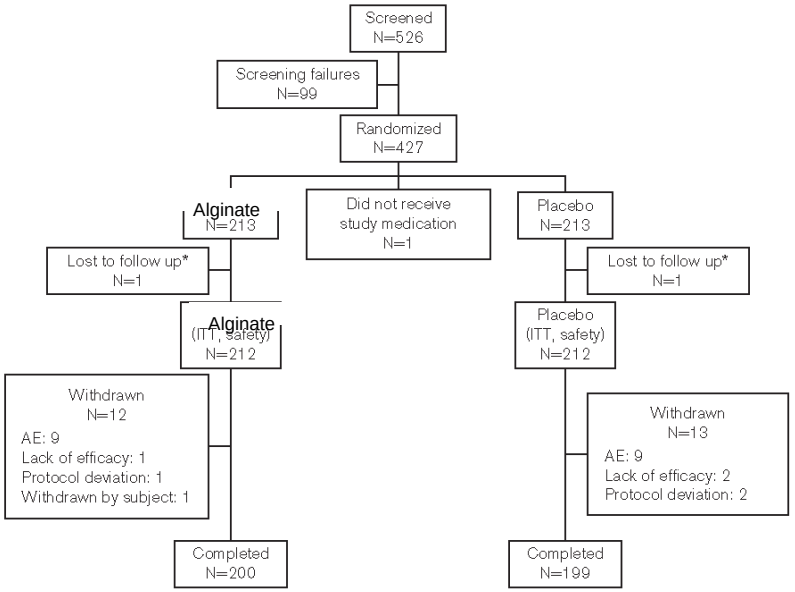
Philip O. Katz, MD, MACG[1], Kerry B. Dunbar, MD, PhD[2,3], Felice H. Schnoll-Sussman, MD, FACG[1], Katarina B. Greer, MD, MS, FACG[4], Rena Yadlapati, MD, MSHS[5] and Stuart Jon Spechler, MD, FACG[6,7]

11. We recommend against routine addition of medical therapies in PPI nonresponders (conditional recommendation, moderate level of evidence).

15. We do not recommend sucralfate for GERD therapy except during pregnancy (strong recommendation, low level of evidence).

Antacids are used exclusively for on-demand symptom relief with little evidence to favor 1 type over another. Studies with an alginic acid preparation suggest potential efficacy in Symptom relief compared with other products, but alginate content of preparations sold in other countries is variable

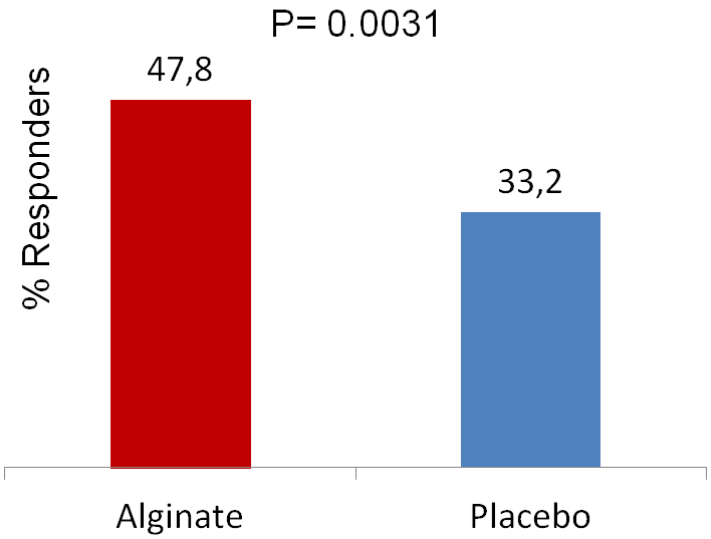
Alginate tablets to reduce reflux symptoms



Multicentre, randomized, double-blind, two-arm, parallel-group, placebo-controlled

Primary efficacy: Reflux Disease Questionnaire gastro-oesophageal reflux disease response (intent-to-treat population)

	Alginate (*N* = 212)	Placebo (*N* = 212)
Responders[a] (*N*)	111	80
LS proportion (95% CI)	47.84 (39.48–56.33)	33.15 (25.69–41.55)
Odds ratio (95% CI)	0.92 (0.65–1.29)	0.50 (0.35–0.71)
Alginate vs. placebo		
Odds ratio (95% CI)	1.85 (1.23–2.78)	
P value	0.0031	



European Journal of Gastroenterology & Hepatology 2019, 31:86–93

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v18.i32.4371

World J Gastroenterol 2012 August 28; 18(32): 4371-4
ISSN 1007-9327 (print) ISSN 2219-2840 (onli

BRIEF ARTI

Alginate controls heartburn in patients with erosive and nonerosive reflux disease

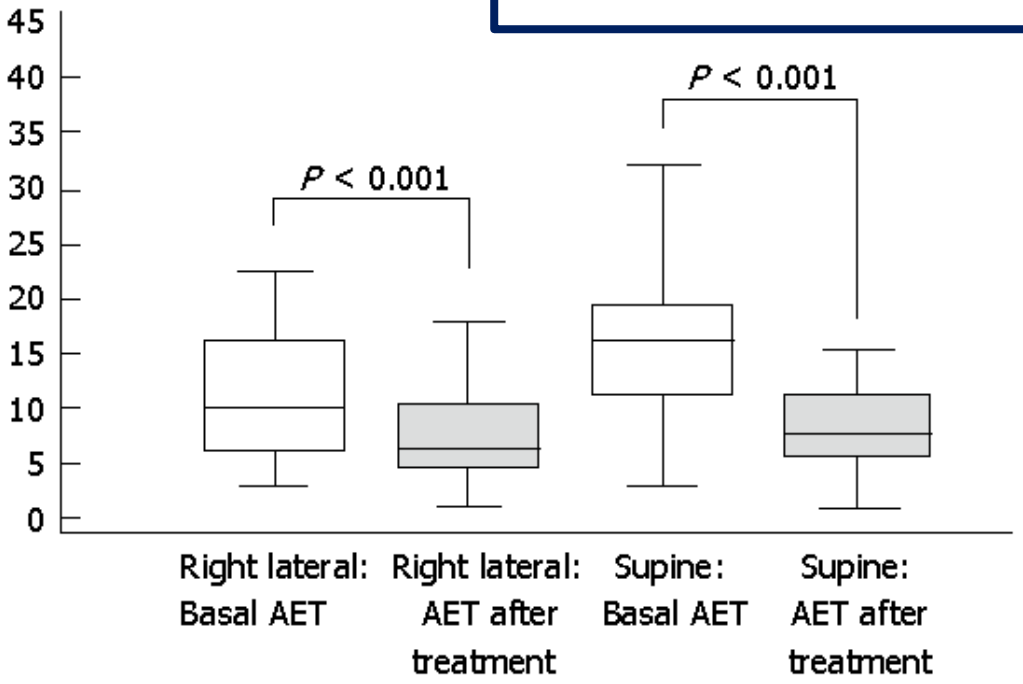
Edoardo Savarino, Nicola de Bortoli, Patrizia Zentilin, Irene Martinucci, Luca Bruzzone, Manuele Furnari, Santino Marchi, Vincenzo Savarino

Sodium bicarbonate and alginate

- neutralize gastric acidity and to create an alginate-based raft that remains in the upper part of the stomach as a physical barrier capable of preventing reflux episodes

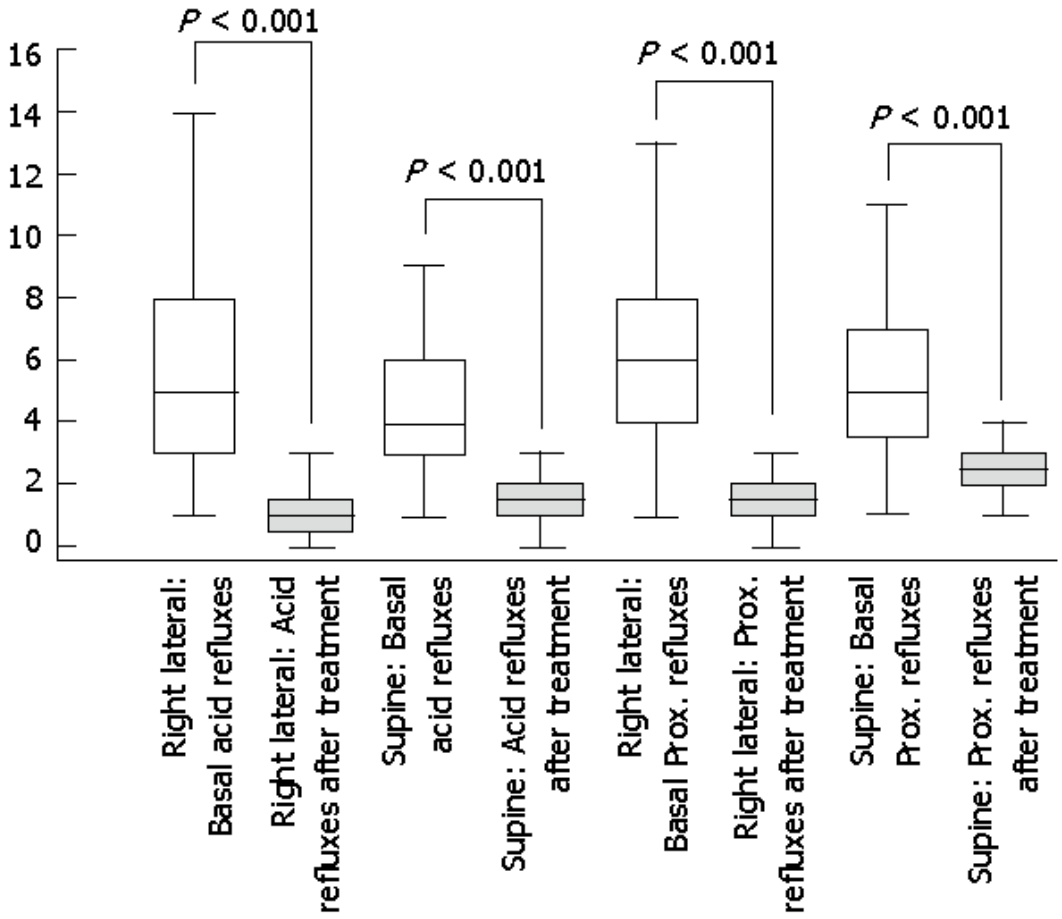
Herbal components (i.e., honey chamomille or *Matricaria recutita L., Calendula officinalis, Aloe vera, Propolis gel)*

- associated with mild anti-inflammatory and analgesic effects, and it has been suggested that they may favor the healing of human mucosa



Median esophageal acid exposure under basal conditions and after alginate intake in the two decubitus positions.

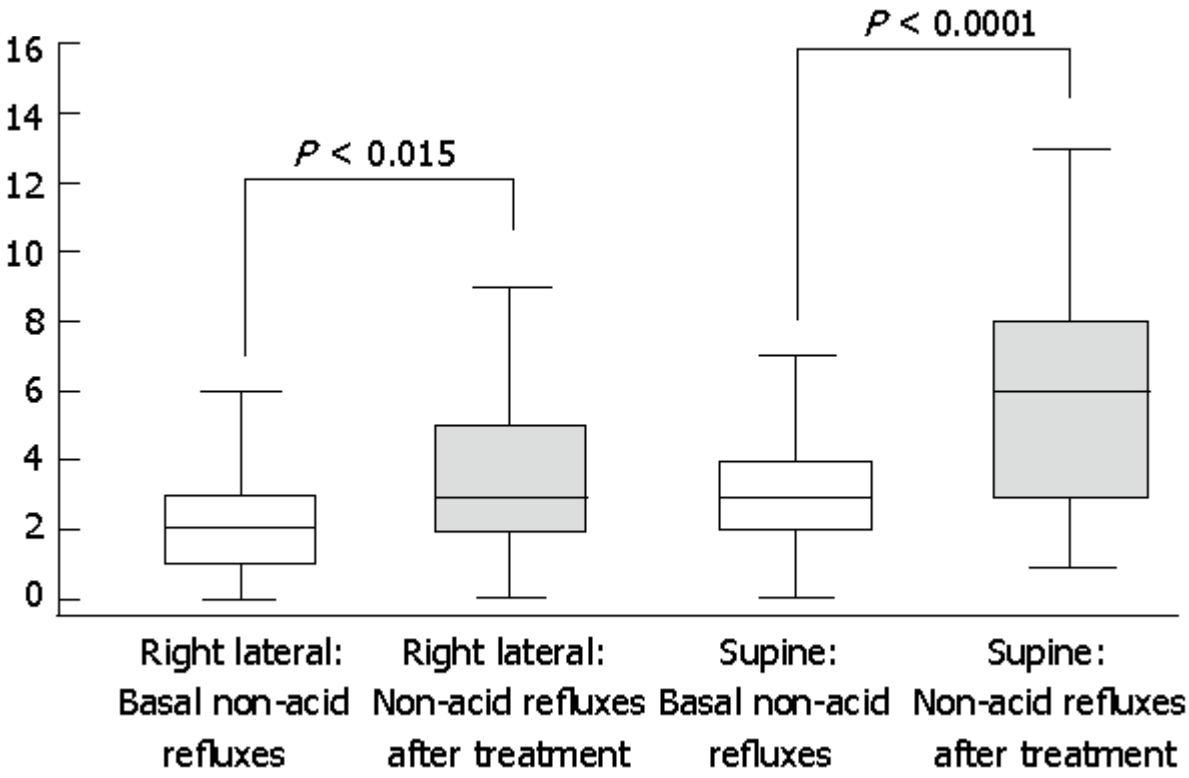
Alginate-based formulation



Number of acid reflux episodes under basal conditions and after Alginate intake in the two decubitus positions

World J Gastroenterol 2012 August 28; 18(32): 4371-4378

Alginate-based formulation



Number of non acid reflux episodes under basal conditions and after Alginate intake in the two decubitus positions

World J Gastroenterol 2012 August 28; 18(32): 4371-4378

Diseases of the Esophagus (2011) ••, ••–••
DOI: 10.1111/j.1442-2050.2011.01276.x

DISEASES OF THE ESOPHAGUS

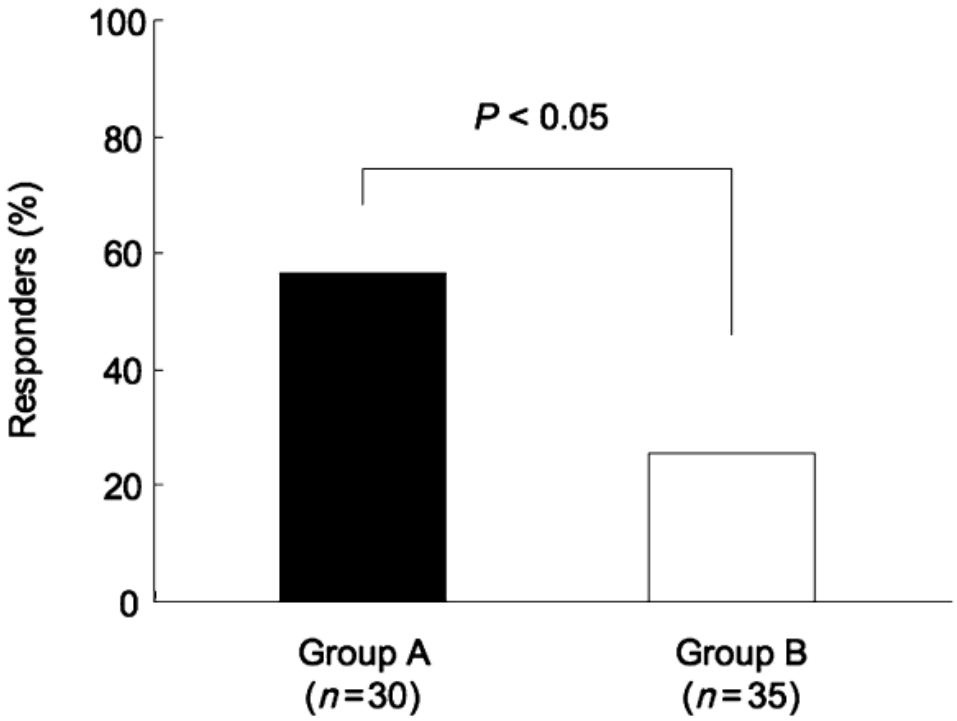
Original article

Efficacy of adding sodium alginate to omeprazole in patients with nonerosive reflux disease: a randomized clinical trial

N. Manabe,[1] K. Haruma,[2] M. Ito,[3] N. Takahashi,[6] H. Takasugi,[7] Y. Wada,[3] H. Nakata,[8] T. Katoh,[9] M. Miyamoto,[4] S. Tanaka[5]

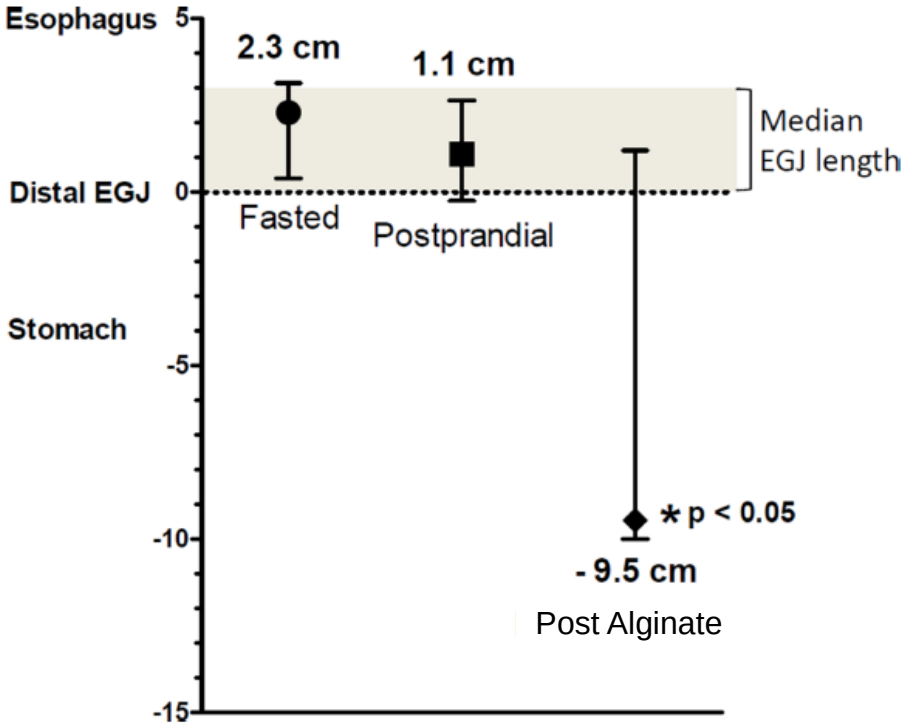
Group A
omeprazole 20 mg plus 30 mL qid of sodium alginate

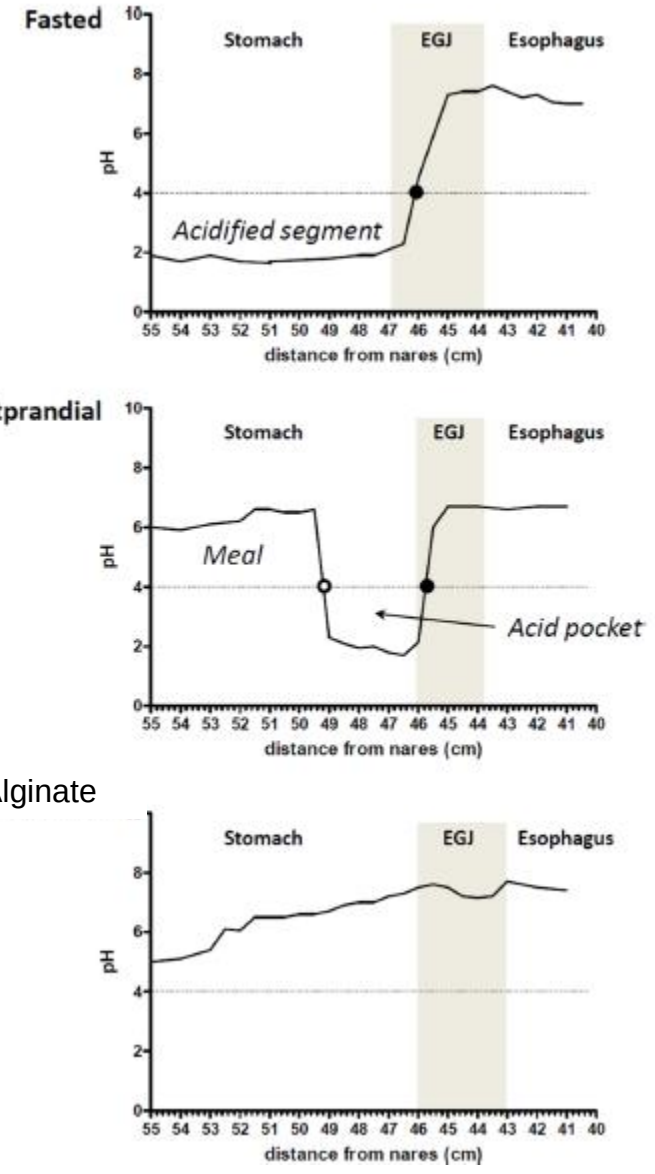
Group B
Omeprazole 20 mg



Rate of complete resolution of heartburn for 7 consecutive days up to the last day of medication. There were significantly more responders in group A than in group B.

Alginate and Acid Pocket





Proximal pH transition point location relative to the distal margin of the EGJ fasting, postprandially, and after dosing with alginate. Alginate neutralized the acidified segment, eliminating the “acid pocket” indicated by the significant relocation of the pH transition point away from the EGJ.

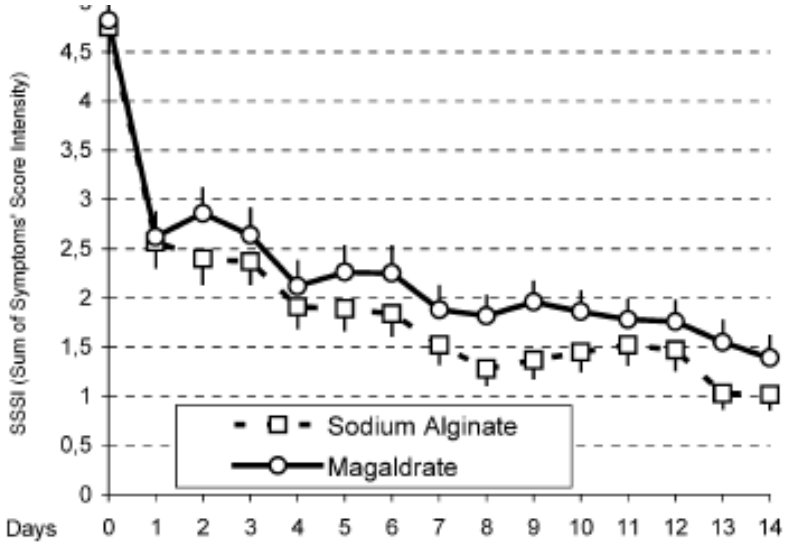
Aliment Pharmacol Ther. 2011 July ; 34(1): 59–66.

Dig Dis Sci (2006) 51:1904–1909
DOI 10.1007/s10620-006-9284-0

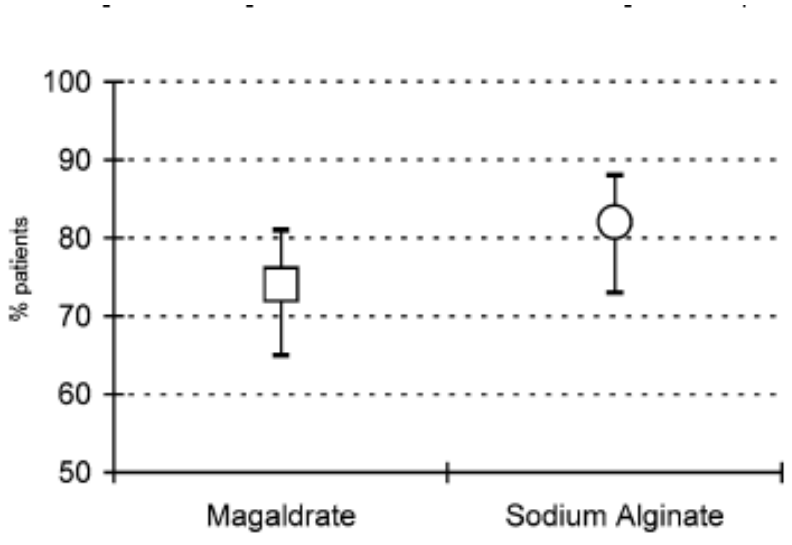
ORIGINAL PAPER

A Comparison Between Sodium Alginate and Magaldrate Anhydrous in the Treatment of Patients with Gastroesophageal Reflux Symptoms

Edoardo G. Giannini · Patrizia Zentilin · Pietro Dulbecco · Elena Iiritano · Claudio Bilardi · Edoardo Savarino · Carlo Mansi · Vincenzo Savarino

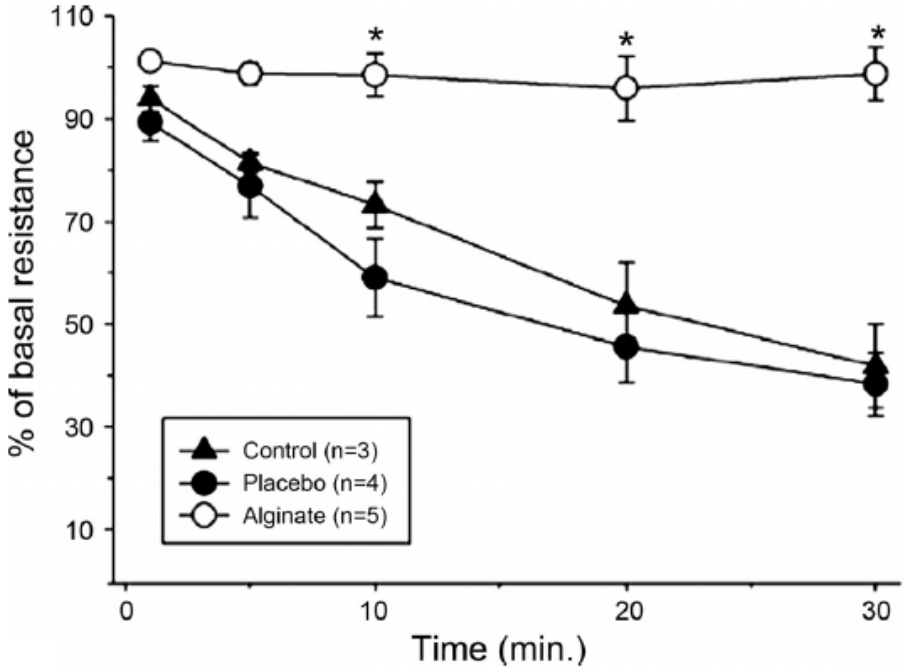


Results of the sum of symptom score intensity (SSSI) in the ITT population (SE in bars)

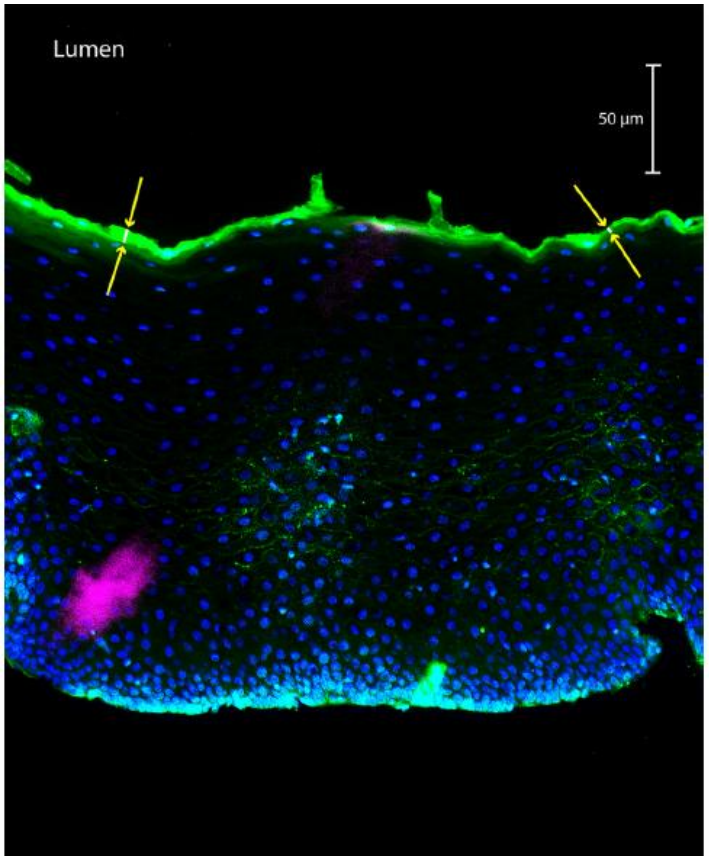


Percentage of patients (95% CI in bars) with symptom disappearance during the treatment phase

Alginate and esophageal mucosal protective effect



Percentage of baseline transepithelial electrical resistance (TER) of 3D human esophageal cell culture after 30 min exposure of pH 3 + 0.5 mM taurodeoxycholic acid solution after application of protectant.



Fluorescein-labeled alginate on the luminal surface of the biopsy mucosa after 1 h washing in neutral solution

Am J Physiol Gastrointest Liver Physiol 308: G975–G980, 2015.

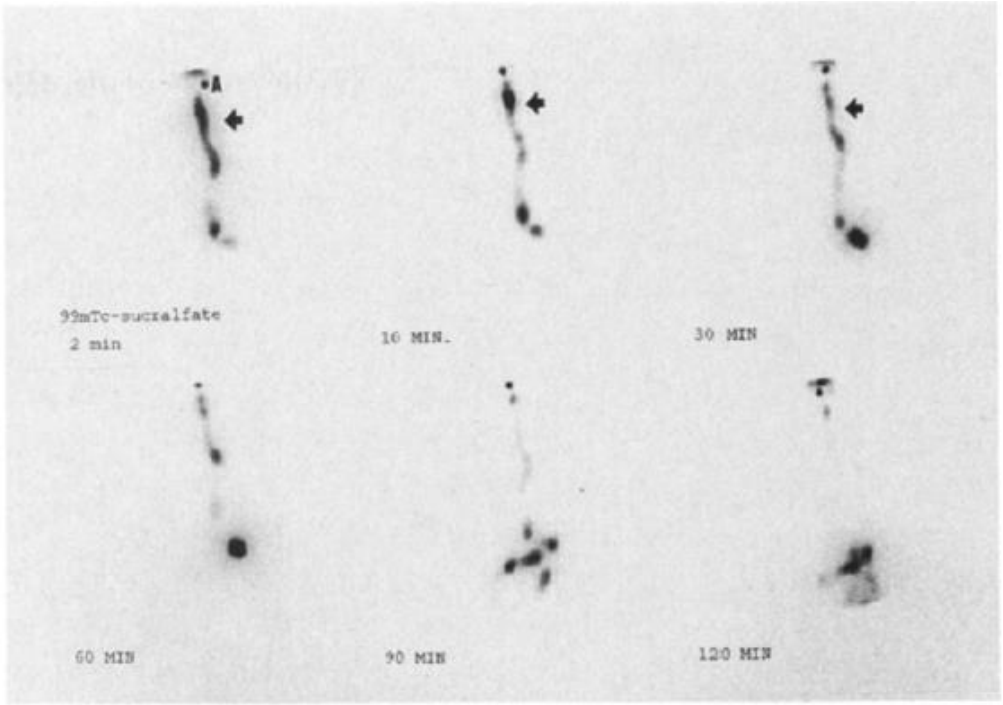
Sucralfate and mucosal protective effect

Macromolecular compound composed of sulphate and aluminium hydroxide exerting a mucosal protective action through different mechanisms:

✓creation of a physical barrier that blocks the diffusion of gastric juices through the esophageal mucosa and mitigates the erosive damage (YK Wang et al, 2013);

✓the aluminum salt of sucrose sulfate, able to adsorb bile acids and forms stable complexes with protein molecules, which in turn are resistant to the proteolytic action of pepsin;

✓stimulation of ulcer repair



Static images of ^{99m}Tc-sucralfate *(arrow)* at regular intervals up to 2 hours. At 2, 10, and 30 minutes, accumulation in the affected segment is seen as a sign of coating *(arrows)*, but activity decreases considerably after 60 minutes. Some persistent activity is also notable at the esophagocardiac junction. The *A* marks the cricoid cartilage.

(Gastrointest Endosc 1995;41:109-14.)

A limitation of sucralfate as a therapy for GERD is its relatively poor mucosal adherence.

Dilated Intercellular Spaces: A Morphological Feature of Acid Reflux–Damaged Human Esophageal Epithelium

NELIA A. TOBEY,* JOHNNY L. CARSON,‡ RADWAN A. ALKIEK,* and ROY C. ORLANDO*

*Department of Medicine, Tulane University School of Medicine, and Veterans Administration Medical Center, New Orleans, Louisiana; and ‡Department of Pediatrics and the Center for Environmental Medicine and Lung Biology, University of North Carolina School of Medicine, Chapel Hill, North Carolina

Transmission Electron Microscopy Scores in Mean and Maximum Measurement of Degrees of Dilated Intercellular Spaces in Biopsy Specimens From Controls and Patients With Reflu Eosphagitis

Patients	Mean scores (μm)	Maximum scores (μm)
Controls (n = 13)	0.46 ± 0.06	1.45 ± 0.15
Erosive reflu (n = 6)	0.80 ± 0.12°	2.89 ± 0.26°
Nonerosive reflu (n = 5)	1.00 ± 0.15°	2.78 ± 0.45°

NOTE. Values are means ± SEM.
°$P < 0.05$ compared with controls.

It is hypothesized that this is a morphological representation of a defective barrier that permits permeation of noxious substances (such as acid) into the deeper epithelium where they can stimulate nociceptive afferents.

Drug/ Supplement/Medical device

Current definition

"Pharmacological means" is understood as an interaction between the molecules of the substance in question and a cellular constituent, usually referred to as a receptor, which either results in a direct response, or which blocks the response to another agent. Although not a completely reliable criterion, the presence of a dose-response correlation is indicative of a pharmacological effect.

Definition of "medical device" under the Medical Devices Regulation (EU) 2017/745

Typically, the medical
device function is achieved by physical means (including mechanical action, physical barrier, replacement of or support to organs or body functions).

Surface acting compounds

Hyaluronic acid-chondroitin sulfate based bioadhesive formulation has been developed to create a barrier on the esophageal mucosa to reduce contact with refluxate.

- **Hyaluronic acid**, mainly present in the extracellular matrix of soft connective tissues, is involved in several key processes such as control of epithelial cells turnover, favouring re-epithelization and mucosal hydratation in ulcer healing
- **Chondroitin-sulphate** is a safe glycosaminoglycan, main component of mucous secretion of parietal cells, able to inhibit pepsin induced damage of the gastroduodenal mucosa. It may be of benefit in disease where inflammation is an essential marker. Interact with a wide variety of molecules including (but not limited to) matrix molecules, growth factors, protease inhibitors, cytokines, chemokines and adhesion molecules via nonspecific/specific saccharide domains within the chains

BMJ 2020;371:m3786 | doi: 10.1136/bmj.m3786

Surface acting compounds

Combination of hyaluronic acid and chondroitin-sulphate (HA+CS) in a bioadhesive carrier may constitute a modern approach to GERD cardinal symptoms relief.

Effect of HA+CS combined with PPI therapy, on primary and secondary endpoints in patients with NERD: ITT analysis

Trial endpoints	PPI + HA+CS		PPI + Placebo		P value
	n/N	%	n/N	%	
Primary					
No of patients with TSS reduction of at least 3 points	40/76	52.6	25/78	32.1	0.01
Secondary					
No of patients with 50% reduction of TSS	29/76	38.2	18/78	23.1	0.042
No of patients with TSS reduction at final visit	60/76	78.9	44/78	56.4	0.003
TSS (±s.d.) before and after treatment	Before	After	Before	After	
	8.53 ± 2.6	5.42 ± 2.1	8.03 ± 2.7	6.49 ± 2.6	
Change (±s.d.) in TSS	−3.11 ± 3.1		−1.54 ± 3.0		0.002

TSS, total symptom (heartburn, retrosternal pain, regurgitation, acid taste) score.

A randomized, double blind trial of 154 patients with NERD showed that the combination of the mucosal protectant and acid suppression improved symptom relief in NERD patients compared with acid suppression alone (53% *v 32%, P<0.01).*

Aliment Pharmacol Ther 2017; 45: 631–642

Medical device made of natural substances

(Polysaccharides, flavonoids, minerals)

Protection of esophageal mucosa in vitro evaluation

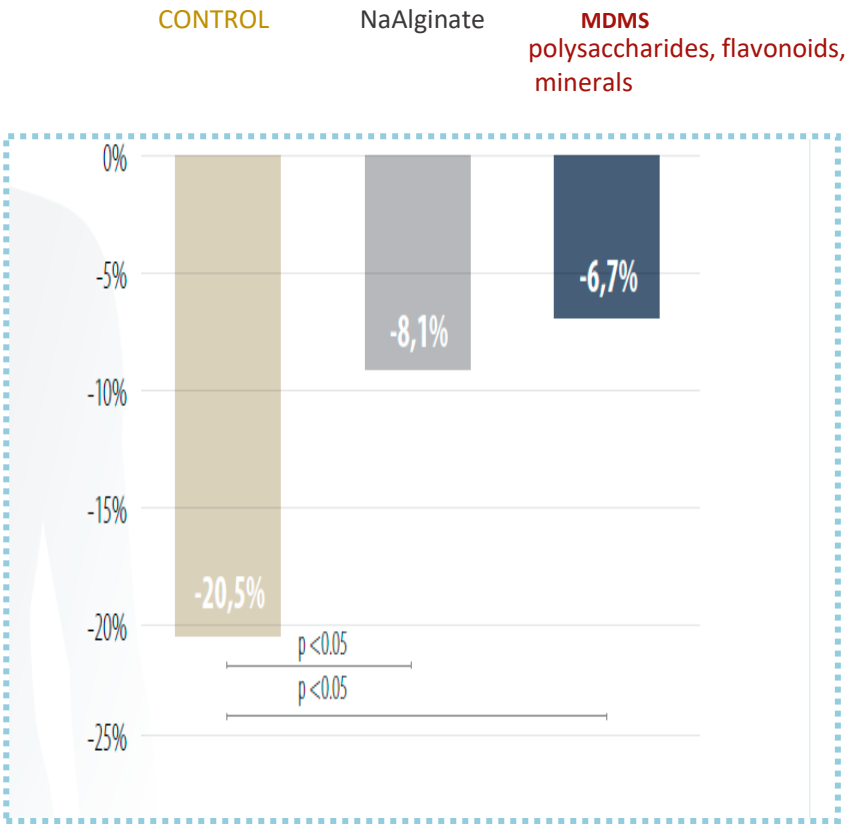
Components	Specific ingredient
Polysaccharides	aloe leaves dehydrated gel (*Aloe vera*), marshmallow root dry extract (*Althaea Officinalis*), mallow leaves dry extract (*Malva sylvestris*)
mineral substances	nahcolite (natural sodium bicarbonate), limestone (natural calcium bicarbonate)
antioxidants	chamomile flowers freeze-dried extract (*Matricaria recutita*), licorice root freeze-dried extract (*Glycyrrhiza glabra*)

Three distal esophageal biopsies of 12 healthy patients were analyzed.

Topical treatment significantly reduced the impairment of the esophageal mucosa barrier induced by an acidic-peptic solution

TRANSEPITHELIAL ELECTRICAL RESISTANCE (TER)

PERCENTAGE DECREASE OF TER INDUCED BY ACIDIC SOLUTIONS
(Krebs – Henseleit pH2 +porcine pepsin + taurodeoxycholic acid)

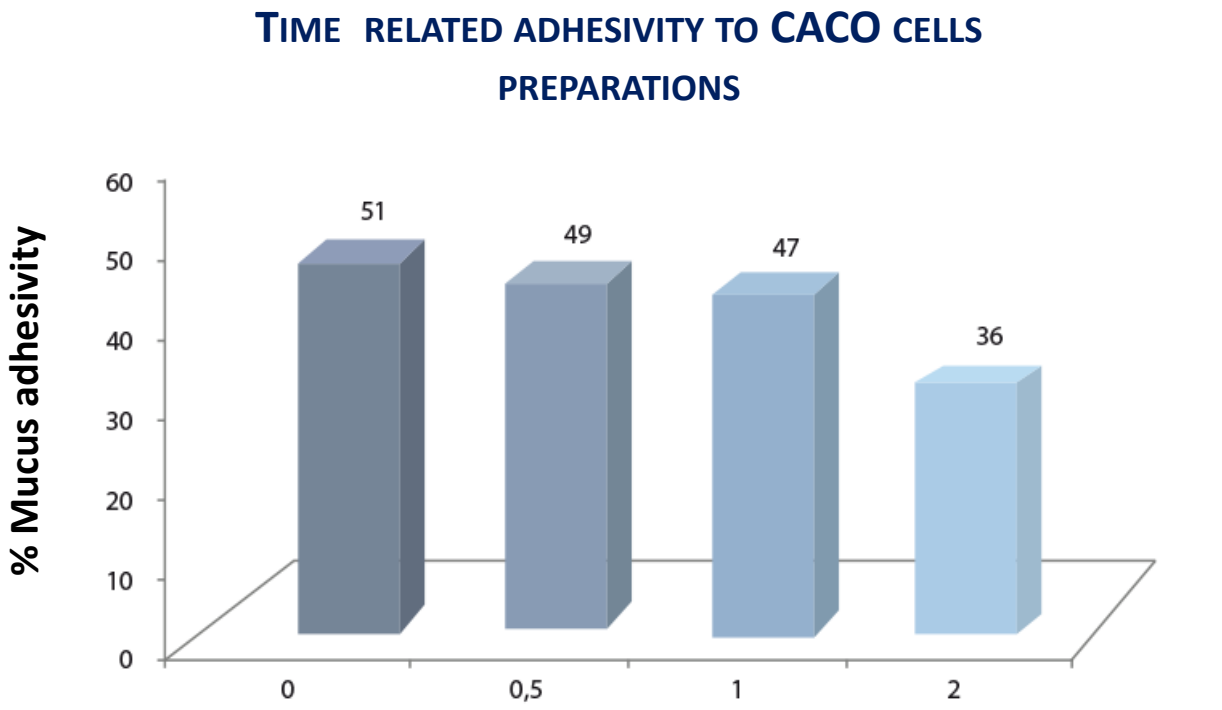


G. Liguori et al, Digestive and Liver Disease 50/S2 (2018)

Medical device made of natural substances

(Polysaccharides, flavonoids, minerals)

Mucosal Adhesivity



Time related polysaccharide mucus adhesivity (hr), diluted 1:5 and washed with gastric-like acidic solution (pH 3.5)

G. Liguori et al, Digestive and Liver Disease 50/S2 (2018)

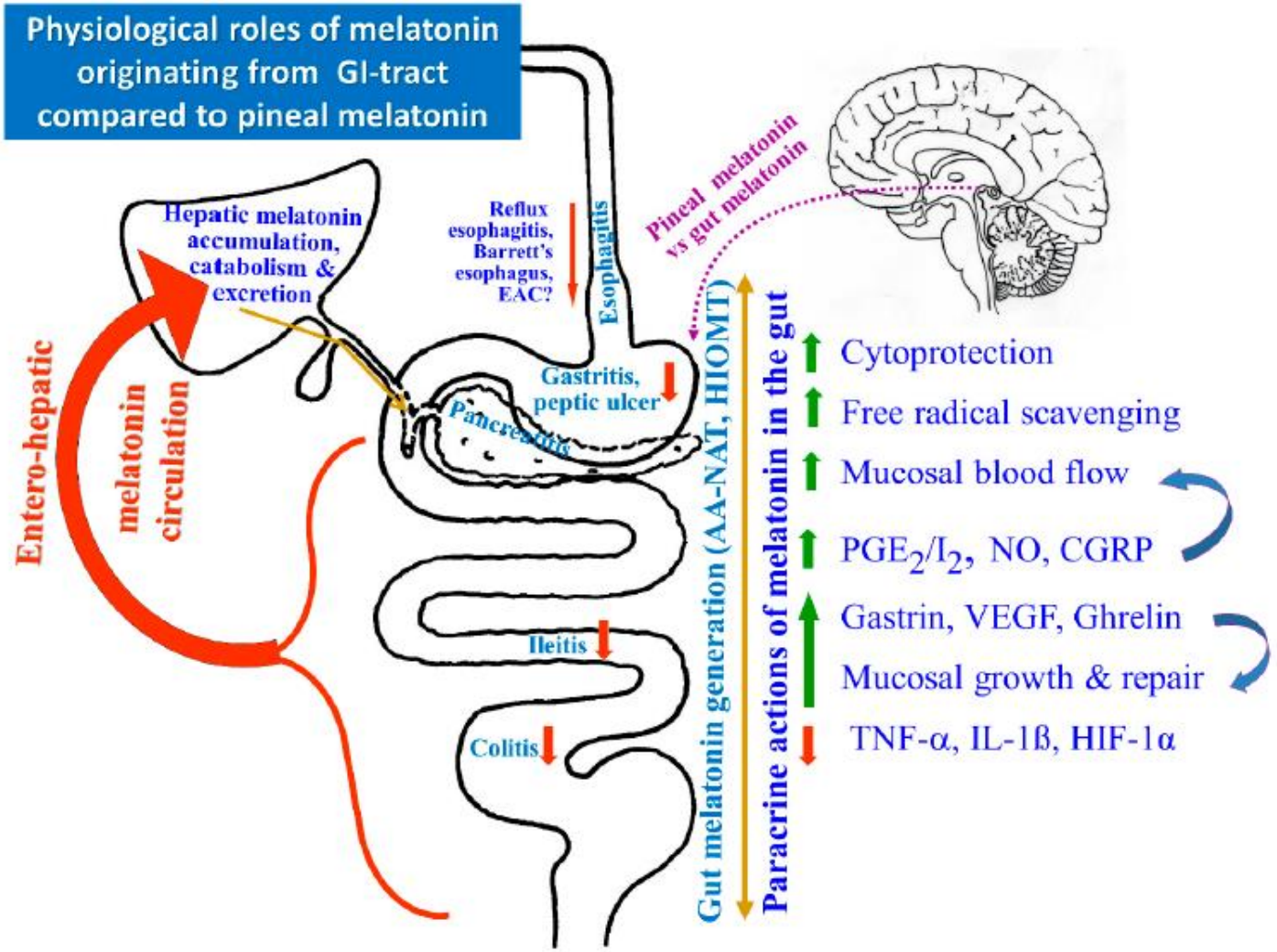


Figure 1. The mechanistic effects of endogenous melatonin produced in the pineal gland or gastrointestinal tract (GI-tract) and exogenous melatonin in attenuation of inflammatory reaction and protection of GI-organs including the esophagus, stomach and intestine.

Melatonin on patients witg GERD

Table 2 Effects of melatonin on patients with GERD group II (n = 9)

	Pretreatment with melatonin	4 weeks Post treatment with melatonin	8 weeks Post treatment with melatonin
Symptoms:			
1-Heart burn:			
Yes	7	3 (57.1%)	0 (100%)
Duration(months)	1.3 + 0.4		
2-Epigastric pain:			
Yes	6	3 (50%)	1 (83%)
Duration(months)	1.4 + 0.5		
B)LES Study:			
1-LES pressure(mmHg)	10 + 1.58	14.5 + 1.58[a]	20.2 + 1.56 [ab]
2-Residual pressure (mmHg)	0.012 + 0.52	0.2 + 0.016	0.32 + 0.013[a]
3-Relaxation duration (seconds)	6.8 + 0.12	5.9 + 0.16 [a]	5.3 + 0.12 [a]
4-Relaxation %	86 + 0.87	90 + 0.86 [a]	100 + 0.00 [ab]
C) PH (at 5 cm above the LES):	2.3 + 0.36	5.2 + 0.5 [a]	6.7 + 0.65 [ab]
D) BAO (mmol/h)	24.7 + 0.5	20.1 + 0.4 [a]	16.6 + 0.6 [ab]
E) Serum Gastrin(pg/ml)	22.1 + 3.2	27.2 + 2.3 [a]	32.3 + 2.1 [ab]
D) Melatonin level at day time (pg/ml):	18.2 + 5.54	28.26 + 2.26 [a]	34.5 + 2.35 [ab]

a: $p < 0.05$ relative to pretreatment with melatonin
b: $p < 0.05$ relative to 4 weeks post treatment with melatonin

Kandil et al. BMC Gastroenterology 2010, 10:7

Take home message

Why a Medical Device for Therapy

1. DRUGS ARE NOT SUFFICIENTLY EFFICACIOUS
2. DRUGS ARE NOT ALWAYS RECOMMENDED

   (childhood, pregnancy, if there are risks of complications)
3. DRUG SIDE EFFECTS ARE INTOLERABLE OR CAN BE SEROIUS
4. FOR MAINTENANCE THERAPY IN MILD SYMPTOMS
5. MOST EFFECTIVE WHEN COMBINED WITH PROTON PUMP INHIBITORS
6. IN THE PRESENCE OF SUPRA- OESOPHAGEAL SYMPTOMS (CHRONIC COUGH, DYSPHONIA, PHARYNGEAL BOLUS AND HOARSENESS)
7. USED IN THE LONG TERM, MIGHT PROLONG REMISSION AND DELAY RELAPSE

Take home message

➢The mucosal protective devices were shown to be capable of achieving a significant and quick symptom relief in patients with NERD.
➢given as add-on medications –proved to be capable of improving symptom controll
➢They suggest a potential for an exciting treatment approach to GERD based on topical mucosal protection

Limitation

- taken several times a day
- Action limited to about 3 hours after intake of the product
- Costly
- The studies on bioadhesive properties are in vitro model and as such is not a true reflection of physiological conditions.
- In vivo gravity, saliva swallowing and mucus could act to dislodge the MD from the esophageal mucosa.

Are necessary well designed clinical trials