Kako nastaje GERB – šta se krije iza gorušice?

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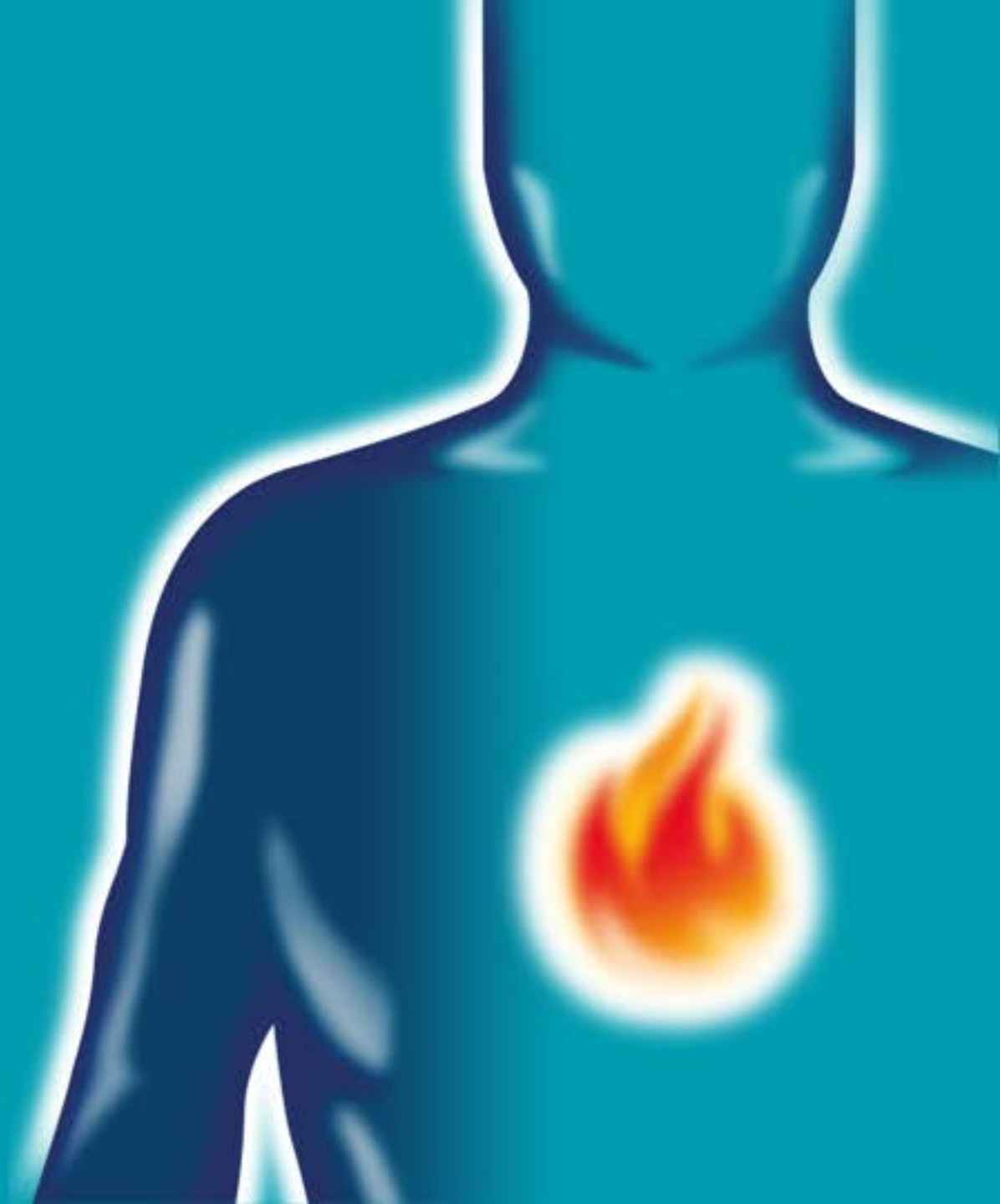


Učestalost GERB-a

- Gorušica je česta
  - 25% jednom mesečno
  - 12% jednom nedeljno
  - 5% svakodnevno
- • Jedna od dve najčešće gastroenterološke dijagnoze među ambulantnim pacijentima

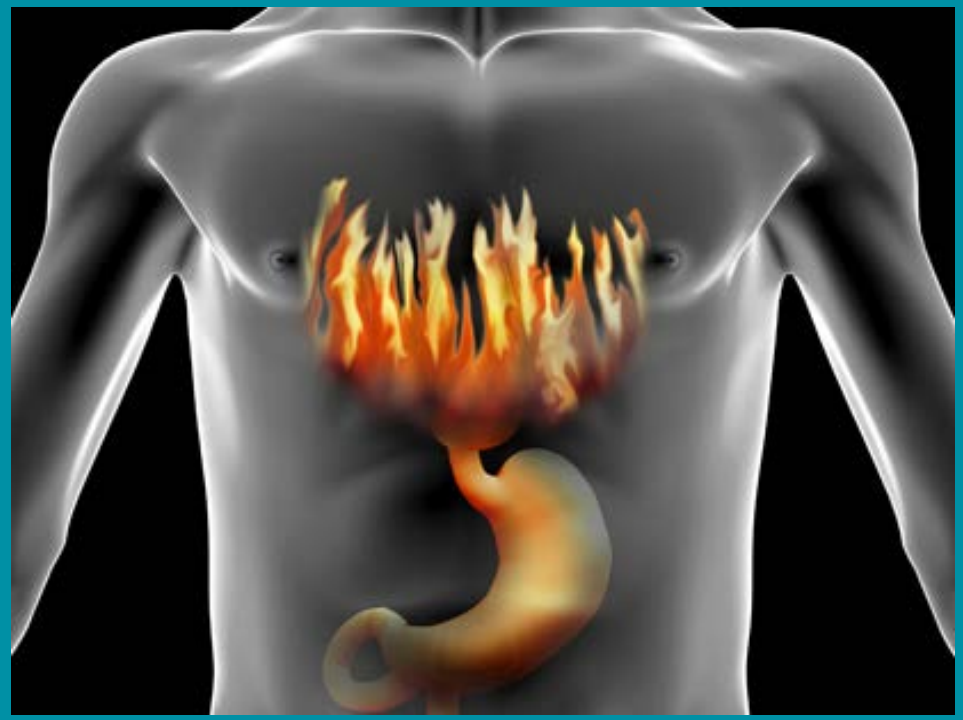
Shaheen NJ et al. Am J Gastroenterol 2006;101:1-11.

Prevalencija GERB u opštoj populaciji

- GERB prevalencija 31,5%

Uključujući nekiseli (alkalni) refluks, ezofagitis

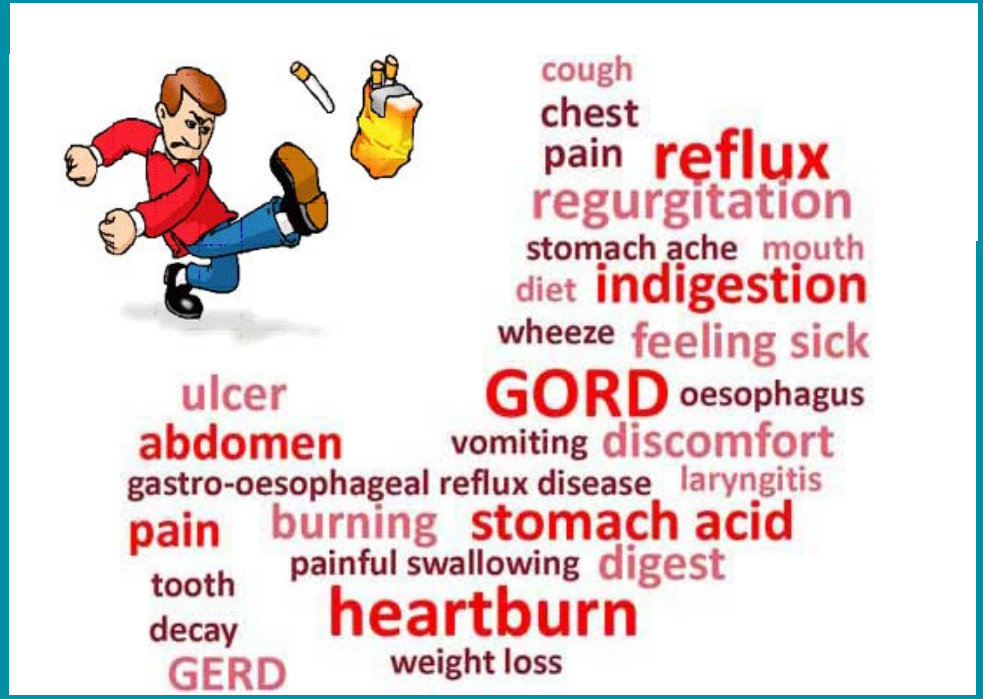
i Barretov jednjak



Zagari et al. GUT 2008

Faktori rizika

- Muški pol
- Godine starosti
- Gojaznost
- Hijatusna hernija
- Pušenje cigareta
- Kafa
- Alkohol
- Lekovi
- Helicobacter pylori

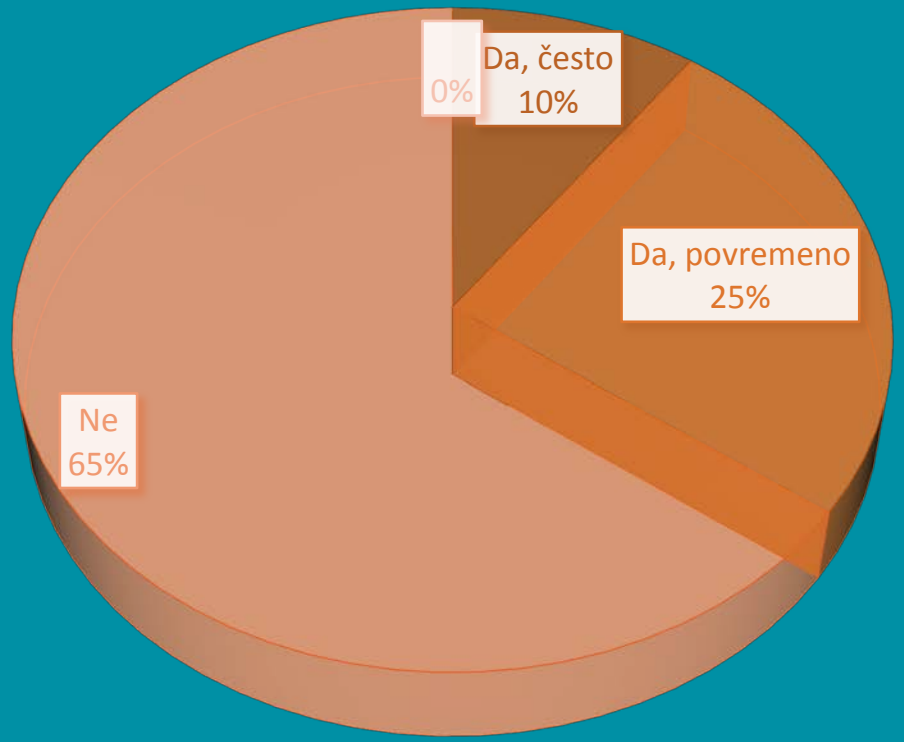


Da li Vi lično patite od problema kao što su bolovi u trbuhu, gorušica, nadimanje, mučnina?

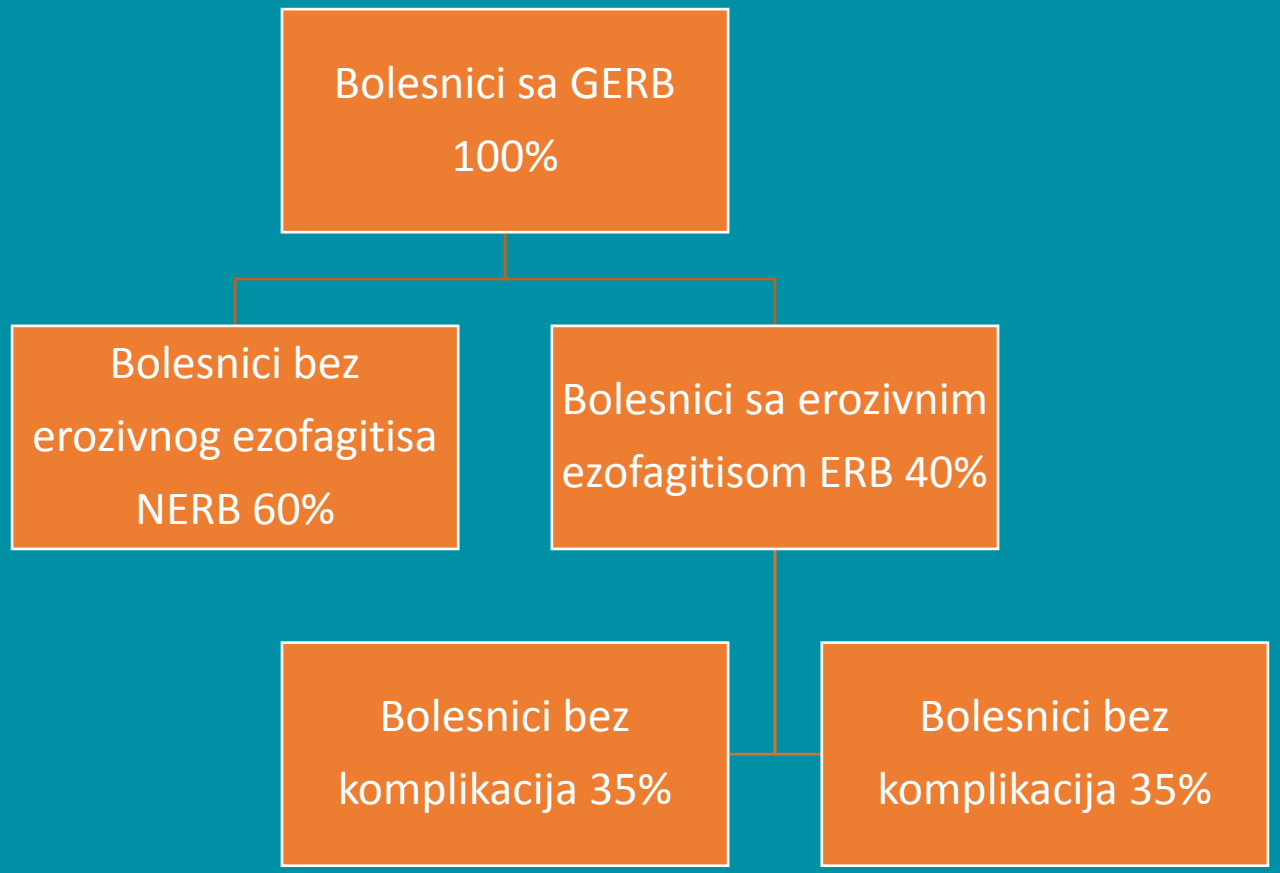
Nešto više od trećine punoletnih građana Srbije ima želudačne tegobe (N=3041)

Značajno prisutnije kod žena nego muškaraca a najčešće u starosnoj dobi od 40 – 49 godina

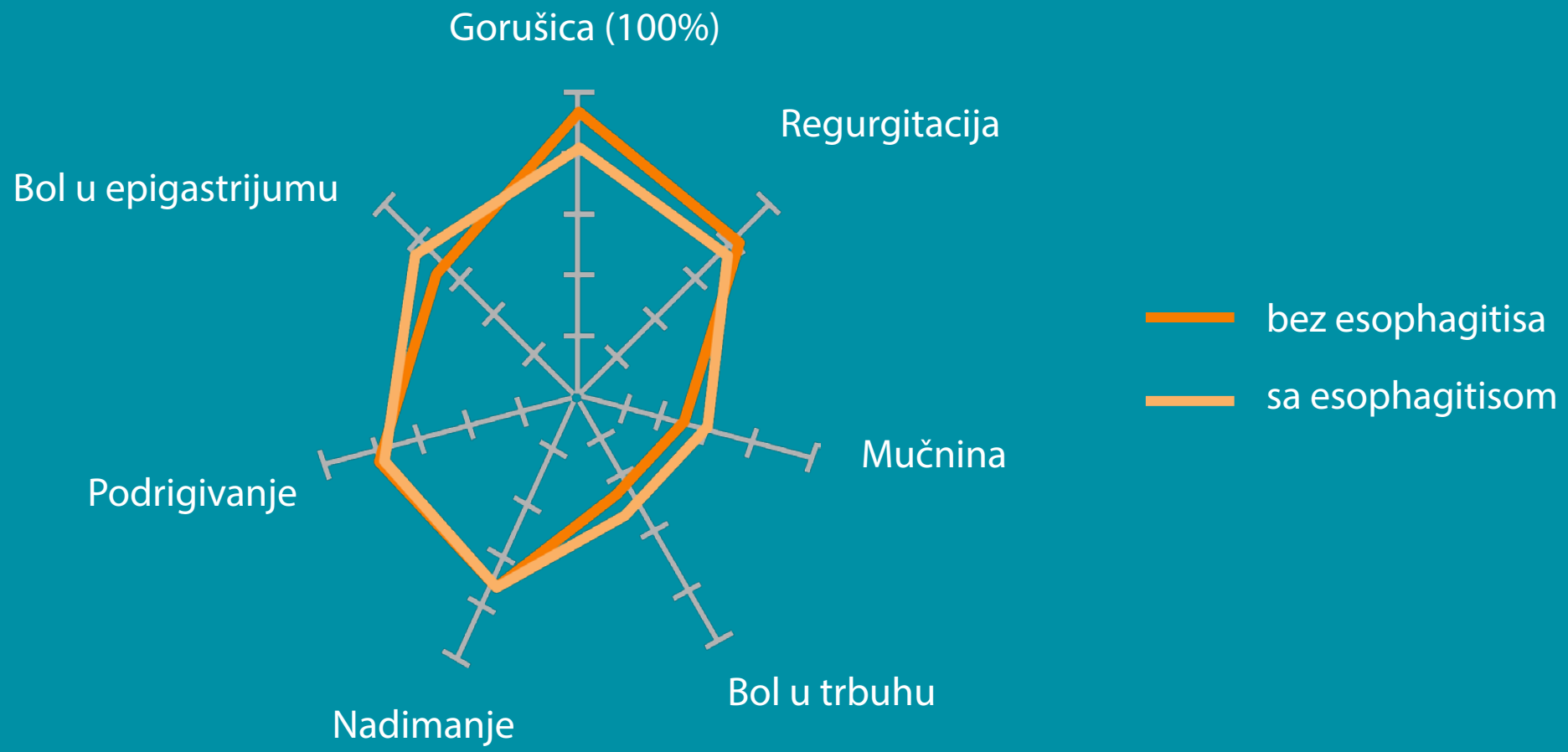
- 45% pati od nadimanja
- 53% imaju želudačne tegobe bar jednom nedeljno
- 3/10 dijagnostikovano je neko oboljenje;
- 6/10 bar nekad koristi lekove.



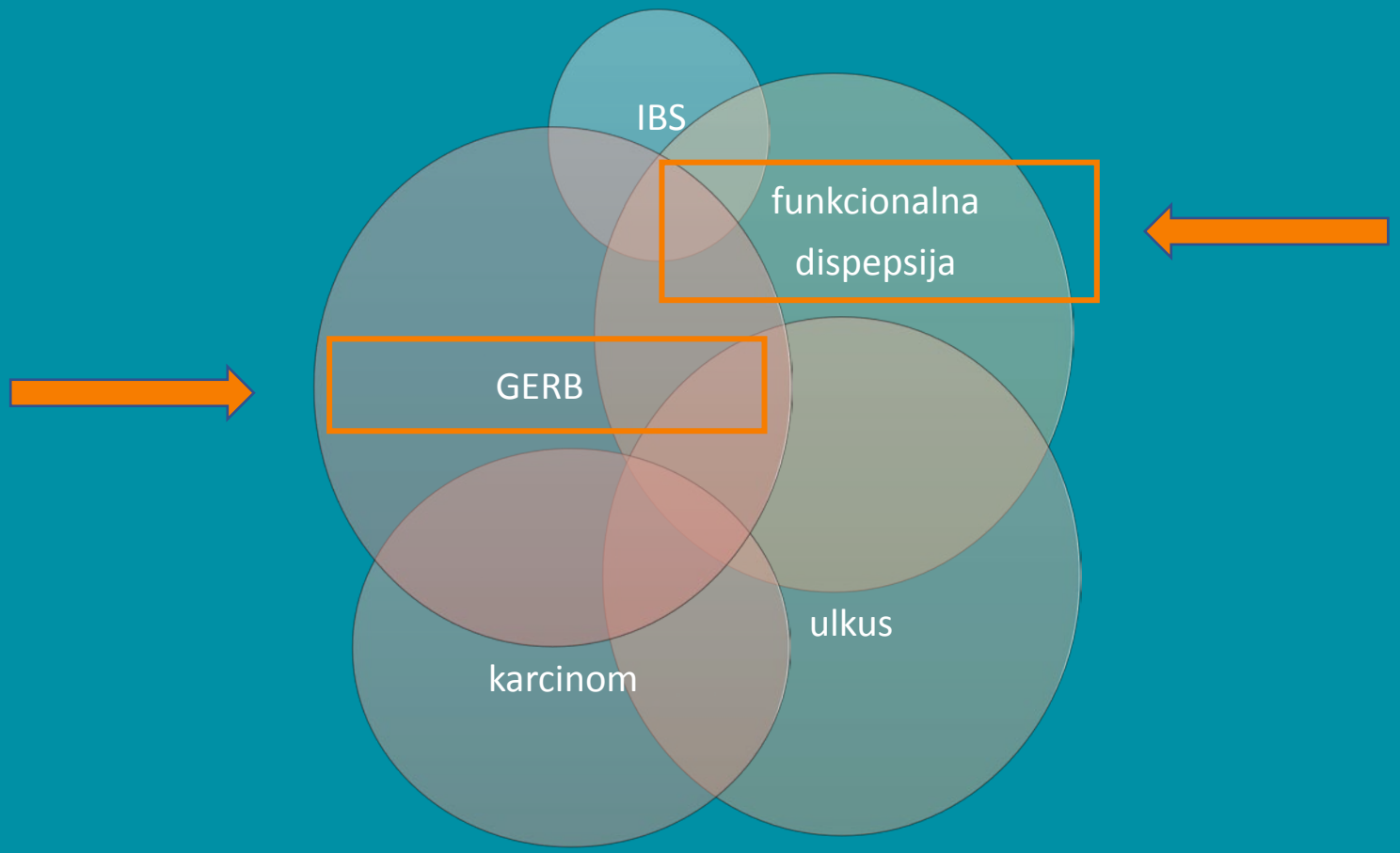
GERB: dve glavne kategorije



GERB simptomi su slični u bolesnika sa i bez erozivnog ezofagitisa



Preklapanje bolesti - klinički izazov



Stangellini V et al. Dig Liver Dis 2003;35:843-848

GERB

- Klinička dijagnoza GERB-a
  - Tipični simptomi
  - Bez alarmnih simptoma
  - < 50 godina

Greška br 1. Postavljanje dijagnoze na osnovu kliničke slike, upitnika i odgovora na IPP terapiju

- Klinička slika
- Podaci iz upitnika

} (70% senzitivnost; 67% specifičnost)

- Odgovor na antisekretornu terapiju (71% senzitivnost; specifičnost 44%)
- **Pojedinačno nisu dovoljni da bi se postavila dijagnoza GERB-a**

…mogu biti od koristi u proceni da li je potrebno dalje ispitivanje

Diamond Study. Gut 2010;59:714–21.

Jones R,et al. Development of the GerdQ, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary care. APT 2009;30:1030–8.

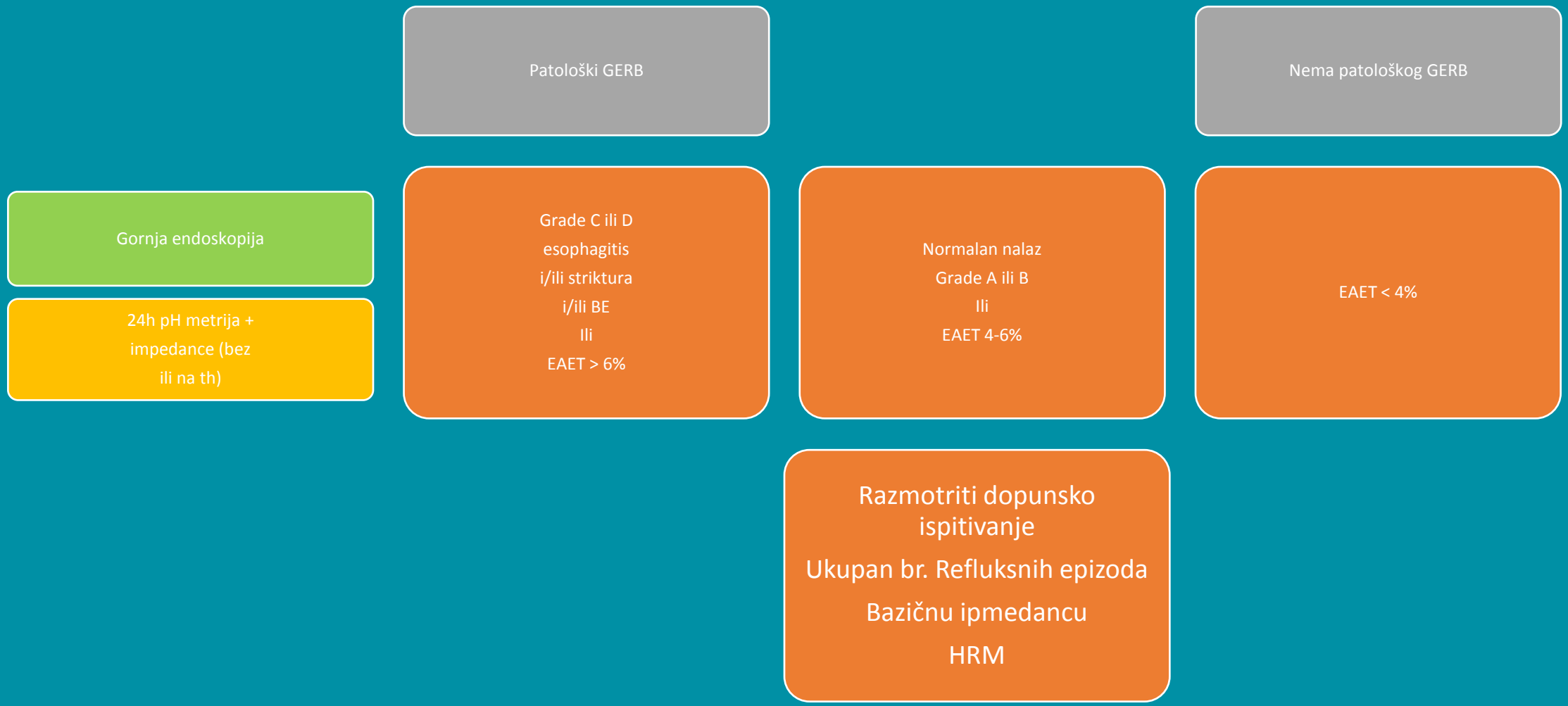
Bolier et al. Systematic review: questionnaires for assessment of gastroesophageal reflux disease. Dis Esophagus 2015;28:105–20.

Greška br 1. Postavljanje dijagnoze GERB-a samo na osnovu odgovora na terapiju IPP

- Probna terapija sa IPP pragmatičan pristup u dijagnozi GERB-a
  - Diamond studija
  - 2-nedelje probna terapija
  - Bolesnici sa GERB-om: **69%**
  - Bolesnici bez GERB-a: **51%**
- Probna terapija IPP nije pouzdana za dijagnozu GERB-a
- Pozitivan odgovor ne znači patološki GERB
- Može biti i nešto drugo (funkcionalna gorušica, ruminacija, achalasia…)

Diamond Study. Gut 2010;59:714–21.

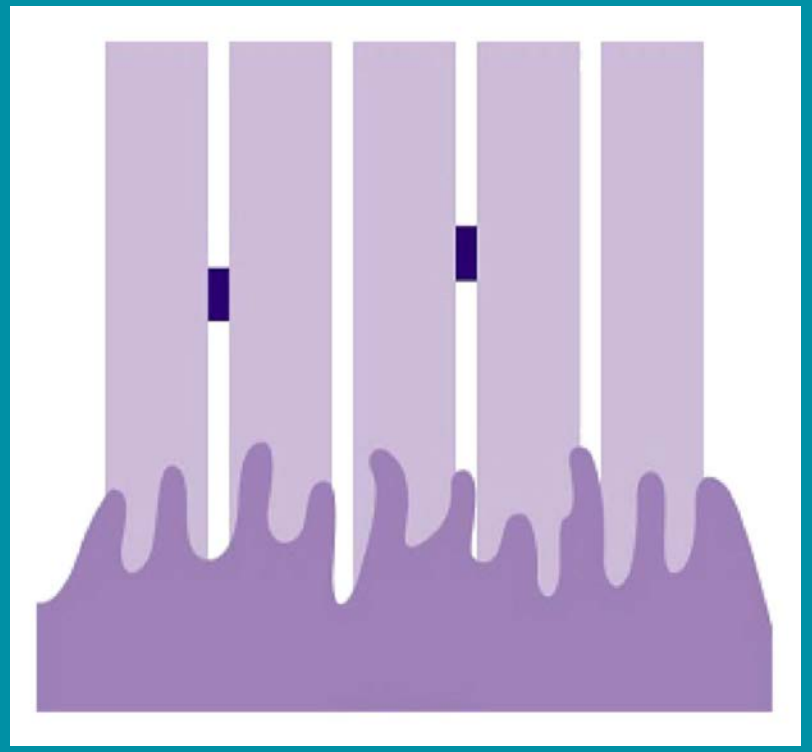
Dijagnoza GERB-a: Lyon konsenzus

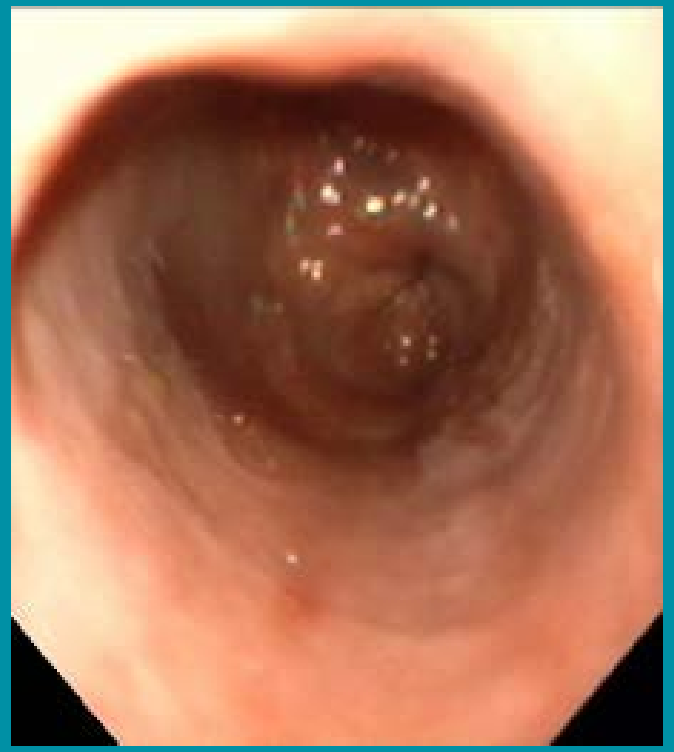


Gut 2018 Jul;67(7):1351-1362

LA - A

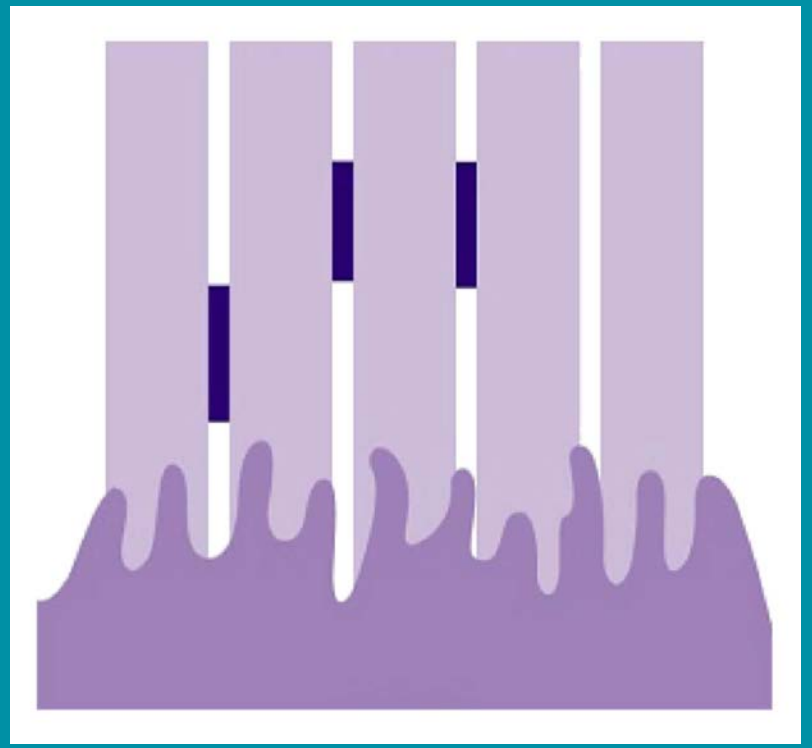
- **Gradus A**:
  - **Jedna ili više erozija sluznice ne dužih od 5 mm na dva odvojena nabora sluznice.**

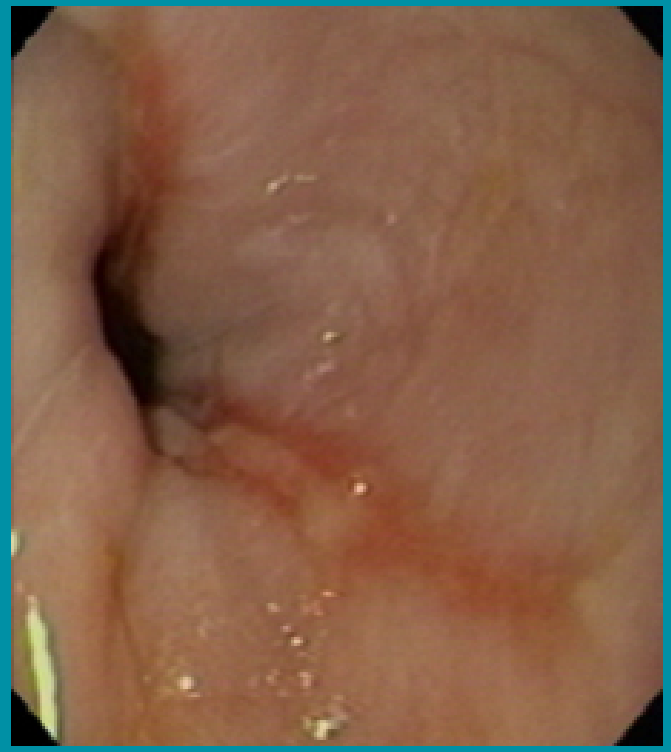




LA - B

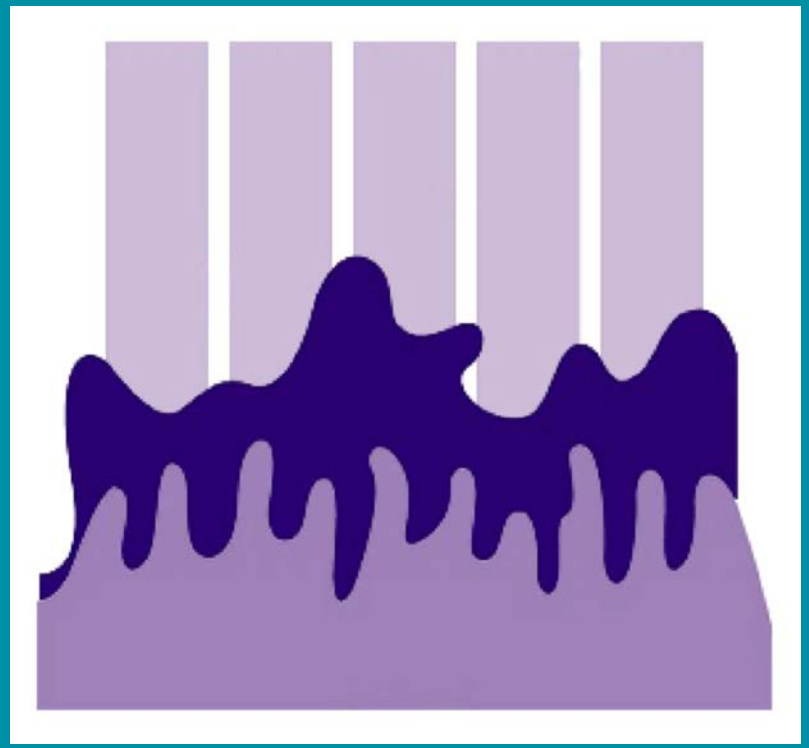
- **Gradus B**:
  - **Jedna ili više erozija sluznice dužih od 5 mm na dva odvojena nabora sluznice.**

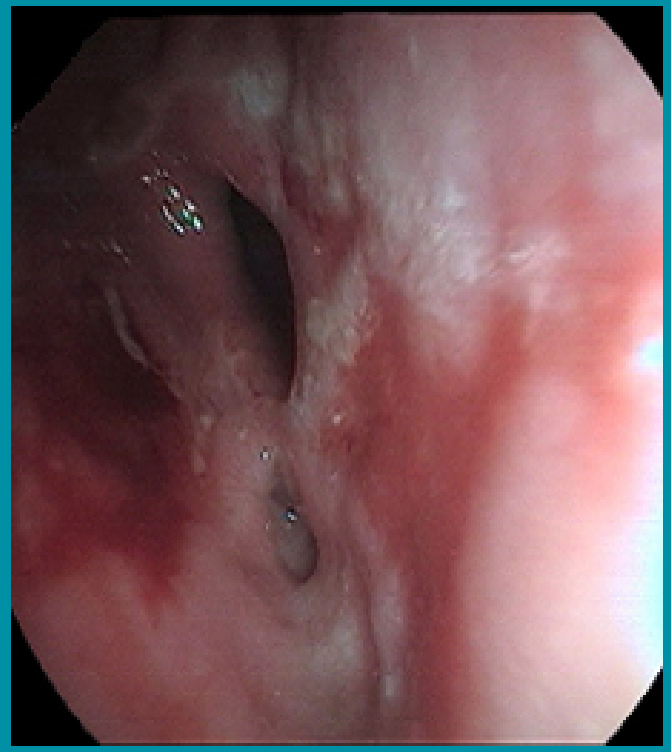




LA - D

- **Gradus D**:
  - Jedna ili više erozija sluznice koje zahvataju najmanje 75% cirkumferencije.

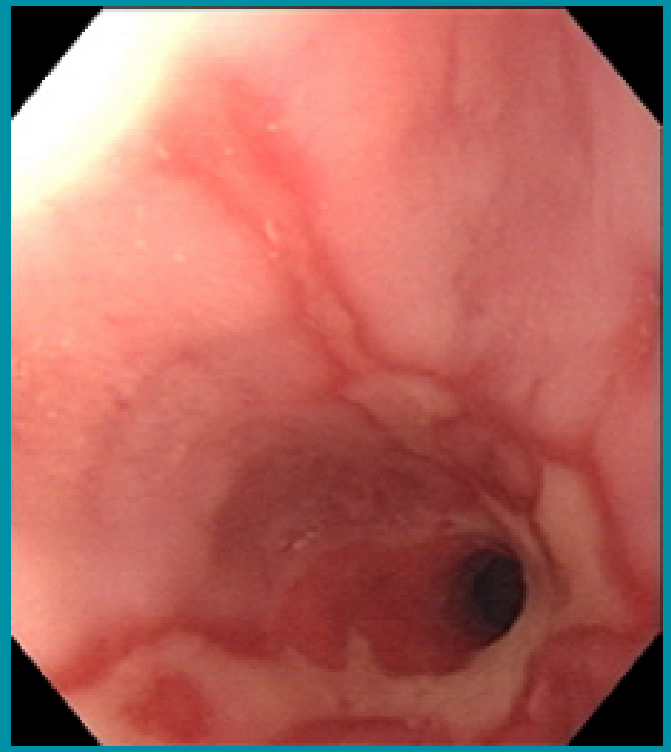




LA - C

Gradus C:

- Jedna ili više erozija sluznice u kontinuitetu na dva ili više nabora sluznice ali koje ne zahvatuju više od 75% cirkumferencije



Uvod

- Klinička dijagnoza GERB-a
  - Tipični simptomi
  - Bez alarmnih simptoma
  - < 50 godina

Praktično ali ne i najpouzdanije

- Indikacije za ispitivanje refluksa
  - Alarmni simptomi
  - Atipični simptomi
  - Ne-reagovanje na terapiju IPP
  - Pre anti-refluksne hirurgije (ARS)

Povećan rizik

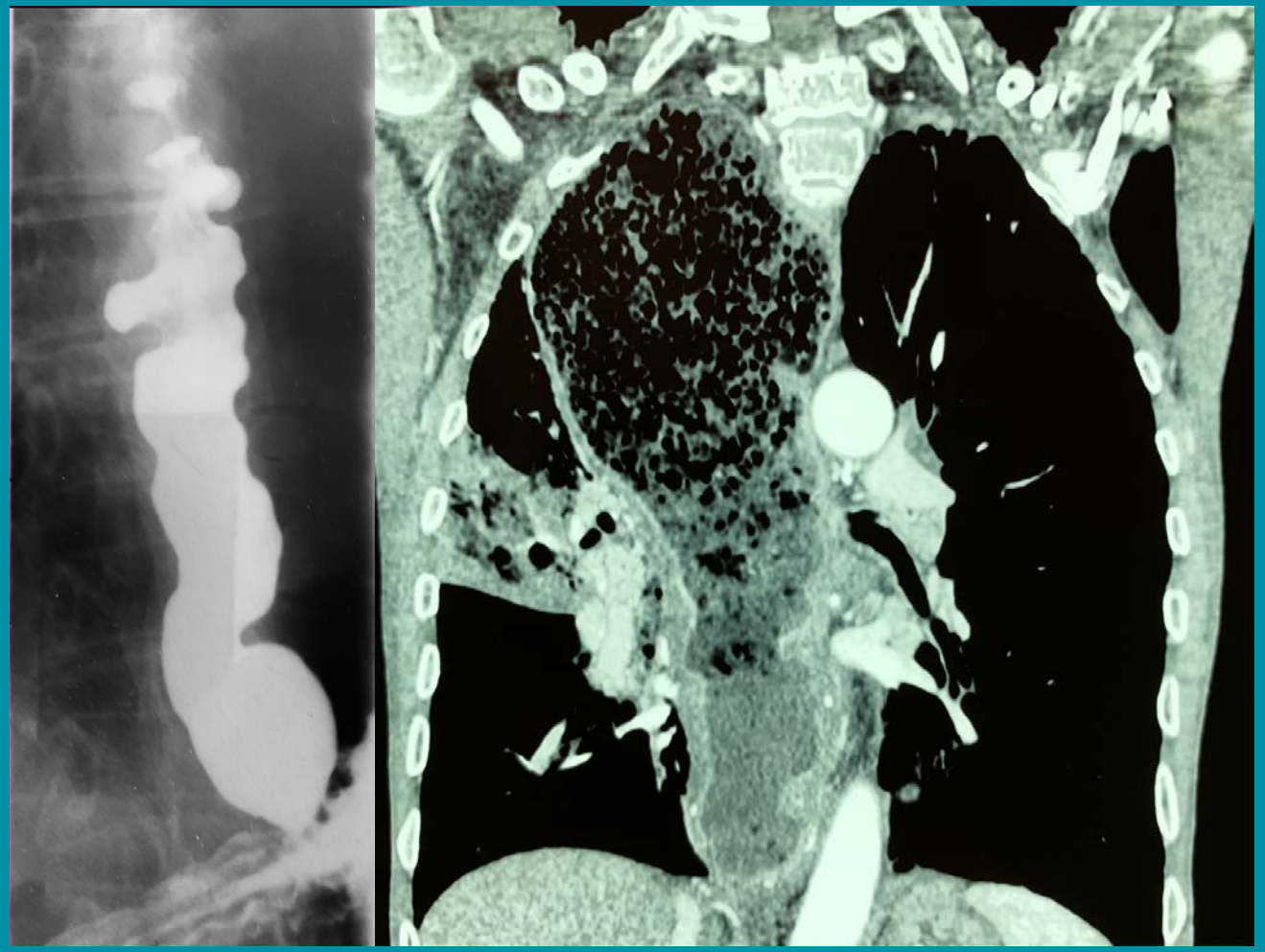
1. Hronični (>5 godina) GERB simptomi
2. Godine starosti (>50 godina)
3. Muški pol
4. Pušenje
5. Centralni tip gojaznosti

Greška br 2. Pretpostavka da upala i bol u grlu mogu biti posledica GERB-a

- GERB ☞ ORL simptomi: teško proceniti
  - Hiperemija/edem glasnica, larinksa, hipertrofija zadnje komisure, granulomi, gust sekret, pseudosulcus vocalis (mukozna membrana na glasnicama)
- Specifičnost mala (< 70%)
  - ORL simptomi + laringoskopski znaci nisu dovoljnji za dijagnozu GERB-a
- Odgovor na probnu terapiju IPP nije pouzdan
  - Izražen placebo
- Dijagnoza GERB-a (preporuka)
  - pH ili pH-impedance monitoring

Greška br 3. Zaboravljena dijagnoza- Achalasia

- Achalasia (redak) motorni poremećaj
  - Nekompletna relaksacija DES
  - Odsustvo peristaltike
- • Najčešći simptomi
  - Disfagija i bol u grudima
  - Regurgitacija-smanjen *clearance*
  - Simptomi noću (regurgitacija)
    - Jedina manifestacija



Greška br 4. Zaboravljena dijagnoza- Sy ruminacije (pre i post-prandijalne regurgitacije)

- Funkcionalni poremećaj
  - nenamerno i bez napora vraćanja hrane u usnu duplju/ponovno gutanje ili ispljuvavanje
- Bolesnici prijavljuju tegobe "kao refluksne"
- Anamneza veoma važna
  - Početak: obično < 10 min. po završetku obroka/Završetak: kada refluksat postane kiseo
  - Ne javlja se tokom noći
  - Nema boljitka na antirefluksnu th i lekove protiv mučnine

Murray HB et al. Diagnosis and Treatment of Rumination Syndrome: A critical review. Am J Gastro Feb. 2019

Greška br 5. Upućivanje svih bolesnika sa simptomima GERD-a rezistetntnim na IPP na ARS

- ~ 60% GERB bolesnika nije zadovoljno sa terapijom IPP
  - Stalna izloženost jednjaka kiselini uprkos terapiji
  - Hipersenzitivnost
  - Funkcionalni simptomi
- > 1/3 koji ne reaguju na terapiju IPP imaju funkcionalne smetnje
- Ne upućivati na ARS
- Preporuka: testiranje (pH metrija +/- impedance)

Greška br 6. Preterano podrigivanje

- Često udruženo sa dispepsijom i GERB-om
- Dva moguća mehanizma
  - Želudačno (gastrično)
    - refleks koji dovodi do relaksacije DES
  - • Supragastrično (većina)
    - Bihevioralna komponenta (gutanje i izbacivanje vazduha pre nego dospe u želudac)
    - Prekida se kada su usta otvorena (npr. “grickanje olovke”)-test

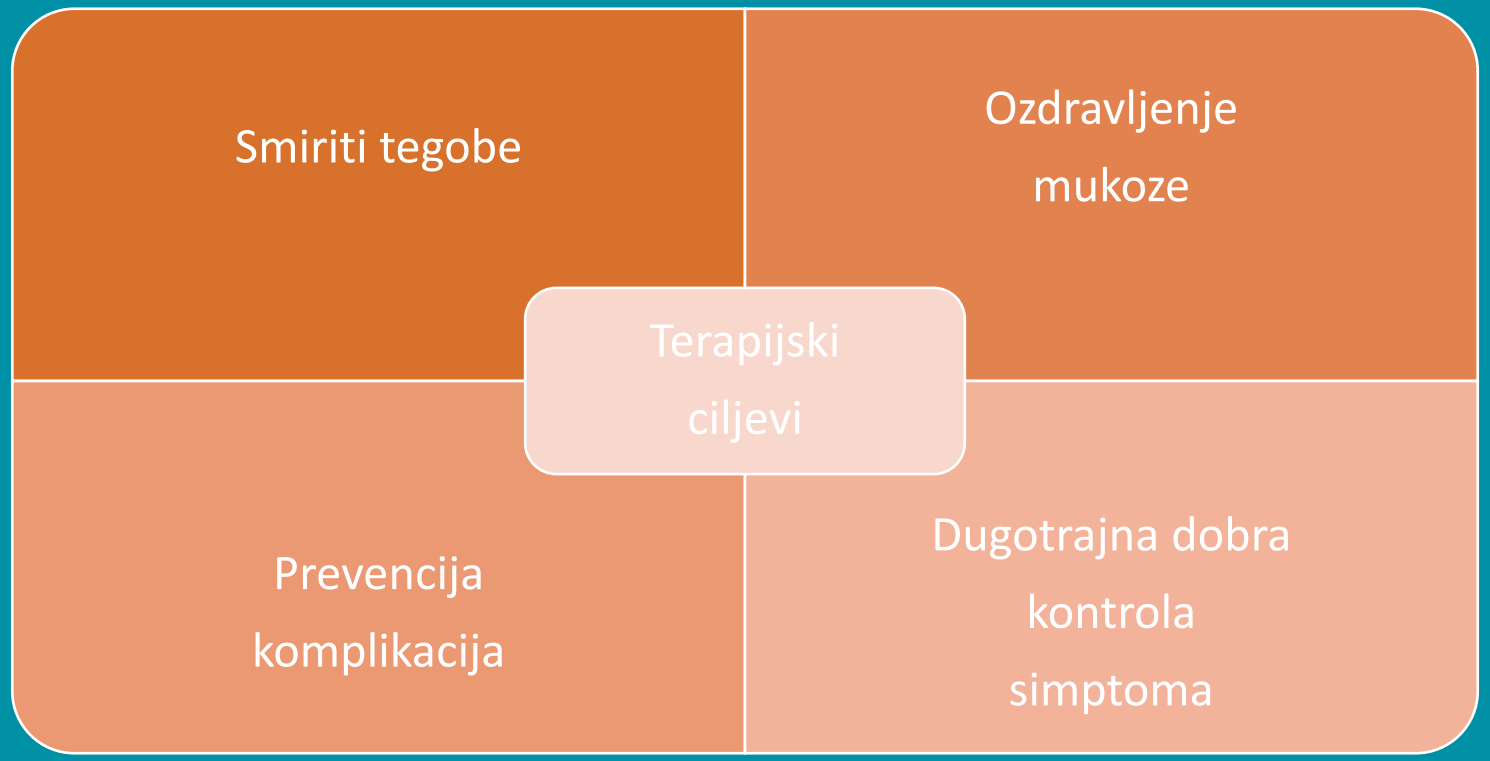
Greška br 7. Razlikovanje GERB-a od EoE

- Eozinofilni esophagitis (EoE)
  - Infiltracija esofagealne mukoze Eo (15/HPF)
  - Disfagija i impakcija hrane (većina)
  - Gorušica i regurgitacija
- GERB ~ EoE
  - Eo se nalaze u mukozi i kod GERB-a
  - IPP efikasan i u EoE u odsustvu GERB-a
  - PPI-responsive eosinophilia (? Podgrupa EoE)
    - Odgovor na IPP nije sigurni način razlikovanja GERB-a od EoE

Greška br. 8. Zanemariti postojanje GERB-a nakon hirurške intervencije

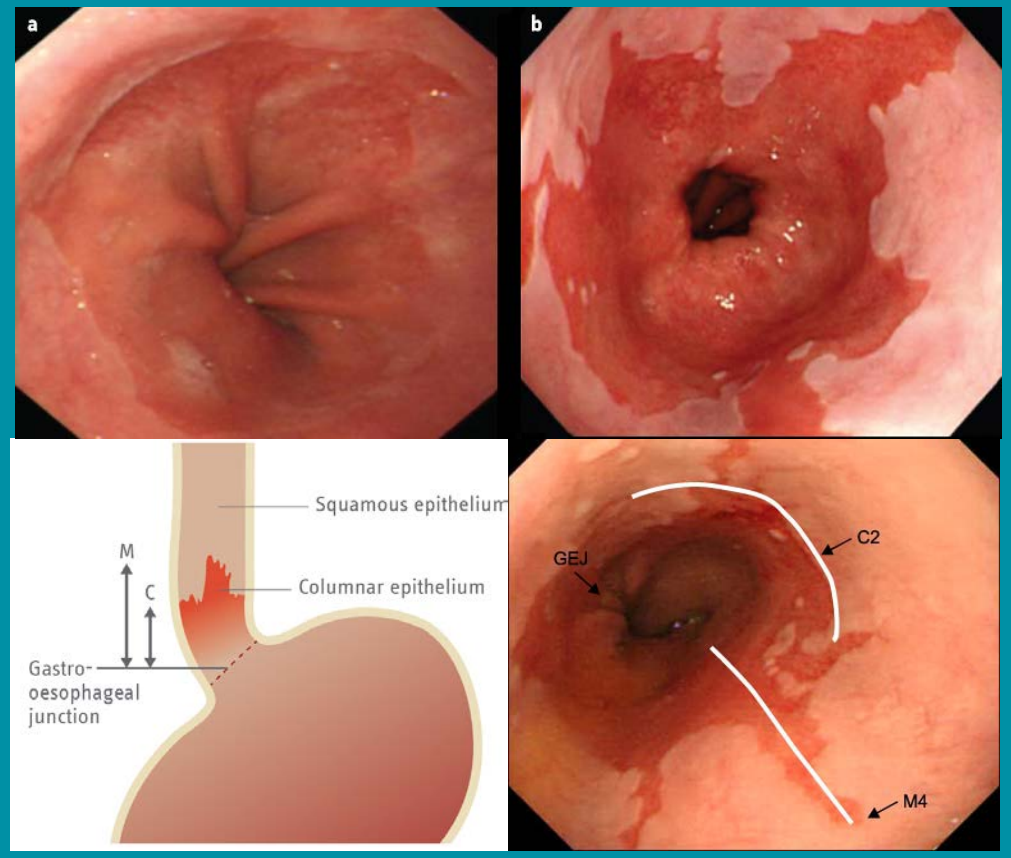
- Refluksni simptomi se javljaju nakon ARS i barijatrijskih procedura
- Sekundarno
  - usled opstrukcije na nivou anastomoze
  - *Sleeve* gastrectomy (povećan intragastrični pritisak)
  - *Kinks* (EGJ i incisura angularis)
- Endoskopija

Terapijski ciljevi u GERB



Kada je empirijska terapija GERB preporučljiva?

- Kada postoje tipični simptomi (gorušica, regurgitacija ...)
- Kada nema alarmnih simptoma:
  1. Otežano gutanje
  2. Povraćanje krvi ili crnog sadržaja
  3. Crna stolica
  4. Anemija
  5. Učestalo povraćanje
  6. Gubitak telesne mase
  7. Palpabilna masa u trbuhu



Refraktorni GERB

- *….patients with GERD who exhibit partial or lack of response to proton pump inhibitor (PPI) once (twice) daily are considered to have refractory GERD therapy…*
- Učestalost: 10-40%

Sifrim D, Zerbib F. Gut 2012; 61:1340

Fass R, Talley N, Grover S. UpToDate March 6th , 2018.

Uzroci refraktornog GERB-a

- Eosinophilic esophagitis
- Achalasia
- Pill-esophagitis
- ZE Sy
- AI bolesti sa ezofagealnim manifestacijama
- Sy ruminacije
- NSAIL
- Karcinom
- Kaustično oštećenje
- Infektivni ezofagitis
- Postiradiacioni ezofagitis

- **Psihološki poremećaji**

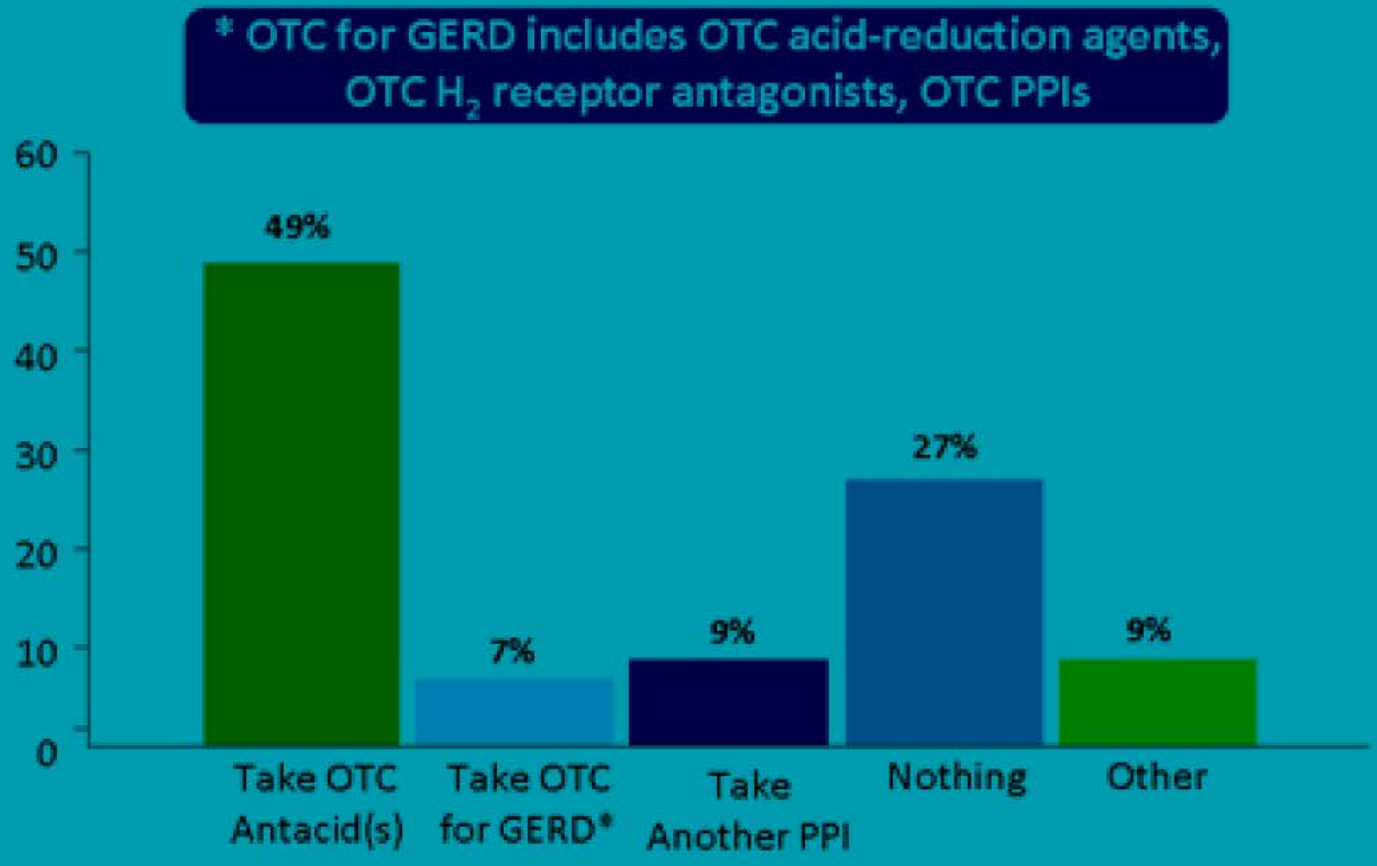
- Nedovolja supresija HCL
  - Komplijansa
  - Nepravilno vreme doziranja

- Smanjenja bioraspoloživost IPP
- Brz metabolizam IPP

- Slabo kiseli refluks
- Alkalni reflux
- Residualni kiseli reflux
- Usporeno pražnjenježeluca

Mermelstein J et al. Clinical and Experimental Gastroenterology 2018:11 119–134

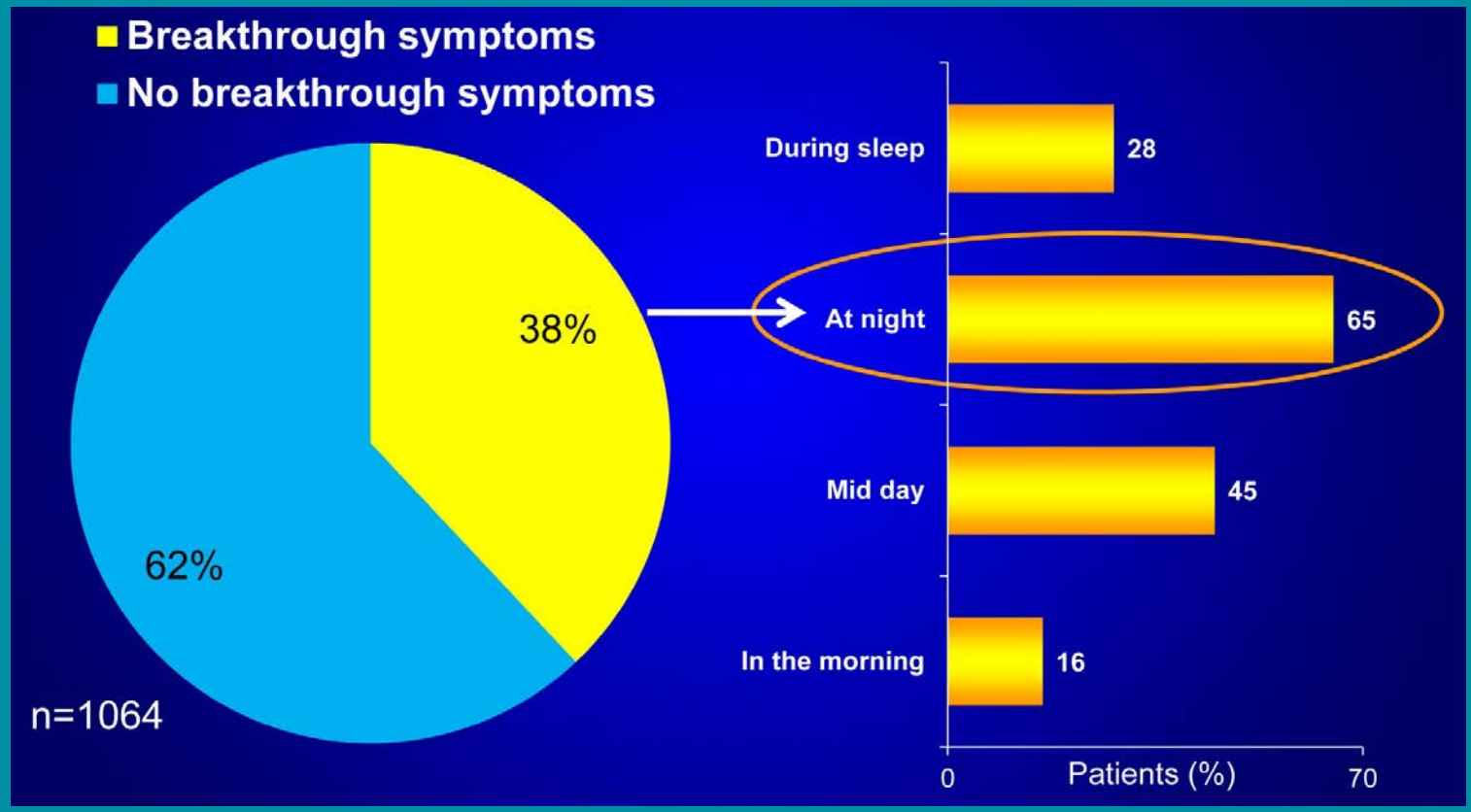
Use of OTC Products



AGA Institute/Harris Interactive Inc. *GERD Patient Study: Patients and Their Medications*. 2008. http://www.gastro.org/user-assets/Documents/13_Media/GERD_Survey_Final_Report_2.pdf

MedscapeCME

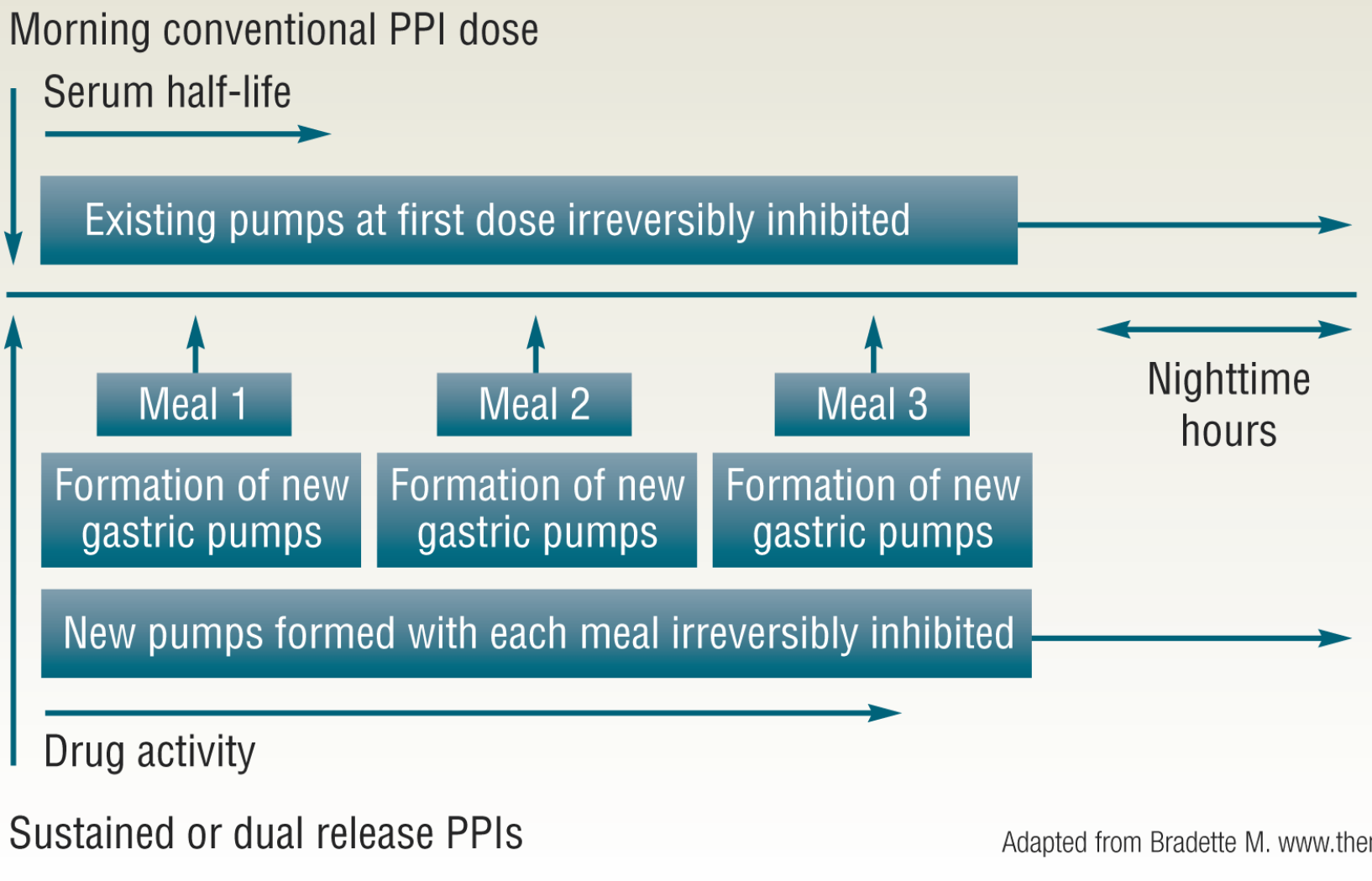
Noćni proboj kiseline-jednom dnevno doziranje IPP



AGA. GERD Patient Study: Patients and Their Medications. Harris Interactive Inc; 2008

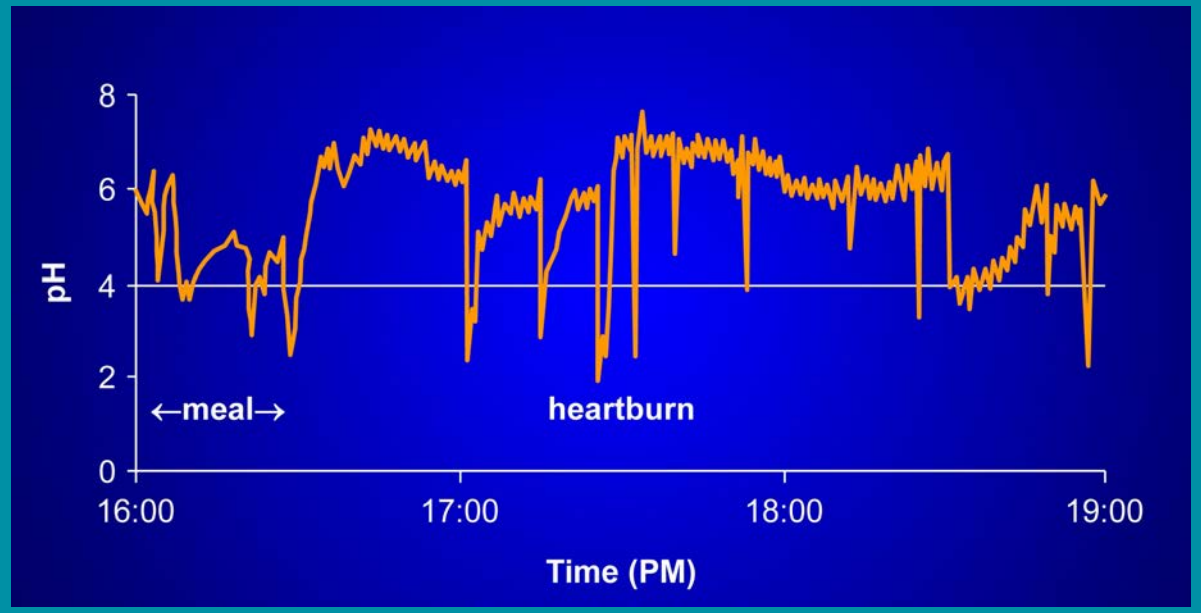
FIGURE 4.

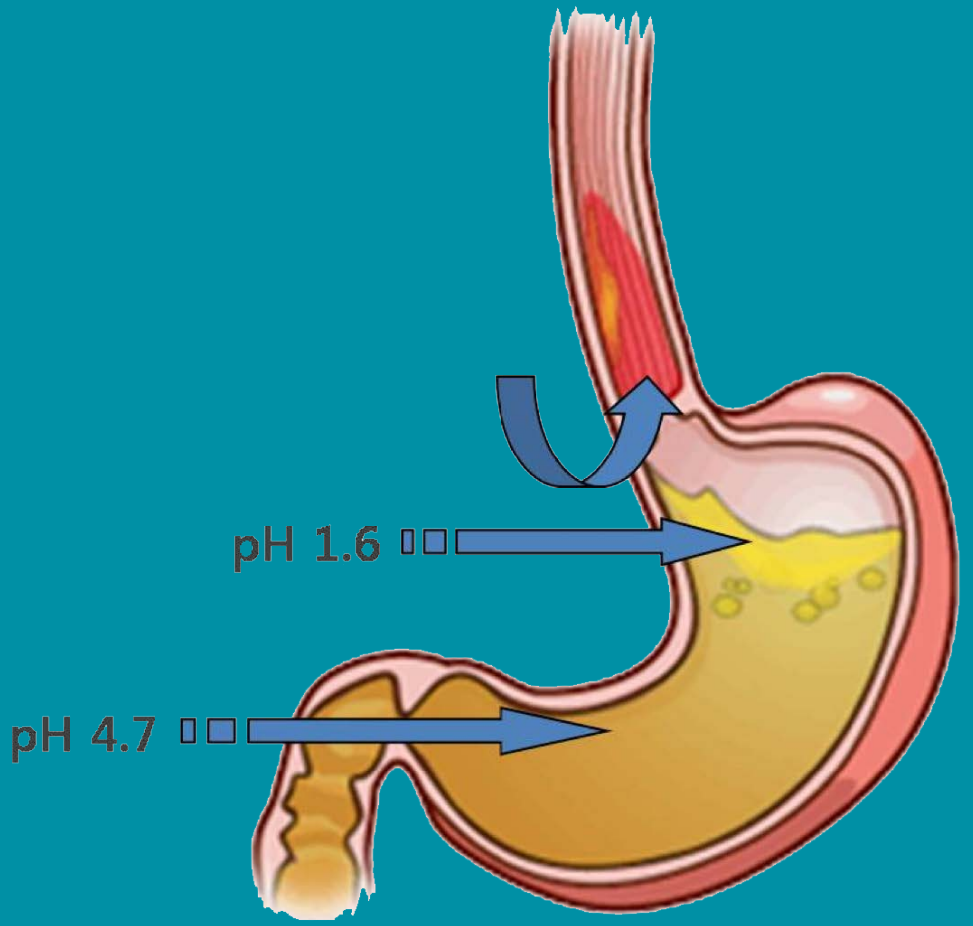
Control of Nocturnal GERD May Depend on Longer PPI Duration of Action



Adapted from Bradette M. www.themedicalxchange.com.

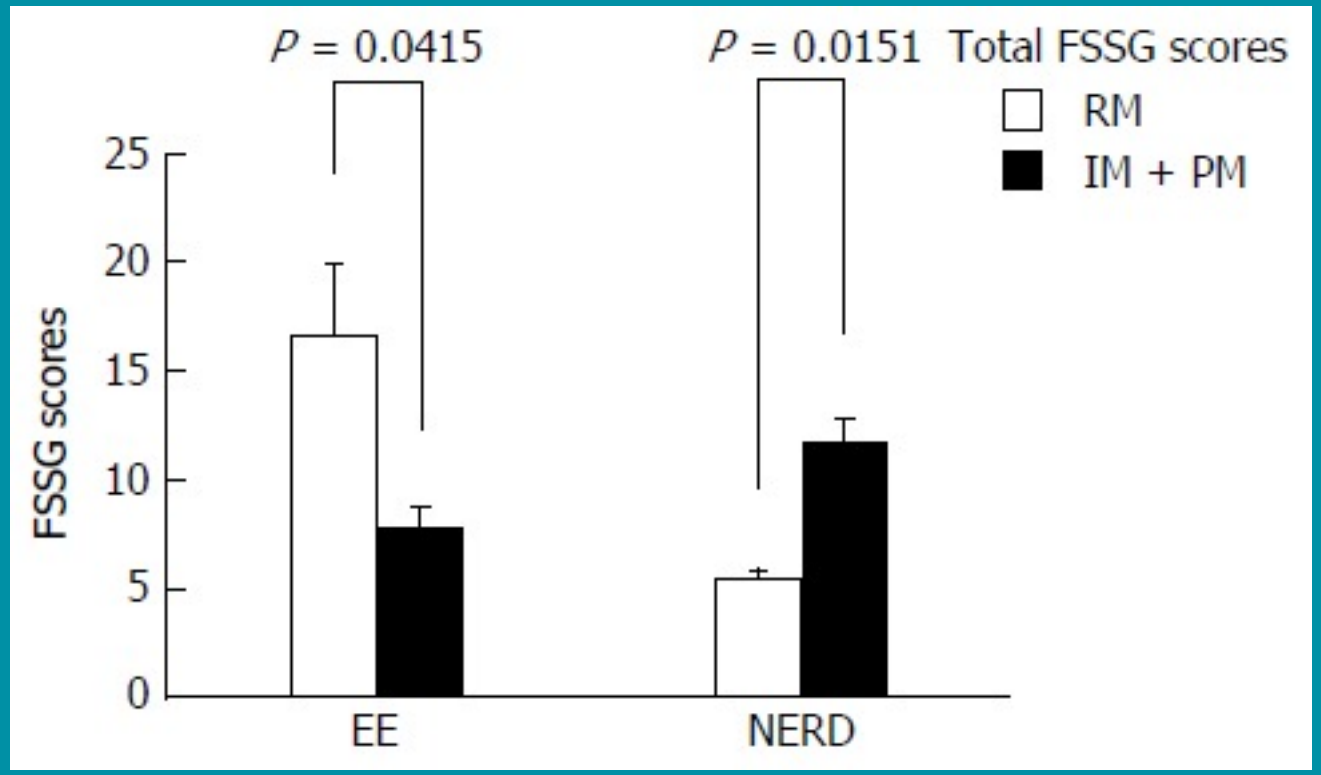
Postprandijalna gorušica
Rezidualni kiseli sadržaj





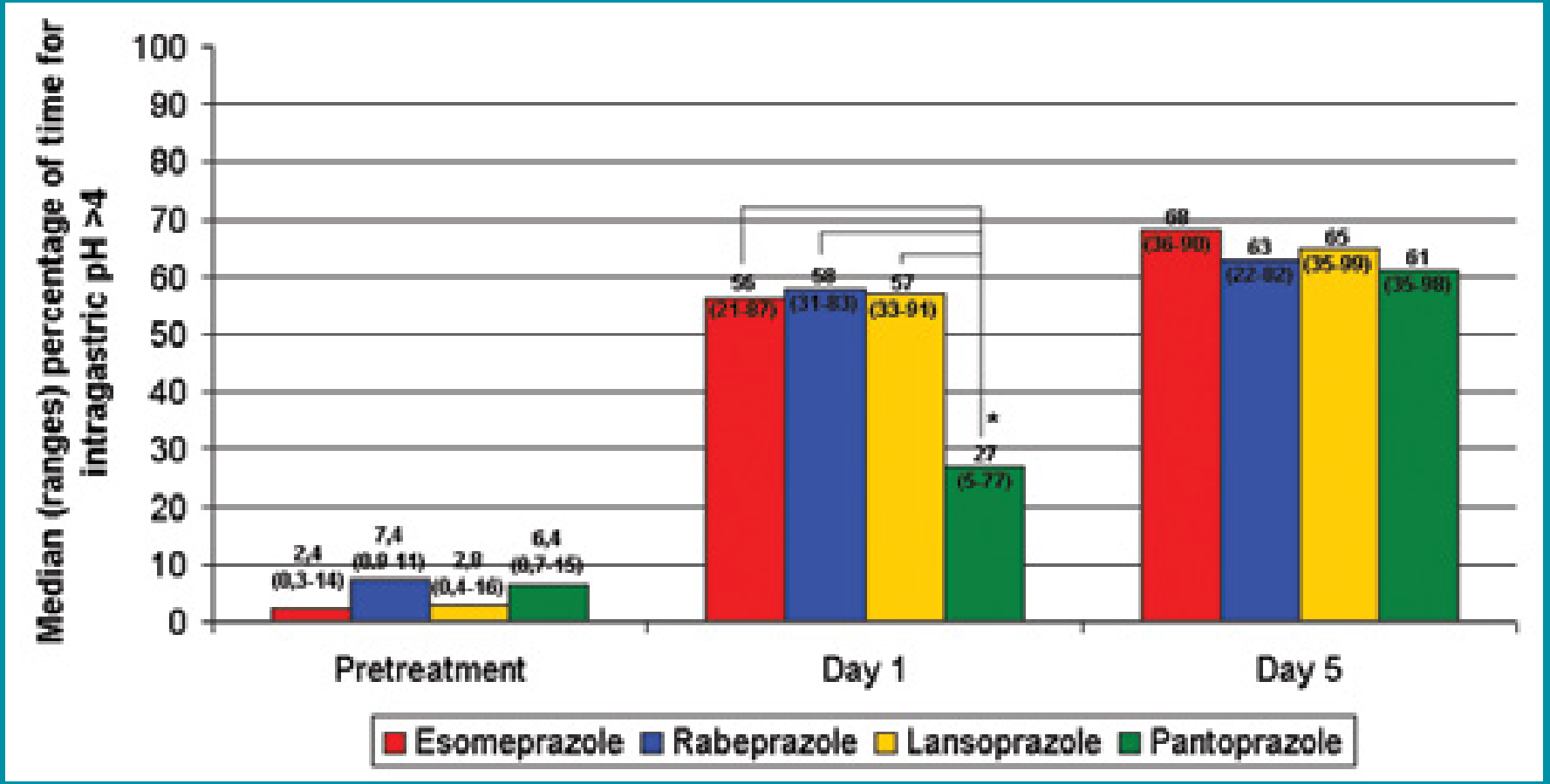
Kahrilas PJ, Boeckxstaens G. Failure of reflux inhibitors in clinical trials: bad drugs or wrong patients? *Gut.* 2012;61(10):1501-1509

CYP2C19 Polimorfizam
Kawara F et al. WJG 2017; Mar 21; 23: 2060–67.

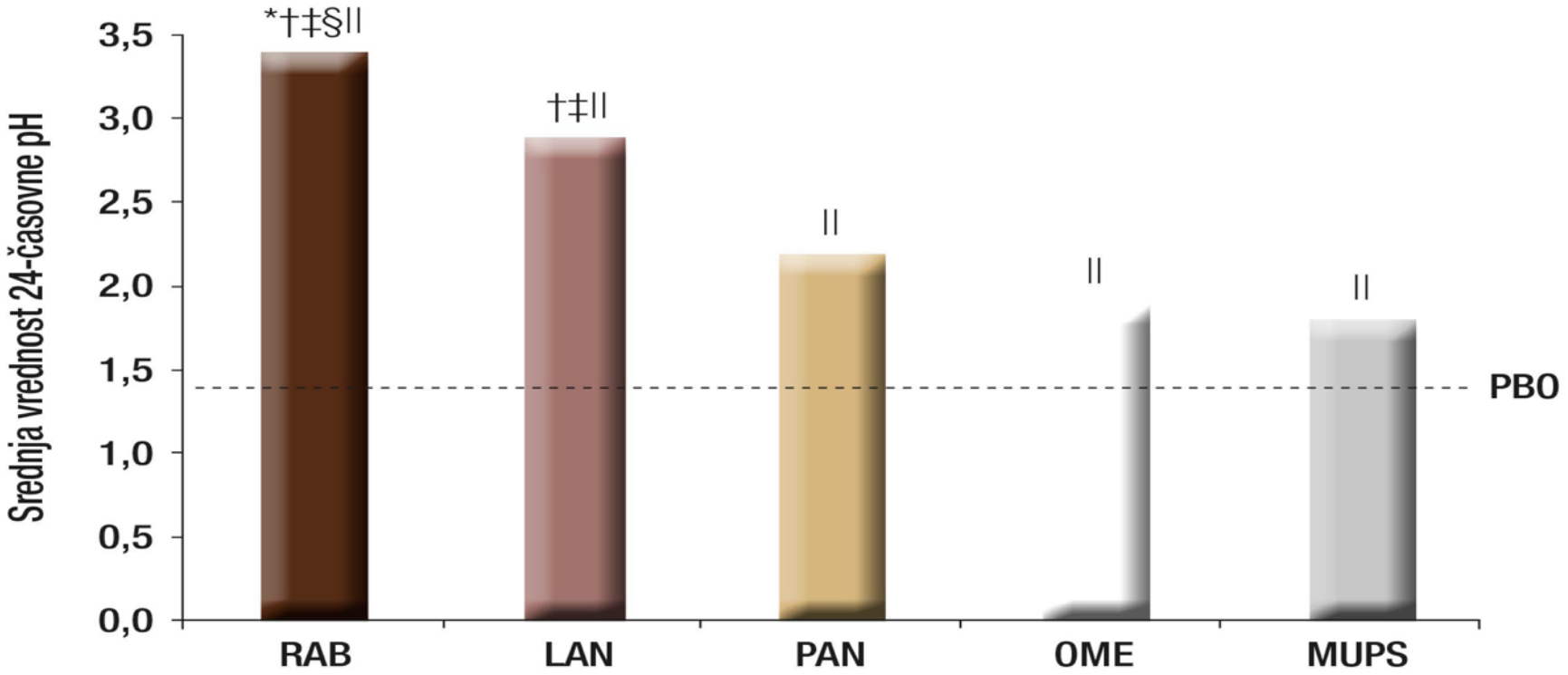


Correlation between the cytochrome P450 2C19 genotype and the total frequency scale for symptoms of gastroesophageal reflux disease score in the erosive esophagitis and non-erosive reflux disease patients. FSSG: Frequency scale for symptoms of gastroesophageal reflux disease; EE: Erosive esophagitis; NERD: Non-erosive reflux disease; RM: Rapid metabolizer; IM: Intermediate metabolizer; PM: Poor metabolizer.

CYP2C19 polimorfizam direktno utiče na metabolizam IPP

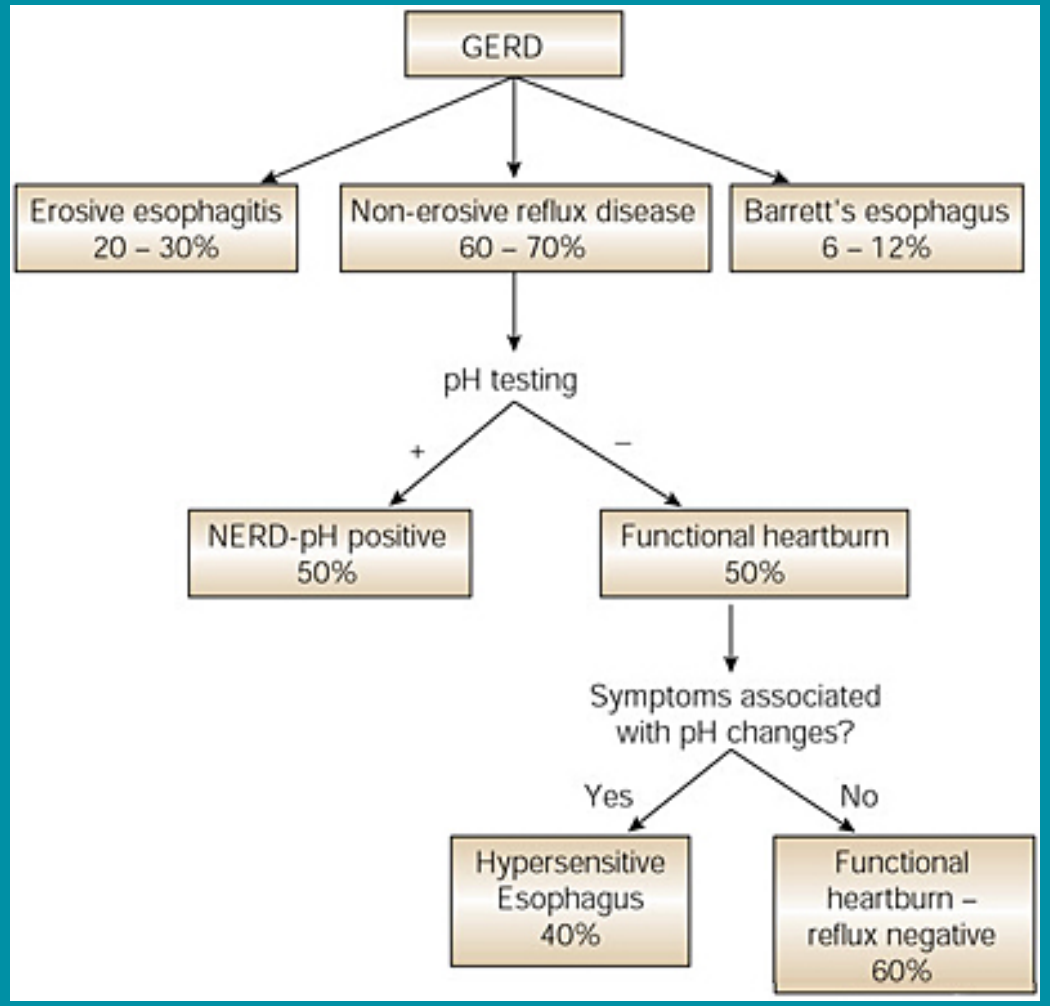


Celebi et al. Turk J Gastroenterol 2016; 27: 408-14



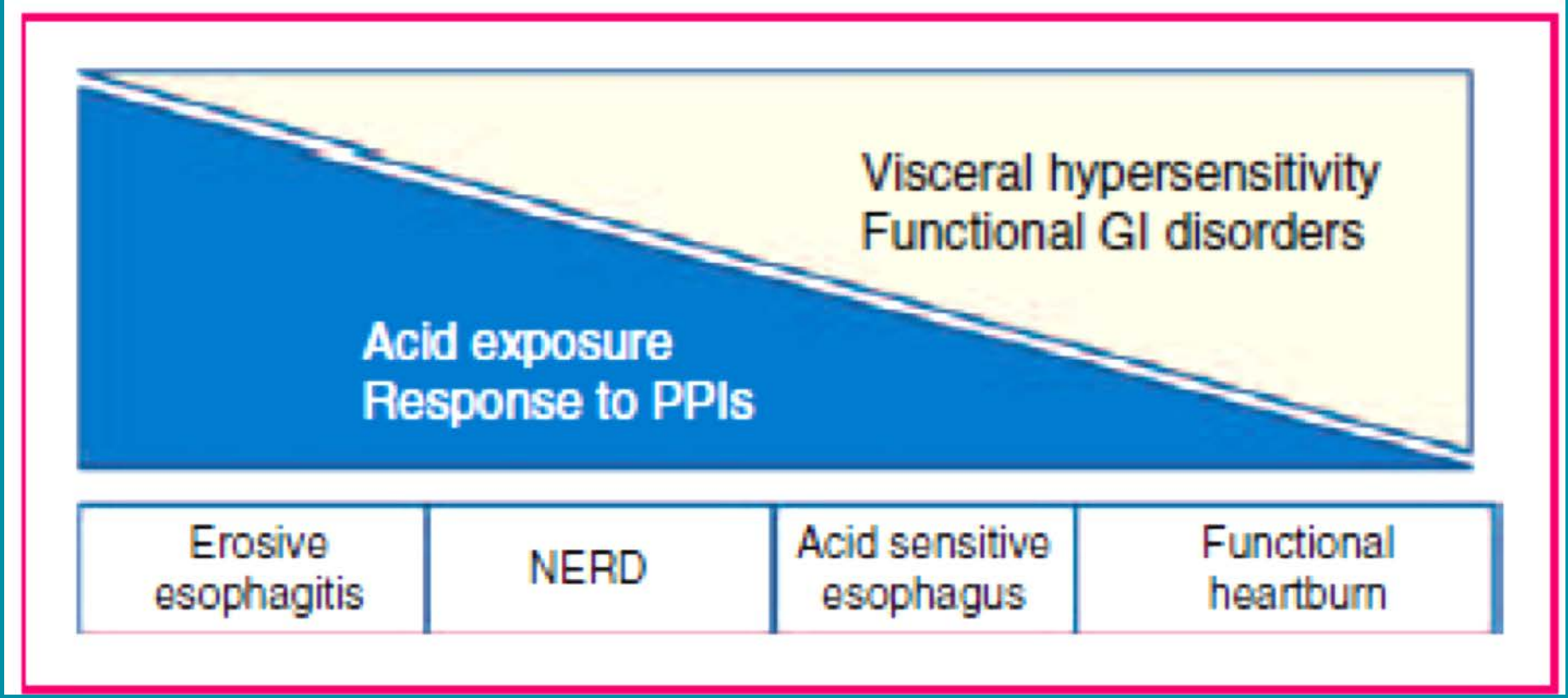
Antisekretorna aktivnost inhibitora protonske pumpe nakon primene pojedinačne doze (dan 1. lečenja), prikazana kroz srednju vrednost pH merene tokom 24 h. LAN, lansoprazol 30 mg; MUPS, omeprazol 20 mg višepeletni sistem; OME, omeprazol 20 mg; PAN, pantoprazol 40 mg; PBO, placebo; RAB, rabeprazol 20 mg. *P ≤ 0.03 vs. LAN; †P ≤ 0.03 vs. PAN; ‡P ≤ 0.02 vs. OME; §P ≤ 0.04 vs. MUPS, ||P ≤ 0.04 vs. PBO.

Fenotipske karakteristike GERB-a



GI Motility online doi:10.1038/gimo42

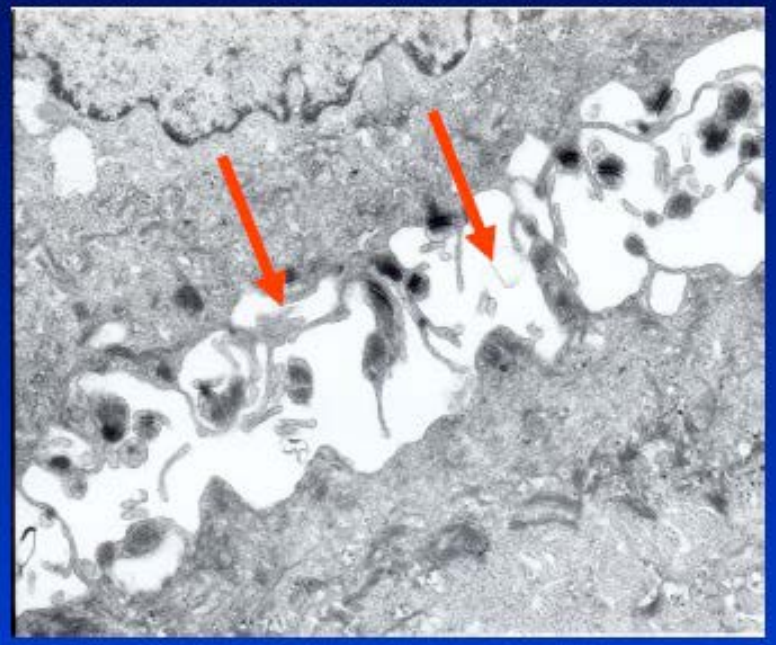
Uloga kiseline i hipersenzitivnosti na različite fenotipove GERB-a i njihov odgovor na IPP



Changes on electron microscopic examination

control

NERD



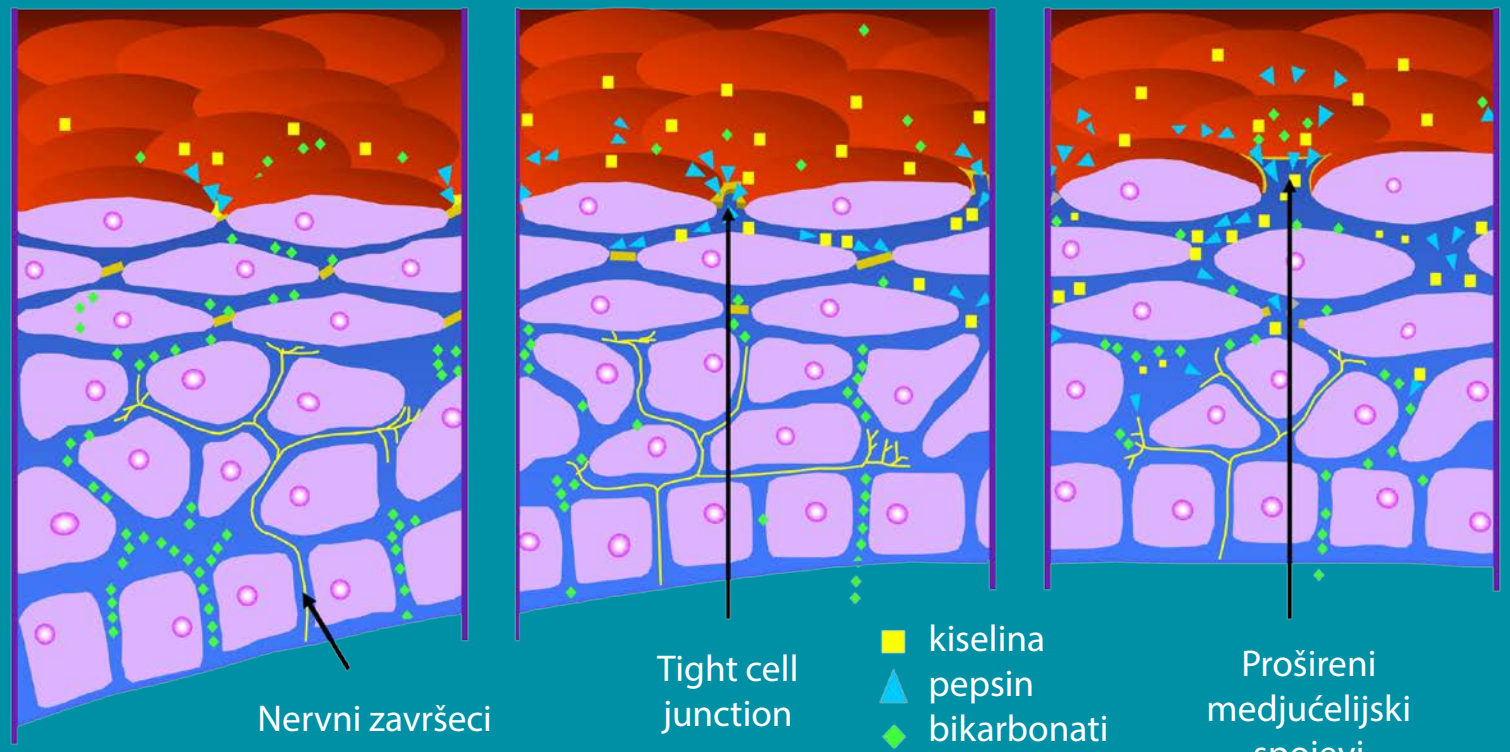
Neumann, Mönkemüller et al. DDS 2008

Kiselina i pepsin iz želudačnog refluksata oštećuju jednjak

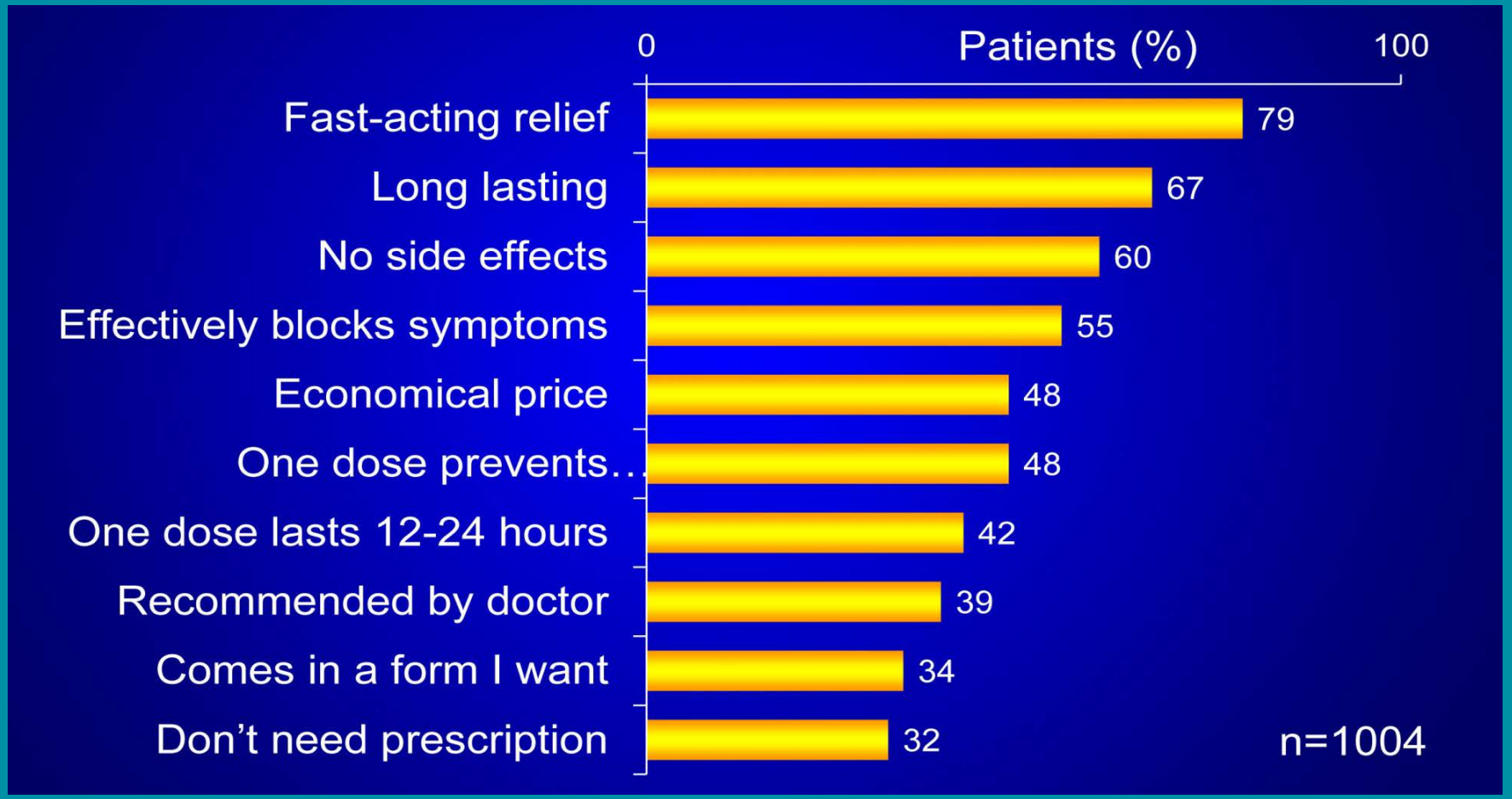
Dejstvo kiseline i pepsina slabi medjućelijske spojeve...

...dovodi do širenja medjućelijskih prostora..

i omogućava prolazak kiseline u dublje slojeve mukoze.

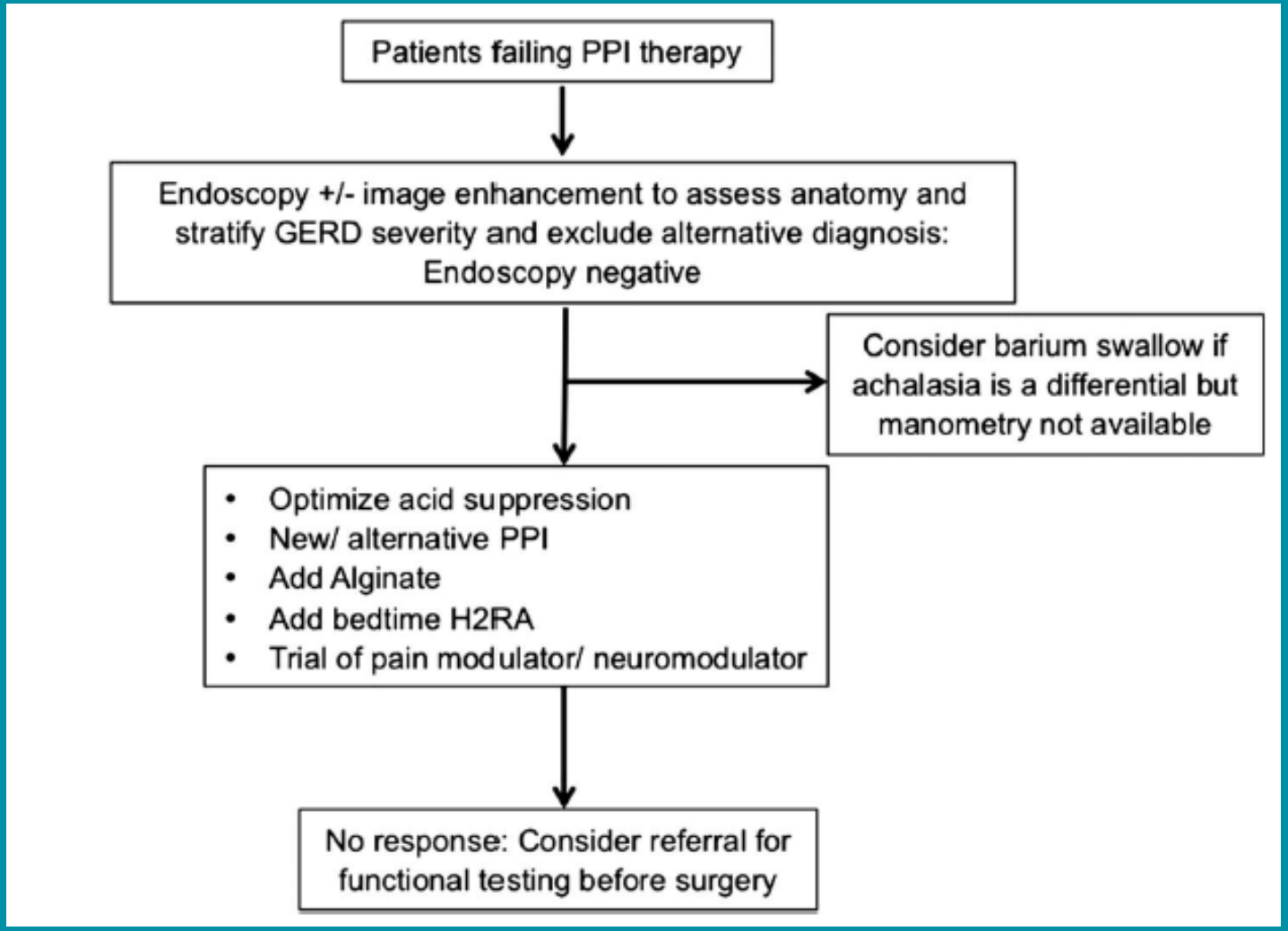


Očekivanja bolesnika veoma važna pri izboru leka



Gallup Organization. The 2000 Gallup Study of Consumers' Use of Stomach Relief Products

Lečenje refraktornog GERB-a i BE- konsenzus



Fock KM, et al. Gut 2016:65:1402-15

Optimizacija terapije

- Drugi IPP
- Večernja doza
- Adjuvantna terapija
  - Alginati
  - Hijaluronska kiselina/Hondroinat sulfat
  - TCA

Potencijalni neželjeni efekti dugotrajne terapije IPP

- Poremećaj metabolizma minerala
- Osteoporoza
- Frakture kuka
- Poremećaj apsorpcije vitamina i Fe
- Crevne infekcije
- Ne-crevne infekcije
- Intereakcija sa clopidogrelom
- Rebound fenomen sekrecije želudačne kiseline
- Hipomagnesemia
- Mikro kopski colitis
- CDAD

Patientćs Perception of PPI Risk and Attempts at Discontinuation. Am J Gastro Mart 08, 2019

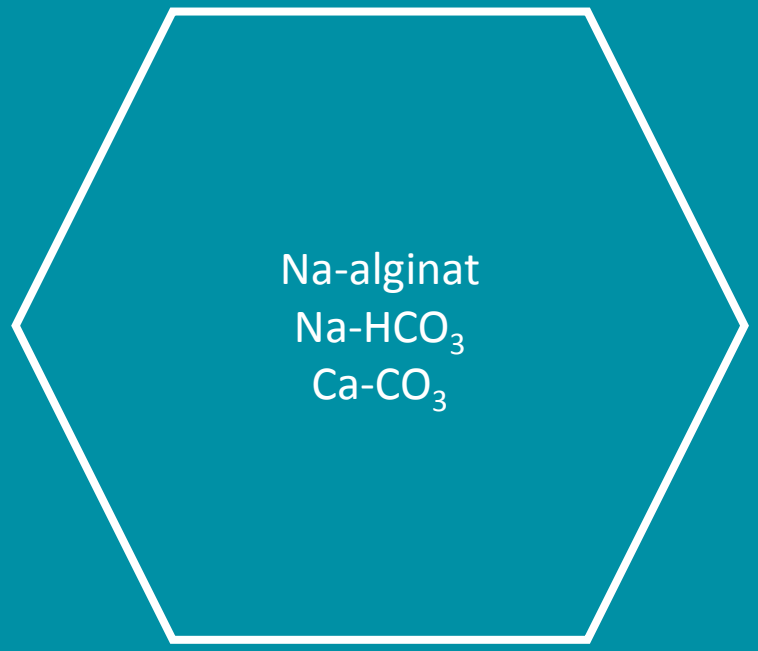
- TAKE-HOME MESSAGE
  - An online survey of adults who use proton pump inhibitors (PPIs) for gastroesophageal reflux disease (GERD) was conducted to ascertain the level of concern patients have regarding the adverse effects of PPIs and whether their concerns are associated with attempts to discontinue the drugs. Nearly **25% of patients discussed the risks and benefits of PPIs with a healthcare provider, and 9% were recommended to discontinue PPIs.** However, of the **39% who attempted to discontinue PPIs, 83% did so without a provider's recommendation**. The strongest factors for discontinuation attempts include a provider's recommendation, concern about adverse effects, and female gender.

Alginati - *Laminaria hiperboreea 1881*

- Prehrambena industrija (napici, kremovi, pudinzi, sladoledi, sosevi, pivo – za održavanje pene!)
- Medicina: stomatološki materijali, hirurške komprese (za opekotine)

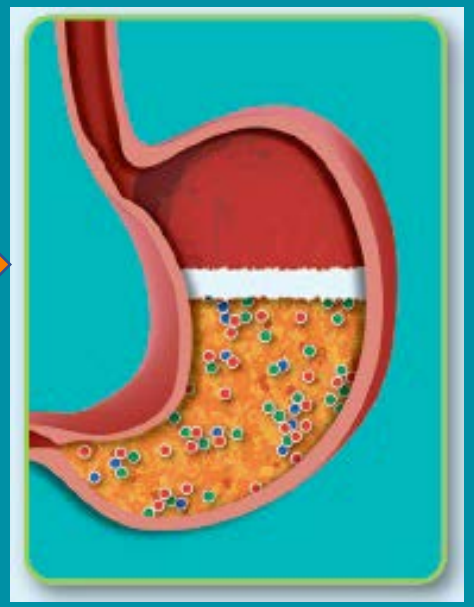
Alginati – način delovanja

- Na-alginat + želudačni sadržaj
  - tanak sloj gela na površini želudačnog sadržaja
- $NaHCO_3$ + HCl
  - CO_2
- Gel + CO_2
  - Pena koja pluta na površini želudačnog sadržaja
- $CaC0_3$ + gel
  - Čvršća struktura
- Sprečava vraćanje želudačnog sadržaja u jednjak

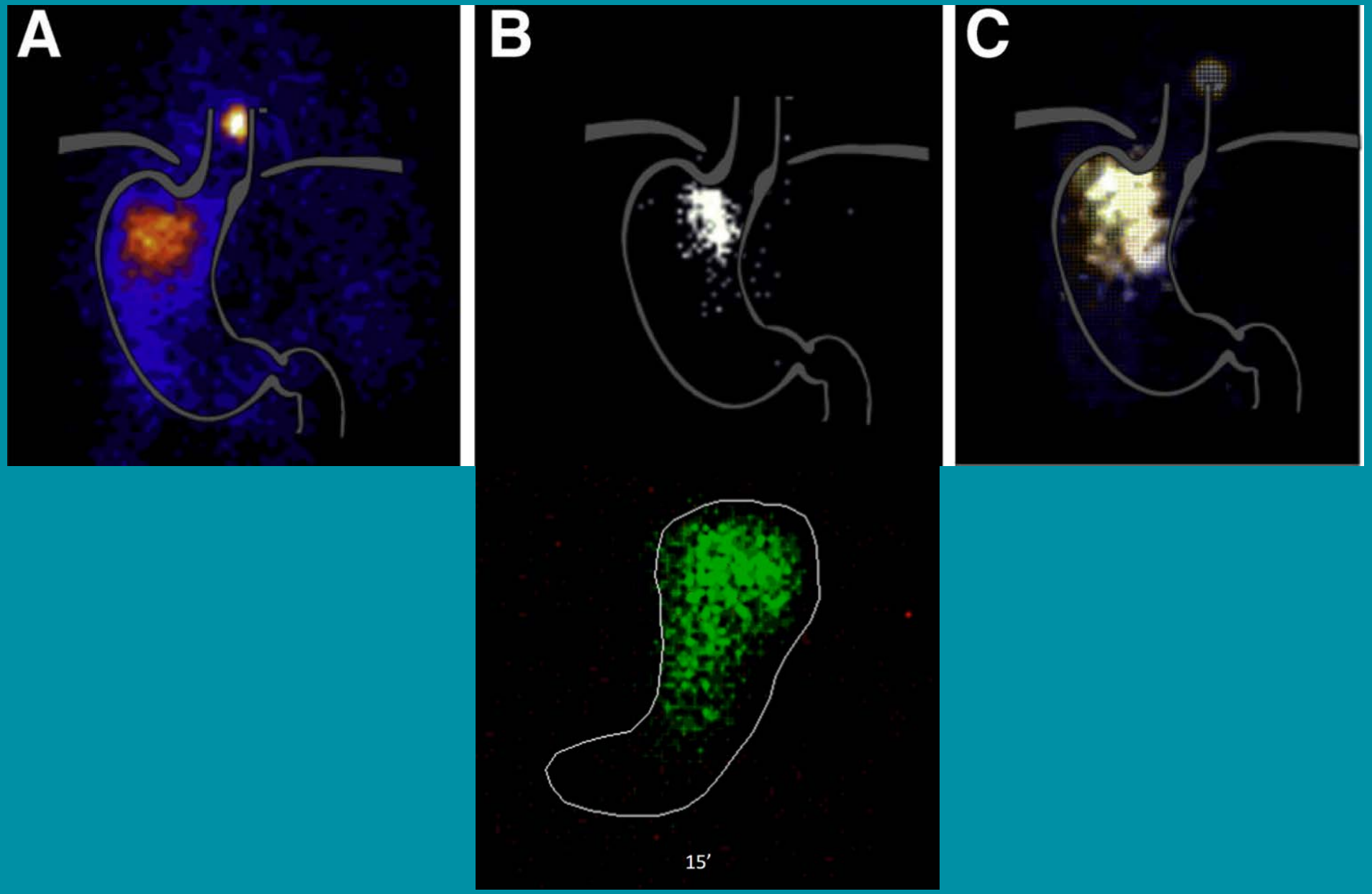


Refluks želudačnog sadržaja - gorušica

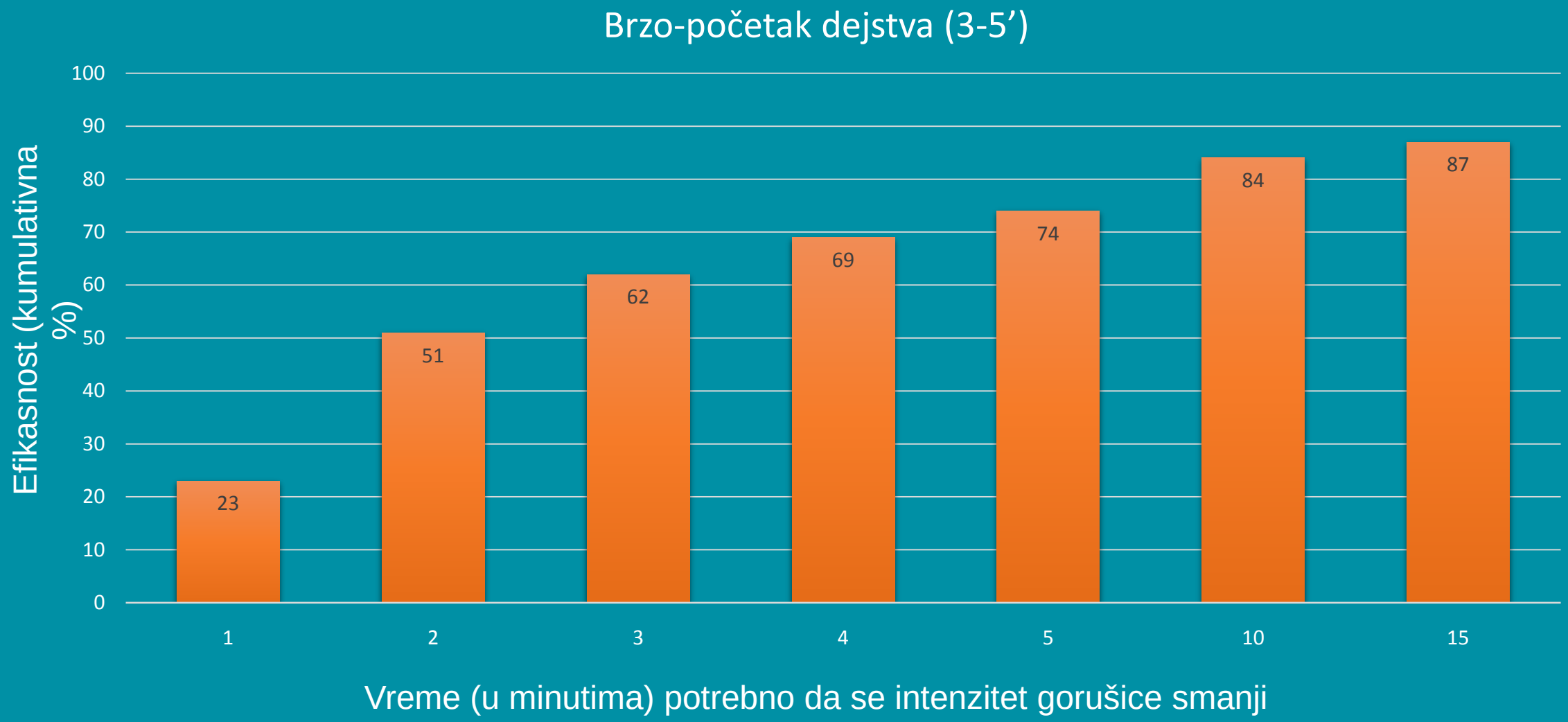
Učinak na simptome već nakon 3 minuta



Formirani penasti sloj na površini želudačnog sadržaja sprečava refluks


A
B
C
15’

Alginati


Brzo-početak dejstva (3-5’)
Efikasnost (kumulativna %)
100
90
80
70
60
50
40
30
20
10
0
23
51
62
69
74
84
87
1
2
3
4
5
10
15
Vreme (u minutima) potrebno da se intenzitet gorušice smanji

Diseases of the Esophagus (2017) **30**, 1–9
DOI: 10.1093/dote/dow020

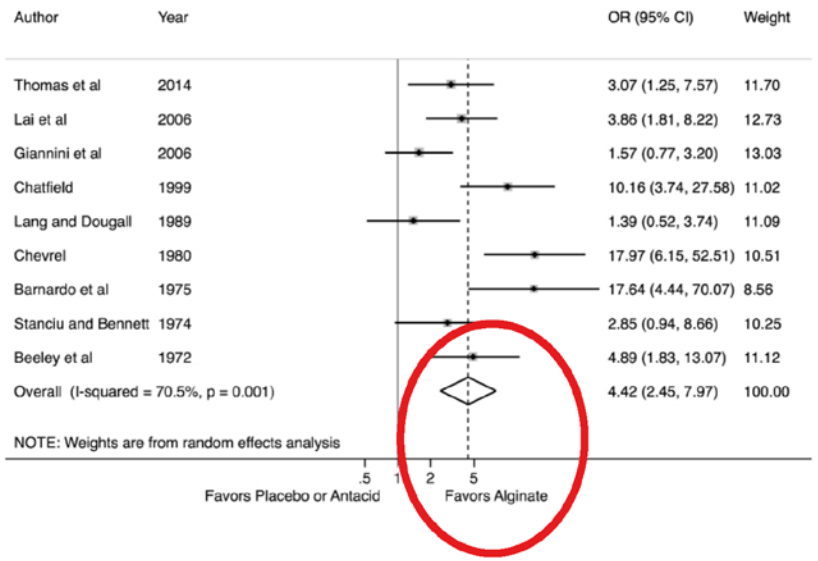
DISEASES OF THE ESOPHAGUS

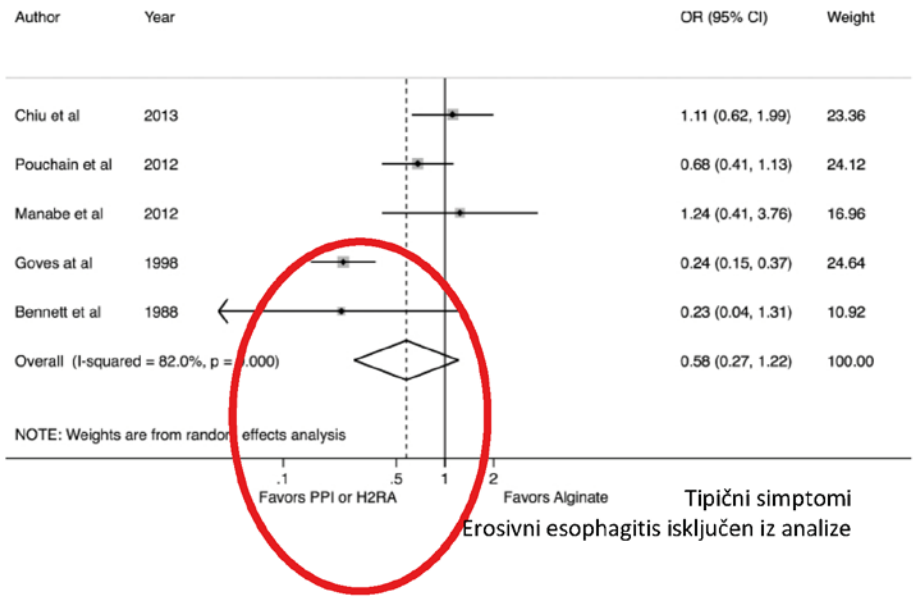
ISDE The International Society for Diseases of the Esophagus

Original Article

Alginate therapy is effective treatment for GERD symptoms: a systematic review and meta-analysis

D. A. Leiman,[1] B. P. Riff,[2] S. Morgan,[3] D. C. Metz,[4] G. W. Falk,[4] B. French,[3,5,6,7] C. A. Umscheid,[3,5,6,7,8] J. D. Lewis[4,5,6,7]





Tipični simptomi
Erosivni esophagitis isključen iz analize

Alginati efikasni u terapiji simptomatskog GERB-a
Potreba RCTs u proceni efikasnosti alginate +/IPP kod refraktornog GERB-a

Alginati

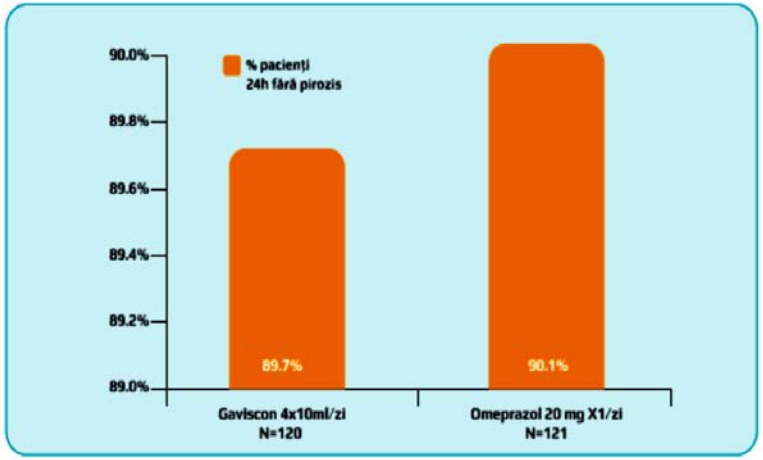
Gaviscon(R) vs. Omeprazole in symptomatic treatment of moderate gastroesophageal reflux. A direct comparative randomised trial

BMC Gastroenterology 2012, **12**:18

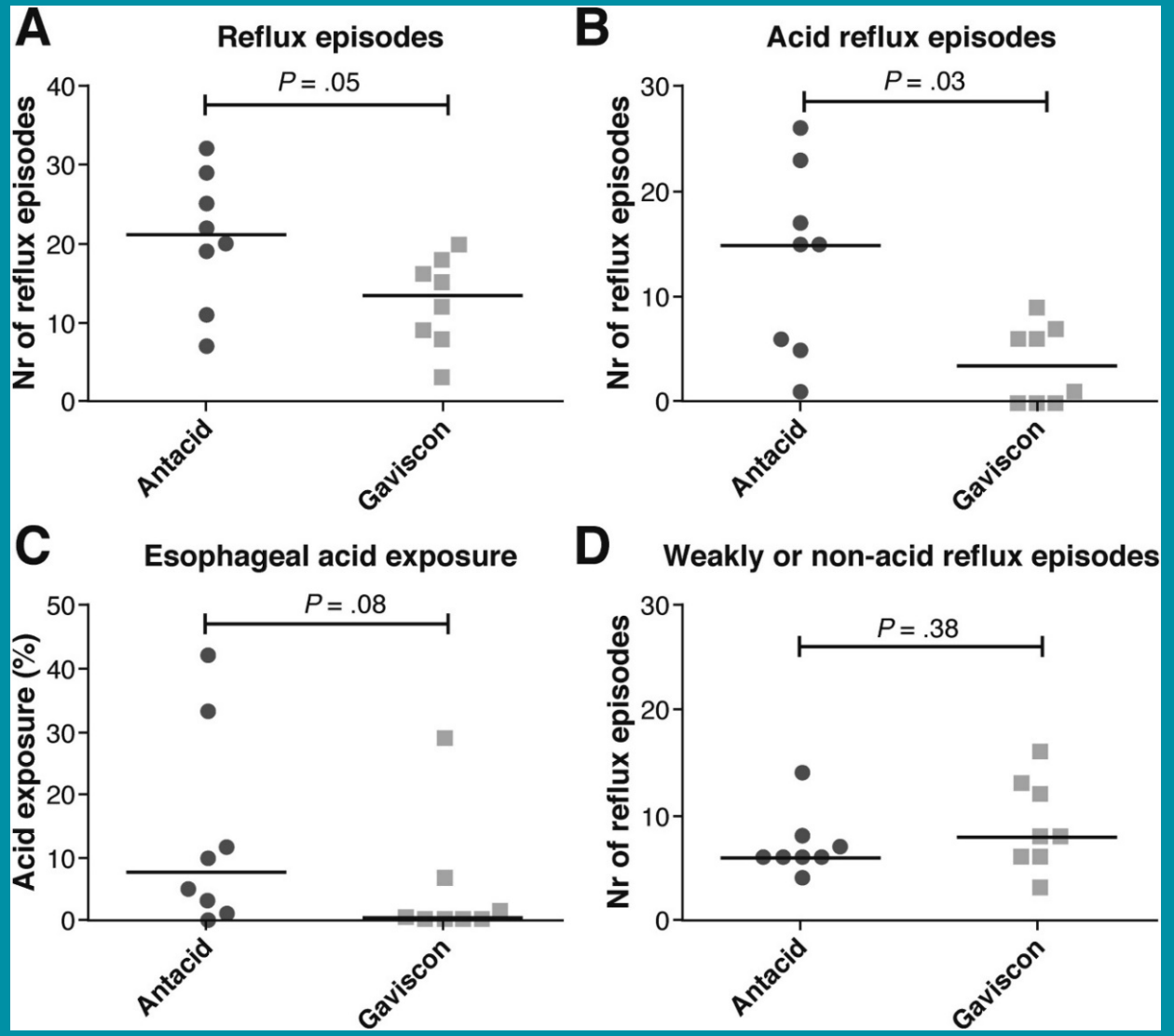
GOOD study, 2012:

Conclusion

In a general practice setting for patients complaining of moderate heartburn, Gaviscon® (4×10 mL/day) is an effective short-term treatment option in mild-to-moderate GERD, in terms of onset of a first 24-h heartburn-free period after initial dosing. It proved non-inferior to omeprazole 20 mg/day, and is thus a relevant and effective alternative treatment in case of moderate and episodic symptoms of GERD as managed in general practice.



Alginati vs. antacidi



Clinical Gastroenterology and Hepatology 2013 11, 1585-1591DOI: (10.1016/j.cgh.2013.04.046)

AP&T Alimentary Pharmacology and Therapeutics

Randomised clinical trial: alginate vs. placebo as add-on therapy in reflux patients with inadequate response to a once daily proton pump inhibitor

C. Reimer*, A. B. Lødrup[†,‡], G. Smith[§], J. Wilkinson[§] & P. Bytzer[†,‡]

Conclusion

In patients with residual reflux symptoms despite PPI treatment, adding an alginate offers additional decrease in the burden of reflux symptoms (EudraCT/IND Number: 2011-005486-21).

Aliment Pharmacol Ther 2016; **43:** 899–909

Thieme

Alginat bei Bedarf als Add-on bei unzureichendem Effekt von Protonenpumpen-Hemmern bei Patienten mit gastroösophagealer Reflux-Krankheit

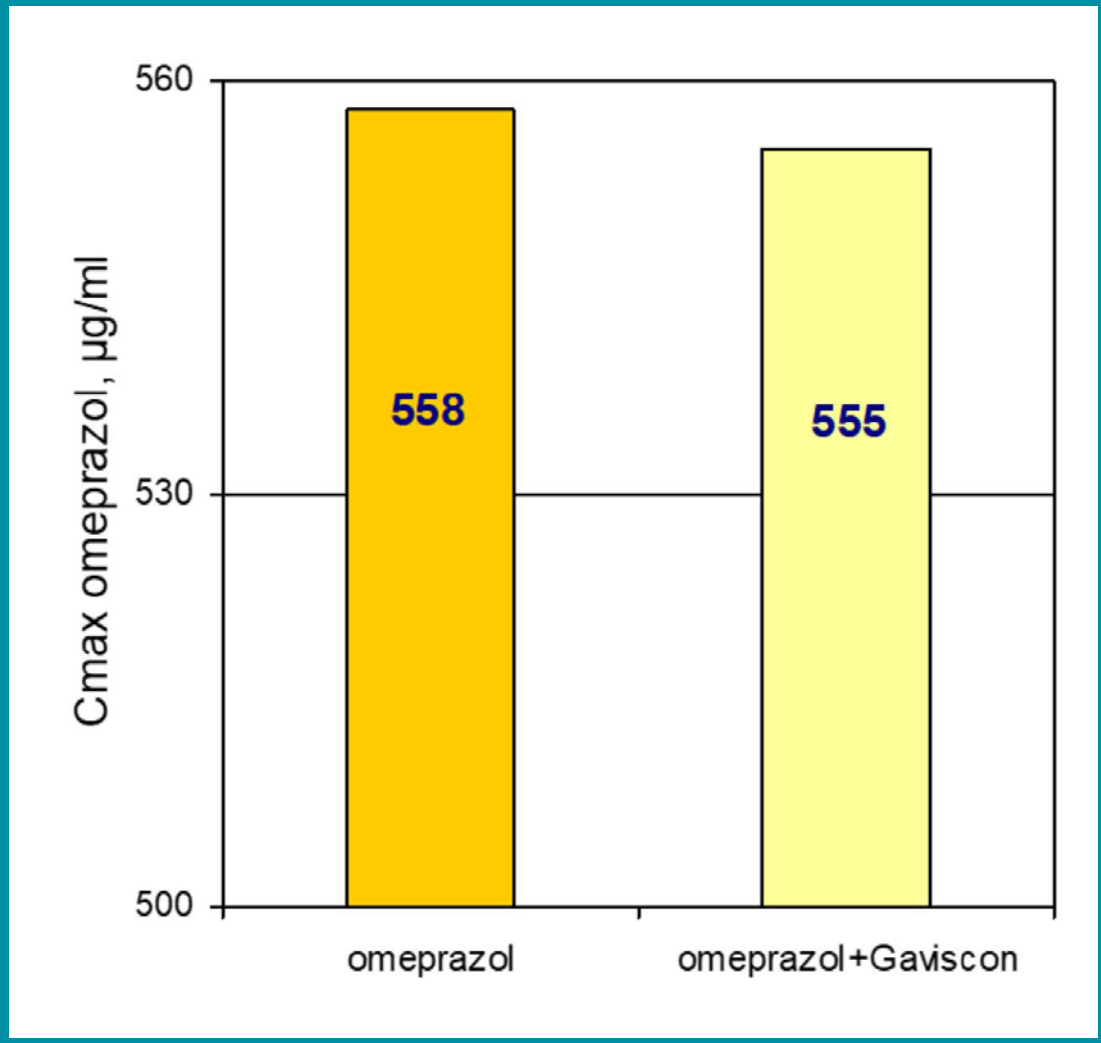
Alginate on demand as add-on for patients with gastro-oesophageal reflux disease and insufficient PPI effect

Conclusions A reflux blocking alginate taken on demand is an effective and safe option for the treatment of break-through symptoms in GERD patients on PPI.

Müller M et al. Alginat bei Bedarf… Dtsch Med Wochenschr 2019; 144: e30–e35

Alginati

- Ne utiče na farmakokinetiku IPP i blokatora H2 receptora
- Formiranje gel strukture i mehaničke barijere nije pod uticajem H2 blokatora i IPP



Dettmar et al 2004: N=24 ;20 mg omeprazolumx1/day + 10 ml Gavisconx4/day, 3 days; evaluation of blood Cmax of omeprazolum in day 3 (with & without Gaviscon co-administration)

Dettmar et al 2005: N=12 volunteers (18-40 yo); 20 mg omeprazolumx1/day, 3 days; Gaviscon raft onset evaluation while co-administrating omeprazolum and without

Alginati

Randomised, controlled, crossover study to assess the suppression of gastro-oesophageal reflux (GOR) by sodium alginate formulations in the form of liquid and tablets

ECM THOMAS,[2] J SYKES,[2] P BERRY,[2] V STRUGALA,[1] PW DETTMAR[1]

[1]*Technostics Lt*
Healthcare (UK)

Gaviscon Tablet and Liquid formulations were shown to significantly suppress postprandial GOR compared to control when measured objectively by oesophageal pHmetry. New formulation Tablet was equally as successful at suppressing GOR as the established Liquid formulation. Effective OTC treatment of GOR is possible using the convenient tablet format with the same efficacy as the liquid format.

© 2010 Journal of Gastroenterology and Hepatology Foundation and Blackwell Publishing Asia Pty Ltd

Journal of Gastroenterology and Hepatology 2010; **25** (Suppl. 2): A79–A176

Alginati

- Postepeno obustavljanje terapije IPP

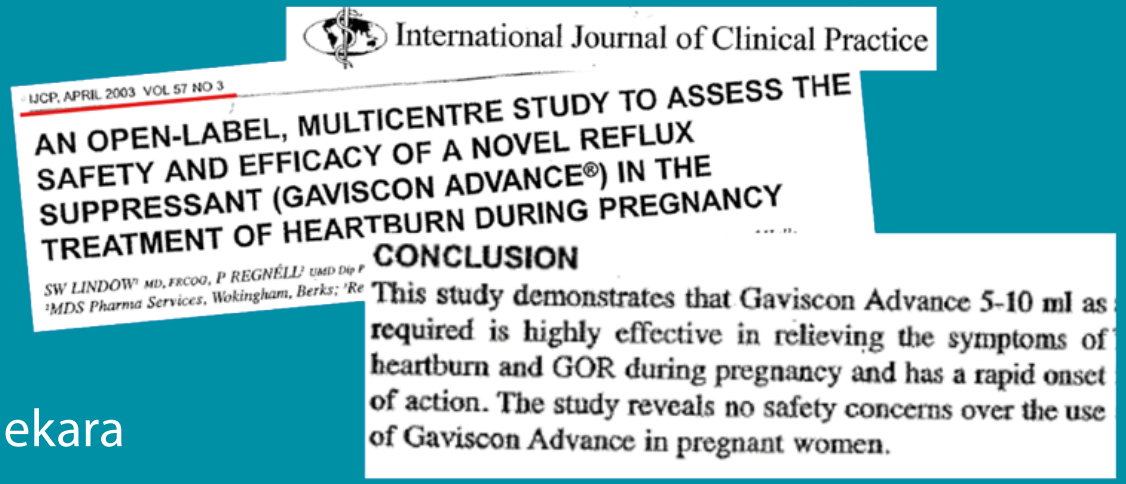
  - Izbegavanje *rebound* fenomena

  - Dovoljno u 58% bolesnika
  - Dobra kontrola simptoma gorušice
  - Smanjeni troškovi lečenja

Cawston & Wood 2003: N=10,000 GORD patients previously treated with PPI (51% lansoprazolum – minimum 8 months, 58% rabeprazolum – minimum 10 months), multi-centric study.

Alginati

- Bezbedna primena
  - Trudnice, stariji pacijenti, deca – po preporuci lekara
  - > 98% smanjenja trajanja i učestalosti simptoma refluksa u toku trudoće.
  - Terapija se dobro podnosi.



International Journal of Clinical Practice

IJCP, APRIL 2003 VOL 57 NO 3

AN OPEN-LABEL, MULTICENTRE STUDY TO ASSESS THE SAFETY AND EFFICACY OF A NOVEL REFLUX SUPPRESSANT (GAVISCON ADVANCE®) IN THE TREATMENT OF HEARTBURN DURING PREGNANCY

SW LINDOW[1] MD, FRCOG, P REGNÉLL[2] UMD Dip P

[1]MDS Pharma Services, Wokingham, Berks; [2]Re

CONCLUSION

This study demonstrates that Gaviscon Advance 5-10 ml as required is highly effective in relieving the symptoms of heartburn and GOR during pregnancy and has a rapid onset of action. The study reveals no safety concerns over the use of Gaviscon Advance in pregnant women.

Alginati

- Oprez- sadrži Natrijum
  - Stariji
  - HBI
  - KVS
  - Srčana slabost

Alginati

- Brzo deluju
- Dugotrajno dejstvo > 4h
- Pogodan za primenu kod trudnica i dece
- Samostalno ili u kombinaciji sa IPP
- Efikasan kod postprandijalne gorušice
- Izlazna strategije lečenja IPP
- Lečenje i kiselog i alkalnog refluksa