Development of urinary incontinence in a 7-year old boy after therapy with proton pump inhibitors and complete resolution of his clinicopathologic features of eosinophilic esophagitis after H2-receptor antagonist treatment: A case report

Klinični primer razvoja urinske inkontinence pri 7-letnem fantu med zdravljenjem z inhibitorjem protonske črpalke in izginotje kliničnopatoloških znakov eozinofilnega ezofagitisa po zdravljenju z antagonisti H2 receptorjev

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gastroezofagealna refluksna bolezen; otrok; inhibitorji protonske črpalke; H2-blokatorji; eozinofilni ezofagitis; na inhibitor protonske črpalke odzivna ezofagealna eozinofilija

Abstract

Background: Several diseases result in profound infiltration of esophageal mucosa by eosinophilic granulocites, with gastroesophageal reflux disease (GERD), eosinophilic esophagitis (EoE) and proton-pump-inhibitor-responsive esophageal eosinophilia (PPI-REE) being the most prevalent. Proton-pump-inhibitor-responsive esophageal eosinophilia (PPI-REE) is a newly recognized entity that must be differentiated from eosinophilic esophagitis (EoE).

Case presentation: A 7-year old Slovenian male presented with a few-month history of chest pain, regurgitation and heartburn. First endoscopy was performed and revealed pronounced longitudinal furrows, and on hystology examination > 70 eosinophils per high power field were found through the entire thickness of epithelium and in the submucosis with eosinophilic microabscess formation. Results of 24-hour pH-monitoring (without impedance monitoring) excluded pathologic acid reflux. All allergy tests were negative. The patient started treatment with proton pump inhibitors (PPIs) for three times, twice with pantoprazole before the endoscopy and once with esomeprasole after it to exclude the diagnosis of GERD and PPI-REE. Urinary incontinence reappeared each time just few days after starting treatment and disapeared few days after stopping it. Therefore, urinary incontinence was considered as a plausible adverse effect of therapy with PPIs. As treatment with PPIs was not tolerated, a therapy with H2-receptor antagonists ranitidine was applied for more than 2 months followed by a second endoscopy. Both symptoms and esophageal eosinophilia completely resolved with ranitidine. The resolution of esophageal eosinophilia in PPI-REE has been atributed to proton pump independent antiinflammatory effects of PPIs. No such effects have been described in H2-receptor antagonists.

Conclusions: Two unique phenomena were observed in the pediatric patient with profound esophageal eosinophilia: urinary incontinence as an adverse effect of therapy with PPIs, and complete resolution of esophageal eosinophilic inflammation with typical features of EoE after treatment with H2-receptor antagonists.

Key words:
gastroesophageal reflux disease; child; proton pump inhibitors; H2-blocker; eosinophilic esophagitis; PPI-responsive esophageal eosinophilia

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Izvleček

Izhodišča: Mnoge bolezni lahko privedejo do obsežne infiltracije sluznice požiralnika z eozinofilnimi granulociti. Med njimi so najbolj pogoste gastroezofagealna refluksna bolezen, eozinofilni ezofagitis in na inhibitor protonske črpalke odzivna ezofagealna eozinofilija.

Prikaz primera: 7-letni fantek iz Slovenije je imel več mesecev trajajoče epizode bolečin v prsnem košu, regurgitacije in pekočega občutka za prsnico. Izvedena je bila prva endoskopija, ki je prikazala izrazite vzdolžne brazde, histološki izvid je prikazal več kot 70 eozinofilcev na polje velike povečave, ki so bili prisotni čez celotno debelino epitela, v submukozi pa so bili pristoni eozinofilni mikroabscesi. 24-urno merjenje pH (brez merjenja impedance) je izključilo patološki kisli refluks. Vsa alergološka testiranja so bila negativna. Bolnik je prejemal terapijo z inhibitorji protonske črpalke trikrat, dvakrat je prejemal pantoprazol pred prvo endoskopijo in enkrat esomeprazol po prvi endoskopiji za izključitev gastroezofagealne refluksne bolezni in na inhibitor protonske črpalke odzivne ezofagealne eozinofilije. Pri bolniku se je nekaj dni po začetku terapije z inhibitorjem protonske črpalke vedno pojavila urinska inkontinenca, ki je izginila nekaj dni po prenehanju jemanja zdravil. Zato se je le-ta zdela zelo verjeten stranski učinek zdravljenja. Glede na slabo prenašanje zdravljenja z inhibitorjem protonske črpalke smo uvedli zdravljenje z antagonistom H2-receptorjev ranitidinom. Simptomi in ezofagealna eozinofilija so po zdravljenju z ranitidinom izginili.

Dobro znani so protivnetni učinki inhibitorjev protonske črpalke, v smislu resolucije ezofagealne eozinofilije pri bolnikih, odzivnih na ezofagealno eozinofilijo po jemanju inhibitorja protonske črpalke. Pri antagonistih receptorjev H2 takšnih učinkov še niso opisali.

Zaključek: Pri bolniku smo opazili dva pojava: urinsko inkontinenco kot stranski učinek zdravljenja z inhibitorji protonske črpalke in popolno remisijo ezofagealnega eozinofilnega vnetja po zdravljenju z antagonisti H2-receptorjev.

1 Introduction

The range of GERD prevalence estimates in adults is 8.8 %-25.9 % in Europe and is considerably lower than that in the population of children over 1 year of age (1). Until mid-nineties, infiltration of esophageal mucosa with eosinophils has been regarded as hallmark of gastroesophageal reflux disease (GERD) as several studies revealed a correlation between the density of esophageal eosinophilia and esophageal acid exposure (2,3). Esophageal eosinophilic infiltration(EEI) is observed in several conditions, including gastroesophageal reflux disease(GERD), eosinophilic esophagitis(EoE), celiac disease, infections, Crohn's disease, achalasia, drug hypersensitivity, vasculitis and graft-versus-host disease (4). Observations that a proportion of these patients who did not respond to anti-secretory therapy got into remission when put on the elemental formula eliminating all food antigens lead to a discovery of a novel disease, EoE (5). According to current guidelines, EoE is defined as a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by esophageal infiltration with at least 15 eosinophils per high-power field(HPF) (6,7). Immune reactions to food antigens, and in some cases maybe also to aeroalergens, are regarded to play crucial role in its development (6,8,9). For confirming a diagnosis of EoE, other diseases that may result in esophageal eosinophilia, especially GERD, should be excluded. While previous guidelines required exclusion of GERD by negative results of esophageal pH-monitoring (10), this is not necessary any more, as both diseases may be present simultaneously. Consequently, absence of re-

sponse – both symptomatic and histologic – to acid suppression with proton pump inhibitors (PPIs) became a recommended method for discrimination between EoE and GERD (6,7). However, a proportion of patients with apparent clinical and histologic signs of EoE and normal esophageal acid exposure (absence of GERD) get into remission with PPI therapy (11,12). This recently recognized entity of esophageal eosinophilia is defined as PPI-responsive esophageal eosinophilia (PPI-REE) (6,7). Retrospective studies have demonstrated that 39 % to 71 % of children and adults with EEI have PPI-REE (13). At the moment, it is not clear whether it represents a part of EoE spectrum, GERD spectrum or a completely independent disease. More than forty patients with EoE were treated at our Pediatric Gastroenterology Unit in recent years, as a majority of patients with EoE in our country are treated at a tertiary level hospital.

It has been proposed that anti-inflammatory effects of PPIs in addition to their inhibition of acid secretion may be involved in PPI-REE (14-19). To the best of our knowledge, resolution of extreme esophageal eosinophilia including other typical hallmarks of EoE with H2-receptor antagonists has never been reported. Therefore, we present a case of a boy with extensive esophageal eosinophilia in whom therapy with PPIs was impossible due to a peculiar adverse reaction, urinary incontinence, and was therefore treated with alternative anti-secretory drug, H2-receptor antagonists, and got into complete clinical and histologic remission.

2 Case Presentation

A 7-year-old white Slovenian male presented with a history of approximately one year of chest pain, regurgitation and heartburn with worsening in the last few months. In the past, he had several episodes of laryngitis and pneumonia that remained etiologically unexplained despite comprehensive diagnostic workout by pulmologist, allergologist and otorhynolaryngologist. Family history was negative for gastrointestinal diseases but positive for allergic diseases (his father has hay fever).

According to the symptoms suggestive for GERD, one-month therapeutic trial with PPI (pantoprazole 1 mg/kg) was prescribed by the boy's primary pediatrician. Symptoms improved, however, approximately a week after starting therapy, nighttime and daytime urinary incontinence appeared, with the boy reporting loss of feeling for the fullness of the bladder and urge for urination. As he had no previous history of urinary incontinence, the parents attributed incontinence to the adverse effects of pantoprazole and stopped the medication. Few days after cessation of the therapy incontinence disappeared, but soon after GERD symptoms reappeared. Thus, the boy was referred to the Pediatric Gastroenterology Unit.

Considering good symptomatic response to the short treatment and no data in the literature about urinary incontinence being an adverse effect of PPIs, therapy with pantoprazole was reconsidered. Again, a week after pantoprazole introduction urinary incontinence reappeared and parents stopped the therapy with the disappearance of incontinence few days after that. Because of persistent chest pain, regurgitation and heartburn the boy was admitted to the hospital 2 months later for esophagogastroduodenoscopy under sedation. Endoscopy was performed which revealed pronounced longitudinal furrows but no erosions of the esophagus, while stomach and duodenal mucosa appea-

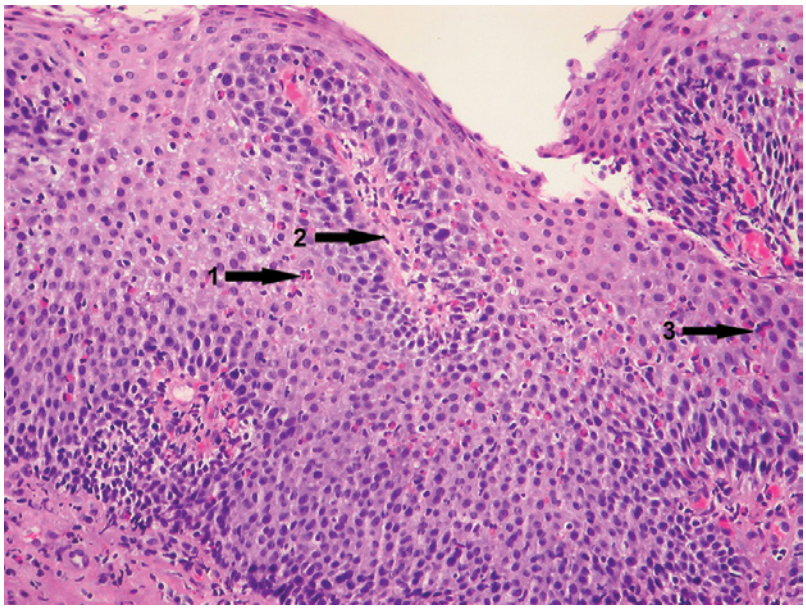

Figure 1: Esophageal biopsy of our patient before treatment with H2-receptor antagonists, eosin hematoxylin staining. High number of eosinophils (1) through entire thickness of esophageal epithelium with degranulation and eosinophilic microabscesses (3), basal cell hyperplasia and elongation of papillae (2).

red normal. A diagnosis of EoE was suspected and biopsies were taken from the duodenum, stomach and esophagus, two from the distal and two from the proximal third. On histology examination of the esophageal biopsy specimen, eosinophils were prominent through the entire thickness of the epithelium and eosinophils were also found in the submucosa with peak eosinophil count of 70 eosinophils per HPF. In addition, eosinophilic microabscesses in the surface layers, degranulation of eosinophils, basal cell hyperplasia and elongation of lamina propria papillae were confirmed (Figure 1).

With strong suspicion of EoE, the boy was referred to an allergologist. Laboratory testing revealed slightly elevated serum immunoglobulin E level (81 kU/L), however specific IgEs, as well as skin prick and patch tests for food allergens were negative. Because of the history of urinary incontinence during PPI therapy, a comprehensive nephrologic and urologic workout was performed. All examinations were normal, including abdominal and urinary tract ultrasound, urinalysis and kidney function tests. No invasive urologic procedures were performed.

In accordance with the recommendations, a two-month treatment with PPI was prescribed to exclude PPI-REE. However, despite the use of esomeprazole instead of pantoprazole, a week after the beginning of treatment urinary incontinence reappeared, and the treatment was stopped. Nine months after PPI treatment, a 24-hour esophageal pH-monitoring (without impedance monitoring) excluded pathologic acid reflux (GERD) as reflux index was 3.6 % (normal <5 %) and DeMeester score was 12.59 (normal 14.7). As urinary incontinence occurred after the treatment with two different types of PPIs, a treatment with ranitidine 75 mg/day was proposed. The patient had no urinary incontinence and his esophageal symptoms resolved completely.

A control endoscopy was performed four months after the first one while the patient was treated with H2-receptor antagonist for more than two months. Macroscopic appearance of the esophagus as well as of the rest of the upper GI tract was completely normal. Four biopsy specimens of the proximal and distal esophagus revealed changes suggesting GERD, while no changes suggesting esophageal eosinophilia were found (there were no eosinophils in the epithelium or in the submucosa, no microabscesses in the surface layers and no degranulation of eosinophils was found). The peak eosinophil count was < 5 per HPF. The patient continues with H2-blocker therapy and is symptom free.

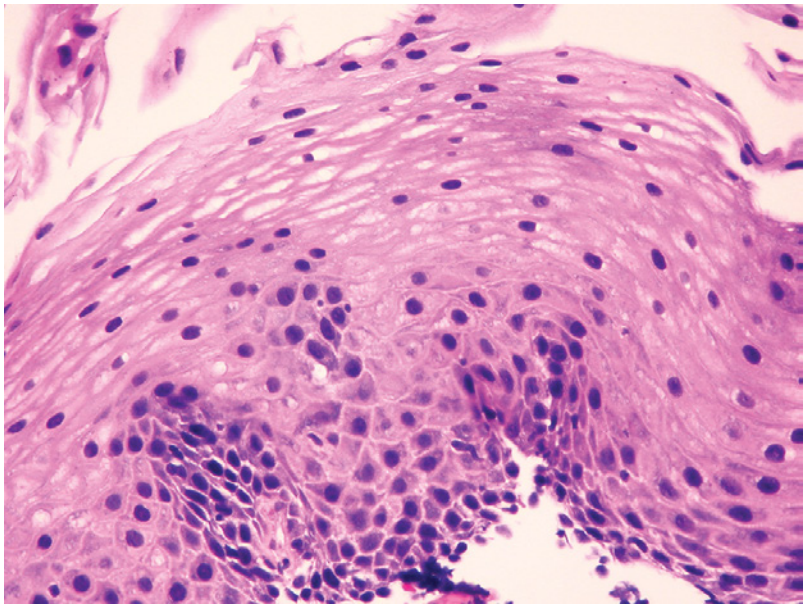

Figure 2: Control esophageal biopsy of our patient after treatment with H2-receptor antagonists, Kreyberg staining. There are no eosinophils, no microabscesses, basalification is absent.

3 Discussion

The presented case is interesting for two reasons. The first is day- and night--time urinary incontinence appearing for three times only a few days after starting PPI therapy and disappearing shortly after its cessation, regardless of whether pantoprazole or esomeprazole was used. The patient had never experienced urinary incontinence before and complete diagnostic workout for potential urologic or neurologic disorders was negative. Although potential "placebo" adverse reaction to drugs could be a possible explanation, it does not seem very probable, as there was no incontinence during a several-month therapy with H2-receptor antagonists ranitidine, and the boy was much too young to discriminate between pharmaceutical aspects of PPIs and H2-receptor antagonists. Therefore, urinary incontinence could be considered as a plausible but extremely rare adverse effect of therapy with PPIs.

PPIs have proven to have a very favorable safety profile. It is known that they can cause dark-colored urine, interstitial nephritis, urinary tract infection and frequent urination (20-22), but to the best of our knowledge and available data, this is the first report of a possible association between urinary incontinence and treatment with PPIs. The underlying mechanism remains unexplained. It has been revealed that both gastric and non-gastric type of hydrogen/potassium adenosine triphosphatase (H+/K+-exchanging ATPase) is present in various tissues including cochlear lateral wall, polymorphonuclear leukocytes, kidney, brain, placenta and colon but its functional role has not been well studied (14,23,24).

However, it is our second observation in this patient, the disappearance of both symptoms and esophageal eosinophilia with H2-receptor antagonist therapy that may be even more interesting. Esophageal eosinophilia is present in many different diseases of the esophagus, with GERD, EoE and PPI-REE being the most prevalent ones. Patient's symptoms were suggestive of GERD and they always practically disappeared with a short-term anti-secretory therapy. However, the symptoms of EoE, especially in young children, can be very atypical and practically indistinguishable from GERD symptoms (25,26). In addition, all other features, such as acid exposure within normal limits during 24-hour pH--monitoring, endoscopic appearance of the esophagus with longitudinal furrows and particularly histology findings, favored the diagnosis of EoE. On the other side, EoE is regarded an immune allergen-driven disease. With the exception of a weak family and potential personal (recurrent laryngitis) history as well as

slightly elevated immunoglobulin E level, there was no evidence supporting such etiology. All specific allergen hypersensitivity tests were negative and both clinical and histologic remission was achieved without therapies recognized as effective in EoE, elimination diet or steroids.

Since recognition that a subgroup of patients with typical features of EoE without evidence of GERD achieve clinicopathologic remission with PPI treatment, this has been defined as PPI-REE (5,6). In addition to the inhibition of the proton pump in the parietal gastric cells, a number of potential direct anti-inflammatory effects of PPIs have been suggested (16-19). It was demonstrated that PPIs inhibit the secretion of eotaxin-3, the most potent chemo-attractant for eosinophils, by esophageal epithelial cells (15). PPIs have been found to have anti-oxidant properties and direct effects on granulocytes, endothelial and epithelial cells that might prevent inflammation and they may reduce esophageal eosinophilia, at least in part, by inhibiting VCAM-1 production by esophageal endothelial cells (18). They inhibit the production of pro-inflammatory cytokines that recruit inflammatory cells to diseased tissues, block IL-8 production, possibly by interfering with the nuclear factor-κB and they decrease levels of a number of proinflammatory cytokines including IL-6, IL-8 and tumor necrosis factor-α (18).

The possibility that three very short treatment courses with PPIs, with two of them even before the first endoscopy revealing profound esophageal eosinophilia, played an important role in our case is practically negligible. Therefore, the remission should be attributed to the therapy with ranitidine. However, we could not find any evidence of anti-inflammatory properties of H2-receptor antagonists on esophageal mucosa other than their acid-secretion inhibition in the literature.

This brings us to reconsider the role of GERD, eventually even the one not reaching the arbitrarily set upper limits of normal esophageal acid exposure, as an important factor in the development of EoE. Several mechanisms which may predispose GERD patients for the development of EoE have been described, such as acid peptic damage to the tight junctions between epithelial cells affecting permeability of the esophageal epithelium for allergens (27,28), as well as enhancement of expression of adhesion molecules and production of inflammatory mediators and cytokines that attract and recruit inflammatory cells including eosinophils in the esophagus (29,30).

In conclusion, the presented case supports the potential importance of gastroesophageal reflux in the pathogenesis of EoE. The relations between GERD and EoE are only partially understood and worthwhile to be studied intensively in the future.

4 Consent

Written informed consent was obtained from the patient's legal guardian(s) for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

5 Authors' contributions

RO and JE carried out the clinical and laboratory evaluation of the patient, esophagogastroduodenoscopy and drafted the manuscript. ZDS carried out the histopathological examination of the biopsy specimen and co-drafted the manuscript.

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References

1. El-Serag HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut. 2013;63(6):871–80.
2. Brown LF, Goldman H, Antonioli DA. Intraepithelial eosinophils in endoscopic biopsies of adults with reflux esophagitis. The American Journal of Surgical Pathology. 1984;8(12):899–905.
3. Brown JF, Goldman H, Antonolio DA. Intraepithelial eosinophils in endoscopic biopsies of adults with reflux esophagitis. Am J Surg Pathol. 1984 Dec; 8(12):899–905.
4. Fujiwara Y, Sugawa T, Tanaka F, Tatsuwaki H, Okuyama M, Hayakawa T, et al. A Multicenter Study on the Prevalence of Eosinophilic Esophagitis and PPI-Responsive Esophageal Eosinophilic Infiltration. Internal Medicine. 2012;51(23):3235–9.
5. Kelly KJ, Lazenby AJ, Rowe PC, Yardley JH, Perman JA, Sampson HA. Eosinophilic esophagitis attributed to gastroesophageal reflux: Improvement with an amino acid-based formula. Gastroenterology. 1995;109(5):1503–12.
6. Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA. ACG clinical guideline: evidence based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Am J Gastroenterol. 2013 May;108(5):697–92; quiz 693
7. Papadopoulou A, Koletzko S, Heuschkel R, Dias JA, Allen KJ, Murch SH, et al. Management Guidelines of Eosinophilic Esophagitis in Childhood. Journal of Pediatric Gastroenterology and Nutrition. 2014;58(1):107–18.
8. Spergel JM. Eosinophilic esophagitis in adults and children: evidence for a food allergy component in many patients. Current Opinion in Allergy and Clinical Immunology. 2007;7(3):274–8.
9. Saugnanam KKN, Collins JT, Smith PK, Connor F, Lewindon P, Cleghorn G, Withers G. Dichotomy of food and inhalant allerge sensitation in eosinophilic esophagitis. Allergy. 2007;62:1257–60.
10. Furuta GT, Liacouras CA, Collins MH, Gupta SK, Justinich C, Putnam PE, et al. Eosinophilic Esophagitis in Children and Adults: A Systematic Review and Consensus Recommendations for Diagnosis and Treatment. Gastroenterology. 2007;133(4):1342–63.
11. Moawad FJ, Veerappan GR, Dias JA, Baker TP, Maydonovitch CL, Wong RKH. Randomized Controlled Trial Comparing Aerosolized Swallowed Fluticasone to Esomeprazole for Esophageal Eosinophilia. The American Journal of Gastroenterology. 2013;108(3):366–72.
12. Peterson KA, Thomas KL, Hilden K, Emerson LL, Wills JC, Fang JC. Comparison of Esomeprazole to Aerosolized, Swallowed Fluticasone for Eosinophilic Esophagitis. Digestive Diseases and Sciences. 2009;55(5):1313–9.
13. Jung DH, Yun G-W, Lee YJ, Jo Y, Park H. Clinicopathologic Analysis of Proton Pump Inhibitor-Responsive Esophageal Eosinophilia in Korean Patients. Gut and Liver. 2016;10(1):37.
14. Ritter M, Schratzberger P, Rossmann H, Wöll E, Seiler K, Seidler U, et al. Effect of inhibitors of Na+/H+-exchange and gastric H+/K+ATPase on cell volume, intracellular pH and migration of human polymorphonuclear leucocytes. British Journal of Pharmacology. 1998;124(4):627–38.
15. Cheng E, Zhang X, Huo X, Yu C, Zhang Q, Wang DH, et al. Omeprazole blocks eotaxin-3 expression by oesophageal squamous cells from patients with eosinophilic oesophagitis and GORD. Gut. 2013;62(6):824–32.
16. Huo X, Zhang X, Yu C, Zhang Q, Cheng E, Wang DH, et al. In oesophageal squamous cells exposed to acidic bile salt medium, omeprazole inhibits IL-8 expression through effects on nuclear factor-kappaB and activator protein-1. Gut. 2014;63(7):1042–52.
17. Zhang X, Cheng E, Huo X, Yu C, Zhang Q, Pham TH, et al. Omeprazole blocks STAT6 binding to the eotaxin-3 promoter in eosinophilic esophagitis cells. PloS one. 2012;7(11):e50037.
18. Kedika RR, Souza RF, Spechler SJ. Potential anti-inflammatory effects of proton pump inhibitors: a review and discussion of the clinical implications. Dig Dis Sci. 2009;54(11):2312–7.
19. Handa O, Yoshida N, Fujita N, Tanaka Y, Ueda M, Takagi T, et al. Molecular mechanisms involved in anti-inflammatory effects of proton pump inhibitors. Inflammation research : official journal of the European Histamine Research Society [et al]. 2006;55(11):476–80.
20. Simpson IJ, Marshall MR, Pilmore H, Manley P, Williams L, Thein HLA, et al. Proton pump inhibitors and acute interstitial nephritis: Report and analysis of 15 cases. Nephrology. 2006;11(5):381–5.
21. Drugs.com. (n.d.). Nexium side effects. Available from: http://www.drugs.com/sfx/nexium-side-effects.html-
22. Drugs.com.(n.d.).Pantoprazole side effects. Available from: http://www.drugs.com/sfx/pantoprazole-side-effects.html-
23. Shibata T, Hibino H, Doi K, Suzuki T, Hisa Y, Kurachi Y. Gastric type H+,K+-ATPase in the cochlear lateral wall is critically involved in formation of the endocochlear potential. AJP: Cell Physiology. 2006;291(5):C1038-C48.
24. Pestov NB, Romanova LG, Korneenko TV, Egorov MV, Kostina MB, Sverdlov VE, et al. Ouabain-sensitive H,K-ATPase: tissue-specific expression

of the mammalian genes encoding the catalytic alpha subunit. FEBS letters. 1998;440(3):320–4.
25. Mulder DJ, Hurlbut DJ, Noble AJ, Justinich CJ. Clinical features distinguish eosinophilic and reflux--induced esophagitis. J Pediatr Gastroenterol Nutr. 2013;56(3):263–70.
26. Aceves SS, Newbury RO, Dohil MA, Bastian JF, Dohil R. A symptom scoring tool for identifying pediatric patients with eosinophilic esophagitis and correlating symptoms with inflammation. Annals of Allergy, Asthma & Immunology. 2009;103(5):401–6.
27. Tobey NA, Carson JL, Alkiek RA, Orlando RC. Dilated intercellular spaces: A morphological feature of acid reflux— damaged human esophageal epithelium. Gastroenterology. 1996;111(5):1200–5.
28. Katzka DA. The Complex Relationship between Eosinophilic Esophagitis and Gastroesophageal Reflux Disease. Digestive Diseases. 2014;32(1–2):93–7.
29. Barthel SR, Annis DS, Mosher DF, Johansson MW. Differential Engagement of Modules 1 and 4 of Vascular Cell Adhesion Molecule-1 (CD106) by Integrins 4beta1 (CD49d/29) and Mbeta2 (CD11b/18) of Eosinophils. Journal of Biological Chemistry. 2006;281(43):32175–87.
30. Rafiee P, Theriot ME, Nelson VM, Heidemann J, Kanaa Y, Horowitz SA, et al. Human esophageal microvascular endothelial cells respond to acidic pH stress by PI3K/AKT and p38 MAPK-regulated induction of Hsp70 and Hsp27. AJP: Cell Physiology. 2006;291(5):C931-C45.