

Treatment of GERD

Bojan Tepeš
AM DC Rogaška,
Slovenia

1. Introduction

Gastroesophageal reflux disease (GERD) is a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications (Vakil, et al , 2006a). GERD results from the combination of excessive gastroesophageal reflux of gastric juice and impaired esophageal clearance of the refluxate. The three dominant pathophysiologic mechanisms causing gastroesophageal junction incompetence are: transient lower esophageal sphincter relaxations (tLESRs), a hypotensive lower esophageal sphincter (LES), and anatomic disruption of the gastroesophageal junction, often associated with a hiatal hernia. The dominant mechanism varies as a function of disease severity with tLESRs predominating with mild disease and mechanisms associated LES dysfunction and hiatus hernia predominating with more severe disease (Bardham CP, et al, 1995).

According to Montreal classification we divide GERD into esophageal and extraesophageal syndromes, with extraesophageal syndromes divided into established and proposed associations (Vakil,et al. 2006; figure 1,2).

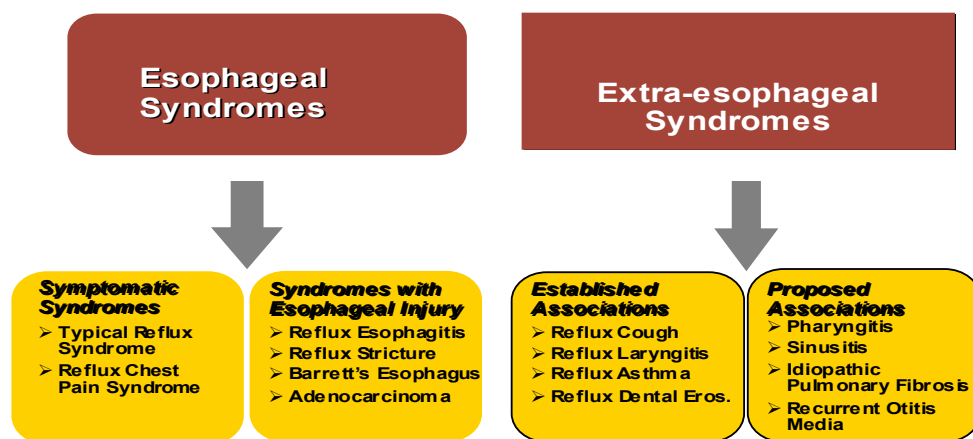


Fig. 1. Montreal classification of GERD

The prevalence of GERD is the greatest in developed world from 10 % in UK and Spain to 29 % in the USA (Dent, et al, 2005). Nonerosive reflux disease (NERD) is the most prevalent

form of GERD with prevalence between 50 % and 70 % (Johansson KE, et al 1986 ; Jones RH, et al.1995).According to Rome III. criteria NERD is further subdivided to thru NERD and functional heartburn (Drossman D, 2006; figure 2).

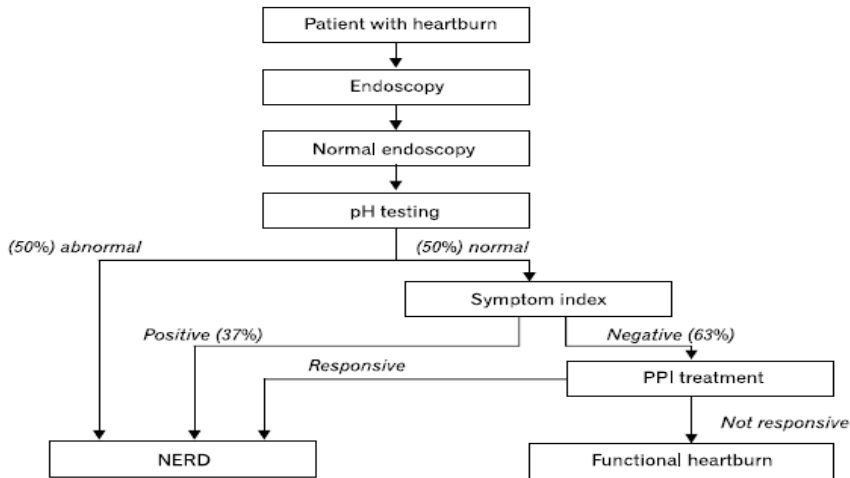


Fig. 2. Diagnostic algorithm for NERD

With medical therapy we can act on the acidity of refluxat (proton pump inhibitors - PPI, H2 blockers, antacids) or with surgery on mechanical reasons for reflux (laparoscopic or open surgical technics). At the moment we don't have medicines in routine clinical practice that can correct the basic reasons for pathologic gastric reflux into the esophagus. In this chapter I would like to address some questions about GERD therapy in different subtypes of GERD and in some specific conditions (gravidity) as well as about long term therapy of GERD and potential side effects of long term PPI therapy.

2. GERD therapy

In the medical management of GERD we can use a "step up" approach (beginning with lifestyle and dietary measures and increasing the treatment from antacids to H 2 blockers and finally to proton pump inhibitors or a "step down" approach (beginning with potent antisecretory agents- PPIs to achieve rapid symptom control and then incrementally decreasing the intervention until patients remain in remission).

We always have to inform patients about necessary lifestyle modifications and about use of antacids and alginates for acid breakthrough symptoms. PPIs are the therapy of choice for GERD patients.

2.1 Lifestyle modifications

GERD is a chronic disease with frequent relapses. Patients should be informed about preventive measures - lifestyle modifications that can have an important influence on their GERD symptoms (Kahrilas, et al, 2008).

Head of bed elevation for 6-8 inches is important for individuals with nocturnal or Extraesophageal syndromes. Patients should refrain from assuming a supine position after meals and avoid having meals three hours before bedtime, both of which will minimize reflux. Obesity is a risk factor for GERD, erosive esophagitis, and esophageal adenocarcinoma. However, improvement in symptoms following weight loss is not uniform. Nevertheless, because of a possible benefit, and because of its other positive effects on human health, weight loss should be recommended (Hampel H, et al, 2005). Patients should be informed that alcohol use and smoking should be stopped, because of its harmful effect on mucosa and because smoking diminishes salivation.

Other measures includes avoidance of reflux-inducing foods (fatty foods, chocolate, peppermint, and excessive alcohol) which may reduce lower esophageal sphincter pressure. Patient should selectively avoid food known to cause symptoms like colas, red wine, and orange juice (pH 2.5 to 3.9).

A systematic review of the articles published on lifestyle modification concluded that at the moment, data support only positive impact of weight loss and head of bed elevation. (Kaltenbach T, et al, 2006).

2.2 Medical therapy of GERD and NERD

The severity of symptoms does not correlate with the presence or with severity of subtypes of GERD (Smout AJPM, 1997).

Treatment of GERD should aim at the relief of symptoms and healing of mucosal injury. There is no difference in therapeutic approach to erosive esophagitis (ERD) or nonerosive esophagitis (NERD) patients.

Antacides and alginate antacids provide only temporal benefit and are ineffective in healing of esophageal mucosal injury. They can be used alone only in case of infrequent postprandial symptoms.

Prokinetic drugs enhance gastrointestinal motility. These drugs can theoretically be useful adjuncts in the treatment of GERD by increasing lower esophageal sphincter pressure, enhancing gastric emptying, or improving peristalsis. They can be used only in some special circumstances: in case of delayed gastric emptying or duodenogastroesophageal reflux (Kahrilas PJ, et al, 2008).

H₂ receptor antagonists (H₂ blockers) inhibit acid secretion by blocking histamine H₂ receptors on the parietal cell. H₂ blockers heal 52 % of patients with esophagitis compared to 8% with placebo. (NNT is 5 for H₂ blockers compared to placebo in healing of GERD) (Khan M, et al 2007, Moayyedi P & Talley NJ, 2006). The problem of H₂ blockers is tachyphylaxis (reduction in therapeutic effect) after one week of therapy. The therapeutic effect of H₂ blockers drop to approximately 50 % after 7 days of therapy (Sachs et al 2006).

Proton pump inhibitors (PPIs) are prodrugs which are activated in the stomach by a two step process. First step is conversion of PPI to its sulfenamide derivative and in the second step sulfenamid is protonated to benzimidazole, which binds irreversibly to the H⁺/K⁺ ATPase. That blocks the H⁺/K⁺ exchange and prevent parietal cell from producing acid. PPIs concentrate in the parietal cell secretory canaliculus, where pH is approximately 1,0 (the

second step in PPI activation needs pKa close to 1). Renal medulla and resorbative surface of bone (osteoclasts have proton pump) do not have a low pH enough to permit the second step of PPI activation. Elsewhere in the body PPIs follow first-order kinetics. Blood levels of PPIs decrease as the drugs are metabolized in the liver and then excreted primarily in the urine or stool (Shi S&Klotz U, 2008, Shin JM,&Sachs G, 2008, Sachs G, et al. 1995, Sachs G, et al 2006).

We have several PPIs with different daily doses recommended by manufacturer (table 1) NNT is 2 for PPI compared to placebo in healing of GERD (Khan M , et al 2007, Moayyedi P & Talley NJ, 2006).

- Delayed release:

Omeprazole	20 mg qd
Lansoprazole	30 mg qd
Rabeprazole	20 mg qd
Pantoprazole	40 mg qd
Esomeprazole	40 mg qd
- Immediate release: Omeprazole + bicarbonate 40 mg qd
- Dual delayed release: Dexlansoprazole 60 mg qd

Table 1. Different Proton pump inhibitors and recommended daily doses

PPIs inhibit only active pumps. A single dose of a PPI does not inhibit all pumps and does not result in profound inhibition of acid secretion. Acid production is inhibited with subsequent PPI doses, taking 5-7 days to achieve a steady state. Acid inhibition is never complete because of continued synthesis of new proton pumps. When PPIs are given twice daily, more active proton pumps are exposed to drug, and steady-state inhibition of gastric acid secretion is achieved more rapidly and more complete (Bell NJV, et al 1992).

PPIs are usually prescribed once daily, usually in the morning. Food affects the bioavailability of each molecule, so it is our practice to recommend that all PPIs should be given prior to meals for optimal efficacy. Results of intragastric pH studies showed that superior daytime pH control (time intragastric pH>4) was seen when the PPI was taken before breakfast compared to after meal. PPIs are responsible for inhibiting gastric acid secretion, thereby decreasing potential damage to the esophageal mucosa. In addition, by raising gastric pH, the conversion of pepsinogen to pepsin, another player of mucosal damage, is inhibited. (Hatlebakk JG, et al , 2000).

In a large meta analysis of 136 randomized controlled trials involving 35 978 patients with esophagitis, the healing rate among those patients treated with PPIs was 83 %. In all trials antacids were used to treat breakthrough symptoms. There were no major differences in efficacy among standard dose of various PPI.

PPIs are better in healing erosive esophagitis than in controlling GERD symptoms. In a large patient unmet needs survey, patients on PPIs reported the highest level of satisfaction (57,9 %) , followed by H-2 blockers (46,1 %; Crawley MS&Schmitt CM, 2000).

FDA approved dosing of PPIs in GERD patients is once daily. In our daily practice we know that substantial number of patients (32 %) on once daily PPI continue to demonstrate abnormal distal esophageal acid exposure and this proportion can be lowered to less than 10 % by increasing standard therapy of PPI to BID (Charbel S, et al , 2006). There is no supporting data for the use of nocturnal dose of a H₂ blocker to twice daily PPI therapy (Vakil N, et al , 2006b). Dosing a PPI before dinner is significantly more effective for nocturnal acid control than dosing before breakfast (Hatlebakk JG,et al, 1998) .The American College of Gastroenterology currently recommends dosing PPIs before evening meal if nighttime acid controlled is needed (DeVault KR& Castell DO , 2005) Because of the short plasma half-life of the PPIs, loss of nocturnal acid control occurs approximately 7 hours after evening dose (Peghini PL,et al 1998).

Patients with GERD (erosive or nonerosive) should be treated with standard dose of PPIs for at least 2-3 months.

The proportion of NERD patients responding to a standard dose of PPI is approximately 20-30% lower than what has been documented in patients with erosive esophagitis. In a systematic review of the literature, PPI symptomatic response pooled rate was 36.7% (95% CI: 34.1-39.3) in NERD patients and 55.5% (95% CI: 51.5-59.5) in those with erosive esophagitis.(Dean BB , et al , 2004). The greater the distal esophageal acid exposure, the higher the proportion of NERD patients reporting symptom resolution.(Lind T, et al, 1997) Patients with NERD also demonstrate longer lag time to sustained symptom response when compared to patients with erosive esophagitis (2 to 3-fold). Furthermore, patients with NERD demonstrate similar symptomatic response to half and full standard dose of PPI, unlike patients with erosive esophagitis who demonstrate an incremental increase in healing and symptom resolution with standard dose compared to half dose of PPIs (Richter JE,et al , 2000). The reason for the differences in therapeutic response between NERD and erosive esophagitis is primarily due to the common inclusion of functional heartburn subjects in the NERD group. However, because most NERD patients demonstrate only modest abnormal esophageal acid exposure, even after excluding functional heartburn patients, the NERD symptomatic response rate to PPI remains lower that what has been observed in erosive esophagitis patients (Hershovici T & Fas R, 2010).

The most common side effects of proton-pump inhibitors are headache, diarrhea, constipation, and abdominal pain. Although in clinical trials these symptoms were not significantly more common with proton-pump inhibitors than with placebo, they have been confirmed in some patients with a test-retest strategy.

2.3 GERD and pregnancy

The smooth muscle relaxation as well as the increased intraabdominal pressure that occurs during pregnancy predisposes to gastroesophageal reflux (Katz PO& Castell DO, 1998). The greatest experience with pharmacologic acid-suppressive therapy in pregnant women has been with the H₂ receptor antagonists ranitidine and cimetidine, which appear to be safe during pregnancy (Larson JD, et al, 1997). There is less experience using proton pump inhibitors during pregnancy, but they are probably safe. A meta-analysis of seven studies (involving a total of 1530 exposed and 133,410 non-exposed pregnant women) found no significant difference in the risk for major congenital birth defects, spontaneous abortions, or preterm delivery (Gill SK,et al, 2009).

2.4 Medical therapy of extraesophageal syndromes

Astma, cronic cough, laryngitis and non cardiac chest pain (esophageal syndrome) are among the conditions where an association with GERD is well established. On the other side GERD can be just one of possible etiologic factors for that diseases. The causal relationship of GERD with with this nonspecific syndromes in absence of a concomitant esophageal GERD syndrome remains controversial and unproven.

In the pro-GERD study that included 6215 patients in Europe 34,9 % of patients with GERD and 30,5 % of patients with NERD have some Extraesophageal Syndromes (Jaspersen D, et al. 2003).

In patients with chronic cough, asthma and laryngeal symptoms PPI standard dose BID is usally prescribed. With this approach likelihood of normalizing esophageal acid exeposure is 93% - 99 % (Charbel S, et al, 2005). Therapy is usually prescribed for 3 months. Studies to support this approach are open label and uncontrolled (Kahrilas Pa, et al, 2008; Tepeš B, 2006). Patients with extraesophageal syndromes can be treated with PPIs only if concomitant esophageal GERD syndrome is present.

2.5 NCCP

Chest pain indistinguishable from ischemic cardiac pain can be caused by GERD - noncardiac chest pain / NCCP (Vakil, et al, 2006a). Community prevalence rates of NCCP are from 23% to 33% (Locke GR, et al, 1997; Eslick GD, et al, 2003). In patients with chest pain ischemic heart disease must be excluded first, GERD is the next most likely pathology. PPIs BID for 8 weeks are recommended in patients with NCCP. Those patients with a good therapeutic response need maintenance therapy with PPIs. If patients do not response to PPIs manometry testing is necessary and specific therapy for motility disorders if proven are needed.

2.6 Maintenance therapy of GERD

Patients with erosive esophagitis have up to 80 % chance of recurrence within 12 months of treatment discontinuation (Johnson DA, et al, 2001; Vakil NB, et al, 2001). GERD recurrence is dramatically decreased by PPI treatment (Donnellan C, et al, 2005, Tepeš , et al, 2009). A systematic review of 17 studies (15 of which were randomized controlled trials) showed that subjects with either nonerosive or uninvestigated GERD did well with on-demand regimens (Pace F, et al, 2007). In study where patients with known erosive esophagitis after being healed with PPI therapy were randomized to either continuous or on-demand therapy, recurrence of erosive disease was higher in subjects treated with on-demand compared continuous therapy (42% vs 19% at 6 months; $P < .00001$). On-demand therapy cannot be recommended for maintaining healing of erosive esophagitis (Sjostedt S, et al ,2005).

In our experience patients with GERD LA C and LA D need standard PPI dose or even higher dose as a maintenance therapy, patients with GERD LA B need standard dose of PPI and in those with GERD A can be put on half a standard dose of PPI (Figure 3,4 Tepeš, et al 2009).

Maintenance therapy should be prescribed to all patients with Barrett oesophagus. Some uncontrolled studies showed that PPI therapy can in part prevent progression of Barrett esophagus to dysplasia and adenocarcinoma (El Serag HB, et al, 2004).

Recommendations regarding maintenance therapy in group of patients with Extraesophageal syndromes are based on expert opinion , because we do not have data from prospective control trials. Step-down therapy should be attempted in all patients with extraesophageal reflux syndromes after empirical twice-daily three months PPI therapy. Continuing maintenance PPI therapy should be predicated on either the requirements of therapy for concomitant esophageal GERD syndromes or extraesophageal syndrome symptoms. In both cases, maintenance therapy should be with the lowest PPI dose necessary (Kahrilas PJ, et al, 2008) .

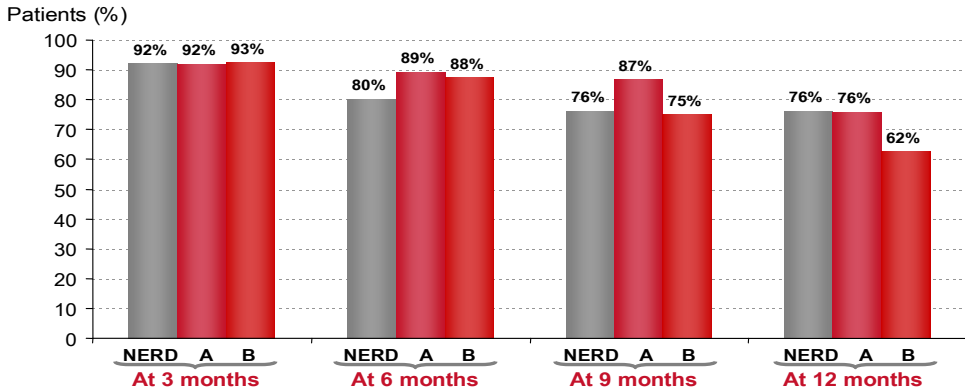


Fig. 3. Cumulative percent of patients in remission in group A2 (omeprazole 10 mg daily) at 3, 6, 9, and 12 months of maintenance therapy by baseline number of patients with a specific grade of disease (intention-to-treat, ITT)

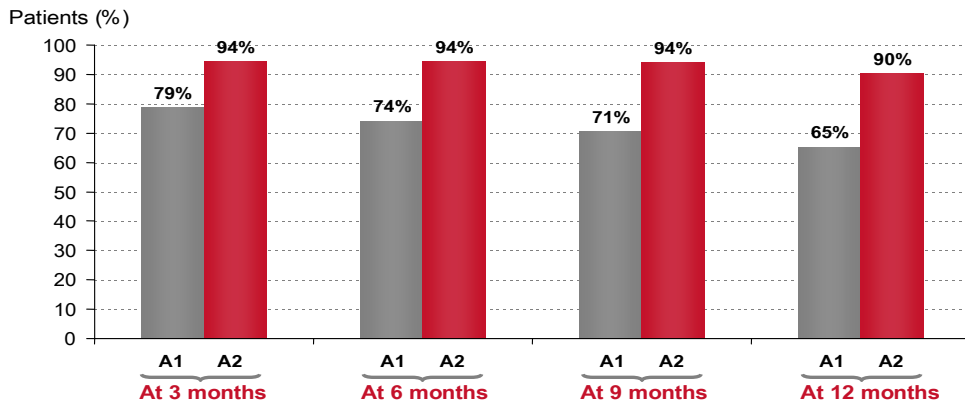


Fig. 4. Cumulative percent of patients with esophagitis grade A in remission in groups A1 (omeprazole 20 mg on demand) and A2 (omeprazole 10 mg QID) at 3, 6, 9, and 12 months of maintenance therapy by number of patients with esophagitis grade A concluding the study in these groups (per-protocol)

2.7 PPI refractory GERD

Patient with GERD are named refractory to PPIs when they do not respond to PPI standard dose BID . Potential etiologies may be gastrointestinal (GI) or non-GI related. The GI etiologies can be esophageal or nonesophageal, and the former may be reflux or nonreflux related.

There are 3 major categories of reflux related causes:

1. First category is reflux with ongoing acid exposure. Etiologies include incorrect medication dose timing, medication noncompliance, residual pathologic acid secretion, rapid PPI metabolism, a hypersecretory state, a significant anatomic abnormality like a large hiatal hernia, excess reflux during tLESRs, or defective esophageal mucosal barrier function.
2. Second category is reflux of nonacid material from either the stomach or the duodenum (e.g., bile).
3. Third category is reflux of normal amounts of weakly acidic or alkaline contents into a hypersensitive esophagus.

The non-reflux-related esophageal causes include dysmotility syndromes such as achalasia, esophageal spasm, or scleroderma; eosinophilic esophagitis; pill esophagitis; and infectious esophagitis.

In the absence of structural, motility, or inflammatory causes, functional heartburn or function chest pain should be considered.

Nonesophageal causes of reflux-type symptoms include gallbladder disease, malignancy in the GI system or surrounding organs, cardiovascular disease, and musculoskeletal disease (Dellon ES & Shaheen NJ, 2010).

After we are sure that patient adheres to the treatment recommendations and PPIs are prescribed BID, further diagnostic procedures are necessary. It is beyond the scope of this Chapter to discuss this procedures in more detail.

2.8 Surgery and GERD

Surgery is a therapeutic option in patients with GERD if GERD has been objectively confirmed. Surgery is an option in individuals who:

1. Have failed medical management (inadequate symptom control, several regurgitation in case of big hiatal hernias, medication side effects).
2. Do not want to be on life long PPI treatment.
3. Have extraesophageal GERD syndrome (asthma, hoarseness, chronic cough, NCCP, aspiration) and have a positive response to PPI therapy.

Preoperatively workup includes: esophagogastroduodenoscopy, pH-metry, esophageal manometry, barium swallow. Patient should be operated in high volume centers with experiences in GERD laparoscopic surgery. The Nissen fundoplication has, in many series, been found superior to other procedures, with symptomatic improvement occurring in 85 % to 90 % of patients. This procedure originally involved passage of the gastric fundus behind the esophagus to encircle the distal 6 cm of the esophagus. Most surgeons choose to perform

a loose ("floppy") Nissen fundic wrap that is about 1 to 2 cm in length including a posterior crural repair. (Ellis FH Jr, 1992). In patients with weak propulsive peristalsis a partial fundoplication is recommended (anterior fundoplication, Toupet partial posterior fundoplication).

Up to 20 % of patients will have postoperative dysphagia or gas-bloat syndrome and up to 10 % will need revisional surgery after laparoscopic fundoplication (Lamb PJ, et al. 2009).

Several randomized controlled trials have compared surgical therapy with medical therapy with a follow-up from 1 to 10,6 years. The majority of studies showed that patients need PPIs after operation in up to 21 % of cases, one study showed that this percentage is much higher -62 % (Spechler SJ, et al, 2001; Dassinger MS, et al, 2004; Kamolz T, et al. 2005; Zaninotto G, et al, 2007).

There has been some randomized controlled trials evaluating cost between medical (omeprazole) and surgical therapy (open total and partial fundoplication) over a period up to 10 years. One modeling study found that the cost-equivalency point for medical and surgical therapy was at 10 years (Heudebert GR, et al, 1997) , whereas another still reported lower cost with medical therapy at 10 years (Arguedas MR, et al, 2004).

Barrett's esophagus is present in 1.65% of the general population, in 8.6% of symptomatic GERD patients presenting to a tertiary care center, and in 10.8% of patients undergoing antireflux surgery . Barrett's esophagus (neoplasia not present) is associated with a significantly increased risk for developing esophageal adenocarcinoma (approximately 100-fold) over that of the general population (Ronkainen J, et al, 2005; Rex DK, et al, 2003, Attwood SE, et al, 2008). Antireflux surgery does not alter the need for continued surveillance endoscopy in patients with Barrett's esophagus. The available evidence is inconclusive about the effect of antireflux surgery on patients with Barrett's esophagus.

3. Side effects of long term PPI therapy

The risk of minor adverse effects from proton pump inhibitors use is 1%-3%, with rates of withdrawal from clinical research studies being 1%-2%, with no significant differences noted between the PPIs (Langtry HD, & Wilde ML, 1997; Laine L, et al 2000). The most common side effects of PPI therapy are: headache, diarrhea and abdominal pain with frequency up to 4 %, what is less than in H₂ blockers (Relly JP, 1999).

Serious adverse effects are rare. Acute interstitial nephritis is a rare complication of PPI treatment (a class effect) which can be potentially reversible if we think on it early enough. Otherways it can lead to acute renal failure. PPIs' metabolites most probably act as a hapten in an autoimmune process in renal interstitium (Geevasinga N, 2006). Hepatitis or disrupted visual disturbances are very rare adverse effect of PPI use (Koury SI, et al ,1998; Garcia Rodrigues LA, et al 1996).

PPI are very frequent used as a maintenance therapy in some indications listed above. They are also very frequently used without proper indication, what can be a reason for mayor concern. Up to 60 % of PPI prescriptions, especially in primary care, are without appropriate indications (Nardino RJ, et al, 2000 ;Batuwitage BT, et al, 2007).

Long term PPI use can have influence on human physiology in different ways:

1. long term hypochlorhydria can influence Ca, Fe, Mg, Vit B12 absorption, and can increase risk for enteric infections
2. hypergastrinemia can have an effect on parathyroid gland, enterochromaffin cells, or gastric histology
3. interactions with other drugs through cytochrome P450
4. idiosyncratic effects

3.1 Effects of PPIs on absorption of minerals and vitamins

Calcium - Calcium solubility is important for its absorption. Acid facilitates release of ionized calcium from insoluble calcium salts (Nordin BE, 1997; Sheikh MS, et al 2007). Several studies have tried to evaluate the importance of acid for calcium absorption. Four out of five studies found decreased absorption of calcium in older patients on PPI therapy (Graziani G, et al, 1995; Graziani G, et al, 2002; Hardy P, et al, 1998; O'Connell MB, et al, 2005; Serfaty-Lacrosniere C, et al, 1995).

Iron- Nonheme iron is a major source of dietary iron and is predominantly in the form of ferric iron. Iron absorption is directly related to the capacity of gastric juice to release iron contained in food (Chorad ME & Shade SG, 1968; Bezwoda W, et al, 1978).

In a group of patients with Zollinger Ellison syndrome on long term PPI therapy for an average of 6 years, no association was found with decreased stores of body iron or iron deficiency (Stewart CA, et al 1998).

Magnesium - several cases of hypomagnesaemia were associated with long term PPI treatment. Prompt resolution of normal magnesium concentration occurred in two weeks after PPI discontinuation or switch to H2 receptor antagonist. The pathophysiologic mechanism for magnesium deficiency is not understood (Epstein M, et al, 2006; Cuny T & Disdsanayake A, 2008;).

Vitamin B 12- gastric acid and pepsin release vit B12 from protein in food and allows vit B12 to bind to R protein and to intrinsic factor in duodenum (Doscherholmen A & Swaim WR, 1973; Festen HP, 1991). The majority of studies did not find that longterm PPI use reduce the vitamin B12 reabsorption. Only in the study which included older patients with Zollinger Ellison syndrome, vitamin B 12 serum concentration was significantly reduced. (Schenk BE, et al, 1999; Insogna KL, 2009; McColl KE, 2009;).

3.2 Effect on bone metabolism

Long term PPI therapy can affect bone metabolism and cause osteoporosis through three potential mechanisms:

- calcium absorption,
- hypergastrinemia
- vitamin B12 deficiency.

The effect of PPI therapy on calcium metabolism has been already described. Hypergastrinemia can lead to parathyroid hyperplasia which can increase bone resorption and reduce cortical bone mineral density, but clinical data are limited. (Mizunashi K, et al,

1993). Vitamin B12 is involved in osteoblast activity and bone formation. Patients with marginally low levels of vitamin B12 were 4.5 fold more likely to have osteoporosis than those with normal levels (Stone KL, et al, 2004; Tucker KL; Dhonukshe-Rutten RA, et al, 2003). Vitamin B12 deficiency can lead to neurologic complications that can also increase the risk of falls (Sato Y, et al, 2005).

Several epidemiologic studies on the use of PPIs and risk for osteoporotic hip fractures have been published. A population based study using UK general practice research database (UK GPRD) observed a 44 % increased risk for hip fractures among patients older than 50 years on PPIs, with significant dose- and duration- response effects (Yang YX, et al, 2006). A population based study from Canada (Targownik LE, et al, 2008) associated long-term PPI exposure with a significant increase in risk of osteoporotic fractures (> 7 years of PPI exposure: OR, 1.92; 95% CI, 1.16 -3.18; hip fractures > 7 years of PPI exposure: OR, 4.55; 95% CI, 1.68 -12.29). The problem of retrospective studies is bias due to confounding. In the nested case control studies using UK GPRD, Kaye et al did not find increased risk of fractures in patients on PPI therapy. Factors such as osteoporosis, vitamin B12 deficiency and prior fractures were among the leading reasons for exclusion, what makes it difficult to generalize the findings (Kaye JA & Jick H. 2008). Targownik et al conducted a cross-sectional and longitudinal analysis of patients referred for dual-energy X-ray absorptiometry scan. They did not associate PPI therapy with prevalent osteoporosis or with significant decreases in BMD over time (Targownik LE, et al, 2010).

3.3 PPIs and infection

Gastric acid acts as a barrier that keeps bacteria from colonizing the upper gastrointestinal tract. The increased bacterial colonization of the stomach observed in PPI users might be associated with pulmonary micro aspiration (Laheij RJ, et al, 2004; Theisen J, et al, 2000). Two retrospective studies found an increased risk for community-acquired pneumonia with current use of PPI (Laheij RJ, et al, 2004; Gulmez SE, et al, 2007). Both studies observed an inverse relationship between the magnitude of the association and the duration of PPI exposure. The weakest association was observed among current users who used the drug for the shortest duration. A third study conducted using the UK GPRD did not find an association between current use of PPIs and a significant increase in risk of community-acquired pneumonia. (Sarkar M, et al, 2007) This study accounted for several highly influential confounders that were not considered in the previous studies. It also showed the inverse relationship between duration of current PPI therapy and risk of pneumonia by demonstrating the greatest increase in risk of community-acquired pneumonia in individuals who were issued a new PPI prescription in the past 48 hours. A similar pattern of risk increase was observed with H2RAs. These observations are inconsistent with a causal association mediated by acid suppression or immunosuppression. In fact, they indicate a protopathic bias (ie, drugs given to relieve early symptoms might be temporally associated with the subsequent illness).

Several studies and a meta analysis by Leonard have observed a 2 to 3 fold increase in the risk of nosocomial or community associated *Clostridium difficile* or other enteric infections in patients on PPI therapy (Leonard J, et al, 2007; Wilcox MH, et al, 2008; Elphick DA, et al, 2005). All the studies are retrospective and some have small number of patients included.

At the moment no PPIs given as once-daily dose truly increase gastric pH >4 for more than 15 hours per day. A large randomized control trials are needed before PPIs can be blamed for increased infection risk.

3.4 PPIs and gastric mucosa

Fundic gland polyps can appear after long term PPI therapy. Patients on PPIs have fourfold increased incidence of fundic glands polyps, which have no malignant potential (El-Zimaity HM, et al 1997; Raghunath AS, et al, 2005;).

If a patients on PPI therapy have *Helicobacter pylori* (*H pylori*) infection, antrum predominant inflammatory phenotype can change to corpus predominant, what can accelerate atrophy and intestinal metaplasia. (Uemura N, et al, 2000). The first Maastricht Consensus recommended *H pylori* eradication in all GERD patients before they are embarked to PPI maintenance therapy (EHPG, 1997).

H pylori eradication may cause regression of gastric atrophy or intestinal metaplasia (Tepes B, et al 1999; Sung JJ, et al 2000; Rocco A, et al, 2002; Ito M & Haruma K, 2002).

Mild / modest hypergastrinemia is a physiologic response to reduction in acid secretion due to PPI therapy. Diffuse linear or micronodular hyperplasia of enterochromaffin like cells is observed in 10 % to 30 % of patients on chronic PPI therapy, mainly in *H pylori* positive patients. Dysplasia or carcinoid have never been described in long term PPI users (Solcia E, et al, 1992; Genta RM, et al, 2003).

Gastrin has trophic effect on tissues through the gastrointestinal tract (Wang TC, et al, 1996). In several studies no increase in colorectal polyps or cancer have been noticed in patients on maintenance PPI therapy (Robertson DJ, et al, 2007; Singh M, et al, 2007; Van Soest EM, et al, 2008).

3.5 PPIs and clopidogrel

PPIs are metabolized by hepatic cytochrome P 450 system, predominantly by CYP2C19, and to lesser extent by CYP3A4 (Ishiazaki T& Horai Y, 1999). Clopidogrel is a pro-drug converted to an active metabolite by cytochrome P450 CYP2C19. Clopidogrel active metabolite irreversibly binds to the platelet adenosine diphosphate P2Y receptor and inhibits platelet aggregation (Gurbel PA, et al, 2009). The common metabolic pathway can theoretically be a reason for drug-drug interaction that can have an impact on clopidogrel activity.

The OCLA study first showed that omeprazole significantly decreased clopidogrel inhibitory effect on platelet P2Y₁₂ as assessed by VASP phosphorylation test (Gilard M, et al, 2008). In in vitro study Di Angiolillo found that metabolic drug-drug interaction exists between clopidogrel and omeprazole but not between clopidogrel and pantoprazole (Angiolillo DJ, et al, 2011).

Several retrospective studies pointed out that concomitant use of PPI and clopidogrel may be associated with adverse cerebrovascular events and myocardial infarction (Gupta E, et al, 2009; Ho PM, et al, 2009; Juurlink DN, et al, 2009; Pezalla E, et al, 2008; Rassen JA, et al, 2009). Meta analysis of 13 studies by Kwork showed no significant association between PPI

use and clopidogrel and overall cerebrovascular or cardiovascular mortality (Kwork CS, et al, 2010).

The only two randomized prospective clinical trials, Triton TIMI 38 and Cogent (O'Donoghue ML, et al, 2009; Bhatt DL, et al, 2010) did not find any association between PPI use and risk of cerebrovascular or cardiovascular morbidity or mortality. Cogent data indicated that use of omeprazole with clopidogrel reduced the risk of gastrointestinal events compared with clopidogrel plus placebo, without increasing the risk of cardiovascular events.

4. Conclusions

PPIs are the therapy of choice for GERD patients. Usually PPIs are prescribed QID for two to three months. One third of patients will need PPI BID. All GERD patients with Extraesophageal syndromes will need PPI BID for three to six months. Patients should be informed about lifestyle modifications and use of antacids for acid breakthrough. Those patients with ERD, Extraesophageal syndromes and Barrett esophagus need maintenance treatment with the lowest dose of PPI that keep them in remission.

Surgery is a therapeutic option for patients who do not have complete therapeutic response with PPI therapy, who do not want to take PPIs lifelong or for those with proven GERD and Extraesophageal syndromes. Long term therapy can have some side effects especially on bone metabolism and can increase risk of enteric infections. The majority of long term side effects data are from epidemiologic or retrospective studies. To be able to clearly answer those questions we need prospective randomized controlled studies.

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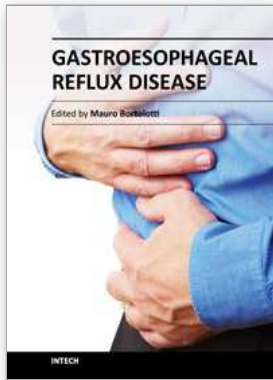
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Gastroesophageal reflux disease affects many patients. This disease not only lowers their quality of life, but it also threatens some of them with an underhand risk of cancer. Additionally, it becomes an economic burden for the patients and society. The aim of this book on gastroesophageal reflux disease is to provide advice and guidance to gastroenterologists to help them understand and manage some aspects of this proteiform disease.

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Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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Phone: +86-21-62489820
Fax: +86-21-62489821

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