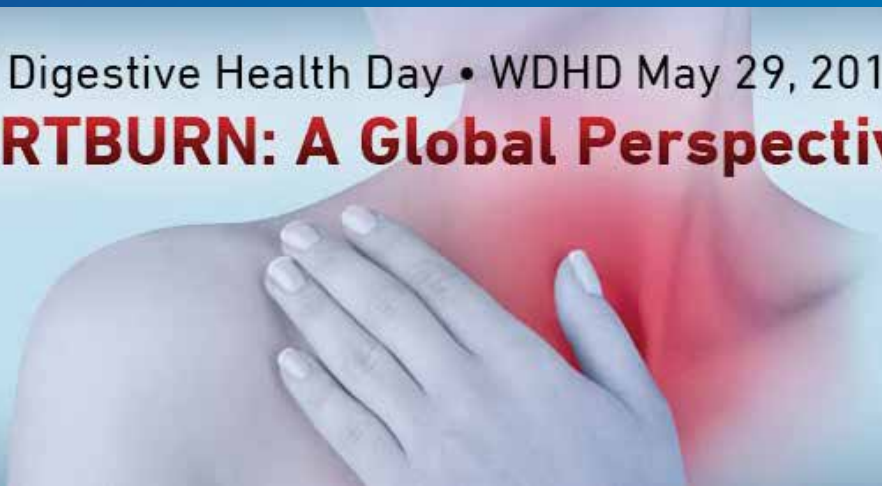World Digestive Health Day • WDHD May 29, 2015
HEARTBURN: A Global Perspective

WGO Handbook on HEARTBURN:
A Global Perspective

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HEARTBURN

Message from the Chair

Heartburn has been identified, in numerous high-impact guidelines, as one of the cardinal symptoms of gastro-esophageal reflux disease (GERD). Indeed, for practical purposes, heartburn, with or without regurgitation, is considered to be diagnostic of GERD, at least as a basis for initial management.

The prevalence of GERD is increasing worldwide although there are marked differences in the reported prevalence, ranging from 2.5% to 6.6% in Eastern Asia up to 13.8% to 25.8% in North America. The reason for the increasing prevalence of GERD is not entirely clear, but it appears to be correlated with the increasing prevalence of obesity in many countries and perhaps to other dietary factors. GERD is associated with a significant impact on health-related quality of life and reduction in personal and work-related productivity; it is also associated with a greater risk of Barrett's esophagus, a pre-malignant condition that may progress to esophageal adenocarcinoma. Fortunately, GERD can generally be treated safely and effectively with acid suppression medications whilst surgical anti-reflux therapy is also effective. However, the investigation and treatment of GERD can be costly and the management of GERD patients has to be optimized in many jurisdictions in the context of the many other pressures on the healthcare system.

Heartburn is thus the key presenting symptom of a very common condition – GERD – that has major implications for individuals and healthcare systems. Despite this, the sensitivity and specificity of heartburn rarely exceed 70-75% for the diagnosis of GERD; a substantial proportion of GERD patients do not have heartburn and, conversely, a substantial proportion of individuals with heartburn do not have GERD. It is, therefore, important to recognize that heartburn may be the presenting feature of other conditions ranging from functional heartburn to eosinophilic esophagitis and motility disorders such as achalasia, as well as extra-esophageal conditions, including ischemic heart disease. Furthermore, although the term 'heartburn' is widely recognized, it may be understood differently by different patients and healthcare providers in different linguistic, social and cultural settings.

The World Gastroenterology Organisation (WGO) wishes to raise awareness of heartburn and to provide a broad overview on this common symptom by providing gastroenterologists and, hence their patients and the lay public, with an understanding of the latest basic and clinical research in the pathogenesis, investigation and treatment of esophageal symptoms. "Heartburn: A Global Perspective," the WGO campaign for World Digestive Health Day 2015, seeks to translate research into clinical practice and facilitate communication between healthcare providers, healthcare payers and heartburn sufferers to ensure that patients receive appropriate dietary and lifestyle advice as well as appropriate investigations and treatment relevant to their condition and circumstances. The WGO's task will be supported by the development of educational and training materials around the world in collaboration with WGO Member Societies and by the concurrent development and publication of the WGO Cascades Guidelines on the Management of Gastroesophageal Reflux Disease.

My colleagues and I from the WDHD 2015 Steering Committee wish to thank you for a productive and successful campaign in providing a global perspective on the management of heartburn.

Yours sincerely,

David Armstrong, MA, MB BChir
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Chair, WDHD 2015

2015 Steering Committee

The World Digestive Health Day Campaign is led by the following individuals representing a global view and expertise in heartburn. They will guide the course of the campaign, leading in the development of tools and activities throughout 2015 and beyond.

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From the Past Chair and Vice Chair of the WGO Foundation

World Digestive Health Day (WDHD) was initiated several years ago by the World Gastroenterology Organisation in order to highlight important global issues in digestive diseases. As WDHD has evolved over the years it has developed from a one day event to a year-long campaign which engages with gastroenterologists, doctors, health care professionals and the general public on many aspects of the prevalence, prevention, diagnosis and management of common gastrointestinal and liver symptoms and disorders. Through direct collaboration with our member societies in over 100 countries around the world and with the support of other professional societies with similar interests, non-governmental agencies, governments and industry, we have helped to promote understanding and raise awareness on these issues.

It may come as a surprise to many that, up until this year, WGO has not addressed one of the most common gastrointestinal symptoms in the world: heartburn. In this handbook, Professor David Armstrong and his team of international experts set out to rectify this omission. This is an opportune time to address this symptom and its related disorders given that we now have so much information on the varying prevalence, clinical presentation and impact of heartburn in different areas of the world. Indeed, it turns out that heartburn and its related syndrome, gastroesophageal reflux disease (GERD), represents a wonderful example of variations in disease expression, not only in different populations, but also between individuals in the same population. These variations have considerable implications for the assessment and management of heartburn; for example, the approach to a middle aged male from Western Europe or North America with a long history of heartburn will be very different to how a young female from China will be investigated and managed. We all have much to learn from these geographical and inter-individual variations in disease phenotype associated with a single, though highly prevalent, symptom: heartburn. This very same symptom provides a perfect platform for the CASCADE approach developed and honed by the WGO guidelines committee over the past decades and, through this handbook, the task force presents a monograph on heartburn that will resonate with WGO members worldwide.

On behalf of the WGO Foundation we congratulate Professor Armstrong and the 2015 Steering Committee and fellow authors on this wonderful work which we hope that you will not only enjoy but find helpful.

Sincerely,

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Past Chair, WGO Foundation

Richard Hunt, MD
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Investigations in Heartburn

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Heartburn and regurgitation are classic symptoms of gastro-esophageal reflux disease (GERD). Investigating GERD remains a challenge as both invasive methods and symptom-based strategies have limitations.

A large number of tests is available for evaluating patients with GERD. Many times, these tests are unnecessary because the classic symptoms of heartburn and acid regurgitation are sufficiently specific to identify reflux disease and begin medical treatment. However, this is not always the case and, on occasion, the clinician must decide which test to choose to make a diagnosis in a reliable, cost-effective and timely manner.

Questionnaires

Current international guidelines recommend symptom-based diagnosis and therapy unless alarm symptoms such as dysphagia, weight loss or hemorrhage mandate prompt endoscopy.

Consequently, there is a need for optimizing the management of GERD patients by implementing symptom based management algorithms, preferably facilitated by a patient-completed questionnaire. Several different questionnaires have been developed to facilitate the diagnosis of GERD, but many of them lack proper validation or lack the simplicity required to be an integrated part of routine care. The GerdQ is a self-administered six-item questionnaire that was recently developed by combining six questions from three different validated patient reported outcome (PRO) questionnaires (GERD Impact Scale – GIS; Gastrointestinal Symptom Rating Scale – GSRS; Reflux Disease Questionnaire – RDQ) to improve and standardize symptom-based diagnosis and evaluation of treatment response in patients with GERD.

Endoscopy

Upper endoscopy is commonly used in the diagnosis and management of GERD. Evidence demonstrates that it is indicated only in certain situations; inappropriate use generates unnecessary costs and exposes patients to harm without improving outcomes.

After a review of evidence regarding the indications for, and yield of, upper endoscopy in GERD, the Clinical Guidelines Committee of the American College of Physicians recommended that upper endoscopy is indicated for:

1. Heartburn and alarm symptoms (dysphagia, bleeding, anemia, weight loss, recurrent vomiting).

2. Typical GERD symptoms that persist despite a therapeutic trial of 4 to 8 weeks of twice-daily proton-pump inhibitor (PPI) therapy.
   Severe erosive esophagitis after a 2-month course of PPI therapy to assess healing and rule out Barrett's esophagus. Recurrent endoscopy after this follow-up examination is not indicated in the absence of Barrett's esophagus.
   A history of esophageal stricture with recurrent symptoms of dysphagia.

3. Men >50 years with chronic GERD symptoms (>5 years) and additional risk factors (nocturnal reflux symptoms, hiatal hernia, elevated body mass index, tobacco use, intra-abdominal distribution of fat) to detect esophageal adenocarcinoma and Barrett's esophagus.
   Surveillance evaluation in men and women with a history of Barrett's esophagus. In the absence of dysplasia, surveillance examinations should occur at intervals no more frequently than 3 to 5 years. More frequent intervals are indicated in patients with Barrett's esophagus and dysplasia.

Histology

Like endoscopy, the role of esophageal biopsies in evaluating GERD has evolved over the years. There is little value for histologic examination of normal-appearing squamous mucosa to diagnose GERD; however, this dictum must now be tempered by the need to differentiate eosinophilic esophagitis from GERD,

Variable	Frequency score (points) for symptom			
Question	0 day	1 day	2–3days	4–7 days
1. How often did you have a burning feeling behind your breastbone (heartburn)?	0	1	2	3
2. How often did you have stomach contents (liquid or food) moving upwards to your throat or mouth (regurgitation)?	0	1	2	3
3. How often did you have a pain in the center of the upper stomach?	3	2	1	0
4. How often did you have nausea?	3	2	1	0
5. How often did you have difficulty getting a good night's sleep because of your heartburn and/or regurgitation?	0	1	2	3
6. How often did you take additional medication for your heartburn and/or regurgitation, other than what the physician told you to take? (such as Tums, Rolaids, Maalox?)	0	1	2	3

GERDQ Table
GerdQ symptom scores:
GerdQ < 8: low probability for GERD
GerdQ ≥ 8 and ≤ 3 on questions 5 and 6 (impact questions): GERD with low impact on daily life
GerdQ ≥ 8 and ≥ 3 on questions 5 and 6 (impact questions): GERD with high impact on daily life

particularly in patients complaining of dysphagia. In patients with classic erosive reflux esophagitis, biopsies are rarely taken, except to exclude neoplasm and infection. In summary, the current primary indication for esophageal biopsy is to define Barrett's epithelium and to exclude eosinophilic esophagitis.

pH monitoring

Ambulatory intra-esophageal pH monitoring is still the gold standard for establishing pathologic acid reflux; clinical indications for this test are now well-established.

Before fundoplication, pH testing should be performed in patients with a normal endoscopy to confirm pathologic acid reflux and establish a firm diagnosis of GERD. After anti-reflux surgery, persistent or recurrent symptoms warrant repeat esophageal pH testing.

Esophageal reflux testing is particularly helpful in evaluating patients with a normal endoscopy. However, here there is controversy whether this should be done on or off PPI therapy to define two populations: those with and those without continued abnormal acid or non-acid exposure times

Finally, ambulatory esophageal pH testing may help to identify patients who have extra-esophageal manifestations of GERD. In this situation, pH testing is often done with additional pH probes in the proximal esophagus or pharynx.

In addition to various types of catheter-based pH monitoring systems, there are:

(1) a catheter-free system using a wireless pH capsule that is affixed to the esophageal mucosa with a delivery system that drives a small needle into the epithelium and transmits pH data to a portable receiver using radiofrequency signals, and

(2) a catheter-based system which combines impedance monitoring with pH testing, allowing the measurement of acid and non-acid reflux.

A critical limitation of esophageal pH monitoring is that there are no absolute threshold values that can identify GERD patients, reliably. Under these circumstances, statistical evaluation of esophageal pH recordings using, for example, the symptom association probability (SAP) or symptom index (SI), can define an association between symptom complaints and GER; however, only a treatment trial can address the critical clinical issue of causality.

Manometry

The advent of multichannel, high-resolution manometry (HRM) has revolutionized esophageal motility testing. With 32 to 36 pressure transducers spanning the entire esophagus, HRM can now accurately assess LES pressure and relaxation, as well as peristaltic activity, including contraction amplitude, duration, and velocity. However, esophageal manometry is generally not indicated in the evaluation of the uncomplicated GERD, because most GERD patients have a normal resting LES pressure and it is difficult to evaluate transient lower esophageal sphincter relaxations (TLESRs) in short-term HRM studies. Having said this, esophageal manom-

etry is, traditionally, recommended to document adequate esophageal peristalsis and exclude variants of achalasia and scleroderma before anti-reflux surgery.

Radiology

The barium esophagogram is an inexpensive, readily available and non-invasive esophageal test. It is most useful in demonstrating anatomic narrowing of the esophagus and assessing the presence and reducibility of a hiatal hernia. Schatzki's rings, webs or minimally narrowed peptic strictures may only be seen with an esophagogram, being missed by endoscopy, which may not adequately distend the esophagus. Giving a 13-mm radiopaque pill or marshmallow along with the barium liquid can help to identify these subtle narrowing's. The spontaneous reflux of barium into the proximal esophagus is very specific for reflux, but is not sensitive and it does not, necessarily, indicate that the patient's symptoms are caused by GER. Provocative manoeuvres (e.g. leg lifting, coughing, Valsalva manoeuvre or water siphon) can elicit stress reflux and improve the sensitivity of barium esophagogram, but some argue that these manoeuvres also decrease its specificity. In general, barium contrast studies are not used to make a diagnosis of GERD but rather to identify structural lesions that may be associated with alarm features.

Conclusion

National guidelines recommend that GERD can be diagnosed, clinically, without the need for formal investigations. Structured questionnaires are cumbersome to use in clinical practice and add little to the accuracy of clinical diagnosis. Diagnostically, upper endoscopy is indicated primarily for patients who have alarm features or who have not responded to a 4-8 week course of twice-daily PPI therapy; esophageal biopsies are not needed to make a diagnosis of GERD but are appropriate if there is a suspicion of eosinophilic esophagitis or Barrett's esophagus. Esophageal pH monitoring, with or without luminal impedance monitoring may be helpful before anti-reflux surgery or for patients with persistent symptoms despite therapy, as may esophageal manometry, especially if there is a suspicion of an underlying motility disorder. Upper GI contrast radiology has a limited role for the diagnosis of GERD and is useful, primarily, if there is a strong suspicion of an underlying structural lesion.

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Heartburn – Underlying Mechanisms

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Heartburn is the cardinal symptom of GERD, particularly in developed, Western countries (1); however, heartburn is not synonymous with GERD (2). Heartburn can occur, for a variety of reasons, in the absence of gastroesophageal reflux (GER) or GERD and, conversely, GER or GERD may exist in the absence of heartburn or, indeed, other symptoms.

To understand the mechanisms underlying heartburn, one must appreciate how the esophagus is exposed to refluxed gastric contents, how gastric refluxate may cause heartburn and other symptoms and how other mechanisms may cause reflux-like symptoms.

Gastroesophageal Reflux

In health, the reflux of gastric contents into the esophagus is prevented or minimized by the anti-reflux barrier which comprises the combined effects of the lower esophageal sphincter (LES), the crural diaphragm and the 'flap valve' effect of the angle of His at the gastroesophageal junction (3). It is worth noting that the reflux of gastric contents into the esophagus is a normal phenomenon in that esophageal acid exposure, measured 5 cm above the LES, is considered to be normal if esophageal pH is below 4 for less than 4% (55-60 minutes) of a 24-hour recording (4).

Pathogenesis of Gastroesophageal Reflux

Disruption of the anti-reflux barrier can occur if the neuromuscular function of the LES is impaired or if the anatomical location of the LES changes relative to the crural diaphragm. If LES function is impaired, the sphincter opens inappropriately or fails to close appropriately, allowing gastric contents to reflux into the esophagus. If the LES is located proximal to the crural diaphragm, the combined effects of the LES and the diaphragm are separated and, furthermore, the musculo-mucosal flap valve at the angle of His is effaced or reduced.

The LES is a ring of smooth muscle that extends 3-4 cm across the gastro-esophageal junction (GEJ) at the level of the diaphragmatic hiatus, encircled by the crural diaphragm. The location of the LES, relative to the diaphragm, is maintained by the phreno-esophageal ligament which can accommodate positional changes that occur with swallow-induced esophageal shortening and with diaphragmatic movements during breathing, coughing and physical exertion. Disruption of the phreno-esophageal ligament allows the gastroesophageal junction to move proximally, into the chest, leading to formation of a hiatus hernia.

Lower esophageal sphincter

The LES is, normally, tonically-contracted with a resting pressure that is 10-30 mm Hg above intragastric pressure. Basal LES pressure (LESP) is dependent on both intrinsic, myogenic factors and extrinsic, neural factors; variations in LESP can be caused by a variety of factors including food, medications, gastric distension, raised intra-abdominal pressure and neuro-hormonal factors.

Marked reductions in resting LESP may play a role in GER and GERD but reflux episodes are rare despite short duration increases in intra-abdominal pressure if the resting LESP is greater than 10 mm Hg and 'free reflux', that occurs in the absence of increased intragastric pressure, is rare if the resting LESP is greater than 5 mm Hg. The effect of reduced basal LESP is exacerbated if there is a co-existing hiatus hernia.

Relaxations of the LES occur commonly and appropriately to allow transit of a swallowed bolus into the stomach; these relaxations are not, generally, associated with GER. In addition, swallow-independent, transient LES relaxations (TLESR), occur about 3 to 6 times per hour, triggered by gastric distension; TLESRs are thought to allow physiological venting or decompression of the stomach and may be associated with audible belching. TLESRs are identifiable by esophageal manometry as a rapid decrease in LES pressure that is not triggered by swallowing; they are mediated by a vago-vagal reflux starting with activation of proximal gastric receptors which relay signals, via afferent sensory vagal fibres to the nucleus tractus solitarius (NTS) and, thence, to the dorsal motor nucleus (DMN) of the vagus nerve. These areas coordinate activity of the LES and the crural diaphragm which are innervated by the vagus and phrenic nerves, via the myenteric plexus of the esophagus and LES. The modulation of TLESRs is affected by a variety of neurotransmitters including acetyl choline, CCK, opioids, cannabinoids, nitric oxide, gamma-aminobutyric acid (GABA) and glutamate. Especially when accompanied by inhibition of the crural diaphragm, TLESRs are the major mechanism associated with episodes of GER although TLESRs occur with comparable frequency in GERD patients and healthy subjects; this suggests that other factors, such as the pressure gradient across the LES or the compliance of the GEJ, are important in permitting the occurrence of GER. TLESRs terminate with the onset of secondary or, less commonly, primary esophageal peristalsis.

Crural diaphragm

The esophagus passes from the thorax to the abdomen via the esophageal hiatus in the diaphragm; the right crus of the diaphragm encircles the LES and, provided that there is no hiatus hernia, it contracts at the level of the LES to augment the anti-reflux barrier during inspiration. In health, the LES is maintained in position, relative to the diaphragm, by the phreno-esophageal ligament; disruption of the phreno-esophageal ligament predisposes to an esophageal hiatus hernia with migration of the LES proximally, into the thoracic cavity.

Hiatus hernia

The role of the hiatus hernia in facilitating GER has been recognized, anew, over the last 15-20 years as studies with newer manometric techniques have demonstrated two contributors to the GEJ pressure zone: the LES and the crural diaphragm. The contribution of the crural diaphragm and flap valve to the anti-reflux barrier is

impaired by the development of a hiatus hernia, consistent with research demonstrating that esophageal acid exposure, esophagitis severity and the prevalence of Barrett's epithelium are all greater if a hiatus hernia is present. Impaired coordination or summation of the effects of the LES and the crural diaphragm are such that reflux in patients with hiatus hernia is associated, to a greater extent, with swallowing, straining and a low basal LES pressure.

Gastric emptying

Delayed gastric emptying does not appear to be a major etiological factor in GERD although a proportion of GERD patients demonstrated slow emptying of the proximal stomach, possibly in relation to dietary or obesity-related factors; it is speculated that this may predispose to an increased propensity for GER or to changes in the position of the 'acid pocket', an area of increased acidity located on top of other gastric luminal contents.

Heartburn

Heartburn was defined, in the Montreal Definition and Classification of GERD, as a 'burning sensation in the retrosternal area (behind the breastbone)' (1) because the term 'heartburn' has not been recognized or defined in a standard fashion across the world. Heartburn and regurgitation (the perception of flow of refluxed gastric content into the mouth or hypopharynx) were, further, defined as the characteristic symptoms of the typical reflux syndrome although it was acknowledged that other symptoms, such as epigastric pain or dyspepsia, are also, commonly, indicative of GERD. Furthermore, although GER is the most common cause of heartburn, refluxed gastric acid is not the only cause and, in addition to non-acid refluxate, other non-reflux-related causes have been implicated, including inflammation and dysmotility of the esophagus, ingested materials and esophageal hypersensitivity.

Pathogenesis of Heartburn

Heartburn, as the characteristic symptom of GER and GERD, is thought to occur because the esophageal epithelium is exposed to refluxed gastric content and, particularly, to refluxed gastric acid. In a high proportion of symptomatic individuals, heartburn is ameliorated by therapy that neutralize refluxed acid or reduce acid reflux by decreasing gastric acid secretion (5,6), suggesting that it is acid-mediated symptom.

However, esophageal acid exposure, measured by intra-luminal pH-metry, is not as well-correlated with heartburn as it is with reflux-related esophageal injury such as erosive reflux esophagitis or Barrett's esophagus. This may be due, in part, to the fact that the pH electrode is placed, by convention, 5 cm above the LES; in consequence, if the proximal extent of the refluxed gastric acid is distal to the electrode, the patient may report symptoms in the absence of any detectable reflux. In addition, symptoms are more common if the reflux episode extends more proximally, if it is longer or if there is a greater degree of prior acid exposure. These observations do not, however, prove that it is acid which causes symptoms; for example, GER includes pepsin which is active in an acidic environment, below pH 4, and it may be pepsin, rather than acid which causes symptoms.

Regardless of what causes the symptoms, it is not clear how symptoms are generated. Intuitively, one might expect GER symptoms to occur the sub-epithelial layers are exposed to luminal acid because of 'mucosal breaks' or erosions; however, if this is the case, one must determine why at least half of individuals with GERD have NERD (non-erosive reflux disease) and why an appreciable proportion of patients with erosions do not report symptoms. It has been proposed that symptoms occur due to functional disruption of the epithelial barrier demonstrable as dilated intercellular spaces (DIS) which are a marker of compromised intercellular tight junctions and a consequent loss of a barrier which should, in health, prevent acid and other noxious molecules from activating chemosensitive nociceptors in the sub-epithelial layers (7,8). DIS are triggered, not only, by luminal acid but, also, by pepsin in an acidic environment, by bile acids and by other systemic factors such as cytokines; thus, DIS may be a non-specific response to injury that does not, necessarily, cause symptoms.

As in other parts of the gastrointestinal tract, esophageal symptoms may indicate local, visceral hypersensitivity leading to a heightened perception of various luminal stimuli. The underlying mechanisms may be central or systemic, mediating the documented effect of stress on patients' perception of heartburn. It is, also, possible that heartburn, whether reflux-related or functional, may be due to up-regulation of nociceptors such as TRPV1, a transient receptor potential (TRP) channel, acid-sensitive ion channels (ASIC) or ionotropic purinergic receptors (P2X) (8). Esophageal symptoms have also been linked to other abnormalities, including sustained esophageal contractions (SEC) observed in the longitudinal muscle layer (9) and esophageal inflammation, diagnosed increasingly commonly, in eosinophilic esophagitis.

Summary

There are multiple mechanisms underlying the pathogenesis of gastro-esophageal reflux disease and its characteristic symptom, heartburn. Heartburn is a symptomatic manifestation of refluxed gastric contents that elicit responses from esophageal nociceptors. The frequency, duration and severity of patients' heartburn are correlated, to some extent, with esophageal acid exposure and, in a large proportion of GERD patients, therapeutic reduction in esophageal acid exposure is associated with a marked reduction in heartburn. However, it is possible that other refluxed gastric contents, in addition to acid, may cause heartburn just as some foods and drinks can cause retrosternal burning symptoms, en route to the stomach. Furthermore, there are other central and local mechanisms that may cause or contribute to heartburn, some by sensitizing the esophagus to apparently normal degrees of reflux and others by eliciting nociceptive responses in the absence of GER. An understanding of the multiple mechanisms underlying GER and heartburn is an important basis for managing GERD in view of the fact that symptom-based diagnosis of GERD has limited sensitivities and specificities of 62-67% and 63-70%, respectively (2).

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Worldwide Epidemiology of Gastroesophageal Disease

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Gastroesophageal reflux disease (GERD) is one of the most common chronic diseases in adults. It affects not only the esophagus but also the upper airways and it is associated with a wide range of extra-esophageal symptoms. Therefore, treating GERD requires collaboration among many different disciplines, including Gastroenterology, ENT, Pulmonary Medicine, General Surgery, Pediatrics, Internal Medicine and General Practice.

Approximately 4650 publications can be found in PubMed by using the terms "GERD" and "prevalence" as keywords. However, it is difficult to compare the epidemiologic studies for several reasons;

1) Studies have been performed using at least 10 different questionnaires, including the Mayo GERD Questionnaire, GERD-Q, DIGEST-Q and RDQ;

2) Various definitions and criteria for GERD have been used in both different and the same questionnaires, but the most common definition is heartburn and/or acid regurgitation once a week or more frequently;

3) Some studies have used non-validated questionnaires;

4) The randomization methodology and response rates differ across studies; and

5) The word "reflux" does not exist in some languages.

Gastroesophageal reflux symptom prevalence

High-quality prevalence studies from Western countries have been undertaken since the 1990s and similar studies were only performed in the 2000s in eastern countries. Because one of the most common questionnaires is the Mayo GERD Questionnaire, the prevalence studies that used this questionnaire and implemented the same diagnostic criteria are summarized in Table 1.

If all of the published studies are considered, the worldwide prevalence of GERD is approximately 15-25%. Although there are major discrepancies between Western and Eastern countries, it is not clear exactly where to divide the world. Western European countries, the USA, and Canada can be pooled in the same group because they share similar cultural and social characteristics. Additionally, these countries have low *Helicobacter pylori* rates and better health care facilities.

The highest numbers are observed in the USA (26.2%), Norway (26%) and Sweden (25.9). Different rates have been reported within these countries, but the differences were not significant. An interesting finding from the USA concerned different ethnic groups: the prevalence rates were 38% in Hispanics, 14.7% in Asians, 29.9% in Caucasians and 22.1% in African-Americans. In a pivotal study, Locke et al administered the Mayo questionnaire to 1511 subjects in Olmsted County by mail. They found that the subjects experienced the following symptoms at least once weekly: heartburn (17.8%), regurgitation (6.3%) and either symptom (19.8%).

If all of the studies from Western countries were evaluated cumulatively, the prevalence of heartburn was 23%, and that of acid regurgitation was 16%.

The majority of studies from Eastern countries originate from South-East and East Asian populations; the prevalence of GERD (common heartburn and/or acid regurgitation that is experienced once a week) in these populations is 2.5–8.2%, which is markedly lower than that reported in the Western studies. One of the first large-scale randomized studies in China that used the Mayo questionnaire via phone interview found a very low prevalence of GERD (2.5%). Subsequent studies showed a meaningful increase of this rate to 6.2%. Japan is the only exception among the Far East countries: a study performed using QUEST showed a high GERD prevalence of 16.5%, one of the highest figures among the Far East countries.

Other Eastern countries have added more data through studies, particularly within the last 5 years. Iran, for example, presents different profiles, and the prevalence rates range from 2.7% to 33%. One recent study performed using the Mayo Questionnaire in Eastern Iran showed a prevalence rate of 25.7% for GERD and regurgitation and noted that regurgitation was more common than heartburn (the heartburn rate was not reported). Two studies from India, which addressed subjects who were admitted to the hospital, reported similar values: 5.3% and 7.1%. Very limited data exist from the southern and eastern parts of the Mediterranean. One study, in Tunisia, defined GERD as occurring once a year or more frequently; therefore, the prevalence rate reached 24.8%. Another study, conducted in Israel via telephone surveys, reported lower figures: 12.5% of the respondents reported weekly or more frequent symptoms.

Compared with prevalence, there are far fewer studies regarding the incidence of GERD. However, it has been shown that the incidence of the disease is on the rise.

Symptom profile

According to epidemiologic studies, one of the major differences between Western and Eastern countries is the prevalence of typical symptoms of GERD. Western countries primarily report heartburn, whereas nearly all other countries predominantly report acid regurgitation. Only a minority of countries (such as Russia and Argentina) have similar rates for both symptoms (Table 1).

These differences are likely underestimated but important because acid regurgitation represents a different therapeutic profile than heartburn. The modality of these differences is not clear but may be due to less overall medicine consumption, decreased obesity, genetic factors (low acid output), dietary factors (such as low consumption of hot or carbonated drinks), low fat meals, and decreased alcohol and tobacco product consumption. Most

importantly, there is an exceedingly high prevalence of *Helicobacter pylori* (*Hp*) in under-resourced populations. It is possible that *Hp* infection may, in some manner, affect the prevalence or mode of presentation of GERD or it may be that higher living standards lead, independently, to a decreased risk of *Hp* infection and an increased food intake and obesity.

Extraesophageal and additional symptoms

As previously mentioned, GERD affects different organ systems and may be related to different conditions, such as cough, asthma, or hoarseness (Table 2). There is no study comparing the atypical symptoms between different countries, but studies that were performed using the same questionnaire have yielded different results. For example, the prevalence of asthma among GERD patients ranges from 0.8% to 9.3%. The prevalence of other symptoms, such as dyspepsia, also differs markedly, ranging from 10.6% to 60.2%.

Conclusions

1) The prevalence of GERD is higher in Western countries (15-25%) than in Eastern countries (3%-16%).

2) The symptom profile of GERD is different: heartburn is more prevalent in Western countries, whereas regurgitation is the predominant symptom in the East.

3) Additional and extra-esophageal symptoms are common in GERD subjects, but the prevalence of each symptom varies significantly among studies.

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Figure-1 The prevalence of gastroesophageal reflux disease (courtesy of Turkish GERD consensus group and Elif Saritas MD)

Table 1: The prevalence of GERD and typical symptoms in studies performed using the Mayo Questionnaire

Place	Author	No of subjects	Heartburn	Regurgitation	GERD
Olmsted (USA)	Locke	1511	17.8	6.3	19.8
Moscow (Russia)	Bor, Lazebnik	1065	17.6	17.5	23.6
Turkey	Bor	3214	9.3	16.6	22.8
Argentina	Chiocca	839	16.9	16.5	23
Eastern Iran	Vossoughinia	1637	NA	25.7	25.7
Olmsted (USA)	Jung	2273	NA	NA	18
Philadelphia (USA)	Yuen	1172	NA	NA	26.2
Madrid (Spain)	Rey	709	NA	NA	8.5
Spain	Diaz-Rubio	2500	NA	NA	9.8
China	Wong	2209	NA	NA	2.5

Table 2: The prevalence of additional symptoms in studies performed using both the same questionnaire and the same diagnostic criteria (Bor et al. Dis Esoph. 2015)

	Olmsted (USA)	Moscow (Russia)	Izmir (Turkey)	Argentina	NW China
NCCP	23.1	15.5	37.3	37.6	34.7
Dysphagia	13.5	25.5	35.7	26.8	6.5
Odynophagia	-	34.4	35.7	-	10.7
Globus	7.0	25.5	23.8	26.3	15.2
Dyspepsia	10.6	60.2	42.1	38.7	29.3
Belching	-	43.0	24.6	-	-
Nausea	-	53.8	60.3		-
Vomiting	-	29.1	38.1	-	-
Hiccup	-	6.8	9.5	-	-
Cough	-	36.7	19.8	-	8.9
Asthma	9.3	-	0.8	6.7	4.2
Pharyngeal symptoms & Hoarseness	14.3	10.4	28.6	21.8	9.4

Treatment of GERD: Overview for Patients

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Lifestyle modifications (LSMs) play a minor role in the management of heartburn [1]. A number of LSMs have been recommended in the past including smoking cessation, dietary modifications *etc*. These often make sense from a general medical perspective but there is not much solid evidence that they substantially improve heartburn or other GERD symptoms. Of the various LSMs that have been studied, the best evidence is for weight reduction in the overweight and obese, and elevation of the head end of the bed while sleeping. However, the latter is seldom done because it is viewed as impractical.

In many countries around the world, people with heartburn have access to over-the-counter (OTC) medicines that they can purchase without first seeing a physician. OTC medicines for heartburn may comprise antacids, H_2-receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs) although not all of these may be available OTC in some countries. People with typical heartburn often use these medicines without seeing a doctor – or may use them before they see a doctor. Different countries' regulatory agencies have made different recommendations about the use of OTC medicines for heartburn, so it would be wise to check on the situation in individual countries. In some countries, H_2RAs and PPIs may still only be available with a doctor's prescription and may not be available for OTC purchase.

Antacids work quickly by neutralizing stomach acid that has come into contact with the lining of the esophagus. These medicines have been used for many years and are generally safe. If these medicines alone are sufficient to control a person's heartburn, no further medical treatment may be necessary. They are suitable for people with mild intermittent heartburn, especially if it is triggered by over-eating. Antacids may contain aluminum, magnesium or calcium. Those with aluminum or calcium may cause constipation; those with magnesium may cause diarrhea. Otherwise, antacids are generally safe and without significant side effects. Sodium bicarbonate can be absorbed into the circulation. It should not be used repeatedly as it can cause sodium overload in some people (for example, those with heart, kidney or liver problems or high blood pressure).

H_2RAs were first developed in the 1970s to treat stomach ulcers. Since then, millions of patients worldwide have received these medicines, which are considered to be extremely safe [2]. They work on the cells in the stomach that produce acid. H_2RAs reduce the production of stomach acid. When less stomach acid is produced, there is less likelihood of acid-related heartburn. H_2RAs in prescription or OTC doses may be effective for the treatment of heartburn in people with GERD. However, they are probably best suited for people who are having relatively mild heartburn – and not necessarily on a daily basis. The effectiveness of H_2RAs on heartburn may reduce or wear off over time if they are taken on a regular daily basis [4]. For that reason, some people find these drugs to be useful if taken only intermittently – and especially on occasions when a particularly large or heavy meal has been eaten. Examples of H_2RAs (not all of which may be available in all countries) include cimetidine, ranitidine, famotidine and nizatidine. In both prescription and OTC forms, these may have different trade names in different countries.

PPIs also work by reducing the amount of acid produced by the stomach. However, they work differently from the H_2RAs and they reduce acid production by a greater amount. They are generally highly effective for treating heartburn that is due to reflux of stomach acid into the esophagus [2, 3]. For most people, a PPI only needs to be taken once-daily; generally, these medicines are best taken 30 – 60 minutes before a meal. Some people take these medicines twice-daily if they do not get adequate heartburn relief from a once-daily dose. These medicines may take a few days to reach their maximum effect. Examples of PPIs that may be available for prescription use or OTC purchase include omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole and dexlansoprazole. Not all of these will be available in all countries and some that are available may not be for OTC purchase. The trade names of these medicines may vary among different countries.

While PPIs are generally considered to be very safe drugs, there have been some recent safety concerns. Long term use of these drugs may be associated with a slight increase in the risk of bone fractures although the mechanism of this is unknown. People at risk of fracture (for example, women who have gone through menopause) should take all necessary measures such as calcium and vitamin D supplements although no additional measures are needed because of PPI use. PPIs may also increase the risk of certain intestinal infections including *C. difficile*. Again, the level of risk is small [5]. As with all medicines, PPIs should be taken in the lowest effective dose.

Both PPIs and H_2RAs have been associated with some interactions with other medicines. Therefore, it is always important to discuss use of these drugs with a doctor. Most of the interactions with H_2RAs, PPIs and other drugs are not serious. However, it is likely that at least some PPIs may reduce the effectiveness of clopidogrel, which is a medicine that reduces blood clotting activity and is used for people with certain heart or blood vessel problems. People taking clopidogrel should probably avoid certain PPIs and should certainly discuss this with their physicians.

Prokinetic drugs are used in some countries as part of the treatment of heartburn. They are used in an attempt to limit the amount of stomach acid getting into the esophagus and / or to move any acid in the esophagus back into the stomach. Currently available prokinetic drugs are not particularly reliable or effective. They are only used in some countries and generally only by prescription.

Apart from LSMs and medicines, heartburn can also be treated with endoscopic procedures or surgery. Different procedures that can be performed at endoscopy may or may not be available in different countries. These are designed to tighten the sphincter that separates the stomach and esophagus so that the reflux of stomach contents into the esophagus is reduced. They have had limited and variable success and there have been serious side effects from some procedures. Choosing to have one of these procedures is a difficult decision that must be discussed in detail with the doctor performing the procedure. This must include an understanding of the possible risks of the procedure. These procedures may be helpful in improving regurgitation, which is otherwise not well controlled with medicines.

Endoscopic treatment may also be used in some countries for the treatment of some patients with Barrett's esophagus (BE) and even early stages of the cancer that can arise from BE – called esophageal adenocarcinoma (EAC). (See elsewhere in this handbook for more information on BE and EAC.) BE that is at high risk of developing into EAC can be treated endoscopically by a procedure called radiofrequency ablation (RFA), although this may not be generally available in all countries.

Surgery is also an option for some people with troublesome heartburn and other symptoms of GERD [6]. Various surgical operations can tighten the sphincter separating the esophagus and stomach so as to limit the total amount of reflux from the stomach. This is highly specialized and is not done by all general surgeons. People having surgical treatment for GERD should be managed in a specialist center by a surgeon with a lot of experience with this type of surgery. The people who do best with surgery are generally young and otherwise healthy (without significant heart or lung problems, for example). Also, it is important to understand that surgery is most helpful for people whose heartburn improved during treatment with a PPI. This is not always well understood by patients and their doctors. People with heartburn that did not improve with PPI treatment probably do not have GERD and should avoid surgical treatment for GERD. (There is more information on non-GERD conditions that may be confused with GERD elsewhere in this handbook.)

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The Family Practitioner's Approach to Heartburn

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Family Practitioners or Primary Care Physicians (PCPs) are used to dealing with symptoms and are not always as enthusiastic as gastroenterologists in providing diagnostic labels. Thus, Gastro-Oesophageal Reflux Disease (GORD or GERD), a label beloved of gastroenterologists, is not necessarily as well recognized in primary care practice even though heartburn, reflux and other upper abdominal and chest symptoms are commonly seen and dealt with.

The concept of "GORD" [1] is in any case a bit of a problem – the traditional perception has been that this is essentially an acid-related disorder, possibly related to "excessive" acid in the esophagus, together with a picture of a failing gastro-esophageal valve, with or without impaired gastric emptying. This is handy for providing an explanation to the patient but none of these concepts is completely true in GORD. It is hardly surprising that many PCPs are confused about the true cause and nature of symptoms such as heartburn.

The situation has been compounded by the assumption that acid suppression would resolve these symptoms and it has been a problem that a large proportion of patients do not actually benefit from this. A common experience in primary care is the variable response of GORD symptoms, including heartburn, to proton pump inhibitors (PPI). It was initially assumed that this was due to therapy adherence shortcomings and inadequate or badly timed dosing but adjustments here have provided only marginal improvements. Indeed, in primary care practice, the majority of patients on long-term acid suppression continue to suffer moderate to severe symptoms [2]. This experience is mirrored in secondary care where the more symptom-resistant patients are likely to be seen. In a seminal study on patients on high dose PPIs for GORD, Mainie et al [3] discovered that 86% had continuing symptoms and, with esophageal pH measurements, they deduced that only 8% of them had acid reflux, 35% had non-acid reflux and that in 57% their symptoms did not appear to be related to reflux at all. This challenges the Montreal Consensus on GORD [1] which described this as "a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications". PCPs, at the sharp end of clinical practice, have long been aware of our inadequacies in managing GORD symptoms effectively.

The value and meaning of symptoms themselves is confusing. In the Diamond study [4] the researchers critically assessed the value of symptoms in patients judged as having GORD, through independent assessment and investigations. GORD was considered to be present in only 65% of those diagnosed initially and only 49% of patients selected heartburn or regurgitation, the so called cardinal symptoms, as their most troublesome symptom. The value of these, essentially clinician-led descriptors, has been further questioned in a large international study across 13 countries [5] where sufferers used a far wider variety of descriptors and where our traditionally used clinical terms did not tally with their experiences. In short, people presenting in primary care do not necessarily present using terms such as "heartburn" and it is more likely that these are categorized as such by the clinician. Even those saying they have "heartburn" might actually have some other meaning in mind.

Incorrectly interpreting the symptoms can present a nightmare scenario – getting it wrong can be dangerous – for the PCP who has to be on the lookout for cardiac problems, amongst other things. With their innately holistic approach to patients' problems, PCPs are also aware of the overlap of symptoms from different causes, including the functional disorders. The label of functional heartburn is only sparsely used in primary care but associations with IBS and with other non-GI functional disorders, such as fibromyalgia and non-cardiac chest pain are common. In the possible presence of circumstantial psychological stress, anxiety and depression in the patient, the PCP has to grapple with a multiplicity of problems. Specific, single symptoms such as heartburn are sometimes relegated to a lower order of priority.

Meanwhile, and this impacts heavily on primary care, the prevalence of GORD is increasing. The Norwegian HUNT Research Centre [6] reported a 31% increase in the prevalence of gastro-esophageal symptoms over ten years to 2009 with a corresponding 47% increase in the frequency of symptoms. Startlingly, the increase was most strongly marked in those over 60 years, a stage at which the possibility of cancer becomes a greater issue. Thus, the size of the problem as well as the need for vigilance in the older age group, is important for PCPs.

In terms of investigations, in the UK, priority in gastroenterology resources and effort has shifted to colonoscopy for the earlier detection of lower GI cancer. This has reduced the emphasis on gastroscopy. Gastroscopy is now reserved, essentially, for those in high-risk groups, such as those with red flag symptoms or older patients and is not recommended for the investigation of GORD symptoms in younger people. Although PCPs, as in many other western countries, have the right of direct access to gastroscopy they are subject to review and possible sanction from their Clinical Commissioning Groups (CCGs), the purchasers of clinical services on their behalf. Trends in gastroscopy numbers are, therefore, downwards compared with previous years and the approach to management is based on an empirical approach rather than on initial investigation.

The mainstay of treatment of heartburn (or GORD in the wider sense) amongst PCPs, following advice and initiatives towards lifestyle measures and antacids and alginates, remains acid suppression therapy. Most consulters are at the stage where they are seeking active treatment. PPIs remain the mainstay of acid suppression therapy, despite the difficulties outlined above in relation to limited success. In previous years, debate around the management of

upper GI symptoms using PPIs was related to their relatively high cost and the large proportion of the health budget they took up. With the availability of cheap generics this is no longer an issue. The role of surgery, essentially fundoplication, is not as prevalent in the UK as in many other European countries and the USA and is normally initiated by a gastroenterologist with a referral to a surgeon, rather than directly from a PCP.

However, whilst the cost and use of PPIs in the initial management of heartburn is not a major issue for PCPs, there are concerns about their long-term use because of possible significantly detrimental side effects. A substantial proportion of the population is taking PPIs, ranging between 2-15% of the Western population depending on definitions of long-term [7] and the numbers are increasing. In many parts of the world, PPIs are available without a prescription and the rates of usage are even higher. It is hard to determine if there is a strong element of over-prescribing by PCPs because of the widened indications for them – essentially concurrently for gastroprotection with NSAIDs and aspirin. With an increasing elderly population taking such drugs, there has been a steep rise in the use of long-term PPIs. In the UK, PCPs are required to audit their long-term prescribing and to monitor patients for appropriate clinical indications. At the same time, it would appear that patients with GORD are relatively adherent to their medication, even if symptom control is variable, and that severe symptoms and Barrett's esophagus are associated with increased adherence [8]. However, few data are available on the rate of success of strategies to reduce or stop treatment for heartburn or GORD specifically.

In summary, a number of problems and questions remain in relation to the PCPs' responses to heartburn and its management. These include whether the interpretation of the presenting problem was accurate; if the presenting symptom was the issue that needed chief attention or if there were other factors that were key. Additionally, is the level of control of symptoms considered satisfactory and what might be gained from a secondary care opinion?

Heartburn remains, essentially, a primary care problem and its interpretation and context within a mix of other symptoms creates a complex issue. What has changed is that it is much less likely to be investigated than in previous years and there is less optimism about the power of PPIs to solve the problem. Nonetheless, the size of the problem is growing and vigilance is needed in at risk groups.

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Role of Dietary Factors in Gastroesophageal Reflux Disease

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Various foods are thought to be associated with gastroesophageal reflux disease (GERD) or to aggravate its symptoms. In routine clinical practice, suspected food products are often restricted in the diet. GERD symptoms generally occur during the post-prandial period, indicating that diet is an important factor in the development of symptoms (1). However, there are controversial reports about the foods that aggravate GERD.

Although Nebel et al. (2) showed that fried and spiced food products and alcohol precipitate pyrosis most, there was no control group in their study and amount consumed of these food products was not stated, raising questions about the generalizability of the study results. In their epidemiological study in a large population, Ruhr et al. investigated the role of fat-rich diet in erosive esophagitis but they did not find a meaningful relationship (3). On the other hand, Shapiro et al. reported that attacks of reflux were more frequent in individuals who were taking a fat-rich diet (4). Similarly, in their large scale, case-control study, El-Serag et al. documented the relation between the total amount of daily consumed fat and both non-erosive GERD and erosive esophagitis (5). Furthermore, Shapiro et al. showed that a diet rich in cholesterol and fatty acids and a high ratio of fat to daily calorie consumption led to an increased risk of episodes of GERD (4).

In a Swedish monozygotic twin study, Zheng et al. found no relation between GERD and the consumption of vegetables, fruits, fish, red meat, rice, pasta, milk, sandwich, potato or grilled food (6).

As for the effect of alcohol consumption, in their case control study with more than 40,000 individuals, Nilsson et al. found no association between alcohol intake and GERD symptoms (7). Similarly, in another population-based study, El-Serag et al. found no association between total amount of daily consumed alcohol and either non-erosive or erosive GERD development (5). Consistent with the findings of these large scale population studies, Shapiro et al. showed that alcohol consumption did not increase the risk of GERD episodes (OR:0.26, CI:0.05-1.3) (4).

However, there are studies suggesting that smoking may play an aggravating role in GERD pathogenesis although the mechanism or mechanisms underlying this observation have not, yet, been clarified. Various studies have shown sudden decreases in lower esophageal sphincter pressure (LESP) during smoking but these studies, also, determined that LESP returned completely to normal, 5-8 minutes after cessation of smoking (8,9).

Several large scale clinical studies have demonstrated the association between smoking and GERD. Nilsson et al. reported that smoking 6 or more cigarettes per day was an independent risk factor for GERD development. Furthermore, they demonstrated that the number of cigarettes smoked daily was directly proportional to the increased risk (7). In their study investigating the association between lifestyle related factors and GERD in monozygotic twins involving more than 25,000 participants, Zheng et al. found an increase in the risk of GERD development in active smokers, 37% in women and 53% in men; this increased risk was, also, shown to be dose-dependent (6). In different population based studies, smoking was detected as a risk factor for GERD development and it was, also, shown to cause more serious symptoms in patients who already have GERD (10,11). Schindlbeck et al. found more reflux episodes in smokers compared to non-smokers, but determined that neither having a history of smoking, nor being an active smoker had an effect on esophageal acid exposure time (12).

Zheng et al. showed, as in the case of alcohol consumption, that there was no association between coffee consumption and development of GERD symptoms (6). Nilsson et al. determined that even consumption of more than 7 cups of coffee did not lead to an increased risk of developing GERD symptoms (7). In a case control study, it was documented that coffee consumption did not increase either the duration of post-prandial acid reflux or the number of reflux episodes. Furthermore, coffee consumption did not affect post-prandial LESP in the same study (13).

The relation between salt consumption and reflux symptoms has been documented in various studies. Consumption of salted fish or meat twice a week and the addition of extra salt to meals were found to be risk factors for development of reflux symptoms (7).

Increased consumption of dietary fiber has been claimed to reduce the risk of reflux-related esophageal adenocarcinoma development (14). Moreover, there is evidence suggesting that a fiber-rich diet is an important protective factor against the development of reflux. In the population based study by Nilsson et al., there was a reduced risk of reflux development in individuals whose dietary fiber intake exceeded 4% of their diet; this risk decreased further, as they increased their fiber consumption (7).

Murphy et al., in 1988, reported that chocolate decreased basal LESP and they confirmed, by intra-esophageal pH monitoring, that esophageal acid reflux increased after chocolate consumption (15). However, to date, no clinical study has investigated the association between chocolate and GERD. Apart from chocolate, there are limited data from clinical studies to suggest an association of carbonated soft drinks with reflux symptoms although, in a multivariate analysis, Fass et al. reported that consumption of carbonated soft drinks increased nocturnal reflux symptoms (16).

The speed with which food is consumed is another risk factor for the development of GERD symptoms. Wildi et al. compared individuals who consumed a specified amount of food over 5 minutes with those who consumed it over 30 minutes; they detected that the median number of reflux episodes observed during a 2-hour, post-prandial period was significantly higher in those individuals who ate more rapidly (14 vs. 10, p=0.02) (17).

Acknowledgement

This manuscript was derived from the Turkish GERD consensus group data.

Recommendations

- There is insufficient evidence in studies to confirm which foods can trigger reflux.

- There are data to suggest an association between the development of reflux and the consumption of salt and salted foods, chocolate, fatty foods and carbonated soft drinks.

- Eating small amounts, frequently and slowly, should be recommended

- The consumption of fiber-rich foods should be recommended.

- There are inter-individual differences in the effects of various foods on the development of GERD symptoms. Therefore, large-scale, randomized trials are necessary to show whether reflux symptoms improve after the removal of dietary factors that could pose a risk for an individual.

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Extra-esophageal manifestations of gastro-esophageal reflux disease

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Introduction

While heartburn and regurgitation are the classical, esophageal manifestations of gastro-esophageal reflux disease (GERD), some individuals may suffer from extra-esophageal manifestations (EEMs).[1] EEMs represent a wide spectrum of symptoms, mainly related to the upper and the lower respiratory tracts, such as laryngitis, chronic cough, chest pain, bronchial asthma, oral ulcers, and sleep disturbances.[2-3] Whilst the evidence is sufficient to label some conditions, such as reflux cough syndrome, reflux laryngitis syndrome, reflux asthma syndrome and reflux chest pain syndrome, as established EEMs of GERD, other symptoms, such as pharyngitis, sinusitis, idiopathic pulmonary fibrosis and recurrent otitis media are labeled as proposed EEMs of GERD because there is only weak or limited evidence to suggest that they are caused by GERD.

Table: Extra-esophageal manifestations of GERD

	Established manifestations	Proposed manifestations
Bronchopulmonary	Reflux cough syndrome	Pneumonia
	Reflux asthma	Pulmonary fibrosis
Oto-rhino-laryngeal	Reflux laryngeal syndrome	Sinusitis
		Otitis media
		Rhinitis
Oral cavity		Halitosis
		Mouth ulcers
		Dysgeusia
		Glossodynia
		Water brash
Others	Non-cardiac chest pain	Dental enamel erosion
		Dental caries

Mechanisms of EEMs of GERD

There are two proposed mechanisms for the occurrence of EEMs in patients with GERD: i.e direct reflux-induced or indirect reflex-induced.[2-3] In the first case, direct reflux of gastric contents into the proximal esophagus, secondary to disruption of the mechanical barrier for reflux (lower esophageal sphincter) or esophageal dysmotility, may expose the oropharyngeal or tracheobronchial structures to acid and pepsin (reflux theory). Alternatively, more limited reflux of gastric acid and/or pepsin into the esophagus may, also, stimulate the vagus nerve. Because of the common embryological origin of the esophagus and the bronchial tree, stimulation of vagus nerve may lead to reflex bronchoconstriction and other extra-esophageal symptoms (reflex theory).

EEMs are more common in erosive than in non-erosive reflux disease. The economic burden of caring for patients with suspected extra-esophageal reflux is almost five times higher than that for patients with typical GERD.[4]

In this short review, we have summarized both established and proposed EEMs of GERD.

Extra-esophageal manifestations of GERD: Established

Reflux laryngitis syndrome

GERD is one of the important causes of laryngeal inflammation. Patients with reflux laryngitis can present with symptoms such as change in voice, intermittent change in the tone of the voice, loss of strength of voice, hoarseness, persistent cough or foreign body sensation in the throat or repetitive clearance of phlegm. Such symptoms are not specific for reflux-induced laryngitis; laryngeal inflammation can be caused or aggravated by many other factors such as dust, smoking or viral infections. It is, therefore, important for a clinician to judge whether GERD, really, is the cause of the problem when a patient presents with laryngeal symptoms. The symptoms of reflux laryngitis due to GERD are more often present in the day-time and in the upright position. Some other clues, which may help a clinician to attribute laryngeal symptoms to GERD are the presence of concomitant symptoms of GERD such as heartburn or regurgitation, the demonstration of reflux or reflux-induced mucosal changes at upper endoscopy or the confirmation of abnormal esophageal acid exposure by mean of a 24-hour pH study. Surprisingly, not every patient with laryngeal inflammation due to GERD has typical GERD symptoms, endoscopic esophagitis or abnormal reflux on 24-hour pH-metry.[5]

Furthermore, features of laryngeal inflammation such as erythema and edema of the crico-arytenoid folds and posterior portion of the true vocal cords are not specific for reflux-induced laryngitis; these findings may be seen in healthy volunteers and they may be caused, also, by smoking, alcohol, post-nasal drip, vocal strain and certain medications.[2] It has also been proposed that laryngeal inflammation in patients with GERD can be caused by non-acid reflux, detectable by combined esophageal pH-impedance monitoring.[6-7] An assay to detect pepsin in sputum or saliva, collected at the time of symptoms, has also been described recently to determine whether laryngeal in-

flammation is caused by gastroesophageal reflux, on the assumption that pepsin originates only in the stomach.[8]

A therapeutic trial with a proton pump inhibitor (PPI), twice-daily, for 4-8 weeks in patients who have GERD and reflux laryngitis syndrome, and observation of their symptomatic response, is a reasonable approach. If symptoms improve, the therapy may need to be prolonged for an additional 2 to 3 months to allow healing of laryngeal inflammation, after which the dose of PPI should be tapered to the minimum level of acid suppression needed to maintain their response.[9-11] Upper endoscopy and 24-hour esophageal pH and/or impedance monitoring should be reserved for patients in whom GERD is still suspected because of persistent symptoms despite appropriate therapy.[10]

Reflux cough syndrome

Chronic cough (a cough lasting for more than 8 weeks) is a frequent symptom in patients suffering from GERD. Gastric refluxate may trigger a chronic cough either directly, by irritating the upper airway or, indirectly, by stimulating an esophago-bronchial reflex. Chronic cough in the general population is caused by many conditions, other than GERD; in a patient who is a non-smoker and has a normal chest X-ray, the four most important causes of a chronic cough are GERD, postnasal drip syndrome, asthma and angiotensin converting enzyme (ACE) inhibitors. There are certain characteristics which may suggest that a cough is caused by GER: these include day-time cough, cough in upright position, cough during phonation, cough during eating or cough when rising from bed. It is worth noting that GERD may induce a cough which can, then, increase intra-abdominal pressure, thereby inducing further reflux which may aggravate the cough still more.

A systematic approach should be followed for patients with chronic cough. Common causes, such as medication (ACE inhibitors), postnasal drip and asthma must be excluded. In patients who have concomitant heartburn and/or regurgitation or those with high degree of suspicion for GERD, an empiric trial of a PPI, twice-daily, for 1 to 2 months is a reasonable approach. Upper endoscopy and 24-hour esophageal pH and/or impedance monitoring should be reserved for patients in whom GERD is still suspected and for whom treatment does not eliminate cough.[10] A lack of response to empiric PPI trial may be an indicator that cough is not caused by GERD, and other causes of chronic cough should be sought.

Reflux asthma syndrome

Epidemiological studies suggest an association between bronchial asthma and GERD. Not only is there an association between the two conditions but each of two conditions or their treatment can aggravate the other. Whilst GERD can induce bronchial asthma by a vagally-mediated reflex or by a micro-aspiration-induced reflux mechanism, as discussed above, bronchial asthma, itself, can enhance reflux by creating a negative intra-thoracic pressure; in addition, medications (e.g. theophylline, beta-2 adrenergic agonists) used to treat bronchial asthma can cause relaxation of the lower esophageal sphincter (LES). Both GERD and bronchial asthma are common in the community and they may, also, co-exist independent of each other.

How, then, does a clinician establish that asthma in a given patient is caused by GERD? Patients with bronchial asthma whose symptoms are worse after meals, or those who do not respond to traditional asthma medications should be suspected of having GERD. Patients who have heartburn and regurgitation before the onset of asthma symptoms may also be suspected of having reflux-induced asthma symptoms.[1-3]

As for patients with reflux-induced laryngitis, the yield of diagnostic tests such as upper endoscopy or 24-hour pH metry is not very encouraging. Furthermore, the response in the outcome parameters of bronchial asthma with treatment of GERD is not uniform. A Cochrane review of GERD treatment for patients with bronchial asthma found only minimal improvement of asthma symptoms following treatment for GERD.[12] A recent, controlled trial in asthmatics has, however, suggested that there is therapeutic benefit from PPIs in a sub-group of asthmatics who have both nocturnal respiratory and GER symptoms.[13]

Therefore, the current recommendation in patients with asthma (with or without concomitant heartburn or regurgitation) is similar to those for patients with chronic cough and laryngitis; that is, an initial empirical trial of twice-daily PPI therapy for 2-3 months. [2,3,14] In those responsive to therapy for both heartburn and/or asthma symptoms, the PPI should be tapered to the minimal dose necessary to control symptoms.[2,3,11] In unresponsive patients, testing for reflux by pH testing and/or impedance-pH monitoring may be considered to confirm the continued reflux of acid or non-acid material which might still be responsible for the patients' asthma symptoms.

Reflux-induced chest pain

Non-cardiac chest pain (NCCP) is a recurring, angina-like, retrosternal chest pain in patients in whom cardiac evaluation is within normal limits. Clinically, cardiac chest pain and chest pain of esophageal origin often present with similar symptoms (often described as burning, pressure-like, sub-sternal or occurring with exercise) and the symptoms may improve with similar treatments (i.e., nitroglycerin); thus, it may be difficult for a clinician to differentiate chest pain of esophageal origin from that of cardiac origin. Pain that is post-prandial, continues for hours, is retrosternal without radiation and is relieved with antacids, and pain that disturbs sleep makes the diagnosis of GER-related chest pain more likely. Obviously, classic reflux symptoms such as heartburn and regurgitation, in the absence of cardiac disease, make the diagnosis more likely. In fact, the symptoms of GERD are found in majority of patients with chest pain due to GERD.[15] Furthermore, NCCPis reported in one third of patients who are frequent refluxers compared to only 7.9% of patients reporting no GERD symptoms.[16]

Direct contact of the esophageal mucosa with gastro-duodenal contents, such as acid, pepsin or bile, leads to stimulation of the vagus nerve which, in turn, most likely causes chest pain. NCCP can also be caused by other esophageal disorders such as nutcracker esophagus or diffuse esophageal spasm; thus, for patients with persistent NCCP despite appropriate GERD therapy, esophageal motility studies should be considered.[17]

NCCP patients without dysphagia can be treated empirically with PPIs for 8 weeks or until symptoms remit; the PPI dose should, then, be tapered to the lowest dose that controls the symptoms. Diagnostic testing with ambulatory pH or impedance monitoring and esophageal motility testing should usually be reserved for those who continue to be symptomatic despite initial empiric trial of PPI.

Surgical treatment

Surgical fundoplication should not be considered in patients who are unresponsive to prolonged, high-dose (twice-daily) PPI therapy.[18-19] Fundoplication may be beneficial in patients who respond to anti-secretory agents but require continuous, high-dose PPI therapy to control symptoms, and in those with large hiatal hernia.

Extra-esophageal manifestations of GERD: Proposed

Oral manifestations of GERD

Oral manifestations of GERD include dental erosions, halitosis, water brash, mouth ulceration, taste disturbance and glossodynia. Dental erosions occur due to erosive potential in the oral cavity from intrinsic and extrinsic acid that exceeds the buffering capacity of saliva.

Other oto-rhino-pharyngeal manifestations of GERD

Other proposed oto-rhino-pharyngeal manifestations of extra-esophageal GERD include chronic rhino-sinusitis and otitis media. Nasopharyngeal exposure to reflux has been found in patients with rhino-sinusitis. GERD treatment with PPI may improve the symptoms of sinusitis.

Pulmonary fibrosis

There is some evidence to suggest that recurrent micro-aspirations of gastric refluxate can lead to pulmonary fibrosis.

Sleep disturbances and GERD

Nocturnal reflux is associated with esophageal injury as well as a higher prevalence of laryngeal and pulmonary manifestations. GERD can affect the quality of sleep by awakening patients from sleep due to nocturnal heartburn and reflux may result in amnestic arousals. Abnormal esophageal acid exposure is also associated with obstructive sleep apnea.[20]

Conclusions

Extra-esophageal manifestations such as chronic cough, reflux laryngitis syndrome, reflux induced chest pain and reflux-induced bronchial asthma are common in patients with GERD. These manifestations can occur in in patients with co-existent other diseases. A trial of PPI therapy, twice-daily for 2-3 months, and evaluation of their response to therapy, is the preferred initial approach to diagnosis and management.

Figure: Treatment algorithm for extra-esophageal manifestations of GERD
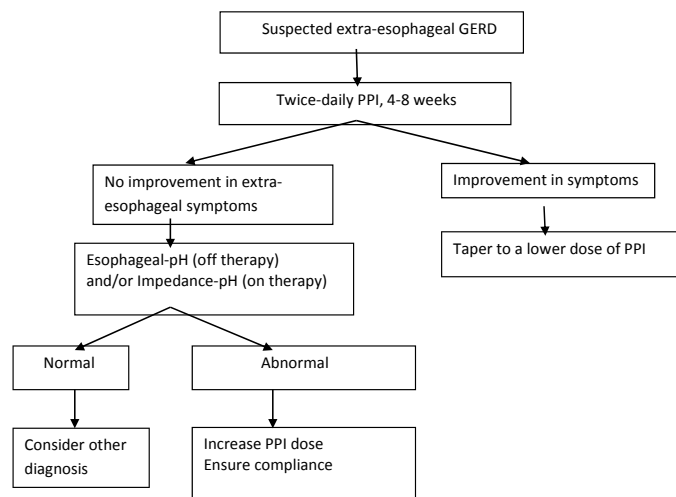
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The Pharmacist's Approach to Heartburn

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The accessibility of pharmacists generally offers the public the opportunity to have their minor ailments[1] assessed: to receive advice, treatment options - non-pharmacological or pharmacological, or to be referred to another health care provider.

Superficially, heartburn – a burning sensation of mid-chest discomfort radiating to throat and neck – may be considered a minor ailment. Regardless of the number of people reporting heartburn symptoms, most of them indicate a waxing and waning of symptoms that may or may not require some treatment option. However, proper triage will help confirm the absence or presence of underlying health issues.

In addition to applying the Connect and Care[2] concept of greeting, listening and assisting the patient with heartburn (Figure 1), the role of the pharmacist, through appropriate questioning[3] (Figure 2) will be to ensure that the patient receives the best treatment option or referral. The patient may have only a single complaint – heartburn – or the heartburn may be one complaint that leads to a broader discussion. In addition, the role of the pharmacist (Figure 3) is to ensure the responsible use of medicine, optimize patient safety, and guide the patient in what to expect from the elected treatment options[4]

Figure 1 Connect and Care Model [2]

Figure 2 Questions to consider when assessing for Heartburn [3]

Figure 3 The role of the pharmacist [4]

If the patient has been referred to the pharmacist by another healthcare provider, the pharmacist should clarify the patient's understanding of, and support that referral. If the patient is seeking pharmacist advice on a primary care basis, the assessment of the patient will include frequency of attacks, intensity and duration. Various patient assessment aids, either electronic or paper, are available (see Figure 11 at end). The patient's assessment of symptom severity will range from 'nuisance' to 'disruption of daily quality of life'. One key consequence of heartburn, for some patients, may be sleep interference.

The pharmacist will query the patient on risk factors[5] (Figure 4). The pharmacist may wish to not only list the risk factors, but also to explain in what way they may affect heartburn.

Figure 4 Risk factors that may contribute to Heartburn [5]

Alcohol can: 1 - increase the relaxation of the lower esophageal sphincter (LES). Gastric acid can then reflux into the esophagus when it normally would not, thereby irritating the esophageal wall; 2 - cause the progressive contractions that occur with swallowing to become erratic. An irregular rhythm can allow acid to enter the esophagus or impair its clearance, thereby triggering heartburn symptoms; 3 - increase the amount of acid produced in the stomach; and 4 - make the esophagus more sensitive to acid and cause inflammation or swelling in its protective lining.

Pregnancy: Heartburn may affect pregnant women due to the effects of progesterone levels on the LES. Pregnancy hormones slow the entire digestive process leading to indigestion and other gastrointestinal problems that may exacerbate heartburn. The crowding of internal organs from the expanding uterus may force stomach fluids up, in a retrograde manner, into the esophagus.

Obesity: increases intra-abdominal pressure and promotes reflux of acidic gastric contents into the esophagus, resulting in heartburn.

Fat: relaxes the LES and delays gastric emptying; both of these factors may promote reflux causing heartburn.

Medications: Anticholinergics, caffeine, ethanol, calcium channel blockers, nicotine and opioids lower LES pressure. Other medications such as bisphosphonates, ASA, clindamycin, NSAIDs, potassium salts and Iron are direct irritants.

Stress: is not a direct cause, but leads to trigger behaviors that may aggravate heartburn and other conditions.

Tobacco use: Smoking can reduce the effectiveness of the LES and slow the production of saliva which helps neutralize stomach acid that has refluxed into the esophagus.

Patients may initially prefer to self-medicate, with or without professional advice. The opportunity for patients to speak with a pharmacist may yield medication or non-medication (life-style) solutions or it may lead to a referral to another professional. It is hoped that pharmacists will access evidence-based medication and therapeutic guidelines to provide best care to their patients. One example of objective comparative drug information can be found through the academic detailing program RxFiles.ca[6]

If the patient has been assessed by the pharmacist, there are 3 options to discuss with the patient - referral to another healthcare provider, recommendation of a non-pharmacological treatment or recommendation of a pharmacological treatment. **The pharmacist** may need to refer the patient to another healthcare practitioner if the patient has any of the risks or warning signs for Gastroesophageal Reflux Disease (GERD) or its complications (Figure 5).
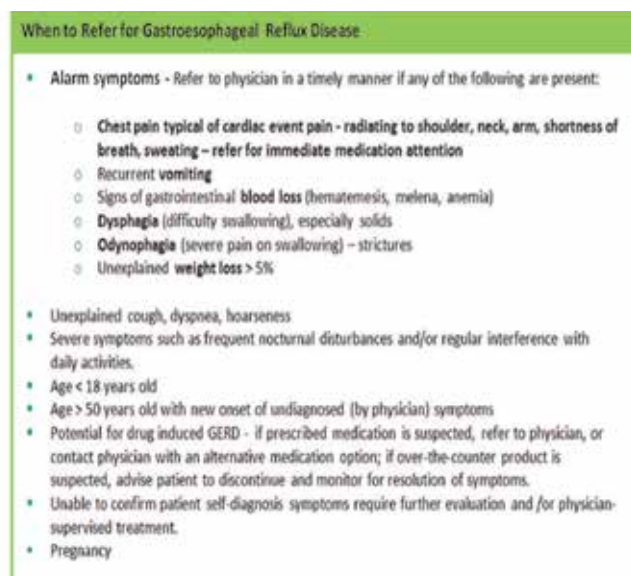
Figure 5 Referral considerations for GERD [1]

The pharmacist may indicate to the patient the benefit from non-pharmacological treatment options. For lifestyle modification (Figure 6), broadly speaking, there are 3 categories:

1. Avoidance of foods that may precipitate reflux (e.g., coffee, alcohol, chocolate, mint, fried or fatty foods)

2. Avoidance of acidic foods that may precipitate heartburn (e.g., citrus, tomato, garlic, onions, carbonated drinks, spicy foods)

3. Adoption of behaviors that may reduce esophageal acid exposure (e.g., weight loss, smoking cessation, eating smaller more frequent

Lifestyle Modifications That May Benefit Patients With Heartburn

- Avoid eating large meals
- Avoid foods, beverages, and activities that promote reflux
- If possible, avoid the use of medications that may aggravate heartburn
- If nocturnal symptoms are present:
  - Avoid lying down for at least 3 hours after eating
  - Elevate the head of the bed 6–10 inches using blocks, or use a foam wedge
- Lose weight if overweight
- Stop or reduce cigarette smoking*
- Wear loose-fitting clothing

*Nicotine may decrease lower esophageal sphincter pressure; the act of smoking decreases salivation.

Figure 6   Lifestyle Modifications for Heartburn [5]

meals, raising the head of the bed, and avoiding recumbence for 2–3 hours after meals).

The pharmacist may indicate to the patient the benefit of pharmacological treatment options from 3 general classes of medicines, Antacids and Alginates, H_2RA Receptor Blockers (H_2RA) and Proton Pump Inhibitors (PPI) (see Figure 9 at end).

Antacids and alginates. Antacids provide rapid, albeit, temporary relief of mild short-term or infrequent heartburn. Antacids are salt compounds of aluminum, magnesium and/or calcium. Viscous alginates, generally provided in combination with an antacid, create a protective barrier on top of gastric contents. Magnesium-containing antacids should be avoided in patients with impaired renal function. If antacids are needed for >2 days a week, the patient may require an OTC H_2RA or PPI. Antacids may provide neutralizing and protective effects depending upon their ingredients. Antacids appear to primarily exert their action in the esophageal lumen.

Selected Medications That Should Not Be Administered Concurrently with Antacids

- Azithromycin
- Dasatinib
- Digoxin
- Fluoroquinolones
- Iron
- Isoniazid
- Itraconazole
- Ketoconazole
- Mycophenolic acid
- Tetracyclines
- Tipranavir

Figure 7   Selected medicine interactions with Antacids [5]

Antacids are capable of interacting with a wide variety of drugs through three primary mechanisms: 1) Binding of another drug in the intestinal tract, 2) Changes in GI pH, and 3) Changes in urinary pH. To prevent the most common and potentially detrimental interactions, patients should not use antacids within 2 hours of enteric-coated products or any of the drugs listed in Figure 7. Antacid-induced alkalinization of the urine may increase blood concentrations of amphetamines and quinidine and decrease concentrations of salicylates. Antacids and alginates are preferred in pregnancy; *OTC H_2RAs are comparable but not superior to antacids for episodic heartburn and GERD.*

H_2RAs. Histamine H_2-receptor antagonists work as selective antagonists at the histamine H_2-receptor, which is located on the basolateral aspect of the parietal cell. The H_2RAs suppress acid production by parietal cells—but to a much lesser degree than the PPIs. Even during treatment with an H_2RA, acid production by the parietal cells can be stimulated by the ingestion of food. Since much reflux (and, therefore, heartburn) occurs in the few hours after meals, this helps to explain why PPIs have proven to be more effective for managing heartburn than the H_2RAs.

OTC H_2RAs (cimetidine, famotidine, nizatidine, ranitidine) are effective for the treatment of mild-to-moderate infrequent heartburn. The lower OTC dosages should be used for mild symptoms, whereas the higher dosages are used for patients with moderate symptoms. The onset of symptom relief is 30–45 minutes, and their effects last ≤10 hours.

H_2RAs should be taken on a "when-needed" basis, as tolerance (tachyphylaxis) may develop to their anti-secretory effect if they are taken every day. An H_2RA may be taken 30–60 minutes prior to eating or exercise to prevent anticipated symptoms. H_2RAs are well-tolerated and have a low incidence of side effects such as headache, diarrhea and constipation.

H_2RAs have advantages (some of which are particularly important for patients in developing countries): faster onset of action, no need to time administration before meals, lower cost, no fear of interaction with clopidogrel, probably safer in pregnancy. Furthermore, they can be used in patients who cannot tolerate PPIs because of side effects.[7] The interaction that occurs with theophylline and warfarin when the cytochrome P-450 enzyme system is inhibited by cimetidine and ranitidine requires monitoring.[8] Evidence, to date, indicates that famotidine does not bind to cytochrome P-450 to a significant extent.

Proton Pump Inhibitors (H+/K+ ATPase Inhibitors). The effects of PPIs can last up to 24 hours. Standard dose, once-daily PPI is more efficacious than an H_2RA. Therapy may be continued for 2-8 weeks, whereupon treatment can be stopped; therapy can be restarted if symptoms recur. There are no clinically important differences among standard doses of PPIs. PPIs are usually well-tolerated with few short-term side effects. Some concerns have arisen regarding an association with some long-term adverse events[9] (Figure 8). When PPIs are strongly indicated, their benefits far outweigh their theoretical risks. However, in cases where PPIs do not have a clear ongoing indication, it is prudent to

consider discontinuing therapy. When stopping a PPI in someone who has been on therapy for several months, some symptomatic rebound acid secretion is a possibility. This could be misinterpreted as a need for ongoing therapy. It is reasonable to taper the PPI over time although evidence is lacking regarding an optimal tapering process. In general, when tapering one may either: a) decrease the PPI dose by 50% for a few weeks or, b) increase the interval between doses to every 2 or more days. This approach may be preferred for PPIs if the lower dose formulation is, relatively, more costly. Antacids or an H$_2$RA such as ranitidine may be used during the taper. In most patients taking long-term PPI therapy for uncomplicated, symptomatic GERD, it is reasonable to attempt to stop or reduce the dose of the PPI at least once per year. Two main concerns with OTC PPI and other therapies are the possibility of misdiagnosis or the under-treatment of patients with severe GERD who require supervised medical care rather than OTC therapy, hence the significance of a 2 week trial period.[10]

Omeprazole may interact with other medications that depend on hepatic CYP 2C19 for metabolism; in particular, it can delay the clearance of diazepam, phenytoin, and warfarin. Because PPIs cause such a profound inhibition of gastric acid secretion, they may interfere with the absorption of drugs for which gastric pH is an important determinant of bioavailability (e.g., ketoconazole, digoxin).[11] There has been some concern with the concomitant use of clopidogrel and medications that are CYP-2C19 inhibitors. Douglas et.al.[12] report that the interaction between clopidogrel and PPIs is clinically unimportant. Clinicians may prefer Ranitidine and Pantoprazole. There have been reports of hypomagnesaemia with some long term users of PPIs. Patients experiencing muscle cramps, palpitations, tremor, and/or dizziness may have their magnesium levels checked.[13] It will always be important to assess the benefit of the chosen therapy (Figure 10).

Figure 10 Patient benefit assessment Heartburn and GERD [1]

Herbal Remedies: There isn't much research into herbal products for heartburn. While there is some evidence for the benefit of a few natural products[14] (e.g., Angelica, Artichoke, Caraway, German Chamomile and Lemon Balm) for dyspepsia, there is no, or limited, evidence for natural products to treat heartburn. Bitter Orange, Capsicum, Fenugreek and Turmeric for example have no convincing evidence. Just because herbal remedies may be seen as 'natural', they can still interfere with other medicines.

Can drinking milk or chewing gum help heartburn? While milk may temporarily buffer stomach acid, nutrients in milk, particularly fat, will stimulate the stomach to produce more acid. Overfilling the stomach may increase heartburn. It may sound strange but gum stimulates the production of saliva, which is an acid buffer. Peppermint free chewing gum also makes you swallow more often, which could improve the clearance rate of reflux within the esophagus.[15] It has been suggested that yogurt and papaya or papaya juice may reduce heartburn.

In summary, pharmacists with access to evidence based treatment guidelines, an understanding of heartburn and related illnesses, and an understanding of available medicines can assist any patient in the caring for their heartburn.

Adverse effect	Comment	References
Enteric infections	Mostly retrospective studies; suppression of acidity by PPIs might predispose to bacterial enteric infection by raising intragastric pH; absolute risk is low	44-47
Community-acquired pneumonia (CAP)	Reduction of gastric acid secretion might predispose to gastric colonization with bacteria that may trans-migrate to the lungs. Note that GERD *per se* is a risk factor for pneumonia. PPI taking may be a surrogate for GERD. No increased risk of CAP seen with long-term PPI use in one study	44, 45, 48, 49
B$_{12}$ malabsorption	Suppression of gastric acidity might impair the ability to extract dietary vitamin B$_{12}$ from food proteins. B$_{12}$ deficiency attributable solely to PPI taking has not been described	44, 45
Hip fracture	The mechanism of this observed effect is unknown. Quantitative risk is low. No evidence that PPIs increase rate of osteoporosis or accelerate bone demineralization	44, 45, 50-54

Figure 8 Potential consequences of long-term use of proton pump inhibitors [9]

Figure 9 Advice to patient for Heartburn and GERD [1]

Figure 11 Patient assessment tool for Heartburn and GERD [1]

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Differential Diagnosis of Heartburn

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Clinical evaluation

Heartburn is characterized by retrosternal burning pain or discomfort that originates high in the epigastrium with intermittent cephalad retrosternal radiation. Although translations and interpretations of the term "heartburn" may vary among countries and languages, typical heartburn is traditionally considered as a specific symptom for gastro-esophageal reflux disease (GERD), thus allowing diagnosis without the need for any further invasive investigation [1]. This assumption remains valid in the majority of patients especially in the primary care setting. In clinical practice, many patients are referred for "heartburn" which appears to be, after a careful interview, either epigastric burning or sore throat. In these patients, the probability of GERD-related symptoms and the response rates to PPIs are probably much lower compared than in patients with actual heartburn [2]. In patients with heartburn, empirical treatment with PPIs provides symptom relief in 50-70% of cases. In cases of treatment failure, physicians should check for compliance to therapy before embarking for additional investigations. Compliance to once-daily PPI in GORD has been reported to be lower in patients with refractory symptoms (46-55%) as compared to patients with adequate relief (84%)[3]. In addition to compliance, the time of dosing should also be checked since taking PPIs 15 minutes before a meal results in a better gastric pH control [4] although it has not been clearly demonstrated yet that this is associated with improved clinical efficacy.

Physicians have to keep in mind that the failure of therapy in patients with heartburn is often related to the absence of reflux-related symptoms, and that additional investigations are mandatory.

Endoscopy

Upper GI endoscopy must be performed in patients who have refractory heartburn, despite therapy, or alarm symptoms. Endoscopy can confirm the diagnosis of GERD when erosive esophagitis or Barrett's esophagus is present. However, the prevalence of erosive esophagitis in patients previously treated with PPIs is below 10% [5] and may reflect poorly-controlled acid reflux. Esophageal biopsies samples should be obtained regardless of the gross appearance of the esophageal mucosa, to rule out eosinophilic esophagitis. Eosinophilic esophagitis is an allergic disorder defined by symptoms related to esophageal dysfunction and characterized by an eosinophil-predominant inflammation on analysis of esophageal biopsy samples [6]. Mucosal eosinophilia is usually isolated to the esophagus, characteristically consisting of a peak value of ≥15 eosinophils per high-power field. In adults, dysphagia is the most frequent symptom of this disorder but in case of heartburn not responding to PPI therapy, upper endoscopy with biopsies may diagnose eosinophilic esophagitis in 1 to 4% of patients [5, 7, 8]. It is important is to look for endoscopic esophageal features of eosinophilic esophagitis such as concentric rings (trachealisation), exudates (white spots), furrows or edema, but the endoscopic appearance of the esophageal mucosa may be normal in 10–25% of patients [9].

Finally, endoscopy can also demonstrate the presence of a severe esophageal motor disorder, such as achalasia, if there is esophageal stasis in a dilated esophagus associated with a 'tight' esophago-gastric junction [9].

Esophageal manometry

All patients who have failed empirical management should have esophageal manometry before reflux monitoring to position pH sensors (especially when recordings are performed in patients taking a PPI) and to rule out achalasia or severe esophageal motor disorders. Indeed, the prevalence of heartburn has been reported to be as high as 35% in achalasia [10, 11].

## Ambulatory monitoring for reflux

Once persisting erosive esophagitis, eosinophilic esophagitis and esophageal motility disorders have been ruled out, a patient with refractory heartburn should be investigated for reflux in ambulatory conditions. The aim of reflux testing is to demonstrate the presence of abnormal reflux (either acid or non-acid) and/or the temporal association between symptoms and reflux events. If GERD has never been previously demonstrated (absence of esophagitis or abnormal pH monitoring), a 24-h pH monitoring without treatment is indicated. If investigations have documented GERD (esophagitis or abnormal pH monitoring), reflux testing should be performed on therapy to assess the residual reflux events and their correlation with symptoms. It is now well demonstrated that testing on therapy should be performed by pH-impedance monitoring which allows the detection of both acid and non-acid reflux events [12]. These investigations will help to distinguish patients with GERD-associated symptoms from those whose symptoms are not GERD-related. In the first group, patients may have either increased acid exposure ("non-erosive reflux disease" or "true refractory GERD" when performed on PPIs) or normal acid exposure but positive symptom-reflux association (the so-called "reflux hypersensitivity" or "esophageal hypersensitivity"). In the second group, patients have normal acid exposure and reflux events and no association between reflux and symptoms: this is the current definition of "functional heartburn". Functional heartburn is likely to represent less than 10% of heartburn patients presenting to gastroenterologists [13], but the proportion may vary between primary care settings and tertiary centers. In a population of 100 patients referred to tertiary centers for reflux testing with pH-impedance monitoring off therapy, the reported prevalence of functional heartburn was 21% in patients refractory to PPIs [14]. The mechanism of symptom perception in functional heartburn is unclear. The prevailing view considers altered visceral perception as a major determinant, but the trigger stimuli provoking heartburn

are unclear, since triggering by any form of reflux events rules out the diagnosis of functional heartburn. The treatment of functional heartburn remains largely empirical, and an individualized approach is therefore recommended. The clinician should provide reassurance and refrain from performing repeated invasive procedures. Since the pathophysiology of functional heartburn mainly involves visceral hypersensitivity, use of pain modulators like low dose tricyclic antidepressants and possibly selective serotonin reuptake inhibitors is reasonable.

Table - Differential diagnosis of heartburn as a gastro-esophageal reflux symptom

Epigastric pain
Sore throat
Eosinophilic esophagitis
Esophageal motility disorders (incl. achalasia of the cardia)
Reflux hypersensitivity (hypersensitive esophagus)
Functional heartburn
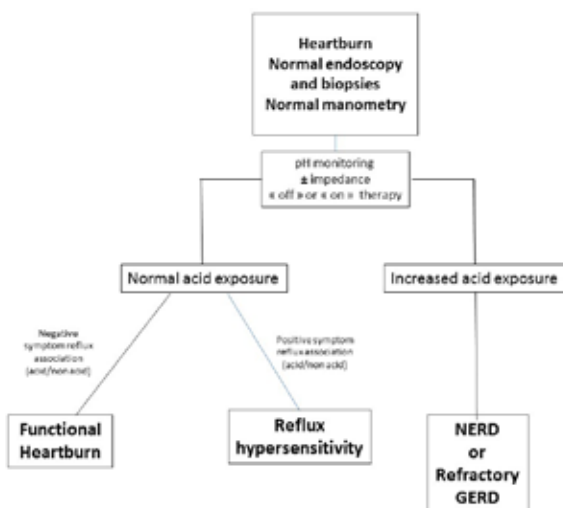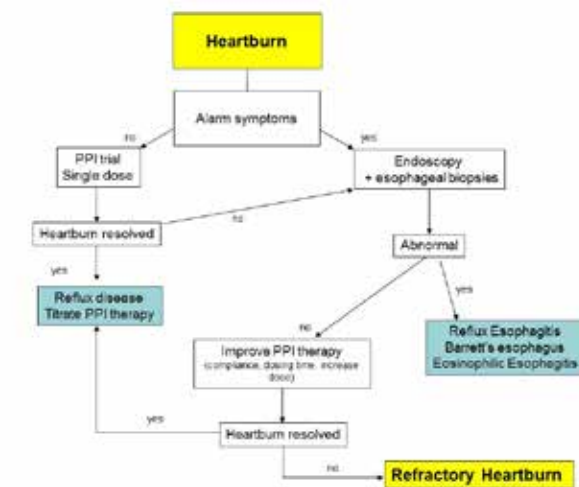
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WGOF-0116-517