REVIEW ARTICLE

Guidelines on gastroesophageal reflux disease

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Abstract

Gastroesophageal reflux disease (GERD) is the most common acid-related disorder encountered during clinical practice in Pakistan and is associated with significant impairment of health-related quality of life. A number of guidelines and recommendations for the diagnosis and management of GERD have been published in different countries, but a Pakistani accepted directive by the standards of evidence-based medicine is still lacking. Our aim was to create an understanding of the natural history and presentations of reflux disease; evaluating possible treatment options available for the patients with complex and uncomplicated reflux ailments with the development of current and up to date evidence based endorsement, relevant to the needs of Pakistani health care providers in order to treat oesophageal manifestations of GERD. In order to make such guidelines, a comprehensive literature search was conducted with pertinent evidence reviewed, and quality of relevant data assessed. The resultant conclusions were based on the best available evidence and expert opinion of the authors of technical review panel.

Keywords: Gastroesophageal reflux disease, Pakistan.

Introduction

In order to create an understanding of the natural history and presentations of reflux disease; evaluating possible treatment options available for the patients with complex and uncomplicated reflux ailments with the development of current and up-to-date evidence-based endorsement relevant to the needs of Pakistani healthcare providers to treat oesophageal manifestations of gastroesophageal reflux disease (GERD), the current literature review was planned. In order to generate guidelines, a comprehensive literature search was conducted with pertinent evidence reviewed, and quality of relevant data was assessed. The resultant conclusions were based on the best available evidence and expert opinion of the authors of technical review panel. The quality of methodology was evaluated based on the user's guide for medical literature for therapeutics and prevention study.[1] Levels of evidence and recommendations grades were defined according to the classification of the Oxford Centre for Evidence-based Medicine[2] (Table-1). Grade A is "highly recommended" and is applied to studies with grade 1 evidence (systematic reviews of randomised controlled trials [RCTs] or large randomised trials with a low

Table: Grade of recommendation and levels of evidence.

Recommendation Grade	Levels of evidence	Types of study
A	1	
	1a	Systematic review of homogeneous RCTs with good methodological quality
	1b	Individual RCTs with narrow confidence intervals
	1c	Uncontrolled studies (dramatic findings)
B	2	
	2a	Systematic review of cohort studies (with homogeneity)
	2b	Individual cohort studies (including low quality RCTs, e.g. <80% follow-up)
	2c	Uncontrolled cohort studies/ecological studies
	3	
	3a	Systematic review of case control studies (with homogeneity)
	3b	Individual case control studies
C	4	Poor quality case series / cohort studies or case control studies
D	5	Expert opinion without explicit or physiology-based critical evaluation; Laboratory research or "first principles"

RCT: Randomized clinical trial.

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probability of bias or without bias).[2]

The Consensus group

The prime intention of Pakistan Society of Gastroenterology (GERD Consensus Group) was to create guidelines for the diagnosis, investigation, symptoms and management of GERD by strictly using evidence-based approach. This criterion, set of standards and recommendations can be clinically applied by primary care physicians and specialists, and would embrace the essentials of physicians, investigators and monitoring bodies. A steering committee comprising invited experts in the area of GERD management, evidence-based medicine and continuing medical education (CME) joined a multidisciplinary consensus group that comprised 14 participants and discussed GERD.

Definition

There can be no standard definition of GERD because the threshold distinction between physiological reflux and reflux disease is still subjective. Hence, these queries can only be answered by judgment or opinion. The Montreal consensus panel defined GERD as "a condition which cultivates when the reflux of stomach contents causes troublesome symptoms and/or complications.[3] "Oesophageal GERD syndromes are classified as those that are symptom-based and those that are defined by tissue damage. In contrast, the extra-oesophageal syndromes are classified as having established or proposed association with GERD.[3]

Prevalence

Around 44% of the US adult population has heartburn at least once a month, 14% have symptoms weekly and 7% experience symptoms on daily basis. Most patients have a tendency to self-diagnose and treat the disease themselves.[4] In Asian countries the frequency of GERD remains significantly lower than that seen in Western regions.[3] A study conducted by Riaz et al, showed percentage of Pakistani students having weekly episodes of heart burn is significantly higher than that in general Asian population.[5]

Demographic factors and GERD

A study by Dent et al. shows the incidence and severity of GERD symptoms in relation to socio-demographic parameters.[4] In this study, there was no difference between males and females having GERD symptoms, but GERD symptoms were more common among older subjects (p=0.0002). The results of the study represent a particular group and cannot be translated to other parts of the world. But surely, these results give us a picture about the demographic relation with GERD.[4] Association with age, gender and pregnancy is questionable. On the contrary, there was a strong association of GERD with high body mass index (BMI) and white race. The incidence of GERD is on the rise in Asians, especially in women. However, men over the age of 60 develop more complications.[6] GERD and Helicobacter (H) Pylori have shown inverse time trends; epidemiological data and research suggests that GERD patients with oesophagitis are less likely to have H. Pylori infection.[5] Factors

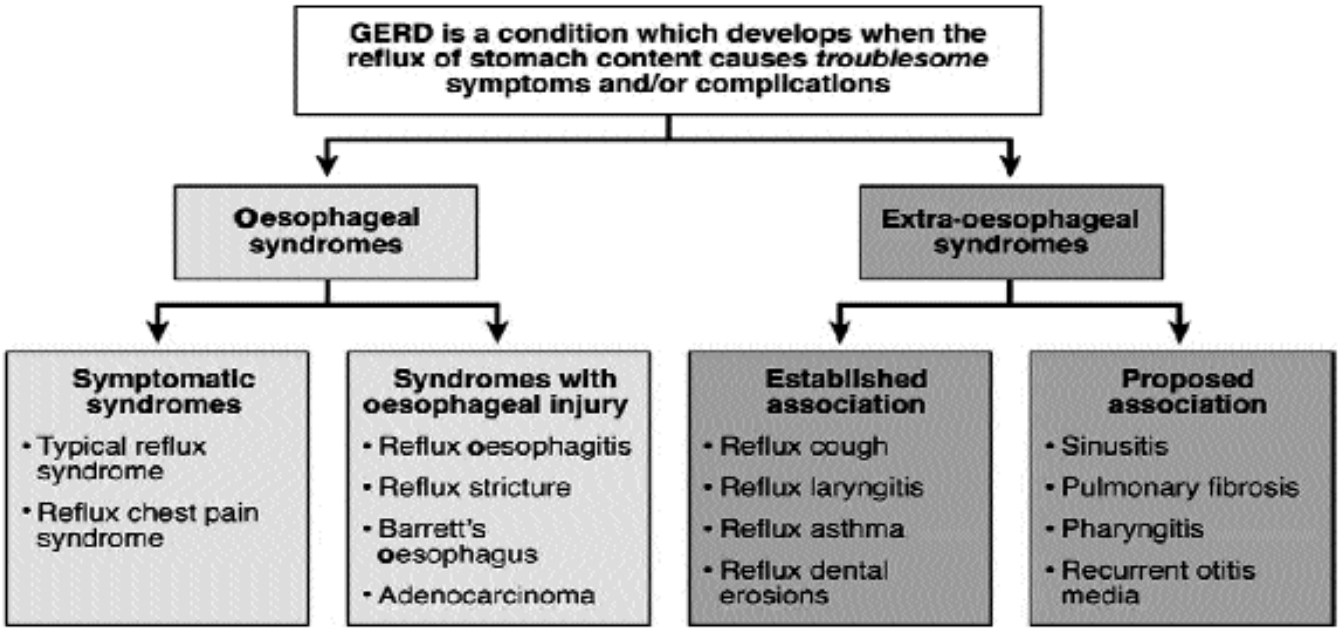

Figure-2: Factors associated with GERD.

associated with GERD are several (Figure-2).[3] Behavioural factors such as cigarette smoking and coffee utilisation are thought to trigger GERD.[7] Peptic ulcer, anxiety and unhappiness are associated with an increased incidence of GERD.[8,9] A study by Jafri et al, has shown that GERD is quite common in the urban population of Pakistan.[10]

Pathophysiology

Transient relaxation of the lower oesophageal sphincter (LES) is an important cause of reflux events both in normal individuals and in patients with oesophagitis. Newer evidence suggests that the frequency of these transient relaxations is not higher in GERD patients than normal, but when relaxations do occur, they are more likely to be associated with reflux of acid in GERD patients.[11] Few episodes of reflux are due to abrupt increases in intra-abdominal pressure that overcomes LES pressure. This is probably a greater factor in patients with more severe grades of oesophagitis than in those with mild disease.[12] Transient relaxation is not the mechanism of GERD in hiatus hernia.[13] Hiatal hernia has been convincingly implicated as a contributor to reflux. Hiatal hernia interferes with this increased LES pressure, and the larger the hernia, the smaller the benefit of the crus in preventing reflux.[14] About 30% of patients with heartburn severe enough to require self-medication with antacids have sensitivity to oesophageal acid infusion or balloon distension despite normal endoscopies and pH probes.[15]

Symptoms

History of the patient should identify the characteristic symptom and define their intensity, duration and frequency; uncover the triggering and relieving factors and determine the pattern of evolution of the disorder over time, as well as its impact on the patient's quality of life (QOL). In this context, it is important to consider patient's age and the presence or absence of alarm manifestations, which include dysphagia, odynophagia, weight loss, gastrointestinal (GI) bleeding, nausea and/or vomiting and a family history of cancer. On the other hand, the absence of typical symptoms does not exclude the diagnosis of GERD. Oesophagogastricendoscopy can reveal reflux oesophagitis or eosinophilicoesophagitis.[16-17]

Functional heartburn should be ruled out in all patients; burning retrosternal discomfort/pain; absence of evidence that GERD is the cause of symptoms; and the absence of histopathology-based oesophageal motility disorder. The above-mentioned criteria should be fulfilled for the preceding 3 months, with symptom onset of at least 6 month prior to diagnosis.[18] Rome III Criteria for Non-Erosive Reflux Disease (NERD) is an abnormal acid exposure or a positive symptoms-reflux association in the absence of macroscopic endoscopic signs of reflux oesophagitis.[19]

Diagnosis

Endoscopy

Endoscopy is indicated mainly in two situations; when the so-called warning symptoms (dysphagia, odynophagia, weight-loss, signs of GI blood loss) are present and in patients thought to be at risk for Barrett oesophagus. Patients with warning symptoms should be easily identified with a carefully obtained history, but who to screen for Barrett oesophagus is more problematic. A recent study suggests that endoscopy in GERD patients with refractory symptoms may reveal eosinophilicoesophagitis in a subset.[20] oesophagitis is only diagnosed if there are breaks in the mucosa of the oesophagus and should be graded using an accepted scale.[7] The extent of columnar replacement of oesophageal mucosa should be clearly described and measured. The distance from the teeth to the oesophagogastric junction should be recorded. A retroflexed view is obtained and any hernia should be described and measured. The ability to image the oesophagus in a less invasive and perhaps less expensive manner remains a goal of several research programmes. A disposable oesophageal pill camera has been developed and marketed. In early, very small studies, this device had impressive sensitivity and specificity when compared to routine endoscopy.[21]

Recommendations

1. Signs and symptoms are insufficient to establish a conclusive diagnosis of GERD, regardless of their frequency and intensity, resulting in a diagnostic certainty of around 40% (A 1/a).

2. Endoscopy is not usually performed in young adult patients with typical history of GERD since it does not alter the clinical evolution when compared to the empiric treatment (A 1/c).

3. Endoscopy can identify oesophageal complications of GERD, including oesophageal ulceration and stricture, Barrett's oesophagus, and oesophageal adenocarcinoma (B 1/a).

4. Alarm symptoms that suggest these complications include long duration (>10 years) of typical symptoms, dysphagia, haematemesis or melena, and weight-loss. The presence of these symptoms is a strong indication for diagnostic testing, especially endoscopy. Male gender, middle age and nocturnal heartburn may be associated with a higher risk of oesophagitis and its

complications (B 1/a).

Ambulatory Reflux Monitoring

There have been several methods developed to test for reflux from the stomach to the oesophagus. Traditionally, these have consisted of a tube with an electrode that measure pH passed through the nose into the oesophagus. Recently, both a tubeless pH monitoring device and impedance based devices (to evaluate non-acid reflux) have been developed. Ambulatory reflux tests are most useful in patients with GERD symptoms that have not responded to empiric therapy and to confirm GERD in patients under evaluation for endoscopic or surgical therapy.[22]

Recommendations

1. pH monitoring (proton-pump inhibitors [PPI] therapy withheld for 7 days) should be used to evaluate patients with a suspected oesophageal GERD syndrome; who have not responded to an empirical trial of PPI therapy, have normal findings on endoscopy, and have no major abnormality on manometry (A 1/b).

2. In patients with atypical manifestations, the impedance-pH-metry substantially contributes to the diagnosis of GERD. However, the examination is costly and scarcely available in our country (A 1/c).

Other Tests

Barium studies do not provide accurate data in the evaluation of GERD and should not be routinely used outside of patients with dysphasia and in some selected patients prior to endoscopic or surgical therapy. While oesophageal motility testing will reveal abnormalities in LES pressure and oesophageal peristalsis in many GERD patients, the use of this test is restricted to finding the location of the LES to facilitate accurate placement of reflux monitoring probes and perhaps to help guide anti-reflux surgery. Likewise, some patients with GERD will have evidence of delayed gastric emptying with nuclear medicine testing, but testing for this is not routinely recommended. Patients who are at risk for cardiac disease may need additional testing to rule out coronary artery disease (CAD).[22]

Recommendations

1. Gastroesophagealscintigraphy is used rarely to demonstrate gastroesophageal reflux or aspiration. The test may be more useful in patients who have concomitant symptoms of delayed gastric emptying (B/2b).

2. Manometry may be used to evaluate patients with suspected oesophageal GERD syndrome who have not responded to an empirical trial of twice-daily PPI therapy and have normal findings on endoscopy. Manometry will serve to localise the LES for potential subsequent pH monitoring, to evaluate peristaltic function preoperatively, and to diagnose subtle presentations of the major motor disorders. Evolving information suggests that high-resolution manometry has superior sensitivity to conventional manometry in recognizing atypical cases of achalasia and distal oesophageal spasm. (A 2/b)

Therapeutics

Lifestyle Changes

Education of the patient about factors that may precipitate reflux remains reasonable.[23,24] Numerous studies have indicated that elevation of the head of the bed, decreased fat intake, cessation of smoking, and avoiding recumbency for 3 hours postprandially all decrease distal esophageal acid exposure, although data reflecting the true efficacy of these maneuvers in patients is almost completely lacking. Certain foods (chocolate, alcohol, peppermint, coffee, and perhaps onions and garlic) have been noted to lower LES pressure, although randomised trials are also not available to test the efficacy of these manoeuvres.[25-29] Many authors assume that 20% to 30% placebo response rate, seen in most randomised trials, is due to lifestyle changes, but this has not been rigorously tested. The potential negative effect of lifestyle changes on a patient's quality of life has also not been examined.[30-33]

Recommendations

1. Weight-loss should be advised for overweight or obese patients with oesophageal GERD syndromes (A /3a).

2. Elevation of the head of the bed for selected patients who are troubled with heartburn or regurgitation when recumbent. Other lifestyle modifications including, but not limited to, avoiding late meals, avoiding specific foods, or avoiding specific activities should be tailored to the circumstances of the individual patient (A 2b).

Anti-refluxants and Antacids

Alginate-based formulations have been available for the past 30 years. Alginates act by a unique mechanism in which the alginate precipitates in the presence of gastric acid forming a gel. The gel then traps carbon dioxide creating foam that floats on the surface of gastric contents like a raft on water.[34-37] They are inexpensive and have a very rapid onset i.e. within 3 minutes.[38,39] Antacids are better than placebo in achieving relief of heartburn.[40]

Recommendations

1. Alginates are an effective treatment in mild to moderate GERD, especially in primary care and should be preferred as first line of therapy (B/3a).

2. Alginates and Antacids could be considered in special situations (such as the occurrence of adverse events with histamine 2 receptor antagonists [H2RA] or PPI) to provide transient symptomatic relief (C/4).

Acid Suppression

Acid suppression is the mainstay of GERD therapy. This has evolved quickly over the past few decades. H2RAs were introduced in the 1980s and, for the first time, provided a specific pharmacological approach to control acid secretion. H2RAs are relatively effective in treating heartburn symptoms with a rapid onset of action. Patients who continue to have heartburn after 6 weeks of treatment with H2RAs are unlikely to respond to prolonged courses or increased dosages. These agents have various approved doses and there are small differences in side effects, but overall, their efficacy is quite similar.[41-43]

In 1989, the first PPI (omeprazole) was developed. This was followed by the introduction of three additional agents (lansoprazole, pantoprazole and rabeprazole) with similar efficacies. A review of 33 randomised trials, including over 3000 patients, showed that symptomatic relief can be expected in 27% of patients treated with placebo, 60% treated with H2RAs, and 83% treated with PPIs.[44] Of those patients with oesophagitis, 24% treated with placebo, 50% treated with H2RAs, and 78% treated with PPI had mucosal healing. The best dose timing for maximum serum concentration and efficacy is when the largest numbers of proton pumps are active. Meals stimulate proton pumps, so dosing the drug 15-60 min prior to a meal produces the most effective acid suppression.[45] It has been suggested that patients on once-daily PPIs take the dose prior to breakfast. Once-daily PPI therapy suppresses gastric acid for 11.2 to 15.3h during a 24h day.[46] More recently, an optically pure preparation of omeprazole was tested and approved as a different agent (esomeprazole).[47] Omeprazole was combined with an antacid and alginate in a new formulation that may have some advantages over the parent compound including the ability to be taken without meals and perhaps more rapid onset of action.[48]

Recommendations

1. Anti-secretory drugs for the treatment of patients with oesophageal GERD syndromes (healing oesophagitis, symptomatic relief, and maintaining healing of oesophagitis). In these uses, PPIs are more effective than H2RAs, which are more effective than placebo (A 1a).

2. Long-term use of PPIs for the treatment of patients with oesophagitis once they have proven clinically effective. Long-term therapy should be titrated down to the lowest effective dose based on symptom control (A 1b).

Prokinetic (Motility) Therapy

Prokinetic drugs are appealing in the treatment of GERD as they may increase gastric emptying, improve peristalsis and increase LES pressure. Unfortunately, these agents are typically not effective as mono-therapy and their side effect profiles often limit their use.[48,49]

Recommendations

1. Prokinetics are inferior to PPI's for the treatment of GERD symptoms in patients without documented erosive esophagitis (A 1/c).

2. Prokinetics are considered to be the second-line therapy in patients with GERD (B 1/b).

Long-term (Maintenance) Therapy

Many patients with GERD require long-term, possibly life-long, therapy; therefore maintenance therapy to keep symptoms comfortably under control and prevent complications is a major concern.[50-53] This will vary in each patient and may require only antacids and lifestyle modifications in up to 20% patients. Patients whose disease has required PPIs for control often will have symptomatic relapses and failure of healing of oesophagitis on standard dose, or even higher dose H2RA and/or prokinetic therapy.[54-57] A full dose of H2RA given once daily, though effective for peptic ulcer disease, is not appropriate for GERD. There does not appear to be a safety advantage with using a lower PPI dose for maintenance, but the indication for some PPIs do suggest a lower maintenance dose (esomeprazole 20mg and lansoprazole 15mg are examples). Ultimately, whatever dose of medication is needed to control symptoms is the dose that should be used and may include full or even increased dose PPI in many patients.[58] There is clear data that full dose PPIs lengthen the interval between symptomatic relapses in patients with oesophageal strictures requiring dilation.[59] There is one retrospective study suggesting less dysplasia in patients with Barrett who take PPI,[60] but this needs confirmation in a large, properly-designed trial. Since many patients will be treated with PPI on a long-term basis, safety is a major concern. Several retrospective studies have recently suggested small but significant increases in community-acquired pneumonia,[61]

clostridium difficile infection[62] and hip fractures[63] in patients on PPI (particularly higher than indicated doses). Atrophic gastritis in chronic omeprazole users is common, but it seems to occur predominantly in patients who are infected with H. pylori.

Recommendations

1. Twice-daily PPI therapy for patients with an oesophageal syndrome with an inadequate symptom response to once-daily PPI therapy (B/2a).

2. Short course (8 weeks) of anti-secretory therapy is recommended in patients with a symptomatic oesophageal syndrome. For a short course of therapy, PPIs are more effective than H2RAs, which are more effective than placebo (A/1c).

3. As needed, use of anti-secretory drugs in patients with a symptomatic oesophageal syndrome without oesophagitis when symptom control is the primary objective. For a short course of therapy, PPIs are more effective than H2RAs, which are more effective than placebo (B/2a).

Endoscopic and Surgical Approaches

The vast majority of GERD patients will have mucosal disease and the majority of symptoms controlled with medical therapy. There is a small subset with symptoms that either are, or appear to be, refractory to medical therapy. A trial that randomised 310 patients between surgery and PPIs found surgery to be slightly superior to omeprazole at the end of 7 years in terms of controlling GERD symptoms although there were more bothersome side effects in the surgical group.[64] Proper selection and preoperative evaluation of patients is very important. In a study of 100 patients, the best predictors of a good outcome were age less than 50 years and typical reflux symptoms that had completely resolved on medical therapy.[65] It is also clear that these typical reflux symptoms are more likely to resolve after surgery than the other atypical and supra-oesophageal symptoms. If typical reflux oesophagitis is not present endoscopically, ambulatory pH testing should be performed to confirm the disease.

Recommendation

1. When a patient with an oesophageal GERD syndrome is responsive to, but intolerant of, acid suppressive therapy, who want to discontinue maintenance treatment or when the reflux of stomach contents causes troublesome symptoms and/or complications, anti-reflux surgery should be recommended as an alternative if adequate and safe surgical expertise is available (A 1b).

2. Preoperatively, it is important to verify that the patient's symptoms in fact are due to reflux. This is accomplished by documenting reflux oesophagitis and a response to PPI therapy or by confirming the pathological degree of reflux with a 24-hour pH assessment while the patient is not receiving therapy (A/1b).

3. Preoperative oesophageal manometry has been widely recommended. It identifies a severe motility disturbance such as achalasia or connective tissue disease, and some surgeons want confirmation of a weak lower oesophageal sphincter, if present (A/1c).

Complications of GERD

Apart from typical reflux symptoms and oesophagitis, the clinical presentation of GERD can be dominated by mucosal complications of reflux:

- Barrett's oesophagus (BE)

- Oesophageal adenocarcinoma

- Peptic structure

- Extra-oesophageal syndromes, most notably asthma, laryngitis or chronic cough.

Frequency of BE in patients with symptoms of gastroesophageal reflux disease is 6-14% in Pakistan.[66] Risk factors for BE are age >40, male gender, long duration of GERD symptoms, hiatal hernia and high BMI.[67] The diagnosis should be made with endoscopy and biopsy of columnar lined oesophagus only. The natural history of asymptomatic BE is unknown.[68] BE is histologically classified into three categories, depending on whether or not they exhibit dysplasia:

(1) BE without dysplasia

(2) BE with low-grade dysplasia (LGD), and

(3) BE with high-grade dysplasia (HGD)

Diagnosis of dysplasia in BE should be confirmed by second specialised pathologist.[69] Rates of progression from LGD to either HGD or oesophageal adenocarcinoma range from 0.5%to 13.4% per patient per year, depending on the pathological confirmation of dysplasia. Risk of progression from HGD to cancer is 6% per patient per year. Surveillance endoscopy in patients with BE is controversial due to lack of randomised trials. Literature review does not suggest a survival benefit with endoscopic surveillance.[70] PPI therapy can be used to control reflux symptoms. Retrospective studies showed a decrease in development of dysplasia in

patient with BE on PPIs. Current data does not support the use of high-dose anti-secretory therapy.[71] Patients with BE should be referred to specialised centres for endoscopic therapy. Multi-centre randomised controlled trials support the use of endoscopic eradication in HGD. Endoscopic eradication therapy with radiofrequency ablation (RFA), photodynamic therapy (PDT), endoscopic mucosal resection (EMR) or cryotherapy for HGD is recommended.[72,73] Anti-reflux surgery does not decrease the rate of adenocarcinoma in patients with reflux. Majority of data does not provide support that fundoplication prevents oesophageal adenocarcinoma. A meta-analysis found similar cancer incidence rates between the surgical and the medical groups (3.8/1000 patient-years vs. 4.2/1000 patient-years).[74]

Recommendations

1. Screening of the general population with GERD for BE is not recommended (A 2/a).

2. Patients with multiple risk factors (age $\geq$40 years, male gender, chronic GERD, hiatal hernia and elevated BMI), screening for BE is recommended (C/4).

3. Diagnosis of dysplasia in BE should be confirmed by second specialised pathologist (1B).

4. At present, endoscopic surveillance should not be performed in patients with BE (A2a).

5. Patients with BE, PPI therapy in a dose to treat GERD symptoms and to heal reflux oesophagitis is indicated. High-dose anti-secretory therapy is not indicated (A/1b).

Extra-oesophageal symptoms of GERD are not uncommon and the treatment is of inconsistent benefit.[75]

Recommendations

1. Asthma, laryngitis, and chronic cough are associated with GERD (A2b).

2. Extra-oesophageal manifestations of GERD are usually multifactorial (A2b).

3. Treatment benefit for extra-oesophageal GERD manifestations is less predictable than for heartburn or oesophagitis (A1b).

Peptic oesophageal stricture occurs as a consequence of chronic GERD and is the most common cause of benign oesophageal strictures. They account for 90% of benign oesophageal strictures.[76] Peptic strictures occur usually at the squamocolumnar junction and measure 1-4 cm in length. Dysphagia is the predominant symptom due to narrowing of oesophageal lumen usually up to 13mm or less in diameter.[77] In the era before anti-secretory drugs, medical therapy had little role in the management of peptic oesophageal strictures. Recent studies have shown that PPIs both improve dysphagia and decrease the need for subsequent oesophageal dilations in patients with peptic oesophageal strictures.[78] Endoscopic dilatation is the first line of treatment for benign oesophageal strictures. Endoscopic dilation with bougies or balloons is the standard treatment for such lesions. There are mainly three types of dilators Maloney or Hurst dilators, Savary-Gilliard dilators and balloon dilators. The rate of perforation after dilation is low;one study reported only one perforation in 400 patients dilated with polyvinyl dilators.[79] A prospective, randomised, double-blind, placebo-controlled trial suggested that steroid injection into the stricture combined with acid suppression significantly improved dysphagia, and decreased both the need for repeat dilation and the average time to repeat dilation compared to sham injection and acid suppression alone.[80] The efficacy of fully covered self-expanding removable stents (SERS) in benign refractory stricture is 46.2%; it is associated with migration rate of 26.4% reported in meta-analysis.[81]

Recommendations

1. In patients with peptic oesophageal stricture, PPI therapy improves dysphagia and decreases the need for subsequent oesophageal dilations (A 2/b).

2. Oesophageal stricture dilatation is effective in relieving dysphagia with lower risk of perforation (A 2/c).

3. Endoscopic steroid injection therapy for refractory oesophageal peptic strictures improves dysphagia, and decreasesthe frequency of dilation (C I/b).

4. Efficacy of oesophageal stenting with SERS is not promising and migration rate is high, hence it is not recommended currently (A I/c).

5. Comparing with balloon dilators, Savary dilators have shown similar stricture recurrence rate in the first year, but lower in the second year and less number of sessions are required to relieve dysphagia (C1b).

Conclusion

GERD is a common disease in this part of the world that imparts a high socioeconomic burden. These guidelines may be useful for diagnosing GERD and performing clinical and research assessments in the Pakistani population. When the benefits and risks, together with the cost-effectiveness, are taken into consideration, early diagnosis and treatment should be offered to the

patients with GERD, in order to decrease the socioeconomic burden and complications related to this disorder.

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