



On Gastro-oesophageal Reflux-Induced Diseases

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This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded one CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 31 March 2008.

Gastro-oesophageal reflux-induced diseases (GERD) are commonly encountered gastro-intestinal disorders and classical symptoms include heartburn, acid regurgitation and atypical chest pain. Oesophageal manifestations and complications of GERD include erosive oesophagitis, oesophageal stricture, Barrett's oesophagus and oesophageal adenocarcinoma. The wide range of extra-oesophageal associations includes sleep disturbance, cough, laryngitis, laryngeal cancer, hoarseness, asthma, sinusitis and dental erosion. There is a perception that the prevalence of GERD is increasing in Asia and the prevalence assessed at two time-points in one city was rising in China and Singapore¹. Obesity, hiatus hernia, smoking and psychosocial factors like heavy workload, anxiety, divorce have been shown to be associated with GERD or heartburn². Although the prevalence of Barrett's oesophagus and adenocarcinoma of oesophagus is still low in HK Chinese, unexpectedly high figures were reported in Xi'an³ and Japan⁴.

1. Pathophysiology of GERD

The contribution of hiatus hernia to GERD is well known. The hiatus hernia eliminates the contribution of the crural diaphragm to lower oesophageal sphincter function and thereby promotes gastro-oesophageal reflux, especially when intragastric pressure is increased due to distension or straining of the abdominal musculature. The most common cause of GERD in the West is an excessive exposure of the oesophagus to acid and pepsin during transient lower oesophageal sphincter relaxation (TLESR). These periods last for 10-30 seconds in normal persons to help to vent gas from the stomach but they are frequently associated with acid reflux in GERD patients. Once gastric acid is in the oesophagus, clearance mechanisms are activated to rapidly propel the acid back to the stomach and in patients with impaired oesophageal motility, they are more prone to develop GERD. Gastric factors also play a role. Abnormal postprandial distribution of meal in the stomach and delayed gastric emptying are associated with reflux. A recent study from HK⁵ reported that impaired oesophageal acid clearance was the major mechanism of GERD.

2. Clinical approach to patients with classical GERD symptoms

Empiric trial of proton pump inhibitors (PPI) or a high dose PPI b.d. as a diagnostic test is widely recommended

as the initial treatment. In a study of Chinese patients with GERD symptoms⁶ using high dose PPI for 2 weeks and a 50% reduction of symptoms as a positive response, the sensitivity and specificity of the high dose PPI test were reported to be 84% and 71% respectively, based on endoscopy or 24 hour pH study as gold standard. Endoscopy is usually reserved for refractory patients or those with alarm signs or symptoms such as anaemia, weight loss or dysphagia. An Asia consensus group⁷ recommended endoscopy for patients older than 35 years of age. Endoscopy allows identification of other benign or malignant diseases (e.g. oesophageal candidiasis), diagnosis of Barrett's oesophagus and classification of patients into those with mucosal disease (reflux oesophagitis) and those without (NERD). Those with mucosal disease required high dose PPI for at least 8 weeks as a recent study on low dose PPI for 8 weeks only led to complete mucosal healing in 48% of patients⁸. Patients with NERD can be managed with step down or step up approach with PPI on a p.r.n. basis. Dietary advice and weight reduction may help some patients. Fortunately most patients with GERD in HK belong to mild erosive disease or NERD but stricture is occasionally encountered (Figure 1).



Figure 1. A 38 year old Chinese lady with long history of SLE complained of acid regurgitation and dysphagia. Endoscopy with pediatric endoscope showed a stricture at the oesophago-gastric junction. The stricture responded to a course of PPI therapy.



3. Extra-oesophageal manifestations of GERD

Convincing evidence exists linking each extra-oesophageal manifestation to reflux in some patients. However a causal relationship remains difficult to establish. The three most commonly investigated conditions are atypical chest pain, asthma and otolaryngeal manifestations. Data substantiating a significant beneficial effect of reflux treatment on symptoms are weak. Symptom relief may be incomplete for several reasons. First, these patients have heightened sensitivity to many different stimuli in the oesophagus. Consequently small amounts of acid could trigger these symptoms. Complete symptom control may be accomplished only by elimination of reflux which is rarely possible with even the best medical or surgical therapy. Secondly, these extra-oesophageal syndromes are usually multi-factorial with GERD as one of the several potential aggravating cofactors.

3a. Atypical chest pain

Individuals with acid reflux may also experience atypical chest pain, i.e. chest pain in patients for whom the results from cardiac work up were negative. It is believed to be one of the most common extra-oesophageal manifestations of acid reflux disease. In a local study⁹ based on telephone interview, 50% of patients with atypical chest pain had symptoms of GERD. A simple approach is to give high dose PPI for 1-2 weeks and a 50% reduction of symptoms is regarded as positive response. Endoscopy or 24 hour pH study or manometry are reserved for refractory cases.

3b. Asthma and chronic cough

Surveys suggested that 30-90% of asthmatic adults had reflux symptoms or abnormal oesophageal acid exposure and many studies showed an association between these two conditions. The value of identifying reflux in individual patients with asthma is now becoming more widely recognised. The recognition of reflux in asthma patients is important because some bronchodilators, which are often used to treat asthma symptoms, may themselves exacerbate reflux by contributing to relaxation of the lower oesophageal sphincter. Such commonplace asthma therapy may therefore indirectly exacerbate respiratory symptoms in some patients with asthma. Several mechanisms might link reflux with asthma. As well as reflux bronchoconstriction caused by the aspiration of refluxed stomach contents into the bronchi, small amount of acid regurgitation in the oesophagus may cause increased bronchial reactivity via a vagally transmitted reflex. The clinical benefits of PPI therapy on asthma patients in randomised trials are however not as great as expected. There is a significant benefit in improving symptoms and reducing asthma medications usage but no objective improvement in pulmonary function test. Those patients with nocturnal respiratory symptoms and GERD symptoms seem to respond best. A subset of patients responded dramatically to anti-reflux surgery with complete asthma resolution¹⁰ but the criteria for selection of patients for surgery is still unclear.

Gastro-oesophageal reflux may also be responsible for some cases of chronic cough but complete treatment response to medical treatment is rare in randomised controlled trials. The only strong support for the link comes from surgical studies that reported a significant

resolution of symptoms in a subgroup of patients¹¹ after laparoscopic fundoplication. Again, the criteria for selection of patients for surgery is not yet clear.

3c. Laryngeal signs and symptoms associated with gastro-oesophageal Reflux

Four to ten per cent of patients in the West presenting to otolaryngologists have reflux symptoms, and reflux is associated with hoarseness, chronic laryngitis, vocal cord ulceration and even carcinoma of the larynx. In a local study of 28 patients with throat symptoms like globus, throat discomfort, burping or cough lasting more than 1 month together with signs of laryngitis, 14% of patients showed objective evidence of acid reflux by pH monitoring¹². In another local study¹³ on 26 patients with globus, objective evidence of GERD was found in 30.8%. Similar to chronic cough, anti-reflux treatment only provides partial improvement in symptomatology and in some cases laryngoscopic appearance. There are probably many other co-factors in the aetiology of chronic laryngitis. Since pH study is not widely available, long term anti-reflux medication should only be continued for patients with both symptoms of GERD and/or signs of chronic laryngitis.

3d. Sleep disturbance

Insomnia, interrupted or poor quality sleep, is a common complication of gastro-oesophageal reflux. Recent data suggested that 50-80% of reflux patients might have disturbed sleep¹⁴. Some cases appear to be associated with a nocturnal breathing disorder such as snoring or obstructive sleep apnoea. Many others are probably simply due to full or partial awakening in response to reflux-induced thoracic discomfort such as regurgitation or heartburn.

4. Management of refractory GERD patient

After a 4-8 week course of morning dose of PPI, 25-42% of patients may still have reflux symptoms. At this point, the physician should ensure the patient's drug compliance and review the timing of the PPI dose (taken 30-60 minutes before meal). Endoscopy should be considered if not yet done. Some patients have predominantly nocturnal symptoms and one option includes changing the timing of the once daily dose from o.m. to before dinner. This would be based on intragastric pH data showing that overnight intragastric pH control is greater when once daily PPI is given before the evening meal, compared to the morning dose. Increasing the patient's proton pump inhibitors to b.d. is another obvious and straightforward choice but the cost of drug will be high. Another choice would be to use an H₂ blocker at bed time but tachyphylaxis occurred rapidly. Performing a 24 hour pH study may help to analyse the relationship between pH and symptoms. The result of 24 hr pH study of a patient with atypical chest pain who failed to respond to once daily PPI is shown in Figure 2. The overall 24 hr acid output is within normal limits in this patient but there is a good correlation between chest pain and acid reflux. The result suggests acid sensitive oesophagus and the patient responds to a higher dose of PPI given twice daily.

For patients who have refractory oesophagitis despite a b.d. dose of PPI, there are however several differential diagnosis such as drug-induced oesophagitis, skin disease associated oesophagitis, hypersecretory state



such as Zollinger-Ellison syndrome, genotypic differences and eosinophilic oesophagitis (diagnosed by biopsy). Endoscopy appearance of drug associated oesophagitis may range from one or more discrete ulcers to diffuse inflammation with exudates, or even stricture and pseudo-tumour formation. The most common site is the junction of the proximal and middle third of the oesophagus where peristalsis is weaker and where the aorta crosses the oesophagus. Common drugs include doxycycline and tetracycline, alendronate, aspirin and NSAID, potassium chloride, ascorbic acid, quinidine and ferrous sulphate. A variety of skin diseases may also cause oesophagitis such as lichen planus, pemphigus and pemphigoid. About 12-20% of Asians are said to be fast metabolisers of PPI. To date, all studies have been done with once daily dose of PPI and it is unknown if twice daily dosing may overcome the problem.

5. Barrett's oesophagus and oesophageal adenocarcinoma

In some patients with abnormal gastro-oesophageal reflux, the oesophageal mucosa responds with the development of metaplastic columnar-specialised intestinal epithelium (Barrett's oesophagus see Figure 3) an assumed risk factor for the development of oesophageal adenocarcinoma. In a recent American Society of Gastrointestinal Endoscopy guidelines¹⁵, some of the recommendations for Barrett's oesophagus are as follows:

- A. Screening gastroscopy for Barrett's oesophagus should be considered in selected patients with chronic long standing GERD. After a negative screening examination, further screening is not indicated.
- B. For patients with established Barrett's oesophagus, biopsy should be taken to look out for dysplasia. After 2 consecutive negative examinations for dysplasia in 1 year, further examination after 3 years is acceptable.
- C. For patients with low grade dysplasia, further surveillance is recommended although the interval of surveillance is controversial.
- D. For patients with high grade dysplasia, there is a significant risk for cancer and management options including frequent repeat endoscopy, oesophagectomy, endoscopic photodynamic therapy, endoscopic mucosal resection(EMR) should be discussed with patients.

In U.S, the pillcam (capsule endoscopy for the oesophagus) has been licensed to detect Barrett's oesophagus without the need of invasive endoscopy but it's not yet available in HK. Many new modalities like narrow band imaging (available in many hospitals already), magnifying endoscopy, chromoendoscopy and endo-microscopy have been developed to help to locate areas of suspicion of high grade dysplasia for biopsy and endoscopic treatment like mucosal resection or photodynamic therapy are options with variable success rate. Fortunately, the incidence of oesophageal adenocarcinoma is still low in HK but a rising trend is observed in Xi'an and Japan.

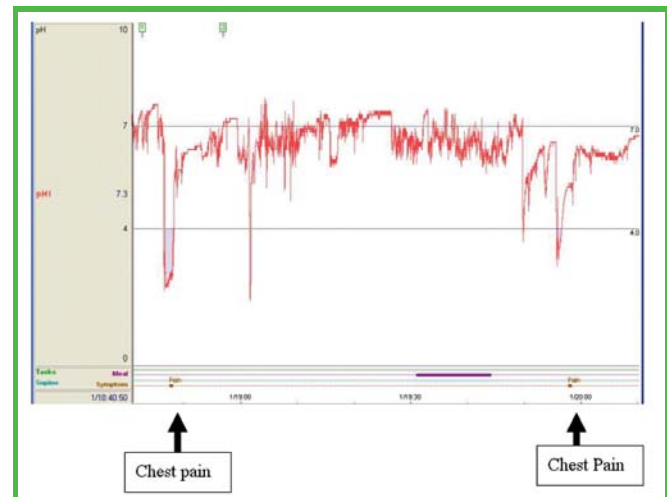


Figure 2. This was the result of 24 hour pH study of a 35 year old gentleman who complained of chest discomfort. His symptoms did not respond to once daily PPI therapy. The 24 hour acid reflux was within normal limits but there was a good correlation between acid reflux below 4 and 2 episodes of chest pain. He responded to twice daily dose of PPI.

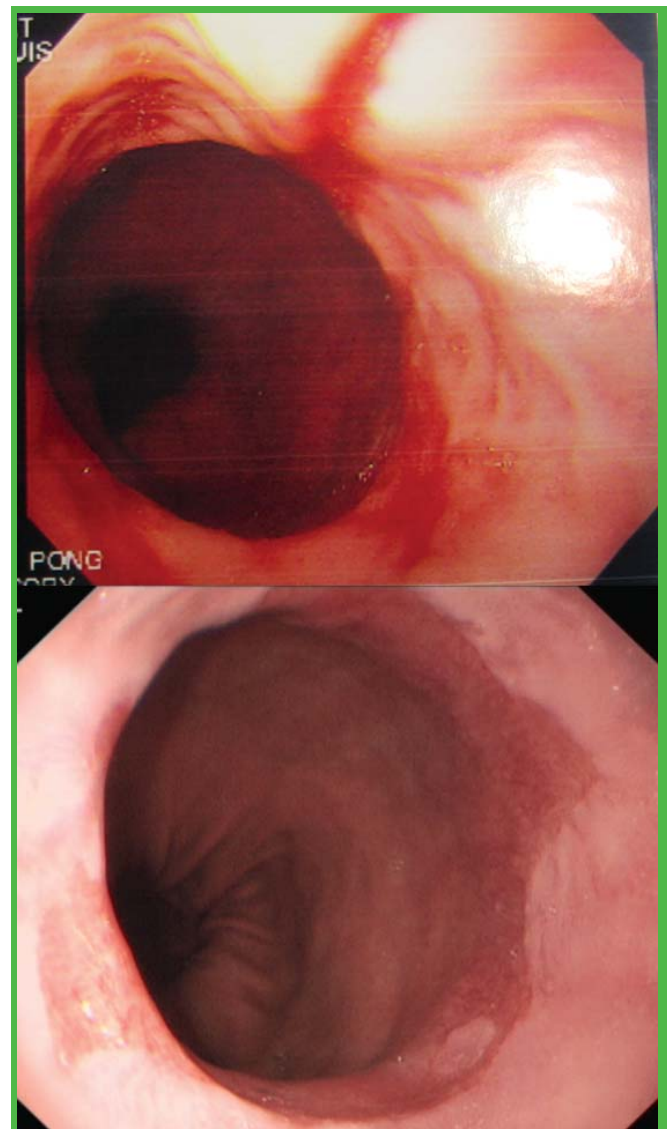


Figure 3. A 35 year old Caucasian patient complained of infrequent mild acid regurgitation and heartburn. Endoscopy showed reflux oesophagitis and hiatus hernia in the upper photo and 3 months after PPI therapy, oesophagitis resolved and biopsy confirmed Barrett's oesophagus without dysplasia in the lower photo.

6. New advances in pH and impedance study

More recently wireless bravo chip is available that can be affixed to the lower oesophagus. 48-72 hour pH data can be recorded via a portable data loggers and analysed by computerised devices. The bravo system has been shown to improve patients' compliance as compared to conventional pH study and allows greater patient freedom to continue normal daily activities. Extended 48 hour pH study is useful as around 25% of cases may have excessive acid reflux in a single day only. However, early detachment within 16 hours resulting in shorter period of recording and technical failure (e.g. batteries) are not infrequently reported. Chest discomfort has also been reported after bravo capsule attachment, possibly due to stimulated oesophageal contraction and occasionally requires removal of the chip. The device is also not widely available. The new multi-channel intraluminal impedance (MII) and pH study catheter can measure both acidic and non-acidic reflux at the same time and research is on-going to study its impact on clinical management.

7. Long term complication of PPI

Recently a retrospective data analysis¹⁶ showed that long term PPI was associated with hip fracture. People over 50 years of age who took the drug for more than one year had a 44% increased risk of hip fracture. Taking PPI at higher dose and for longer periods pushed up the risk of hip fracture to 245%. The authors speculate that PPI stops gastric acid which is required for calcium absorption and they urge doctors to use the lowest effective dose of the drug. Other associations like *Clostridium difficile* associated diarrhoea and pneumonia have also been reported but the relationship remains speculative.

8. Endoscopic and surgical treatments for GERD

The Stretta procedure is an endoluminal radio-frequency energy delivery system for the treatment of GERD and obtained FDA approval in US since 2000. In a study up to 4 years¹⁷, 75% of patients treated with Stretta procedure required no or fewer medications than before at the end of assessment. There is also a favourable impact on lower oesophageal sphincter pressure, oesophageal acid reflux and symptom scores as well. Over four thousand procedures had been performed and unfortunately, a few perforations and two deaths were reported in the early post-marketing phase. Preliminary experience in Japan¹⁸ is promising and bigger studies in Asia are awaited. Other procedure like NDO plicator which can create a full thickness serosa-to-serosa apposition of the proximal cardia has also been approved in US but experience in Asia is limited.

Laparoscopic fundoplication has evolved as the surgical procedure of choice for patients with GERD. Although the durability of surgical treatment has been questioned, experienced surgeons achieve long term reflux cure rates of about 85-95%. Success with medical therapy is the only thing that predicts a successful surgical outcome. The only possible exception is in asthmatic patients where reduction of oral steroids was possible in a small series of Caucasian patients after surgery. Similar data from Asia are lacking. It is an option for patients who do not wish to take long term medications. Performance of bariatric surgery and

fundoplication can also be done at the same time for patients with morbid obesity and GERD.

9. GERD and *H. pylori*

A negative correlation between GERD and *H. pylori* is observed in many Asian countries, suggesting a protective role of *H. pylori* against GERD. Although eradication of *H. pylori* may increase basal gastric acidity and reduce the efficacy of PPI therapy in some patients, the bacteria should still be eradicated to protect the patient from *H. pylori* associated gastric diseases.

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