Consensus of gastroesophageal reflux disease in Taiwan with endoscopy-based approach covered by National Health Insurance

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Summary  Background and aims: Gastroesophageal reflux disease (GERD) is emerging as a clinical complication in the Orient. The consensus comprises recommendations to GERD control under the advantage of endoscopy-based approach covered by the Taiwan National Health Insurance. Methods: The steering committee defined the consensus scope to cover diagnostic, therapeutic, unresolved, controversial, or long-term proton pump inhibitor-related issues to GERD. The
Introduction

Diagnosis and treatment of gastroesophageal reflux disease (GERD) are becoming more important [1–4]. GERD has not only chronic recurrent bothersome clinical symptoms, but also long-term impacts on the quality of life and performance of diseased individuals. In the Western world, due to a low prevalence of esophageal cancer and upper gastrointestinal malignancy, empiric antisecretory medication, such as proton pump inhibitors (PPIs), has been widely applied for patients with typical presentations such as acid regurgitation or heart burn sensation at the epigastric or midchest regions to indicate reflux-related disorders [4–8]. Nevertheless, the current role of esophageal endoscopy remains helpful to confirm the diagnosis of erosive esophagitis and then to validate the degree of esophageal mucosal defects according to the Los Angeles grading classification [9–14]. The different disease spectrums, such as erosive or nonerosive GERD, will have different treatment modalities. Accordingly, even PPI can be empirically started in the Western world, the role of endoscopic-based approach for GERD shall remain with more accurate diagnostic determination to the disease spectrum and to exclude the malignant potentials of upper gastrointestinal tract in the Eastern world with high cancer endemics.

In Taiwan, endoscopy can be covered by the Taiwan National Health Insurance program, and based on the endoscopic findings to define the disease spectrum of GERD, PPIs can be allowed for durations ranging from at least 4 months up to 12 months. Accordingly, a nationwide model is required to offer an objective evidence of erosive GERD control. The advantage of the current consensus is that it offers Taiwanese experts’ experiences with endoscopic-based approach supported by the National Health Insurance in a near 95% nationwide coverage. The current consensus has provided a strong evidence of its validity for GERD management in a nationwide cohort setting, including the diagnostic approach and therapeutic assessment. The consensus also addressed important concerns to highlight the unresolved, controversial, and long-term issues of GERD for future improvement in such endemic area with upper gastrointestinal cancers.

Methods

Steering committee set the consensus scope and structure

To establish the expert consensus of GERD in Taiwan, the steering committee was initiated by J.T. Lin, chaired by B.S. Sheu along with eight other opinion leaders from the Gastroenterological Society of Taiwan (C.T. Chiu, Y.C. Lee, G.Y. Chang, D.C. Wu, C.M. Liou, M.S. Wu, W.L. Chang, and C.Y. Wu). The steering committee defined the scope sessions of the consensus, conducted a literature search and review, formulated draft statements, and defined the statement evidence level.

Steering committee members to conduct literature search and review

The literature searches included Medline, Embase, the Cochrane Central Register of Controlled Trial, and ISI Web of Knowledge, with manual searches of bibliographies of key articles and proceedings of abstracts of major gastroenterology conferences held over the past 7 years. The key words used in the search included gastroesophageal reflux, PPI, Barrett’s esophagus, extraesophageal symptoms, narrow band image, upper gastrointestinal endoscopy, etc. The members of the steering committee summarized the findings in the three scope sessions of this consensus: (1) diagnostic approach; (2) therapeutic assessment; and (3) unresolved, controversial, or long-term PPI-related issues associated with GERD. Based on the review of the literature, the draft statements of the consensus were...
were obtained from all experts prior to voting. Mandatory written disclosures of financial conflicts of interest were refined at the steering committee meeting held in Kaohsiung, Taiwan during June 2014.

Expert group meeting to achieve agreement of statement and recommendation grading

A total of 35 experts (the names are listed in the supplementary data), including 10 members in the steering committee and 25 members who accepted the invitation of the steering committee, comprised the expert group of the Taiwan GERD consensus. The draft statements from the four session groups were sent to all the experts, together with pertinent literature, prior to the consensus meeting in Kaohsiung in August 2014.

During the 2-day consensus meeting, for each draft statement from the four scope sessions, the supporting evidence from the keynote literature summary by the steering committee was presented serially in the following order: cover diagnostic, therapeutic, unresolved, controversial, long-term PPI-related issues for GERD. Based on a modified Delphi process through two separate iterations, all participants voted anonymously for the first round of statements and modified the statements through discussion. The modified statements were followed by a second round of voting with electronic keypads until a consensus was reached at the agreement percentage of \( \geq 80\% \). If the agreement was \(< 80\% \), the statement was rejected. The expert members also discussed the level of evidence suggested by the steering committee and then graded the recommendation level by voting for each statement. The grade of recommendation ranged from A to D, as was used in our previous consensus in Taiwan [15]. The level of recommendation was defined as the grade with the highest number of votes of the expert group members. The conferences were underwritten by unrestricted grants from the Gastroenterological Society of Taiwan. Mandatory written disclosures of financial conflicts of interest within the period of 3 years prior to the meetings were obtained from all experts prior to voting.

Consensus statements

Section I: diagnostic approach

**Statement I-1:** In Taiwan, the prevalence of GERD is increasing while that of Helicobacter pylori infection is declining. (agreement: 100\%, level of evidence: 2a, recommendation: A)

Several validated questionnaires have been developed for the assessment of GERD. Clinical applications of the GERD questionnaires may include the diagnosis of GERD, assessment of treatment response, and evaluation of GERD symptoms and their effects on the quality of life. For example, the GERD Questionnaire has been proved to be a useful tool to diagnose GERD with an area under the receiver operating characteristic curve of 0.7 [21]. A higher GERD Questionnaire score is significantly correlated with a higher risk of erosive esophagitis [22]. The Reflux Disease Questionnaire, which includes both the presence of symptoms and the severity/frequency of GERD, has been found to be useful in monitoring its therapeutic response to PPIs [23,24]. The Short-Form 36 questionnaire has been used in the evaluation of health status and quality of life in GERD patients [25].

**Statement I-2:** The validated questionnaire is useful in the diagnosis of GERD, monitoring of treatment response, and evaluation of quality of life. (agreement: 100\%, level of evidence: 3b, recommendation: A)

In Taiwan, concomitant GERD symptoms are commonly observed in patients with upper aerodigestive tract neoplasms, and approximately two-thirds of the patients with fresh hypopharyngeal cancer have erosive esophagitis, active H. pylori infection, or gastric/duodenal ulcers [26]. In patients with gastric cancer, similarly, concomitant GERD/dyspepsia symptoms are very common [27]. Therefore, in this population with prevalent upper GI malignancies, upper endoscopy is well accepted by gastroenterologists as the first-line diagnostic tool for the evaluation of GERD symptoms, categorization of disease spectrum of GERD (such as erosive GERD and non-erosive reflux disease (NERD)), and most importantly, exclusion of the possibility of upper GI tract cancer.
PPIs are the most effective drugs to suppress gastric acid secretion and relieve reflux symptoms. Therefore, an empirical short course (usually 7–14 days) of PPIs, the so-called PPI test, is useful in the diagnosis of GERD. In patients with GERD symptoms, a previous meta-analysis has shown pooled sensitivity and specificity of 71% and 41%, respectively. The data indicated that the PPI test was sensitive, but less specific. In patients with noncardiac chest pain, the PPI test showed pooled sensitivity and specificity of 80% and 74%, respectively, to confirm GERD. A meta-analysis indicated that the optimal duration may be 1 week and the optimal cutoff value should be a decrease of heartburn score by >75%.

Image-enhanced endoscopy provides a significant improvement over standard white-light imaging for the diagnosis of nonerosive GERD, with better visualization of subtle erosive changes in the esophagus. The sensitivity and specificity of narrow-band images in differentiation of nonerosive reflux diseases and controls were 65% and 83%, respectively, based on the presence of dilated intrapapillary capillary loops under endoscopic magnification. The inter- and intraobserver agreement in the grading of endoscopic esophagitis could be improved when image-enhanced endoscopy was used. Certain specific narrow band image findings can even correlate with a positive therapeutic response.

In patients with atypical or refractory GERD symptoms, it is important to identify those with true GERD and other etiology mimicking GERDs such as atypical presentation of achalasia and some of esophageal motility disorders. Additional diagnosis with esophageal manometry and 24-hour pH monitoring is required to detect other disease entities that may manifest like GERD. The addition of impedance to conventional 24-hour pH monitoring improves diagnosis by showing weak acidic and nonacidic refluxes. In patients with refractory GERD symptoms, the true diagnosis of GERD can be confirmed by abnormal acid exposure on 24-hour PH monitoring. By contrast, negative results of PH monitoring suggest that symptoms are unlikely due to acid reflux.

Traditional diagnoses of GERD, including endoscopy, manometry, and pH studies, may be cumbersome in some cases, such as in patients who have undergone total or proximal gastrectomy, those with nasogastric tube or gastrostomy, and children. Esophageal radiographic or scintigraphic studies can be an alternative choice to define the presence of GERD. More specifically, radionuclide scintigraphy may provide important diagnostic clues under special conditions, and the reported sensitivities of esophageal scintigraphy in the diagnosis of GERD could be up to 76%.

Persistent heartburn and other upper gastrointestinal symptoms despite PPI therapy have become clinical problems that are increasing in gastroenterology practices. Approximately 25% of PPI recipients will require higher doses than initially prescribed because of insufficient control of GERD symptoms or lack of healing of the esophageal mucosa. A randomized control trial suggested that double dosing of lansoprazole or switching to esomeprazole can deal with patients suffering from persistent symptoms despite lansoprazole therapy. More studies confirming similar effectiveness of double dosing or switching to a different PPI can really be helpful.
Several studies showed that there are no differences in symptomatic remission and improvement of quality of life between on-demand and continuous therapy with PPIs for GERD [50–52]. However, continuous therapy has a higher healing rate of erosive esophagitis [53,54]. However, most of the studies focus on mild GERD cases. Further studies should be undertaken to investigate severe GERD.

**Statement II-3:** The response to PPI therapy for symptoms relief in patients with non-erosive reflux disease is generally lower than that in those with erosive esophagitis.  
(agrément: 97%, level of evidence: 1a, recommendation: A)

A multicenter study showed that the heartburn resolution rates at 4 weeks were higher for patients with erosive esophagitis than for those with nonerosive esophagitis [55]. A systemic review reveals that PPI can provide higher therapeutic gain for heartburn resolution in patients with nonerosive reflux disease than in those with erosive esophagitis.

**Statement II-4:** PPI therapy for NERD patients may be augmented with prokinetics and alginites.  
(agrément: 82%, level of evidence: 1b recommendation: B)

Administration of mosapride citrate in addition to omeprazole improved GERD symptoms and gastric emptying in PPI-resistant nonerosive GERD patients with delayed gastric emptying [56]. Another study illustrated that omeprazole combined with sodium alginate provided higher resolution of heartburn than omeprazole alone in patients with nonerosive GERD [57]. Due to the limited case numbers in the previous two studies, more evidence is anticipated in future studies.

**Statement II-5:** GERD patients with higher BMI will have poorer symptoms relief by PPI treatment.  
(agrément: 97%, level of evidence: 2a, recommendation: A)

There was a strong positive association between body mass index (BMI) and symptoms of GERD in a large cohort of women [58]. For Los Angeles Grade A or B reflux esophagitis, a higher BMI decreases the rate of sustained symptomatic response after 8 weeks of esomeprazole therapy, and increases the need for medication and the failure rate of on-demand therapy [13]. In addition, a BMI of >25 kg/m² is an independent risk factor to determine the healing of Los Angeles Grade C or D reflux esophagitis by esomeprazole [14]. Reducing BMI to >1.5 kg/m², especially for those with an initial BMI of >25 kg/m², could be promising to improve the healing of RE-CD by esomeprazole [14].

The prevalence of Barrett’s esophagus in Taiwan was 0.06–2.0%, and it varies with study design [59–62]. Chen et al [16] found that the prevalence of Barrett’s esophagus did not change over time, although the prevalence of GERD was increasing. Chang et al [61] used a prospective design with a standardized biopsy protocol and histological confirmation for Barrett’s esophagus to include both symptomatic and asymptomatic patients from a large ethnic Chinese population. The prevalence (0.85%) of Barrett’s esophagus in this study is lower than that in Western countries. The prevalence of Barrett’s esophagus varies from 2.4% to 13.6% in Western countries, according to some studies [63–66], using the same design (prospective enrollment, endoscopic biopsy from standard four quadrants, pathological confirmation, and a large case number).

**Statement II-6:** Barrett’s esophagus remains uncommon in Taiwan compared with Western countries.  
(agrément: 100%, level of evidence: 3a, recommendation: A)

The utility of Prague C and M criteria has been proved by a large prospective study in Taiwan [61]. A multinational endoscopic study showed that the intraclass correlation coefficient value for the scores of the C value was 0.92 and that for M value was 0.94, indicating an excellent interobserver agreement [67]. In other words, Prague C and M criteria have good validity and reliability for description of Barrett’s esophagus. However, a long-term follow-up study should be conducted to verify the relationship between the clinical outcome of Barrett’s esophagus and the severity of Prague C and M values.

**Statement II-7:** Prague C and M criteria is recommended in the endoscopic description of Barrett’s esophagus.  
(agrément: 94%, level of evidence: 3a, recommendation: B)

The prevalence of Barrett’s esophagus in Taiwan was 0.06–2.0%, and it varies with study design [59–62]. Chen et al [16] found that the prevalence of Barrett’s esophagus did not change over time, although the prevalence of GERD was increasing. Chang et al [61] used a prospective design with a standardized biopsy protocol and histological confirmation for Barrett’s esophagus to include both symptomatic and asymptomatic patients from a large ethnic Chinese population. The prevalence (0.85%) of Barrett’s esophagus in this study is lower than that in Western countries. The prevalence of Barrett’s esophagus varies from 2.4% to 13.6% in Western countries, according to some studies [63–66], using the same design (prospective enrollment, endoscopic biopsy from standard four quadrants, pathological confirmation, and a large case number).

**Section III:** unresolved, controversial, or long-term care issues

Extraesophageal syndromes, including chronic cough, asthma, and chronic laryngitis, are present in a substantial proportion of patients with gastroesophageal reflux disease [68]. However, management of these extraesophageal symptoms remains debatable in clinical practice [68–73]. Whether PPI therapy is beneficial in the management of these symptoms has attracted much attention. Whether long-term PPI therapy and surveillance programs may reduce the risk and mortality of esophageal adenocarcinoma, respectively, in patients with Barrett’s esophagus are also important clinical issues [74–77]. Whether long-term PPI users have a higher risk of potential adverse effects, such as fracture and enteric infection, is also a controversial issue [78–84]. Another important issue is
whether screening and eradication of \( H. pylori \) are indicated in patients receiving long-term PPI therapy for GERD.

**Statement III-1:** Proton pump inhibitor therapy may reduce cough in patients with typical reflux symptoms and chronic cough.

(Feasibility: 94%, level of evidence: 1a, recommendation: B)

Of the nine adult studies that compared PPI with placebo for various outcomes, four (\( N = 116 \) and \( N = 75 \) for PPI and placebo groups, respectively) assessed the clinical failure defined as still coughing at the end of the trial or reporting period [2]. A meta-analysis showed no significant difference between PPI therapy and placebo in total resolution of cough (odds ratio 0.46; 95% confidence interval 0.19–1.15) [68]. However, a significant improvement in cough scores was observed in cross-over trials [68]. Nevertheless, the small sample size and the use of different outcomes were the major limitations of this meta-analysis. Further well-designed large clinical trials on this issue are warranted.

**Statement III-2:** In adult asthma patients with typical reflux symptoms, proton pump inhibitor therapy may improve pulmonary function.

(Feasibility: 82%, level of evidence: 1a, recommendation: B)

A meta-analysis including 2524 patients showed that PPI therapy may improve the morning peak expiratory flow, as compared to placebo, in adult asthma patients with reflux symptoms [69]. However, PPI therapy was not effective in asthma patients who did not report reflux symptoms and in pediatric asthma patients [69–72]. Besides, the clinical significance of the magnitude of this improvement remains debatable [69,70]. Further trials are warranted to identify the subgroup of patients that might benefit more from PPI therapy.

**Statement III-3:** There is insufficient evidence to support proton pump inhibitor therapy can improve laryngeal symptoms in suspected GERD-related chronic laryngitis.

(Feasibility: 97%, level of evidence: 1a, recommendation: B)

A meta-analysis failed to show a significant symptom reduction by PPI therapy in patients with chronic laryngitis [73]. However, the study scale is limited in usual and definition of chronic laryngitis with diversity among different studies in meta-analysis [73,74].

**Statement III-4:** Long-term proton pump inhibitor therapy may reduce the risk of high grade dysplasia and esophageal adenocarcinoma in patients with Barrett’s esophagus.

(Feasibility: 91%, level of evidence: 2a, recommendation: B)

A meta-analysis of five cohort studies (\( N = 1666 \)) and two case-control studies (\( N = 1147 \)) showed that long-term PPI therapy was associated with a 71% reduction in the risk of high-grade dysplasia and esophageal adenocarcinoma in patients with Barrett’s esophagus [75]. There was also a trend that the benefit was more prominent in patients receiving PPI therapy for longer than 2–3 years [75], but randomized trials on this issue are lacking.

**Statement III-5:** Endoscopic surveillance in patients with Barrett’s esophagus is recommended for high risk groups, although the cost-effectiveness remains debatable.

(Feasibility: 100%, level of evidence: 2b, recommendation: A)

Nationwide population-based cohort studies showed that the annual incidence of esophageal adenocarcinoma ranged from 0.15% to 0.19% in males and from 0.05% to 0.08% in females in unselected patients with Barrett’s esophagus [76]. A retrospective cohort study showed that the proportion of high-grade dysplasia and esophageal adenocarcinoma detected was higher among patients with low-grade dysplasia who underwent endoscopic surveillance every 3 months or less [77]. Considering the low incidence of esophageal cancer and high cost of endoscopy, endoscopic surveillance is recommended only for high-risk patients. Risk factors for progression to esophageal cancer include male gender, longer duration of Barrett’s esophagus, higher BMI, higher waist-to-hip ratio, longer length of the Barrett’s esophagus segment, presence of hiatal hernia, visible nodularity detected by endoscopy, higher degree of dysplasia, etc. [76,77]. Future prospective cohort studies and intervention trials are warranted to suggest the optimal intervals of endoscopic surveillance for Barrett’s esophagus.

**Statement III-6:** Although observational studies showed the association of long-term use of proton pump inhibitor with hip and vertebral fracture, the causal relationship remains uncertain.

(Feasibility: 100%, level of evidence: 2a, recommendation: B)

A meta-analysis of four cohort studies and six case-control studies, including 223,210 fracture cases, showed increased risks of hip and vertebral, but not of wrist/forearm, fractures in PPI users [77]. However, PPI use was not
associated with osteoporosis and low bone mineral density [78,79,84]. Therefore, the causal relationship of the association detected by observational studies remains uncertain because the possibility of confounding by indication could not be excluded. Therefore, well-designed randomized trials are warranted to clarify the causal relationships of the association.

Statement III-7: Although observational studies showed the association of long-term use of proton pump inhibitor with Clostridium difficile associated diarrhea, the causal relationship remains uncertain. (agreement: 94%, level of evidence: 2a, recommendation: B)

A meta-analysis of six cohort studies and 17 case-control studies, including close to 300,000 patients, showed increased risks of Clostridium difficile-associated diarrhea among patients on long-term PPI therapy [79,80]. Similarly, randomized trials are warranted to confirm or refute the causal relationships of the association.

Statement III-8: Eradication of Helicobacter pylori improves gastritis and prevents progression of gastric atrophy and intestinal metaplasia and is recommended in patients on long-term proton pump inhibitor therapy. (agreement: 94%, level of evidence: 1a, recommendation: A)

Earlier observational studies showed an increased risk of atrophic gastritis in patients with reflux esophagitis and Helicobacter pylori infection that were treated with PPI therapy [82]. The subsequent four randomized control trials that included 546 patients further showed that gastric inflammation could be reduced by H. pylori eradication [3,82—84]. Longer follow-up periods are warranted to assess whether the risk of atrophic gastritis or intestinal metaplasia in long-term PPI users can really be controlled by H. pylori eradication.

Dissemination strategies and legal issues

These statements are based on the best available evidence to pursue better quality of care and will be updated every 5 years. They are not suitable for deciding the standard of care in specific cases. This consensus statement will be disseminated through the following: (1) presentations given at the annual society meeting of Taiwan Digestive Week in 2014; (2) release of the copies of these statements in electronic and paper format to national societies/associations of gastroenterologists for their iterations; and (3) release on the website of our society link.

Conflicts of interest

All authors declare no conflicts of interest.

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References


[44] Akbunar AT, Alper E, Nak SG, Konuk N, Erkal B, Tamgac F. A simple method to increase the diagnostic efficiency of...


