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SPECIAL ARTICLE

Evidence-based clinical practice guidelines for peptic ulcer disease 2015

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Abstract The Japanese Society of Gastroenterology (JSGE) revised the evidence-based clinical practice guidelines for peptic ulcer disease in 2014 and has created an English version. The revised guidelines consist of seven items: bleeding gastric and duodenal ulcers, *Helicobacter pylori* (*H. pylori*) eradication therapy, non-eradication therapy, drug-induced ulcer, non-*H. pylori*, non-nonsteroidal anti-inflammatory drug (NSAID) ulcer, surgical treatment, and conservative therapy for perforation and stenosis. Ninety clinical questions (CQs) were developed, and a literature search was performed for the CQs using the Medline, Cochrane, and Igaku Chuo Zasshi databases between 1983 and June 2012. The guideline was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Therapy is initially provided for ulcer complications. Perforation or stenosis is treated with surgery or conservatively. Ulcer bleeding is first treated by endoscopic hemostasis. If it fails, surgery or interventional radiology is chosen. Second, medical therapy is provided. In cases of NSAID-related ulcers, use of NSAIDs is stopped, and anti-ulcer therapy is provided. If NSAID use must continue, the ulcer is treated with a proton pump inhibitor (PPI) or prostaglandin analog. In cases with no NSAID use, *H. pylori*-positive patients receive eradication and anti-ulcer therapy. If first-line eradication therapy fails, second-line therapy is given. In cases of non-*H. pylori*, non-NSAID ulcers or *H. pylori*-positive patients with no indication for eradication therapy, non-eradication therapy is provided. The first choice is PPI therapy, and the second choice is histamine 2-receptor antagonist therapy. After initial therapy, maintenance therapy is provided to prevent ulcer relapse.

Keywords Peptic ulcer · Gastric ulcer · Stomach ulcer · Duodenal ulcer · *Helicobacter pylori* eradication · Nonsteroidal anti-inflammatory drug · Cyclooxygenase-2 · Low-dose aspirin

Introduction

In 2009, the Japanese Society of Gastroenterology (JSGE) developed the evidence-based clinical practice guideline for peptic ulcer disease, and this guideline was revised in 2014. A working committee (chair, Yoshino J., vice-chair, Satoh K., Akamatsu T., Itoh T., Kato M., Kamada T., Takagi A., Chiba T., Nomura S., Mizokami Y., and Murakami K.) and an evaluation committee (chair, Sakamoto C., vice-chair, Hiraishi H., Ichinose M., Uemura N., Goto H., and Jo T.) collaborated to create the guideline. The revised guideline consists of seven items, newly including non-*Helicobacter pylori* (*H. pylori*), non-nonsteroidal anti-inflammatory drug

The original version of this article appeared in Japanese as "Shokasei Kaiyo Sinryo Guideline 2015" from the Japanese Society of Gastroenterology (JSGE), published by Nankodo, Tokyo, 2015. Please see the article on the standards, methods, and process of developing the Guidelines (doi:10.1007/s00535-014-1016-1).

The members of the Guidelines Committee are listed in the Appendix in the text.

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(NSAID) ulcer. For drug-induced ulcers, their epidemiology and pathophysiology were also examined. Ninety clinical questions (CQs) were developed, and a literature search was performed for the CQs using the Medline, Cochrane, and Igaku Chuo Zasshi databases for the period between 1983 and June 2012. The CQs mainly relate to treatment, with no CQs about diagnosis. The guideline was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [1]. The quality of evidence was graded as A (high), B (moderate), C (low), and D (very low). The strength of a recommendation was indicated as either "1" (strong recommendation) or "2" (weak recommendation) [1]. Consensus was previously defined as 70 % or more votes in agreement.

1. Bleeding gastric and duodenal ulcers

Endoscopic therapy

CQ. Is endoscopic therapy effective in treating peptic ulcer bleeding?

- Endoscopic therapy for peptic ulcer bleeding is superior to pharmacotherapy alone with regard to initial hemostasis and re-bleeding. Endoscopic therapy decreases the need for surgery and mortality versus pharmacotherapy alone. Recommendation 1, 100 % agreed, evidence level A.

Comment: Sachs et al. [2] reported in their meta-analysis that endoscopic therapy at peptic ulcer bleeding significantly decreased continued bleeding, re-bleeding, and transfer to emergency surgery vs. standard therapy. In meta-analysis of Barkun et al. [3], endoscopic therapy decreased re-bleeding, the need for surgery, and mortality versus pharmacotherapy alone. Meta-analysis of Barkun et al. was different from Sachs's report with respect to significant improvement in mortality. Result of Barkun's meta-analysis reflects to our statement.

CQ. What type of peptic ulcer bleeding is indication for endoscopic hemostasis?

- Active bleeding and ulcer with non-bleeding visible vessel is a good indication for endoscopic hemostasis. Recommendation 1, 100 % agreed, evidence level A.

Comment: In meta-analysis of Sachs et al. [2], they defined cases of peptic ulcer with active bleeding and non-bleeding visible vessels were indication for endoscopic hemostasis.

Two non-randomized control studies [4, 5] reported endoscopic therapy of nonbleeding adherent clots significantly reduced ulcer re-bleeding rates in high-risk patients compared with medical therapy alone. On the other hand, randomized study reported effect of combination therapy [endoscopic hemostasis +proton pump inhibitor (PPI)] with nonbleeding adherent clots had no difference with that of PPI alone [6]. We do not recommend endoscopic hemostasis as peptic ulcer with adherent clots because treatment of patients with adherent clots on ulcer remains controversial.

CQ. Is endoscopy for hemostasis confirmation (second look) necessary?

- Second-look endoscopy is recommended to confirm recurrent bleeding of high-risk patients. Recommendation 1, 100 % agreed, evidence level A.

Comment: In meta-analysis of Tsoi et al. [7], second-look endoscopy with thermal coagulation reduced re-bleeding, but second-look with injection provided no significant improvement in re-bleeding. The author suggested that routine second-look endoscopy was not useful. With respect to medical economic benefit, routine second-look endoscopy could not recommend for all patients with endoscopic therapy.

Systematic review of Elmunzer et al. [8] indicated the independent pre-endoscopic predictors of re-bleeding were hemodynamic instability and comorbid illness. In their review, the independent endoscopic predictors of re-bleeding were active bleeding at endoscopy, large ulcer size, posterior duodenal ulcer, and lesser gastric curvature ulcer. Second-look is useful to patients with pre-endoscopic or endoscopic predictors.

Non-endoscopic therapy

CQ. Is medication with antacid agents required after endoscopic treatment for hemorrhagic peptic ulcers?

- Medication with antacid agents is strongly recommended after endoscopic treatment for hemorrhagic peptic ulcers. Recommendation 1, 100 % agreed, evidence level A.

Comment: Compared with placebo, intravenous PPI therapy after endoscopic treatment for hemorrhagic peptic ulcers has been proven to reduce the rate of re-bleeding, the volume of blood transfusion, the period of admission, and the rate of converting to surgery in two meta-analyses [9, 10] and some randomized controlled trials (RCTs). High-dose PPI therapy was more effective in reducing the volume of blood transfusion compared with ordinary-dose of PPI therapy [11]. There was no significant difference between intravenous and oral PPI therapy.

The effectiveness of an intravenous medication of histamine 2-receptor antagonist (H_2RA) therapy after endoscopic treatment for hemorrhagic peptic ulcers is controversial. Selby et al. [10] reported that H_2RA therapy significantly reduced the rate of converting to surgery compared with placebo, while Carr-Loche et al. [12] reported that H_2RA therapy did not reduce it.

PPI therapy has been considered more effective than H_2RA therapy with respect to the rate of re-bleeding [13], volume of blood transfusion [9], period of admission [9], rate of conversion to surgery, suppression of gastric acid, arterial bleeding, and gastric ulcer after endoscopic treatment for hemorrhagic peptic ulcers in foreign studies. However, there has been no significant difference in efficacy after endoscopic treatment for hemorrhagic peptic ulcers between intravenous PPI and H_2RA therapy in Japan [14]. The reasons for this difference between foreign counties and Japan were thought to be as follows: (1) PPIs are usually administered in foreign countries at twice the dose as in Japan; and (2) endoscopic hemostatic techniques are better in Japan than in foreign countries.

CQ. How should we deal with patients with hemorrhagic peptic ulcer if they were taking anti-coagulant and/or anti-platelet agents?

- It was strongly recommended that anti-platelet agents should be continued for patients with high-risk conditions for thromboembolism associated with their withdrawal. Recommendation 1, 100 % agreed, evidence level A.
- It was proposed to change anti-coagulant agents to heparin or to resume anti-coagulant agents as soon as possible after confirming the arrest of bleeding for patients with high-risk conditions for thromboembolism associated with their withdrawal. Recommendation 2, 100 % agreed, evidence level C.

Comment: We should consider both the risk of re-bleeding due to continuing anti-coagulant and/or anti-platelet agents and the risk of thromboembolism associated with their withdrawal. The high-risk conditions for thromboembolism associated with withdrawal of antithrombotic therapy were shown in the Table 3 of Guidelines of Japan Gastroenterological Endoscopy Society [Dig Endosc: 2014; 26:1–14 (a paper that was out of the searched period)].

Mortality was significantly lower in the group continuing anti-platelet agents compared with the group with withdrawing them among patients with hemorrhagic peptic ulcer with cardiovascular and/or cerebrovascular diseases [15]. On the other hand, we can suspend anti-platelet agents in patients with low-risk conditions for thromboembolism.

Concerning anti-coagulant agents, there has been no high-level evidence corresponding to the same situation [16].

CQ. Is eradication of *H. pylori* required for the prevention of re-bleeding in patients with hemorrhagic peptic ulcer?

- *H. pylori* eradication therapy is strongly recommended in the *H. pylori*-infected patients with hemorrhagic peptic ulcers cured by conservative treatment. Recommendation 1, 100 % agreed, evidence level A.

Comment: The effectiveness of *H. pylori* eradication therapy after healing of a hemorrhagic peptic ulcer to reduce re-bleeding was proven by two meta-analyses [17, 18] and some RCTs. Furthermore, *H. pylori* eradication therapy has been shown to decrease the cost per year in patients [18]. Maintenance treatment such as antacid agents is not required after cure of *H. pylori* infection.

2. *H. pylori* eradication therapy

Initial treatment

CQ. Are *H. pylori* eradication and additional treatment of ulcer healing after eradication therapy necessary in *H. pylori*-positive patients with an active gastric or duodenal ulcer?

- Eradication therapy in *H. pylori*-positive patients with an active gastric or duodenal ulcer is performed as initial treatment, because successful eradication of *H. pylori* accelerates gastric or duodenal ulcer healing.

  Recommendation 1, 100 % agreed, evidence level A.

- After *H. pylori* eradication therapy, additional treatment for ulcer healing is recommended.

  Gastric ulcer, Recommendation 1, 100 % agreed, evidence level A;

  Duodenal ulcer, Recommendation 2, 100 % agreed, evidence level C.

Comment: Successful *H. pylori* eradication was reported to provide a benefit for gastric or duodenal ulcer healing. Successful eradication of *H. pylori* accelerates gastric or duodenal ulcer healing compared with unsuccessful eradication [19, 20]. The gastric or duodenal ulcer healing rate by *H. pylori* eradication therapy without concomitant acid suppression was not significantly different from that with PPI treatment [21, 22]. However, a Japanese randomized study showed that 1-week triple therapy healed gastric ulcers of less than 1 cm in diameter, but not gastric ulcers equal to or more than 1.5 cm in diameter [23]. Follow-up treatment to suppress acid is needed for larger gastric ulcers after *H. pylori* eradication therapy. Additional treatment with mucosal protective drugs after *H. pylori* eradication has been proven to promote gastric ulcer healing in Japanese randomized studies [24, 25]. Therefore, additional treatment for ulcer healing is recommended after *H. pylori* eradication therapy. In duodenal ulcer, additional treatment with PPIs after 1-week eradication of *H. pylori* did not increase the ulcer healing rate [26]. Therefore, additional treatment with PPIs is not always necessary in active duodenal ulcer cases. However, follow-up therapy

with PPIs after *H. pylori* eradication should be considered for the cases that fail eradication therapy.

Eradication regimen

CQ. Which regimens are effective for first-line *H. pylori* eradication therapy?

- Triple therapy using PPI, amoxicillin, and clarithromycin is effective as first-line *H. pylori* eradication therapy. Recommendation 2, 100 % agreed, evidence level A.
- A high-dose of PPIs increases the efficacy of triple therapy. Recommendation 2, 100 % agreed, evidence level A.
- There are no significant differences in cure rates among PPIs (omeprazole, lansoprazole, rabeprazole, and esomeprazole). Recommendation 2, 100 % agreed, evidence level A.
- Sequential therapy and concomitant quadruple therapy are equally effective for *H. pylori* eradication in treatment-naive patients. Recommendation 2, 100 % agreed, evidence level A.

Comment: In Japan, triple therapy consisting of a PPI, amoxicillin, and clarithromycin has been used as first-line eradication therapy for *H. pylori* infection. Since a decline in the eradication rate of standard triple therapy was observed in Japan due to clarithromycin resistance [27], the recommendation in the 2015 version of the guideline was changed to a level lower than in the previous version of the guideline. According to the Maastricht IV Consensus report for the management of *H. pylori*, triple therapy with a PPI should be used in areas where clarithromycin resistance is low (<15 %) [28].

Triple therapy with a PPI (lansoprazole 30 mg twice daily, omeprazole 20 mg twice daily, rabeprazole 20 mg twice daily, or esomeprazole 20 mg twice daily), amoxicillin (750 mg twice daily), and clarithromycin (200 mg twice daily) seems to be equally effective for eradication [29–32]. A meta-analysis showed that the cure rate of high-dose PPI was 583/711 (82 %) compared to 734/992 (74 %) with standard-dose PPI (RR 1.09; 95 % CI 1.01–1.17) [33]. In addition, a recent meta-analysis has shown that the maximal effect was seen in the studies comparing a high dose of the more potent second-generation PPIs [34]. A pooled analysis demonstrated the superiority of sequential therapy over 7-day triple therapy with an RR of 1.23 (95 % CI 1.19–1.27) [35]. However, sequential therapy is relatively complex, requiring the patients to switch from dual to triple therapy. A PPI, clarithromycin, metronidazole, and amoxicillin regimen as a four-drug, three-antibiotic, non-bismuth-containing quadruple regimen is proposed. Pooled estimates of the five RCTs showed superiority of non-bismuth-containing quadruple therapy over triple therapy with an OR of 2.86 (95 % CI 1.73–4.73) [36].

Very recently, a newly developed potassium-competitive acid blocker, vonoprazan, has been reported to have a superior eradication rate, especially in clarithromycin-resistant patients [37].

Second-line eradication therapy

CQ. What kind of regimen should we choose for second-line eradication therapy?

- Triple therapy with moxifloxacin is suggested.
  Recommendation 2, 100 % agreed, evidence level A
- In Japan, triple therapy with PPI, amoxicillin, and metronidazole is recommended.
  Recommendation 1, 100 % agreed, evidence level A

Comment: Some meta-analyses [38, 39] showed that levofloxacin-based and moxifloxacin-based triple therapies were more effective than other therapies, including bismuth-based triple therapy or quadruple therapy. However, these drugs have not been approved for *H. pylori* eradication therapy in Japan. The rate of *H. pylori* showing primary resistance to levofloxacin is high in Japan. The eradication rate of triple therapy with PPI, amoxicillin, and metronidazole is still high in Japanese patients after failure of first-line therapy.

Third-line eradication therapy

CQ. What kind of regimen should we choose for third-line eradication therapy?

- No regimens are recommended.

Comment: A Japanese RCT of third-line therapy showed that the eradication rate of triple therapy with sitafloxacin was 70 % [40]. Because the rate was not high enough, no regimens were recommended in this guideline.

Prevention of ulcer recurrence

CQ. Does eradication therapy of *H. pylori* prevent ulcer recurrence?

- Eradication of *H. pylori* is recommended as a preventive care for the recurrence of peptic ulcer. Recommendation 1, 100 % agreed, evidence level A.

Comment: In the NIH consensus meeting in 1994, it was concluded that all peptic ulcers infected by *H. pylori* were to be eradicated regardless of whether it was a primary or recurrent ulcer [41]. In Europe and the United States, the incidence of duodenal ulcer constitutes a significant

percentage compared with the other peptic ulcers and a lot of evidence that recurrence could be inhibited by eradicating duodenal ulcer has been stored [42, 43]. However, there was a moment when a question was raised as to whether eradication was truly effective for inhibiting recurrence of gastric ulcer or not [44].

Afterward, many reports from home and abroad suggested that *H. pylori* eradication clearly inhibited gastric ulcer from recurring and it accomplished better results than the traditional maintenance treatment using acid reducer. In the case of gastric ulcer, it is also clear that eradicating *H. pylori* prevents ulcers from recurring as well as the case of duodenal ulcers [45].

The group of Hulst provided eradication treatment to 45 cases of gastric ulcer. From the results of a long-term follow-up spent 2.5 years on average and 9.8 years at the longest, they stated that they did not find any recurrences of gastric ulcer from successfully eradicated groups as well as the case of duodenal ulcers [45]. According to the recent meta-analysis of 52 clinical tests conducted around the world, it is effective to eradicate to inhibit both duodenal ulcer and gastric ulcer from recurring [20].

It is confirmed that eradication has an effect on inhibiting recurrence of gastric ulcers here in Japan as well [46]. At 1 year after the combined treatment of lansoprazole/amoxicillin/clarithromycin, in the successfully eradicated group, it showed that the cumulative recurrence risk of each gastric ulcer and duodenal ulcer was 11 and 6 %. In contrast, in the unsuccessfully eradicated group, it showed a significantly higher rate of each of 65 and 85 %. Also, over 4,000 multicenter studies spent 4 years in Japan [47] indicated that the recurrence ratio of gastric ulcer or duodenal ulcer is only 1–2 % per annum after eradication. Therefore, we should conduct an infection diagnosis on the cases of gastric or duodenal ulcer which have neither active hemorrhage nor are associated with NSAID, and also we should conduct eradication treatment on the cases infected by *H. pylori*.

Ulcer recurrence after eradication

CQ. How frequent would ulcer recur after successful eradication and how do we prevent it?

- Ulcers recur after eradication in only 0–2 % of cases. We should eliminate the possible causes of recurrence such as reinfection with *H. pylori*, smoking habit, or NSAID administration. Recommendation 2, 100 % agreed, evidence level B.

Comment: In Japan, it is reported that in the cases at 1 year after the successful eradication, the cumulative recurrence risk of each gastric ulcer and duodenal ulcer is 11 and 6 % [46], however, in theses recurrences, some cases that are difficult to be distinguished from erosive lesion are also included. Furthermore, over 4,000 multicenter studies spent 4 years in Japan indicated that the recurrence ratio of gastric ulcer or duodenal ulcer is only 1–2 % per annum after eradication [47]. We found NSAID meditation records and habit of smoking or drinking alcohol more significantly in the recurrence cases of gastric ulcer; 93.1 % of gastric ulcer recurred as gastric ulcer, and all duodenal ulcers recurred as duodenal ulcers. Smoking, drinking alcohol, and NSAID meditation were seen as background factors of gastric ulcer recurrence, so it is possible that some other factors other than reinfection with *H. pylori* have a larger influence on gastric ulcers than on duodenal ulcer.

Although it is uncommon that ulcers recur after eradication, reinfection with *H. pylori*, smoking habit, and NSAID administration are certainly considered to be risks of ulcers to recur.

3. Non-eradication therapy

Initial therapy

CQ. What is the first-line drug for the initial non-eradication treatment of gastric ulcers?

- PPIs are recommended. Recommendation 1, 100 % agreed, evidence level A.
- If PPIs cannot be prescribed, H_2RAs are recommended. Recommendation 1, 100 % agreed, evidence level B.
- If PPIs cannot be prescribed, drugs such as pirenzepine, sucralfate, and misoprostol are recommended. Recommendation 2, 100 % agreed, evidence level B.

Comment: We recommend PPIs because several meta-analyses demonstrated that the ulcer-healing rate of PPIs was significantly higher than that of H_2RAs [48–51]. When PPIs cannot be prescribed due to allergy, for example, H_2RAs are recommended. With respect to the ulcer-healing rate, there were no significant differences between H_2RAs [52–59]. Moreover, pirenzepine [60], sucralfate [61–68], and misoprostol [69, 70] are recommended because each of their ulcer-healing rates was equivalent to those of H_2RAs. Although vonoprazan could not be cited because the literature was searched from 1983 to 2012, vonoprazan has been receiving much attention in recent years because of its high ulcer-healing rate for gastric ulcers compared with lansoprazole [71].

CQ. For the initial non-eradication treatment of gastric ulcers, is combination therapy of gastric secretion inhibitors and mucosa-protecting agents effective?

- For PPIs, single administration is recommended. Recommendation 2, 100 % agreed, evidence level C.

- For H_2RAs, several combination therapies such as cimetidine and egualen sodium (Recommendation 2, 100 % agreed, evidence level B), ranitidine and teprenone (Recommendation 2, 100 % agreed, evidence level C), and cimetidine and ecabet sodium (Recommendation 2, 100 % agreed, evidence level C) are recommended.

Comment: We recommend single administration of PPIs because mucosa-protecting agents do not enhance the healing of gastric ulcers [72]. Several combination therapies such as cimetidine and egualen sodium [73], ranitidine and teprenone [74], and cimetidine and ecabet sodium [75] enhance the healing of gastric ulcers.

CQ. What is the first-line drug for the initial non-eradication treatment of duodenal ulcers?

- PPIs are recommended. Recommendation 1, 100 % agreed, evidence A.
- If PPIs cannot be prescribed, H_2RAs are recommended. Recommendation 1, 100 % agreed, evidence level B.
- If PPIs cannot be prescribed, drugs such as pirenzepine, sucralfate, and misoprostol are recommended. Recommendation 2, 100 % agreed, evidence B.

Comment: We recommend PPIs because a meta-analysis demonstrated that the ulcer-healing rate of PPIs was significantly higher than that of H_2RAs [76]. When PPIs cannot be prescribed due to allergy, for example, H_2RAs are recommended. About the ulcer-healing rate, there were no significant differences between H_2RAs [77–79]. Moreover, pirenzepine [80], sucralfate [81–85], and misoprostol [86] are recommended, because each of their ulcer-healing rates was equivalent to those of H_2RAs. Although vonoprazan could not be cited because the literature was searched from 1983 to 2012, vonoprazan has been receiving much attention in recent years because of its high ulcer-healing rate for duodenal ulcers compared to lansoprazole [71].

CQ. For the initial non-eradication treatment of duodenal ulcers, is combination therapy of gastric secretion inhibitors and mucosa-protecting agents effective?

- For PPIs, single administration of PPIs is recommended. Recommendation 2, 100 % agreed, evidence level C.
- For H_2RAs, combination therapy with cimetidine and aldioxa is recommended. Recommendation 2, 100 % agreed, evidence level C.

Comment: We recommend single administration of PPIs because mucosa-protecting agents do not enhance the healing of duodenal ulcers [72]. Combination therapy with cimetidine and aldioxa enhances the healing of duodenal ulcers [87].

Maintenance therapy

CQ. Is maintenance treatment necessary for non-eradication therapy in gastric ulcer patients?

- In non-eradication therapy for gastric ulcers, maintenance treatment is effective for the prevention of ulcer recurrence in healed gastric ulcers, and this treatment is recommended. Recommendation 1, 100 % agreed, evidence level A.

Comment: In recent years, *H. pylori* eradication therapy is a first step treatment for gastric ulcer patients. Because it has been shown that *H. pylori* eradication therapy prevents peptic ulcer recurrence, gastric ulcer patients for whom non-eradication therapy is appropriate are few. Hentschel et al. [88] entered that 108 patients with healed gastric ulcers into a 1-year, double-blind study to compare the effect of cimetidine maintenance therapy (400 mg at night) with placebo. The total ulcer recurrence rate was significantly lower in the cimetidine-treated group (14 %) than in the placebo-treated group (55 %). Other RCTs comparing placebo also concluded that maintenance treatment is effective for sustaining remission in patients with gastric ulcers [89, 90].

CQ. What drugs should be selected for non-eradication therapy (maintenance treatment) in gastric ulcer patients?

- In non-eradication therapy (maintenance treatment) for gastric ulcers, H_2RA and sucralfate are recommended. Recommendation 1, 100 % agreed, evidence level A.

Comment: A placebo-controlled RCT showed that the recurrence rate of gastric ulcers was significantly lower in the cimetidine-treated group (400 mg at night) than in the placebo-treated group [88]. The drugs that are effective as maintenance treatment to prevent gastric ulcers are cimetidine 400 or 800 mg, ranitidine 150 mg, famotidine 20 mg, roxatidine acetate 75 mg, nizatidine 150 mg, and sucralfate 2, 3, and 4 g [61, 88, 91–94].

CQ. Is maintenance treatment necessary for non-eradication therapy in duodenal ulcer patients?

- In non-eradication therapy for duodenal ulcers, maintenance treatment is effective for the prevention of ulcer recurrence in healed duodenal ulcers, and this treatment is recommended. Recommendation 1, 100 % agreed, evidence level A.

Comment: In recent years, *H. pylori* eradication therapy is a first-step treatment for duodenal ulcer patients. Because it has been shown that *H. pylori* eradication therapy prevents

peptic ulcer recurrence, duodenal ulcer patients for whom non-eradication therapy is appropriate are few. Sontag et al. [95] examined that 370 patients with healed duodenal ulcers who entered a 1-year, double-blind study to compare the effect of cimetidine maintenance therapy (400 or 600 mg) with that of placebo. The total ulcer recurrence rate was significantly lower in the cimetidine-treated group than in the placebo-treated group. Other placebo-controlled RCTs also concluded that maintenance treatment is effective for sustaining remission in patients with duodenal ulcers [96, 97].

CQ. What drugs should be selected for non-eradication therapy (maintenance treatment) in duodenal ulcer patients?

- In non-eradication therapy (maintenance treatment) for duodenal ulcers, PPI, H_2RA, and sucralfate are recommended. Recommendation 1, 100 % agreed, evidence level A.

Comment: A placebo-controlled RCT showed that the duodenal ulcer recurrence rate was significantly lower in the cimetidine-treated group (400 or 600 mg) than in the placebo-treated group [95]. The drugs that are effective as maintenance treatment for preventing duodenal ulcers are cimetidine 400 or 600 mg, ranitidine 150 mg, famotidine 20 or 40 mg, roxatidine acetate 75 mg, nizatidine 150 mg, sucralfate 2 g, omeprazole 20 mg, and lansoprazole 15 mg [95–98].

4. Drug-induced ulcer

Non-selective NSAID-induced ulcer

CQ. How should NSAID-induced ulcers be treated?

- NSAIDs should be discontinued, and administration of anti-ulcer drugs is recommended. Recommendation 1, 100 % agreed, evidence level A.
- If NSAIDs cannot be discontinued, administration of PPIs or prostaglandin (PG) analog is recommended. Recommendation 1, 100 % agreed, evidence level A.

Comment: Gastric and duodenal ulcer to be found in NSAIDs user heal to a high rate only by NSAIDs withdrawal [99].

The healing rate of gastric and duodenal ulcers with misoprostol 800 μg/day was significantly higher than with placebo [100].

In the comparative studies of PPIs vs. H_2RA (lansoprazole 15 mg or 30 mg/day vs. ranitidine 300 mg/day [101]), and PPIs vs. PG analog (omeprazole 20 mg or 40 mg/day vs. misoprostol 800 μg/day [102]), the healing rate of gastric and duodenal ulcers was higher in the PPI groups in all of these studies.

CQ. Does eradication of *H. pylori* increase the healing rate of NSAID-induced ulcers?

- When NSAID-induced ulcers do not lead to healing, eradication of *H. pylori* cannot accelerate the ulcer-healing process. Thus, *H. pylori* eradication therapy is not recommended. Recommendation 2, 100 % agreed, evidence level A.

Comment: Many studies show that eradication of *H. pylori* has no effect on treatment of NSAID-induced ulcers [103]. Some reports indicate that *H. pylori* eradication therapy delays the healing of these ulcers. Because none of the previous studies reported that *H. pylori* eradication therapy facilitates the healing of NSAID-related ulcers, *H. pylori* eradication therapy is not recommended.

CQ. If a patient receiving NSAIDs tests positive for *H. pylori* infection, should *H. pylori* eradication therapy be administered?

- Eradication of *H. pylori* is recommended for prevention of ulcers in patients starting treatment with NSAIDs (e.g., NSAID-naive patients).

  Recommendation 1, 100 % agreed, evidence level A.
- Eradication of *H. pylori* is not recommended for prevention of ulcers in patients who are already being treated with NSAIDs. Recommendation 1, 100 % agreed, evidence level A.

Comment: With regard to the usefulness of *H. pylori* eradication therapy in patients starting treatment with NSAIDs (e.g., NSAID-naive patients), Chan et al. [104] reported data at 8 weeks and 6 months after eradication of *H. pylori*. A significant preventative effect was not observed in patients who were being treated with NSAIDs; moreover, the results indicate that PPIs are more useful. The result of a meta-analysis [105] shows that *H. pylori* eradication therapy reduces the incidence of ulcers in patients receiving NSAIDs as a whole; however, an effect of *H. pylori* eradication therapy cannot be expected during NSAIDs therapy. Instead, the efficacy of PPIs was observed. The results of the meta-analysis reported in 2012 [106] also shows that the efficacy of *H. pylori* eradication therapy for prevention of NSAID-induced ulcers was comparable to that of the previously reported result; however, the efficacy of *H. pylori* eradication therapy was observed primarily in Asian patients.

CQ. Is preventative therapy for NSAID-induced ulcers necessary in patients with no history of ulcers?

- Prevention of NSAID-induced ulcers is necessary and recommended even in patients with no history of ulcers. Recommendation 2, 100 % agreed, evidence level A.

Comment: In patients receiving long-term NSAID therapy (more than 3 months), the efficacy of PG analog (misoprostol 400–800 μg/day) [107], PPIs (omeprazole 10 mg and 20 mg/day), or high-dose H_2RA (famotidine 80 mg/day) [108] given as primary prevention has been reported in many RCTs and meta-analyses. These studies show that even in patients with no history of ulcers, if patients are elderly or have a history of cardiovascular events, the concomitant use of PPI was associated with a two-thirds reduction in the risk for serious NSAID ulcer complications [109].

CQ. How should NSAID-induced ulcers be prevented in patients receiving high-dose NSAIDs or combination of antithrombotic drugs or glucocorticoids or bisphosphonates; or for patients who are elderly or having severe complications?

- In patients receiving combinations of NSAIDs and low-dose aspirin (LDA), administration of PPIs or PG analog is recommended for ulcer prevention. Recommendation 1, 100 % agreed, evidence level A.
- In elderly patients, administration of PPIs and PG analog is recommended for prevention of NSAID-induced bleeding ulcer.

Recommendation 1, 100 % agreed, evidence level A.

Comment: In patients with a history of ulcer who are receiving combinations of NSAIDs and LDA, the preventive effect up to 12 weeks was observed in patients who received a half dose or regular doses of PPI (lansoprazole 15 or 30 mg/day), or 800 μg/day of misoprostol [110]. The risk of ulcer complications increases when NSAIDs are administered with glucocorticoids or anticoagulants; however, no RCT has been conducted to investigate ulcer prevention in patients receiving such drug combinations. The efficacy of PPIs and PG analog for prevention of complications such as bleeding in elderly patients has been demonstrated in many studies [109].

CQ. How should recurrence be prevented in patients with a history of ulcers or bleeding ulcers who are starting NSAID therapy?

- PPIs and PG analog effectively prevent NSAID-induced ulcers in patients with a history of ulcers; thus, concomitant administration of a PPI is recommended as the first-line drug. Recommendation 1, 100 % agreed, evidence level A.
- Concomitant administration of the selective cyclooxygenase (COX)-2 inhibitor celecoxib and a PPI is recommended for preventing recurrence of bleeding NSAID-induced ulcers in patients with a history of bleeding ulcers. Recommendation 1, 100 % agreed, evidence level A.

Comment: The efficacy of PG analog [111] and PPIs [112] for secondary prevention was observed in high-risk patients (elderly or with a history of peptic ulcer).

Moreover, in a Japanese study of 24-week monitoring of patients with a history of ulcers, the usefulness of lansoprazole, as compared to placebo (mucosal protective drugs), was observed [113]. One study showed that when the NSAID-induced ulcer was healed, all patients started a combination of celecoxib plus esomeprazole or placebo. Over a 13-month observation period, the ability to prevent hemorrhagic ulcers was significantly higher with the combination of celecoxib plus esomeprazole [114].

In Japan, the efficacy of esomeprazole for the secondary prevention of NSAID-induced ulcers was reported in 2012 (Aliment Pharmacol Ther 2012; 36:115–25). Moreover, a new class of acid suppressants; a potassium-competitive acid blocker (PCAB: vonoprazan) became available in February, 2015. For the secondary prevention of NSAID-induced ulcers, the non-inferiority of PCAB to PPIs has been demonstrated. (Gastroenterology, Vol. 146, Issue 5, S-739 Published in issue: May 2014)

Selective NSAID (COX2-selective inhibitor)-induced ulcer

CQ. Is preventive medication with anti-ulcer agents required for patients taking a COX-2 selective inhibitor?

- Preventive medication with anti-ulcer agents is recommended for patients taking COX-2 selective inhibitors with a past history of peptic ulcer. Recommendation 1, 100 % agreed, evidence level A.
- No preventive medication of anti-ulcer agents is recommended for patients taking COX-2 selective inhibitors without a past history of peptic ulcer. Recommendation 1, 100 % agreed, evidence level A.

Comment: The incidence rate of relapsing peptic ulcer or complications due to peptic ulcer has been reported to range from 3.7 to 24.1 % when patients with a past history of peptic ulcer take a COX-2 selective inhibitor without preventive medication with anti-ulcer agents [112]. On the other hand, preventive medication with PPIs has been proven to significantly reduce the incidence rate of relapsing peptic ulcer when patients with a history of peptic ulcer take a COX-2 selective inhibitor [112].

In patients without a past history of peptic ulcer, no significant difference in the incidence rate of peptic ulcer between taking a COX-2 selective inhibitor and a placebo has been reported [115].

CQ. Does medication with a COX-2 selective inhibitor reduce the incidence rate of NSAID-induced peptic ulcers?

- Medication with COX-2 selective inhibitors is recommended because it reduces the incidence rate of NSAID-induced peptic ulcer. Recommendation 1, 100 % agreed, evidence level A.

Comment: In Western countries, the incidence rate of peptic ulcers has been reported to be significantly lower in patients taking a COX-2 selective inhibitor than in patients taking non-selective NSAIDs [116]. Furthermore, COX-2 selective inhibitor therapy has been proven useful to prevent re-bleeding after the healing of a hemorrhagic peptic ulcer, and to have the same incidence rate of non-selective NSAIDs with a PPI [117].

In Japan, celecoxib is reported to be as effective as loxoprofen in the treatment of rheumatoid arthritis and osteoarthritis with a lower incidence of gastrointestinal events [118]

LDA-induced ulcer

CQ. How should LDA-related peptic ulcers be treated?

- LDA with concomitant use of PPI is recommended for treating LDA-related peptic ulcers. Recommendation 1, 100 % agreed, evidence A.

Comment: Long-term therapy with LDA is associated with a significant increase in the incidence and recurrence of gastrointestinal (GI) hemorrhage [119], whereas continuous LDA therapy reduces mortality rates related to cardiovascular (CV) events [15]. In the incidence of recurrent ulcer bleeding and peptic ulcer healing rates, there were no differences between the PPI and PPI-plus-LDA [120]

CQ. What kind of concomitant use of medicine should be effective for reduced incidence and prevalence rate of LDA-related peptic ulcers?

- Acid-suppressive treatment is recommended for the reduction of the incidence and prevalence rate of LDA-related peptic ulcers. Recommendation 1, 100 % agreed, evidence A.

Comment: LDA treatment is associated with high prevalence and incidence of peptic ulcers [121]. Esomeprazole reduces the occurrence of peptic ulcers in patients taking LDA [122], and esomeprazole was superior to famotidine in preventing upper GI complications related to LDA, clopidogrel, and thrombolytics [123]. Famotidine was effective in the prevention of new gastric and duodenal ulcers compared to placebo in patients on LDA without ulcers on endoscopy at baseline [124]. Furthermore, esomeprazole reduces the risk of developing gastric and/or duodenal ulcers associated with the continuous use of LDA in patients older age without preexisting gastroduodenal ulcers [125].

CQ. What kind of concomitant use of medicine should be effective for reduced incidence and prevalence rate of LDA-related peptic ulcer bleeding?

- Acid-suppressive treatment is recommended for the reduction of the incidence and prevalence rate of LDA-related peptic ulcer bleeding. Recommendation 1, 100 % agreed, evidence A.

Comment: LDA treatment is associated with a high prevalence and incidence of peptic ulcer bleeding [126–128]. Among patients receiving LDA and clopidogrel, prophylactic use of PPI reduced the rate of upper GI bleeding (UGIB) [129]. In a meta-analysis, PPI use reduced the risk of GI bleeding in patients with given LDA [128].

CQ. What kind of concomitant use of medicine should be effective for reduced incidence and prevalence rate of recurrent LDA-related peptic ulcer bleeding?

- PPI in addition to the eradication of *H. pylori* infection is recommended compared to eradication alone for the reduction of the incidence and prevalence rate of LDA-related peptic ulcer bleeding. Recommendation 1, 100 % agreed, evidence A.

Comment: The overall relative risk of Upper GI complications is associated with LDA use [130]. Among those taking LDA, especially references with respect to the probability of recurrent bleeding, the eradication of *H. pylori* is equivalent to treatment with omeprazole [131]. In patients who had ulcer complications related to the long-term use of LDA, treatment with lansoprazole in addition to the eradication of *H. pylori* significantly reduced the rate of recurrence of ulcer bleeding compared to placebo plus *H. pylori* eradication [132]. The combination of esomeprazole and LDA is superior to clopidogrel in preventing ulcer complications in patients who have a past history of LDA-related peptic ulcer bleeding [133, 134]. The long-term incidence of recurrent ulcer bleeding with LDA use is low after *H. pylori* eradication [135].

CQ. How should an LDA-related peptic ulcer recurrence be prevented in patients with a history of peptic ulcers?

- PPI is recommended for the reduction of the recurrence rate of LDA-related peptic ulcers. Recommendation 1, 100 % agreed, evidence A.

Comment: In patients with LDA-related peptic ulcers, high-dose famotidine therapy is inferior to pantoprazole in preventing recurrent bleeding ulcers continued to receive LDA [136]. Lansoprazole was superior to gefarnate in reducing the risk of gastric or duodenal ulcer recurrence in patients with a definite history of gastric or duodenal ulcers who required long-term LDA therapy [137]. Rabeprazole is more effective than gefarnate in reducing the risk of recurrence of peptic ulcer in LDA users [138]. Esomeprazole is efficacious and well tolerated in reducing the recurrence of peptic ulcer with a history of ulcers who are taking LDA [139]. Vonoprazan was effective for the prevention of peptic ulcer recurrence and hemorrhage in patients with a defined history of peptic ulcers who required LDA (Gastroenterology, Vol. 146, Issue 5, S-739 Published in issue: May 2014).

CQ. In patients without a history of peptic ulcer and with no risk of peptic ulcer, is the prevention of LDA-related peptic ulcers necessary?

- Acid-suppressive treatment is recommended for the reduction of the incidence and prevalence rate of LDA-related peptic ulcers without a history of ulcers (a primary protection). Recommendation 1, 100 % agreed, evidence A.

Comment: Famotidine was effective in the prevention of new gastric and duodenal ulcers compared to placebo in patients on LDA without ulcers on endoscopy at baseline [124].

CQ. How should a peptic ulcer be prevented with NSAID treatment in patients taking LDA?

- PPI is recommended for the preventing gastric ulcers concomitant use of LDA with NSAIDs. Recommendation 1, 100 % agreed, evidence A.

Comment: NSAIDs plus LDA caused a greater increase in gastric ulcers than LDA alone [140]. COX-2 selective inhibitors were associated with a lower risk of peptic ulcers and UGIB than non-selective NSAIDs in taking with LDA [141, 142], whereas in patients at high risk for recurrence of gastric ulcer taking with NSAIDs plus LDA, use of co-therapy with misoprostol or lansoprazole significantly lowered the risk for gastric ulcer recurrence [110]. Then, in LDA users, naproxen plus esomeprazole was associated with a lower combined incidence of gastric ulcers compared to naproxen [143]. Moreover, in patients with taking LDA, the use of celecoxib or naproxen plus lansoprazole resulted in similar rates of gastroduodenal ulceration [144].

5. Non-*H. pylori*, non-NSAID ulcer

CQ. How should non-*H. pylori*, non-NSAID ulcers be treated?

- In the treatment of non-*H. pylori* and non-NSAID ulcers, PPI therapy is advised. Recommendation 2, 100 % agreed, evidence level C.

Comment: Since the discovery of *H. pylori* infection in the stomach, both *H. pylori* infection and NSAID use had been considered to be the two main causes of peptic ulcer diseases. However, there have been recent reports of an increase in the proportion of peptic ulcers without these known risk factors; these are termed idiopathic peptic ulcers [145–147]. Advanced age, serious systemic complications, and psychological stress are considered to be the potential risk factors for idiopathic ulcers. The management of idiopathic peptic ulcers is poorly defined. Because early studies suggested that some of these patients had increased gastrin and acid hypersecretion, PPI therapy is advised for idiopathic peptic ulcers. Compared to *H. pylori*-positive ulcers, idiopathic ulcers showed more recurrences and bleeding, and acid suppressive therapy is needed to prevent ulcers [146]. In addition, a recent study showed that gastroprotective agents do not reduce the risk of recurrent bleeding or mortality for patients with *H. pylori*—negative idiopathic bleeding ulcers [147]. In the future, RCTs are needed to investigate the effect of PPIs on the long-term risk of recurrent bleeding and mortality in idiopathic ulcers.

6. Surgical treatment

CQ. What is the surgical indication for peptic ulcer perforation?

- Early operation is recommended for peptic ulcer perforation when it has been a long time after perforation or there is massive ascites, or a full stomach. Recommendation 1, 100 % agreed, evidence level B.
- Early operation is recommended for peptic ulcers when the patient is over 70 years old or with a general disorder, or the vital signs are unstable. Recommendation 1, 100 % agreed, evidence level C.

Comment: Even when surgery is not indicated based on the above statements, follow-up CT is needed for patient

observation [148]. If the patient's state is not improved at follow-up, the surgery is indicated.

CQ. What is the surgical indication for peptic ulcer bleeding?

- Surgery is recommended when the bleeding cannot be easily controlled by endoscopy. When the patient is old, earlier operation is recommended [149]. Recommendation 1, 80 % agreed, evidence level B.

Comment: Endoscopic treatment is commonly used today, but there is a report from abroad that endoscopic treatment increased mortality. It is important to go to surgery when it is appropriate.

Interventional radiology is reported to be useful. However, institutions that can perform interventional radiology are few.

CQ. What is the best surgical procedure for peptic ulcer perforation?

- The surgical procedure most recommended for gastroduodenal peptic ulcer perforation is peritoneal lavage + closure of the perforated hole + omental patch. Recommendation 1, 100 % agreed, evidence level A.

Comment: There are many reports of comparisons between open laparotomy and laparoscopic surgery. Laparoscopic surgery is superior with respect to pain and surgical site infection, but it has a longer operation time. All the trials were limited to patients in good general condition. Whether laparoscopic surgery is possible in the emergent setting depends on the institution, and laparoscopic surgery is not included in the statement.

CQ. What is the best surgical procedure for peptic ulcer bleeding?

- Gastrostomy + suturing hemostasis + suturing closure of the ulcer bed is recommended. Recommendation 1, 100 % agreed, evidence level C
- The Dubois operation is recommended for chronic bleeding duodenal ulcer. Recommendation 1, 100 % agreed, evidence level C.

Comment: When the recommended operation, gastrostomy + suturing hemostasis + suturing closure of the ulcer bed, cannot control bleeding, gastrectomy is one of the choices for bleeding control. There is a report of a case series of the Dubois operation being useful for chronic bleeding duodenal ulcer [150].

CQ. What are the surgical procedures for stenosis caused by a chronic peptic ulcer?

- Gastro-duodenal side-to-side anastomosis is recommended for a stenosis caused by a chronic peptic ulcer. Recommendation 1, 100 % agreed, evidence level B.
- Distal gastrectomy is also recommended for a stenosis caused by a chronic peptic ulcer. Recommendation 1, 100 % agreed, evidence level C.
- The Findterer–Bancroft operation is recommended for the cases with difficult duodenal stump closure. Recommendation 1, 100 % agreed, evidence level C.

Comment: Highly selective vagotomy plus Jaboulay is reported to be useful [151]. This was reported in 1995, when *H. pylori* eradication and PPI therapy were uncommon, and it is a question of whether highly selective vagotomy is still needed.

CQ. Is *H. pylori* eradication needed after surgery for peptic ulcer?

- Eradication is recommended if the patient is positive for *H. pylori* after the omental patch procedure for peptic ulcer. Recommendation 1, 100 % agreed, evidence level A.

Comment: Almost all reports are in concordance for eradication after gastric preserving surgery [152]. There is no agreement about eradication after distal gastrectomy. Early eradication is reported to accelerate ulcer healing.

7. Conservative therapy for perforation and stenosis

CQ. What condition is an indication of medical therapy for perforated peptic ulcer?

- We propose an indication of medical therapy for the perforated peptic ulcer is mild localized peritonitis. The criteria of medical therapy contain onset within 24 h, onset at hunger, stable condition without severe complication, symptom of peritoneal irritation localized in the upper quadrant, and a small amount of ascites. Recommendation 2, 100 % agreed, evidence level D.
- The therapy of perforated peptic ulcer gives priority to surgical therapy in patients over 70 years old. Recommendation 2, 100 % agreed, evidence level C.

Comment: Indication of medical therapy for perforated peptic ulcer is mild localized peritonitis. Crofts et al. [148] reported patients below 70 years old were significantly less likely to transfer to surgical therapy than older patients. Many studies reported that age of indication for conservative therapy was less than 70 years.

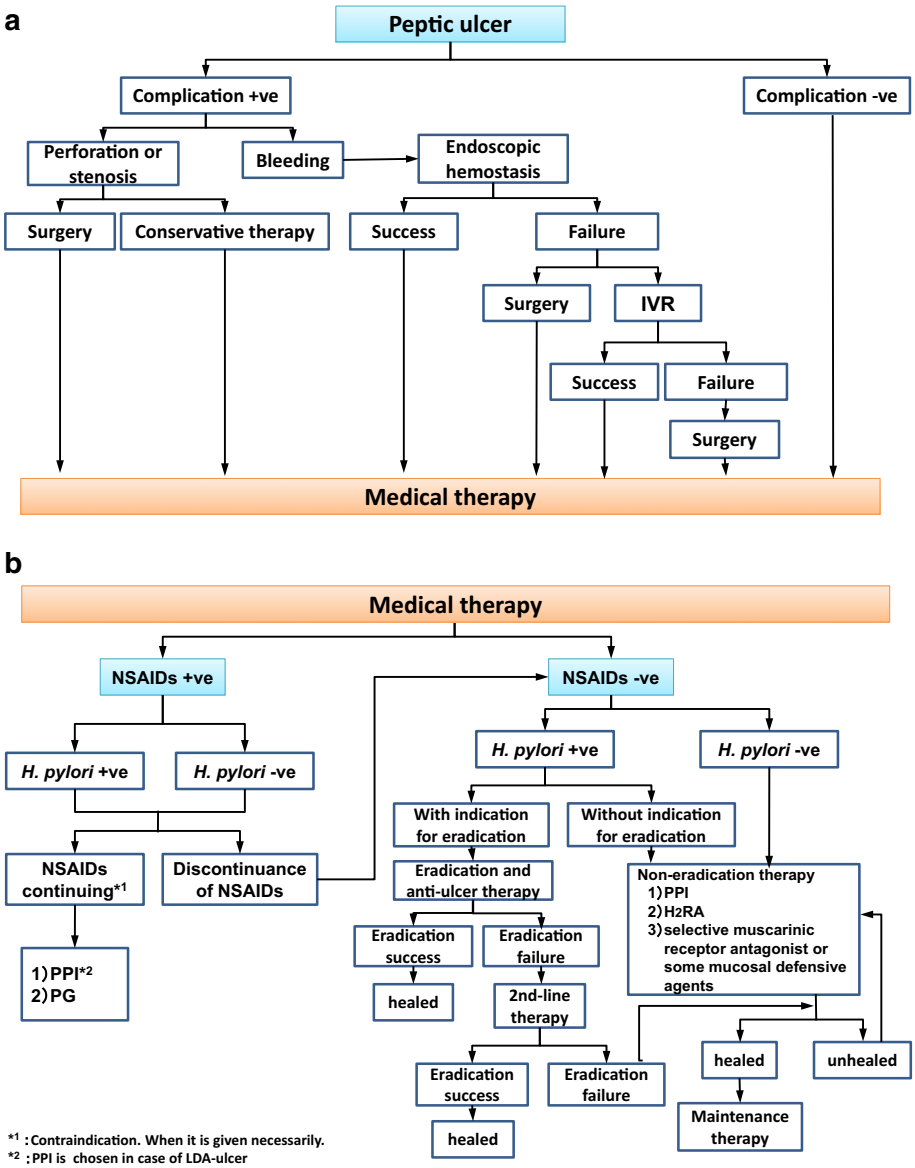

Fig. 1 **a**, **b** Therapeutic algorithms. *IVR* interventional radiology

CQ. Which timing is medical therapy for the perforated peptic ulcer shifted to surgical therapy?

- We propose that perforated peptic ulcer be treated with surgical therapy when clinical and imaging findings have no improvement after 24 h. Recommendation 2, 100 % agreed, evidence level D.

Comment: Some studies reported the time point of operation beyond 12 or 24 h at onset worsen outcome of surgical therapy. Many authors suggested surgical therapy should be performed within 24 h.

CQ. What kind of therapy is selected for stenosis of peptic ulcer?

- Endoscopic balloon dilation is recommended for maintenance therapy with stenosis of peptic ulcer. Recommendation 2, 100 % agreed, evidence level D.

Comment: Stenosis of peptic ulcer is almost stenosis of the pyloric ring. Endoscopic balloon dilation obtained a good success rate [82 (range, 75–100) %] in a short time, but the long-term (for 2 years) outcome decreased to 53 (range, 49–83) %.

Therapeutic algorithm

Figure 1 shows the algorithms for the treatment of peptic ulcer disease. Initially, ulcer complications are treated. Perforation or stenosis is treated with surgery or conservatively. Ulcer bleeding is first treated by endoscopic hemostasis. When it fails, surgery or interventional radiology is chosen.

Second, medical therapy is provided. In cases of NSAID-related ulcers, the use of NSAIDs is stopped, and

anti-ulcer therapy is provided. If NSAID use must continue, the ulcer is treated with a PPI or PG analog.

In cases without NSAID use, the patient is evaluated for *H. pylori* infection. *H. pylori*-positive patients with an indication for eradication therapy receive eradication and anti-ulcer therapy. If ulcers are scarred after *H. pylori* eradication, the disease is healing. If first-line eradication therapy fails, second-line therapy is given.

In cases of non-*H. pylori*, non-NSAID ulcers or *H. pylori*-positive patients without an indication for eradication therapy, non-eradication therapy is provided. The first choice is a PPI. The second choice is an H_2RA. The third choice is a selective muscarinic receptor antagonist or some mucosal defensive agents. After initial therapy, maintenance therapy is provided for prevention of ulcer relapse.

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Appendix

Members of the Guidelines Committee who created and evaluated the JSGE "Evidence-based clinical practice guidelines for peptic ulcer disease" are listed below.

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The Japanese Society of Gastroenterology

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