Review Article

Diagnosis, Treatment, and Outcome in Patients with Bleeding Peptic Ulcers and *Helicobacter pylori* Infections

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Upper gastrointestinal (UGI) bleeding is the most frequently encountered complication of peptic ulcer disease. *Helicobacter pylori* (*Hp*) infection and nonsteroidal anti-inflammatory drug (NSAID) administration are two independent risk factors for UGI bleeding. Therefore, testing for and diagnosing *Hp* infection are essential for every patient with UGI hemorrhage. The presence of the infection is usually underestimated in cases of bleeding peptic ulcers. A rapid urease test (RUT), with or without histology, is usually the first test performed during endoscopy. If the initial diagnostic test is negative, a delayed ¹³C-urea breath test (UBT) or serology should be performed. Once an infection is diagnosed, antibiotic treatment is advocated. Sufficient evidence supports the concept that *Hp* infection eradication can heal the ulcer and reduce the likelihood of rebleeding. With increased awareness of the effects of *Hp* infection, the etiologies of bleeding peptic ulcers have shifted to NSAID use, old age, and disease comorbidity.

1. Introduction

Left untreated, peptic ulcer diseases (PUD) will cause major complications, such as hemorrhage, perforation, or obstruction in 20–25% of patients. Among these complications, upper gastrointestinal (UGI) bleeding is the most frequently encountered, accounting for about 70% of cases [1, 2]. With the discovery of *Helicobacter pylori* (*Hp*) [3], the pathogenic relationship between PUD and *Hp* infection has come into focus. Worldwide consensus guidelines recommend the mandatory eradication of *Hp* in patient with PUD [4–13].

Another independent risk factor for PUD and subsequent UGI bleeding is the administration of nonsteroidal anti-inflammatory drugs (NSAIDs) [14]. Those patients requiring long-term NSAID treatment should be screened for *Hp* status, and *Hp* eradication is suggested before administering NSAIDs [8]. Writing prescriptions for aspirin and antiplatelet agents is a common clinical scenario that creates new challenges related to UGI bleeding in gastroenterological

practices [15, 16]. However, the relationship between the use of these medications and UGI bleeding is beyond the scope of this paper. Here, we will elucidate the relationship between bleeding peptic ulcers and *Hp* infection from the chronological perspective with an emphasis on diagnosis, treatments, and outcomes.

2. Materials and Methods

We searched Pubmed (to 15 March 2014). Overall, we identified 708, 526, and 120 with the following key word combinations: “bleeding peptic ulcer AND *Helicobacter pylori* diagnosis,” “bleeding peptic ulcer AND *Helicobacter pylori* treatment,” and “bleeding peptic ulcer AND *Helicobacter pylori* outcome,” respectively.

Medical subject headings (MeSH) terms were employed to assist the search, and the results were reviewed by the authors. We also conducted a manual search of material

from several congresses. The paper selection criteria included (1) discussion with diagnosis, treatment, or outcome of bleeding peptic ulcers and *Hp* infection and (2) publication in full manuscript form in English. Finally, 129 articles were selected, and their reference lists were checked for other possible studies for inclusion.

3. Results and Discussion

3.1. Diagnosis. The diagnosis of *Hp* infection is based on both invasive and noninvasive methods. Endoscopy is an invasive method, which includes a rapid urease test (RUT), histology, culturing, and polymerase chain reaction (PCR). The noninvasive methods include serology antibody assessment, ¹³C-urea breath test (UBT), and stool antigen testing. There are only minimal differences in the accuracies of the invasive tests. Among them, the RUT is the most frequently used. The UBT is the recommended noninvasive test [17]. Recently, the monoclonal stool antigen test has also been suggested [18]. The prevalence of *Hp* infection in noncomplicated PUD has been reported to be high in duodenal ulcer patients and moderate in gastric ulcer patients, regardless of which test is performed [19, 20]. However, there have been discrepant test results among patients with bleeding peptic ulcers. The individual diagnostic tests are discussed below.

3.1.1. RUT. The RUT is the most common examination for patients with UGI bleeding because endoscopy is always performed in such cases. An early study from Hong Kong disclosed a high false-negative rate for urease tests from antral biopsies in bleeding ulcer patients [21]. Almost simultaneously, we reported delayed positive results on the CLO test (color change after 24 hours) in our bleeding peptic ulcer patients if there was blood in the gastric antrum [22]. Another study from Greece demonstrated similar results at the same meeting [23]. These studies were further elucidated in subsequently published full articles [24–26].

Because there is always blood in the stomachs of patients with bleeding peptic ulcers, interference with RUT results by blood components is a concern. Several mechanisms have been suggested, including the bactericidal effect of serum inducing a transient decrease in bacterial density, the presence of anti-*Hp* antibodies inhibiting urease production, suppressed urease activity by serum enzymes or electrolytes, various buffering systems (e.g., albumin, bicarbonate, and phosphate) interfering with the pH level of the RUT reagent, and concomitant administration of NSAIDs or proton pump inhibitors (PPIs). In one in vitro study [27], a false-negative RUT result was caused by the buffering effects of serum albumin on the pH indicator but not on urease activity. Another in vitro study concluded that large gastric lavage before endoscopy can cause a false-negative RUT result [28]. However, our study found no influence on the likelihood of a false-negative result if the gastric antral biopsy specimen was cleansed by normal saline before inoculating the wells for the CLO test [29]. Similarly, another study concluded that an artificial blood-soaked antral specimen did not influence the results of two RUTs [30]. The bactericidal effect of human

plasma [31, 32] and the reduction in bacterial load by PPIs [33] have been demonstrated.

In subsequent studies worldwide [34–40], RUT was further confirmed to be less sensitive than other tests in the diagnosis of *Hp* infection in bleeding peptic ulcers. Another consideration is that *Hp* bacterial density may be patchy, and only using samples from the gastric antrum may be inadequate. Inappropriate biopsy site and inadequate specimens are other explanations of false-negative results of RUT in patients with UGI bleeding. (Blood in stomach could induce *Hp* migration to corpus and fundus and the decrease of bacterial density in the antrum. Fewer amounts of specimens are obtained during emergent endoscopy procedure.) Simultaneous antral and body specimens or multiple biopsies have been found to produce more positive RUTs [41, 42]. Most authors concluded that the RUT cannot be the only diagnostic test in such circumstances [43]. If the initial diagnostic test is negative, a delayed test 4–8 weeks later can have up to an 80% positive rate in previously negative patients [44].

3.1.2. Histology. Different studies have reported low sensitivity with histologic methods, which is consistent with RUT sensitivity. This suggests that histology cannot reliably exclude *Hp* infection in patients with bleeding peptic ulcers [24, 34]. However, other studies have reported that histology is more sensitive than RUT [24, 25, 35, 36]. As previously mentioned, patchy distribution of bacterial density can be one factor, but the staining method and pathologist's interpretations also influence the results [45]. Others have suggested that the prevalence of *Hp* infection is probably the same among bleeding and nonbleeding patients [46]. The sensitivity of histology also relies on the experience of the endoscopist to take the biopsy from the appropriate site. Some publications had shown that atrophic change, rugal hyperplasia, edema, and spotty erythema are valuable endoscopic findings of *Hp* infection. It is very important to avoid false-negative histology finding by taking the biopsy from RAC (regular arrangement of collecting venules) negative site [47]. Therefore, combination tests should be performed to achieve a more precise diagnosis [48].

3.1.3. Culturing and PCR. Culturing *Hp* in patients with bleeding peptic ulcers produced a low yield in several studies [24, 34]. The reasons for its infrequent use include the time-consuming nature of the process due to the microanaerobic pathogen characteristics and the lack of time to perform the procedure during endoscopy.

Mucosal PCR has been used as an invasive test to diagnose *Hp* infection. In one study, this test was less sensitive in patients with bleeding peptic ulcers than for those with nonbleeding peptic ulcers and chronic gastritis [49]. However, another study reported that PCR had higher sensitivity than other biopsy-based tests and similar sensitivity to noninvasive tests [50]. The authors also demonstrated that blood may reduce the sensitivities of all biopsy-based tests. A study using real-time PCR can improve *Hp* detection in a histology-negative, formalin-fixed, and paraffin-embedded

biopsy and is superior to immunohistochemical staining [51]. Modified PCR could improve diagnostic accuracy in patients with UGI bleeding [52].

3.1.4. UBT. Many studies have confirmed that the ^{13}C -UBT can accurately diagnose *Hp* infection [53, 54]. This statement also applies to patients with UGI bleeding [24, 26, 35, 36, 38]. The test's sensitivity is not affected by blood in the stomach and is higher than those of biopsy-based methods and other noninvasive tests [55–57].

Because a subject must drink a urea-containing solution in conjunction with a test meal or citric acid, one might question whether this method is suitable for bleeding patients. Most UBTs are done when patients resume eating, or the UBT is reserved as a delayed test if the initial invasive methods are negative. However, using low-dose encapsulated ^{13}C -urea has proven to be feasible in fasting patients or even before an endoscopy because it only takes a small amount of water to swallow a pill [58].

3.1.5. Stool Antigen Test. The stool *Hp* antigen test has been introduced as an accurate noninvasive test [59]. It can be performed by enzyme-linked immunosorbent assay (ELISA) with monoclonal or polyclonal antibodies or by immunochromatographic assay with monoclonal antibodies. The sensitivity of this method is reduced by UGI bleeding when polyclonal ELISA or immunochromatographic stool antigens are used [38, 60, 61]. Furthermore, it is not reliable in patients with bleeding peptic ulcers [62]. Another study reported a high number of false-positive results in patients with UGI bleeding due to a cross-reaction with the blood [63]. Therefore, the stool *Hp* antigen diagnostic test is not recommended for use in patients with UGI.

3.1.6. Serology. We [24] and others [34] have demonstrated that serology is more sensitive than other invasive tests in cases of bleeding peptic ulcer. It can be used as the initial invasive test, as an alternative test, or when the UBT test is negative. However, commercial serological tests must be confirmed by a local laboratory before they are used in an individual hospital [64]. Additionally, if patients have been treated for *Hp* infection, serological tests have revealed that serum antibodies may last for up to a year [65]. This fact must not be overlooked when interpreting the results.

3.1.7. NSAIDs, PPI, and Other Drugs with Bleeding PUD on Diagnosis Tests. No matter which diagnostic tests are employed in patients with bleeding PUD, physicians should preclude NSAID use. Many studies have confirmed the influence of NSAIDs on the sensitivities of the test results [66–68]. *Hp* infection and NSAID use are two independent factors related to bleeding peptic ulcers [69]. In patients who are already on long-term NSAIDs, *Hp* eradication does not prevent the peptic ulcer from bleeding. Nevertheless, patients who require long-term NSAID medications should be tested for *Hp* infection in advance. *Hp* eradication can decrease the

incidence of peptic ulcer bleeding. But in patients with long-term NSAIDs use, the cause of peptic ulcer bleeding should be NSAIDs use, not *H. pylori* status.

Another frequently encountered scenario is that most patients are given PPIs either intravenously or orally at the initial presentation of UGI bleeding, even before an endoscopic examination. There is concern over whether the recent use of a PPI interferes with the diagnostic accuracy for *Hp* infection. One study with a 3-day dosage of intravenous PPI in a bleeding peptic ulcer case found that a high infusion dose significantly impacts negative histology and RUT results as compared to a regular daily dose [70]. Dose-dependent PPIs do produce short-term effects on *Hp* diagnosis. Recent PPI use may induce false-negative results on both invasive tests [35] and noninvasive tests, such as the UBT [71–74] and stool *Hp* antigen test [75]. The duration of PPI administration can variably affect diagnostic accuracy. Usually, discontinuation of the drug for 2 weeks is recommended before performing any test, except serology.

Antisecretory medication is mandatory in patients with bleeding peptic ulcers. H₂-receptor antagonists (H₂RA) may be an alternative regimen. There are several studies evaluating H₂RA and *Hp* diagnostic accuracy. Conflicting results exist, but most data indicate that these drugs have little influence on the *Hp* diagnosis [76, 77].

3.1.8. Summary. A systematic review and meta-analysis explored the accuracies of *Hp* diagnostic tests in patients with bleeding peptic ulcers [78]. The authors found that biopsy-based methods had low sensitivity and high specificity; UBT had high accuracy; stool antigen tests were less accurate; and serology, though not influenced by UGI bleeding, was not recommended as the first test. Pooled data on sensitivity, specificity, and positive and negative likelihood ratios are shown in Table 1. Because the positive likelihood ratio is high, positive invasive tests or UBT requires no further confirmation of *Hp* infection. However, the other delayed tests should not be overlooked.

A recent meta-regression study [79] suggested that the low prevalence of *Hp* infection in patients with bleeding peptic ulcers might be related to the methodology of the studies and to the patients' characteristics. The authors found a higher prevalence of *Hp* infection when a delayed test was performed and when younger patients were included. They concluded that the prevalence of *Hp* infection had been underestimated in patients with bleeding peptic ulcers. They also suggested that a delayed diagnostic test should be carried out if the initial diagnostic test is negative, as recommended by the International Consensus [11].

3.2. Treatment

3.2.1. *Hp* Eradication. *Hp* infection is still an important factor in peptic ulcer development. Eradication therapy is suggested for both duodenal and gastric ulcers in patients infected with *Hp* [13], regardless of whether they have complications. Although there is no direct causal relationship between *Hp* infection and early rebleeding in patients with peptic

TABLE 1: Accuracies of different diagnostic tests based on pooled data of different studies of patients with bleeding peptic ulcers [78].

Diagnostic test	Number of studies	Pooled patients	Sensitivity	Specificity	Positive LR	Negative LR
RUT	16	1,417	0.67	0.93	9.6	0.31
Histology	10	827	0.70	0.90	6.7	0.23
Culture	3	314	0.45	0.98	19.6	0.31
UBT	8	520	0.93	0.92	9.5	0.11
Stool Ag	6	377	0.87	0.70	2.3	0.2
Serology	9	803	0.88	0.69	2.5	0.25

Ag: antigen; LR: likelihood ratio; RUT: rapid urease test; UBT: urea breath test.

ulcer bleeding [80, 81], empirical *Hp* eradication as soon as patients resume eating is the most cost-effective strategy for preventing recurrent hemorrhage [82].

Many studies in the 1990s demonstrated the benefit of *Hp* eradication in decreasing peptic ulcer recurrences, as well as in bleeding cases. Using antibiotics to kill the bacteria was proven effective in preventing ulcer rebleeding in early studies [83, 84]. Other regimens using omeprazole and amoxicillin can also reduce the recurrence of peptic ulcer bleeding as compared to omeprazole or ranitidine alone [85–88]. The results were the same when the antibiotics were changed [89].

With the introduction of the ideal eradication regimen for *Hp* infection, triple therapy has been applied worldwide [90–92]. We previously reported that triple therapy can achieve a 91.3% eradication rate and a 97.1% ulcer healing rate in bleeding peptic ulcers [93]. One study found that as long as antibiotic eradication or *Hp* infection suppression is achieved, bleeding can be reduced [94]. Subsequent studies also confirmed that *Hp* eradication improves healing and decreases rebleeding [95–97].

The current dogma is that *Hp* eradication in bleeding peptic ulcers is superior to simple ulcer healing in preventing further ulcer hemorrhages [98, 99]. Therefore, testing for the presence of *Hp* infection and eradicating it are both mandatory and cost effective [100]. While there has been concern over whether maintenance antisecretory treatment was necessary, the current position is that, as long as *Hp* is eradicated, peptic ulcer rebleeding is virtually eliminated. Therefore, antisecretory therapy is no longer required [101–104]. However, maintenance antisecretory therapy should be considered for *Hp*-eradicated patients who did not stop NSAID use.

We performed a prospective 5-year followup of patients after *Hp* eradication and assessed the healing of bleeding peptic ulcers [101]. We randomized 82 consecutive patients into 4 different groups after 1 week of triple therapy and 3 weeks of PPI treatment. Despite 4 months of different maintenance regimens among the four groups (antacid suspension, colloidal bismuth, famotidine, or a placebo treatment), all the patients remained ulcer free with no evidence of reinfection. In recent pooled data of 1000 patients from 10 Spanish university hospitals and a total of 3253 patient-years of long-term followup, maintenance antiulcer treatment was not indicated once *Hp* had been eradicated [104]. However,

the recent Maastricht IV/Florence Consensus suggested that while maintenance antiulcer treatment is not needed for bleeding duodenal ulcers, it should be continued for gastric ulcers [13].

PPI treatment is usually administered to patients with bleeding peptic ulcers, even before endoscopic examination. This treatment can facilitate the endoscopic hemostatic effect in reducing short-term rebleeding [105, 106]. PPI treatment also has benefits for *Hp* eradication. One study demonstrated that intravenous omeprazole can decrease the risk of peptic ulcer rebleeding and may even improve the *Hp* eradication rate of the subsequent triple therapy [107].

Hp eradication after peptic ulcer bleeding reduces recurrence. Is confirmation of eradication of *Hp* worthwhile? One study using the Markov model proved that confirmation of *Hp* eradication after completion of antibiotic treatment in peptic ulcer bleeding is cost effective [108].

3.2.2. Summary. Eradication therapy is suggested in *Hp*-infected bleeding peptic ulcers. Triple therapy including a PPI and two antibiotics is the primary regimen. However, the rising antibiotic resistance rate should be taken into consideration in specific regions. Concomitant triple therapy, sequential therapy, bismuth- or non-bismuth-based quadruple therapy, and levofloxacin-based regimens are appropriate alternatives. After eradication, prolonged acid-suppressive therapy for duodenal ulcers is unnecessary, but gastric ulcers may require additional acid-suppressive therapy for 4–8 weeks due to their slow healing time and larger size.

3.3. Outcome

3.3.1. Outcome with/without *Hp* Eradication. Among patients with peptic ulcer diseases, 20–25% develop bleeding, perforation, or obstruction. In patients with bleeding peptic ulcers, approximately 33% develop recurrent bleeding within 1–2 years if left untreated after the ulcer heals [117]. Consequently, *Hp* eradication reduces the recurrence rate of peptic ulcers [118]. As mentioned previously, several studies have also reported a low rebleeding rate after *Hp* eradication, even without acid-suppressive drug maintenance [83–89, 95, 96, 101, 109, 111–116]. A multicenter Spanish cohort study with similar findings was published recently, and comparative results with other studies are shown in Table 2.

TABLE 2: Incidence of rebleeding in *Hp*-eradicated patients with no maintenance acid-suppressive therapy among different studies [104].

Author	Year and area	Ulcer type	Regimen	ER number	Mean F/U (M)	Rebleeding number (%)
Graham et al. [83]	1993, USA	PU	Triple	17	12	0 (0%)
Labenz and Borsch [84]	1994, Germany	PU	7 different protocols	42	17	0 (0%)
Jaspersen et al. [86]	1995, Germany	PU	Dual	24	12	0 (0%)
Jaspersen et al. [109]	1995, Germany	DU	Dual	29	12	1 (3.4%)
Rokkas et al. [85]	1995, Greece	DU	Dual	13	12	0 (0%)
Santander et al. [87]	1996, Spain	PU	Dual or triple	84	12	2 (2.3%)
Riemann et al. [88]	1997, Germany	PU	Dual	42	19	2 (4.8%)
Sung et al. [89]	1997, Hong Kong	PU	Triple	108	12	0 (0%)
Macri et al. [110]	1998, Italy	DU	Quadruple	21	48	0 (0%)
Amendola et al. [111]	1999, Argentina	PU	PPI 1-week regimen	42	24	0 (0%)
Gisbert et al. [112]	1999, Spain	DU	Triple or dual	111	12	0 (0%)
Lai et al. [113]	2000, Hong Kong	DU	Triple	41	53	2 (4.9%)
Vergara et al. [95]	2000, Spain	PU	Triple or quadruple	93	27	0 (0%)
Pellicano et al. [114]	2001, Italy	DU	Antibiotics	46	47	0 (0%)
Capurso et al. [115]	2001, Italy	DU	Dual or triple	83	36	3 (3.3%)
Arkkila et al. [96]	2003, Finland	PU	Quadruple or dual	176	12	2 (1.1%)
Liu et al. [101]	2003, Taiwan	PU	Triple	26	56	0 (0%)
Horvat et al. [116]	2005, Croatia	GU	Triple	43	12	1 (2.3%)
Gisbert et al. [104]	2012, Spain	PU	Triple*	1000	39	5 (0.5%)

DU: duodenal ulcer; ER: eradication; F/U: followup; GU: gastric ulcer; PU: peptic ulcer (gastric or duodenal ulcer).

*Triple therapy first followed by 2nd-, 3rd-, or 4th-line treatment.

Posttreatment *Hp* status has been found to be an independent predictor of duodenal ulcer bleeding recurrence [113]. Followup *Hp* testing after eradication in cases of bleeding peptic ulcers is therefore beneficial [108]. Because recrudescence is more common than reinfection [119], physicians should use combined tests or select a much lower cut-off value for ¹³C-UBT to verify eradication success.

Is there a trend toward decreasing *Hp*-related bleeding peptic ulcers today? The answer is yes. After the global implementation of *Hp* eradication for PUDs, the incidence of *Hp*-infected UGI hemorrhage has decreased. A 10-year nationwide database from Taiwan also demonstrated 42–48% and 41–71% decreases in the incidence of hospitalization for

gastric ulcers and duodenal ulcers, respectively, and these rates included uncomplicated and complicated cases [120]. Similar results have also been reported in other countries [121].

Nevertheless, bleeding peptic ulcers remain a worldwide problem. The increasing use of NSAIDs is considered to be an important underlying cause. Many studies have confirmed that current UGI bleeding in patients can be attributed to NSAID usage [122–126]. One study from the United States found that admission for PUD-related complications has not decreased despite decreasing *Hp* prevalence and increasing *Hp* eradication [127], and the authors proposed that this could be due to NSAID use. Meanwhile, *Hp* eradication

can decrease the long-term incidence of recurrent ulcer bleeding in low-dose aspirin users [128]. Eliminating one independent risk factor can attenuate the effect of another independent factor on inducing peptic ulcer bleeding. A recent study found that patients with bleeding peptic ulcers and concurrent *Hp* infection have a more favorable outcome than those without [129].

3.3.2. Summary. *Hp* infection is an independent risk factor for bleeding duodenal ulcers. *Hp*-infected gastric ulcers in combination with old age and NSAID or aspirin therapy may increase the bleeding risk. Eradication treatment can decrease the likelihood of peptic ulcer rebleeding and associated complications. Admissions for bleeding peptic ulcers have not decreased despite the eradication of *Hp* infections. Concomitant administration of NSAIDs, old age, and comorbidities are currently considered as risk factors for UGI bleeding.

4. Conclusions

Three decades after the discovery of *Hp*, the etiologies of bleeding peptic ulcers are changing. However, diagnosis of *Hp* infection is still the first priority in these patients. Invasive RUT is most frequently used, but this methodology is hampered by a high rate of false-negative results, especially in patients with UGI bleeding. Other delayed tests should be performed if the initial diagnostic test is negative. Eradication of *Hp* infection can reduce the risk of rebleeding and should be started as soon as patients resume eating. Concomitant use of NSAIDs, aspirin, or other antiplatelet drugs associated with old age and comorbidities is the most likely etiology for current bleeding peptic ulcers. *Hp* eradication is beneficial for patients who require the long-term administration of these drugs.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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References

- [1] L. Laine and W. L. Peterson, "Bleeding peptic ulcer," *The New England Journal of Medicine*, vol. 331, no. 11, pp. 717–727, 1994.
- [2] J. S. Barthel, "Bleeding ulcers and *Helicobacter pylori*," *Gastrointestinal Endoscopy*, vol. 46, no. 4, pp. 371–375, 1997.
- [3] B. J. Marshall and J. R. Warren, "Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration," *The Lancet*, vol. 1, no. 8390, pp. 1311–1314, 1984.
- [4] NIH Consensus Conference, "NIH Consensus Development Panel on *Helicobacter pylori* in peptic ulcer disease. *Helicobacter pylori* in peptic ulcer disease," *The Journal of the American Medical Association*, vol. 272, no. 1, pp. 65–69, 1994.
- [5] P. Malfertheiner, "Current European concepts in the management of *Helicobacter pylori* infection. The Maastricht consensus report. European *Helicobacter Pylori* Study Group," *Gut*, vol. 41, no. 1, pp. 8–13, 1997.
- [6] S. K. Lam and N. J. Talley, "Report of the 1997 Asia Pacific Consensus Conference on the management of *Helicobacter pylori* infection," *Journal of Gastroenterology and Hepatology*, vol. 13, no. 1, pp. 1–12, 1998.
- [7] P. Malfertheiner, F. Mégraud, C. O'Morain et al., "Current concepts in the management of *Helicobacter pylori* infection—the Maastricht 2-2000 Consensus Report," *Alimentary Pharmacology and Therapeutics*, vol. 16, no. 2, pp. 167–180, 2002.
- [8] P. Malfertheiner, F. Megraud, C. O'Morain et al., "Current concepts in the management of *Helicobacter pylori* infection: the Maastricht III Consensus Report," *Gut*, vol. 56, no. 6, pp. 772–781, 2007.
- [9] W. D. Chey and B. C. Y. Wong, "American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection," *The American Journal of Gastroenterology*, vol. 102, no. 8, pp. 1808–1825, 2007.
- [10] K. M. Fock, P. Katelaris, K. Sugano et al., "Second Asia-Pacific consensus guidelines for *Helicobacter pylori* infection," *Journal of Gastroenterology and Hepatology*, vol. 24, no. 10, pp. 1587–1600, 2009.
- [11] A. N. Barkun, M. Bardou, E. J. Kuipers et al., "International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding," *Annals of Internal Medicine*, vol. 152, no. 2, pp. 101–113, 2010.
- [12] J.-J. Sung, F.-K. Chan, M. Chen et al., "Asia-Pacific Working Group consensus on non-variceal upper gastrointestinal bleeding," *Gut*, vol. 60, no. 9, pp. 1170–1177, 2011.
- [13] P. Malfertheiner, F. Megraud, C. A. O'Morain et al., "Management of *Helicobacter pylori* infection—the Maastricht IV/Florence consensus report," *Gut*, vol. 61, no. 5, pp. 646–664, 2012.
- [14] M. E. van Leerdam and G. N. J. Tytgat, "Review article: *Helicobacter pylori* infection in peptic ulcer haemorrhage," *Alimentary Pharmacology and Therapeutics*, vol. 16, supplement 1, pp. 66–78, 2002.
- [15] K. Barada, H. Abdul-Baki, I. I. El Hajj, J. G. Hashash, and P. H. Green, "Gastrointestinal bleeding in the setting of anticoagulation and antiplatelet therapy," *Journal of Clinical Gastroenterology*, vol. 43, no. 1, pp. 5–12, 2009.
- [16] P.-I. Hsu, "New look at antiplatelet agent-related peptic ulcer: an update of prevention and treatment," *Journal of Gastroenterology and Hepatology*, vol. 27, no. 4, pp. 654–661, 2012.
- [17] S. Redéen, F. Petersson, E. Törnkrantz, H. Levander, E. Mårdh, and K. Borch, "Reliability of diagnostic tests for *Helicobacter pylori* infection," *Gastroenterology Research and Practice*, vol. 2011, Article ID 940650, 6 pages, 2011.
- [18] J. P. Gisbert and J. M. Pajares, "Diagnosis of *Helicobacter pylori* infection by stool antigen determination: a systematic review," *American Journal of Gastroenterology*, vol. 96, no. 10, pp. 2829–2838, 2001.
- [19] M. E. van Leerdam, "Epidemiology of acute upper gastrointestinal bleeding," *Best Practice and Research: Clinical Gastroenterology*, vol. 22, no. 2, pp. 209–224, 2008.
- [20] G. Castillo-Rojas, M. A. Ballesteros, S. Ponce de León, R. Morales-Espinosa, A. Cravioto, and Y. López-Vidal, "Bleeding peptic ulcers and presence of *Helicobacter pylori* by various tests: a case-control study," *European Journal of Gastroenterology and Hepatology*, vol. 14, no. 10, pp. 1113–1118, 2002.

- [21] K.-C. Lai, W.-M. Hui, and S.-K. Lam, "Bleeding ulcers have high false negative rates for antral *Helicobacter pylori* when tested with urease test," *Gastroenterology*, vol. 110, no. 4, p. A167, 1996.
- [22] C.-L. Lee, T.-C. Tu, R.-N. Yang et al., "Does blood in the stomach influence the diagnosis of *H. pylori* infection in patients with bleeding peptic ulcer?" *Gut*, vol. 41, supplement 1, p. A76, 1997.
- [23] A. Archimandritis, M. Tzivras, S. Souyioultzis et al., "High rates of false negative rapid urease test (CLO) in patients with upper gastrointestinal bleeding (UGB)," *Gut*, vol. 41, supplement 1, p. A76, 1997.
- [24] T.-C. Tu, C.-L. Lee, C.-H. Wu et al., "Comparison of invasive and noninvasive tests for detecting *Helicobacter pylori* infection in bleeding peptic ulcers," *Gastrointestinal Endoscopy*, vol. 49, no. 3 I, pp. 302–306, 1999.
- [25] A. Archimandritis, M. Tzivras, S. Sougioultzis et al., "Rapid urease test is less sensitive than histology in diagnosing *Helicobacter pylori* infection in patients with non-variceal upper gastrointestinal bleeding," *Journal of Gastroenterology and Hepatology*, vol. 15, no. 4, pp. 369–373, 2000.
- [26] C.-C. Liao, C.-L. Lee, Y.-C. Lai et al., "Accuracy of three diagnostic tests used alone and in combination for detecting *Helicobacter pylori* infection in patients with bleeding gastric ulcers," *Chinese Medical Journal*, vol. 116, no. 12, pp. 1821–1826, 2003.
- [27] W. K. Leung, J. J. Y. Sung, K. L. K. Siu, F. K. L. Chan, T. K. W. Ling, and A. F. B. Cheng, "False-negative biopsy urease test in bleeding ulcers caused by the buffering effects of blood," *The American Journal of Gastroenterology*, vol. 93, no. 10, pp. 1914–1918, 1998.
- [28] G. T. Fantry, A. H. Rosenstein, and S. P. James, "Confounding factors in the detection of *Helicobacter pylori* infection in patients with upper gastrointestinal bleeding," *The American Journal of Gastroenterology*, vol. 94, no. 5, pp. 1421–1422, 1999.
- [29] T.-C. Tu, C.-L. Lee, and C.-H. Wu, "False negative CLO test in bleeding ulcers can't be corrected by cleansing the implanted specimen," *Gut*, vol. 45, supplement 5, p. A121, 1999.
- [30] L. Laine, O. Sidhom, S. Emami, R. Estrada, and H. Cohen, "Effect of blood on rapid urease testing of gastric mucosal biopsy specimens," *Gastrointestinal Endoscopy*, vol. 47, no. 2, pp. 141–143, 1998.
- [31] J. Houghton, R. Ramamoorthy, H. Pandya, R. Dhirmalani, and K. H. Kim, "Human plasma is directly bacteriocidal against *Helicobacter pylori* in vitro, potentially explaining the decreased detection of *Helicobacter pylori* during acute upper GI bleeding," *Gastrointestinal Endoscopy*, vol. 55, no. 1, pp. 11–16, 2002.
- [32] G. Gonzalez-Valencia, G. I. Perez-Perez, R. G. Washburn, and M. J. Blaser, "Susceptibility of *Helicobacter pylori* to the bactericidal activity of human serum," *Helicobacter*, vol. 1, no. 1, pp. 28–33, 1996.
- [33] D. Y. Graham, A. R. Opekun, F. Hammoud et al., "Studies regarding the mechanism of false negative urea breath tests with proton pump inhibitors," *The American Journal of Gastroenterology*, vol. 98, no. 5, pp. 1005–1009, 2003.
- [34] R. Colin, P. Czernichow, V. Baty et al., "Low sensitivity of invasive tests for the detection of *Helicobacter pylori* infection in patients with bleeding ulcer," *Gastroenterologie Clinique et Biologique*, vol. 24, no. 1, pp. 31–35, 2000.
- [35] P. Griño, S. Pascual, J. Such et al., "Comparison of diagnostic methods for *Helicobacter pylori* infection in patients with upper gastrointestinal bleeding," *Scandinavian Journal of Gastroenterology*, vol. 36, no. 12, pp. 1254–1258, 2001.
- [36] I. K. Chung, S. J. Hong, E. J. Kim et al., "What is the best method to diagnose *Helicobacter* infection in bleeding peptic ulcers?: a prospective trial," *The Korean Journal of Internal Medicine*, vol. 16, no. 3, pp. 147–152, 2001.
- [37] D. Schilling, A. Demel, H. E. Adamek, T. Nüsse, E. Weidmann, and J. F. Riemann, "A negative rapid urease test is unreliable for exclusion of *Helicobacter pylori* infection during acute phase of ulcer bleeding. A prospective case control study," *Digestive and Liver Disease*, vol. 35, no. 4, pp. 217–221, 2003.
- [38] P. Griño, S. Pascual, J. Such et al., "Comparison of stool immunoassay with standard methods for detection of *Helicobacter pylori* infection in patients with upper-gastrointestinal bleeding of peptic origin," *European Journal of Gastroenterology and Hepatology*, vol. 15, no. 5, pp. 525–529, 2003.
- [39] J. H. Tang, N. J. Liu, H. T. Cheng et al., "Endoscopic diagnosis of *Helicobacter pylori* infection by rapid urease test in bleeding peptic ulcers: a prospective case-control study," *Journal of Clinical Gastroenterology*, vol. 43, no. 2, pp. 133–139, 2009.
- [40] Y. J. Choi, N. Kim, J. Lim et al., "Accuracy of diagnostic tests for *Helicobacter pylori* in patients with peptic ulcer bleeding," *Helicobacter*, vol. 17, no. 2, pp. 77–85, 2012.
- [41] L. Laine, D. Chun, C. Stein, I. El-Beblawi, V. Sharma, and P. Chandrasoma, "The influence of size or number of biopsies on rapid urease test results: a prospective evaluation," *Gastrointestinal Endoscopy*, vol. 43, no. 1, pp. 49–53, 1996.
- [42] R. M. Zagari and F. Bazzoli, "*Helicobacter pylori* testing in patients with peptic ulcer bleeding," *Digestive and Liver Disease*, vol. 35, no. 4, pp. 215–216, 2003.
- [43] H. L. Chan, J. C. Wu, F. K. Chan et al., "Is non-*Helicobacter pylori*, non-NSAID peptic ulcer a common cause of upper GI bleeding? A prospective study of 977 patients," *Gastrointestinal Endoscopy*, vol. 53, no. 4, pp. 438–442, 2001.
- [44] M. Güell, E. Artigau, V. Esteve, J. Sánchez-Delgado, F. Junquera, and X. Calvet, "Usefulness of a delayed test for the diagnosis of *Helicobacter pylori* infection in bleeding peptic ulcer," *Alimentary Pharmacology and Therapeutics*, vol. 23, no. 1, pp. 53–59, 2006.
- [45] D. Vaira, L. Gatta, C. Ricci, and M. Miglioli, "Review article: Diagnosis of *Helicobacter pylori* infection," *Alimentary Pharmacology and Therapeutics, Supplement*, vol. 16, supplement 1, pp. 16–23, 2002.
- [46] J. P. Gisbert, L. Gonzalez, A. de Pedro et al., "*Helicobacter pylori* and bleeding duodenal ulcer: prevalence of the infection and role of non-steroidal anti-inflammatory drugs," *Scandinavian Journal of Gastroenterology*, vol. 36, no. 7, pp. 717–724, 2001.
- [47] K. Watanabe, N. Nagata, R. Nakashima et al., "Predictive findings for *Helicobacter pylori*-uninfected, -infected and -eradicated gastric mucosa: validation study," *World Journal of Gastroenterology*, vol. 19, no. 27, pp. 4374–4379, 2013.
- [48] C. A. Fallone, "Detection of *Helicobacter pylori* in the setting of acute upper gastrointestinal bleeding," *Journal of Clinical Gastroenterology*, vol. 37, no. 1, pp. 6–8, 2003.
- [49] H.-J. Lin, W.-C. Lo, C.-L. Perng, G.-Y. Tseng, A.-F. Li, and Y.-H. Ou, "Mucosal polymerase chain reaction for diagnosing *Helicobacter pylori* infection in patients with bleeding peptic ulcers," *World Journal of Gastroenterology*, vol. 11, no. 3, pp. 382–385, 2005.
- [50] C.-C. Lo, K.-H. Lai, N.-J. Peng et al., "Polymerase chain reaction: a sensitive method for detecting *Helicobacter pylori* infection in bleeding peptic ulcers," *World Journal of Gastroenterology*, vol. 11, no. 25, pp. 3909–3914, 2005.

- [51] M. J. Ramírez-Lázaro, S. Lario, A. Casals et al., "Real-time PCR improves *Helicobacter pylori* detection in patients with peptic ulcer bleeding," *PLoS ONE*, vol. 6, no. 5, Article ID e20009, 2011.
- [52] J. Saez, S. Belda, M. Santibáñez et al., "Real-time PCR for diagnosing *Helicobacter pylori* infection in patients with upper gastrointestinal bleeding: comparison with other classical diagnostic methods," *Journal of Clinical Microbiology*, vol. 50, no. 10, pp. 3233–3237, 2012.
- [53] R. P. H. Logan, "Urea breath tests in the management of *Helicobacter pylori* infection," *Gut*, vol. 43, supplement 1, pp. S47–S50, 1998.
- [54] J. P. Gisbert and J. M. Pajares, "Review article: 13C-urea breath test in the diagnosis of *Helicobacter pylori* infection—a critical review," *Alimentary Pharmacology and Therapeutics*, vol. 20, no. 10, pp. 1001–1017, 2004.
- [55] M. Wildner-Christensen, A. T. Lassen, J. Lindebjerg, and O. B. Schaffalitzky De Muckadell, "Diagnosis of *Helicobacter pylori* in bleeding peptic ulcer patients, evaluation of urea-based tests," *Digestion*, vol. 66, no. 1, pp. 9–13, 2002.
- [56] B. Velayos, L. Fernández-Salazar, F. Pons-Renedo et al., "Accuracy of urea breath test performed immediately after emergency endoscopy in peptic ulcer bleeding," *Digestive Diseases and Sciences*, vol. 57, no. 7, pp. 1880–1886, 2012.
- [57] J. P. Gisbert, C. Esteban, I. Jimenez, and R. Moreno-Otero, "13C-urea breath test during hospitalization for the diagnosis of *Helicobacter pylori* infection in peptic ulcer bleeding," *Helicobacter*, vol. 12, no. 3, pp. 231–237, 2007.
- [58] M. Winiarski, W. Bielanski, M. Plonka et al., "The usefulness of capsulated 13C-urea breath test in diagnosis of *Helicobacter pylori* infection in patients with upper gastrointestinal bleeding," *Journal of Clinical Gastroenterology*, vol. 37, no. 1, pp. 34–38, 2003.
- [59] J. P. Gisbert and J. M. Pajares, "Stool antigen test for the diagnosis of *Helicobacter pylori* infection: a systematic review," *Helicobacter*, vol. 9, no. 4, pp. 347–368, 2004.
- [60] U. Peitz, A. Leodolter, S. Kahl et al., "Antigen stool test for assessment of *Helicobacter pylori* infection in patients with upper gastrointestinal bleeding," *Alimentary Pharmacology & Therapeutics*, vol. 17, no. 8, pp. 1075–1084, 2003.
- [61] J. P. Gisbert, M. Trapero, X. Calvet et al., "Evaluation of three different tests for the detection of stool antigens to diagnose *Helicobacter pylori* infection in patients with upper gastrointestinal bleeding," *Alimentary Pharmacology and Therapeutics*, vol. 19, no. 8, pp. 923–929, 2004.
- [62] H.-J. Lin, W.C. Lo, C.-L. Perng et al., "Helicobacter pylori stool antigen test in patients with bleeding peptic ulcers," *Helicobacter*, vol. 9, no. 6, pp. 663–668, 2004.
- [63] M. E. van Leerdam, A. van der Ende, F. J. W. Ten Kate, E. A. J. Rauws, and G. N. J. Tytgat, "Lack of accuracy of the noninvasive *Helicobacter pylori* stool antigen test in patients with gastroduodenal ulcer bleeding," *The American Journal of Gastroenterology*, vol. 98, no. 4, pp. 798–801, 2003.
- [64] C. T. Loy, L. M. Irwig, P. H. Katelaris, and N. J. Talley, "Do commercial serological kits for *Helicobacter pylori* infection differ in accuracy? A meta-analysis," *The American Journal of Gastroenterology*, vol. 91, no. 6, pp. 1138–1144, 1996.
- [65] W.-M. Wang, C.-Y. Chen, C.-M. Jan et al., "Long-term follow-up and serological study after triple therapy of *Helicobacter pylori*-associated duodenal ulcer," *The American Journal of Gastroenterology*, vol. 89, no. 10, pp. 1793–1796, 1994.
- [66] A. S. Taha, J. Reid, P. Boothmann et al., "Serological diagnosis of *Helicobacter pylori*—evaluation of four tests in the presence or absence of non-steroidal anti-inflammatory drugs," *Gut*, vol. 34, no. 4, pp. 461–465, 1993.
- [67] J. M. Kang, N. Kim, B. H. Lee et al., "Risk factors for peptic ulcer bleeding in terms of *Helicobacter pylori*, NSAIDs, and antiplatelet agents," *Scandinavian Journal of Gastroenterology*, vol. 46, no. 11, pp. 1295–1301, 2011.
- [68] F. Manguso, E. Riccio, G. de Nucci et al., "*Helicobacter pylori* infection in bleeding peptic ulcer patients after non-steroidal antiinflammatory drug consumption," *World Journal of Gastroenterology*, vol. 17, no. 40, pp. 4509–4516, 2011.
- [69] A. K. Henriksson, A.-C. Edman, I. Nilsson, D. Bergqvist, and T. Wadström, "Helicobacter pylori and the relation to other risk factors in patients with acute bleeding peptic ulcer," *Scandinavian Journal of Gastroenterology*, vol. 33, no. 10, pp. 1030–1033, 1998.
- [70] M. Udd, P. Miettinen, A. Palmu, and R. Julkunen, "Effect of short-term treatment with regular or high doses of omeprazole on the detection of *Helicobacter pylori* in bleeding peptic ulcer patients," *Scandinavian Journal of Gastroenterology*, vol. 38, no. 6, pp. 588–593, 2003.
- [71] J. P. Gisbert and J. M. Pajares, "13C-urea breath test in the management of *Helicobacter pylori* infection," *Digestive and Liver Disease*, vol. 37, no. 12, pp. 899–906, 2005.
- [72] K. Murakami, R. Sato, T. Okimoto et al., "Influence of anti-ulcer drugs used in Japan on the result of 13C-urea breath test for the diagnosis of *Helicobacter pylori* infection," *Journal of Gastroenterology*, vol. 38, no. 10, pp. 937–941, 2003.
- [73] F. Parente, M. Sainaghi, O. Sangaletti et al., "Different effects of short-term omeprazole, lansoprazole or pantoprazole on the accuracy of the 13C-urea breath test," *Alimentary Pharmacology and Therapeutics*, vol. 16, no. 3, pp. 553–557, 2002.
- [74] S. J. Connor, F. Seow, M. C. Ngu, and P. H. Katelaris, "The effect of dosing with omeprazole on the accuracy of the 13C-urea breath test in *Helicobacter pylori*-infected subjects," *Alimentary Pharmacology & Therapeutics*, vol. 13, no. 10, pp. 1287–1293, 1999.
- [75] L. Gatta, N. Vakil, C. Ricci et al., "Effect of proton pump inhibitors and antacid therapy on 13C urea breath tests and stool test for *Helicobacter pylori* infection," *American Journal of Gastroenterology*, vol. 99, no. 5, pp. 823–829, 2004.
- [76] S. J. Connor, M. C. Ngu, and P. H. Katelaris, "The impact of short-term ranitidine use on the precision of the 13C-urea breath test in subjects infected with *Helicobacter pylori*," *European Journal of Gastroenterology and Hepatology*, vol. 11, no. 10, pp. 1135–1138, 1999.
- [77] K. Adachi, H. Fujishiro, T. Mihara, Y. Komazawa, and Y. Kinoshita, "Influence of lansoprazole, famotidine, roxatidine and rebamipide administration on the urea breath test for the diagnosis of *Helicobacter pylori* infection," *Journal of Gastroenterology and Hepatology*, vol. 18, no. 2, pp. 168–171, 2003.
- [78] J. P. Gisbert and V. Abaira, "Accuracy of *Helicobacter pylori* diagnostic tests in patients with bleeding peptic ulcer: a systematic review and meta-analysis," *The American Journal of Gastroenterology*, vol. 101, no. 4, pp. 848–863, 2006.
- [79] J. Sánchez-Delgado, E. Gené, D. Suárez et al., "Has *H. pylori* prevalence in bleeding peptic ulcer been underestimated? A meta-regression," *The American Journal of Gastroenterology*, vol. 106, no. 3, pp. 398–405, 2011.
- [80] D. Schilling, A. Demel, T. Nüsse, E. Weidmann, and J. F. Riemann, "Helicobacter pylori infection does not affect the

- early rebleeding rate in patients with peptic ulcer bleeding after successful endoscopic hemostasis: a prospective single-center trial," *Endoscopy*, vol. 35, no. 5, pp. 393–396, 2003.
- [81] I. Rácz, K. Bircher, T. Kárász, and A. Németh, "The influence of *Helicobacter pylori* infection on early rebleeding rate in patients with peptic ulcer bleeding," *Endoscopy*, vol. 36, no. 5, pp. 461–462, 2004.
- [82] E. Gené, J. Sanchez-Delgado, X. Calvet, J. P. Gisbert, and R. Azagra, "What is the best strategy for diagnosis and treatment of helicobacter pylori in the prevention of recurrent peptic ulcer bleeding? A cost-effectiveness analysis," *Value in Health*, vol. 12, no. 5, pp. 759–762, 2009.
- [83] D. Y. Graham, K. S. Hepps, F. C. Ramirez, G. M. Lew, and Z. A. Saeed, "Treatment of *Helicobacter pylori* reduces the rate of rebleeding in peptic ulcer disease," *Scandinavian Journal of Gastroenterology*, vol. 28, no. 11, pp. 939–942, 1993.
- [84] J. Labenz and G. Borsch, "Role of *Helicobacter pylori* eradication in the prevention of peptic ulcer bleeding relapse," *Digestion*, vol. 55, no. 1, pp. 19–23, 1994.
- [85] T. Rokkas, A. Karameris, A. Mavrogeorgis, E. Rallis, and N. Giannikos, "Eradication of *Helicobacter pylori* reduces the possibility of rebleeding in peptic ulcer disease," *Gastrointestinal Endoscopy*, vol. 41, no. 1, pp. 1–4, 1995.
- [86] D. Jaspersen, T. Koerner, W. Schorr, M. Brennenstuhl, C. Raschka, and C. H. Hammar, "Helicobacter pylori eradication reduces the rate of rebleeding in ulcer hemorrhage," *Gastrointestinal Endoscopy*, vol. 41, no. 1, pp. 5–7, 1995.
- [87] C. Santander, R. G. Grávalos, A. Gómez-Cedenilla, J. Cantero, and J. M. Pajares, "Antimicrobial therapy for *Helicobacter pylori* infection versus long-term maintenance antisecretion treatment in the prevention of recurrent hemorrhage from peptic ulcer: prospective nonrandomized trial on 125 patients," *The American Journal of Gastroenterology*, vol. 91, no. 8, pp. 1549–1552, 1996.
- [88] J. F. Riemann, D. Schilling, P. Schauwecker et al., "Cure with omeprazole plus amoxicillin versus long-term ranitidine therapy in *Helicobacter pylori*-associated peptic ulcer bleeding," *Gastrointestinal Endoscopy*, vol. 46, no. 4, pp. 299–304, 1997.
- [89] J. J. Y. Sung, W. K. Leung, R. Suen et al., "One-week antibiotics versus maintenance acid suppression therapy for *Helicobacter pylori*-associated peptic ulcer bleeding," *Digestive Diseases and Sciences*, vol. 42, no. 12, pp. 2524–2528, 1997.
- [90] F. Bazzoli, R. M. Zagari, S. Fossi et al., "Short-term low-dose triple therapy for the eradication of *Helicobacter pylori*," *European Journal of Gastroenterology and Hepatology*, vol. 6, no. 9, pp. 773–777, 1994.
- [91] M. M. Yousfi, H. M. T. El-Zimaity, M. T. Al-Assi, R. A. Cole, R. M. Genta, and D. Y. Graham, "Metronidazole, omeprazole and clarithromycin: an effective combination therapy for *Helicobacter pylori* infection," *Alimentary Pharmacology & Therapeutics*, vol. 9, no. 2, pp. 209–212, 1995.
- [92] T. Lind, S. V. van Zanten, P. Unge et al., "Eradication of *Helicobacter pylori* using one-week triple therapies combining omeprazole with two antimicrobials: the MACH I study," *Helicobacter*, vol. 1, no. 3, pp. 138–144, 1996.
- [93] C. Lee, T. Tu, C. Wu et al., "One-week low-dose triple therapy is effective in treating *Helicobacter pylori*-infected patients with bleeding peptic ulcers," *Journal of the Formosan Medical Association*, vol. 97, no. 11, pp. 733–737, 1998.
- [94] A. Sonnenberg, C. A. Oison, and J. Zhang, "The effect of antibiotic therapy on bleeding from duodenal ulcer," *The American Journal of Gastroenterology*, vol. 94, no. 4, pp. 950–954, 1999.
- [95] M. Vergara, F. Casellas, E. Saperas et al., "Helicobacter pylori eradication prevents recurrence from peptic ulcer haemorrhage," *European Journal of Gastroenterology and Hepatology*, vol. 12, no. 7, pp. 733–737, 2000.
- [96] P. E. T. Arkkila, K. Seppälä, T. U. Kosunen et al., "Eradication of *Helicobacter pylori* improves the healing rate and reduces the relapse rate of nonbleeding ulcers in patients with bleeding peptic ulcer," *The American Journal of Gastroenterology*, vol. 98, no. 10, pp. 2149–2156, 2003.
- [97] J. P. Gisbert, X. Calvet, F. Feu et al., "Eradication of *Helicobacter pylori* for the prevention of peptic ulcer rebleeding," *Helicobacter*, vol. 12, no. 4, pp. 279–286, 2007.
- [98] J. P. Gisbert, S. Khorrami, F. Carballo, X. Calvet, E. Gene, and E. Dominguez-Muñoz, "Meta-analysis: *Helicobacter pylori* eradication therapy vs. antisecretory non-eradication therapy for the prevention of recurrent bleeding from peptic ulcer," *Alimentary Pharmacology & Therapeutics*, vol. 19, no. 6, pp. 617–629, 2004.
- [99] V. K. Sharma, A. V. Sahai, F. A. Corder, and C. W. Howden, "Helicobacter pylori eradication is superior to ulcer healing with or without maintenance therapy to prevent further ulcer haemorrhage," *Alimentary Pharmacology and Therapeutics*, vol. 15, no. 12, pp. 1939–1947, 2001.
- [100] J. Ofman, J. Wallace, E. Badamgarav, C.-F. Chiou, J. Henning, and L. Laine, "The cost-effectiveness of competing strategies for the prevention of recurrent peptic ulcer hemorrhage," *The American Journal of Gastroenterology*, vol. 97, no. 8, pp. 1941–1950, 2002.
- [101] C. C. Liu, C. L. Lee, C. C. Chan et al., "Maintenance treatment is not necessary after *Helicobacter pylori* eradication and healing of bleeding peptic ulcer a 5-year prospective, randomized, controlled study," *Archives of Internal Medicine*, vol. 163, no. 17, pp. 2020–2024, 2003.
- [102] J. P. Gisbert, S. Khorrami, F. Carballo, X. Calvet, E. Gené, and J. E. Dominguez-Muñoz, "H. pylori eradication therapy vs. antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy) for the prevention of recurrent bleeding from peptic ulcer," *Cochrane Database of Systematic Reviews*, no. 2, Article ID CD004062, 2004.
- [103] A. Kikkawa, R. Iwakiri, H. Ootani et al., "Prevention of the rehaemorrhage of bleeding peptic ulcers: effects of *Helicobacter pylori* eradication and acid suppression," *Alimentary Pharmacology and Therapeutics, Supplement*, vol. 21, supplement 2, pp. 79–84, 2005.
- [104] J. P. Gisbert, X. Calvet, A. Cosme et al., "Long-term follow-up of 1,000 patients cured of helicobacter pylori infection following an episode of peptic ulcer bleeding," *The American Journal of Gastroenterology*, vol. 107, no. 8, pp. 1197–1204, 2012.
- [105] N. Liu, L. Liu, H. Zhang et al., "Effect of intravenous proton pump inhibitor regimens and timing of endoscopy on clinical outcomes of peptic ulcer bleeding," *Journal of Gastroenterology and Hepatology*, vol. 27, no. 9, pp. 1473–1479, 2012.
- [106] A. Sreedharan, J. Martin, G. I. Leontiadis et al., "Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding (review)," *Cochrane Database of Systematic Reviews*, vol. 7, no. 7, Article ID CD005415, 2010.
- [107] B.-S. Sheu, C.-H. Chi, C.-C. Huang, A.-W. Kao, Y.-L. Wang, and H.-B. Yang, "Impact of intravenous omeprazole on *Helicobacter pylori* eradication by triple therapy in patients with peptic ulcer bleeding," *Alimentary Pharmacology and Therapeutics*, vol. 16, no. 1, pp. 137–143, 2002.

- [108] H. Pohl, S. R. G. Finlayson, A. Sonnenberg, and D. J. Robertson, "Helicobacter pylori-associated ulcer bleeding: should we test for eradication after treatment?" *Alimentary Pharmacology and Therapeutics*, vol. 22, no. 6, pp. 529–537, 2005.
- [109] D. Jaspersen, T. Korner, W. Schorr, M. Brennenstuhl, and C. Heinz-Hammar, "Omeprazole-amoxycillin therapy for eradication of *Helicobacter pylori* in duodenal ulcer bleeding: preliminary results of a pilot study," *Journal of Gastroenterology*, vol. 30, no. 3, pp. 319–321, 1995.
- [110] G. Macri, S. Milani, E. Surrenti, M. T. Passaleva, G. Salvadori, and C. Surrenti, "Eradication of *Helicobacter pylori* reduces the rate of duodenal ulcer rebleeding: a long-term follow-up study," *The American Journal of Gastroenterology*, vol. 93, no. 6, pp. 925–927, 1998.
- [111] M. Amendola, R. Farias, J. Katz et al., "Absence of bleeding recurrence of peptic ulcer after long term follow-up of successful eradication of *Helicobacter pylori*," *Acta Gastroenterologica Latinoamericana*, vol. 29, no. 2, pp. 47–50, 1999.
- [112] J. P. Gisbert, D. Boixeda, R. Aller et al., "Helicobacter pylori and bleeding duodenal ulcer: Prevalence of the infection, efficacy of three triple therapies and role of eradication in the prevention of recurrent hemorrhage," *Medicina Clinica*, vol. 112, no. 5, pp. 161–165, 1999.
- [113] K. C. Lai, W. M. Hui, W. M. Wong et al., "Treatment of *Helicobacter pylori* in patients with duodenal ulcer hemorrhage—a long-term randomized, controlled study," *The American Journal of Gastroenterology*, vol. 95, no. 9, pp. 2225–2232, 2000.
- [114] R. Pellicano, S. Peyre, N. Leone et al., "The effect of the eradication of *Helicobacter pylori* infection on hemorrhage because of duodenal ulcer," *Journal of Clinical Gastroenterology*, vol. 32, no. 3, pp. 222–224, 2001.
- [115] G. Capurso, B. Annibale, J. Osborn et al., "Occurrence and relapse of bleeding from duodenal ulcer: respective roles of acid secretion and *Helicobacter pylori* infection," *Alimentary Pharmacology and Therapeutics*, vol. 15, no. 6, pp. 821–829, 2001.
- [116] D. Horvat, A. Včev, I. Soldo et al., "The results of *Helicobacter pylori* eradication on repeated bleeding in patients with stomach ulcer," *Collegium Antropologicum*, vol. 29, no. 1, pp. 139–142, 2005.
- [117] L. A. Laine, J. Goldstein, J. Barkin, R. Hunt, S. Crowe, and D. Cave, "Helicobacter pylori and complicated ulcer disease," *The American Journal of Medicine*, vol. 100, supplement 5, pp. 52S–59S, 1996.
- [118] R. J. Hopkins, L. S. Girardi, and E. A. Turney, "Relationship pylori and reduced and ulcer recurrence: a review," *Gastroenterology*, vol. 110, no. 4, pp. 1244–1252, 1996.
- [119] J. P. Gisbert, "The recurrence of *Helicobacter pylori* infection: incidence and variables influencing it. A critical review," *The American Journal of Gastroenterology*, vol. 100, no. 9, pp. 2083–2099, 2005.
- [120] C. Wu, M. Wu, C. Wang, J. Cheng, K. N. Kuo, and J. Lin, "A nationwide population-based cohort study shows reduced hospitalization for peptic ulcer disease associated with *H pylori* eradication and proton pump inhibitor use," *Clinical Gastroenterology and Hepatology*, vol. 7, no. 4, pp. 427–431, 2009.
- [121] K. Åhsberg, W. Ye, Y. Lu, Z. Zheng, and C. Staël von Holstein, "Hospitalisation of and mortality from bleeding peptic ulcer in Sweden: a nationwide time-trend analysis," *Alimentary Pharmacology and Therapeutics*, vol. 33, no. 5, pp. 578–584, 2011.
- [122] K. M. Fock, "Peptic ulcer disease in the 1990s: an Asian perspective," *Journal of Gastroenterology and Hepatology*, vol. 12, no. 6, pp. S23–S28, 1997.
- [123] D. Ramsoekh, M. E. van Leerdam, E. A. J. Rauws, and G. N. J. Tytgat, "Outcome of peptic ulcer bleeding, nonsteroidal anti-inflammatory drug use, and *Helicobacter pylori* infection," *Clinical Gastroenterology and Hepatology*, vol. 3, no. 9, pp. 859–864, 2005.
- [124] N. J. Liu, C. S. Lee, J. H. Tang et al., "Outcomes of bleeding peptic ulcers: a prospective study," *Journal of Gastroenterology and Hepatology*, vol. 23, no. 8, part 2, pp. e340–e347, 2008.
- [125] J.-Y. Lau, J. Sung, C. Hill, C. Henderson, C. W. Howden, and D. C. Metz, "Systematic review of the epidemiology of complicated peptic ulcer disease: incidence, recurrence, risk factors and mortality," *Digestion*, vol. 84, no. 2, pp. 102–113, 2011.
- [126] H. Fujinami, T. Kudo, A. Hosokawa et al., "A study of the changes in the cause of peptic ulcer bleeding," *World Journal of Gastrointestinal Endoscopy*, vol. 4, no. 7, pp. 323–327, 2012.
- [127] D. Manuel, A. Cutler, J. Goldstein, M. B. Fennerty, and K. Brown, "Decreasing prevalence combined with increasing eradication of *Helicobacter pylori* infection in the United States has not resulted in fewer hospital admissions for peptic ulcer disease-related complications," *Alimentary Pharmacology and Therapeutics*, vol. 25, no. 12, pp. 1423–1427, 2007.
- [128] F. K. L. Chan, J. Y. L. Ching, B. Y. Suen, Y. K. Tse, J. C. Y. Wu, and J. J. Y. Sung, "Effects of *Helicobacter pylori* infection on long-term risk of peptic ulcer bleeding in low-dose aspirin users," *Gastroenterology*, vol. 144, no. 3, pp. 528–535, 2013.
- [129] R. D. Chason, J. S. Reisch, and D. C. Rockey, "More favorable outcomes with peptic ulcer bleeding due to *helicobacter pylori*," *The American Journal of Medicine*, vol. 126, no. 9, pp. 811.e1–818.e1, 2013.