DYSPEPSIA AND NON-INFECTIOUS PEPTIC ULCER

CHI Formulary Indication Review

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INDICATION UPDATE

ADDENDUM- October 2023

To the CHI Original Dyspepsia and Non-infectious Peptic Ulcer Clinical Guidance- Issued January 2020

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Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

Abbreviations

CHI	Council of Health Insurance
COX-2	Cyclooxygenase-2
CPG	Clinical Practice Guideline
DOAC	Direct oral anticoagulants
EPS	Epigastric pain syndrome
ESGE	European Society of Gastrointestinal Endoscopy
ESNM	European Society for Neurogastroenterology and Motility
F	Forrest
FD	Functional dyspepsia
H2RA	Histamine type 2 receptor antagonist
IDF	CHI Drug Formulary
JSGE	Japanese Society of Gastroenterology
LDA	Low-dose aspirin
NSAID	Non-steroidal anti-inflammatory drug
NVUGIH	Nonvariceal upper gastrointestinal hemorrhage
P-CAB	Potassium-competitive acid blocker
PCC	Prothrombin complex concentrate
PDS	Postprandial distress syndrome
PPI	Proton pump inhibitor
PUB	Peptic ulcer bleeding
TAE	Transcatheter angiographic embolization
UEG	United European Gastroenterology
UGIH	Upper gastrointestinal hemorrhage
VKA	Vitamin K antagonist
VPZ	Vonoprazan

Executive Summary

Dyspepsia is a term used to describe a diverse range of symptoms experienced in the upper abdomen, which can have various underlying causes. Patients often don't specifically use the word "dyspepsia" but instead describe their abdominal symptoms as discomfort, pain, aching, bloating, fullness, burning, or indigestion.

Dyspepsia is a highly prevalent gastrointestinal disorder worldwide, affecting a significant number of individuals. However, despite its widespread occurrence, ranging from 1.8% to 57% across different populations, there has been no research conducted to determine its prevalence specifically in Saudi Arabia. A questionnaire was filled by 778 individuals in 2020 in Saudi Arabia, and showed a female predominance, with women representing 68% of those surveyed. The prevalence of dyspepsia was found to be 92.4%, with 719 out of 778 individuals experiencing the condition[1].

The most common symptoms include upper gastrointestinal complaints, such as belching, postprandial fullness, early satiety, epigastric pain, and epigastric burning. The cause of dyspepsia has not been clearly defined, but several pathophysiologic mechanisms, primarily focusing on the gastroduodenal pathways, have been suggested to explain this condition. Treatment options include proton pump inhibitors (PPIs), H2-receptor antagonists (H2RAs), prokinetics, phytotherapy, antidepressants, and psychotherapy[2].

CHI issued Dyspepsia and Non-infectious Peptic Ulcer clinical guidance after thorough review of renowned international and national clinical guidelines in January 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Dyspepsia and Non-infectious Peptic Ulcer clinical guidance and seeks to offer guidance for the effective management of Dyspepsia and Non-infectious Peptic Ulcer. It provides an **update on the** Dyspepsia and Non-Infectious Peptic Ulcer **Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, being **the issuance of updated versions of previously reviewed guidelines** namely Endoscopic diagnosis and management of nonvariceal upper gastrointestinal hemorrhage (NVUGIH): **European Society of Gastrointestinal Endoscopy (ESGE)** Guideline – Update **2021** and Management of Nonvariceal Upper Gastrointestinal Bleeding: Guideline Recommendations from the **International Consensus Group (2021)**. Moreover, new guidelines are added to the report such as **British Society of Gastroenterology**

guidelines on the management of functional dyspepsia **(2022)**, **Japanese Society of Gastroenterology (JSGE)** Evidence-based clinical practice guidelines for functional dyspepsia **2021**, **United European Gastroenterology (UEG), European Society for Neurogastroenterology and Motility (ESNM) consensus** on functional dyspepsia **(2020)** and Perforated and Bleeding Peptic Ulcer: **World Society of Emergency Surgery (WSES) Guidelines (2020)**.

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is advisable to (Concurrent Use) was removed for histamine type 2 receptor antagonists (H2RAs) such as cimetidine and nizatidine since they can also be used alone for the treatment of dyspepsia and peptic ulcer. There have been no updates made to any of the previously listed drugs in terms of drug information and prescribing edits since January 2020.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the Gastric and Esophageal Cancers therapeutic management.

Below is a table summarizing the major changes based on the different dyspepsia and peptic ulcer guidelines used to issue this report.

Table 1. General Recommendations for the Management of Dyspepsia and Non-Infectious Peptic Ulcer

Management of Dyspepsia and Non-infectious Peptic Ulcer		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
Changes in lifestyle and dietary adjustments have shown effectiveness in the management of functional dyspepsia (FD).	Recommendation Strong (100%), evidence level B	Japanese Society of Gastroenterology (JSGE)[2]
PPIs are effective in treating FD. There doesn't appear to be a dose-response relationship, so the lowest effective dose should be used. PPIs are well tolerated.	Recommendation: strong, quality of evidence: high	British Society of Gastroenterology guidelines[3]
H2RAs present a potentially effective treatment choice for FD and are generally well-tolerated.	Recommendation: weak, quality of evidence: low	British Society of Gastroenterology guidelines[3]

Tricyclic antidepressants and anxiolytics, such as tandospirone, have shown efficacy in treating FD and are suggested as potential treatment options for FD patients.	Recommendation Weak (92%), evidence level A for tricyclic antidepressants and B for anxiolytics such as tandospirone	Japanese Society of Gastroenterology (JSGE) guidelines[2]
While certain prokinetic drugs have demonstrated effectiveness in treating FD, their efficacy varies depending on the drug class, and many of these medications are not widely accessible outside of Asia and the USA. However, most prokinetic drugs are generally well tolerated.	Recommendation: weak, evidence quality: low for acotiamide, itopride, and mosapride. Recommendation: strong, evidence quality: moderate for tegaserod	British Society of Gastroenterology guidelines[3]
For patients with acute upper gastrointestinal bleeding (UGIH), it is advised to contemplate the use of a high dose of intravenous proton pump inhibitor (PPI) therapy before undergoing endoscopy. This approach aims to lessen the severity of endoscopic findings and potentially reduce the need for endoscopic intervention.	Strong recommendation, moderate quality evidence	European Society of Gastrointestinal Endoscopy (ESGE) Guideline[4]
In cases of ulcers caused by Nonselective NSAID usage, it is strongly recommended to discontinue the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and, instead, choose anti-ulcer medications as an alternative treatment.	Recommendation: strong, 100% consensus, supported by evidence level A	Japanese Society of Gastroenterology (JSGE) guidelines[5]
It is highly recommended to use proton pump inhibitors (PPIs) alongside continuous low-dose aspirin (LDA) therapy to prevent peptic ulcers caused by LDA.	Recommendation: strong, 100% agreed, evidence level A	Japanese Society of Gastroenterology (JSGE) guidelines[5]

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in **dyspepsia and non-infectious peptic ulcer clinical and therapeutic management.**

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: one part includes recommendations from **updated versions of guidelines** mentioned in the previous CHI dyspepsia and non-infectious peptic ulcer report, and another part includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines mentioned in the January 2020 CHI dyspepsia and non-infectious peptic ulcer report and the corresponding recommendations:

Table 2. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
1.1 **American College of Gastroenterology** Guidelines: Dyspepsia Management **(2017)**	N/A*
1.2 **European Society of Gastrointestinal Endoscopy** Guidelines of Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage **(2015)**	1.1.1 Endoscopic diagnosis and management of nonvariceal upper gastrointestinal hemorrhage (NVUGIH): **European Society of Gastrointestinal Endoscopy (ESGE) Guideline** – Update (**2021)**
1.3 **NICE Guidelines** for managing peptic ulcer disease in adults **(2019)**	N/A*
1.4 **NICE Guidelines** for Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management **(2019)**	N/A*
1.5 **International Consensus** Recommendations on the Management	1.1.2 Management of Nonvariceal Upper Gastrointestinal Bleeding: Guideline

of Patients with Non-variceal Upper Gastrointestinal Bleeding **(2010)**	Recommendations from **the International Consensus Group (2019)**

**: The published version of the guideline is the most recent one, and there are no updates available.*

1.1.1 Endoscopic Diagnosis and Management of Nonvariceal Upper Gastrointestinal Hemorrhage (NVUGIH): European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2021

*Please refer to **Section 1.2** of CHI Dyspepsia and Non-infectious Peptic Ulcer original clinical guidance.*

The 2021 revised edition of European Society of Gastrointestinal Endoscopy (ESGE) Guideline: Endoscopic diagnosis and management of nonvariceal upper gastrointestinal hemorrhage (NVUGIH): European Society of Gastrointestinal Endoscopy[4] introduced a set of recommendations accompanied by a grading scheme, outlined as follows:

Table 3. European Society of Gastrointestinal Endoscopy (ESGE) Grading Scheme for Recommendations

Grading Scheme for Recommendations	
Very low	The true effect is probably markedly different from the estimated effect.
Low	The true effect might be markedly different from the estimated effect.
Moderate	The authors believe that the true effect is probably close to the estimated effect.
High	The authors have a lot of confidence that the true effect is similar to the estimated effect.

Table 4. European Society of Gastrointestinal Endoscopy (ESGE) Quality of Evidence

Quality of evidence	
Weak	There is likely to be an important variation in the decision that informed persons are likely to make
Strong	All or almost all persons would choose that intervention

Pre-endoscopy management

- The ESGE suggests promptly evaluating the hemodynamic condition of individuals experiencing acute upper gastrointestinal hemorrhage (UGIH) and, if there's hemodynamic instability, initiating rapid intravascular volume replenishment with crystalloid fluids. (Strong recommendation, low quality evidence)
- The ESGE advises that, for patients with acute upper gastrointestinal hemorrhage (UGIH) who are stable in terms of their hemodynamics and have no prior cardiovascular disease, a conservative approach to red blood cell (RBC) transfusions is recommended. This involves maintaining a hemoglobin level of 7 g/dL or lower as the threshold for initiating RBC transfusions, with a target post-transfusion hemoglobin concentration in the range of 7 to 9 g/dL. (Strong recommendation, moderate quality evidence.)
- In the case of hemodynamically stable patients experiencing acute upper gastrointestinal hemorrhage (UGIH) and having a history of acute or chronic cardiovascular disease, the ESGE suggests a more lenient approach to red blood cell (RBC) transfusions. Specifically, they recommend initiating RBC transfusions when the hemoglobin level falls at or below 8 g/dL and aim for a post-transfusion target hemoglobin concentration of at least 10 g/dL. (Strong recommendation, low quality evidence.)
- The ESGE advises using the Glasgow–Blatchford Score (GBS) for the pre-endoscopy assessment of risk in patients with acute upper gastrointestinal hemorrhage (UGIH). Patients with a GBS score of 1 or less are categorized as being at an extremely low risk for rebleeding, mortality within 30 days, or requiring hospital-based intervention. Consequently, these patients can be safely managed as outpatients and can undergo endoscopy on an outpatient basis. (Strong recommendation, moderate quality evidence)
- ESGE advises that patients experiencing acute upper gastrointestinal bleeding (UGIH) who are on low-dose aspirin for primary cardiovascular prophylaxis should temporarily discontinue aspirin. However, the decision to restart aspirin should be made carefully after re-evaluating its clinical indication. (Strong recommendation, low quality evidence)
- ESGE advises that patients with acute upper gastrointestinal bleeding (UGIH) who are taking low-dose aspirin as the sole therapy for secondary cardiovascular prophylaxis should not discontinue aspirin. If, for any reason, aspirin is temporarily interrupted, it should be resumed as soon as possible, preferably within 3-5 days. (Strong recommendation, moderate quality evidence)

- For patients on dual antiplatelet therapy (DAPT) for secondary cardiovascular prophylaxis, aspirin should not be interrupted during acute UGIH. The second antiplatelet agent should be interrupted but restarted as soon as possible, preferably within 5 days. Cardiology consultation is suggested. (Strong recommendation, low quality evidence)
- The ESGE advises against routinely administering platelet transfusions to individuals with acute non-variceal upper gastrointestinal hemorrhage (NVUGIH) who are currently using antiplatelet medications. (Strong recommendation, low quality evidence.)
- The use of tranexamic acid is not recommended for patients with acute non-variceal UGIH (Strong recommendation, high quality evidence)
- For patients on vitamin K antagonists (VKAs) with acute UGIH, the anticoagulant should be withheld. (Strong recommendation, low quality evidence)
- In patients on VKAs with acute UGIH and hemodynamic instability, low-dose vitamin K supplemented with intravenous prothrombin complex concentrate (PCC); fresh frozen plasma (FFP) can be administered if PCC is not available. However, this should not delay endoscopy or, if required, endoscopic hemostasis. (Strong recommendation, low quality evidence)
- For patients on direct oral anticoagulants (DOAC) with acute UGIH, the anticoagulant should be withheld, and endoscopy should not be delayed. In patients with severe ongoing bleeding, consideration can be given to the use of a DOAC reversal agent or intravenous PCC. (Strong recommendation, low quality evidence)
- It is recommended to consider administering a high dose of intravenous proton pump inhibitor (PPI) therapy prior to endoscopy in patients with acute upper gastrointestinal bleeding (UGIH). This approach aims to reduce the severity of endoscopic findings and potentially minimize the requirement for endoscopic intervention. (Weak recommendation, high quality evidence)
- ESGE advises against the use of somatostatin or its analogue octreotide in patients with non-variceal upper gastrointestinal bleeding (NVUGIH). (Strong recommendation, low quality evidence).
- ESGE does not recommend the routine use of nasogastric or orogastric aspiration/lavage in patients presenting with acute UGIH. (Strong recommendation, moderate quality evidence).
- ESGE strongly advises against routine preventative endotracheal intubation to protect the airway before performing upper endoscopy in patients with acute

upper gastrointestinal hemorrhage (UGIH). (Strong recommendation, high quality evidence).

- ESGE recommends prophylactic endotracheal intubation for airway protection before upper endoscopy only in specific cases of acute UGIH. These cases include individuals who are currently experiencing ongoing active hematemesis, agitation, or encephalopathy with an inability to adequately control their airway. (Strong recommendation, low quality evidence).
- Regarding prokinetic medications, ESGE strongly recommends the administration of intravenous erythromycin before endoscopy in selected patients with clinically severe or ongoing active UGIH. (Strong recommendation, high quality evidence).

Endoscopic management

- ESGE provides the following definitions for the timing of upper GI endoscopy in acute UGIH relative to patient presentation: Urgent endoscopy should be performed within 12 hours, early endoscopy within 24 hours, and delayed endoscopy after 24 hours. (Strong recommendation, moderate quality evidence).
- Following hemodynamic resuscitation, ESGE strongly recommends performing early upper GI endoscopy, defined as within 24 hours. (Strong recommendation, high quality evidence).
- ESGE does not recommend urgent upper GI endoscopy (within 12 hours) since it does not lead to improved patient outcomes compared to early endoscopy. (Strong recommendation, high quality evidence).
- Similarly, ESGE does not recommend emergent upper GI endoscopy (within 6 hours) as it may be associated with worse patient outcomes. (Strong recommendation, moderate quality evidence).
- ESGE advises against using the use of antiplatelet agents, anticoagulants, or a predetermined international normalized ratio (INR) cutoff level to define or guide the timing of upper GI endoscopy in patients with acute UGIH. (Strong recommendation, low quality evidence).
- Regarding on-call GI endoscopy resources, ESGE strongly recommends having both an on-call GI endoscopist skilled in endoscopic hemostasis and on-call nursing staff with technical expertise in the use of endoscopic devices available 24/7. (Strong recommendation, low quality evidence).
- ESGE strongly recommends using the Forrest (F) classification in all patients with peptic ulcer hemorrhage to differentiate between low-risk and high-risk endoscopic stigmata. (Strong recommendation, high quality evidence).

- ESGE also recommends that peptic ulcers with spurting or oozing bleeding (FIa and FIb, respectively) or with a nonbleeding visible vessel (FIIa) should receive endoscopic hemostasis because these lesions are at high risk for persistent bleeding or recurrent bleeding. (Strong recommendation, high quality evidence).
- ESGE suggests that peptic ulcers with an adherent clot (FIIb) should be considered for endoscopic clot removal. Once the clot is removed, any identified underlying active bleeding (FIa or FIb) or nonbleeding visible vessel (FIIa) should receive endoscopic hemostasis. (Weak recommendation, moderate quality evidence).
- ESGE advises against performing endoscopic hemostasis in patients with peptic ulcers displaying a flat pigmented spot (FIIc) or a clean base (FIII) as these characteristics are associated with a low risk of adverse outcomes. In specific clinical scenarios, these patients may be considered for expedited hospital discharge. (Strong recommendation, moderate quality evidence).
- ESGE does not recommend the routine utilization of a Doppler endoscopic probe to assess the endoscopic stigmata of peptic ulcer bleeding. (Strong recommendation, low quality evidence).
- ESGE does not recommend the routine application of capsule endoscopy technology for assessing acute upper gastrointestinal hemorrhage (UGIH).(Strong recommendation, low quality evidence.)
- For peptic ulcer hemorrhage with active bleeding (FIa, FIb), ESGE recommends a combination therapy approach involving epinephrine injection along with a second hemostasis method, which can be either contact thermal therapy or mechanical therapy. (Strong recommendation, high quality evidence).
- In selected cases of actively bleeding ulcers (FIa, FIb), particularly those larger than 2 cm, featuring a substantial visible vessel (> 2mm), or located in high-risk vascular areas (e.g., gastroduodenal or left gastric arteries), or excavated/fibrotic ulcers, ESGE suggests considering endoscopic hemostasis using a cap-mounted clip as the primary treatment. (Weak recommendation, low quality evidence).
- For ulcers with a non-bleeding visible vessel (FIIa), ESGE recommends various options for treatment, including contact or non-contact thermal therapy, mechanical therapy, or injection of a sclerosing agent, either as monotherapy or in combination with epinephrine injection. (Strong recommendation, high quality evidence).

- ESGE does not recommend using epinephrine injection as a sole endoscopic treatment. If used, it should be combined with a second endoscopic hemostasis method. (Strong recommendation, high quality evidence).
- The ESGE defines persistent bleeding as ongoing active bleeding that does not respond to standard hemostasis techniques. (Strong recommendation, high quality evidence).
- In patients with persistent bleeding that does not respond to standard hemostasis methods, ESGE suggests considering the use of a topical hemostatic spray/powder or cap-mounted clip. (Weak recommendation, low quality evidence).
- For patients with persistent bleeding unresponsive to all forms of endoscopic hemostasis, ESGE recommends considering transcatheter angiographic embolization (TAE). Surgery should be considered when TAE is not available locally or after failed TAE. (Strong recommendation, moderate quality evidence).
- ESGE also suggests contemplating the use of hemostatic forceps as an alternative option for endoscopic hemostasis in peptic ulcer hemorrhage. (Weak recommendation, moderate quality evidence).

Post-endoscopy management

- ESGE recommends high-dose proton pump inhibitor (PPI) therapy for specific cases of upper gastrointestinal bleeding. This includes patients who have undergone endoscopic hemostasis and those with specific ulcer stigmata. The recommended PPI therapy involves an initial intravenous bolus followed by continuous infusion (e.g., 80mg as a bolus followed by 8mg per hour) for 72 hours post-endoscopy. Alternatively, other high-dose PPI regimens given twice-daily intravenously or orally may be considered. (Strong recommendation, high quality evidence)
- ESGE does not recommend routine second-look endoscopy as part of the management of NVUGIH. (Strong recommendation, high quality evidence).
- ESGE recommends that recurrent bleeding be defined as bleeding following initial successful endoscopic hemostasis. (Strong recommendation, high quality evidence).
- ESGE recommends that patients with clinical evidence of recurrent bleeding should receive repeat upper endoscopy with hemostasis if indicated. (Strong recommendation, high quality evidence).
- ESGE recommends that in the case of failure of this second attempt at endoscopic hemostasis, transcatheter angiographic embolization (TAE)

should be considered. Surgery is indicated when TAE is not locally available or after failed TAE. (Strong recommendation, high quality evidence).

- ESGE recommends that for patients with clinical evidence of recurrent peptic ulcer hemorrhage, use of a cap-mounted clip should be considered. In the case of failure of this second attempt at endoscopic hemostasis, transcatheter angiographic embolization (TAE) should be considered. Surgery is indicated when TAE is not locally available or after failed TAE. (Strong recommendation, moderate quality evidence).
- ESGE recommends that in patients who have had acute NVUGIH and require ongoing dual antiplatelet therapy (DAPT), PPI should be given as co-therapy. (Strong recommendation, moderate quality evidence)
- ESGE recommends that in patients who need to continue anticoagulation therapy after experiencing acute non-variceal upper gastrointestinal bleeding (NVUGIH), such as peptic ulcer hemorrhage, anticoagulation should be resumed promptly once the bleeding has been controlled. Ideally, this should occur within or shortly after 7 days of the bleeding event, considering the thromboembolic risk. It is important to consider the rapid onset of action of direct oral anticoagulants (DOACs) in comparison to vitamin K antagonists (VKAs) in this context. (Strong recommendation, low quality evidence)
- ESGE recommends PPIs for gastroduodenal prophylaxis in patients requiring ongoing anticoagulation and with a history of NVUGIH. (Strong recommendation, low quality evidence)

1.1.2 Management of Nonvariceal Upper Gastrointestinal Bleeding: Guideline Recommendations from the International Consensus Group (2019)

*Please refer to **Section 1.5** of CHI Dyspepsia and Non-infectious Peptic Ulcer original clinical guidance.*

The 2019 guidelines published by the International Consensus Group introduced a set of recommendations accompanied by a grading scheme, outlined as follows[6]:

Table 5. International Consensus Group Quality of Evidence for the Recommendations

Quality of evidence and definitions	
Very low	Any estimate of effect is very uncertain
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
High	Further research is very unlikely to change our confidence in the estimate of effect

Table 6. International Consensus Group Grade of Recommendations

Grades of recommendations and definitions	
Conditional	The strength of the recommendation would default (without a vote), “we suggest”
Strong	If the statement warranted a vote and at least 75% of the participants voted “strong”, “we recommend”

- The routine use of promotility agents before endoscopy to enhance the diagnostic yield is not recommended.
- Pre-endoscopic PPI therapy may be considered to reduce the severity of the endoscopic lesion and decrease the need for endoscopic intervention but should not delay endoscopy.
- H2RAs are not recommended for patients with acute ulcer bleeding.
- In patients with acute ulcer bleeding, the use of somatostatin and octreotide is not routinely recommended.
- In patients with bleeding ulcers displaying high-risk stigmata who have undergone successful endoscopic therapy, it is recommended to utilize intravenous proton pump inhibitor (PPI) therapy, administered via a loading dose followed by a continuous intravenous infusion. This approach is preferred over no treatment or the use of H2 receptor antagonists (H2RAs). (GRADE: strong recommendation, moderate-quality evidence. Vote on PICO question: yes, 100%)
- In patients who have high-risk ulcer bleeding, requiring endoscopic therapy and 3 days of high-dose proton pump inhibitor (PPI) therapy, it is suggested to use twice-daily oral PPIs (compared to once-daily) for a duration of 14 days, followed by a once-daily regimen. (GRADE: conditional recommendation, very low-quality evidence. Vote on PICO question: yes, 95%; uncertain/neutral, 5%)
- In patients with previous ulcer bleeding who require a non-steroidal anti-inflammatory drug (NSAID), the combination of a PPI and a COX-2 inhibitor is recommended to reduce the risk for recurrent bleeding from that of Cyclooxygenase-2 (COX-2) inhibitors alone.

- In patients who are on low-dose aspirin (ASA) therapy and experience acute ulcer bleeding, it is recommended to resume ASA therapy once the risk of cardiovascular complications is deemed to be greater than the risk of bleeding.
- In patients who have previously experienced ulcer bleeding and are undergoing cardiovascular prophylaxis with either single or dual antiplatelet therapy, it is recommended to use proton pump inhibitor (PPI) therapy rather than no PPI therapy. (GRADE: conditional recommendation, low-quality evidence. Vote on PICO question (single): yes, 95%; uncertain/neutral: 5%. Vote on PICO question (double): yes, 100%)
- For patients who have previously experienced ulcer bleeding and require ongoing cardiovascular prophylaxis with anticoagulant therapy such as vitamin K antagonists or direct oral anticoagulants (DOACs), it is recommended to use proton pump inhibitor (PPI) therapy rather than no PPI therapy. (GRADE: conditional recommendation, very low-quality evidence. Vote on PICO question: yes, 85%; uncertain/neutral, 15%)
- In patients with previous ulcer bleeding who require cardiovascular prophylaxis, it should be recognized that clopidogrel alone has a higher risk for rebleeding than ASA combined with a PPI.

1.2 Additional Guidelines

This section includes the added guidelines to the previous CHI Dyspepsia and Non-infectious Peptic Ulcer report, along with their recommendations.

Table 7. List of Additional Guidelines

Additional Guidelines
British Society of Gastroenterology guidelines on the management of functional dyspepsia **(2022)**
Japanese Society of Gastroenterology (JSGE) Evidence-based clinical practice guidelines for functional dyspepsia **(2021)**
United European Gastroenterology (UEG) and **European Society for Neurogastroenterology and Motility (ESNM)** consensus on functional dyspepsia **(2020)**
Perforated and Bleeding Peptic Ulcer: **World Society of Emergency Surgery (WSES)** Guidelines **(2020)**

1.2.1 British Society of Gastroenterology Guidelines on the Management of Functional Dyspepsia (2022)

The British Society of Gastroenterology guidelines on the management of functional dyspepsia (2022)[3] introduced a set of recommendations accompanied by a grading scheme, outlined as follows:

Table 8. British Society of Gastroenterology Guidelines Quality of Evidence

Grading Scheme for Recommendations	
Very low	The true effect is probably markedly different from the estimated effect
Low	The true effect might be markedly different from the estimated effect
Moderate	The authors believe that the true effect is probably close to the estimated effect
High	The authors have a lot of confidence that the true effect is similar to the estimated effect

Table 9. British Society of Gastroenterology Guidelines Strength of Recommendations

Grading scheme for recommendations	
Weak	There is likely to be an important variation in the decision that informed persons are likely to make
Strong	All or almost all persons would choose that intervention

- In the absence of upper gastrointestinal alarm symptoms or signs, it is recommended that clinicians diagnose FD when patients present with bothersome epigastric pain or burning, early satiation, and/or postprandial fullness persisting for more than 8 weeks. (recommendation: strong, quality of evidence: very low)

The Rome criteria, currently in their fourth iteration, are the gold-standard symptom-based diagnostic criteria for FD. Details are found in table 10.

Table 10. The Rome IV Criteria for the Diagnosis of Functional Dyspepsia. Retrieved from Black CJ, Paine PA, Agrawal A, et al. British Society of Gastroenterology guidelines on the management of functional dyspepsia. Gut. 2022;71(9):1697-1723. doi:10.1136/gutjnl-2022-327737.

Diagnostic criteria for functional dyspepsia	
One or more of the following: ► Bothersome epigastric pain. ► Bothersome epigastric burning. ► Bothersome postprandial fullness. ► Bothersome early satiation. ► Symptom onset at least 6 months prior to diagnosis. ► Symptoms should be active within the past 3 months. ► And, no evidence of structural disease (including at upper endoscopy) likely to explain the symptoms.	
Diagnostic criteria for epigastric pain syndrome (EPS)	**Diagnostic criteria for postprandial distress syndrome (PDS)**
Must include *one* or *both* of the following symptoms at least 1 day a week. 1. Bothersome epigastric pain (ie, severe enough to impact on usual activities). 2. Bothersome epigastric burning (ie, severe enough to impact on usual activities). Supportive criteria: 1. Pain may be induced by ingestion of a meal, relieved by ingestion of meal or may occur while fasting. 2. Postprandial epigastric bloating, belching and nausea can also be present. 3. Persistent vomiting likely suggests another disorder;. 4. Heartburn is not a dyspeptic symptom, but may often coexist. 5. The pain does not fulfil biliary pain criteria. 6. Symptoms that are relieved by evacuation of faeces or gas generally should not be considered as part of dyspepsia. 7. Other digestive symptoms (such as gastro-oesophageal reflux disease and irritable bowel syndrome) may coexist with the EPS.	Must include one or both of the following symptoms at least 3 days a week: 1. Bothersome postprandial fullness (ie, severe enough to impact on usual activities). 2. Bothersome early satiation (ie, severe enough to prevent finishing a regular sized meal). Supportive criteria: 1. Postprandial epigastric pain or burning, epigastric bloating, excessive belching, and nausea can also be present. 2. Vomiting warrants consideration of another disorder. 3. Heartburn is not a dyspeptic symptom, but may often coexist. 4. Symptoms that are relieved by evacuation of faeces or gas should generally not be considered as part of dyspepsia. 5. Other individual digestive symptoms or groups of symptoms (such as gastro-oesophageal reflux disease and irritable bowel syndrome) may coexist with PDS.

- It is strongly recommended to offer empirical acid suppression therapy to patients without H. pylori infection. (recommendation: strong; quality of evidence: high)
- Referral of patients with FD to gastroenterology in secondary care is appropriate in cases of diagnostic uncertainty, severe symptoms, treatment resistance, or patient request for specialist opinion. (recommendation: weak, quality of evidence: low)
- Routine gastric emptying testing or 24-hour pH monitoring is not recommended for patients with typical symptoms of FD. (recommendation: strong, quality of evidence: very low)
- Ideally, patients with FD referred to secondary care should be managed in a specialized clinic, with access to healthcare professionals knowledgeable in the field, dietetic and lifestyle support, and various effective treatment options including medications and gut-brain behavioral therapies. (recommendation: strong, quality of evidence: very low)
- It is strongly recommended that all patients with FD are advised to engage in regular aerobic exercise. (recommendation: strong, quality of evidence: very low)

- There is insufficient evidence to support the recommendation of specific dietary therapies, including a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs), for FD. (recommendation: weak; quality of evidence: very low)
- Eradication therapy is an effective treatment for patients with FD who test positive for Helicobacter pylori (H. pylori) infection. However, adverse events are more common compared to control therapy. (recommendation: strong; quality of evidence: high)

First-line treatment of FD

- H2RAs may be an effective treatment option for FD, and they are generally well tolerated. (recommendation: weak, quality of evidence: low).
- PPIs are effective in treating FD. There doesn't appear to be a dose-response relationship, so the lowest effective dose should be used. PPIs are well tolerated. (recommendation: strong, quality of evidence: high)
- Some prokinetic drugs may be effective in treating FD, but their efficacy varies based on the drug class, and many of these drugs are not readily available outside of Asia and the USA. Most prokinetic drugs are well tolerated. (recommendation: weak, quality of evidence: low for acotiamide, itopride, and mosapride. (recommendation: strong, quality of evidence: moderate)
- However, there is a shortage of placebo-controlled trials for commonly accessible prokinetics like domperidone or metoclopramide. As a result, it remains uncertain whether these medications are effective in treating FD.

Second-line treatment of FD

- Tricyclic antidepressants (TCAs) used as gut-brain neuromodulators are an effective treatment option for FD when other treatments have not been successful. They can be initiated in either primary or secondary care settings, but it is important to provide a clear explanation to patients regarding the reason for their use and to discuss potential side effects. TCAs should be started at a low dose, such as 10 mg of amitriptyline taken once daily, and the dosage should be gradually increased up to a maximum of 30-50 mg once daily. (recommendation: strong, quality of evidence: moderate)
- As a second-line treatment for FD, antipsychotics such as sulpiride (100 mg four times a day) or levosulpiride (25 mg three times a day) may potentially be effective. However, careful explanation regarding their use and counseling on potential side effects are necessary. (recommendation: weak, quality of evidence: low)

- There is a lack of evidence supporting the effectiveness of selective serotonin reuptake inhibitors (SSRIs) used as gut-brain neuromodulators as a second-line treatment for global symptoms in FD. (recommendation: weak, quality of evidence: moderate).
- There is insufficient evidence to support the effectiveness of serotonin norepinephrine reuptake inhibitors (SNRIs) used as gut-brain neuromodulators as a second-line treatment for global symptoms in FD. However, considering their efficacy in other chronic painful conditions, further trials are needed to evaluate the potential effectiveness of these drugs in FD. (recommendation: weak, quality of evidence: low).
- Tandospirone (10 mg three times a day) may be an effective second-line treatment for FD, but there is insufficient evidence to support the efficacy of other 5-hydroxytryptamine-1A agonists like buspirone (10 mg three times a day). Additional trials for these drugs are needed. (recommendation: weak, quality of evidence: low)
- Pregabalin (75 mg once daily) may be effective as a second-line treatment for FD, but further randomized controlled trials (RCTs) are required. Given its controlled drug status, it is advised to use pregabalin only in specialist settings. (recommendation: weak, quality of evidence: low)
- Mirtazapine (15 mg once daily) may be an effective second-line treatment for patients with FD experiencing early satiation and weight loss. However, more RCTs are needed to provide stronger evidence. (recommendation: weak, quality of evidence: very low)

Gut–brain behavioral therapies in FD

- Interpersonal psychodynamic informed psychotherapy may potentially be an effective treatment for global symptoms in FD. (recommendation: weak, quality of evidence: very low)
- Cognitive-behavioral therapy (CBT) and metacognitive therapy are suggested as potential treatments for global symptoms in FD. (recommendation: weak, quality of evidence: very low)
- Stress management approaches are also considered as potential treatments for global symptoms in FD. (recommendation: weak, quality of evidence: very low)
- Hypnotherapy may be an effective treatment for global symptoms in FD. (recommendation: weak, quality of evidence: very low)

Management of severe or refractory FD

- It is strongly recommended to involve a multidisciplinary support team for patients with severe or refractory FD. (recommendation: strong, quality of evidence: low).
- To minimize iatrogenic harm, opioids and surgery should be avoided in patients with severe or refractory FD. (recommendation: strong, quality of evidence: very low)
- Patients with severe or refractory FD who experience weight loss and food restriction should be evaluated for eating disorders and disordered eating, including avoidant restrictive food intake disorder (ARFID). (recommendation: strong, quality of evidence: very low)
- Early involvement of a dietitian is recommended for patients with severe or refractory FD to prevent an overly restrictive diet. (recommendation: strong, quality of evidence: very low)

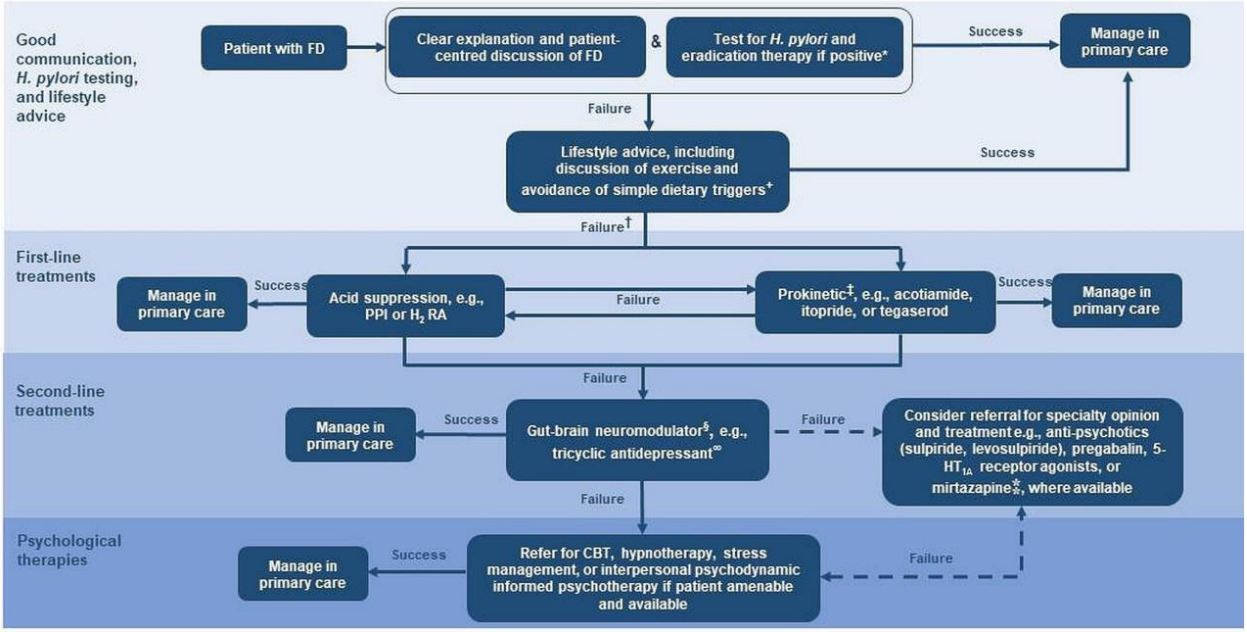

Figure 1. *Treatment Algorithm for Functional Dyspepsia. Adapted from Black CJ, Paine PA, Agrawal A, et al. British Society of Gastroenterology guidelines on the management of functional dyspepsia. Gut. 2022;71(9):1697-1723. doi:10.1136/gutjnl-2022-327737.*

1.2.2 The Japanese Society of Gastroenterology (JSGE) Evidence-Based Clinical Practice Guidelines for Functional Dyspepsia (2021)

The Japanese Society of Gastroenterology (JSGE) Evidence-based clinical practice guidelines for functional dyspepsia 2021[7] introduced a set of recommendations accompanied by a grading scheme, outlined as follows:

Table 11. JSGE Grading Scheme for Recommendations

Grading Scheme for Recommendations	
A	The data were derived from multiple randomized clinical trials or meta-analyses
B	The data were derived from one randomized trial or from nonrandomized studies
C	The data were derived from expert opinions, case studies, or standards of care

Table 12. JSGE Quality of Evidence for the Recommendations

Quality of evidence	
Weak	"We suggest"
Strong	"We recommend"

First-line treatment

- Modifications in lifestyle and diet have proven to be effective in managing FD. [Recommendation Strong (100%), evidence level B]
- The treatment of FD can be effectively accomplished using PPIs and H2RAs. [Recommendation Strong (100%), evidence level A]
- Due to limited evidence available, the efficacy of potassium-competitive acid blockers (P-CABs) cannot be adequately evaluated. [Recommendation Weak (77%), evidence level C]
- Acotiamide, an acetylcholinesterase (AChE) inhibitor, has demonstrated usefulness in the treatment of certain conditions, and its use is recommended. [Recommendation Strong (100%), evidence level A]
- The Japanese herbal medicine rikkunshito is an effective treatment for FD, and its use is recommended. [Recommendation Strong (92%), evidence level A]

Second line treatment

- Dopamine receptor antagonists have shown utility in clinical practice, and their use is suggested. [Recommendation Weak (85%), evidence level B]
- Similarly, serotonin-4 (5-HT4) receptor agonists have demonstrated usefulness, and their use is also suggested. [Recommendation Weak (85%), evidence level B]
- Tricyclic antidepressants and anxiolytics, such as tandospirone, have shown efficacy in treating FD and have been suggested as treatment options for FD patients. [Recommendation Weak (92%), evidence level A for TCAs and B for anxiolytics such as tandospirone]

Alternative or complementary therapy

- The effectiveness of antacids, prostaglandin analogs (e.g., misoprostol), and gastroprotective agents (e.g., sucralfate and rebamipide) as treatments for functional dyspepsia (FD) remains unclear. [Recommendation NA, evidence level B]
- The implementation of psychosomatic internal medical treatment has been proposed as an effective approach for managing FD. [Recommendation Weak (100%), evidence level B]

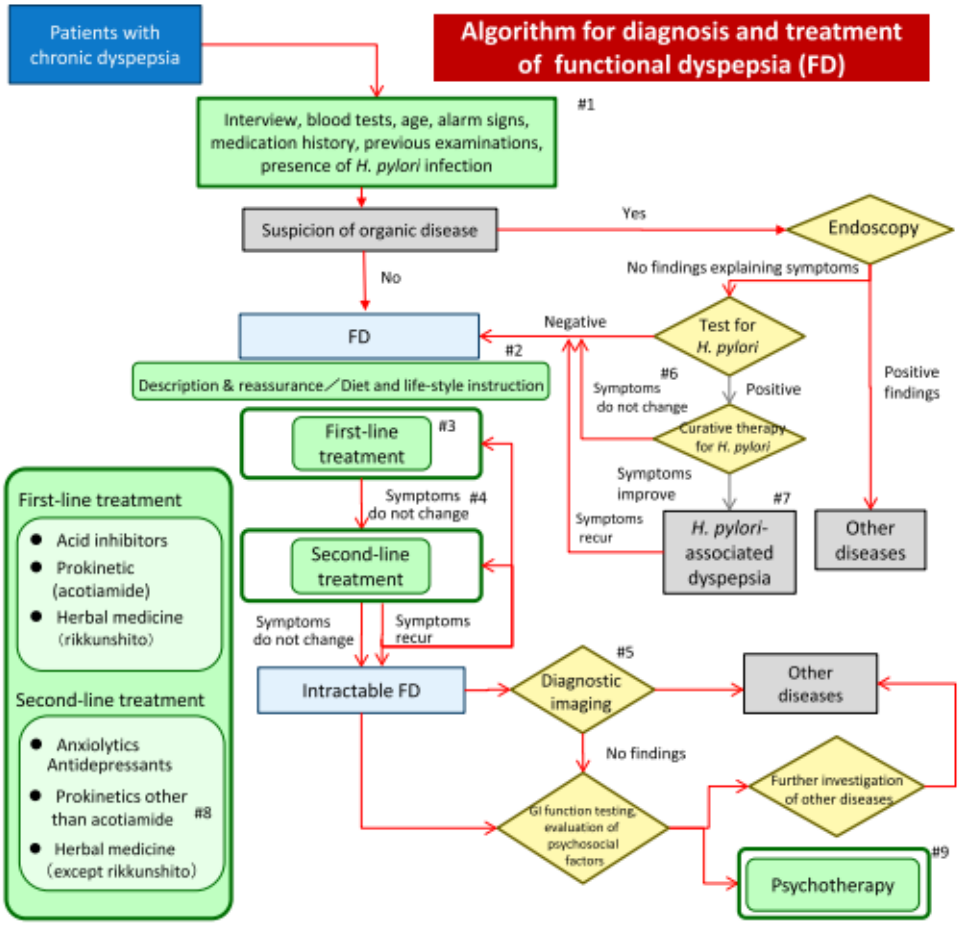

Figure 2. *Algorithm for the Diagnosis and Treatment of Functional Dyspepsia (FD). Adapted from Miwa H, Nagahara A, Asakawa A, et al. Evidence-based clinical practice guidelines for functional dyspepsia 2021. J Gastroenterol. 2022;57(2):47-61. doi:10.1007/s00535-021-01843-7.*

1.2.3 United European Gastroenterology (UEG) and European Society for Neurogastroenterology and Motility (ESNM) Consensus on Functional Dyspepsia (2020)

The United European Gastroenterology (UEG) and European Society for Neurogastroenterology and Motility (ESNM) (2020)[8] consensus introduced a set of grading scales outlined as follows:

Table 13. Six-Point Likert Scale

Point	Description
A+	Agree strongly
A	Agree with minor reservation
A−	Agree with major reservation

D−	Disagree with minor reservation
D	Disagree with major reservation
D+	Disagree strongly

Table 14. United European Gastroenterology (UEG) and European Society for Neurogastroenterology and Motility (ESNM) (2020) Grading of Recommendations Assessment, Development, and Evaluation System

Code	Quality of evidence	Definition
A	High	Further research is very unlikely to change our confidence in the estimate of effect. • Several high-quality studies with consistent results • In special cases: one large, high-quality multicenter trial
B	Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. • One high-quality study • Several studies with some limitations
C	Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. • One or more studies with severe limitations
D	Very Low	Any estimate of effect is very uncertain. • Expert opinion • No direct research evidence • One or more studies with very severe limitations

Definitions and symptoms descriptors

- Dyspepsia refers to a symptom or set of symptoms that is (are) considered to originate from the gastroduodenal region. STATEMENT ENDORSED, overall agreement 98%, GRADE B

- The main symptoms of dyspepsia according to the Rome IV criteria include early satiation, postprandial fullness, epigastric pain, and epigastric burning. STATEMENT ENDORSED, overall agreement 98%, GRADE B
- Functional dyspepsia is a condition characterized by chronic dyspeptic symptoms in the absence of organic, systemic, or metabolic condition(s) that is (are) likely to explain symptoms STATEMENT ENDORSED, overall agreement 93%, GRADE A

Epidemiology and risk factors

- (Functional) Dyspepsia occurs at all ages but the highest incidence is in the middle age. STATEMENT NOT ENDORSED, overall agreement 73%, GRADE B
- (Functional) Dyspepsia is more prevalent in women than me. STATEMENT ENDORSED, overall agreement 83%, GRADE A
- Acute gastrointestinal infection is a risk factor for development of functional dyspepsia. STATEMENT ENDORSED, overall agreement 90%, GRADE A
- NSAID intake is a risk factor for the development of functional dyspepsia. STATEMENT NOT ENDORSED, overall agreement 61%, GRADE C
- Antibiotic therapy is a risk factor for the development of functional dyspepsia. STATEMENT NOT ENDORSED, overall agreement 37%, GRADE C
- Anxiety is a risk factor for development of functional dyspepsia. STATEMENT ENDORSED, overall agreement 93%, GRADE A
- Depression is a risk factor for the development of functional dyspepsia. STATEMENT NOT ENDORSED, overall agreement 76%, GRADE B
- Smoking is a risk factor for the development of functional dyspepsia. STATEMENT NOT ENDORSED, overall agreement 37%, GRADE C.

Impact of functional dyspepsia

- Functional dyspepsia is a major source of healthcare costs. STATEMENT ENDORSED, overall agreement 98%, GRADE A
- Functional dyspepsia is a major source of self-costs to patients. STATEMENT ENDORSED, overall agreement 93%, GRADE B
- Functional dyspepsia is an important source of loss of work productivity. STATEMENT ENDORSED, overall agreement 88%, GRADE B
- Functional dyspepsia is associated with a significant decrease in quality of life. STATEMENT ENDORSED, overall agreement 100%, GRADE A

- Functional dyspepsia is associated with psychosocial co- morbidities such as anxiety and depression. STATEMENT ENDORSED, overall agreement 100%, GRADE A
- Weight loss can be a consequence of FD. STATEMENT ENDORSED, overall agreement 90%, GRADE B
- In case of weight loss, eating disorders must be ruled out. STATEMENT NOT ENDORSED, overall agreement 73%, GRADE C

Pathophysiology of functional dyspepsia

- Dietary factors underlie symptom generation in functional dyspepsia. STATEMENT NOT ENDORSED, overall agreement 51%, GRADE C
- H. pylori is a cause of symptoms in a subgroup of patients with dyspepsia and normal endoscopy. STATEMENT ENDORSED, overall agreement 81%, GRADE B
- Impaired gastric accommodation is a pathophysiological mechanism in functional dyspepsia. STATEMENT ENDORSED, overall agreement 93%, GRADE B
- Delayed gastric emptying is a pathophysiological mechanism in functional dyspepsia. STATEMENT ENDORSED, overall agreement 85%, GRADE B
- Rapid gastric emptying is a pathophysiological mechanism in functional dyspepsia. STATEMENT NOT ENDORSED, overall agreement 32%, GRADE C
- Hypersensitivity to gastric distention is a pathophysiological mechanism in functional dyspepsia. STATEMENT ENDORSED, overall agreement 93%, GRADE B
- Duodenal mucosal alterations are a pathophysiological mechanism in functional dyspepsia. STATEMENT NOT ENDORSED, overall agreement 76%, GRADE B
- Altered gastric acid secretion is a pathophysiological mechanism in functional dyspepsia. STATEMENT NOT ENDORSED, overall agreement 29%, GRADE C
- Altered release of peptide hormones is a pathophysiological mechanism in functional dyspepsia. STATEMENT NOT ENDORSED, overall agreement 24%, GRADE C
- Increased sensitivity to duodenal luminal content is a pathophysiological mechanism in functional dyspepsia. STATEMENT NOT ENDORSED, overall agreement 68%, GRADE C

- Altered duodenal microbiota composition is a pathophysiological mechanism in functional dyspepsia. STATEMENT NOT ENDORSED, overall agreement 34%, GRADE C
- Impaired vagus nerve function is a pathophysiological mechanism in functional dyspepsia. STATEMENT NOT ENDORSED, overall agreement 46%, GRADE C
- Anxiety and stress are pathophysiological mechanisms in functional dyspepsia. STATEMENT NOT ENDORSED, overall agreement 66%, GRADE B
- Depression is a pathophysiological mechanism in functional dyspepsia. STATEMENT NOT ENDORSED, overall agreement 54%, GRADE B
- Disordered central processing of incoming signals from the gastroduodenal region is a pathophysiological mechanism in functional dyspepsia. STATEMENT ENDORSED, overall agreement 85%, GRADE C
- Genetic factors determine the susceptibility to functional dyspepsia. STATEMENT NOT ENDORSED, overall agreement 37%, GRADE C

Diagnosis

- Upper gastrointestinal endoscopy is mandatory for establishing a diagnosis of functional dyspepsia. STATEMENT ENDORSED, overall agreement 80%, GRADE A
- In primary care, uninvestigated dyspepsia can be managed without endoscopy if there are no alarm symptoms or risk factors. STATEMENT ENDORSED, overall agreement 93%, GRADE A
- Upper gastrointestinal endoscopy is mandatory if there are alarm symptoms or risk factors. STATEMENT ENDORSED, overall agreement 93%, GRADE A
- Screening blood tests are useful when considering a diagnosis of functional dyspepsia. STATEMENT NOT ENDORSED, overall agreement 46%, GRADE B
- Every patient with dyspeptic symptoms should be tested for Helicobacter pylori (non-invasively or at gastroscopy). STATEMENT ENDORSED, overall agreement 81%, GRADE A
- Patients with dyspepsia and H. pylori-positive gastritis should be considered to have functional dyspepsia just if symptoms persist 6 to 12 months after H. pylori eradication. STATEMENT ENDORSED, overall agreement 83%, GRADE B
- Patients with dyspepsia and H. pylori-negative gastritis should be considered to have functional dyspepsia. STATEMENT ENDORSED, overall agreement 85%, GRADE B

- Functional dyspepsia should be subdivided into EPS and PDS for further diagnostic and therapeutic approach. STATEMENT ENDORSED, overall agreement 83%, GRADE B
- Upper abdominal ultrasound is useful when considering a diagnosis of functional dyspepsia. STATEMENT NOT ENDORSED, overall agreement 27%, GRADE B
- A gastric emptying test is useful when considering a diagnosis of functional dyspepsia. STATEMENT NOT ENDORSED, overall agreement 34%, GRADE B
- Esophageal pH monitoring is useful in functional dyspepsia to rule out GERD. STATEMENT NOT ENDORSED, overall agreement 37%, GRADE B
- Increased duodenal eosinophil count is a marker of functional dyspepsia. STATEMENT NOT ENDORSED, overall agreement 20%, GRADE C

Treatment

- Symptom improvement in functional dyspepsia (FD) can be achieved through dietary adjustments. STATEMENT NOT ENDORSED, overall agreement 73%, GRADE C
- Proton pump inhibitor (PPI) therapy is considered the most suitable initial treatment for functional dyspepsia (FD). STATEMENT NOT ENDORSED, overall agreement 73%, GRADE B
- PPI therapy is the most effective therapy for EPS. STATEMENT NOT ENDORSED, overall agreement 59%, GRADE C
- Prokinetic therapy is an effective therapy for FD. STATEMENT NOT ENDORSED, overall agreement 54%, GRADE B
- Prokinetic therapy is the most effective therapy for PDS. STATEMENT NOT ENDORSED, overall agreement 54%, GRADE B
- Efficacy of prokinetics is not related to their enhancement of gastric emptying rate. STATEMENT NOT ENDORSED, overall agreement 56% GRADE B
- Itopride is effective for FD patients. STATEMENT NOT ENDORSED, overall agreement 56%, GRADE C
- Mirtazapine is effective for post-prandial distress syndrome patients with weight loss. STATEMENT NOT ENDORSED, overall agreement 68%, GRADE B
- 5-HT1A agonists (tandospirone, buspirone.) are effective for PDS. STATEMENT NOT ENDORSED, overall agreement 56%, GRADE B
- Herbal therapies are effective for FD patients. STATEMENT NOT ENDORSED, overall agreement 37%, GRADE B

- Tricyclic antidepressants (TCAs) are effective for EPS. STATEMENT NOT ENDORSED, overall agreement 78%, GRADE B
- TCAs are effective for PDS. STATEMENT NOT ENDORSED, overall agreement 32%, GRADE B
- TCAs are not effective for PDS. STATEMENT NOT ENDORSED, overall agreement 39%, GRADE B
- Serotonin reuptake inhibitors are effective for FD. STATEMENT NOT ENDORSED, overall agreement 20%, GRADE B
- Serotonin reuptake inhibitors are not effective for FD. STATEMENT NOT ENDORSED, overall agreement 54%, GRADE B
- Serotonin noradrenaline reuptake inhibitors are effective for FD. STATEMENT NOT ENDORSED, overall agreement 17%, GRADE C
- Serotonin noradrenaline reuptake inhibitors are not effective for FD. STATEMENT NOT ENDORSED, overall agreement 49%, GRADE C
- Iberogast (STW-5) is effective for FD patients. STATEMENT NOT ENDORSED, overall agreement 54%, GRADE B
- Rifaximin is effective for FD patients. STATEMENT NOT ENDORSED, overall agreement 19%, GRADE C
- Hypnotherapy is effective for FD patients. STATEMENT NOT ENDORSED, overall agreement 29%, GRADE B
- Cognitive–behavioral therapy (CBT) is effective for FD patients. STATEMENT NOT ENDORSED, overall agreement 42%, GRADE B
- Acupuncture is effective for FD patients. STATEMENT NOT ENDORSED, overall agreement 27%, GRADE B
- Mindfulness is effective for FD patients. STATEMENT NOT ENDORSED, overall agreement 27%, GRADE B
- In case of severe weight loss in FD, nutritional support may be needed. STATEMENT ENDORSED, overall agreement 90%, GRADE B

1.2.4 The Japanese Society of Gastroenterology (JSGE) Evidence-Based Clinical Practice Guidelines for Peptic Ulcer Disease (2020)

The Japanese Society of Gastroenterology (JSGE) Evidence-based clinical practice guidelines for peptic ulcer disease 2020[5] introduced a set of recommendations accompanied by the same grading scheme detailed in tables 3 and 4 above.

- It is strongly recommended to continue aspirin for conditions with a high risk of thromboembolic events. (Recommendation: strong, 100% agreed, evidence level B)
- It is suggested to switch antiplatelet agents to aspirin in patients with conditions at high risk of thromboembolic events. (Recommendation: weak, 100% agreed, evidence level D)
- It is also suggested to temporarily suspend antiplatelet agents, except for patients at high risk of thromboembolic events. (Recommendation: weak, 100% agreed, evidence level D.
- In patients undergoing endoscopic hemostasis, it is strongly recommended to suspend warfarin if necessary. If warfarin is discontinued, heparin can be used or warfarin can be resumed once hemostasis is established. (Recommendation: strong, 100% agreed, evidence level C)
- For patients receiving direct oral anticoagulants (DOACs) and undergoing endoscopic hemostasis, it is weakly suggested to resume DOACs early (within 1-2 days) after confirming hemostasis. (Recommendation: weak, 100% agreed, evidence level D)
- In patients on both antiplatelet agents and warfarin, it is suggested to switch antiplatelet agents to aspirin or cilostazol, or to continue warfarin with appropriate prothrombin time-international normalized ratio (PT-INR), or to switch warfarin to heparin. (Recommendation: weak, 100% agreed, evidence level D)
- In patients who are taking dual antiplatelet agents, it is recommended to continue with aspirin alone. (Recommendation: strong, 100% agreed, evidence level D)
- To enhance treatment outcomes, it is recommended to administer proton pump inhibitors (PPIs) following endoscopic treatment for hemorrhagic peptic ulcers. (Recommendation: strong, 100% agreed, evidence level A)
- For patients on dual antiplatelet therapy (DAPT), it is strongly recommended to use proton pump inhibitors (PPIs) in combination to prevent upper gastrointestinal bleeding (UGIB). (Recommendation: strong, 100% agreed, evidence level A)
- If patients are taking warfarin along with antiplatelet drugs or non-steroidal anti-inflammatory drugs (NSAIDs), it is suggested to use PPIs to prevent UGIB. (Recommendation: weak, 100% agreed, evidence level C)

First-line treatment for the initial non-eradication treatment of gastric and duodenal ulcers

- It is strongly recommended to use either proton pump inhibitors (PPIs) or potassium-competitive acid blockers (P-CABs). (Recommendation: strong, 100% agreed, evidence level A)
- If PPIs and P-CABs are not suitable options, histamine-2 receptor antagonists (H2RAs) are recommended. (Recommendation: strong, 100% agreed, evidence level B)
- In cases where both PPIs and P-CABs are not feasible, the use of pirenzepine, sucralfate, and misoprostol is suggested. (Recommendation: weak, 100% agreed, evidence level B)

Nonselective NSAID-induced ulcer treatment

- It is strongly recommended to discontinue the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and instead, administer anti-ulcer drugs. (Recommendation: strong, 100% agreed, evidence level A)
- If discontinuing NSAIDs is not possible, the first-line therapy is the administration of proton pump inhibitors (PPIs). (Recommendation: strong, 100% agreed, evidence level A)
- It is necessary and recommended to administer proton pump inhibitors (PPIs) for the prevention of NSAID-induced ulcers, even in patients with no prior history of ulcers. (Recommendation: weak, 100% agreed, evidence level A)
- To prevent ulcers induced by nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with a history of ulcers, proton pump inhibitors (PPIs) are recommended as the primary choice. Specifically, it is suggested that vonoprazan (VPZ), a type of PPI, be used for this purpose. (Recommendation: weak, 100% agreed, evidence level B)
- In cases where there has been bleeding from NSAID-induced ulcers in the past, it is recommended to administer a selective cyclooxygenase (COX)-2 inhibitor in combination with a PPI. (Recommendation: strong, 100% agreed, evidence level B)
- For patients who are taking a combination of nonsteroidal anti-inflammatory drugs (NSAIDs) and either glucocorticoids or antithrombotic drugs, it is advised to administer a selective cyclooxygenase-2 (COX-2) inhibitor as a preventive measure against ulcers. (Recommendation: strong, 100% agreed, evidence level B)
- Additionally, in elderly patients or those with severe complications, the use of proton pump inhibitors (PPIs) is recommended to prevent the occurrence of ulcers caused by NSAIDs. (Recommendation: strong, 100% agreed, evidence level A)

- COX-2 selective inhibitors are recommended for the prevention of NSAID-induced ulcers. (Recommendation: strong, 100% agreed, evidence level)
- Patients who have a history of peptic ulcers or hemorrhage and are taking COX-2 selective inhibitors should be prescribed anti-ulcer agents for prevention. (Recommendation: strong, 100% agreed, evidence level B)
- On the other hand, patients who are taking COX-2 selective inhibitors but do not have a history of peptic ulcer are not recommended to receive preventive treatment with anti-ulcer agents. (Recommendation: strong, 100% agreed, evidence level B)

Low-dose aspirin (LDA)-induced ulcer

- It is recommended to use proton pump inhibitors (PPIs) alongside continuous low-dose aspirin (LDA) therapy to prevent peptic ulcers caused by LDA. (Recommendation: strong, 100% agreed, evidence level A)
- PPIs or H2RAs are recommended for the reduction of the incidence and prevalence of LDA-related peptic ulcers. (Recommendation: strong, 100% agreed, evidence level A)
- PPIs or VPZ is recommended for the reduction of the incidence and prevalence of LDA-related Peptic ulcer bleeding (PUB) (Recommendation: strong, 100% agreed, evidence level A)
- To lower the likelihood of recurrent LDA-related peptic ulcers, the use of proton pump inhibitors (PPIs) or vonoprazan (VPZ) is strongly recommended. (Recommendation: strong, 100% agreed, evidence level A)
- Furthermore, histamine H2 receptor antagonists (H2RAs) are suggested as an alternative option to reduce the recurrence rate of LDA-related peptic ulcers. (Recommendation: weak, 100% agreed, evidence level C)
- For individuals without a history of ulcers who are at risk of developing LDA-related peptic ulcers, proton pump inhibitors (PPIs) are recommended as a means of primary prevention. (Recommendation: strong, 82% agreed, evidence level A)
- Compared to nonselective NSAIDs, COX-2 selective inhibitors decrease the risk of peptic ulcers and bleeding in patients who are taking low-dose aspirin (LDA). (Recommendation: strong, 100% agreed, evidence level A)
- To prevent gastric injury in patients who have a moderate or lower risk of peptic ulcers and require both LDA and NSAIDs, it is recommended to use celecoxib in combination with proton pump inhibitors (PPIs). (Recommendation: strong, 100% agreed, evidence level A)

- To prevent the recurrence of peptic ulcers after NSAID treatment in patients who are also taking low-dose aspirin (LDA), it is recommended to use celecoxib along with proton pump inhibitors (PPIs). (Recommendation: strong, 100% agreed, evidence level A)

1.2.5 Perforated and Bleeding Peptic Ulcer: World Society of Emergency Surgery (WSES) Guidelines (2020)

The World Society of Emergency Surgery (WSES) guidelines on the diagnosis and management of on perforated and bleeding peptic ulcer (2020)[9] introduced a set of recommendations accompanied by a grading scheme, outlined as follows:

Table 15. Quality of Evidence and Strength of Recommendations

Quality of Evidence	
High quality	A
Moderate quality	B
Low quality	C
Very low quality	D
Strength of Recommendations	
Strong recommendation for using an intervention	1
Weak recommendation for using an intervention	2
Weak recommendation against using an intervention	2
Strong recommendation against using an intervention	1

I. Perforated Peptic Ulcer

Diagnosis

- For individuals who are suspected of having gastroduodenal perforation, we advise conducting standard laboratory tests and arterial blood gas analysis as a regular practice. (strong recommendation based on very low-quality evidences, 1D).
- For individuals experiencing an acute abdomen due to a suspected perforated peptic ulcer, our recommendation is to undergo a CT scan for imaging purposes. (Strong recommendation based on low quality evidences, 1C).
- For individuals experiencing an acute abdomen due to a suspected perforated peptic ulcer, we recommend initiating diagnostic assessment with a chest and abdominal X-ray as the first step, especially if a CT scan is not

readily accessible. (Strong recommendation based on low-quality evidences, 1C).

- In cases where imaging does not reveal free air, but there remains a persistent suspicion of a perforated peptic ulcer, we suggest further imaging using water-soluble contrast, either administered orally or through a nasogastric tube. (Weak recommendation based on very low-quality evidences, 2D).

Resuscitation

- We advise conducting a **swift assessment** and **timely identification** of patients who have sepsis associated with a perforated peptic ulcer. This proactive approach aims to prevent additional organ failure and decrease the likelihood of mortality. (strong recommendation based on moderate-quality evidences, 1B).
- We recommend considering the use of **scoring systems** such as the Sequential Organ Failure Assessment (SOFA) and the Quick Sequential Organ Failure Assessment (qSOFA) to gauge and evaluate the severity of the disease in individuals diagnosed with a perforated peptic ulcer. (Weak recommendation based on low-quality evidences, 2 C).
- For unstable patients diagnosed with a perforated peptic ulcer, we strongly advise immediate resuscitation to reduce mortality. (strong recommendation based on low quality evidences, 1C).
- In cases of unstable patients with a perforated peptic ulcer, we recommend restoring physiological parameters to include a mean arterial pressure of at least 65 mmHg, a urine output of at least 0.5 ml/kg/h, and normalization of lactate levels. (strong recommendation based on low-quality evidences,1C).
- We suggest employing various types of hemodynamic monitoring, whether invasive or non-invasive, to optimize fluid and vasopressor therapy and tailor the resuscitation strategy to the individual patient. (strong recommendation based on low quality evidences, 1C).
- For individuals with a perforated peptic ulcer, we recommend caution against routinely opting for non-operative management. Instead, non-operative management (NOM) should only be contemplated in highly specific cases where it has been verified through a water-soluble contrast study that the perforation has naturally sealed. (weak recommendation based on low-quality evidences, 2C).
- For individuals diagnosed with a perforated peptic ulcer, we recommend refraining from using endoscopic treatments like clipping, sealing with fibrin

glue, or employing stents. (Weak recommendation based on low-quality evidences, 2C)

Surgery

- For individuals diagnosed with a perforated peptic ulcer and displaying substantial pneumoperitoneum, extraluminal contrast leakage, or peritonitis symptoms, we strongly advise pursuing operative treatment. (Strong recommendation based on low-quality evidences, 1C)
- Furthermore, we recommend conducting surgery at the earliest opportunity, particularly in cases of delayed presentation and in patients aged over 70 years old. (strong recommendation based on moderate-quality evidences, 1B)
- For stable patients with a perforated peptic ulcer, we recommend considering a laparoscopic approach. However, in cases where the necessary laparoscopic expertise and equipment are not available, we advise opting for an open surgical approach. (weak recommendation based on moderate-quality evidences, 2B).
- For patients with a perforated peptic ulcer who are in an unstable condition, we strongly recommend undergoing open surgery. (strong recommendation based on very low-quality of evidences, 1D).
- For patients who have a perforated peptic ulcer measuring less than 2 cm, our suggestion is to proceed with primary repair. However, there is insufficient evidence to make a definitive recommendation regarding whether the use of an omental patch can offer additional protection for the repair in such cases. (weak recommendation based on low-quality evidences, 2C)
- For the treatment of perforated peptic ulcers larger than 2 cm, we propose a personalized approach, taking into account the specific location of the ulcer. When dealing with sizable gastric ulcers that raise concerns about potential malignancy, we recommend considering resection, with the inclusion of contextual operative frozen pathologic examination whenever it is feasible. In the case of substantial duodenal ulcers, we advise evaluating the necessity for resection or repair, potentially with or without pyloric exclusion and external bile drainage. Duodenostomy should be reserved for extremely rare and exceptional circumstances. (weak recommendations based on very low-quality evidences, 2D).
- For patients suffering from septic shock as a result of a perforated peptic ulcer and exhibiting significant physiological distress, we recommend implementing a damage control strategy. (weak recommendation based on very low-quality of evidences, 2D)

Antimicrobial therapy

- For patients diagnosed with a perforated peptic ulcer, we advise administering broad-spectrum antibiotics. (strong recommendation based on low-quality evidences, 1C)
- We recommend collecting samples for microbiological analysis, including both bacteria and fungi, from all patients undergoing surgery, followed by appropriate adjustments to antibiotic therapy based on the results. (strong recommendation based on low-quality evidences, 1C)
- We recommend against routinely administering antifungal agents as standard empiric therapy for patients with perforated peptic ulcers. Instead, antifungal treatment should be considered for patients at high risk of fungal infection, such as those who are immunocompromised, elderly, have comorbidities, experienced prolonged ICU stays, or have unresolved intra-abdominal infections. (weak recommendation based on low-quality evidences, 2C)
- For patients with perforated peptic ulcers, we recommend initiating an empiric broad-spectrum antibiotic regimen as early as possible. This regimen should target a combination of Gram-negative, Gram-positive, and anaerobic bacteria. Ideally, this treatment should be initiated after peritoneal fluid has been collected for analysis. (Strong recommendation based on low-quality evidences, 1C)
- For patients with perforated peptic ulcers, we recommend considering a short-course antibiotic therapy lasting 3 to 5 days or until inflammatory markers return to normal levels. (weak recommendation based on low-quality evidences, 2C).

II. Bleeding peptic ulcer

Diagnosis

- For patients suspected to have a bleeding peptic ulcer, we advise conducting blood-typing, hemoglobin and hematocrit measurements, electrolyte assessments, and coagulation evaluations. (strong recommendation based on very low-quality evidences, 1D).
- When endoscopy is not readily available for patients with suspected bleeding peptic ulcers, we recommend considering a contrast-enhanced CT scan as an alternative diagnostic approach. (weak recommendation based on very low-quality evidences, 2D)
- For patients with suspected bleeding peptic ulcers, we strongly recommend conducting an endoscopy as promptly as possible, particularly in high-risk individuals. (strong recommendation based on low-quality evidences, 1C).

- We recommend using recent hemorrhage stigmata observed during endoscopy as a guide for making management decisions because they can serve as predictors of the risk of future bleeding. (strong recommendation based on low-quality evidences, 1C).

Resuscitation

- We recommend a swift and thorough evaluation by both surgical and medical teams for patients with bleeding peptic ulcers. This approach aims to prevent further bleeding and reduce mortality. (strong recommendation based on very low-quality evidences, 1D).
- We recommend evaluating multiple factors, including symptoms, signs, and laboratory findings, to assess the stability or instability of patients with bleeding peptic ulcers when they are referred to the emergency department (ED). (strong recommendation based on low quality evidences, 1C).
- In patients with bleeding peptic ulcers, we recommend considering the evaluation of patients using the Rockall and Glasgow-Blatchford scoring systems. These scoring systems can help assess the severity of the disease and guide appropriate therapy. (weak recommendation based on low-quality evidences, 1C).
- We recommend utilizing resuscitation targets that are akin to those employed in damage control resuscitation for patients with bleeding peptic ulcers. (weak recommendation based on low-quality evidences, 1C).
- For patients with bleeding peptic ulcers, we recommend maintaining a hemoglobin (Hb) level of at least greater than 7 g/dl during the resuscitation phase. (strong recommendation based on moderate-quality evidences, 1B).

Non-operative management—endoscopic treatment

- For patients experiencing bleeding peptic ulcers, our primary recommendation following endoscopy is to opt for non-operative management as the initial approach. (strong recommendation based on low-quality evidences, 1C).
- In patients with bleeding peptic ulcers, we recommend the use of endoscopic treatment to achieve hemostasis. This approach helps reduce the risk of re-bleeding, the necessity for surgery, and mortality. (strong recommendation based on low-quality evidences, 1C)
- We recommend stratifying patients based on the Blatchford score and adopting a management approach that takes into account their individual risk levels. (weak recommendation based on very low-quality evidences, 2D)

    - For patients classified as being in the very low-risk group, we recommend considering outpatient endoscopy as a suitable approach. (weak recommendation based on low-quality evidences, 2C).
    - For patients classified as low-risk, we recommend early inpatient endoscopy, ideally within 24 hours of admission. (strong recommendation based on low-quality evidences, 1C).
    - For patients categorized as high-risk, we strongly recommend urgent inpatient endoscopy, preferably within 12 hours of admission. (strong recommendation based on low-quality evidences, 1C)
- For patients with spurting ulcers (Forrest 1a), oozing ulcers (Forrest 1b), and ulcers with non-bleeding visible vessels (Forrest 2a), it is recommended to perform endoscopic hemostasis. (strong recommendation based on low-quality evidences, 1C).
- For patients with bleeding peptic ulcers, we recommend considering a dual-modality approach for endoscopic hemostasis. (weak recommendation based on moderate-quality evidences, 2B)
- In cases of bleeding peptic ulcers, it is advisable to consider Doppler probe-guided endoscopic hemostasis if the expertise for this technique is available.
- In patients with bleeding peptic ulcers, we recommend considering the administration of erythromycin before performing an endoscopy. (weak recommendation based on moderate-quality evidences, 2B).
- For patients with bleeding peptic ulcers, we recommend initiating proton pump inhibitor (PPI) therapy as soon as possible. (weak recommendation based on moderate-quality evidences, 2B).
- Following successful endoscopic hemostasis in patients with bleeding peptic ulcers, we recommend administering a high-dose proton pump inhibitor (PPI) as a continuous infusion for the initial 72 hours. (weak recommendation based on moderate-quality evidences, 2B)
- For patients with bleeding peptic ulcers who have undergone endoscopic treatment, we recommend using a proton pump inhibitor (PPI) for a duration of 6 to 8 weeks. Long-term PPI use is not recommended unless the patient continues to use nonsteroidal anti-inflammatory drugs (NSAIDs) or has other specific indications for extended PPI therapy. (strong recommendation based on moderate-quality evidences, 1B)
- For patients experiencing recurrent bleeding from a peptic ulcer, we recommend considering endoscopy as the initial and primary treatment option. (strong recommendation based on low-quality evidences, 1C).

- In cases of recurrent bleeding, we recommend considering transcatheter angioembolization as an alternative option, particularly when the necessary resources and expertise are available. (weak recommendation based on very low-quality evidences, 2D).

Angiography, embolization

- For patients with bleeding peptic ulcers, we recommend considering angiography for diagnostic purposes as a secondary investigative option when endoscopy has yielded negative results. (weak recommendation based on low-quality evidences, 2C).
- There is insufficient evidence to provide a recommendation regarding the use of provocation angiography in the management of bleeding peptic ulcers.
- For hemodynamically stable patients with bleeding peptic ulcers, when endoscopic hemostasis has failed twice or is not possible or feasible, we recommend considering angiography with angioembolization as an alternative approach, provided that the necessary technical skills and equipment are available. (weak recommendation based on very low-quality evidences, 2D).
- We advise against the routine use of angioembolization in unstable patients with bleeding peptic ulcers. Angioembolization in unstable patients should be considered only in selected cases and within facilities that are equipped to handle such procedures safely and effectively. (weak recommendation based on very low-quality evidences, 2D).
- For patients experiencing rebleeding from a peptic ulcer, we recommend considering angioembolization as a viable and feasible option. (weak recommendation based on low-quality evidences, 2C).
- Numerous techniques and materials are available for use in the embolization of bleeding duodenal ulcer disease. We recommend adopting a customized approach guided by a multidisciplinary team that takes into account the patient's individual factors, the nature of the pathology, and environmental considerations. (weak recommendation based on low-quality evidences, 2C)

Surgery

- For patients with bleeding peptic ulcers, if repeated endoscopy fails, we recommend considering surgical hemostasis as the next step. Alternatively, if angiographic embolization is immediately available and the necessary skills are present, it can be a suitable option. However, in patients who have hypotension, hemodynamic instability, or ulcers larger than 2 cm at the initial endoscopy, we recommend surgical intervention without the need for

repeated endoscopy. (strong recommendation based on very low-quality evidences, 1D)

- For patients with refractory bleeding peptic ulcers, we recommend considering surgical intervention with open surgery as the appropriate course of action. (weak recommendation based on very low-quality evidences, 2D).
- For patients who have undergone surgery for a bleeding peptic ulcer, we suggest performing intra-operative endoscopy. This procedure can help in precisely identifying and localizing the bleeding site during the surgery. (weak recommendation based on very low-quality evidences, 2D).
- We recommend selecting the surgical procedure based on factors such as the location and extent of the ulcer and the specific characteristics of the bleeding vessel. This approach allows for a more tailored and effective treatment strategy. (weak recommendation based on low-quality evidences, 2C).
- The recommendation for an immediate or delayed biopsy depends on the clinical context and the specific circumstances of the case. (weak recommendation based on low-quality evidences, 2C).
- For patients with hemorrhagic shock and signs of severe physiological derangement, we recommend considering damage control surgery. This approach is aimed at rapidly addressing the bleeding and facilitating prompt admission to the intensive care unit (ICU) for further management. (weak recommendation based on very low-quality evidences, 2D).

Antimicrobial therapy

- Empirical antimicrobial therapy is not recommended for patients with bleeding peptic ulcers. (strong recommendation based on low-quality evidences, 1C).
- We recommend conducting Helicobacter pylori testing in all patients diagnosed with bleeding peptic ulcers. (strong recommendation based on low-quality evidences, 1C).

Section 2.0 Drug Therapy in Dyspepsia and Non-Infectious Peptic Ulcer

This section comprises three subsections: the first contains the newly recommended drugs, the second covers drug modifications, the third outlines the drugs that have been withdrawn from the market, and the fourth details other drugs that are not currently SFDA registered as of June 2023 (it is advised to refer to the SFDA drug list website[10] for the most recent updates regarding drug registration).

2.2 Additions

After January 2020, there have been no new drugs for dyspepsia and non-infectious peptic ulcer that have received SFDA approval.

2.3 Modifications

- For **H2RAs** (nizatidine): **CU (Concurrent use)** removed since they can be used as monotherapy.
- PA (Prior Authorization) was replaced by MD (Physician Specialty) for metoclopramide and domperidone:
    - Metoclopramide: should be prescribed by a gastroenterologist who should monitor and clear the risks of tardive dyskinesia or dystonia, verify if there are any drug-drug interactions, and should confirm to be used as a step therapy in case of undiagnosed and functional dyspepsia in patients < 60 years who are not responding to PPI or H. Pylori eradication therapy.
    - Domperidone: should be prescribed by a specialist to confirm its use only in patients with gastroparesis.

2.3 Delisting

Ranitidine should be delisted from the SFDA list since it was withdrawn from the market and is no longer SFDA registered.

Cimetidine is no longer SFDA registered and is delisted as well.

Alternatives still registered include famotidine and nizatidine.

2.4 Other Drugs

On December 17, 2021, **glycopyrrolate** ODT orally disintegrating tablets (not SFDA registered), in adults to reduce symptoms of a peptic ulcer as an adjunct to treatment of peptic ulcer[11].

Section 3.0 Key Recommendations Synthesis

- It is highly recommended that individuals diagnosed with functional dyspepsia (FD) are encouraged to participate in consistent aerobic exercise. (Recommendation: Strong, Quality of evidence: Very low)[3]
- The evidence available is insufficient to support the recommendation of specific dietary interventions, such as a low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) diet, for the management of FD. (Recommendation: Weak, Quality of evidence: Very low)[3]
- Lifestyle and dietary adjustments have demonstrated effectiveness in the management of FD. [Recommendation: Strong (100%), Evidence level: B] [7]
- H2-RAcan be considered as a potential treatment choice for functional dyspepsia (FD), and they are generally well tolerated. (Recommendation: Weak, Quality of evidence: Low) [3]
- PPIs are an effective treatment for FD. There is no observed dose-response relationship, so the minimum effective dose should be utilized. PPIs are well tolerated. (Recommendation: Strong, Quality of evidence: High)[3]
- Tricyclic antidepressants and anxiolytics, including tandospirone (*not SFDA registered*), have demonstrated effectiveness in the treatment of functional dyspepsia (FD) and have been proposed as potential therapeutic choices for patients with FD. [Recommendation: Weak (92%), Evidence level A for tricyclic antidepressants and B for anxiolytics such as tandospirone][7]
- Acotiamide (*not SFDA registered*), an inhibitor of acetylcholinesterase (AChE), has proven to be valuable in treating specific conditions and is highly recommended for use. [Recommendation Strong (100%), evidence level A] [2]
- The efficacy of antacids, prostaglandin analogs (such as misoprostol), and gastroprotective agents (like sucralfate and rebamipide) in treating functional dyspepsia (FD) is still uncertain. [Recommendation NA, evidence level B][2]
- Before conducting endoscopy in patients with acute upper gastrointestinal bleeding (UGIH), it is suggested to contemplate the use of a high dose of intravenous proton pump inhibitor (PPI) therapy. This strategy aims to lessen

the severity of endoscopic findings and potentially reduce the need for endoscopic intervention. (Weak recommendation, high quality evidence) [4]

- In patients with previous ulcer bleeding who require a non-steroidal anti-inflammatory drug (NSAID), the combination of a PPI and a COX-2 inhibitor is recommended to reduce the risk for recurrent bleeding from that of Cyclooxygenase-2 (COX-2) inhibitors alone.[6]
- According to ESGE guidelines, patients with acute upper gastrointestinal bleeding (UGIH) who are solely on low-dose aspirin for secondary cardiovascular prophylaxis should not stop taking aspirin. In case aspirin is temporarily interrupted for any reason, it should be resumed as soon as possible, preferably within 3-5 days. (Strong recommendation, moderate quality evidence)[4]
- For patients undergoing dual antiplatelet therapy (DAPT) for secondary cardiovascular prophylaxis, aspirin should not be interrupted during acute UGIH. However, the second antiplatelet agent should be paused but restarted promptly, preferably within 5 days. It is advisable to seek cardiology consultation. (Strong recommendation, low quality evidence)
- For nonselective NSAID-induced ulcer treatment, there is a strong recommendation to cease the usage of NSAIDs and instead, opt for anti-ulcer drugs. (Recommendation: strong, 100% agreed, evidence level A)[5].
- For nonselective NSAID-induced ulcer treatment, if discontinuing NSAIDs is not feasible, the first-line treatment involves administering proton pump inhibitors (PPIs). (Recommendation: strong, 100% agreed, evidence level A)[5].
- To prevent peptic ulcers caused by continuous low-dose aspirin (LDA) therapy, it is strongly advised to use proton pump inhibitors (PPIs) concurrently. (Recommendation: strong, 100% agreed, evidence level A)[5].
- PPIs or H2-RAs (histamine-2 receptor antagonists) are recommended to lower the occurrence and prevalence of LDA-related peptic ulcers. (Recommendation: strong, 100% agreed, evidence level A)[5].
- It is highly recommended to use proton pump inhibitors (PPIs) alongside continuous low-dose aspirin (LDA) therapy to prevent peptic ulcers caused by LDA.
- For patients with bleeding peptic ulcers, we recommend initiating proton pump inhibitor (PPI) therapy as soon as possible. (weak recommendation based on moderate-quality evidences, 2B)[9].

- For patients diagnosed with a perforated peptic ulcer, we advise administering broad-spectrum antibiotics. (strong recommendation based on low-quality evidences, 1C)[9].

Section 4.0 Conclusion

This report serves as **an annex to the previous Dyspepsia and Non-infectious Peptic ulcer report** and aims to provide recommendations to aid in the management of Dyspepsia and Non-infectious Peptic ulcer report. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Dyspepsia and Non-infectious Peptic ulcer report. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

Section 5.0 References

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Dyspepsia and Non-infectious Peptic Ulcer Scope

2020	Changes	2023	Rationale
Section 1.0 Dyspepsia and Non-infectious Peptic Ulcer Clinical Guidelines			
American college of Gastroenterology Guidelines: Dyspepsia Management (2017)	N/A		
European Society of Gastrointestinal Endoscopy Guidelines of Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage (2015)	Updated	Endoscopic diagnosis and management of nonvariceal upper gastrointestinal hemorrhage (NVUGIH): European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2021[4]	• ESGE advises that patients with acute upper gastrointestinal bleeding (UGIH) who are taking low-dose aspirin as the sole therapy for secondary cardiovascular prophylaxis should not discontinue aspirin. If, for any reason, aspirin is temporarily interrupted, it should be resumed as soon as possible, preferably • For patients on dual antiplatelet therapy (DAPT) for secondary cardiovascular prophylaxis, aspirin should not be interrupted during acute UGIH. The second antiplatelet agent should be interrupted but restarted as soon as possible, preferably within 5 days. Cardiology consultation is suggested. • For patients on vitamin K antagonists (VKAs) with acute UGIH, the anticoagulant should be withheld.

			• In patients on VKAs with acute UGIH and hemodynamic instability, low-dose vitamin K supplemented with intravenous prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP) can be administered if PCC is not available. However, this should not delay endoscopy or, if required, endoscopic hemostasis. • For patients on direct oral anticoagulants (DOAC) with acute UGIH, the anticoagulant should be withheld, and endoscopy should not be delayed. In patients with severe ongoing bleeding, consideration can be given to the use of a DOAC reversal agent or intravenous PCC. • ESGE recommends that in patients who need to continue anticoagulation therapy after experiencing acute non-variceal upper gastrointestinal bleeding (NVUGIH), such as peptic ulcer hemorrhage, anticoagulation should be resumed promptly once the bleeding has been controlled. Ideally, this should occur within or shortly after 7 days of the bleeding event, considering the thromboembolic risk. It is important to consider the

			rapid onset of action of direct oral anticoagulants (DOACs) in comparison to vitamin K antagonists (VKAs) in this context. • ESGE recommends PPIs for gastroduodenal prophylaxis in patients requiring ongoing anticoagulation and with a history of NVUGIH.
NICE Guidelines for Managing peptic ulcer disease in adults (2019)	N/A		
NICE Guidelines for Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management (2019)	N/A		
International Consensus Recommendations on the Management of Patients with Non-variceal Upper Gastrointestinal Bleeding (2010)	Updated	Management of Nonvariceal Upper Gastrointestinal Bleeding: Guideline Recommendations From the International Consensus Group (2021)[6]	• The routine use of promotility agents before endoscopy to enhance the diagnostic yield is not recommended. • Pre-endoscopic PPI therapy may be considered to reduce the severity of the endoscopic lesion and decrease the need for endoscopic intervention but should not delay endoscopy.

			• H2-RAs are not recommended for patients with acute ulcer bleeding • In patients with acute ulcer bleeding, the use of somatostatin and octreotide is not routinely recommended. • In patients with bleeding ulcers displaying high-risk stigmata who have undergone successful endoscopic therapy, it is recommended to utilize intravenous proton pump inhibitor (PPI) therapy, administered via a loading dose followed by a continuous intravenous infusion. This approach is preferred over no treatment or the use of H2 receptor antagonists (H2-RAs). • In patients who have high-risk ulcer bleeding, requiring endoscopic therapy and 3 days of high-dose proton pump inhibitor (PPI) therapy, it is suggested to use twice-daily oral PPIs (compared to once-daily) for a duration of 14 days, followed by a once-daily regimen. • In patients who are on low-dose aspirin (ASA) therapy and experience acute ulcer bleeding, it is recommended to resume ASA therapy once the risk of cardiovascular complications is deemed to

			be greater than the risk of bleeding. • In patients who have previously experienced ulcer bleeding and are undergoing cardiovascular prophylaxis with either single or dual antiplatelet therapy, it is recommended to use proton pump inhibitor (PPI) therapy rather than no PPI therapy. • For patients who have previously experienced ulcer bleeding and require ongoing cardiovascular prophylaxis with anticoagulant therapy such as vitamin K antagonists or direct oral anticoagulants (DOACs), it is recommended to use proton pump inhibitor (PPI) therapy rather than no PPI therapy.
	Missing Guideline	British Society of Gastroenterology guidelines on the management of functional dyspepsia (2022)[3]	• It is strongly recommended to offer empirical acid suppression therapy to patients without H. pylori infection. • Referral of patients with functional dyspepsia (FD) to gastroenterology in secondary care is appropriate in cases of diagnostic uncertainty, severe symptoms, treatment resistance, or patient request for specialist opinion. • Routine gastric emptying testing or 24-hour pH monitoring is not

			recommended for patients with typical symptoms of FD. • Ideally, patients with FD referred to secondary care should be managed in a specialized clinic, with access to healthcare professionals knowledgeable in the field, dietetic and lifestyle support, and various effective treatment options including medications and gut-brain behavioral therapies. • In the absence of upper gastrointestinal alarm symptoms or signs, it is recommended that clinicians diagnose functional dyspepsia (FD) when patients present with bothersome epigastric pain or burning, early satiation, and/or postprandial fullness persisting for more than 8 weeks. • It is strongly recommended that all patients with functional dyspepsia (FD) are advised to engage in regular aerobic exercise. • There is insufficient evidence to support the recommendation of specific dietary therapies, including a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs), for FD. • H2-RAmay be an effective treatment option for FD, and

			they are generally well tolerated. • PPIs are effective in treating FD. There doesn't appear to be a dose-response relationship, so the lowest effective dose should be used. PPIs are well tolerated. • Some prokinetic drugs may be effective in treating FD, but their efficacy varies based on the drug class. Most prokinetic drugs are well tolerated. **Second-line treatment of FD** • Tricyclic antidepressants (TCAs) used as gut-brain neuromodulators are an effective treatment option for functional dyspepsia (FD) when other treatments have not been successful. They can be initiated in either primary or secondary care settings, but it is important to provide a clear explanation to patients regarding the reason for their use and to discuss potential side effects. TCAs should be started at a low dose, such as 10 mg of amitriptyline taken once daily, and the dosage should be gradually increased up to a maximum of 30-50 mg once daily. • As a second-line treatment for functional dyspepsia (FD), antipsychotics such as sulpiride (100 mg four times a day) or levosulpiride (25 mg

			three times a day) may potentially be effective. However, careful explanation regarding their use and counseling on potential side effects are necessary. • There is a lack of evidence supporting the effectiveness of selective serotonin reuptake inhibitors (SSRIs) used as gut-brain neuromodulators as a second-line treatment for global symptoms in functional dyspepsia (FD). • There is insufficient evidence to support the effectiveness of serotonin norepinephrine reuptake inhibitors (SNRIs) used as gut-brain neuromodulators as a second-line treatment for global symptoms in functional dyspepsia (FD). However, considering their efficacy in other chronic painful conditions, further trials are needed to evaluate the potential effectiveness of these drugs in FD. • Tandospirone (10 mg three times a day) may be an effective second-line treatment for FD, but there is insufficient evidence to support the efficacy of other 5-hydroxytryptamine-1A agonists like buspirone (10 mg three times a day). Additional trials for these drugs are needed.

			• Pregabalin (75 mg once daily) may be effective as a second-line treatment for FD, but further randomized controlled trials (RCTs) are required. Given its controlled drug status, it is advised to use pregabalin only in specialist settings. • Mirtazapine (15 mg once daily) may be an effective second-line treatment for patients with FD experiencing early satiation and weight loss. However, more RCTs are needed to provide stronger evidence. **Gut–brain behavioral therapies in FD** • Interpersonal psychodynamic informed psychotherapy may potentially be an effective treatment for global symptoms in functional dyspepsia (FD). • Cognitive-behavioral therapy (CBT) and metacognitive therapy are suggested as potential treatments for global symptoms in FD. • Stress management approaches are also considered as potential treatments for global symptoms in FD. • Hypnotherapy may be an effective treatment for global symptoms in FD. **Management of severe or refractory FD**

			• It is strongly recommended to involve a multidisciplinary support team for patients with severe or refractory functional dyspepsia (FD). • To minimize iatrogenic harm, opioids and surgery should be avoided in patients with severe or refractory FD. • Patients with severe or refractory FD who experience weight loss and food restriction should be evaluated for eating disorders and disordered eating, including avoidant restrictive food intake disorder (ARFID). • Early involvement of a dietitian is recommended for patients with severe or refractory FD to prevent an overly restrictive diet.
	Missing Guideline	The Japanese Society of Gastroenterology (JSGE) Evidence-based clinical practice guidelines for peptic ulcer disease 2020[5]	• It is strongly recommended to continue aspirin for conditions with a high risk of thromboembolic events. • It is suggested to switch antiplatelet agents to aspirin in patients with conditions at high risk of thromboembolic events. • It is also suggested to temporarily suspend antiplatelet agents, except for patients at high risk of thromboembolic events. • In patients undergoing endoscopic hemostasis, it is strongly recommended to suspend warfarin if necessary.

			If warfarin is discontinued, heparin can be used or warfarin can be resumed once hemostasis is established. • For patients receiving direct oral anticoagulants (DOACs) and undergoing endoscopic hemostasis, it is weakly suggested to resume DOACs early (within 1-2 days) after confirming hemostasis. • In patients on both antiplatelet agents and warfarin, it is suggested to switch antiplatelet agents to aspirin or cilostazol, or to continue warfarin with appropriate prothrombin time-international normalized ratio (PT-INR), or to switch warfarin to heparin. • In patients who are taking dual antiplatelet agents, it is recommended to continue with aspirin alone. • To enhance treatment outcomes, it is recommended to administer proton pump inhibitors (PPIs) following endoscopic treatment for hemorrhagic peptic ulcers. • For patients on dual antiplatelet therapy (DAPT), it is strongly recommended to use proton pump inhibitors (PPIs) in combination to prevent upper gastrointestinal bleeding (UGIB).

			• If patients are taking warfarin along with antiplatelet drugs or non-steroidal anti-inflammatory drugs (NSAIDs), it is suggested to use PPIs to prevent UGIB. **First-line treatment for the initial non-eradication treatment of gastric and duodenal ulcers** • It is strongly recommended to use either proton pump inhibitors (PPIs) or potassium-competitive acid blockers (P-CABs). • If PPIs and P-CABs are not suitable options, histamine-2 receptor antagonists (H2RAs) are recommended. • In cases where both PPIs and P-CABs are not feasible, the use of pirenzepine, sucralfate, and misoprostol is suggested. **Nonselective NSAID-induced ulcer treatment** • It is strongly recommended to discontinue the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and instead, administer anti-ulcer drugs. • If discontinuing NSAIDs is not possible, the first-line therapy is the administration of proton pump inhibitors (PPIs). • It is necessary and recommended to administer proton pump inhibitors (PPIs) for the prevention of NSAID-

			induced ulcers, even in patients with no prior history of ulcers. • To prevent ulcers induced by nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with a history of ulcers, proton pump inhibitors (PPIs) are recommended as the primary choice. Specifically, it is suggested that vonoprazan (VPZ), a type of PPI, be used for this purpose. • In cases where there has been bleeding from NSAID-induced ulcers in the past, it is recommended to administer a selective cyclooxygenase (COX)-2 inhibitor in combination with a PPI. • For patients who are taking a combination of nonsteroidal anti-inflammatory drugs (NSAIDs) and either glucocorticoids or antithrombotic drugs, it is advised to administer a selective cyclooxygenase-2 (COX-2) inhibitor as a preventive measure against ulcers. • Additionally, in elderly patients or those with severe complications, the use of proton pump inhibitors (PPIs) is recommended to prevent the occurrence of ulcers caused by NSAIDs.

			• COX-2 selective inhibitors are recommended for the prevention of NSAID-induced ulcers. • Patients who have a history of peptic ulcers or hemorrhage and are taking COX-2 selective inhibitors should be prescribed anti-ulcer agents for prevention. • On the other hand, patients who are taking COX-2 selective inhibitors but do not have a history of peptic ulcer are not recommended to receive preventive treatment with anti-ulcer agents. • It is recommended to use proton pump inhibitors (PPIs) alongside continuous low-dose aspirin (LDA) therapy to prevent peptic ulcers caused by LDA. • PPIs or H2RAs are recommended for the reduction of the incidence and prevalence of LDA-related peptic ulcers. • PPIs or VPZ is recommended for the reduction of the incidence and prevalence of LDA-related Peptic ulcer bleeding (PUB) • To lower the likelihood of recurrent LDA-related peptic ulcers, the use of proton pump inhibitors (PPIs) or vonoprazan (VPZ) is strongly recommended.

			• Furthermore, histamine H2 receptor antagonists (H2RAs) are suggested as an alternative option to reduce the recurrence rate of LDA-related peptic ulcers. • For individuals without a history of ulcers who are at risk of developing LDA-related peptic ulcers, proton pump inhibitors (PPIs) are recommended as a means of primary prevention. • Compared to nonselective NSAIDs, COX-2 selective inhibitors decrease the risk of peptic ulcers and bleeding in patients who are taking low-dose aspirin (LDA). • To prevent gastric injury in patients who have a moderate or lower risk of peptic ulcers and require both LDA and NSAIDs, it is recommended to use celecoxib in combination with proton pump inhibitors (PPIs). • To prevent the recurrence of peptic ulcers after NSAID treatment in patients who are also taking low-dose aspirin (LDA), it is recommended to use celecoxib along with proton pump inhibitors (PPIs). (Recommendation: strong, 100% agreed, evidence level A)

	Missing Guideline	The Japanese Society of Gastroenterology (JSGE) Evidence-based clinical practice guidelines for functional dyspepsia 2021[7]	**First-line treatment** • Modifications in lifestyle and diet have proven to be effective in managing functional dyspepsia (FD). • The treatment of functional dyspepsia (FD) can be effectively accomplished using proton pump inhibitors (PPIs) and histamine type 2 receptor antagonists (H2RAs). • Due to limited evidence available, the efficacy of potassium-competitive acid blockers (P-CABs) cannot be adequately evaluated. • Acotiamide, an acetylcholinesterase (AChE) inhibitor, has demonstrated usefulness in the treatment of certain conditions, and its use is recommended. • The Japanese herbal medicine rikkunshito is an effective treatment for FD, and its use is recommended. **Second line treatment** • Dopamine receptor antagonists have shown utility in clinical practice, and their use is suggested. • Similarly, serotonin-4 (5-HT4) receptor agonists have demonstrated usefulness, and their use is also suggested. • Tricyclic antidepressants and anxiolytics, such as tandospirone, have shown efficacy in treating functional

			dyspepsia (FD) and have been suggested as treatment options for FD patients. **Alternative or complementary therapy** • The effectiveness of antacids, prostaglandin analogs (e.g., misoprostol), and gastroprotective agents (e.g., sucralfate and rebamipide) as treatments for functional dyspepsia (FD) remains unclear. • The implementation of psychosomatic internal medical treatment has been proposed as an effective approach for managing FD.
	Missing Guideline	United European Gastroenterology (UEG) and European Society for Neurogastroenterology and Motility (ESNM) consensus on functional dyspepsia (2020)[8]	• Symptom improvement in functional dyspepsia (FD) can be achieved through dietary adjustments. • Proton pump inhibitor (PPI) therapy is considered the most suitable initial treatment for functional dyspepsia (FD). • PPI therapy is the most effective therapy for EPS. • Prokinetic therapy is an effective therapy for FD. • Prokinetic therapy is the most effective therapy for PDS. • Efficacy of prokinetics is not related to their enhancement of gastric emptying rate. • Itopride is effective for FD patients.

			• Mirtazapine is effective for post-prandial distress syndrome patients with weight loss. • 5-HT1A agonists (tandospirone, buspirone.) are effective for PDS. • Herbal therapies are effective for FD patients. • Tricyclic antidepressants (TCAs) are effective for EPS. • TCAs are effective for PDS. • TCAs are not effective for PDS. • Serotonin reuptake inhibitors are effective for FD. • Serotonin reuptake inhibitors are not effective for FD. • Serotonin noradrenaline reuptake inhibitors are effective for FD. • Serotonin noradrenaline reuptake inhibitors are not effective for FD. • Mindfulness is effective for FD patients. • In case of severe weight loss in FD, nutritional support may be needed.

Appendix C. MeSH Terms PubMed

Query	**Search Details**	**Filters**	**Results**
(((Dyspepsia[MeSH Terms]) OR (Dyspepsias[Title/Abstract])) OR (Indigestion[Title/Abstract]))	("dyspepsia"[MeSH Terms] OR "Dyspepsias"[Title/Abstract] OR "Indigestion"[Title/Abstract] OR	Guideline, in the last 5 years	5

OR (Indigestions[Title/Abstract])	"Indigestions"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))		

Appendix D. Treatment Algorithms

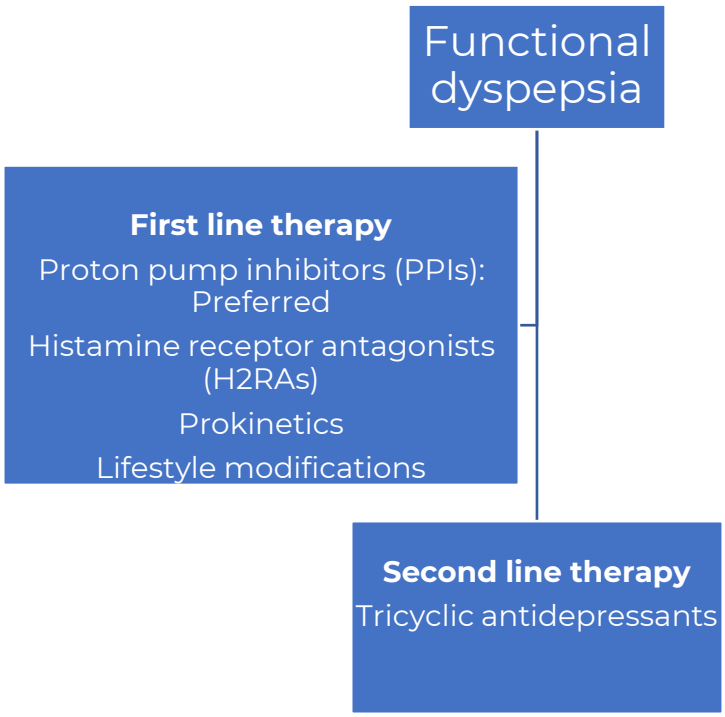

Figure 3. *Treatment Algorithm for Functional Dyspepsia*[2,3,7,8]

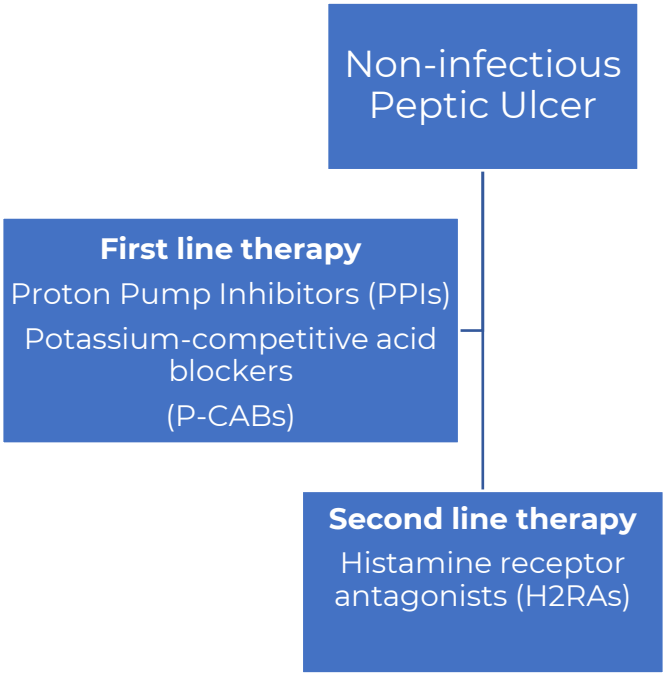

Figure 4. *Treatment Algorithm for Non-Infectious Peptic Ulcer*[5,6,9]