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Expert consensus on medication therapy for acid-related diseases

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ABSTRACT

Acid-related diseases (ARDs) are characterized by high incidence rates and significant disease burden. Excessive gastric acid secretion or heightened gastric acid sensitivity is the common pathogenesis of these conditions, leading to the widespread application of the principle of "treating different diseases with the same therapy" in medication management. With increasing concerns about the risks of inappropriate use of acid-suppressing drugs like proton pump inhibitors (PPIs), there is an urgent need to deepen the systematic understanding of medication therapy for acid-related diseases and to promote rational drug use. This consensus was developed by a multidisciplinary panel of experts in clinical medicine, pharmacy, and methodology. Based on evidence-based medicine, it provides a systematic elaboration on the classification of ARDs, therapeutic drugs, diagnostic methods, and pharmaceutical care services. Additionally, it offers consensus-based recommendations and management strategies for key clinical issues encountered in practice. The release of this consensus is of great significance for establishing a medication therapy management system and promoting rational drug use for acid-related diseases.

Acid-related diseases (ARDs) refer to a group of digestive disorders triggered by excessive gastric acid secretion, abnormal gastric acid exposure, or visceral hypersensitivity to acid. They encompass conditions such as gastroesophageal reflux disease (GERD), peptic ulcer (PU), and functional dyspepsia (FD), with the pathological essence being mucosal damage caused by acid attack or symptom occurrence due to abnormal acid perception.[1] At the epidemiological level, ARDs impose a heavy burden: approximately 13% of the global population experiences typical GERD symptoms (e.g., heartburn and regurgitation) ≥ 1 time per week, and 7.2% of adults suffer from functional dyspepsia. In China, the prevalence (95% confidence interval) of GERD, reflux esophagitis (RE), gastric ulcer (GU), duodenal ulcer (DU), and H. pylori infection was estimated to be 10.5%, 5.4%, 2.5%, 4.5%, and 41.5%, respectively. In addition, the prevalence of FD even exceeds 35.0%, and it often overlaps with other gastrointestinal disorders.[2–7] These conditions are frequently recurrent, not only impairing patients' quality of life but also is associated with an increased risk of gastrointestinal malignancies, thus imposing a significant public health challenge.[4,7] However, current clinical practice is confronted with four major challenges: First, the widely prescribed drug proton pump inhibitors (PPIs) have limitations such as nocturnal acid breakthrough (NAB) and efficacy variability influenced by Cytochrome P450 2C19 (CYP2C19) gene polymorphism.[8,9] Safety concerns are increasingly drawing widespread attention, as long-term exposure may be associated with increased risks of fractures, kidney injury, and infections.[10,11] Second, although acid suppression remains the cornerstone "one-size-fits-all" therapeutic principle for ARDs, the prevalent use of combination and multi-drug regimens increases the risk of clinically significant drug-drug interactions, exemplified by cisapride-associated cardiotoxicity.[12] Third, most existing domestic clinical consensus focus on single diseases or specific drug classes (e.g., PPIs), lack evidence-based support, and thus fail to systematically guide individualized combination therapy.[13] Fourth, there remains insufficient medical evidence to support the use of PPIs for acid-suppressing therapy in special populations, such as children and pregnant women.

Against this backdrop, the development of this consensus holds crucial clinical value. By integrating multidisciplinary expert opinions and evidence-based medicine findings, a systematic drug treatment system for ARDs, including domestic potassium-competitive acid blockers (P-CABs), such as keipulasheng,[14] was established for the first time. This consensus not only standardizes the treatment path based on the principle of "taking acid suppression as the core and implementing individualized combination medication",[4] but also provides pharmaceutical service countermeasures to address drug interactions and long-term safety risks.[12] This will fill the gap in evidence-based medicine in the diagnosis and treatment of ARDs, optimize the allocation of medical resources, guide the drug treatment of ARDs, and improve the prognosis of patients.

Consensus development methodology

Consensus development working group and conflict of interest management

Based on primary functions, the consensus development working group was divided into the following roles: Chief Experts, the Consensus Steering Committee, the Evidence Evaluation Group, the Consensus Panel, the External Review Panel, and the Secretariat. The

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group comprised experts in pharmacy, gastroenterology, and evidence-based medicine. All members of the consensus development working group completed a conflict of interest disclosure form, declaring no financial or non-financial conflicts of interest related to this consensus.

Consensus registration

At the initiation of this consensus, the working group drafted a protocol and completed the registration with the International Practice Guidelines Registry Platform (http://www.guidelines-registry.cn/, Registration No: PREPARE-2025CN153).

Target users and target population

The target users of this consensus are relevant healthcare professionals, including gastroenterologists and clinical pharmacists, at various levels of medical institutions. The target population for the recommendations is patients with acid-related disorders.

Formulation of clinical questions

The formulation of clinical questions for this consensus involved a three-step process: (1) The Evidence Evaluation Group conducted a comprehensive review of domestic and international guidance documents, such as guidelines and consensus statements on acid-related disorders. Combined with expert consultations, 57 clinical questions were initially collected. (2) A questionnaire survey was administered to gastroenterologists and clinical pharmacists. Through merging and deduplication, the 57 questions were consolidated into 17 questions. (3) Based on the previous two steps, a meeting to finalize the clinical questions was held on March 13, 2025. The consensus experts discussed and revised the questions through two rounds of the Delphi method. The questions were then reviewed and approved by the Steering Committee, ultimately finalizing the inclusion of 7 clinical questions.

Evidence search and screening

Following the evidence-based medicine PICO principle (P: Population/Patient, I: Intervention, C: Control/Comparison, O: Outcome), the 7 clinical questions included in the consensus were structured. Search strategies were subsequently developed. The specific databases searched included English-language databases such as PubMed, Embase, the Cochrane Library, and Web of Science, as well as Chinese databases including China National Knowledge Infrastructure (CNKI), Wanfang Data Knowledge Service Platform, VIP Information Network, and the China Biomedical Literature Database (SinoMed). Results from Clinicaltrials.gov were also searched. Additionally, a snowball search was conducted on the references of relevant reviews, systematic reviews or meta-analyses, guidelines, management recommendations, and consensus statements. Included document types were guidance documents (guidelines/consensus), systematic reviews (or meta-analyses), randomized controlled trials, and cohort studies.

Evidence quality assessment and grading

Different quality assessment tools were used to evaluate different types of evidence. The quality of included guidelines/consensus was assessed using the AGREE II instrument. The quality of included systematic reviews or meta-analyses was evaluated using AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews 2).[15] The risk of bias in included randomized controlled trials was assessed using the Cochrane Collaboration's risk of bias (ROB) tool.[16] The methodological quality of cohort studies was evaluated using the Newcastle-Ottawa Scale (NOS).[17] The evaluation process was conducted independently by two reviewers; any disagreements were resolved through discussion or by consulting a third party.

Evidence quality was graded using the GRADE approach,[18] which classifies evidence quality into four levels: high, moderate, low, and very low.

Formulation of recommendations

For each clinical question, the Evidence Evaluation Group prepared evidence summary tables detailing the available evidence from domestic and international sources. Draft recommendations were formulated after review by clinical experts and methodologists. On June 14, 2025, the consensus working group convened a consensus meeting to discuss the recommendations. The Consensus Panel, referencing the GRADE strength of recommendations, fully weighed the benefits and harms, considered patient values and preferences as well as accessibility, and refined the recommendations through discussions based on the Delphi method.

Consensus writing and external review

After consensus was reached on the recommendations, the Evidence Evaluation Group drafted the initial consensus manuscript following the RIGHT (Reporting Items for practice Guidelines in HealThcare)[19] statement. Upon completion, the draft was submitted to the External Review Panel (members not directly involved in the development process) for full-text review and feedback. The Evidence Evaluation Group revised the draft based on the collected external review comments. The Steering Committee further discussed, revised, and refined the full text, ultimately finalizing the recommendations and forming the final version of the consensus.

Overview of acid-related disorders

Classification of ARDs

Based on acid secretion status, anatomical site, and clinical urgency, ARDs are primarily classified as follows:

(1) Esophageal Acid-Related Diseases

Esophageal ARDs primarily involve the esophagus and are further differentiated based on the underlying mechanism of acid involvement.

1) Acid exposure-related esophageal disorders — Gastroesophageal reflux disease (GERD)
   GERD is characterized by the reflux of gastric contents, including acid, into the esophagus, leading to troublesome symptoms and/or mucosal injury. Acid suppression therapy remains the cornerstone of management for symptom relief and mucosal healing. GERD is classified into reflux esophagitis (RE), where mucosal erosion or ulceration is present, and non-erosive reflux disease (NERD), where symptoms occur without visible mucosal breaks.
   Refractory GERD is defined as the persistence of symptoms such as heartburn or regurgitation despite 8 weeks of double-dose PPIs therapy. Contributing factors may be categorized as reflux-related (e.g., inadequate acid suppression, obesity, hiatal hernia) or non-reflux-related (e.g., esophageal motility disorders, other forms of esophagitis, psychosocial factors). Management should be tailored accordingly based on the underlying cause.

2) Acid perception-related esophageal disorders — Functional esophageal disorders

Functional esophageal disorders present with chronic esophageal symptoms in the absence of structural, inflammatory, motility, or metabolic abnormalities. These conditions are often influenced by psychosocial factors and may coexist with organic or mucosal diseases. Acid-suppressive therapy may offer symptomatic benefit in selected patients, particularly those with reflux hypersensitivity. According to the Rome IV criteria, functional esophageal disorders include functional

chest pain, functional heartburn, reflux hypersensitivity, globus, and functional dysphagia.[20]

(2) Gastroduodenal Acid-Related Diseases

Gastroduodenal ARDs involve the stomach and/or duodenum and encompass a range of acid secretory states and underlying etiologies.

1) Hypersecretory conditions
   ① Peptic ulcer (PU) results from the erosive action of gastric acid and pepsin on the mucosal lining. Acid suppression facilitates ulcer healing by reducing intragastric acidity.
   ② Gastrinoma is a functional neuroendocrine tumor characterized by ectopic hypersecretion of gastrin, leading to massive gastric acid production and consequent refractory ulcers, acid reflux, heartburn, and abdominal pain. Potent acid suppression is essential for controlling hypersecretion and preventing complications.
2) Infectious and inflammatory diseases
   ① Helicobacter pylori (H. pylori) infection can alter gastric acid secretion, often resulting in increased acid output in a subset of patients. Eradication therapy restores acid secretory balance and reduces the risk of ulcers and gastritis. Acid-suppressive agents enhance the efficacy of eradication regimens by increasing local antibiotic concentrations, inhibiting H. pylori urease activity, and improving bacterial susceptibility to antimicrobials.
   ② Chronic gastritis refers to persistent inflammation of the gastric mucosa due to various causes. Gastric acid can aggravate mucosal inflammation and erosion. Acid suppression or neutralization is commonly employed to alleviate symptoms and minimize further irritation of the compromised mucosa.
3) Functional gastroduodenal disorders
   In functional gastroduodenal disorders, gastric acid secretion is typically normal, but patients may exhibit visceral hypersensitivity to acid or underlying motility abnormalities. Acid-suppressive therapy is primarily used to relieve symptoms such as heartburn in epigastric pain syndrome (EPS) or rumination syndrome. Based on the Rome IV criteria, functional gastroduodenal disorders include functional dyspepsia (subdivided into postprandial distress syndrome [PDS] and EPS), belching disorders, nausea and vomiting disorders, and rumination syndrome.[20]

(3) Acute Severe Acid-Related Diseases

These conditions are characterized by high clinical urgency and require prompt intervention.

1) Acute upper gastrointestinal bleeding (UGIB), often caused by ulcers or erosions, is closely associated with gastric acid. Acid suppression elevates intragastric pH, thereby promoting platelet aggregation and hemostasis, which reduces the risk of rebleeding and mortality.
2) Acute gastric mucosal lesions may develop under stress or exposure to chemical or physicochemical insults. Acid plays a significant role in mucosal injury, and acid-suppressive therapy is fundamental in management. By increasing gastric pH, it protects the mucosa and helps prevent complications such as bleeding or perforation.

Treatment roadmap and commonly used drugs for ARDs (Table 1, Fig. 1)
Key Diagnostic Methodologies for ARDs[1,21,22]

For the assessment of gastric acid secretion, detection of reflux episodes, evaluation of mucosal damage, and exclusion of other diseases, the diagnosis of ARDs often relies on multiple detection methods. Common methods include the following:

Upper endoscopy (esophagogastroduodenoscopy, EGD)

To confirm and characterize the upper gastrointestinal mucosal injury (e.g., reflux esophagitis, Barrett's esophagus, peptic ulcers) secondary to ARDs, upper endoscopy (esophagogastroduodenoscopy, EGD) is the preferred and often gold-standard diagnostic modality. It enables direct visualization and clear identification of inflammatory, erosive, ulcerative, stenotic, polypoid, and neoplastic lesions within the esophagus, stomach, and duodenum. Furthermore, it allows for histopathological diagnosis via biopsy, which is critical for procedures such as H. pylori detection, differentiation between benign and malignant ulcers, and confirmation of Barrett's esophagus.

Upper gastrointestinal barium meal radiography

Upper gastrointestinal barium meal radiography is a key imaging modality for evaluating structural abnormalities of the upper digestive tract and serves as a valuable adjunct to gastroscopy. This technique involves the dynamic fluoroscopy of the digestive tract under X-ray, enabling clear identification of pathologies such as ulcers, filling defects (suggestive of tumors or polyps), luminal stenosis, hiatal hernias, and gastroesophageal reflux.

Esophageal PH monitoring

Esophageal pH monitoring serves to record the frequency, duration, and severity of acid reflux episodes through continuous pH measurement.

Multichannel intraluminal impedance monitoring

Multichannel intraluminal impedance monitoring detects reflux events by measuring changes in intraluminal impedance and can differentiate between gaseous and liquid reflux.

Supplementary and other diagnostic tests for GERD

The PPI Test (e.g., with omeprazole): This diagnostic trial involves a short course of PPI therapy to observe symptomatic improvement.

Assessment for Duodenogastroesophageal Reflux (DGER): This investigation aims to confirm the duodenal content reflux, including bile, into the esophagus.

Standard Acid Reflux Test: It assesses the frequency and severity of acid reflux.

Acid Perfusion Test (Bernstein Test): It is a provocative test in which an acidic solution is infused into the esophagus to reproduce symptoms and evaluate their correlation with acid reflux.

Radionuclide gastroesophageal scintigraphy

This diagnostic modality utilizes radionuclide imaging to evaluate of reflux via gastroesophageal or duodenogastric reflux scintigraphy.

Esophageal and gastric manometry

This procedure involves esophageal or gastric manometry to assess the motor function of the esophagus or stomach.

Gastric acid determination and monitoring

This involves the collection of gastric or duodenal fluid samples to measure and evaluate gastric acid secretion.

Assessment of gastrointestinal hormones

It evaluates the role of gastrointestinal hormones in ARDs through measurement of their concentrations in blood or tissue.

The aforementioned diagnostic methods each have specific clinical scenarios, advantages, limitations, and indications. Gastroscopy (Esophagogastroduodenoscopy, EGD) and upper gastrointestinal barium meal radiography are the core imaging techniques for

Table 1
Commonly used drugs for the treatment of acid-related diseases.

Drug classification	Subcategory/Representative drug	Main mechanism of action/characteristics
Acid-suppressing drugs	① H_2 receptor antagonist(H_2RA) Cimetidine, ranitidine, famotidine, roxatidine	Block the H_2 receptors of gastric parietal cells and reduce gastric acid secretion
	② **PPIs** Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole, Ilaprazole, Esomeprazole	Inhibits H^+/K^+-ATPase and has a strong acid suppression effect
	③ **P-CAB** Vonoprazan, Tegoprazan, Keverprazan, Linagolide glutarate	Potassium-competitive acid blockers rapidly suppress acid and are not affected by food intake
Antacid drugs	Hydrotalcite, Aluminum hydroxide, Aluminum phosphate gel	It directly neutralizes stomach acid and quickly relieves symptoms
Gastric mucosal protectant	**Exogenous** Sucralfate, Hydrotalcite, Bismuth potassium citrate, Colloidal bismuth pectin	Promote mucus secretion, increase bicarbonate content, and physically cover and protect the mucosa
	Endogenous Teprenone, Rebamipide, Irsogladine, Icabetasodium, Polaprezinc, Gastrointestinal hormones, Glutamine derivatives	Stabilize cell membranes, increase mucosal protective factors, promote blood flow, resist oxidation, and protect the gastric and small intestinal mucosa
Prokinetic agents	①Dopamine D_2 receptor antagonist: Domperidone ②Dual action of dopamine D_2 receptor antagonist and acetylcholinesterase inhibitor: Itopride ③5-HT_4 receptor agonists: Mosapride, Prucalopride ④Dual action of 5-HT_4 receptor and dopamine receptor: Cinitapride, Metoclopramide ⑤Opioid receptor agonist: Trimebutine ⑥Motilin receptor agonist: erythromycin and its derivatives	Enhance gastrointestinal peristalsis, coordinate motor function, and improve indigestion and gastroesophageal reflux
Digestive enzyme preparation	Pancreatin, Pepsin and its compound	Supplement digestive enzymes, promote food breakdown, and alleviate abdominal distension and indigestion caused by enzyme deficiency
TLESR inhibitor	Baclofen	Inhibit transient lower esophageal sphincter relaxations (TLESR) to reduce reflux of gastric contents
Chinese patent medicine	Morodan, Zhizhu Kuanzhong Capsules, Weisu Granules, Dalitong Granules, Modified Zuojin Pills, Biling Weitong Granules, Jinghua Weikang Capsules, Qizhi Weitong Granules, Shugan Jieyu Capsules, Xinwei Zhitong Capsules, Xiangsha Pingwei Granules, Xiangsha Yangwei Pills, Xiangsha Liujunzi Granules, etc	Harmonize the spleen and stomach, soothe the liver and regulate qi, promote blood circulation and relieve pain (Note: The specific mechanism varies depending on the prescription)
Neuromodulator	Flupentixol, melitracen, citalopram, duloxetine, sertraline, paroxetine, mirtazapine, trazodone, lorazepam, etc	Regulate the function of the central nervous system, improve anxiety, depression and the accompanying gastrointestinal symptoms
Antibacterial drugs for eradicating Hp	Amoxicillin, clarithromycin, tetracycline, levofloxacin, metronidazole, furazolidone, etc	Combining PPIs and bismuth agents to eradicate Hp
Antiemetic drugs	①5-HT_3 receptor antagonists: Ondansetron et al. ②Neurokinin NK_1 receptor antagonist: Aprepitant ③Dual action of 5-HT_4 receptor and dopamine receptor: metoclopramide ④Histamine H_1 receptor antagonist: promethazine ⑤Muscarinic M receptor antagonist: scopolamine	It is used as a single agent or in combination to prevent or treat common acute and chronic nausea and vomiting through central or peripheral effects

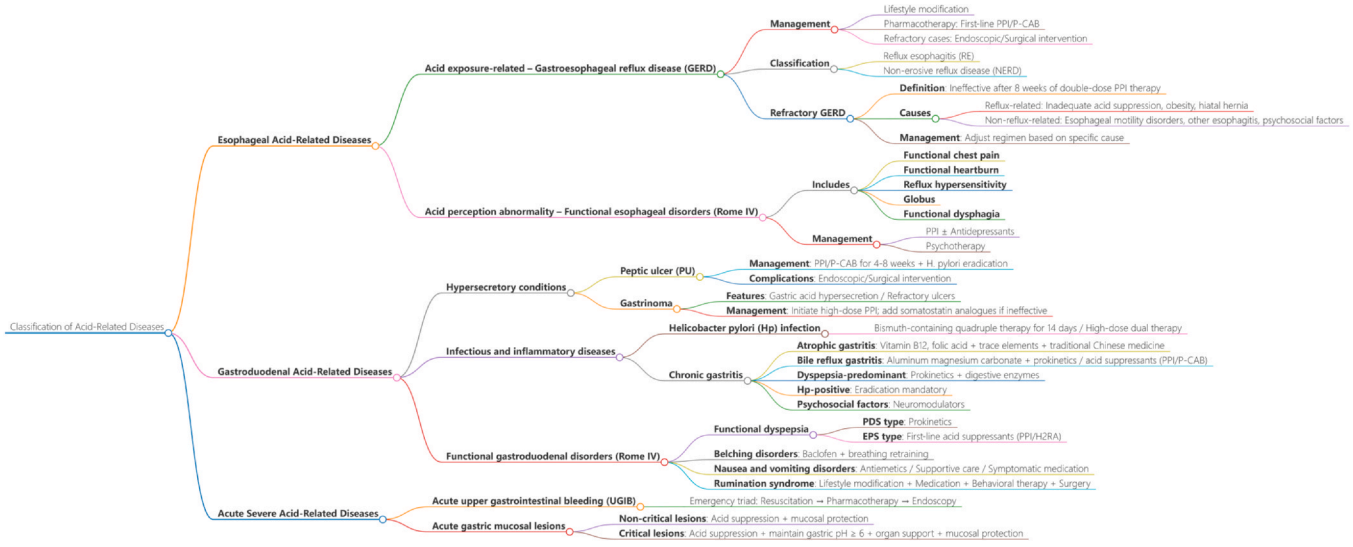

Fig. 1. Classification and Treatment Pathways for ARDs. This roadmap outlines the diagnostic subtypes and corresponding management strategies for acid-related disorders.

evaluating structural abnormalities secondary to ARDs, such as ulcers, reflux esophagitis, Barrett's esophagus, stenotic segments, and neoplastic lesions. They are frequently combined with functional studies, including esophageal pH monitoring and gastric acid secretion testing. Clinicians should tailor the diagnostic strategy by selecting and integrating the appropriate tests based on the patient's specific symptoms, physical findings, preliminary assessment results, as well as the indications and contraindications of each procedure. This comprehensive approach allows for a more accurate diagnosis of ARDs and guides the subsequent formulation of an effective treatment plan.

Tiered strategy for pharmaceutical care

Principles for tiered pharmaceutical care

This consensus establishes a tiered pharmaceutical care system for patients with ARDs. Based on clinical priority and intensity of care required, pharmaceutical care is stratified into three tiers.

Tier 1: Pharmaceutical Care applies to cases involving critically ill patients (with life-threatening or disabling risks) or situations with high medication-related risks (e.g., severe adverse drug reactions). This tier mandates active and prompt intervention by the pharmacist.

Tier 2: Pharmaceutical Care applies to situations of significant clinical importance (which may lead to prolonged hospitalization or increased costs, etc.) but are not immediately life-threatening. This tier requires monitoring of the medication therapy process by the pharmacist or the implementation of preventive measures against irrational drug use.

Tier 3: Pharmaceutical Care applies to patients with stable conditions and no significant therapeutic risks. The pharmacist's primary role in this tier is to ensure the standardization of medication therapy at key stages (e.g., referral, pre-discharge, etc.) and patient adherence.

Reference criteria for tiered pharmaceutical care

The recommended criteria and content for tiered pharmaceutical care for patients with acid-related diseases are outlined in Table 2. The stratification indicators are primarily based on the patient's pathophysiological status and pharmacotherapeutic profile. The assessment of the pharmacotherapeutic profile is conducted from the perspective of medication-related risks, with key considerations including: concomitant medication use or polypharmacy[23,24]; Use of standard versus double or higher drug dosages; Potential or confirmed drug-drug interactions; Severity of adverse events graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.[25]

Key implementation points of pharmaceutical care

In accordance with the Specifications for Pharmaceutical Care Services in Medical Institutions issued by the National Health Commission of the People's Republic of China,[27] pharmaceutical care for hospitalized patients should cover the entire pharmacotherapy process. Following the clarification of pharmaceutical care grading criteria, it is necessary to organize and optimize the monitoring items for the whole treatment process, as detailed in Tables 3 and 4.

Appropriate medication management

The primary objective of pharmaceutical care is to ensure the safety, efficacy, and cost-effectiveness of pharmacotherapy. While delivering patient-centered services, the rational use of medications must be concurrently addressed. Particular emphasis should be placed on the appropriate selection and combination of antacids and acid-suppressing agents. As a general rule, if monotherapy fails to achieve sufficient symptom control, consider adjusting the dosage or switching to an agent with a different mechanism of action. Except in approved compound formulations, the unwarranted combination of an antacid with an acid-suppressive agent or the concomitant use of acid-suppressive agents with distinct mechanisms should be avoided. For patients on long-term therapy, any decision for combination therapy must be supported by clear clinical justification. Furthermore, drug-drug interactions warrant prioritized attention. Through pharmaceutical care, practitioners must conduct systematic assessments and implement timely interventions to prevent adverse events. These events may arise from: altered absorption of concomitant drugs due to drug-induced changes in gastrointestinal pH, or disrupted metabolism/excretion resulting from interactions with hepatic enzymes or drug transporters.

In addition, close attention should be paid to rational medication use indicators. Since H. pylori eradication often requires combination therapy with antimicrobials, the "Antimicrobial Use Density" of different antimicrobial regimens must be monitored. For patients undergoing digestive endoscopic procedures, the rational utilization rate of prophylactic antibiotics for different surgical incision types should be emphasized during the perioperative or periprocedural period; As acid-suppressing therapies are available in multiple formulations, the principle of "oral administration over intravenous infusion whenever possible" should be adhered to, with a focus on monitoring and reducing the intravenous infusion rate, particularly the "Intravenous PPIs Utilization Rate." For patients on long-term medication, the rational utilization rate of medications listed in the National Key Monitoring Catalog, the priority utilization rate of essential medicines, treatment duration, and the "Drug Proportion" should also be assessed. As there are no unified standards for the above-mentioned rational drug use indicators, it is recommended that strategies such as rational drug use decision trees, warning tables for high-risk drug combinations, quantitative scoring criteria for intravenous-to-oral conversion, and priority use matrices for essential drugs be introduced according to the actual needs of the medical institution. Relevant medicines and those with high risks of irrational use should be taken as the focus of pharmaceutical care. The specific content of the pharmaceutical care program should be comprehensively determined by integrating the patient's pathophysiological status and the risks associated with drug therapy.

Recommendations for the pharmacological treatment of acid-related disorders

Clinical question 1: how should pharmacologic therapy be optimized in patients experiencing NAB during PPIs treatment?

Recommendation 1–1: For patients who develop NAB during PPIs therapy, short-term ($\leq$4 weeks) bedtime administration of an H_2RA may be considered (famotidine 10 mg, 20 mg, or 40 mg HS, ranitidine 75 mg, 150 mg, or 300 mg HS, cimetidine 200 mg, 400 mg, or 800 mg HS, or nizatidine 75 mg or 150 mg HS) (High-quality evidence, Strong recommendation).

Recommendation 1–2: For patients with NAB during PPIs therapy, switching from a PPI to a P-CAB may be considered (keverprazan 20 mg QD; vonoprazan 20 mg QD, or 20 mg BID if inadequate response; tegoprazan 50 mg QD) (High-quality evidence, Strong recommendation).

NAB is defined as a period of intragastric pH $<$ 4.0 lasting more than 1 h between 22:00 and 08:00 during PPI therapy.[28–30] Its incidence has been reported to be as high as 70%.[29] NAB is a common phenomenon during long-term PPI therapy, potentially related to suboptimal medication adherence, proton-pump regeneration, and the relatively short half-life of PPIs.[31] Because PPIs require activation in an acidic environment, they should be taken on an empty stomach to inhibit active proton pumps; post-prandial administration markedly reduces bioavailability.

The 2022 ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease recommends that PPIs be administered 30–60 min before meals to achieve optimal acid suppression. For patients with incomplete response to once-daily therapy, the

Table 2
Tiered pharmaceutical care criteria for patients with acid-related diseases.

Indicator Category		Tier 1 Pharmaceutical Care	Tier 2 Pharmaceutical Care	Tier 3 Pharmaceutical Care[a]
Pathophys-iological Status	Special Physiological Status	Perform Tier 1 Care if ANY of the following applies: ① Pregnant or lactating women; ② Neonates or infants (≤ 3 years old).	Perform Tier 2 Care if ANY of the following applies: ① Children (3–18 years old) or elderly (≥65 years old); ② Dysphagia or fasting state.	Abnormal body weight[26] (BMI < 18.5 kg/m^2 or BMI ≥28 kg/m^2).
	Special Pathological Status	Perform Tier 1 Care if ANY of the following applies: ① Severe infection; ② Hematemesis, bloody stools, or active bleeding; ③ Any of the following: circulatory failure, respiratory failure, impaired consciousness, aspiration, OR a Glasgow Blatchford Score (GBS)[b] > 1; ④ Liver cirrhosis or severe hepatic/renal insufficiency[c]; ⑤ Comorbid severe stress states[d] (e.g., major trauma, surgery); ⑥ Patients transferred from intensive care units (ICU) or other critical care departments.	Perform Tier 2 Care if ANY of the following applies: ① Unstable comorbid underlying diseases (e.g., GERD Los Angeles Classification Grade C ~ D); ② Moderate infection; ③ Receiving total parenteral nutrition (TPN) or tube-feeding enteral nutrition support; ④ Nutritional Risk Screening (NRS-2002) score ≥ 3; ⑤ Melena or endoscopic observation of minor bleeding; ⑥ Coagulation dysfunction (International Normalized Ratio (INR) > 1.5); ⑦ Moderate hepatic/renal insufficiency; ⑧ Comorbid sleep disorders or requiring psychiatric/psychological therapeutic intervention; ⑨ History of failed *Helicobacter pylori* eradication.	① Mild infection; ② Positive fecal occult blood test; ③ Mild hepatic/renal insufficiency.
Pharmacotherapy	Medication-Related Risk in Acid-Related Diseases	Perform Tier 1 Care if ANY of the following applies: ① Number of medications[23] ≥ 10; ② Use of acid suppressants/antacids at more than double the standard therapeutic dose; ③ Occurrence of clinically significant drug-drug interactions; ④ Drug Adverse Reactions (ADRs) rated as CTCAE Grade 4–5.	Perform Tier 2 Care if ANY of the following applies: ① Number of medications[23] between 5 and 9 (5 ≤ N < 10); ② Concomitant use of drugs with similar mechanisms of action; ③ Use of acid suppressants/antacids at double the standard therapeutic dose; ④ ADRs rated as CTCAE Grade 2–3; ⑤ Long-term use or in-hospital concomitant use of medications with potential gastrointestinal mucosal damaging effects (e.g., corticosteroids, Non-Steroidal Anti-Inflammatory Drugs(NSAIDs), antiplatelet agents, bisphosphonates, immunosuppressants, chemotherapeutic agents).	① Only potential drug-drug interactions exist; ② Mild ADRs (e.g., CTCAE Grade 1).
	Rational Medication Use & Control	Refer to the relevant control indicators of the respective healthcare institution[e]		

Note: a) Tier 3 Pharmaceutical Care may be implemented based on the presence of the listed issues when criteria for Tier 1 or 2 are not met; b) Glasgow Blatchford Score (GBS) scoring system; c) Refer to the Child-Pugh classification and the staging system of chronic kidney disease; d); Refer to the Trauma Index score or those undergoing Grade III or IV surgery; e) Refer to Section 3 for details.

Table 3
Main implementation items of graded pharmaceutical care.

Monitoring Items		Level 1 Care	Level 2 Care	Level 3 Care
Pharmaceutical Consultation	Timing	On admission / referral or when the patient's condition changes		
Pharmaceutical Ward Round / Whole-process Monitoring	Frequency	≥ 3 times per week	≥ 2 times per week	≥ 1 times per week
	Sub-items	Medical order review; Medication intervention; Case discussion / consultation	Medical order review; Medication intervention	Medical order review
Medication Consultation / Medication Education		Before discharge / when necessary		

guideline suggests increasing to twice-daily dosing; if optimization of dose and timing fails to control symptoms, switching to an alternative PPI is reasonable.[31]

Nevertheless, even after optimized PPI therapy, some patients continue to experience NAB. NAB typically occurs during the interval of suboptimal acid suppression between PPI doses. H_2RAs inhibit basal acid secretion by blocking histamine H_2 receptors, thereby complementing PPIs to fill this pharmacologic gap.[29] The 2022 ACG guideline states that in patients with persistent nocturnal symptoms despite PPI treatment, short-term bedtime H_2RA use may be considered; however, tolerance generally develops within several weeks, so long-term use is not recommended.[32]

A systematic review of eight randomized controlled trials (RCTs) (n = 274) demonstrated that bedtime H_2RA supplementation significantly reduced NAB incidence (RR, 0.48; 95% CI, 0.30–0.75). In subgroup analyses, short-term H_2RA use showed consistent benefit (RR = 0.43, 95% CI, 0.25–0.72), whereas long-term use did not (RR = 0.75, 95% CI, 0.41–1.36).[33]

The same ACG guideline also suggests bedtime administration of immediate-release omeprazole/sodium bicarbonate (IR-OME) for NAB control.[32] This U.S.-marketed formulation lacks an enteric coating and uses sodium bicarbonate to stabilize omeprazole in the stomach, enabling rapid absorption and a pH rise within 15 min, suitable for rapid symptom relief.[34] However, as immediate-release omeprazole is not available in China, and no clinical studies have evaluated sodium bicarbonate alone or combined with PPIs for NAB treatment, this consensus does not recommend its use for NAB control.

PPIs have a short half-life of 2–4 h. In CYP2C19 rapid metabolizers, acid suppression may be reduced, leading to poor efficacy.[35] P-CABs are unaffected by CYP2C19 polymorphisms[35] and do not require acid activation. They competitively bind both resting and active H^+/K^+-ATPase enzymes, are more stable under acidic conditions, and have a longer half-life (6–9 h),[36] making them suitable for NAB prevention.[35]

A systematic review and Bayesian network meta-analysis compared various acid-suppressive agents for NAB control. It included 55 RCTs with 2015 participants. P-CABs achieved the highest rate of nocturnal acid inhibition (≥ 91%), significantly outperforming new-generation PPIs (76.6%), bedtime H_2RAs (61.3%), and isomeric PPIs (38.6%).[37] Subgroup analyses showed consistent superiority of P-CABs in nocturnal dosing, Asian populations, and first-day administration.[37] Another meta-analysis of 12 RCTs evaluating acid-related disorders reported Surface Under the Cumulative Ranking Curve (SUCRA) values of 71.4% for keverprazan 20 mg, 42.4% for vonoprazan 20 mg, and 27.1% for tegoprazan 50 mg.[38] These findings suggest that P-CABs may offer a promising approach for NAB prevention and management, although further clinical data are warranted.

The safety profile of P-CABs is generally comparable to that of PPIs. Most available data are from Asian populations, and long-term safety evidence remains limited. Adverse events associated with P-CABs resemble those of PPIs, including gastrointestinal symptoms, hepatic enzyme elevation, infection risk, neurologic symptoms, and skin reactions. A meta-analysis of 7 Asian RCTs comparing P-CABs with lansoprazole in peptic ulcer treatment found no significant difference in overall treatment-emergent adverse events (TEAEs) (RR = 0.997, 95% CI, 0.949–1.046, P = 0.893). However, serious adverse events occurred in 9.3% of lansoprazole users and 9.6% of P-CAB users, suggesting a slightly higher risk with P-CABs (RR = 1.325, 95% CI, 1.005–1.747, P = 0.046).[39]

A pharmacovigilance study using the Japanese Adverse Drug Event Report (JADER) database identified a possible association between vonoprazan use and nephrotoxicity in Japanese patients, with an incidence comparable to PPIs.[40] P-CABs result in greater gastrin elevation than PPIs[41,42] and may induce more prominent parietal and G-cell hyperplasia.[43] Case reports have suggested a potential association between vonoprazan and hypomagnesemia, warranting vigilance for individual risk.[44,45] Concomitant administration of atorvastatin and vonoprazan significantly increases systemic exposure to atorvastatin and its metabolites.[41]

Clinical Question 2: The Application of Neuromodulators in ARDs.

Recommendation 2–1: For patients with FD refractory to other pharmacological treatments and those with GERD presenting with

Table 4
Core contents of graded pharmaceutical care items.

Monitoring Items	Core Contents
Pharmaceutical Consultation	Verify the patient's basic information and diagnosis, and assess the progression of their condition along with any specific patient needs. Then, evaluate the appropriateness of the medication regimen by applying evidence-based principles and considering thepharmacologic properties of the drugs, in conjunction with the patient's individual pathophysiological characteristics. If any irrational medication use is identified, communicate promptly with the treating clinician.
Pharmaceutical Ward Round / Whole-process Monitoring	1. Efficacy Monitoring: Monitor adjustments to therapy adjustments and review the appropriateness of medication use. Focus on evaluating the elimination of etiological factors (e.g., *Helicobacter pylori* (Hp) eradication), symptom relief (e.g., assess gastroesophageal reflux using tools such as the GERD-Q questionnaire along with objective measures such as 24-hour esophageal pH-impedance monitoring), and improvement in quality of life. If treatment outcomes are unsatisfactory, assess for potential medication-related problems and intervene as needed. 2. Safety Monitoring: Monitor for adverse drug reactions (ADRs). Communicate relevant risks to the healthcare team and implement necessary preventive measures.
Medication Consultation / Medication Education	Educate patients on appropriate medication use and address any unnecessary concerns (e.g., dark stools caused by bismuth agents) to improve medication adherence. For patients with multiple comorbidities and polypharmacy, provide recommendations for medication reconciliation and regimen adjustment.

esophageal hypersensitivity, neuromodulators are recommended to be added based on comorbid conditions (e.g., anxiety, depression). Adverse effects should be closely monitored during treatment (Moderate-quality evidence, strong recommendation).

Recommendation 2–2: For patients with FD, recommended neuromodulators include amitriptyline, flupentixol-melitracen, citalopram, and fluoxetine. For patients with GERD, recommended neuromodulators include flupentixol-melitracen, citalopram, and paroxetine (Moderate-quality evidence, strong recommendation).

Some patients with acid-related disorders, such as FD and GERD, frequently present with comorbid neuropsychiatric symptoms like depression and anxiety. It is recommended that neuromodulators be used as second-line therapy for FD and for GERD patients with esophageal hypersensitivity. Both US and Japanese guidelines recommend tricyclic antidepressants for patients with FD refractory to other therapies.[46,47] A systematic review and meta-analysis of 71 RCTs demonstrated that among various pharmacological agents for treating FD symptoms, tricyclic antidepressants ranked second in efficacy (RR = 0.71; 95% CI, 0.58–0.87) and ranked first when only low-risk-of-bias trials were included, although they were also associated with the highest risk of adverse events.[48] Another systematic review comparing the efficacy of ten psychotropic drugs for FD suggested that flupentixol-melitracen may be the most effective agent in alleviating dyspeptic symptoms.[49] A multicenter, randomized, double-blind, placebo-controlled trial compared the effects of antidepressants in patients with FD across eight research centers. The results demonstrated that both amitriptyline and escitalopram improved patients' overall quality of life, with amitriptyline potentially offering greater benefit (OR = 3.1; 95% CI, 1.1–9.0).[50] A Chinese retrospective cohort study, analyzing clinical data on antidepressant use among outpatient FD patients, indicated that low-dose antidepressants—particularly citalopram and fluoxetine—may be considered for refractory FD.[51] Chinese expert consensus also recommends low-dose neuromodulators for patients with refractory FD or those with comorbid anxiety or depression.[52] Italian guidelines recommend the use of neuromodulators for the treatment of visceral hypersensitivity associated with GERD.[53] Two meta-analyses and one RCT have shown that citalopram can effectively control reflux symptoms in GERD,[54–56] while paroxetine and flupentixol-melitracen are also effective for GERD.[54] However, imipramine was not effective.[55] For patients with refractory GERD, a trial of neuromodulator therapy is recommended if esophageal hypersensitivity is present or comorbid anxiety/depression exists.[57–59]

Clinical Question 3: The overuse of PPIs is a prominent issue. How should they be applied rationally?

Recommendation 3–1: Prophylactic use of PPIs should be strictly limited to patients with well-defined high-risk factors. The oral formulation is preferred, and when clinically feasible, intravenous therapy should be transitioned to oral administration (intravenous-to-oral sequential therapy). The treatment duration should be individualized (Moderate-quality evidence, strong recommendation).

Recommendation 3–2: Long-term PPI use (≥3 months) requires regular monitoring of serum magnesium, vitamin B_{12} levels, renal and hepatic function, electrolytes, and bone mineral density, with timely assessment of the necessity for discontinuation (Moderate-quality evidence, strong recommendation).

(1) Current Status of PPI Overuse

Among hospitalized patients, 78% of PPI prescriptions are for prophylactic purposes, of which 73% lack a clear indication (e.g., absence of high-risk factors for stress ulcers).[60–62] In perioperative patients, only 21.5% meet high-risk criteria (e.g., mechanical ventilation > 48 h). Postoperative prophylaxis often exceeds 7 days, significantly increasing the risk of fractures (RR = 1.20) and *Clostridium difficile* infection (OR = 2.1).[63–66]

(2) Indications for Prophylactic PPI Use

Prophylactic PPI therapy should be strictly reserved for the following high-risk populations:

1) Patients at High Risk for Stress-Related Mucosal Disease (SRMD)[67–69]:
   ①ICU Patients with any of: mechanical ventilation > 48 h, coagulopathy (INR > 1.5 or platelets < 50 × 10^9/L), sepsis/shock, or a history of upper gastrointestinal bleeding within the past 12 months.
   ②Major Surgery Patients: Surgery duration > 4 h, severe burns (> 30% body surface area in adults), traumatic brain injury (GCS ≤10) or cervical spinal cord injury, concurrent shock, or sustained hypotension.
2) Patients at High Risk for Drug-Related Mucosal Injury:
   ①Long-term NSAIDs users with additional risk factors: age > 65 years, history of peptic ulcer/bleeding, gastroesophageal reflux symptoms, use of multiple or high-dose NSAIDs, or concomitant anticoagulant use.[70]
   ②Antiplatelet Therapy: Patients on dual antiplatelet therapy (DAPT), those combining antiplatelets with anticoagulants, or those with additional risk factors such as H. pylori infection, long-term smoking or alcohol use, chronic kidney disease, or multiple bleeding risks.[71–79]
   ③Concomitant use of corticosteroids and NSAIDs (regardless of corticosteroid dose).
3) Other High-Risk Populations:
   Acute respiratory distress syndrome (ARDS), sepsis, septicemia, intestinal obstruction, post-organ transplantation, and post-endoscopic submucosal dissection (ESD) for artificial ulcer prevention (to prevent delayed bleeding).[80,81]

(3) Adverse Effects

Short-term (1%-5% incidence): Diarrhea, nausea, headache, rash, etc. These are mostly mild and self-limiting.[82]

Long-term (≥3 months): Hypomagnesemia, vitamin B_{12} deficiency, *Clostridium difficile* infection, pneumonia, osteoporosis and fractures, chronic kidney disease risk, gastric fundic gland polyps, dementia, among others.

1) Skeletal System: PPI use is associated with a significantly increased risk of hip fracture (RR = 1.20, 95% CI, 1.14–1.28), showing a dose-dependent relationship (high-dose RR = 1.30).[65]
2) Metabolic Abnormalities: PPI use for ≥ 2 years increases the risk of vitamin B_{12} deficiency by 65% (OR = 1.65, 95% CI, 1.58–1.73), with higher risk associated with high-dose therapy (OR = 1.95).[83,84]
3) Infection Risk: Increased risk of *Clostridium difficile* infection (OR = 2.1, 95% CI, 1.2–3.5)[66]; community-acquired pneumonia risk is increased by 37% (OR = 1.37, 95% CI, 1.22–1.53), with short-term use (< 30 days) posing a higher risk (OR = 1.49, 95% CI, 1.34–1.66).[85]
4) Renal Impairment: Increased risk of chronic kidney disease by 17% (HR = 1.17, 95% CI, 1.12–1.23), with twice-daily dosing associated with a higher risk (HR = 1.46, 95% CI, 1.28–1.67).[86]

Clinical Question 4: What treatment regimen is recommended for the eradication of refractory Helicobacter pylori infection (RHPI)?

Recommendation 4–1: For RHPI, empirical eradication therapy with the bismuth quadruple therapy (BQT) regimen containing bismuth, two antibiotics, and an acid suppressant is recommended. The antibiotic combinations including tetracycline, metronidazole, amoxicillin, and furazolidone are considered. For the selection of acid suppressants, PPIs with potent acid-suppressive effects, increased PPI doses, or P-CABs can be used. If bismuth is unavailable, high-dose PPI or P-CAB combined with amoxicillin therapy may be considered (Moderate-quality evidence, strong recommendation).

2022 Chinese National Clinical Practice Guideline on H.pylori Eradication Treatment[87] indicates that for refractory H.pylori infection, the following recommendations are proposed: For empirical eradication therapy, the bismuth quadruple regimen—comprising a PPI, bismuth, and antimicrobial combinations selected from those listed in Table 4—is recommended; Individualized therapy guided by bacterial culture and antimicrobial susceptibility testing should be implemented when conditions permit. The Maastricht VI/Florence Consensus Report[88] and the guidelines from the American Gastroenterological Association (AGA)[89] suggest that high-dose PPI-amoxicillin dual therapy may be considered if bismuth is contraindicated or if first-line bismuth quadruple therapy fails. Several studies have confirmed that the BQT regimen achieves high eradication rates in subjects with previous H. pylori eradication failure, serving as an effective rescue therapy after the failure of clarithromycin or levofloxacin-based regimens with favorable patient compliance and good safety profile[90–98]; thus, BQT is preferentially recommended. In China, the resistance rates to clarithromycin and levofloxacin are relatively high (> 30%).[99–101] If H.pylori treatment fails, antibiotics to which H.pylori may have developed resistance should not be reused. Given the high resistance rates to clarithromycin and levofloxacin, these antibiotics or other members of their classes should not be repeated in subsequent treatment attempts.[89] Except for clarithromycin and levofloxacin, the phenotypic resistance and genotypic resistance of other antimicrobial agents lack good consistency. Most cases of refractory H. pylori infection in China have already developed resistance to clarithromycin and levofloxacin, and the success rate of H. pylori culture after prior treatment may be less than 80%. In clinical practice, antimicrobial susceptibility testing can only provide useful information for a limited number of antibiotics such as clarithromycin, metronidazole, and quinolones. Furthermore, in vitro susceptibility to clarithromycin and metronidazole does not necessarily translate to in vivo eradication, which limits the clinical application of drug susceptibility testing.[102] Therefore, the value of resistance gene testing in patients with refractory H. pylori infection is limited.

In China, the resistance rates to amoxicillin, furazolidone, and tetracycline are relatively low, and these agents can be used as the preferred options for rescue therapy.[103,104] When empirically applying the bismuth quadruple regimen, clinicians should take into account local clinical characteristics (e.g., antibiotic resistance status, clinical drug accessibility) and use the antimicrobial combinations and doses listed in Table 5. The repeated use of previously administered antibiotics should be avoided as much as possible. For patients with rapid PPI metabolism, increasing the PPI dose or replacing PPIs with P-CABs may be considered.[96,105–109] The use of rifabutin-containing eradication regimens is not recommended, as it may further exacerbate the drug resistance situation of tuberculosis, and there is currently a lack of population-specific research evidence from China.

Clinical Question 5: Timing and Strategies of the Combined Use of PPIs for Patients Using NSAIDs.

Recommendation 5–1: For NSAIDs users with high-risk factors for gastrointestinal mucosal damage, concurrent use of a PPI is recommended to prevent upper gastrointestinal ulcers and bleeding (High-quality evidence, strong recommendation).

Recommendation 5–2: For patients on long-term NSAID therapy who are concurrently infected with H.pylori, screening and eradication of H.pylori are recommended (Moderate-quality evidence, strong recommendation).

Recommendation 5–3: Long-term concurrent use of NSAIDs and PPIs may exacerbate small intestinal injury. For high-risk patients, endogenous mucosal protective agents (e.g., teprenone) are recommended to prevent lower gastrointestinal mucosal damage (Moderate-quality evidence, strong recommendation).

Risk factors for NSAID-associated gastrointestinal injury include advanced age (65 years), high-dose NSAID therapy (at the maximum recommended prescribed dose), concomitant use of other medications (low-dose aspirin, corticosteroids, or anticoagulants), past medical history (primarily peptic ulcer disease or upper gastrointestinal bleeding), comorbidities (primarily cardiovascular disease, renal disease, diabetes, hypertension, etc.), and H.pylori infection. Patients with ≥ 2 of the above factors, or a history of complicated ulcers—especially recent ulcer history—are considered high-risk.[71] PPIs are considered first-line agents for the prevention and treatment of NSAID-associated gastrointestinal injury.[110] Multiple domestic and international consensus and guidelines statements recommend PPI prophylaxis for high-risk patients on long-term NSAID therapy to prevent gastrointestinal damage.[71,110,111] Findings from a Cochrane review indicate that PPI significantly reduce the risk of NSAID-associated gastric ulcers (RR = 0.39, 95% CI, 0.31–0.50) and duodenal ulcer events (RR = 0.20, 95% CI, 0.10–0.39).[112] A RCT demonstrated that for long-term NSAID users, lansoprazole achieved a superior gastric ulcer healing rate after 8 weeks of treatment compared to ranitidine ($P < 0.05$).[113]

Eradication of H.pylori significantly reduces the recurrence rate of NSAID-associated ulcers. It is recommended that patients on long-term NSAID therapy be screened for and receive eradication of H. pylori.[114,115] The AGA guidelines also note that H.pylori eradication combined with PPI therapy can reduce the incidence of NSAID-associated ulcers by 50% (RR = 0.5, 95% CI, 0.3–0.8).[71] Meta-analyses indicate that H.pylori-positive individuals have a 1.94 times higher odds ratio of developing low-dose aspirin-induced ulcers compared with H. pylori-negative individuals(95% CI, 1.54–2.46).[116,117] The incidence of ulcer bleeding is significantly lower in patients who undergo H. pylori eradication (HR = 0.35, 95% CI, 0.14–0.89, P = 0.028). However, H. pylori eradication only provides short-term benefit to patients (HR = 1.31, 95% CI, 0.55–3.11, P = 0.54).

Recent international studies have found that PPIs may exacerbate the damage caused by NSAIDs to the small intestinal mucosa. A meta-analysis[118] showed that PPI significantly increase both the prevalence and number of small intestinal injuries in NSAID users (prevalence:OR = 3.00; 95% CI, 1.74–5.16; number: MD = 2.30; 95% CI, 0.61–3.99), but did not alter the risk of small intestinal bleeding (OR = 1.24; 95% CI, 0.80–1.92). An RCT[119] demonstrated that PPIs can increase the risk of short-term NSAID-induced small intestinal injury (relative risk 2.67; 95% CI, 1.08–6.58). Animal studies suggest that the mechanism by which PPIs exacerbate NSAID-induced small intestinal mucosal damage may be associated with alterations in gut microbiota.[120,121] Studies have shown that certain endogenous mucosal protective agents (e.g., teprenone) have a protective effect against NSAID-induced mucosal damage. An RCT involving 40 patients with rheumatic diseases demonstrated that after 12 weeks of combined treatment with teprenone and diclofenac sodium, the rate of small

Table 5
Antimicrobial combinations recommended in BQT regimen for the eradication of RHPI.

Antimicrobial combinations	Antimicrobial 1	Antimicrobial 2
Combination 1	Tetracycline 500 mg, tid ~ qid	Metronidazole 400 mg, qid
Combination 2	Amoxicillin 1.0 g, bid ~ tid	furazolidone 100 mg, bid
Combination 3	Tetracycline 500 mg, tid ~ qid	furazolidone 100 mg, bid
Combination 4	Amoxicillin 1.0 g, bid ~ tid	Tetracycline 500 mg, tid ~ qid
Combination 5	Amoxicillin 1.0 g, bid ~ tid	Metronidazole 400 mg, qid

intestinal mucosal injury was reduced by 75% compared to the control group ($P < 0.01$).[122] A prospective, randomized, double-blind, crossover trial involving 10 healthy male volunteers assessed gastric and small intestinal mucosal damage induced by NSAIDs using capsule endoscopy. The results showed that combined therapy with teprenone and rabeprazole reduced the number of gastrointestinal lesions caused by one week of diclofenac sodium administration (2.6 ± 3.2 vs. 9.5 ± 8.5, respectively; $P = 0.027$).[123]

Clinical Question 6: Can gastrointestinal prokinetic agents be used for GERD? What are the treatment options and duration?

Recommendation 6–1: For GERD treatment, combination therapy with gastrointestinal prokinetic agents can be considered for patients who show an inadequate response to PPI therapy, particularly when associated with delayed gastric emptying (Moderate-quality evidence, strong recommendation).

Recommendation 6–2: The administration of gastrointestinal prokinetic agents should be individualized based on clinical circumstances, with close monitoring for adverse drug reactions. The typical treatment duration is 4–8 weeks, adjusted according to symptom improvement (Moderate-quality evidence, strong recommendation).

For GERD patients with co-existing gastrointestinal dysmotility, monotherapy with acid suppressants may yield inadequate outcomes. The addition of a prokinetic agent as an adjunctive therapy can be beneficial, as it addresses symptoms through mechanisms complementary to acid suppression.[124] Multiple guidelines and consensus statements indicate that combining prokinetics (e.g., mosapride) with PPIs improves select symptoms.[53,59,125–128] The American guidelines do not recommend any kind of gastrointestinal prokinetic agent for GERD therapy unless there is objective evidence of gastroparesis.[32] A detailed medical history must be obtained before prescribing, and the efficacy and safety of the medication must be comprehensively considered, particularly its effects on the cardiovascular and central nervous systems, to avoid contraindications.[129] Metoclopramide readily crosses the blood-brain barrier. Use of high doses or prolonged therapy is associated with an increased risk of extrapyramidal symptoms, particularly in elderly patients. Domperidone, which has limited penetration of the blood-brain barrier, is not associated with central nervous system effects. However, its use may be accompanied by hyperprolactinaemic side effects such as galactorrhoea and breast tenderness, and it carries a risk of serious cardiac arrhythmias. Both mosapride and itopride are generally well-tolerated but can produce gastrointestinal adverse reactions, including diarrhea and abdominal pain. Of note, Itopride offers distinct pharmacological advantages: it is not metabolized by the Cytochrome P450 (CYP450) enzyme system, minimizing the potential for drug-drug interactions. Furthermore, as it lacks affinity for the 5-HT4 receptor, it presents a negligible risk of QT interval prolongation and related serious cardiac events.

A meta-analysis from China demonstrated that although combination therapy with gastrointestinal prokinetic agents (acotiamide, domperidone, mosapride, cisapride, treatment duration 2–8 week) did not result in superior endoscopic mucosal healing rates compared to PPI monotherapy, a statistically significant improvement in symptomatic response was observed ($P = 0.010$).[130] Furthermore, studies indicate that regardless of the class of prokinetic agent combined (mosapride, domperidone, acotiamide, or revexepride), the combination therapy group (treatment duration 2–12 weeks) significantly reduced overall GERD symptoms ($P < 0.0001$), though it did not improve quality of life scores ($P = 0.420$). Regarding overall symptom improvement, combination therapy for at least 4 weeks demonstrated greater benefit than PPI monotherapy.[131] Studies using mosapride or cisapride (treatment duration 2–12 months) showed reduced reflux episodes compared to PPI monotherapy ($P = 0.0003$), but no significant effect on acid exposure time ($P = 0.65$). Adverse reaction rates were significantly higher in the combination therapy group ($P = 0.005$).[132] Furthermore, combination therapy with domperidone for GERD (treatment duration 2–12 weeks) demonstrated superiority over PPI monotherapy in reducing reflux episodes, acid exposure time, and heartburn scores. Adverse reactions were comparable between groups, with both showing diarrhea, regurgitation, headache, nausea with vomiting, and weakness with dizziness.[133]

Clinical Question 7: Is CYP2C19 genotyping required prior to PPI administration?

Recommendation 7–1: For patients requiring long-term/high-dose PPI therapy, those receiving concomitant relevant medications, or those with suboptimal therapeutic efficacy, CYP2C19 genotyping is recommended (Low-quality evidence, weak recommendation).

CYP2C19 genotype significantly influences the metabolism of PPI, resulting in marked differences in plasma drug concentrations among patients with different metabolizer categories (fast, normal, and slow metabolizers).[134,135] Genotyping can guide dose adjustment of therapeutic regimens to improve disease response rates: fast metabolizers (FMs) require dose escalation to enhance efficacy (e.g., for *Helicobacter pylori* eradication),[136] while slow metabolizers (SMs) need dose reduction to mitigate long-term medication risks (e.g., infection, osteoporosis).[135]

CYP2C19 genotyping can predict the risk of drug-drug interactions. For instance, in patients receiving clopidogrel co-administered with PPIs, SMs have an increased risk of cardiovascular events.[137] When omeprazole or other CYP2C19-dependent PPIs are co-administered with CYP2C19 inhibitors (e.g., voriconazole) or inducers (e.g., ritonavir), dose adjustment is required.[138,139]

In specific clinical scenarios (e.g., pediatric eosinophilic esophagitis, treatment of patients with reflux esophagitis, and failed *Helicobacter pylori* eradication therapy), genotyping helps optimize PPI selection or intensify treatment strategies.[136,140,141] However, some studies indicate that CYP2C19 genotyping has limited value in the management of PPI-refractory ulcers and esophagitis in children with esophageal atresia.[142,143] Therefore, clinical decisions should be made based on a comprehensive analysis of multiple lines of evidence.

The AGA Guidelines[89] noted that studies evaluating CYP2C19 genotyping-guided PPI selection and dosing for refractory H.pylori infection have been conducted in the Asia-Pacific population, where the prevalence of the FMs is relatively high. For the management of refractory *Helicobacter pylori* infection, it may be reasonable to empirically adopt strategies that achieve more potent intragastric acid suppression. Such strategies include increasing the dose and/or frequency of first-generation PPIs; using more potent next-generation PPIs; and selecting P-CABs with strong acid-suppressive effects if available.

In summary, the philosophy underlying the pharmacological management of acid-related disorders is evolving from a singular focus on "acid suppression" towards a comprehensive approach emphasizing "standardization, individualization, and safety." This consensus, grounded in evidence-based medicine and integrating the insights of multidisciplinary experts, systematically elaborates on and constructs a pharmacological treatment framework covering aspects such as disease overview, pharmaceutical care, and clinical issues. However, we also acknowledge that several critical scientific questions and clinical challenges remain to be addressed. Future research should strengthen investigations into areas such as the benefit-risk ratio of long-term use of different acid suppressants, comparisons between standard regimens for refractory Helicobacter pylori (Hp) infection and novel dual therapy, the cost-effectiveness of genetic testing, and the risk of interactions associated with multiple medications. In conclusion, this consensus provides practical guidance for medical and pharmaceutical professionals involved in the clinical diagnosis and treatment of acid-related disorders, promoting a more systematic and standardized approach to rational drug use.

Supplementary provisions

Dissemination and implementation of the guidance

This consensus was jointly initiated by the First Affiliated Hospital of Zhengzhou University and the editorial office of Precision

Medication, with the authorization of the Committee of Drug-induced Diseases of the Chinese Pharmacological Society. Once the consensus is officially published, the formulation working group will promote its dissemination and implementation through a variety of channels, including publication in academic journals, development of consensus interpretation and implementation guidance, promotion at academic conferences, holding of promotion and implementation training sessions, as well as publicity on WeChat and multiple other online platforms. Meanwhile, the Chinese version of this consensus will be published simultaneously.

Guidance updates

The consensus working group will continuously monitor research progress in the pharmacological treatment of acid-related disorders. Based on evidence updates, the group will initiate the consensus update process in a timely manner, adhering to relevant update methodologies and procedures during the update process.

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Chief Experts

Yonghong Hu (The First Affiliated Hospital of Zhengzhou University), Hongtao Wen (The First Affiliated Hospital of Zhengzhou University)

Steering Committee

Yinhua Deng (Hunan Provincial People's Hospital), Zhaoshuai Ji (Beijing Tsinghua Changgung Hospital), Hongzhi Lou (The First Affiliated Hospital of Henan University of Science and Technology), Xiaohong Liu (The First Affiliated Hospital of Henan University of Chinese Medicine), Chuanjiang Ma (Affiliated Hospital of Shandong University of Traditional Chinese Medicine), Lei Wang (Henan Provincial People's Hospital), Bowen Yi (Xiyuan Hospital, China Academy of Chinese Medical Sciences), Hong Yin (Chinese PLA General Hospital), Zhikang Ye (McMaster University, Canada), Qingyu Yang (Zhengzhou People's Hospital), Yubing Zhou (The First Affiliated Hospital of Zhengzhou University)

Consensus group

Pharmacy subgroup

Dengta Cai (The First Affiliated Hospital of Henan University), Xiaofei Chen (The First Affiliated Hospital of Henan University of Chinese Medicine), Rui Feng (The Fourth Hospital of Hebei Medical University), Weijie Jiao (Henan Provincial Hospital of Traditional Chinese Medicine), Yonghong Kong (Zhumadian Central Hospital), Xueli Liu (Puyang Oilfield General Hospital), Hailin Mai (The Third Affiliated Hospital of Sun Yat-sen University), Zhe Wang (The Second Affiliated Hospital of Wenzhou Medical University), Xiuqing Wang (Anyang People's Hospital), Junjie Zhao (The First Affiliated Hospital of Zhengzhou University), Jun Zhao (Nanyang Central Hospital), Yang Zhao (The Fifth Affiliated Hospital of Zhengzhou University), Liang Zhang (Hebi People's Hospital), Weiya Yu (The First People's Hospital of Pingdingshan), Ling Zha (Zhoukou Central Hospital)

Gastroenterology subgroup

Bin Jia (Affiliated Hospital of Shandong University of Traditional Chinese Medicine), Dongyan Li (Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology), Xuejin Liu (Zhoukou Central Hospital), Mingjie Qian (The Second Affiliated Hospital of Soochow University), Zhen Sun (Affiliated Hospital of Shandong University of Traditional Chinese Medicine), Lihong Wang (Zhengzhou Central Hospital), Tao Yang (The Second Affiliated Hospital of Guangzhou Medical University)

Secretariat

Xintong Fan (The First Affiliated Hospital of Zhengzhou University), Kefeng Liu (The First Affiliated Hospital of Zhengzhou University), Yongjie Yang (The First Affiliated Hospital of Zhengzhou University)

Evidence Evaluation Group

Yuna Chai (The First Affiliated Hospital of Zhengzhou University), Ya Li (The First Affiliated Hospital of Zhengzhou University), Yingxia Li (The First Affiliated Hospital of Zhengzhou University), Xiaoyun Wang (The First Affiliated Hospital of Zhengzhou University), Jie Yang (The First Affiliated Hospital of Zhengzhou University), Jingmin Zhang (The First Affiliated Hospital of Zhengzhou University), Mingxia Zhou (The First Affiliated Hospital of Zhengzhou University)

External Review Group

Shuang Cai (The First Affiliated Hospital of China Medical University), Guoji Dang (Pingmei Shenma Medical Group General Hospital), Zhongqin Dang (Henan Provincial Hospital of Traditional Chinese Medicine), Jie Pan (The Second Affiliated Hospital of Soochow University), Chengwu Shen (Shandong Provincial Hospital Affiliated to Shandong First Medical University), Yongfang Yuan (Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine)

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Declaration of Competing Interest

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Youhong Hu
China Pharmacological Society Pharmacogenic Diseases Committee, China
E-mail address: hyouhong@163.com