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2022 Chinese national clinical practice guideline on *Helicobacter pylori* eradication treatment

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Abstract

Background: *Helicobacter pylori* (*H. pylori*) infection is an infectious disease with a prevalence rate of up to 50% worldwide. It can cause indigestion, gastritis, peptic ulcer, and gastric cancer. *H. pylori* eradication treatment can effectively control disease progression and reduce the risk of the above conditions. However, the escalating trend of antibiotic resistance presents a global challenge for *H. pylori* eradication. We aim to provide guidance on pharmacological treatment of *H. pylori* infection.

Methods: This clinical practice guideline is developed following the World Health Organization's recommended process, adopting Grading of Recommendations Assessment, Development and Evaluation in assessing evidence quality, and utilizing Evidence to Decision framework to formulate clinical recommendations, minimizing bias and increasing transparency of the clinical practice guideline development process. We used the Reporting Items for practice Guidelines in HealThcare (RIGHT) statement and The Appraisal of Guidelines for Research and Evaluation II (AGREE II) as reporting and conduct guides to ensure the guideline's completeness and transparency.

Results: Though decreasing in developed countries, the prevalence of *H. pylori* remains high in developing countries, causing a major public health burden. This clinical practice guideline contains 12 recommendations concerning pharmacological treatment for *H. pylori* eradication. Among them, it is worth highlighting that bismuth preparations are inexpensive, safe, and effective, consequently making bismuth quadruple therapy a preferred choice for initial and rescue treatment. In empirical treatment, high-dose dual therapy is equally effective compared with bismuth quadruple therapy.

Conclusions: The 12 recommendations in this clinical practice guideline are formed with consideration for stakeholders' values and preferences, resource use, feasibility, and acceptability. Recommendations are generalizable to resource limited settings with similar antibiotic resistance pattern as China, and lower middle-income countries facing comparable sociological and technical challenges.

Registration: Guidelines International Network (GIN) website, https://guidelines.ebmportal.com/node/69996.

Keywords: *Helicobacter pylori*; Peptic ulcer; Guideline; Pharmacological treatment

Introduction

Helicobacter pylori (*H. pylori*) infection is an infectious disease with a prevalence rate of up to 50% in developing countries.[1-3] It is a major cause for indigestion, gastritis, peptic ulcer, and gastric cancer,[4] and is the second most common cause for cancer death in the world with 783,000 reported deaths in 2018 alone.[5]*H. pylori* eradication can reduce gastric inflammation, promote healing of peptic ulcer, and reduce risk of gastric cancer. A randomized clinical trial (RCT) shows *H. pylori* eradication reduced long-term gastric cancer incidence rate by 40% in a 15-year follow-up.[6]

H. pylori eradication rate is, however, declining, while prevalence of antibiotic resistance has been rising.[7] Antibiotic resistance rate in China is around 20% to 40%

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for clarithromycin and levofloxacin, and 60% to 90% for metronidazole.[8-11] Effective initial eradication is thus crucial to ensuring success in battling the infection. Though international guidelines offer advice, it is difficult to achieve lasting success due to regional differences in disease patterns, antimicrobial resistance rates, and accessibility to drug treatments. In recent decades, domestic research and local clinical experience jointly informed management strategies for *H. pylori* infection in China, which produced a satisfactory outcome. To sustain the effort, the Chinese Society of Gastroenterology initiated the current clinical practice guideline (CPG).

The scope of this CPG focuses on pharmacological treatment of *H. pylori* infection. It is produced to offer utility for Chinese clinicians, patients, and their careers in making treatment decisions, to ultimately improve health outcome and quality of life, and achieve cost saving. This article provides a synopsis of 12 key recommendations, along with summaries of clinical study data supporting each recommendation [Table 1]. The current CPG is an update of the previous consensus guideline published in 2018.[12] We aim to review it for update in 2025.

We define relevant clinical terms as the following in this CPG to promote consistency in interpretation and practice [Table 2].

Methods

Guideline development group (GDG) composition

Clinical chair of this CPG recommended a multidisciplinary group of 20 clinicians from across regions in China to form GDG; among them are gastroenterologists, laboratory scientists, pharmacists, and epidemiologists. Their conflicts of interest (CoI) were collected and assessed using a standard form constructed under the guidance of principles listed on Guideline International Network (GIN). All GDG members were free of financial and intellectual CoI and were permitted full participation. China Clinical Practice Guideline Alliance (GUIDANCE) provided methodological expertise and systematic review support. This CPG is registered on GIN website (https://guidelines.ebmportal.com/node/69996).

Table 1: Summary and strength of recommendations.

No.	Recommendation	Strength of recommendation
1	Bismuth quadruple therapy is recommended over triple therapy for initial and second line eradication treatment in people with *H. pylori* infection.	Strong recommendation, moderate certainty of evidence
2	Both bismuth quadruple therapy and high-dose dual therapy are equally suggested for initial and second eradication treatments.	Weak recommendation, low certainty of evidence
3	The GDG suggests against routine use of double dose PPI in bismuth quadruple therapy for people with *H. pylori* infection.	Weak recommendation, moderate certainty of evidence
4	Both standard dose PPI bismuth quadruple therapy and P-CAB bismuth quadruple therapy are equally suggested for initial and second line eradications.	Weak recommendation, low certainty of evidence
5	The GDG recommends antibiotic history guided treatment plan in initial and second line eradications.	Strong recommendation, moderate certainty of evidence
6	The GDG does not suggest routine use of AST guided therapy in initial eradication treatment, but encourages its use in second line treatment or in people with previous history of treatment failure.	Weak recommendation, moderate certainty of evidence
7	The GDG conditionally suggests augmenting Chinese herbal medicine to bismuth quadruple therapy.	Conditional recommendation, low certainty of evidence
8	The GDG conditionally suggests augmenting probiotics to bismuth quadruple therapy in initial and second line treatments.	Conditional recommendation, moderate certainty of evidence
9	The GDG neither supports nor refutes the use of triple therapy combined with probiotics for people with *H. pylori* infection in initial and second line treatments.	No recommendation, very low certainty of evidence
10	The GDG suggests against the use of triple therapy combined with gastric mucosal protective agents for initial and second line eradication treatments.	Weak recommendation, expert consensus
11	The GDG suggests the following treatment for people with refractory *H. pylori* infection: (1) empirical bismuth quadruple therapy with the combination of antibiotics listed in Table 4, in addition to PPI or bismuth; and (2) where possible, apply bacterial culture and AST to guide treatment plan.	Weak recommendation, expert consensus
12	For people with *H. pylori* infection and penicillin allergy, the GDG suggests bismuth quadruple therapy with tetracycline and metronidazole; or bismuth quadruple therapy containing cefuroxime instead of amoxicillin. The GDG suggests against bismuth quadruple therapy with any combinations of clarithromycin, levofloxacin, or metronidazole, with the exception of usage of metronidazole in full dosage (1.5–1.6 g/day).	Weak recommendation, expert consensus

AST: Antibiotic susceptibility test; GDG: Guideline development group; PPI: Proton pump inhibitors; P-CAB: Potassium-competitive acid blocker; *H. pylori*: *Helicobacter pylori*.

Table 2: Definition of clinical terminology.

Term	Definition
Therapy	
High-dose dual therapy	The administration of both amoxicillin (≥3.0 g/day, 1.0 t.i.d., or 0.75 q.i.d.) and PPIs (esomeprazole or rabeprazole, double dose bid or standard dose q.i.d.) for 14 days;
Triple therapy	PPI plus two antibiotics for 7–14 days;
Bismuth quadruple therapy	PPI, bismuth, plus two antibiotics for 14 days;
Non-bismuth quadruple therapy	PPI, plus three antibiotics (amoxicillin, clarithromycin, and metronidazole) for 10–14 days;
Concomitant therapy	PPI plus amoxicillin, clarithromycin, and metronidazole for 10–14 days;
Sequential therapy	Phase 1: PPI plus amoxicillin for 5–7 days; followed by phase 2: PPI plus clarithromycin and metronidazole for 5–7 days;
Hybrid therapy	The combined use of sequential therapy and concomitant therapy. Phase 1: PPI plus amoxicillin for 5–7 days; followed by phase 2: PPI plus amoxicillin, clarithromycin, and metronidazole for 5–7 days;
Population	
Initial treatment	First time receiving *H. pylori* infection eradication treatment;
Second line treatment	Second time treatment for one prior course of unsuccessful *H. pylori* infection eradication;
Refractory infection[105,106]	People with two or more unsuccessful courses of *H. pylori* infection eradication treatments.

H. pylori: *Helicobacter pylori*; PPI: Proton pump inhibitors.

Guideline development

This CPG is developed following the WHO recommended process,[13] adopting Grading of Recommendations Assessment, Development and Evaluation (GRADE) in assessing evidence quality, and utilizing Evidence to Decision framework to formulate clinical recommendations, which minimize bias and increase transparency of the process. Quality of evidence indicates the degree of certainty of findings. GRADE categorizes the quality of evidence into high, moderate, low, and very low, through assessing various aspects of the body of evidence, including risk of bias, inconsistency, indirectness, imprecision, and publication bias. This is taken into account to inform the final recommendation, together with the balance of benefit and harm, stakeholders' values and preferences, cost effectiveness, acceptability, and feasibility. The strength of recommendations in this CPG are categorized into strong, weak, and conditional. The factors that promote strong recommendation include high certainty of evidence, similarity in stakeholders' values and preferences, cost effectiveness, and sharp contrast between benefit and harm.[14]

The GDG identified 12 important clinical questions through discussion, which were later converted into research questions using PICO format (Population, Intervention, Comparator and Outcome) to pave the way for systematic reviews. Under each clinical question, the GDG selected up to seven outcomes through discussion and categorized these into critically important, important, and not important through blind voting. The GDG held seven online meetings between September and November 2021 to review evidence under each PICO question, and to reach a consensus on corresponding recommendations. Consensuses were reached through open discussion and voting, where 80% is adopted as a threshold to pass a recommendation [Supplementary File 1, http://links.lww.com/CM9/B392].

The full CPG report was sent to external guideline methodologists and clinicians without direct involvement in the current CPG for review. Their feedbacks were collected and incorporated as appropriate. We referenced The Appraisal of Guidelines for Research and Evaluation II (AGREE II) before and during the conduct of CPG to ensure quality and followed Reporting Items for practice Guidelines in HealThcare (RIGHT) statement for reporting.[15,16]

Evidence synthesis

The systematic review team searched PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure, VIP, China Biomedical Database, and WanFang between May 20 and 24, 2021 without date or language limit [Supplementary File 2, http://links.lww.com/CM9/B393]. Additionally, reviewers' hand searched references of all included articles for further relevant studies, and contacted clinicians for potentially relevant studies. Two separate sets of searches were carried out to identify studies on efficacy and safety, and studies on other factors including cost-effectiveness, values and preferences, acceptability, and feasibility.

Reviewers worked in pairs to independently carry out reference screening and data extraction, and resolved any disagreements through discussion or consulting a third reviewer. A data extraction form with standardized variable headings was used in this process. We employed Cochrane risk of bias table (RoB, version 1.0) to assess the risk of bias for RCTs, while Newcastle–Ottawa Scale was used for observational studies. We used Review Manager (version 5.4, The Cochrane Collaboration, 2020) to analyze data from controlled clinical studies or RCT and R 4.0.2 for single arm studies. For binary outcome, we calculated risk ratio (RR) and its 95% confidence interval (CI); for continuous outcome, where possible, we calculated mean difference with its 95% CI. We employed

I^2 >50% as a general guide to identify heterogeneity in a pooled analysis, through which subgroup analysis was explored on clinical, methodological, and statistical variations. Quality of evidence is appraised using GRADE, as stated in the preceding section.

Recommendations and Evidence Profile

Should bismuth quadruple therapy be used as initial and second line eradication treatment in people with H. pylori infection?

Recommendation

The GDG recommends bismuth quadruple therapy for initial and second line eradication treatment in people with *H. pylori* infection (strong recommendation, moderate certainty of evidence). Besides proton pump inhibitors (PPI), the antibiotics shown in Table 3 are recommended combinations (strong recommendation, moderate certainty of evidence).

Implementation suggestion

1. Quadruple therapy containing tetracycline and metronidazole is reported to induce severe adverse events in some people, and thus sufficient communication and joint decision making with user is strongly advised.
2. In areas with multi-antibiotic (including clarithromycin, metronidazole, and levofloxacin) resistance, or in people with a history of macrolides, quinolones, and nitroimidazole resistances, where successful eradication is threatened, the GDG suggests bismuth quadruple therapy containing furazolidone. Antibiotic combination in such therapy includes: (1) amoxicillin 1000 mg, b.i.d; furazolidone 100 mg, b.i.d; and (2) tetracycline 500 mg t.i.d or q.i.d; furazolidone 100 mg, b.i.d.

Evidence profile

We included 24 RCTs comparing triple therapy directly with quadruple therapy.[17-40] Settings included China,[21,26-29,32,35,37-40], Iran,[19,33,36] Korea,[24] Malaysia,[25] Iraqi,[17] Turkey,[20,22,23,31,34] Kuwait,[18] and a multi-center trial[30] involving France, Germany, Ireland, Italy, Poland, Spain, and United Kingdom. Relative to triple therapy, bismuth quadruple therapy may improve eradication rate (RCT = 24, N = 7220, RR = 1.12, 95% CI 1.09–1.15, moderate quality evidence, see Supplementary Figure 1, http://links.lww.com/CM9/B394). Such beneficial effect is consistent across subgroup analysis of different antibiotic combinations, for example, in amoxicillin with clarithromycin subgroup (RCT = 6, N = 1373, RR = 1.13, 95% CI 1.06–1.21), amoxicillin with levofloxacin subgroup (RCT = 4, N = 702, RR = 1.09, 95% CI 1.02–1.17), and metronidazole with tetracycline subgroup (RCT = 12, N = 4316, RR = 1.19, 95% CI 1.16–1.23). Bismuth quadruple therapy may also reduce incidence of important adverse events, including allotriogeusia (RCT = 9, N = 3131, RR = 0.48, 95% CI 0.39–0.60, low quality evidence) and diarrhea (RCT = 15, N = 4743, RR = 0.79, 95% CI 0.66–0.95, moderate quality evidence).

Bismuth quadruple therapy may potentially have the following undesirable effects, ie, it may increase risk of dizziness (RCT = 8, N = 2921, RR = 2.35, 95% CI 1.08–3.08), headache (RCT = 8, N = 3134, RR = 2.08, 95% CI 1.48–2.92), treatment cessation due to drug related adverse events (RCT = 9, N = 2910, RR = 1.70, 95% CI, 1.21–2.41), and nausea/vomiting (RCT = 12, N = 4015, RR = 3.05, 95% CI 2.15–4.31). All of the above are of low quality of evidence.

Rational

Average eradication rate is 81.3% in bismuth quadruple group and 71.3% in triple therapy group (RCT = 24, N = 7220). In every 1000 people treated, there likely to be 86 more successful eradications in the quadruple therapy group than in the triple therapy group (RCT = 24, N = 7220, RR = 1.12, 95% CI 1.09–1.15, moderate quality of evidence). Although there might be some increase in some adverse events in the quadruple group, none of these is critical. GDG concludes that the desirable health effect of Bismuth quadruple therapy outweighs the undesirable.

Should high-dose dual therapy be recommended as initial and second line eradication treatment for people with H. pylori infection?

Recommendation

Both bismuth quadruple therapy and high-dose dual therapy are suggested for initial and second eradication treatment (weak recommendation, low certainty of evidence).

Table 3: Recommended antibiotic combinations in bismuth quadruple therapy*.

Therapy	Antibiotic 1	Antibiotic 2
1	Amoxicillin 1000 mg, b.i.d.	Clarithromycin 500 mg, b.i.d.
2	Amoxicillin 1000 mg, b.i.d.	Levofloxacin 500 mg, q.d. or 200 mg, b.i.d.
3	Tetracycline 500 mg, t.i.d. or q.i.d.	Metronidazole 400 mg, t.i.d. or q.i.d.
4	Amoxicillin 1000 mg, b.i.d.	Metronidazole 400 mg, t.i.d. or q.i.d.
5	Amoxicillin 1000 mg, b.i.d.	Tetracycline 500 mg, t.i.d. or q.i.d.

* In compliance with China NMPA's requirement, furazolidone is only recommended for treatment resistant *H. pylori* infection. Standard dose proton pump inhibitors (PPI) includes: omeprazole 20 mg, esomeprazole 20 mg, rabeprazole 10 mg, lansoprazole 30 mg, pantoprazole 40 mg, ilaprazole 5 mg, b.i.d., taken 30 min before meal. Standard dose bismuth is defined as bismuth potassium citrate 220 mg, b.i.d., taken 30 min before meal; dosage of bismuth pectin is to be confirmed. Recommended duration of treatment is 14 days. *H. pylori*: *Helicobacter pylori*; NMPA: National Medical Products Administration.

Evidence profile

Four RCTs from Turkey[41] and China[42-44] provided direct comparison. All three RCTs from China used amoxicillin and clarithromycin in bismuth quadruple therapy, and the other used metronidazole and tetracycline bismuth quadruple therapy. Treatment duration is 14 days for all trials. Relative to bismuth quadruple therapy, high-dose dual therapy may produce trivial benefit in eradication rate (RCT = 4, *N* = 1451, RR 1.02, 95% CI 0.98–1.07, moderate quality evidence, see Supplementary Figure 2, http://links.lww.com/CM9/B394), and may result in further reduction in headache (RCT = 2, *N* = 947, RR = 0.26, 95% CI 0.1–0.7, low quality evidence). On the other hand, there is little to no difference between groups on allotriogeusia (RR = 0.05, 95% CI 0.01–0.27) and arrhythmia (RR = 2.57, 95% CI 0.12–52.99).

The average eradication rate in the bismuth quadruple and high-dose dual therapy groups are 83.6% and 85.3%, respectively (RCT = 4, *N* = 1451). Overall, there is no apparent difference between groups on eradication rate and critical adverse events. Most outcomes are of low or very low quality of evidence, which indicates low certainty on any discriminatory advantages between groups, and thus the GDG concludes that both therapies are reasonable options for initial and second line eradication treatment. It is worth noting that, in China, the clinical accessibility to tetracycline and furazolidone is compromised owing to risk of side effects and the related restrictions imposed by the National Medical Products Administration (NMPA).

Should double dose PPI be recommended in bismuth quadruple therapy for people with H. pylori infection?

Recommendation

The GDG suggests against routine use of double dose PPI in bismuth quadruple therapy for people with *H. pylori* infection (weak recommendation, moderate certainty of evidence).

Implementation suggestion

In situations where the *CYP2C19* genetic test confirms PPI fast metabolism, double dose PPI could be considered in bismuth quadruple therapy. Around 40% of the Chinese population falls in the fast metabolism category,[8] and in theory, these people could benefit from enhanced acid suppression.

Evidence profile

Four RCTs from China[45-48] were included. All used amoxicillin and clarithromycin as choice of antibiotic with treatment duration between 10 and 14 days. Double dose PPI bismuth quadruple therapy may lead to a trivial increase in eradication rate (RCT = 4, *N* = 904, RR = 1.03, 95% CI 0.98–1.08, moderate quality evidence, see Supplementary Figure 3, http://links.lww.com/CM9/B394) and may increase some non-specified adverse events (RCT = 3, *N* = 804, RR = 1.65, 95% CI 1.13–2.40, low quality evidence), relative to standard dose PPI group. Average eradication rate in double dose and standard dose groups are 88.7% and 86.1%, respectively. With consideration to the trivial difference on eradication rate between groups, the GDG concludes that the potential benefit and harm of double dose PPI is similar to that of the standard dose group.

In bismuth quadruple therapy, should PPI or potassium-competitive acid blockers (P-CABs) be recommended?

Recommendation

The GDG suggests that both standard dose PPI bismuth quadruple therapy and P-CAB bismuth quadruple therapy are available treatment options for initial and second line eradication (weak recommendation, low certainty of evidence).

Evidence profile

Three RCTs from China[49,50] and Korea[51] compared standard dose PPI bismuth quadruple therapy with P-CAB bismuth quadruple therapy at a treatment duration of 14 days. Two of the RCTs reported eradication rate, but meta-analysis was not conducted due to insufficient information to ascertain homogeneity. Nevertheless, individual trial data show no apparent differences between groups on eradication rate (RR = 1.05, 95% CI 0.98–1.12; RR = 1.05, 95% CI 0.99–1.13). There is little to no difference on adverse events related (RCT = 1, *N* = 30, RR = 0.80, 95% CI 0.44–1.45) or unrelated to treatment (RCT = 1, *N* = 30, RR = 3.00, 95% CI 0.13–68.26). As evidence around the application of P-CAB accumulates, the direction and magnitude of its effect may indeed become more apparent with future research.[52]

In empirical treatment for people with H. pylori, should treatment plan be guided by history of antibiotic use?

Recommendation

The GDG recommends an antibiotic history guided treatment plan in initial and second line eradication (strong recommendation, moderate certainty of evidence).

Implementation suggestion

History of antibiotic usage based on patient recall may be unreliable or misleading, and thus where possible electronic patient records should be used.

Macrolides (eg, clarithromycin), quinolones (eg, levofloxacine), and nitroimidazole (eg, metronidazole) are known to cause secondary resistance and cross drug resistance, and are thus likely to induce drug resistance in people with previous history of use, ultimately reducing the effectiveness of eradication treatment. In contrast, amoxicillin and tetracycline do not carry a similar risk and can be considered for second line and refractory treatment.

Evidence profile

In light of the growing rate of antimicrobial resistance, and reduced effectiveness of many popular regimens, the ability to quickly ascertain microbial resistance pattern before prescription becomes crucial. A quick and practical way is to ask the patients for history of antibiotics use and check their medical records. A single RCT conducted (Tailored triple plus bismuth therapy based on past medication history for the first-line *H. pylori* eradication in an area with high antibiotic resistance: a randomized controlled trial) in China fulfilled the inclusion criteria. It shows that relative to empirical treatment, people who received treatment guided by history of antibiotic use may achieve an increase in eradication rate (RCT = 1, *N* = 800, RR = 1.10, 95% CI 1.04–1.17, low certainty of evidence). There is little to no difference between groups on adverse events, for example, headache (RR = 0.69, 95% CI 0.2–2.4), skin rash (RR = 0.67, 95% CI 0.15–3.06), and other severe adverse events (RR = 0.75, 95% CI 0.21–2.63).

The average eradication rates in the empirical treatment group and the history of antibiotic use guided treatment group are 81% and 89.5%, respectively, indicating a moderate degree of relative benefit in the later.

Relative to empirical treatment, should antibiotic susceptibility test (AST) be recommended to guide the treatment?

Recommendation

The GDG does not suggest routine use of AST guided therapy in initial eradication treatment (weak recommendation, moderate certainty of evidence), but encourages the use of it in second line treatment or in people with previous history of treatment failure.

Evidence profile

Five RCTs conducted in China[8,32,53-55] are included. Three of these compared culture and standard AST guided quadruple therapy *vs.* empirical treatment,[32,53,54] and the others compared culture and standard AST guided triple therapy *vs.* empirical treatment.[8,32,55] Relative to empirical therapy, AST guided quadruple therapy increased eradication rate, with, on average, 126 more eradications per 1000 people treated (RCT = 3, *N* = 824, RR = 1.18, 95% CI 1.09–1.27, moderate certainty of evidence, see Supplementary Figure 4, http://links.lww.com/CM9/B394). One of the three RCTs[32] caused heterogeneity, and when removed, the magnitude of benefit was slightly reduced to an average of 56 more eradications per 1000 people treated (RR = 1.08, 95% CI 0.99–1.19). There may be little to no difference on adverse events between groups, for example, on diarrhea (RR = 0.80, 95% CI 0.39–1.61), fatigue (RR = 1.18, 95% CI 1.09–1.27), dizziness (RR = 0.51, 95% CI 0.16–1.63), skin rash (RR = 0.86, 95% CI 0.36–2.08), nausea/vomiting (RR = 0.43, 95% CI 0.17–1.04), and severe adverse events (RR = 0.47, 95% CI 0.09–2.38), with mostly very low certainty of evidence.

The direction and magnitude of effect are similar between groups. On average we can expect 83 more eradications (RCT = 3, *N* = 1360, RR = 1.11, 95% CI 1.05–1.17, moderate certainty of evidence) and 50 less nausea/vomiting (RCT = 1, *N* = 310, RR = 0.44, 95% CI 0.17–1.17, moderate certainty of evidence) per 1000 people treated with AST guided triple therapy. There may be little to no difference on other adverse events between groups, such as diarrhea (RR = 0.87, 95% CI 0.63–1.32), dizziness (RR = 0.52, 95% CI 0.15–1.84), fatigue (RR = 0.60, 95% CI 0.25–1.46), and dysgeusia (RR = 0.88, 95% CI 0.63–1.23), all with very low certainty of evidence.

Overall, compared to empirical therapy, AST guided triple therapy and quadruple therapy are likely to bring moderate to large clinical benefit, with, on average, between 56 and 126 more eradications for every 1000 people treated (moderate certainty of evidence). However, in China, antibiotic susceptibility has reduced feasibility and clinical availability, and not all healthcare facilities have the capacity to offer these tests. Routine use of the test may result in inequality in healthcare access. But overall, the GDG concludes that the benefit of using drug susceptibility test guided therapy outweighs the potential harm, and should at least be encouraged for use in people with a previous history of treatment failure.

Should Chinese herbal medicine be augmented to bismuth quadruple therapy in initial and second eradication treatment for people with H. pylori infection?

Recommendation

The GDG suggests augmenting Chinese herbal medicine to bismuth quadruple therapy for people with *H. pylori* infection under the following conditions (conditional recommendation, low certainty of evidence).

(a) When applying empirical therapy in regions where bismuth quadruple therapy has low eradication rate;
(b) When treating people with treatment resistant *H. pylori* infection, clinicians could consider adding Chinese herbal medicine upon discussion with patients;
(c) Chinese herbal medicine can be used as a replacement of bismuth in quadruple therapy for people with bismuth allergy or in regions where bismuth is inaccessible.

Implementation suggestion

It may be beneficial on eradication rate when bismuth quadruple therapy is augmented with the following Chinese herbal medicines: sequentially adding jing-hua-wei-kang capsule (160 mg, t.i.d., or 240 mg b.i.d. for 3–4 weeks), ban-xia-xie-xin decoction, or *Rheum officinale*, rhizoma coptidis, and radix scutellariae dominated TCM prescription. Substitution of bismuth or clarithromycin with the above in quadruple therapy produces an effect similar to bismuth quadruple therapy on eradication rate.

Evidence profile

A total of 22 RCTs[56-77] with an overall sample size of 3602 people were included. All are conducted in China

with a treatment duration of 14 days. A total of 12 RCTs used bismuth quadruple therapy with herbal decoction[58-60,62,67-69,73-77] and the other 10 used patent prescription.[56,57,61,63-66,70-72] Augmenting Chinese herbal medicine may increase eradication by an average of 112 more cases per 1000 people treated (22 RCT, $N = 3602$, RR = 1.15, 95% CI 1.11–1.18, moderate certainty of evidence, see Supplementary Figure 5, http://links.lww.com/CM9/B394). However, there is little to no difference between groups on adverse events, including diarrhea (RR = 0.98, 95% CI 0.49–1.81), nausea (RR = 0.62, 95% CI 0.26–1.48), dizziness (RR = 0.90, 95% CI 0.36–2.25), headache (RR = 0.80, 95% CI 0.22–2.91), fever (RR = 0.33, 95% CI 0.01–8.03), and skin rash (RR = 1.37, 95% CI 0.46–4.06), all are very low certainty of evidence.

Should probiotics be augmented to bismuth quadruple therapy in initial and second eradication treatment for people with H. pylori infection?

Recommendation

The GDG suggests augmenting probiotics to bismuth quadruple therapy in initial and second line treatments for people with *H. pylori* infection, under the following conditions (conditional recommendation, moderate certainty of evidence).

Implementation suggestion

Provided cost and complexity of treatment are not of concern, probiotics can be used in people with unstable intestinal microecology, as evidenced by functional diarrhea and diarrhea-type irritable bowel syndrome, and those exposed to long-term antibiotic use. The GDG suggests a mixed strain containing lactic acid bacteria to be taken before and during eradication treatment for a minimum of 2 weeks.

Evidence profile

Ten RCTs were included[78-87] from China,[78,79,83,84,86] Iran,[82,87] Spain,[80] Thailand,[81] and Italy.[85] Five of these used triple therapy plus compound probiotics,[79,82-84,87] three augmented *Lactobacillus*,[80,81,85] one augmented *Bifidobacterium*,[78] and one augmented *Clostridium butyricum*.[86] Duration of treatment varied between 7 days and 30 days.

Relative to bismuth quadruple therapy used alone, augmenting probiotics may bring small benefit in eradication rate (on average 40 more eradications per 1000 people treated, RCT = 10, $N = 1614$, RR = 1.05 95% CI 1.00–1.10, moderate certainty of evidence, see Supplementary Figure 6, http://links.lww.com/CM9/B394), and may reduce incidence of diarrhea (3 RCT, $N = 472$, RR = 0.14, 95% CI 0.05–0.38, low certainty of evidence). There may be little to no difference between groups on other adverse events, such as stomach-ache (RR = 2.11 95% CI 0.70–6.36) and vomiting (RR = 3.00, 95% CI 0.62–14.47), with very low certainty of evidence.

In conclusion, adding probiotics to bismuth quadruple therapy may produce a small benefit in eradication rate, and may reduce incidence of diarrhea. The acceptability and feasibility of adding probiotic is generally good in most clinical settings. However, there is a lack of evidence on the relative efficacy among the diverse range of probiotics. Overall, the GDG reached consensus that the benefit of adding probiotic may outweigh any potential harm.

Relative to quadruple therapy, should triple therapy combined with probiotics be recommended for people with H. pylori infection?

Recommendation

There is a lack of evidence to either support or refute the use of triple therapy combined with probiotics for people with *H. pylori* infection in initial and second line treatments (no recommendation, very low certainty of evidence).

Evidence profile

Two RCTs from China[88] and Italy[89] were included. One[89] compared bismuth quadruple therapy with triple therapy plus *Lactobacillus* (duration 10 days), while the other[88] compared it with tipple therapy plus *Bifidobacterium* (duration 14 days). Results show that relative to bismuth quadruple therapy, triple therapy plus probiotic makes little to no difference to eradication rate (RR = 1.02, 95% CI 0.92–1.13) or adverse events. There is a lack of evidence to either support or refute the use of triple therapy plus probiotics.

Relative to bismuth quadruple therapy, should triple therapy combined with gastric mucosal protective agents be recommended for initial and second line eradication treatment?

Recommendation

The GDG suggests against the use of triple therapy combined with gastric mucosal protective agents for initial and second line eradication treatments (weak recommendation, expert consensus).

Evidence profile

There were no eligible RCTs with direct comparisons. China, in general, has a high antibiotic resistance rate on clarithromycin, metronidazole, and levofloxacin, and this partially contributed to the progressively declining eradication rate with triple therapy. This, coupled with the limitation in accessing AST, led to a preference among Chinese clinicians to lean toward the use of bismuth quadruple therapy. With consideration to the above, and the lack of evidence proving additional clinical benefit of triple therapy with gastric mucosal protective agents, the GDG concludes that bismuth quadruple therapy has advantage, particularly in acceptability and feasibility, among Chinese stakeholders.

What treatment should be recommended to people with refractory H. pylori infection?

Recommendation

The GDG suggests the following treatment for people with refractory *H. pylori* infection: (1) empirical bismuth quadruple therapy with combination of antibiotics listed in Table 4, in addition to PPI or bismuth; and (2) where possible, application of bacterial culture and AST to guide treatment plan (weak recommendation, expert consensus).

Implementation suggestion

1. With the exception of clarithromycin and levofloxacine, antibiotic resistance gene mutation analysis appears to have relatively limited value due to the lack of consistency between phenotypic resistance and genetic resistance. Since a majority of refractory cases in China are resistant to clarithromycin and levofloxacine, applying the analysis in this group has limited value.
2. With consideration to local clinical features (eg, drug resistance and accessibility), when applying empirical bismuth quadruple therapy, the GDG suggests antibiotic combinations listed in Table 4, and advises against repeated application of previously used antibiotics.
3. The GDG suggests increasing the dosage of PPI or replacing it with P-CAB in people with CYP2C19 rapid metabolizer.
4. The GDG suggests against treatment plans containing rifabutin, since it may further increase drug resistance in people with tuberculosis.
5. Evidence supporting the use of semi-synthetic tetracycline (eg, minocycline) in people with refractory *H. pylori* infection is limited.[90-92]

Evidence profile

Refractory *H. pylori* infection refers to those cases of *H. pylori* infection with at least two unsuccessful eradication treatments. The GDG estimates that at least 5% to 10% of the *H. pylori* infections in Chinese population are refractory cases, which presents a major challenge for treatment. Our search did not find any RCT evidence in this area, and recommendations in Table 4 are drawn with reference to clinical studies in refractory patients in China.[93,94]

What therapy should be recommended to people with H. pylori infection who are allergic to penicillin?

Recommendation

For people with *H. pylori* infection and penicillin allergy, the GDG suggests bismuth quadruple therapy with tetracycline and metronidazole; or bismuth quadruple therapy containing cefuroxime instead of amoxicillin [Table 5]. The GDG suggests against bismuth quadruple therapy with any combinations of clarithromycin, levofloxacin, or metronidazole, with the exception of when metronidazole is used in full dosage (1.5–1.6 g/day) (weak recommendation, expert consensus).

Implementation suggestion

Where possible, the GDG suggests use of individualized therapy guided by genetic testing or strain culture.

Evidence profile

Around 5% to 10% of people with *H. pylori* infection are allergic to penicillin, which presents a challenge to eradication treatment.[95] Clinically, an even greater percentage of people are unable to use amoxicillin for various reasons, for example, history of penicillin allergy, penicillin allergy test positive, lack of allergy test facility, and other adverse reaction. Only a small proportion of these people truly have immune mediated allergy. It is crucial that clinicians thoroughly examine patients' condition and history to exclude the possibility of the above and retain the option of amoxicillin use.[96] In China, antibiotic resistance rate for clarithromycin, levofloxacin, and metronidazole is gradually increasing,

Table 4: Antibiotic combinations in bismuth quadruple therapy for refractory *H. pylori* infection.

Therapy	Antibiotic 1	Antibiotic 2
1	Tetracycline 500 mg, t.i.d. or q.i.d.	Metronidazole 400 mg, q.i.d.
2	Amoxicillin 1000 mg, b.i.d. or t.i.d.	Furazolidone 100 mg, b.i.d.
3	Tetracycline 500 mg, t.i.d. or q.i.d.	Furazolidone 100 mg, b.i.d.
4	Amoxicillin 1000 mg, b.i.d. or t.i.d.	Tetracycline 500 mg, t.i.d. or q.i.d.
5	Amoxicillin 1000 mg, b.i.d. or t.i.d.	Metronidazole 400 mg, q.i.d.

H. pylori: Helicobacter pylori.

Table 5: Antibiotic combinations in bismuth quadruple therapy for people with penicillin allergy.

Therapy	Antibiotic 1	Antibiotic 2
1	Tetracycline 500 mg, t.i.d. or q.i.d.	Metronidazole 400 mg, t.i.d. or q.i.d.
2	Cefuroxime 500 mg, b.i.d.	Levofloxacin 500 mg, q.d.
3	Clarithromycin 500 mg, b.i.d.	Metronidazole 400 mg, q.i.d.

which results in reduced effectiveness of eradication therapies with combinations of these drugs, particularly with pair-wise combinations in the penicillin allergic subgroup population. Options are further restricted for people in initial and second line treatments, as the Chinese regulatory agency (the NMPA) permits furazolidone for use only in refractory infection.

One cohort study[97] demonstrated an acceptable eradication rate with bismuth quadruple therapy containing tetracycline and metronidazole, but the feasibility of this therapy is challenged in China due to the restricted accessibility to tetracycline. Other research investigating alternative options produced inconclusive findings, including replacement of amoxicillin with cefuroxime,[98,99] increasing the frequency and dosage of metronidazole,[100] use of semi-synthetic tetracycline (eg, minocycline),[91] and enhancement of acid suppression using P-CAB.[101]

Discussion

Though decreasing in developed countries, the prevalence of *H. pylori* remains high in developing countries, causing a major public health burden. Adding to the challenge, antimicrobial resistance is disproportionally higher in low-income and middle-income countries.[102] International CPGs cannot fully address the practical needs of clinicians in lower middle-income countries (LMIC), such as China, for they lack consideration of local healthcare features, antibiotic resistance pattern, regional feasibility, and acceptability data.

Globally, bismuth-based triple therapy was the earlier mainstream therapy, whereas classic bismuth-based quadruple therapy (that consists of PPI, bismuth, metronidazole, and tetracycline) has been gaining popularity only in recent years. In contrast, bismuth quadruple therapy (internationally also known as triple therapy plus bismuth) has been the mainstay therapy in China for nearly a decade, almost replacing triple therapy. The mechanism of action of bismuth is not yet fully understood, but its direct antimicrobial activity against *H. pylori* has been demonstrated. Studies from China, Korea, and Europe reported that the addition of bismuth (ie, 14-day triple therapy plus bismuth) can improve eradication rates despite a high prevalence of antimicrobial resistance. It appears that a major benefit of bismuth's effect lies in the fact that it causes a rise in the successful eradication rate among antibiotic resistant infections by an additional 30% to 40%.[103] Bismuth preparations are inexpensive, safe, and effective, and consequently, making bismuth quadruple therapy a preferred choice for initial and rescue treatments is warranted.

Comparing with the recently published Maastricht VI/Florence considerations report[104] on *H. pylori* infection, we observe that the two guidelines are similar and consistent in terms of eradication treatment course, recommendation of some bismuth quadruple regimens, use of acid suppressants (PPI and P-CAB), and recommendation of dual therapy. Due to the different background of drug resistance, the clinical availability of drugs, and the application of previous eradication regimens and research experiences, there are significant differences in the treatment framework, processing flow, drug selection, and so on.

Applicability of Recommendations

Antimicrobial resistant patter and host genotype are two major factors affecting the effectiveness of eradication treatment (eg, *CYPRC19* gene carriers are a PPI fast metabolizer), and many LMIC share a similar antimicrobial resistant pattern with China (eg, high resistance to clarithromycin, metronidazole, and levofloxacin). Health systems in these LMIC often lacks resources and face similar sociological (eg, poor awareness level) and technological (eg, diagnostic/laboratory detection of infection) challenges, which escalates inappropriate antimicrobial use.[103] Therefore, the recommendations in this CPG are applicable to resource-limited settings, and countries with an antibiotic resistance pattern similar to China's.

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Conflicts of interest

None.

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