National Consensus on Management of Dyspepsia and *Helicobacter pylori* Infection

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ABSTRAK

Dispepsia merupakan salah satu dari berbagai keluhan umum yang dapat ditemui oleh dokter di berbagai bidang, tidak terbatas hanya pada ahli saluran cerna saja dalam praktik kesehariannya. Pengertian mengenai patofisiologi dispepsia terus berkembang sejak dimulainya investigasi secara ilmiah pada 1980-an sampai dengan saat ini yang memandang infeksi Helicobacter pylori sebagai salah satu faktor kunci dalam menangani dispepsia, baik terkait ulkus maupun non-ulkus. Penatalaksanaan dispepsia tidak bisa dilepaskan dari penatalaksaan infeksi H.pylori, serta penambahan pengetahuan baru terkait definisi, patofisiologi, diagnosis dan penatalaksanaan dispepsia dan infeksi H.pylori.

Konsensus penatalaksanaan dispepsia dan infeksi H.pylori di Indonesia ini dibuat berdasarkan evidence based medicine, sehingga dapat digunakan sebagai rujukan para dokter dalam menangani kasus-kasus dispepsia dan infeksi H.pylori di tempat praktik sehari-hari. Dengan adanya konsensus terbaru ini diharapkan para dokter dapat lebih meningkatkan pelayanannya kepada pasien-pasien dispepsia dan infeksi H.pylori.

Kata kunci: *dispepsia, H. Pylori, saluran cerna.*

ABSTRACT

Dyspepsia is one of numerous general complaints, which is commonly encountered by doctors of various disciplines. In daily practice, the complaint is not only limited for gastroenterologists. Knowledge on pathophysiology of dyspepsia have been developing continuously since a scientific investigation has been started in 1980's, which considers Helicobacter pylori as one of key factor in managing dyspepsia, either it is associated with ulcer or non-ulcer. The management of dyspepsia cannot be separated from the management of H. pylori and there is an additional new knowledge associated with definition, pathophysiology, diagnosis and treatment of both dyspepsia and H. pylori infection.

This consensus document on the management of dyspepsia and H. pylori infection in Indonesia has been developed using the evidence-based medicine principles; therefore, it can be used as a reference for doctors in dealing with dyspepsia and H. pylori infection cases in their daily practice. It is expected that with the new consensus, doctors can provide greater service to their patients who have dyspepsia and H. pylori infection.

Keywords: *dyspepsia, H. Pylori, gastrointestinal tract.*

INTRODUCTION

Dyspepsia is a common symptom found in daily practice and it has been known for a long period of time. There is a continuously developing definition starting from all symptoms originated from the upper gastrointestinal tract up to the exclusion of reflux symptoms; while the most recent definition refers to the Rome III criteria.[1]

H. pylori (Hp) infection nowadays has been considered as one of important factors in dyspepsia management, both the organic or functional dyspepsia; therefore, any discussion on dyspepsia should be correlated with the management of Hp infection. Various meta-analysis studies have demonstrated that there is a correlation between Hp infection and gastroduodenal diseases, which is characterized by symptoms/signs of dyspepsia.[2,3] The prevalence of Hp infection in Asia is relatively high and thus it should be noticed in the diagnosis approach and management of dyspepsia. Hp eradication has been proven effective in eliminating symptoms of organic dyspepsia; however, for functional dyspepsia, further studies are still necessary.[4]

The consensus is developed to provide a guideline for general physicians, specialists, and consultants regarding the management of dyspepsia. The consensus has combined the management of dyspepsia and Hp infection; therefore, it will achieve better results.

EPIDEMIOLOGY

Dyspepsia is an uncomfortable feeling (discomfort) originated from the upper part of abdomen. The discomfort can be one of or some of following symptoms, i.e. epigastric pain, epigastric burn, feeling of fullness after having meal, early satiated and bloating in the upper gastrointestinal tract area, nausea, vomiting and blurping.[5] For functional dyspepsia, those abovementioned symptoms must occur for at least the last three months with symptom onset of six months before the diagnosis is defined.

The prevalence of dyspepsia in health care units reaches 30% of services offerec by general physicians and 50% of services by gastroenterologists. Most of Asian patients with uninvestigated dyspepsia and without any alarm signs experience functional dyspepsia. The results of studies in Asian countries (China, Hong Kong, Indonesia, Korea, Malaysia, Singapore, Taiwan, Thailand and Vietnam) show that 43 to 79.5% patients with dyspepsia have dysfunctional dyspepsia.[5]

From the results of endoscopy, which had been performed in 550 patients with dyspepsia at some centers in Indonesia between January 2003 and April 2004, there were 44.7% cases with minimal disorder of gastritis and duodenitis; 6.5^ cases with gastric ulcer and 8.2% of normal cases.[6] In Indonesia, the data on prevalence of Hp infection in patients with peptic ulcers (without a history of using non-steroid anti-inflammatory drugs (NSAIDS)) varies between 90 and 100% and for patients with functional dyspepsia, the prevalence is 20-40% with various diagnostic methods (serology examination, culture and histopathology).[7]

The prevalence of Hp infection in patients with dyspepsia who underwent endoscopic examination at various teaching hospital in Indonesia between 2003 and 2004 was 10.2%. A relatively high prevalence was found in Makassar, which was 55% (2011) and in Solo as many as 51.8% (2008). The high prevalence was also found in Yogyakarta of 30.6% and Surabaya of 23.5% in 2013; while the lowest prevalence has been found in Jakarta (8%).[6,8-10]

PATHOPHYSIOLOGY

The pathophysiiology of peptic ulcer caused by Hp and non-steroid anti-inflammatory drugs (NSAID) has been widely known.[1] Functional dyspepsia is caused by some major factors such as gastroduodenal motility disorder, Hp infection, gastric acid, visceral hypersensitivity and psychological factors. Other factors that may have role are genetics, life style, environment, diet and history of previous gastrointestinal infection.[11,12]

The Role of Gastroduodenal Motility Disorders

The gastroduodenal motility disorder consists of reduced gastric capacity in accommodating meal (impaired gastric accommodation), antroduodenal incoordination and slow gastric

emptying. It is also one of main mechanism in the pathophysiology of functional dyspepsia, which is associated with bloating after meal and it may be found in the form of abdominal distension, bloating and fullness.[5,12]

The Role of Visceral Hypersensitivity

Visceral hypersensitivity has an important role in the pathophysiology of functional dyspepsia, particularly in increasing the sensitivity of peripheral and central sensory nerves against chemical and intraluminal receptor stimuli at the proximal part of the stomach. It can cause or aggravate dyspepsia symptoms.[5]

The Role of Psychosocial Factors

Psychosocial disorder is one of inducers that may have roles in functional dyspepsia. The severity of psychosocial disorder is consistent with the severity of dyspepsia. Various studies show that depression and anxiety have roles in the development of functional dyspepsia.[5,12]

The Role of Gastric Acid

Gastric acid may have a role in developing symptoms of functional dyspepsia. It has also becomes an underlying reason for effective treatment using anti-secretory agents as shown by some studies in patients with functional dyspepsia. There is little data of studies on the gastric secretion and some reports in Asia are still controversial.[5]

The Role of Hp Infection

The prevalence of Hp infection in patients with functional dyspepsia varies from 39% to 87%. The correlation between Hp infection and motility disorder is inconsistent; however, eradication of Hp improves the symptoms of functional dyspepsia. Biological markers such as ghrelin and leptin as well as altered expression of muscle-specific microRNAs are correlated with pathophysiological process of functional dyspepsia, which still needs further studies.[5,13]

DIAGNOSIS

Diagnosis of Dyspepsia

Dyspepsia that has been investigated consists of organic and functional dyspepsia. Organic dyspepsia consists of gastric ulcer, duodenal ulcer, erosive gastritis, gastritis, duodenitis and a process of malignancy. Functional dyspepsia refers to the Rome III criteria, which has not been validated in Indonesia. The Asia-Pacific Consensus (2012) has decided to follow the concept in the Rome III diagnosis criteria with some additional symptoms of bloating in the upper abdominal part, which is commonly found as the symptom of functional dyspepsia.[5]

Dyspepsia according to the Rome III criteria is a disease with one or more symptoms associated with gastroduodenal abnormalities of:

- Epigastric pain
- Epigastric burn sensation
- Fullness or discomfort after meal
- Early satiety

The symptoms must occur at least in the last three months with an onset of symptoms in six months before the diagnosis is established.

The Rome III criteria categorize functional dyspepsia into 2 subgroups, i.e. the epigatric pain syndrome and postprandial distress syndrome. However, the most recent evidence demonstrates that there is an overlapping of diagnosis in two third of patients with dyspepsia.[1]

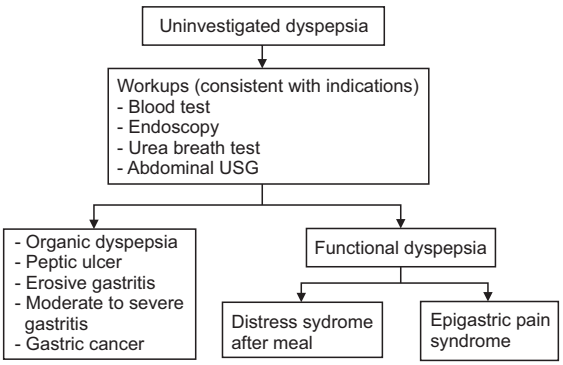


Figure 1. Algorithm for diagnosis of uninvestigated dyspepsia

Evaluation on the alarm signs must always be part of evaluation of the patients who come with a complaint of dyspepsia. The alarm signs for dyspepsia include weight loss (unintended weight loss), progressive dysphagia, recurrent or persistent vomiting, gastrointestinal bleeding, anemia, fever, a mass in the upper abdominal area, a family history of gastric cancer, dyspepsia with new onset in patients aged more than 45 years. Patients with those complaints must be investigated first using endoscopy.[5]

Diagnosis of Hp Infection[14]

Diagnostic test of Hp infection can be performed both directly using endoscopy (rapid urease test, histological test, culture and PCR) and indirectly without endoscopy (urea breath test, stool test, urine test and serology). Urea breat test has now become the gold standard for evaluating Hp. One of the available urea breath tests is the ^{13}CO breath analyzer. There is a requirement for conducting Hp evaluation, i.e. the patient must be free from antibiotic and PPI (proton-pump inhibitor) treatment for 2 weeks and there are some other factors that need to be taken into consideration such as clinical situation, prevalence of the infection, prevalence of the infection in a population, probability of pre-test infection, differences in test performance and factors that can affect the result of the test such as the use of anti-secretory and antibiotic treatment.

MANAGEMENT

The management of dyspepsia is initiated by carrying out efforts on identification of pathophysiology and etiological factors as many as possible.[11] Treatment of dyspepsia can already be started based on the dominant clinical symptoms (although those symptoms have not been investigated) and the treatment is subsequently continued in consistent with the results of investigation.

Tabel 1. A comparison of various diagnostic tests for Hp infection

Tests	Sn	Sp	Notes
With endoscopy			
Rapid urease test	>98%	99%	- Fast and inexpensive - Reduced sensitivity following treatment - Specimens are obtained from antrum
Histology	>95%	>95%	- Increased detection using special staining Warthin- Starry/ hematoxylin-eosin/ Giemsa) - Specimens are obtained from antrum and corpus
Culture			- Very specific, poor sensitivity when transport medium is not available - Requires experience - Expensive, often unavailable - Specimens are obtained from antrum and corpus - Using media such as Sparrow
PCR			- Sensitive and specific - No standard - Specimens were obtained from antrum and corpus - Considered
Without endoscopy			
ELISA serology	85-92%	79-83%	- Less accurate and does not demonstrate active infection - A reliable predictor of infection in developing countries with high prevalencei - It is not recommended for a period after therapy - Inexpensive and available
^{13}C urea breath test (UBT) such as: $^{13}CO_2$ breath analyzer	95%	96%	- It is recommended for establishing the diagnosis of Hp infection before commencing therapy[14] - The test of choice for confirming eradication - Patient is not allowed having PPI and antibiotic treatment for 2 weeks prior to the examination.[15,16] - Varied availability
Fecal antigen	95%	94%	Rarely used although it has high sensitivity and specificity, before and after therapy
Finger-stick serology			Very poor and can not match the ELISA serology
Urinary antibody: Urine-baed Rapid Urine Test[17-19]	73.2-82%	78.6-90.7%	Right now, the urine test has not been available in Indonesia

Sn: sensitivity, Sp: specificity, ELISA: enzyme-linked immunosorbent assay,
PCR: polymerase chain reaction, PPI: proton-pump inhibitor

Uninvestigated Dyspepsia

The optimum management strategy for this phase is by providing empirical therapy for 1-4 weeks before receiving results of initial investigation, i.e. the examination evaluating the evidence of Hp presence.[11,13] For certain region and ethnicity and patients with high risk, the Hp evaluation must be performed earlier. Medications that can be used are antacids, gastric acid antisecretory agents (PPI such as omeprazole, rabeprazole and lansoprazole and/or H2-Receptor Antagonist [H2RA]), prokinetics and cytoprotectors (such as rebamipide), in which the selection of the regimen is based on the dominant symptoms and previous medication. There is an ongoing development of a new drug which acts on the down-regulation proton pump that has been expected to have better mechanism of action than the PPI, i.e. the DLBS.[24,11]

Associated with the high prevalence of Hp infection, the test-and-treat strategy is applied for patients with dyspepsia symptoms without any alarm sign. The test-and-treat strategy is performed for:[20]

- Dyspepsia patients without any complication, who do not response to life style changes, 2-4 weeks of treatment using single PPI and without any alarm sign.
- Patients with a history of gastric or duodenal ulcer, but have never been investigated.
- Patients who will receive NSAID, particularly those with a history of gastroduodenal ulcer.
- Patients with unexplained iron deficiency anemia, idiopathic thrombocytopenic purpura and vitaminB12 deficiency.

Test and treat is NOT performed in:[20]

- Patients with gastroesophageal reflux disease (GERD).
- Children with functional dyspepsia.

Dyspepsia That Has Been Investigated

Dyspepsia patients with alarm signs receive no empirical therapy; instead, they should be investigated first by endoscopy with or without histopathological assessment before they are treated as patients with functional dyspepsia.

After the investigation, it does not exclude the possibility that in some of dyspepsia cases, GERD is found as the abnormality.

Organic Dyspepsia

When a lesion of mucosa (mucosal damage) is found, which is consistent with the endoscopy findings, therapy is given based on the abnormalities that have been found. Abnormalities that have been included into the organic dyspepsia group are gastritis, hemorrhagic gastritis, duodenitis, gastric ulcer, duodenal ulcer or malignancy process. In peptic ulcer (gastric and/or duodenal ulcer), the medication that can be given are a combination of PPI such as rabeprazole 2 x 20 mg or

Table 2. Therapy regimen for Hp eradication[14,23]

Drug	Dose	Duration
First line:		
PPI*	2x1	7-14 days
Amoxicillin	1000 mg (2x1)	
Clarithromycin	500 mg (2x1)	
In an area where resistance to clarithromycin >20%		
PPI*	2x1	7-14 days
Bismuth subsalicylate	2x2 tablet	
Metronidazole	500 mg (3x1)	
Tetracyline	250 mg (4x1)	
When bismuth is not available:		
PPI*	2x1	7-14 days
Amoxicillin	1000 mg (2x1)	
Clarithromycin	500 mg (2x1)	
Second line: this class of drugs is used when there is a failure with clarithromycin-based regimen		
PPI*	2x1	7-14 days
Bismuth subsalicylate	2x2 tablets	
Metronidazole	500 mg (3x1)	
PPI*	2x1	7-14 days
Amoxicillin	1000 mg (2x1)	
Levofloxacin	500 mg (2x1)	
Third line: when the second line regimen fails. Whenever possible, the selection is based on resistance test and/or clinical changes		
PPI*		7-14 days
Amoxicillin	2x1	
Levofloxacin	1000 mg (2x1)	
Rifabutin	500 mg (2x1)	

*PPI agents that have been used are rabeprazole 20 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and esomeprazole 40 mg.
Notes: Sequential therapy (can be given as the first lilne when there is no data about resistance to clarithromycin): PPI + amoxicillin for 5 days followed by PPI + clarithromycin and nitroimidazole (tinidazole) for 5 days.

lanzoprazole 2 x 30 mg and mucoprotectors such as rebamipide 3 x 100 mg.

Functional Dyspepsia

When there is no mucosal damage found after the investigation, the treatment can be given in consistent with the presence of functional dyspepsia.

The use of prokinetics such as metoclopramide, domperidone, cisapride, itopride and others can improve the symptoms of patients with functional dyspepsia. It may be associated with slow gastric emptying as one of pathophysiology in functional dyspepsia. Caution must always be applied when using cisapride as it may have potency for cardiovascular complication.[11]

Data about the use of antidepressants or antianxiolytic in patient siwht functional dyspepsia is still very limited. A recent study in Japan has demonstrated a significant improved symptom in patients with functional dyspepsia who have receivied 5-HT1 agonists compared to placebo. On the other hand, the use of venlafaxin, a serotonine and norepinephrin inhibitor, does not show better results compared to placebo.[5]

Psychological problems as well as sleep disturbance and defects on central serotonin sensitivity may become important factors in the response of antidepressant therapy in patients with functional dyspepsia.[5]

Management of dyspepsia with Hp infection

Hp eradication can provide long-term remission of dyspepsia symptoms.[20] A cross-sectional study conducted in 21 patients at Cipto Mangunkusumo Hospital, Jakarta (2010) found that the eradication therapy had improved the symptoms in a majority of dyspepsia patients with a percentage of symptom improvement as much as 76% and 81% had negative Hp results when they were evaluated using UBT.[21]

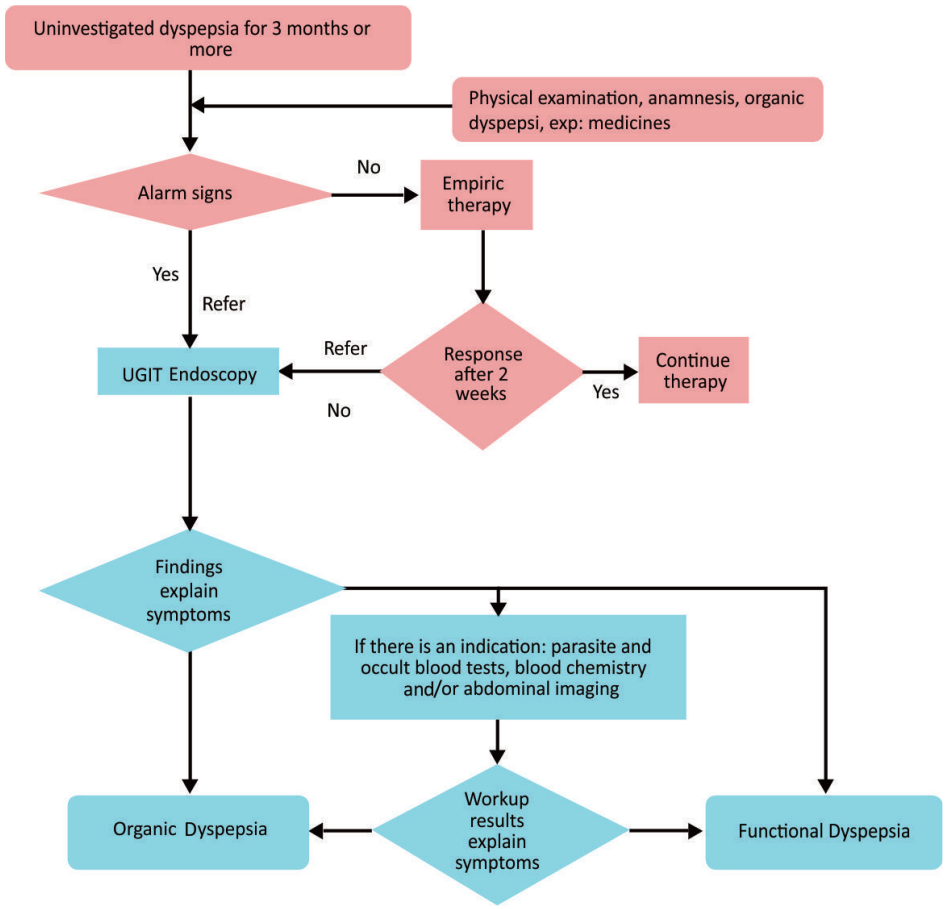
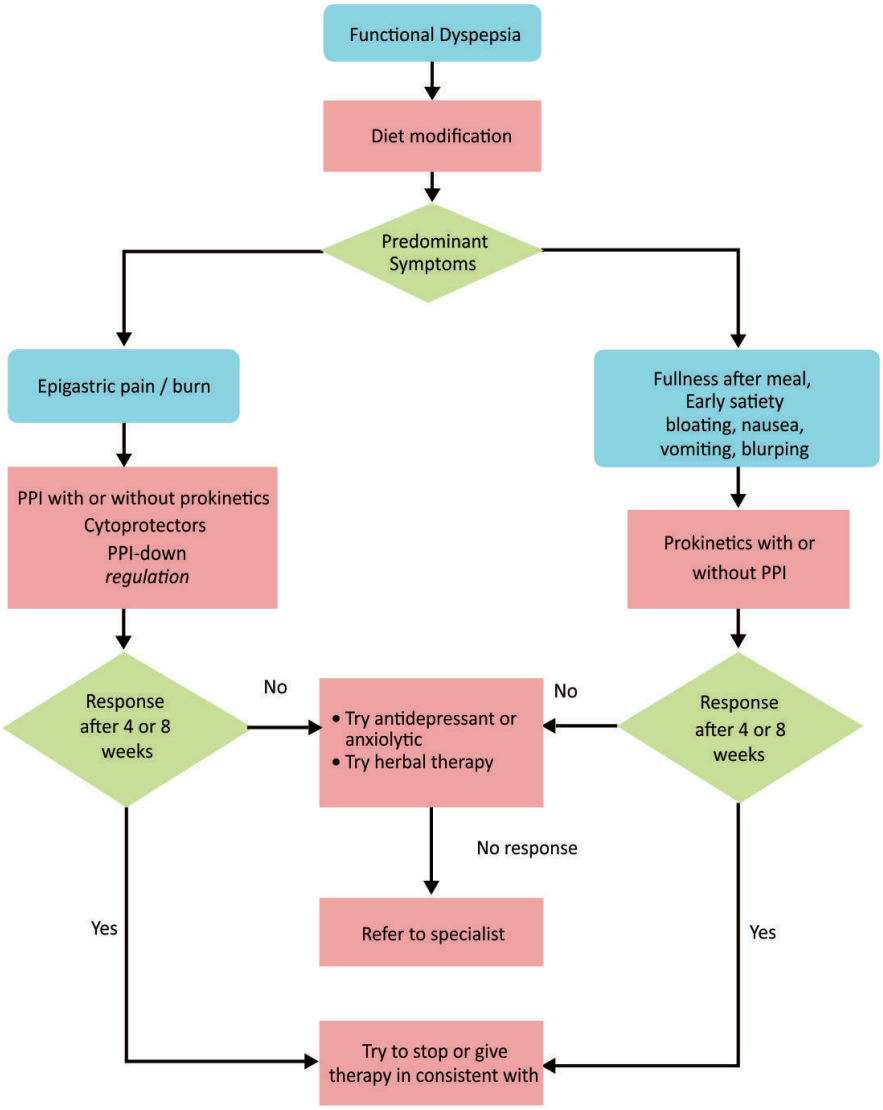


Figure 2. Algorithm of managing dyspepsia at various levels of health care units[5]



*Alarm signs: weight loss (unintended) progressive dysphagia, recurrent/persistent vomiting, gastrointestinal tract bleeding, anemia, fever, upper abdominal mass, family history of stomach cancer, new onset dyspepsia in patients aged >45 years.
PE: physical examination; UGIT: Upper Gastro Intestinal Tract, HCP-1: The First Level Health Care Provider, HCP-2-3: The Second and Third Level of Health Care Providers.

Figure 3. Algorithm of managing functional dyspepsia[5]

A prospective study conducted by Syam AF et al in 2010 showed that Hp eradication therapy using triple therapy (rabeprazole, amoxicillin and clarithromycin) for 7 days was better than the 5-day therapy.[22]

In an area where resistance to clarithromycin is high, we recommend to perform culture and resistance test (using endoscopic specimens) prior to therapy. A molecular test can also be performed to detect Hp and resistance to clarithromycin and/or fluoroquinolone directly through gastric biopsy.

After giving eradication therapy, a confirmation test must be done using UBT or H. pylori stool antigen monoclonal test. The test can be performed within at least 4 weeks after the end of treatment. For HpSA, there is a possibility of false positive result.

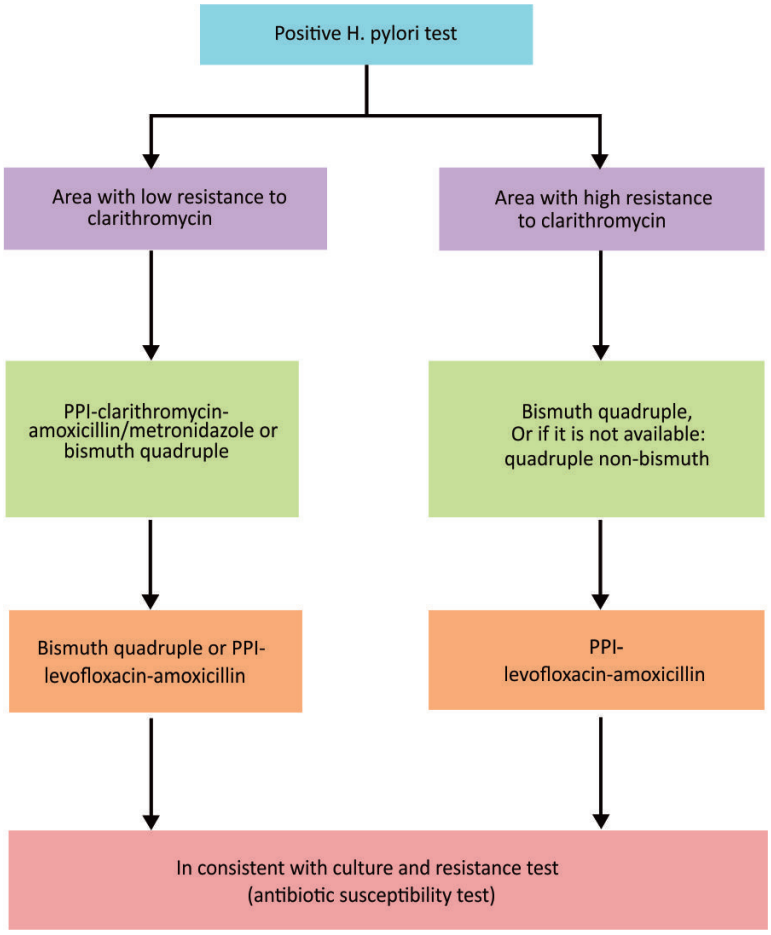


Figure 4. Algorithm of managing eradication of Hp infection[5]

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