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Clinical Practice: Diagnosis and Evaluation of Dyspepsia

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Abstract

The main issue regarding the approach to the patient with uninvestigated dyspepsia are whether the symptoms are the result of important clinical illness which then determines the appropriate management strategy for treatment of the symptoms. A initial trial of empiric anti-secretory drugs is recommended for those without *H. pylori* infection and no alarm symptoms whereas *H. pylori* eradication is recommended for those with an active *H. pylori* infection. Treatment expectations for *H. pylori* infections should theoretically be similar to other common infectious diseases. In most regions clarithromycin resistance has undermined traditional triple therapy such that it is no longer a suitable choice as an empiric therapy. Four drug therapies such as sequential, concomitant, and bismuth-quadruple therapy are generally still acceptable choices as empiric therapies. Post eradication testing is highly recommended to provides early identification of otherwise unrecognized increasing antimicrobial resistance. However, despite the ability to successfully cure *H. pylori* infections, a symptomatic response can be expected in only a minority of those with dyspepsia not associated with ulcers (so called non-ulcer dyspepsia). Overall, from the patients stand point, symptomatic relief is often difficult to achieve and physicians must relay on reassurance along with empiric and individualized care.

Keywords

Dyspepsia; *Helicobacter pylori*; diagnosis; non-ulcer dyspepsia; gastric ulcer; *H. pylori* therapy

Case vignette

Scenario 1

A 57 year old Korean-American man presented with a 6 month history of daily epigastric discomfort relieved by eating. He had not experienced this problem previously. There were no aggravating factors. He was otherwise healthy, had no other gastrointestinal complaints, and had not lost weight. He did not smoke and was a social drinker. He took no drugs. He had been born in Korea and had come to the United States at age 6 as an adoptee. The family history was unknown. Physical examination and basic laboratory tests (complete blood count, basic metabolic panel, and urinalysis) were normal. The stool guaiac was negative.

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Scenario 2

same patient but 25 years old

The clinical problem

Dyspepsia (bad digestion) is a common (ie, 15 to 40% of the population) and perplexing global problem with a broad differential. Initially, patients are characterized as having "uninvestigated" dyspepsia which simply means that the patient has not undergone specific diagnostic investigations most especially upper gastrointestinal endoscopy. After an appropriate evaluation the patient would be recharacterized as either having dyspepsia associated with a specific disease (eg, peptic ulcer disease), condition (eg, NSAID use), or as functional dyspepsia.

Dyspepsia like gastritis is a term has had variable use by both clinicians and patients. Some order was introduced by the ROME meetings on functional gastrointestinal disorders which have since 1988 grappled with bringing order to a variety of common gastrointestinal symptom complexes (1;2). The ROME II criteria defined functional dyspepsia as pain or discomfort centered in the upper abdomen without a definite structural or biochemical explanation. More recent iterations have separated patients with substernal discomfort and typical heartburn from those with dyspepsia. The most recent ROME III criteria reclassified functional dyspepsia with two new symptom entities: epigastric pain syndrome and meal-related symptoms termed postprandial pain syndrome (3;4). These working definitions are expected to continue to evolve as new etiological conditions are identified allowing symptom based definitions to be separated based on specific etiologies.

Strategies and Evidence

The diagnostic and management strategies for patients with dyspepsia are based first on the degree of concern regarding the presence of a serious disease and second on cost effectiveness. The 4 common approaches include: prompt endoscopy, an empiric trial of antisecretory drugs, test for *H. pylori* and treat those who test positive, and test for *H. pylori* and endoscope those who test positive. These approaches have been compared in randomized controlled trials (5-12).

The most common important clinical diagnoses presenting as dyspepsia are gastric-esophageal malignancies and peptic ulcer disease. Because of its better accuracy and the ability to obtain biopsies, upper gastrointestinal endoscopy has generally replaced barium radiographic studies as the diagnostic test of choice. The choice of a particular strategy depends on the pretest probability of finding an serious condition (defined as one in which a definite diagnose might favorably influence outcome). There is now general agreement that prompt endoscopy is the preferred strategy for those over a predefined age (typically 50 or 55) and those with "alarm symptoms" (Table 1) (13-19). The difference in recommended age cut-off is related to the fact that the prevalence of gastric carcinoma varies greatly among population (eg, 45 years in areas where gastric cancer is common and 55 in areas where it is not). Overall, the positive predictive value of alarm symptoms is poor; most will have normal upper endoscopies, and the few malignancies that are found are typically advanced (20;21). For those who do not qualify for prompt endoscopy, the decision to try empiric antisecretory therapy or test for *H. pylori* depends on the prevalence of *H. pylori* in the population. Generally empiric antisecretory therapy is recommended when the prevalence of *H. pylori* is 10% or less (13). In most regions, the prevalence of *H. pylori* is above this threshold and test and treat is the most cost effective strategy (22).

Scenario 1—This patient meets the criteria for early endoscopy based on age and recent onset.

Scenario 2—No alarm features are present; the prevalence of *H. pylori* is likely greater than 10% making the test and treat strategy like the most cost effective.

Diagnosis

Scenario 1—The patient underwent upper gastrointestinal endoscopy which showed a 1.5 cm benign appearing gastric ulcer 1 cm proximal to the angularis incisura. Biopsies of the ulcer edge and base and from the normal appearing mucosa of the antrum and corpus were taken according to the recommendations of the updated Sydney system. “Salvage” cytology was also performed. (23) and was negative for malignancy showing “Mucosecreting epithelia with regressive artifacts and leucocytes”). Histological interpretation was: “Antral biopsy samples shows mild intestinal metaplasia (atrophy +--) coexisting with active and follicular inflammation. The biopsy sample from the transitional zone features hyperplastic epithelial changes, and scattered intestinal metaplasia (+--) (vial 1). Both oxyntic samples (vial 2) show superficial inflammatory infiltrate with no atrophic changes. Biopsy samples obtained from the ulcer edge/base (vial 3) consist of connective tissue, partially covered by columnar hyperplastic epithelia including goblet cells; necrotic debris are also present. In both antral and corpus biopsy samples, bacteria with morphology consistent with *H. pylori* are present (++-)”.

Interpretation of the gastric histology

The histology shows a *H. pylori*-associated gastritis with atrophic gastritis of the antrum, non-atrophic corpus gastritis, coexisting with morphological features indicative of non-malignant active gastric ulcer. The availability of targeted antral and corpus specimens allowed the pathologist to provide an estimate of gastric cancer risk using the newly introduced OLGA staging system (Figure 1) (24). Using only the traditional histology report the clinician might be concerned about the finding of intestinal metaplasia, overestimate the cancer risk, and be unsure about what follow-up might be indicated. This case was assessed as OLGA-Stage II which signifies a low cancer risk.

Scenario 2—The choices for non-invasive testing for *H. pylori* include IgG serology (IgM and IgA anti-*H. pylori* antibody tests are unreliable), stool antigen or urea breath testing. Serologic testing is no longer recommended in part because of lower sensitivity and the presence of serum anti-*H. pylori* antibodies can not distinguish between present and past infection. Both stool antigen testing and the urea breath test detect the presence of active infection and have excellent sensitivity and specificity. Stool antigen tests using monoclonal antibodies are preferred over those using polyclonal antibodies. One caveat is that the use of antibiotics, bismuth, or proton pump inhibitors will reduce the bacterial load in the stomach and may result in false negative results. This is a problem both with non-invasive tests (urea breath test and stool antigen test) and with invasive tests such as histology, rapid urease testing, and culture. It is therefore recommended that when possible testing not be done within one, preferably 2 weeks of the use of any of these drugs. When there is a high pretest probability for *H. pylori* infection (ie, presence of an ulcer) and the tests are negative, the test should be repeated after discontinuing these drugs. H_2-receptor antagonists do not effect the *H. pylori* bacterial load and thus one can temporarily switch from PPI to an H2RA for patients who require continuous antisecretory drug therapy.

The patient in *Scenario 2* received a urea breath test which was positive. In most instances endoscopy would not be done in a young person without alarm systems because even if an ulcer were present, the ulcer disease would be cured along with the *H. pylori* infection.

Management

Scenario 1—The issues that need to be addressed include a strategy for obtaining relief of symptoms, healing of the ulcer, choice of anti-*H. pylori* therapy, deciding on a strategy for confirmation of cure of the infection, and deciding whether endoscopic confirmation of healing of the ulcer was warranted.

The issues for *Scenario 2* would be choice of anti-*H. pylori* therapy, deciding on a strategy for confirmation of cure of the infection (Figure 2).

Choice of anti-*H. pylori* therapy

Both scenario 1 and 2 require choosing an appropriate anti-*H. pylori* therapy. This decision has become increasingly difficult because, with few exceptions, worldwide empiric use of traditional (legacy) triple therapy with a PPI, clarithromycin and amoxicillin no longer provides an acceptable cure rate (ie, cure rates now typically below 80%) (25-33;33-37). This decline in effectiveness is primarily related to the increasing prevalence of clarithromycin resistance. The decline in effectiveness has often been unrecognized by practicing clinicians in part because, in contrast to other common infectious diseases, regional and local data concerning antibiotic resistance patterns is usually unavailable. In addition, post treatment testing for cure is often not routinely done such that clinicians were not alerted to the increasing tide of failures (37-39). Recent expert consensus statements and guidelines have also failed to effectively deal with this issue. They generally have acknowledged that legacy triple therapy should not be used empirically in regions where resistance is common, but fail to note with few exceptions (eg, Northern Eruope) high level resistance is now the rule and not the exception. It is ironic that when increasing resistance results in reduced cure rates for common bacterial infections (eg, *Streptococcus pneumoniae*), previously recommended therapies are rapidly abandoned for therapies that provide high cure rates. In contrast, with *H. pylori* infections, steadily falling cure rates have until recently been accepted and even recommended as first line. The *H. pylori* literature is also replete with examples of comparative trials in region where clarithromycin resistance has made triple therapy ineffective allowing investigators to “prove” that a new therapy A is superior to one with proven unacceptable low cure rates (38). Hopefully, *H. pylori* like other infectious diseases will begin to stress cure rates, only highly successful therapies will be compared, patients will no longer be randomized to known inferior regimens, and meta-analyses will no longer recommend as equivalent therapies that provide less than acceptable cure rates (ie, if both are bad, can one be better) (32-34;37;38;40).

High cure rates for *H. pylori* infections currently consists of multidrug therapies and include an antisecretory drug. Therapy tailored to antimicrobial susceptibility is preferred for all infectious diseases but is not yet widely available (41). Four drug combinations currently provide the best results although studies evaluating dose, duration, formulation, etc. have generally not been done such that the therapy is still more an art than a science (39). The currently best 4 drug combinations are shown in Table 2 and consist of two general combinations A) a PPI, amoxicillin, clarithromycin, metronidazole/tinidazole given either sequentially or concomitantly, or B) a PPI, a bismuth, tetracycline HCl, and metronidazole/tinidazole (37;42). Metronidazole resistance, in contrast to clarithromycin resistance, can be partially over come by increasing the dosage and duration of therapy. Both commercially available bismuth-containing convenience packs available in the United states (Helidac® and Pylera®) contain suboptimal doses of metronidazole (250 mg q.i.d. for Helidac® and 375 t.i.d. for Pylera® and in areas where metronidazole resistance is likely to be prevalent (ie, women, Hispanics, individuals from developing countries), it may be prudent to add an additional prescription to bring the dose up to 500 mg t.i.d. In addition, Pylera® contains a suboptimal dose of tetracycline (375 mg t.i.d.) instead of the recommended 500 mg q.i.d.

Confirmation of cure

As there is no universally effective empiric therapy, post eradication testing is recommended (eg, with a urea breath test or stool antigen test) to both confirm cure and to serve as an early warning of the rise in antibiotic resistance locally (37). Post eradication testing should be delayed a minimum of 4 weeks after the end of therapy to allow regrowth of any remaining bacteria. The caveats regarding avoiding use of antibiotics, bismuth and PPIs mentioned above also applies.

Confirmation of healing of the gastric ulcer

Until recently, it was standard of care to follow-up all gastric ulcers to confirm healing and more importantly to reconfirm that the ulcer was not actually a gastric cancer. This strategy was based on the knowledge that 1 to 5% of benign appearing ulcers are actually gastric cancers (43;44). As a general rule, gastric ulcers should be followed to complete healing confirmed endoscopically. Confirmation of cure of *H. pylori* can be done histologically at the same time. Endoscopic follow-up of duodenal ulcers is unnecessary.

Guidelines

Five guidelines and recommendations for dyspepsia have been published including those from North America, Europe and Asia (13-19) as well as a recent excellent review of the various guidelines (45). The agree on the major points. Differences primarily relate to the initial steps for those without alarm symptoms and these differences generally relate to the differences audiences (general physicians vs. gastroenterologists). There is also a well thought out discussion of dyspepsia associated with non-steroidal anti-inflammatory drug therapy with a useful algorithm (46).

Conclusions and Recommendations

The main issues regarding the approach to a patient with uninvestigated dyspepsia are whether the symptoms are the result of important clinical illness and what is the appropriate management strategy for treatment of the symptoms. A initial trial of empiric anti-secretory drugs is recommended for those without *H. pylori* infection and no alarm symptoms whereas *H. pylori* eradication is recommended for those with an active *H. pylori* infection. *H. pylori* infection is etiologically associated with clinical outcomes such as duodenal ulcer disease, gastric ulcer disease, and atrophic gastritis. Atrophic gastritis in turn may lead to iron and/or vitamin B12 deficiency, gastric adenocarcinoma and/or primary B-cell gastric lymphoma. (47-50). To Eradication is associated with healing of the gastritis prevention or cure of peptic ulcers. If done before the onset of atrophy will likely prevent gastric cancer. Thus, it is recommended for all *H. pylori* infections.

The treatment of *H. pylori* infection is being rethought to bring the expectations into line with other common treatable infectious diseases. It is now recognized that recommendations regarding the continued use of triple therapy are generally not useful for clinicians in that they lack specific details about the global problem of clarithromycin resistance and it deleterious effects on cure rates. In general, recent “consensus” groups and Society guidelines have recommended legacy triple therapy with caveat that if there is a high prevalence of resistance alternate therapy should be used. The general high prevalence of resistance supports the recommendation currently all patients should considered to have clarithromycin resistant *H. pylori* infections and legacy triple therapies should be avoided as an empiric choice (37-39). Hopefully, the next generation of recommendations will focus on empiric therapies that reliably provide high cure rates (Grade A or B results on the scale of A = ≥9% to F ≤80%)(35). The gold standard therapy should be “the one that works locally”. Recent consensus statements and

guidelines agree regarding the importance of diagnostic testing both pre and post therapy (51;52). Post eradication confirmation of cure is especially because it can provide early identification of otherwise unrecognized increasing antimicrobial resistance. However, despite the ability to successfully cure *H. pylori* infections, a symptomatic response can be expected in only a minority of those with dyspepsia not associated with ulcers (so called non-ulcer dyspepsia) (53). Overall, from the patients stand point, symptomatic relief is often difficult to achieve and physicians must relay on reassurance along with empiric and individualized care. For many patients, therapy consists of reassurance along with empiric and individualized.

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Atrophy Score		Corpus			
		No Atrophy (score 0)	Mild Atrophy (score 1)	Moderate Atrophy (score 2)	Severe Atrophy (score 3)
Antrum	No Atrophy (score 0) (including *incisura angularis*)	STAGE 0	STAGE I	STAGE II	STAGE II
	Mild Atrophy (score 1) (including *incisura angularis*)	STAGE I	STAGE I	STAGE II	STAGE III
	Moderate Atrophy (score 2) (including *incisura angularis*)	STAGE II	STAGE II	STAGE III	STAGE IV
	Severe Atrophy (score 3) (including *incisura angularis*)	STAGE III	STAGE III	STAGE IV	STAGE IV

Figure 1.
OLGA staging system for risk of gastric cancer

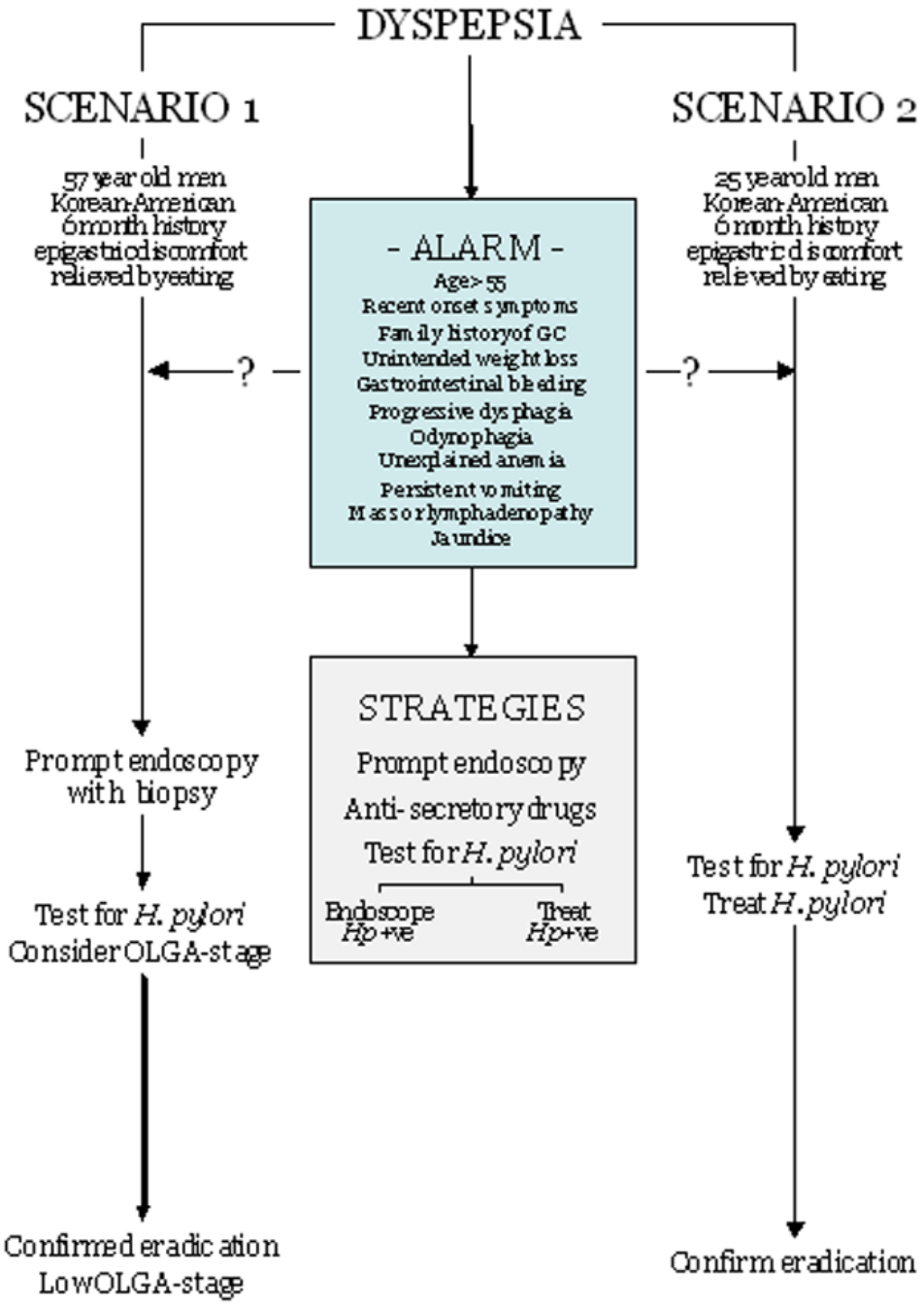

Figure 2.
Schema for evaluation of the patient

Table 1

Alarm symptoms

Age over 55 with new onset symptoms
Family history of gastric cancer
Unintended weight loss
Gastrointestinal bleeding
Progressive dysphagia
Odynophagia
Unexplained iron deficiency anemia
Persistent vomiting
Palpable mass or lymphadenopathy
Jaundice

Table 2

Four-drug therapies for *H. pylori* in the era of prevalent clarithromycin resistance

1	**Sequential regimen**: PPI + 1 gm amoxicillin b.i.d. for 5 days, followed by PPI + 500 mg clarithromycin + 500 mg metronidazole/tinidazole b.i.d. for 5 days)
2	**Concomitant regimen**: PPI + 1 gm amoxicillin + 500 mg clarithromycin + 500 mg metronidazole/ tinidazole all b.i.d. for 10 to 14 days
3	**Bismuth quadruple therapy**: PPI of choice b.i.d., bismuth tablets 2 q.i.d. (420 mg bismuth subcitrate or 524 mg bismuth subsalicylate), tetracycline HCl 500 mg q.i.d., metronidazole/tinidazole 500 gm t.i.d. (drugs often given with meals and when q.i.d. also at bedtime)