Pharmacy Benefits Management
Strategic Health Group and
the Medical Advisory Panel

The Pharmacologic Management of *Helicobacter pylori* in Peptic Ulcer Disease and Dyspepsia

Department of Veterans Affairs
Veterans Health Administration
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Department of
Veterans Affairs

Memorandum

Date: February 24, 1998

From: Under Secretary for Health (10)

Subj: Pharmacologic (Drug) Treatment Guidelines

To: VISN Directors, VISN Clinical Managers, Medical Center Directors,
Chiefs of Staff and Patient Care Staffs

1. To date, I have approved the issuance of eight drug treatment guidelines for the most common diagnoses associated with our patient population, and indicated that other guidelines would follow. Please find the attached drug treatment guideline for the Pharmacologic Management of *Helicobacter pylori* in Peptic Ulcer Disease and Dyspepsia.

2. The Medical Advisory Panel of VHA's Pharmacy Benefits Management Strategic Health Care Group facilitated and coordinated this effort. This guideline and those which will follow in the future months, are intended to promote cost effective, quality patient care for veteran patients throughout the VA health care system.

3. The guidelines are based on nationally recognized treatment guidelines, current literature and expert opinion from clinicians across the VA system. The guidelines are dynamic and will be revised as new clinical data becomes available. Also, the guidelines are not intended to interfere with clinical judgement that might dictate deviation under special circumstances. Rather, they are intended to assist practitioners in providing consistent, high quality care.

4. I commend the efforts put forth in the development of these guidelines and know from the many comments received about them from throughout the VA that they are a welcome tool for both practitioners and managers. I strongly encourage their utilization and will closely follow their implementation, as well as the outcomes associated with their use. They constitute a significant advancement in VHA's evolution toward a truly integrated health care delivery system.

Kenneth W. Kizer, M.D., M.P.H.

Attachment

The Medical Advisory Panel for the Pharmacy Benefits Management Strategic Health Group

Mission

The mission of the Medical Advisory Panel (MAP) for Pharmacy Benefits Management (PBM) includes the development of evidence-based pharmacologic management guidelines for improving quality and providing best-value patient care.

The MAP is comprised of practicing VA physicians from facilities across the nation:

Peter A. Glassman, M.B.B.S., M.Sc.
Chairman, Medical Advisory Panel
Staff Internist , Department of Medicine
VAMC West Los Angeles, CA.
Assistant Professor of Medicine
University of California, Los Angeles

John Booss, M.D.
National Director, Neurology Service
VAMC West Haven, CT.
Professor, Departments of Neurology &
Laboratory Medicine
Yale University School of Medicine

Domenic A. Ciraulo, M.D.
Chief, Psychiatry Service
VAMC Boston, MA.
Professor and Chairman
Division of Psychiatry
Boston University School of Medicine

Barry Cusack, M.D.
Chief, Geriatric Section
VAMC Boise, ID.
Associate Professor of Medicine
Division of Gerontology &
Geriatric Medicine, School of Medicine
University of Washington

Jeff Etchason, M.D.
Director, Health Service Research & Development VAMC
Atlanta, GA.
Director, Program for the Evaluation of Clinical Technologies
and Pharmaceuticals, Emory University Center for Clinical
Evaluation Sciences
Assistant Professor of Medicine
Emory University School of Medicine

C.B. Good, M.D., M.P.H.
Staff Physician, Department of Medicine
VAMC Pittsburgh, PA.
Associate Professor of Medicine
University of Pittsburgh

Patricia S. Hlavin, M.D., MS.
Director Urgent Care Center/Emergency Room
Director, FIRM Blue General Medicine Clinics
VAMC San Diego, CA.
Associate Clinical Professor of Medicine
University of California, San Diego

William Korchik, M.D.
Director, Extended Care Center
Medical Director, Adult Day Health Care
VAMC Minneapolis, MN.
Assistant Professor of Medicine
University of Minnesota

Pharmacy Benefits Management (PBM)
Strategic Health Group (SHG)

VHA's PBM SHG has been directed by the Under Secretary for Health to coordinate the development of guidelines for the pharmacologic management of common diseases treated within the VA, establish a national level VA formulary, and to manage pharmaceutical costs, utilization, and measure outcomes as they apply to patient care. The MAP provides support and direction to the PBM staff, located in Hines, Illinois.

John E. Ogden, R.Ph., M.S.
Chief Consultant, PBM SHG

Andy Muniz, R.Ph., M.S.
Deputy Chief Consultant, PBM SHG

Michael A. Valentino, R.Ph., MHSA
Associate Chief Consultant, PBM SHG

Karen E. Bertch, Pharm.D.
Clinical Specialist

Christine Chandler, Pharm.D.
Clinical Specialist

Elaine M. Furmaga, Pharm D.
Clinical Specialist

Deborah Khachikian, Pharm.D.
Clinical Specialist

Suzanne Lenz, R.Ph.
Pharmacist Specialist / Contract Liaison

Catherine Schranz, Pharm.D., M.S.
Clinical Specialist

Lisa Torphy
Program Specialist

Development of the Guidelines

Whenever possible, the PBM and MAP rely upon evidence-based, multidisciplinary, nationally recognized consensus statements for the basis of VA guidelines. Relevant literature is reviewed and assessed with consideration given to the VA population. Draft guidelines are sent to the field for comments prior to being finalized.

Development of the guidelines relied upon Soll AH, for the Practice Parameters Committee of the American College of Gastroenterology. *Medical treatment of peptic ulcer disease: Practice guidelines.* JAMA 1996;275:622-9, NIH Consensus Development Panel on *Helicobacter pylori* in Peptic Ulcer Disease. *Helicobacter pylori in peptic ulcer disease*. JAMA 1994;272:65-9, and Ofman JJ, Etchason J, Fullerton S et al. *Management strategies for Helicobacter pylori-seropositive patients with dyspepsia: Clinical and economic consequences.* Ann Intern Med 1997;126:280-316.

Use of the Guidelines

The purpose of the guidelines is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. This guideline attempts to define principles of practice which should produce high quality patient care. They are attuned to the needs of a primary care practice but are directed to providers at all levels. The guidelines also serve as a basis for monitoring local, regional and national patterns of pharmacologic care.

Guidelines should not be considered inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the same results. The ultimate judgment regarding the propriety of any course of conduct must be made by the clinician in light of individual patient situations.

Updating the Guidelines

PBM will review the guidelines routinely. Updating will occur as new information is made available from well-designed, scientifically valid studies and as outcome data may direct.

A current copy of the pharmacologic management guidelines can be obtained from the Pharmacy Benefits Management home page at http://www.dppm.med.va.gov

Referencing the Guidelines

This guideline should be referenced as:
Pharmacy Benefits Management-Medical Advisory Panel. The Pharmacologic Management of *Helicobacter pylori* in Peptic Ulcer Disease and Dyspepsia. VHA PBM-SHG Publication No. 98-0009. Hines, IL: Pharmacy Benefits Management Strategic Health Group, Veterans Health Administration, Department of Veterans Affairs. February 1998.

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The PBM/MAP collaborates with VA technical advisory groups and other experts in developing guidelines. We gratefully acknowledge and thank those clinicians for sharing their expertise in this area.

Andrew H. Soll, M.D.
Staff Physician, Division of Gastroenterology
Medical Service
VAMC West Los Angeles, CA.
Professor of Medicine
University of California, Los Angeles

Draft guidelines were disseminated for peer-review through the VISNs, prior to their completion. The PBM and the MAP would like to acknowledge and thank the following individuals who contributed both their time and effort to this process.

Matthew Christianson, R.Ph.
Pharmacy Resident
VA Puget Sound Healthcare System
Seattle, WA

P. Bailey Francis, M.D.
Chief of Staff
Atlanta VAMC
Atlanta, GA

Brett R. Gandhi, M.D.
General Internist
VA Healthcare Network of New England
Manchester, NH

Jerry G. Greene, M.D.
Medical Director
Samuel S. Stratton VAMC
Albany, NY

Ian Gralnek, M.D.
Department of Gastroenterology
West Los Angeles VAMC
West Los Angeles, CA

William Grossman, M.D.
Chief Medical Officer
Wilkes-Barre VAMC
Wilkes-Barre, PA

Daniel Hollander, M.D.
Chief Medical Officer
VHA Sierra Pacific Network
San Francisco, CA

Richard Jesudass, M.D.
Staff Gastroenterologist
Muskogee VAMC
Muskogee, OK

Cyrus Kapadia, M.D.
Associate Chief, Medicine and Digestive Diseases
VA Connecticut Healthcare System (West Haven)
West Haven, CT

Terry Laws, Pharm.D.
Infectious Disease Clinical Pharmacist
Asheville VAMC
Asheville, NC

Thomas Mahl, M.D.
Chief, Gastroenterology and Assistant
Professor of Medicine
Buffalo VAMC
Buffalo, NY

Denis M. McCarthy, M.D.
Chief of Division of Gastroenterology and
Hepatology at University of New Mexico
and Chief of General Internal Medicine
Albuquerque VAMC
Albuquerque, NM

* This list does not represent all the clinicians who reviewed the guideline, rather those who wished to be acknowledged. The Pharmacy Benefits Management and Medical Advisory Panel take full responsibility for the content of this guideline.

II. Acknowledgments Con't*

Anthony Morreale, Pharm.D.
Assistant Chief, Pharmacy Service
San Diego VAMC
San Diego, CA

Peter Mucha, Jr., M.D.
Chief, Surgical Service
Lebanon VAMC
Lebanon, PA

Carrie P. Ogorek, M.D.
Primary Care Physician and
Acting Chief of Gastroenterology
Philadelphia VAMC
Philadelphia, PA

Gary M. Patchin, Pharm.D.
Clinical Pharmacy Specialist
Ioannis A. Lougaris VAMC
Reno, NV

J. David Ranjitsingh, M.D.
Chief, Medical Service
Columbus VAOPC
Columbus, OH

Jean-Pierre Raufman, M.D
Chief, DD&N
Little Rock VAMC
Little Rock, AR

Joseph Rindone, Pharm.D.
Clinical Pharmacist
Prescott VAMC
Prescott, AZ

Michael Rotblatt, M.D.
Clinical Assistant Professor of Medicine
Sepulveda VAMC
Sepulveda, CA

Karine Rozenberg-Ben-Dror, Pharm.D.
Clinical Pharmacy Specialist
VA Chicago Healthcare System
Lakeside Division
Chicago, IL

Richard E. Sampliner, M.D.
Program Director, Gastroenterology Section
Tuscon VAMC
Tuscon, AZ

Jerome M. Sampson, M.D.
Chief, Medical Service
Alexandria VAMC
Alexandria, LA

Marisel Segarra-Newnham, Pharm.D.
Clinical Pharmacist - Infectious Disease
West Palm Beach VAMC
West Palm Beach, FL

Steven I. Shedlofsky, M.D.
Professor of Internal Medicine and
Chief, Gastroenterology
Lexington VAMC
Lexington, KY

Eden A. Suguitan, M.D.
Gastroenterologist
Lebanon VAMC
Lebanon, PA

Jeff Whittle, M.D.
Staff Physician
VA Pittsburgh Health Care System
Pittsburgh, PA

William White, M.D.
Associate Chief of Staff
Little Rock VAMC
Little Rock, AR

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EXECUTIVE SUMMARY

1. The presence of *Helicobacter pylori (H. pylori)* is associated with peptic ulcer disease (PUD). It is detected in 80-95% of duodenal ulcers (DU) and 70-90% of gastric ulcers (GU) not associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs).

2. Invasive and non-invasive *H. pylori* tests are available. Several clinical factors such as recent use of antibiotics or proton pump inhibitors (PPIs), or whether the patient has a planned esophagogastroduodendoscopy (EGD) influence the modality chosen to test for *H. pylori*. No one test can be recommended in all instances, and all tests, except for cultures, have sensitivity and specificity of 90% or greater when used appropriately.

   a. The role of *H. pylori* in patients with documented non-ulcer dyspepsia (NUD) and gastroesophageal reflux disease (GERD) has not been established, and a recommendation regarding testing and management cannot be made at this time.

   b. Testing for *H. pylori* is generally recommended for patients with a history of PUD with recurrent dyspepsia or newly documented PUD, and for patients with recurrent or ongoing uncomplicated dyspepsia that has not yet been investigated or evaluated.

   c. However, in patients with uncomplicated DU who are not taking NSAIDs, the high prevalence of *H. pylori* infection in the population favors empiric *H. pylori* eradication therapy without prior *H. pylori* testing.

3. Current consensus recommends treating *H. pylori*-positive ulcer patients with an appropriate antibiotic-containing eradication regimen to facilitate ulcer healing and reduce the risk of ulcer recurrence.

   a. For patients with uncomplicated dyspepsia and positive *H. pylori* serology, this document recommends treating *H. pylori* without investigation for PUD. This has been demonstrated to be cost-effective based on the principles of decision analysis.

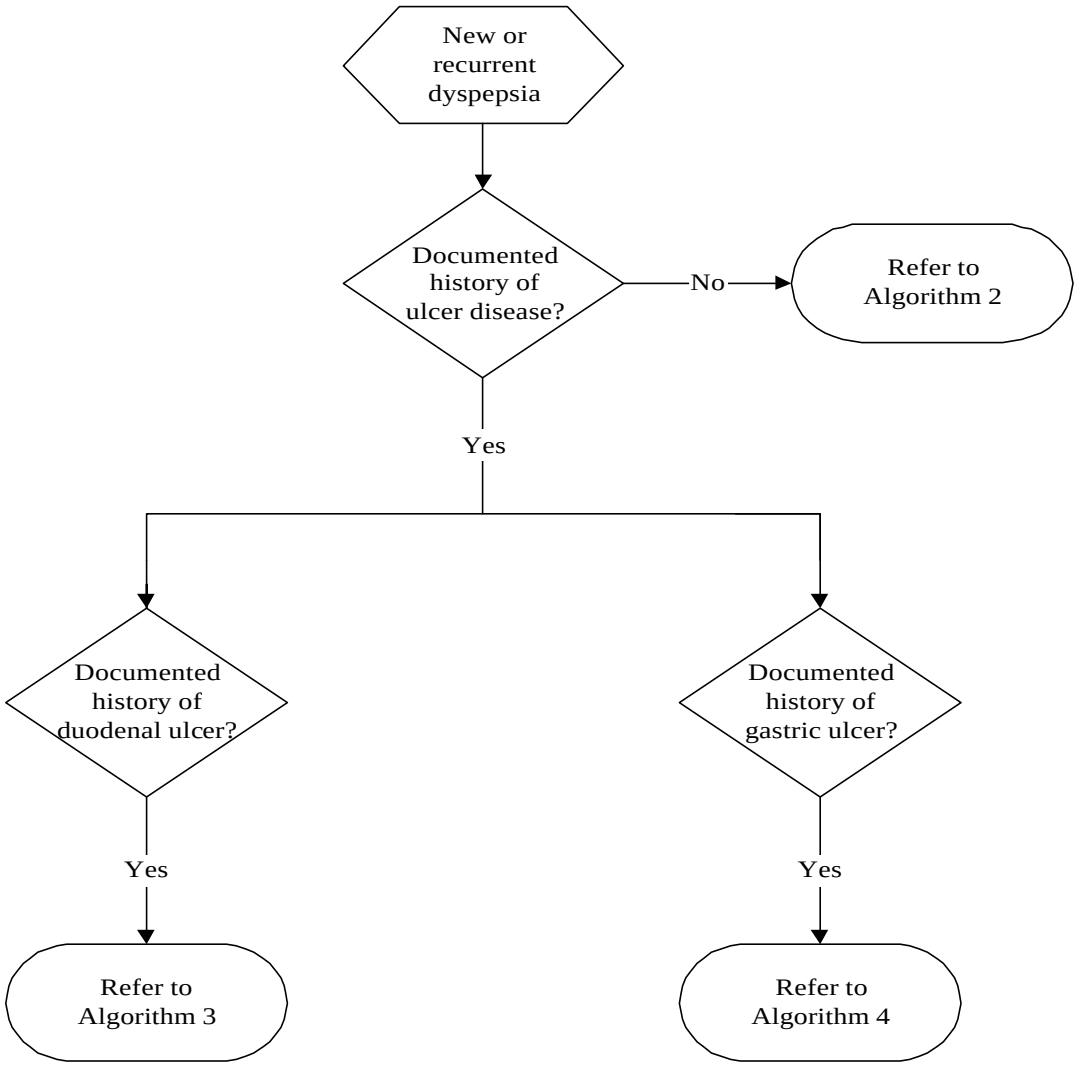
   b. No one regimen has proven to be the most cost-effective in eradicating *H. pylori*, however, single antibiotic containing regimens result in lower overall efficacy and are not recommended.

4. H_2 receptor antagonists (H_2RAs) continue to be the antisecretory agents of choice in ulcer healing and maintenance therapy. PPIs may be reserved for complicated patients.

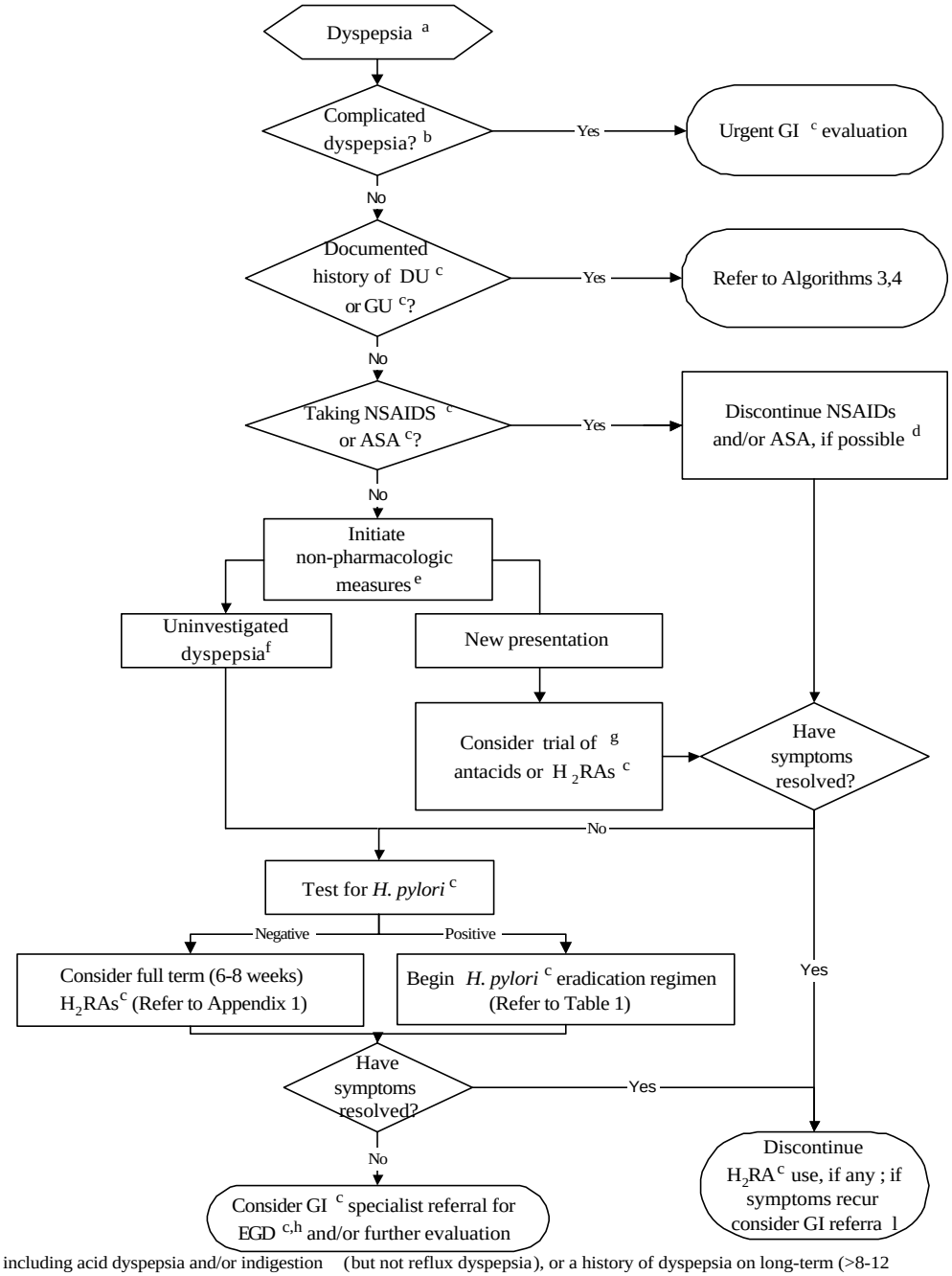
   a. For patients with uncomplicated dyspepsia or uncomplicated ulcer treated with *H. pylori* eradication regimens, antisecretory therapy need not be continued beyond the duration required for ulcer healing (4-12 weeks).

   b. For complicated ulcers, antisecretory therapy should be continued until *H. pylori* eradication is assured.

Algorithm 1. Management of *Helicobacter pylori* in Peptic Ulcer Disease and Dyspepsia



Algorithm 2. New or Recurrent Dyspepsia Without History of Ulcer Disease



[a] Overlapping symptoms including acid dyspepsia and/or indigestion (but not reflux dyspepsia), or a history of dyspepsia on long-term (>8-12 weeks) anti-secretory therapy

[b] Unexplained weight loss, anorexia, nausea/vomiting, dysphagia, melena, heme-positive stool, hematemesis, epigastric mass, iron deficiency, anemia, change in bowel habit, early satiety. New onset in patient > 50 years old should be monitored closely if not referred to GI specialist initially.

[c] DU-duodenal ulcer; GU=gastric ulcer; GI=gastrointestinal; NSAID=Non-steroidal anti-inflammatory drug; ASA=acetylsalicylic acid; H. pylori=Helicobacter pylori; $H_2RA=H_2$ receptor antagonist; EGD=Esophagogastroduodenoscopy

[d] When chronic anti-inflammatory use is necessary, salsalate may be considered

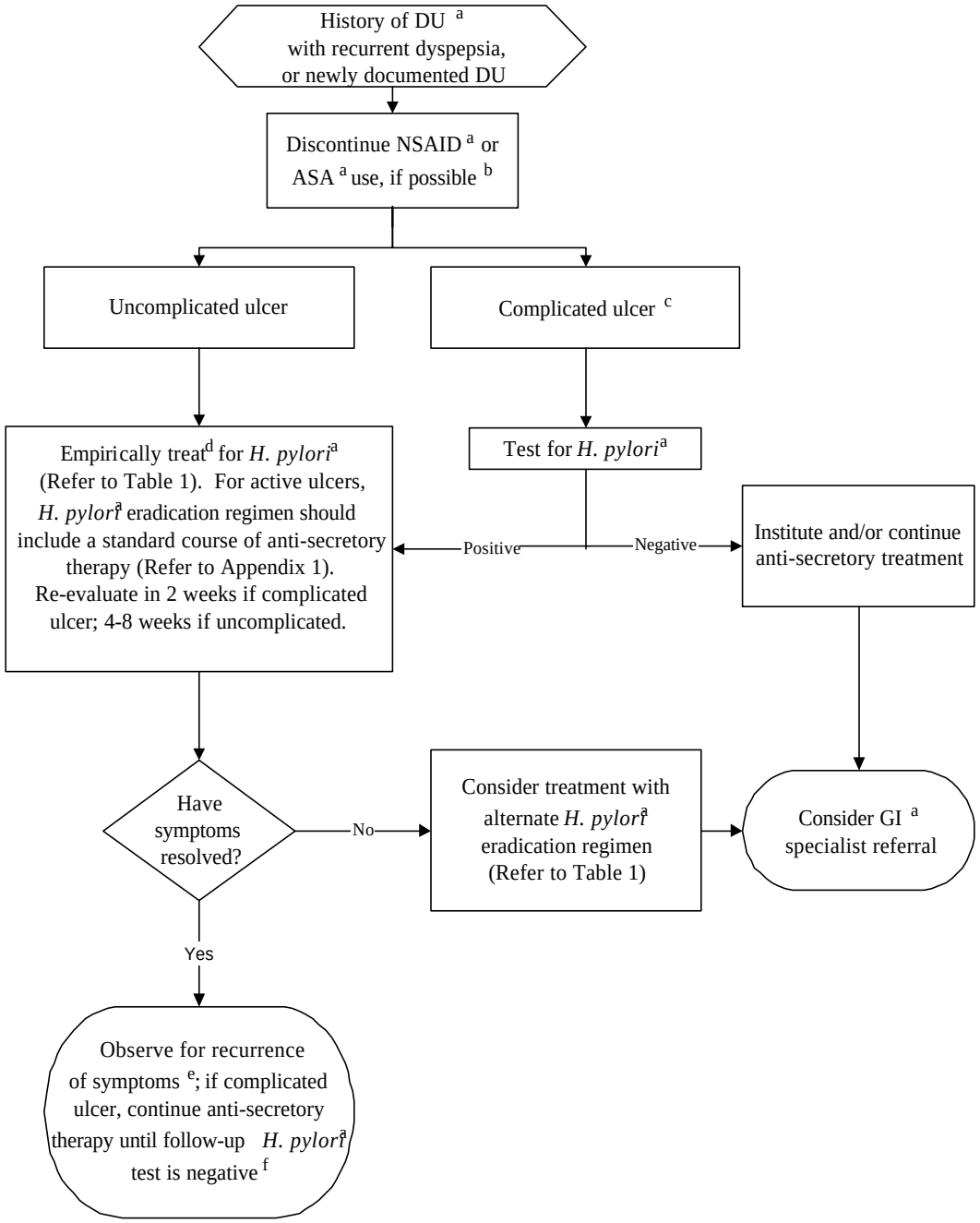
[e] Advise patient to stop smoking and reduce or discontinue use of alcohol

[f] Uninvestigated dyspepsia is defined as recurrent dyspepsia symptoms or ongoing dyspepsia (> 1 month) not yet investigated or evaluated by appropriate studies, including *H. pylori* testing. Many of these patients will have been on various antisecretory regimens with or without response.

[g] Management is controversial; may test and begin therapy simultaneously

[h] EGD is the preferred imaging study except in special instances, when an imaging study is warranted

Algorithm 3. Documented Duodenal Ulcer



[a] DU-duodenal ulcer; NSAID=Non-steroidal anti-inflammatory drug; ASA=acetylsalicylic acid; *H. pylori=Helicobacter pylori*; GI=gastrointestinal

[b] When chronic anti-inflammatory use is necessary, salsalate may be considered

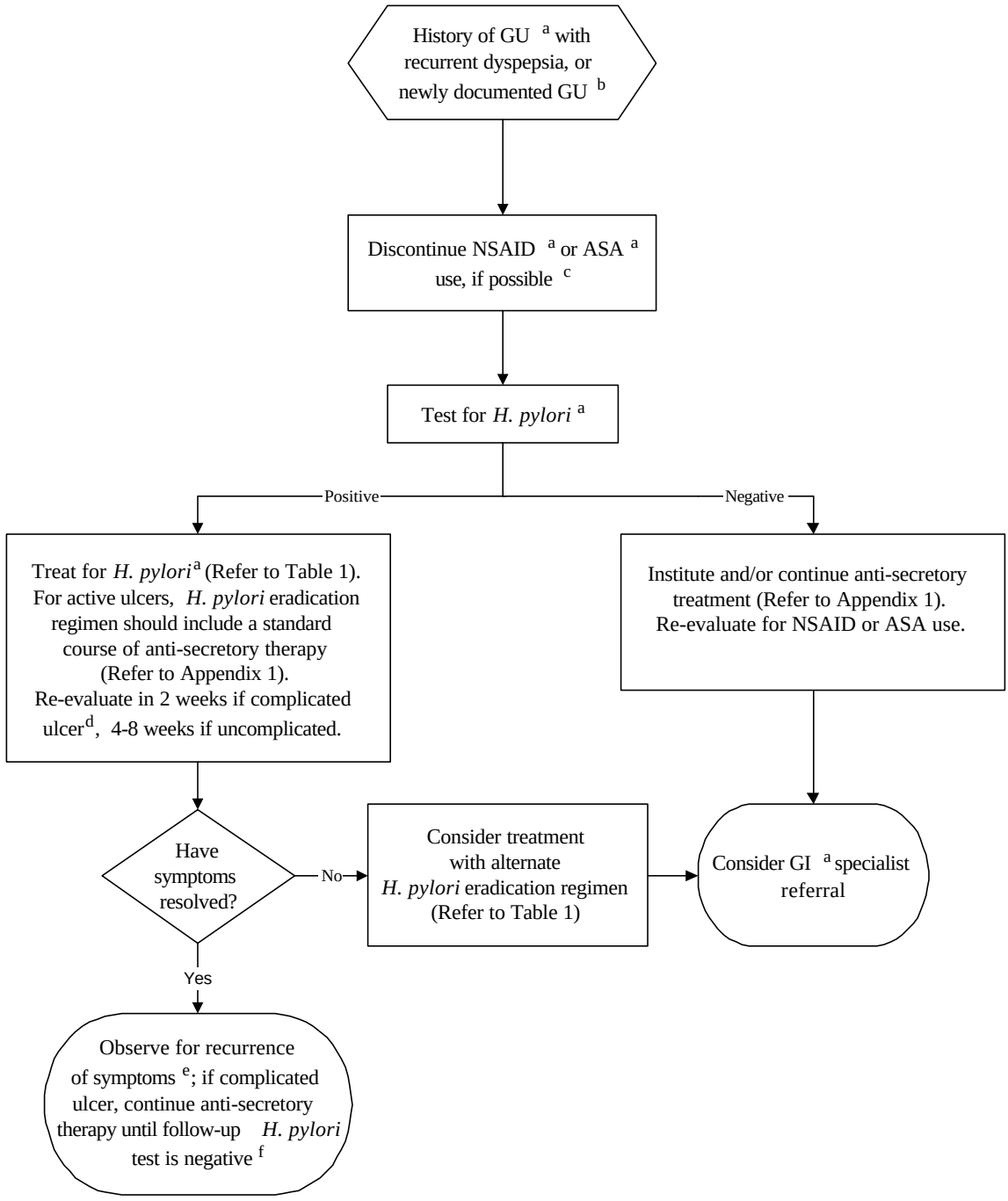
[c] Any history of obstruction, GI bleeding, perforation, duodenal deformity, giant ulcer (> 2cm), or refractory ulcer. Elderly patients with significant co-morbidities, heavy smokers, and/or anticoagulated patients should be treated as if they have complicated ulcers. Active complicated ulcers should be managed in consultation with GI.

[d] Testing for *H. pylori* in uncomplicated patients is controversial due to the potential for false negative results from the urea breath test. Therefore, empiric therapy is preferred, although testing for *H. pylori* remains an option.

[e] If symptoms recur, consider GI specialist referral

[f] Testing should occur 4-12 weeks after completion of *H. pylori* eradication regimen

Algorithm 4. Documented Gastric Ulcer



[a] GU-gastric ulcer; NSAID=Non-steroidal anti-inflammatory drug; ASA=acetylsalicylic acid; *H.pylori=Helicobacter pylori;* GI=gastrointestinal
[b] All documented GU should be (or should have been) referred for evaluation to rule out malignancy
[c] When chronic anti-inflammatory use is necessary, salsalate may be considered
[d] Active complicated ulcer should be treated in conjunction with a GI specialist
[e] If symptoms recur, consider GI specialist referral
[f] Testing should occur 4-12 weeks after completion of *H. pylori* eradication regimen

Table 1. *H. pylori* Eradication Therapy [a]

DRUG REGIMENS[b]	COURSE OF THERAPY [c]	CURE RATE	COMMENTS
Bismuth Subsalicylate 2 tabs qid Metronidazole 250 mg qid Tetracycline 500 mg qid ± H_2RA[d] or PPI[e]	2 weeks	88-90%	• Bismuth Subsalicylate must be chewed or dissolved in mouth before swallowing; can darken the stool; use with caution in patients with aspirin allergy; discontinue if patient experiences tinnitus • Metronidazole should not be taken while drinking alcohol; patient may develop a metallic taste and/or darkened urine • Tetracycline should not be taken with dairy products, antacids, or iron containing products; patient may develop photosensitivity with sunlight/sunlamp exposure or rash • PPI capsules should be swallowed whole, not crushed or chewed; lansoprazole can be opened and sprinkled on applesauce or mixed with applejuice for administration in patients with a nasogastric tube; omeprazole may be opened and the granules mixed with acidic juices or applesauce and administered immediately • Do not substitute antibiotics in these regimens as efficacy may be decreased
Bismuth Subsalicylate 2 tabs qid Metronidazole 250 mg qid Amoxicillin 500 mg qid ± H_2RA[d] or PPI[e]	2 weeks	80-86%	
PPI[e] Metronidazole 500 mg bid Amoxicillin 1 gram bid	1-2 weeks	77-83%	
PPI[e] Metronidazole 500 mg bid Clarithromycin 500 mg bid	1-2 weeks	87-91%	
PPI[e] Clarithromycin 500 mg bid Amoxicillin 1 gram bid	1-2 weeks	86-91%	
PPI[e] Bismuth Subsalicylate 2 tabs qid Metronidazole 250 mg qid Tetracycline 500 mg qid	1-2 weeks	94-98%	

[a] Adapted from: Soll AH, for the Practice Parameters Committee of the American College of Gastroenterology. Medical treatment of peptic ulcer disease: Practice guidelines. JAMA. 1996;275:622-9.

[b] Regimens listed are not all inclusive but reflect the most effective according to the literature at this time. Evaluation of effective drug regimens for *H. pylori* eradication is a dynamic process. These guidelines will be updated periodically. The latest medical literature should be consulted until that time. Refer to Appendices 1-3 for complete prescribing information. All drugs taken with meals except PPI (taken before meals).

[c] Most clinical trials evaluating 1week drug regimens are from trials conducted in Europe. These guidelines advocate using a 2 week regimen which has been shown to be effective in trials conducted in the United States.

[d] Refer to Appendix 1 for recommended dosing of H_2RAs

[e] Recommended PPI is lansoprazole 30mg bid

I. DEFINITIONS

A. Peptic ulcer disease (PUD) is a heterogeneous group of disorders characterized by ulceration of the upper gastrointestinal (GI) tract. The major common forms of peptic ulcer are duodenal ulcers (DU) and gastric ulcers (GU).

B. Dyspepsia occurs in two overlapping patterns: acid dyspepsia (classic ulcer-like hunger pain), and indigestion (belching or epigastric bloating, fullness or pain).

C. Complicated dyspepsia involves any of the following warning features: anemia, weight loss, dysphagia or other signs of serious underlying illness (Refer to Section III).

D. Complicated PUD includes history of obstruction, GI bleeding, perforation, duodenal or gastric deformity, giant ulcer (> 2 cm), refractory ulcer, elderly patients with significant co-morbidities, heavy smoking, or anticoagulated patients on warfarin.

E. Uninvestigated dyspepsia refers to recurrent symptoms of dyspepsia or ongoing dyspepsia (> 1 month) not yet investigated or evaluated by appropriate studies, including *H. pylori* testing. Many of these patients will have been on various antisecretory regimens with or without response.

II. GENERAL PRINCIPLES

A. Patients presenting with PUD/dyspepsia may be categorized as having either new onset, recurrent or uninvestigated dyspepsia or recurrent dyspepsia with a history of PUD. Patients with a complicated presentation require urgent GI evaluation (Refer to Section III).

B. There are several issues to consider in the management of PUD and dyspepsia in relation to *H. pylori*. They include *H. pylori* testing, interpreting the results, treatment, and follow-up.

C. Many patients with uninvestigated dyspepsia/suspected PUD are on long-term (>8-12 weeks) H_2 receptor antagonists (H_2RAs). These patients should not be on antisecretory therapy on a daily (or near-daily basis) for >8-12 weeks without an appropriate evaluation with *H. pylori* testing and/or esophagogastroduodenoscopy (EGD).

D. *H. pylori* eradication regimens differ in the drugs and dosages used, duration of treatment, cost, and eradication rate. No one regimen has been proven to be the most cost-effective, however regimens incorporating only a single antibiotic have less efficacy overall and are not recommended.

E. Current consensus (refer to Soll AH, for the Practice Parameters Committee of the American College of Gastroenterology. *Medical treatment of peptic ulcer disease: Practice guidelines*[18] and NIH Consensus Development Panel on *Helicobacter pylori* in Peptic Ulcer Disease, *Helicobacter pylori in peptic ulcer disease* [14]) supports eradicating *H. pylori* when there is documented PUD. It has been demonstrated to be cost-effective to treat patients presenting with new or uninvestigated dyspepsia if they test positive for *H. pylori* (refer to Ofman JJ et al. *Management strategies for Helicobacter pylori-seropositive patients with dyspepsia: Clinical and economic consequences*[15]).

F. In the evaluation of dyspepsia and suspected PUD, the preferred imaging study, if warranted, is EGD. Under certain circumstances, radiographic studies may be helpful for evaluating dyspepsia (or concomitant dysphagia) or where access to EGD is limited.

III. PATIENT EVALUATION

A. HISTORY

Document the following:

1. Medication history including use of NSAIDs or aspirin, corticosteroids, antisecretory agents (e.g., antacids, H_2RAs, prokinetic agents, proton pump inhibitors, sucralfate) or warfarin
2. Smoking history
3. Alcohol history
4. GI history including previous treatment with *H. pylori* eradication regimen and GI procedures
5. Previous antibiotic therapy with metronidazole or clarithromycin (patients who have previously taken these agents should be considered to have resistant *H. pylori)*

B. PHYSICAL EXAM/PRELIMINARY EVALUATION

Assess for the presence of complicating factors or suggestions of malignancy:

1. Unexplained weight loss or anorexia
2. Persistent nausea and vomiting
3. Dysphagia
4. Melena, heme-positive stool, or hematemesis
5. Epigastric mass
6. Iron-deficiency anemia
7. Change in bowel habit
8. Early satiety
9. New-onset in patient 50 years or older (these patients should be monitored closely if not initially referred to a GI specialist)

IV. TESTS TO GUIDE MANAGEMENT

A. *H. pylori* TESTING

1. All currently available *H. pylori* tests have individual sensitivities and specificities > 90%, except for culture, which has a sensitivity of approximately 70-80%.

2. Tests conducted in the ambulatory setting (noninvasive):

   a. Antibody detection (serology)
      - Qualitative IgG tests provide inexpensive, highly specific serological tests for *H. pylori*, although they are not useful in evaluating the patient for eradication after treatment with an *H. pylori* eradication regimen.

      - Quantitative IgG tests are more precise than qualitative serological tests. They can be used to monitor for a 50% fall in antibodies 3-6 months after treatment, indicating eradication of *H. pylori*. However, this requires sequential testing on specimens stored for 3-6 months making it impractical for many medical centers.

   b. Urea Breath Test
      - Urea breath tests may be useful to confirm *H. pylori* eradication. Tests are usually done 4 to 12 weeks after *H. pylori* treatment in patients with complicated ulcers or for those with recurrent symptoms. Testing within 4 weeks after receiving *H. pylori* eradication therapy or after receiving proton pump inhibitors (PPIs) may give false negative results.

3. Tests obtained by EGD (invasive):

   a. Histology is used to detect acute and/or chronic inflammation or for staining to detect *H. pylori* infection in an untreated patient. *H. pylori* staining provides a more sensitive index of *H. pylori* infection, and in combination with chronic inflammation, is diagnostic in virtually all infected subjects. Therefore, the absence of chronic inflammation on antral biopsies excludes *H. pylori* infection with the highest possible degree of confidence.

   b. Rapid urease tests, such as the CLOtest®, are useful for confirming the presence of *H. pylori*. They should not be used to confirm eradication of *H. pylori* until at least 4-12 weeks following treatment or use of antibiotics, bismuth or PPIs.

B. WHO TO TEST FOR *H. pylori*

1. Patients with uncomplicated dyspepsia, including the following, should be tested:

   a. Patients with new or recurrent dyspeptic symptoms who fail a trial of antisecretory therapy (Refer to Algorithm 2).

   b. Uninvestigated dyspepsia patients, including those on long-term (> 8 to 12 weeks) antisecretory therapy or who have been treated with long-term antisecretory therapy in the past without appropriate evaluation (i.e. *H. pylori* testing and/or EGD; refer to Algorithm 2).

2. Patients with documented active or a past history of GU or complicated DU with recurrent symptoms should be tested:

   a. Patients with complicated DU require testing to determine future management strategy; specifically to provide a baseline value for later comparison to ensure eradication (Refer to Algorithm 3).

   b. Patients with documented GU (complicated or uncomplicated) should be tested for *H. pylori*. Gastric ulcers must also have definitive testing to exclude malignancy (Refer to Algorithm 4).

3. Patients with uncomplicated DU who are not taking NSAIDs have a greater than 80% probability of being *H. pylori* positive. Thus, a negative test has poor predictive value and empiric therapy without testing for *H. pylori* is recommended.

C. HOW TO INTERPRET *H. pylori* TESTS

1. Interpretation of test results depends on the accuracy of the test (e.g., specificity and sensitivity and the pretest probability of disease in a particular patient).

2. In patients with uncomplicated DU who are not taking NSAIDs, interpretation of negative *H. pylori* test results is difficult due to the high prevalence of *H. pylori* and therefore a potential for false negatives.

3. For patients with complicated DU, a negative test should be followed up with a referral to a GI specialist.

4. Although the prevalence of *H. pylori* is lower in GU, negative test results may be false-negative and clinicians may wish to re-test.

5. False negative results to *H. pylori* tests, except serology, may occur if the patient has recently taken antibiotics, PPIs, or bismuth compounds within 4-12 weeks.

V. MANAGEMENT

A. GENERAL APPROACH

1. Empirically treating dyspeptic patients with antibiotic therapy without *H. pylori* testing cannot be recommended at this time.

2. It is clearly beneficial to treat *H. pylori* in PUD.

3. Patients with uncomplicated DU who have not received prior *H. pylori* eradication therapy may be empirically treated with antibiotics.

4. *H. pylori* positive patients with GU should be treated with eradication and anti-secretory therapy. Special attention should be given to rule out cancer due to its association in GU. The same principles for therapy of DU apply to GU.

5. Use of NSAIDs should be discouraged and eliminated wherever possible. When chronic anti-inflammatory use is necessary, salsalate may be considered. If the patient is at risk for ulceration or recurrent ulceration, preventive therapy (e.g., misoprostol, H_2RA, or PPI) may be considered in consultation with a GI specialist.

B. NON-PHARMACOLOGIC THERAPY

1. Advise the patient to stop smoking and discontinue or reduce alcohol intake as these can worsen dyspeptic symptoms and/or increase the risk of ulcer recurrence.

C. PHARMACOTHERAPY

1. *H. pylori* eradication regimens (For specific regimens refer to Table 1; also refer to Appendices 1-3 for additional information)

a. Eradication rates of the various regimens are dependent on both antimicrobial effectiveness as well as patient compliance. Less complicated, more expensive regimens may increase patient compliance, although there is insufficient data to recommend one therapeutic regimen over another.

b. Regimens containing a single antibiotic in combination with antisecretory therapy are not as effective as those containing two or three antimicrobial agents.

c. Recommended regimens should not be substituted, as reduced rates of eradication will result. Specifically, ampicillin should not replace amoxicillin, azithromycin or erythromycin should not replace clarithromycin, and doxycycline should not replace tetracycline.

d. Patients with a documented adverse effect to a specific drug in a *H. pylori* eradication regimen should be placed on a regimen not containing that drug.

e. The patient's medications should be reviewed to assess for potential drug interactions (Refer to Appendices 2-4).

f. Explain to the patient the need for compliance with *H. pylori* eradication regimens. Educate patients regarding minor, generally self-limiting, side effects associated with treatment (Refer to Table 1). Advise patients about rare, potentially serious side effects (e.g. protracted diarrhea) which warrant discontinuing therapy and/or possibly medical attention.

g. Practitioners may empirically treat dyspepsia with a 6-8 week course of H_2RAs (Refer to Appendix 1). If symptoms persist > 2 weeks on treatment or recur at the end of the therapeutic trial, patients should be tested for *H. pylori*.

h. In uncomplicated PUD, antisecretory therapy should be continued for the full course of 4-12 weeks, depending on choice of agent and type of ulcer (Refer to Appendix 1). Patients with complicated ulcers should be continued on antisecrectory therapy until *H. pylori* eradication is confirmed.

i. To facilitate the prescribing process and reduce error, preprinted prescriptions or standing orders for *H. pylori* eradication regimens should be encouraged.

2. H_2RAs (Refer to Appendices 1&2)

a. H_2RAs bind competitively to gastric H_2 receptors to reversibly inhibit acid secretion. Blockade of parietal cell histamine receptors inhibit all phases of gastric acid secretion induced by histamine, gastrin and acetylcholine. The net effect is an increase in the pH of the stomach.

b. All H_2RAs are equally effective and have similar healing rates for the treatment of PUD and maintenance therapy after treatment. The differences between H_2RAs are their side-effects, cost, and drug interaction profiles. All H_2RAs are safe in the treatment of dyspepsia and PUD.

c. At appropriate dosages, treatment duration of DU with H_2RAs in combination with *H. pylori* eradication therapy is approximately 4-8 weeks. GUs heal more slowly than DUs, and may require an increased duration of treatment (8-12 weeks).

d. Maintenance therapy for dyspepsia and uncomplicated ulcers is not required. Single dose therapy at bedtime of an H_2RA at half the treatment dose is reported to be effective in preventing ulcer recurrence. However, benefit of maintenance therapy in a patient with complicated PUD after treatment of *H. pylori* is unknown at this time. Therefore, it is recommended that maintenance therapy be used in consultation with a GI specialist.

e. Cimetidine reduces the hepatic metabolism of certain drugs via inhibition of the cytochrome (CYP) P450 enzyme system (Refer to Appendix 2). Ranitidine has an intermediate affinity for the CYP system. Famotidine and nizatidine do not appreciably

bind to the CYP system and their potential to cause significant inhibition of the CYP system is greatly reduced.

3. PPIs (Refer to Appendices 1&3)

a. PPIs irreversibly inhibit the parietal cell H^+/K^+-ATPase enzyme system. The dose-related effect is to suppress basal and stimulated gastric acid secretion, independent of the stimulus. Inhibition of acid secretion with these agents is more pronounced than with H_2RAs, and because of irreversible binding, results in prolonged inhibition of gastric acid secretion.

b. Overall healing rates following H_2RA or PPI therapy are comparable and depend on the duration of treatment. Due to the increased cost without proven benefit, PPIs may be reserved for complicated patients.

c. PPIs are effective adjuncts in the eradication of *H. pylori*. Because they require an acid environment to be effective, PPIs should **not** be used with other antisecretory agents.

d. Doses administered in the morning result in a higher median 24-hour pH effect than if given at night.

e. At appropriate dosages, treatment duration of PUD with PPIs is approximately 4-8 weeks.

D. FOLLOW-UP

1. Ensure that patients finish their full course of therapy to eradicate *H. pylori*.

2. Monitor for continued symptoms during treatment and recurrent symptoms after eradication of *H. pylori*. In most cases, recurrence of symptoms warrant consultation with a GI specialist.

3. For complicated ulcer patients, *H. pylori* eradication should be verified before stopping antisecretory therapy. Consultation with a GI specialist regarding maintenance therapy should be considered since it remains unclear as to what is the optimal management after *H. pylori* eradication for these patients.

4. Urea breath testing is an easy, non-invasive method for confirming eradication of *H. pylori.* These tests may be falsely negative in about 10% of cases, especially if the patient has been recently treated (< 12 weeks earlier) with a PPI, antibiotics, or bismuth (due to decreased amount of bacteria present to react with reagent).

5. Repeat EGD remains the most reliable way to confidently diagnose *H. pylori* eradication. Although the urease testing on biopsies has a 10% false negative rate (higher with recent PPI, antibiotic or bismuth therapy), a positive result is highly specific and diagnoses the presence of infection nearly 100% of the time.

6. Qualitative serology testing is not useful in confirming eradication of *H. pylori*. Quantitative assays are difficult to conduct since they need to be performed simultaneously on a stored pre-treatment and post-treatment serum sample, drawn 3-6 months after treatment. Eradication is presumed when the assay reveals a > 50% fall in IgG antibody.

VI. SUGGESTED MEASURES FOR EVALUATING IMPLEMENTATION OF *H. PYLORI* IN PUD/DYSPEPSIA GUIDELINE

A. TESTING

1. Patients with uninvestigated dyspepsia (after failing a trial of non-pharmacologic measures, and possibly, antacids or H_2RAs, and discontinuation of NSAIDs and/or aspirin) without a history of documented ulcer disease, should be tested for *H. pylori* .

B. TREATMENT

1. Patients with a positive result for *H. pylori* should receive treatment with a *H. pylori* eradication regimen.

2. Patients with documented ulcer disease need to be treated for *H. pylori* (unless a negative result for *H. pylori* was obtained).

3. Follow-up should be scheduled after treatment for *H. pylori* (2 weeks for complicated ulcer, 4 to 8 weeks for uncomplicated ulcer).

C. OUTCOME

1. Patients with dyspepsia or uncomplicated ulcers should not require maintenance antisecretory therapy after receiving treatment for *H. pylori.*

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Appendix 1. Oral Dosing Regimens of Antisecretory Agents [a,b,c]

DRUG	DUODENAL ULCER		GASTRIC ULCER	*H. pylori* ERADICATION	DAILY DOSE ADJUSTMENT IN RENAL IMPAIRMENT		COMMENTS
	Active	Maintenance			CrCl	Dose	
H_2RAs							Most common side effects include headache, dizziness, diarrhea, constipation and mental status changes
CIMETIDINE[d]	300 mg qid 400 mg bid 800 mg hs x 4-8 wks	400 mg hs	800 mg hs or 300 mg qid x 8-12 wks	Refer to dosing for active DU or GU	> 30 mL/min 15-30 mL/min < 15 mL/min	800 mg HS 600 mg HS 300-400 mg HS	Observe caution with agents metabolized in the liver. May decrease dosage for elderly patients
FAMOTIDINE[d]	40 mg hs 20 mg bid x 4-8 wks	20 mg hs	20 mg bid 40 mg hs x 8-12 wks	Refer to dosing for active DU or GU	< 10 mL/min	20 mg HS or 40 mg qod	
Nizatidine	300 mg hs 150 mg bid x 4-8 wks	150 mg hs	150 mg bid x 8-12 wks	Refer to dosing for active DU or GU	20-50 mL/min < 20 mL/min	150 mg qd - 150 mg qod 150 mg qd - 150 mg q3d	
Ranitidine	300 mg hs 150 mg bid x 4-8 wks	150 mg hs	150 mg bid x 8-12 wks	Refer to dosing for active DU or GU	< 50 mL/min	150 mg HS	
PPIs							Most common side effects include abdominal pain, nausea, and diarrhea
LANSOPRAZOLE[d]	15 mg/d x 4 wks	15 mg/d [e]	30 mg qd x 4-8 wks	30 mg bid x 2 wks	No adjustment necessary		Consider dosage adjustment in severe liver disease, not necessary for elderly patients
Omeprazole	20 mg/d x 4-8 wks	NA[f]	40 mg qd x 4-8 wks	20 mg bid x 2 wks	No adjustment necessary		No adjustment necessary for liver disease or elderly patients

[a] Adapted from: Hebel SK ed. Drug facts and comparisons, St. Louis, MO: Facts and Comparisons, Inc.1997

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[d] Formulary agent

[e] Studies do not extend beyond 12 months of use

[f] Not FDA approved for this indication

Appendix 2. Drug Interactions of H_2RAs[a,b,c]

CIMETIDINE		
INTERACTION	**INTERACTING DRUGS**	**EFFECT**
Inhibit Metabolism	Warfarin[d],Benzodiazepines (diazepam, chlordiazepoxide, alprazolam and triazolam), Carbamazepine, Cisapride, Flecainide, Lidocaine, Nicotine, Oral Sulfonylureas (glyburide, glipizide, tolbutamide), Paroxetine, Phenytoin, Praziquantel, Propafenone, Quinidine, Tacrine, Theophylline, Tricyclic Antidepressants (desipramine, doxepin, imipramine, nortriptyline)	↑ serum levels of interacting drugs; potentiation of therapeutic effects and in some cases, symptoms of toxicity Monitor concurrent therapy with H_2RAs; draw serum levels of interacting drugs if appropriate; change interacting drug if needed
Undetermined	Clozapine, Meperidine	
Reduce Metabolism	Beta Blockers (propranolol, metoprolol, labetalol, and pindolol) Calcium Channel Blockers (verapamil, diltiazem, nifedipine, nimodipine, nisoldipine and nitrendipine)	
Reduced Renal Secretion	Procainamide	
Reduced Absorption (pH)	Fluconazole, Ketoconazole, Itraconazole	↓ serum levels of interacting drugs;

[a] Adapted from: Hansten PD, Horn JR. Drug interactions analysis and management. Vancouver: Applied Therapeutics Inc.; 1997
[b] Adapted from: Hebel SK ed. Drug facts and comparisons, St. Louis, MO: Facts and Comp arisons, Inc.;1997
[c] Appendix 2 lists the more commonly cited drug interactions; this list is not wholly comprehensive
[d] Use combination only if benefit outweighs risk

Appendix 3. Drug Interactions of PPIs [a,b,c,d]

OMEPRAZOLE AND LANSOPRAZOLE		
INTERACTION	**INTERACTING DRUGS**	**EFFECT**
Inhibit Metabolism	Benzodiazepines[e] (diazepam, lorazepam, oxazepam and temazepam), Phenytoin[e], Warfarin[e]	↑ serum levels of interacting drugs; potentiation of therapeutic effects and in some cases, symptoms of toxicity Monitor concurrent therapy with PPIs; draw serum levels of interacting drugs if appropriate; change interacting drug if needed
Inhibit Acid Secretion	Digoxin	↑ bioavailability of interacting drug
Reduced absorption (pH)	Itraconazole, Ketoconazole	↓ serum level of interacting drug due to change in gastric pH

[a] Adapted from: Hansten PD, Horn JR. Drug interactions analysis and management. Vancouver:Applied Therapeutics Inc.; 1997
[b] Adapted from: Hebel SK ed. Drug facts and comparisons, St. Louis, MO: Facts and Comparisons, Inc.; 1997
[c] Spencer CM, Faulds D. Lansoprazole: A reappraisal of its pharmacodynamic and pharmacokinetic properties and its therapeutic efficacy in acid-related disorders. Drugs 1994;48(3):404-30
[d] Appendix 3 lists the more commonly cited drug interactions; this list is not wholly comprehensive
[e] Reported with omeprazole only

Appendix 4. Drug Interactions of Antimicrobials [a,b,c]

CLARITHROMYCIN		
INTERACTION	**INTERACTING DRUGS**	**EFFECT**
Inhibit Metabolism	Cisapride[d], Non-sedating antihistamines (Astemizole, Terfenadine)[d], Theophylline[d], Carbamazepine, Cyclosporine, Digoxin, Indinavir, Tacrolimus, Warfarin	↑ serum levels of interacting drugs; potentiation of therapeutic effects and in some cases, symptoms of toxicity
METRONIDAZOLE		
Inhibit Metabolism	Warfarin[d], Carbamazepine, Phenytoin	↑ serum levels of interacting drugs; potentiation of therapeutic effects and in some cases, symptoms of toxicity
Reduced Clearance	Fluorouracil[d]	
Unknown	Disulfiram	

[a] Adapted from: Hansten PD, Horn JR. Drug interactions analysis and management. Vancouver:Applied Therapeutics Inc.; 1997
[b] Adapted from: Hebel SK ed. Drug facts and comparisons, St. Louis, MO: Facts and Comparisons, Inc.; 1997
[c] Appendix 4 lists the more commonly cited drug interactions; this list is not wholly comprehensive
[d] Use combination only if benefit outweighs risk

Appendix 5. Selected Costs for PUD Drug Therapy (as of February 1998)

For current prices, check the Pharmacy Benefits Management Bulletin Board at 708-531-7947

VHA has awarded a National Contract to cimetidine (Zenith Goldline Pharmaceuticals) as its 1st line H_2RA, famotidine (Pepcidâ) as 2nd line H_2RA, and lansoprazole (Prevacidâ) as its proton pump inhibitor

DRUG	DOSE [a]	DURATION	FEDERAL SUPPLY SCHEDULE (FSS) COST FOR DURATION OF THERAPY
Cimetidine	400 mg bid	4 weeks	$ 3
Famotidine	40 mg hs	4 weeks	$18
Lansoprazole	15 mg qd	4 weeks	$46
Bismuth Subsalicylate Metronidazole Tetracycline	2 tabs qid 250 mg qid with meals and qhs 500 mg qid	2 weeks	$ 7[b]
Bismuth Subsalicylate Metronidazole Amoxicillin	2 tabs qid 250 mg qid, with meals and qhs 500 mg qid, with meals and qhs	2 weeks	$ 9[b]
Lansoprazole Metronidazole Amoxicillin	30mg bid, before meals 500 mg bid, with meals 1 gram bid, with meals	2 weeks	$50
Lansoprazole Metronidazole Clarithromycin	30mg bid, before meals 500 mg bid, with meals 500 mg bid, with meals	2 weeks	$89
Lansoprazole Clarithromycin Amoxicillin	30mg bid, before meals 500 mg bid, with meals 1 gram bid, with meals	2 weeks	$91

[a] Usual doses, does not reflect equivalent doses
[b] Additional cost if cimetidine 400mg bid x 4 weeks ($3), famotidine 40mg qhs x 4 weeks ($18), or lansoprazole 30mg bid x 2 weeks ($46) added to the regimen