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H. Pylori Treatment Regimens

Abbreviations: ACG=American College of Gastroenterology; AMOX=amoxicillin; BID=twice daily; BIS=bismuth subcitrate potassium; BSS=bismuth subsalicylate (*Pepto-Bismol* Regular Strength); CLAR=clarithromycin; DU=duodenal ulcer; ESOMP=esomeprazole; GU=gastric ulcer; IT=intent-to-treat; LANS=lansoprazole; MET=metronidazole; OMP=omeprazole; PANT=pantoprazole; PP=per protocol; PPI=proton pump inhibitor; RAB=Rabeprazole; TIN=tinidazole; QID = four times daily; RIF=rifabutin; TCN=tetracycline; TID=three times daily; TPD=Therapeutic Products Directorate (Health Canada).

NOTE: Not all FDA- or TPD-approved regimens have maximum efficacy. **Regimens with <80%(IT) or 90%(PP) are not recommended.**[2,4]

PPI or H2-Blocker	Antibiotic 1	Antibiotic 2	Bismuth Compound	Duration [2-4]	Comments	Efficacy[a,b]	FDA-Approved (U.S.)	TPD-Approved (Canada)
Recommended Oral Regimens per ACG Guidelines(2007), Canadian Helicobacter Study Group Consensus (2004) and Dyspepsia Working Grp (2005)[2-4]								
ESOMP 20 mg BID **or** ESOMP 40 mg QD	CLAR 500 mg BID	AMOX 1 gm BID		14 days U.S. 7 or 10 days Canada	10-day regimen is FDA approved. FDA-approved *Nexium* 40 mg once daily dosing rather than 20 mg BID.[5] 7-day regimen is TPD approved. Available as *Nexium 1-2-3 A* in Canada.	10-day regimen[5] 84% (PP) 77% (IT) 7-day regimen[6] 86% (PP) 89% (IT)	Yes	Yes
ESOMP 20 mg BID **or** ESOMP 40 mg QD	CLAR 500 mg BID	MET 500 mg BID		14 days U.S. 7 or 10 days Canada		--	No	No

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PPI or H2-Blocker	Antibiotic 1	Antibiotic 2	Bismuth Compound	Duration [2-4]	Comments	Efficacy[a,b]	FDA-Approved (U.S.)	TPD-Approved (Canada)
Recommended Oral Regimens Per ACG Guidelines(2007), Canadian Helicobacter Study Group Consensus(2004) and Dyspepsia Working Grp (2005)[2-4]								
LANS 30 mg BID	CLAR 500 mg BID	AMOX 1 gm BID		14 days U.S. 7 or 10 days Canada	Both 10-day and 14-day regimens are FDA approved.[7,8] 7-day, 10-day, and 14-day regimens are TPD approved.[9] Available as *Prevpac* in U.S. and *Hp-Pac* in Canada.	<u>10-day regimen</u>[7] 84% (PP) 81% (IT) <u>14-day regimen</u>[7] 85-92% (PP) 82-86% (IT)	Yes	Yes
LANS 30 mg BID	CLAR 500 mg BID	MET 500 mg BID		14 days U.S. 7 or 10 days Canada		≥90% (PP)[2] ≥80% (IT)[2]	No	No
OMP 20 mg BID	CLAR 500 mg BID	AMOX 1 gm BID		14 days U.S. 7 or 10 days Canada	10-day regimen is FDA approved.[10] 7-day regimen is TPD approved.[11] Available as *Losec 1-2-3 A* in Canada. Give additional 18 days of OMP 20 mg daily for ulcer healing and symptom relief.[10] Give additional OMP 20 mg daily for up to 3 wk for active DU and OMP 20-40 mg daily for up to 12 wk for active GU.[11]	<u>10-day regimen</u> 77-78% (PP)[10] 69-73% (IT)[10] <u>7-day regimem</u> 91-98% (PP)[11] 94%-96% (IT)[11]	Yes	Yes

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PPI or H2-Blocker	Antibiotic 1	Antibiotic 2	Bismuth Compound	Duration [2-4]	Comments	Efficacy[a,b]	FDA-Approved (U.S.)	TPD-Approved (Canada)
Recommended Oral Regimens Per ACG Guidelines(2007), Canadian Helicobacter Study Group Consensus(2004) and Dyspepsia Working Grp (2005)[2-4]								
OMP 20 mg BID	CLAR 500 mg BID	MET 500 mg BID		14 days U.S. 7 or 10 days Canada	7-day regimen is TPD approved.	91–94% (PP)[11] 87-95% (IT)[11]	No	Yes
PANT 40 mg BID	CLAR 500 mg BID	AMOX 1 gm BID		14 days U.S. 7 or 10 days Canada	7-day regimen is TPD approved.[12]	86%-93% (IT)[12]	No	Yes
PANT 40 mg BID	CLAR 500 mg BID	MET 500 mg BID		14 days U.S. 7 or 10 days Canada	7-day regimen is TPD approved.[12]	83%-96% (IT)[12]	No	Yes
RAB 20 mg BID	CLAR 500 mg BID	AMOX 1 gm BID		14 days U.S. 7 or 10 days Canada	7-day regimen is FDA and TPD approved.[13,14] 7-day regimen is not recommended per 2007 U.S. *H. pylori* treatment guidelines due to lower eradication rates compared to 10- and 14-day treatment regimens.[2]	84% (PP)[13] 77% (IT)[13]	Yes	Yes
RAB 20 mg BID	CLAR 500 mg BID	MET 500 mg BID		14 days U.S. 7 or 10 days Canada		--	No	No

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PPI or H2-Blocker	**Antibiotic 1**	**Antibiotic 2**	**Bismuth Compound**	**Duration** [2-4]	**Comments**	**Efficacy**[a,b]	**FDA-Approved (U.S.)**	**TPD-Approved (Canada)**
Recommended Oral Regimens Per ACG Guidelines(2007), Canadian Helicobacter Study Group Consensus (2004) and Dyspepsia Working Grp (2005)[2-4]								
ESOMP 20 mg BID **or** ESOMP 40 mg QD **or** LANS 30 mg BID **or** OMP 20 mg BID **or** PANT 40 mg BID **or** RAB 20 mg BID	TCN 500 mg QID	MET 250 mg QID	BSS 525 mg QID	10-14 days[2]	BSS/MET/TCN combination is available in U.S. as *Helidac*.[15] Considered a first-line therapy per 2007 U.S. *H. pylor*i treatment guidelines.[2]	--	No	No
OMP 20 mg BID **or** LANS 30 mg BID	TCN 500 mg QID	MET 500 mg TID	BSS 525 mg QID	10-14 days[2]	Considered an alternative to PPI + CLAR + AMOX (or MET) per 2007 Sanford Guide to antimicrobial therapy.[16]	90-99%[16] (not specified PP or IT)	No	No
ESOMP 20 mg BID **or** LANS 30 mg BID **or** OMP 20 mg BID **or** PANT 40 mg BID **or** RAB 20 mg BID	MET 375 mg or 500 mg QID	TCN 375 or 500 mg TID	BSS 525 mg QID	10 or 14 days[4]	Considered a first-line therapy per 2005 Canadian dyspepsia treatment guidelines.[3]	>80% (IT)[4]	No	No

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PPI or H2-Blocker	Antibiotic 1	Antibiotic 2	Bismuth Compound	Duration [2-4]	Comments	Efficacy[a,b]	FDA-Approved (U.S.)	TPD-Approved (Canada)
Recommended Oral Regimens Per ACG Guidelines(2007), Canadian Helicobacter Study Group Consensus (2004) and Dyspepsia Working Grp (2005)[2-4]								
Famotidine 40 mg/day, **or** Nizatidine 300 mg/day, **or** Ranitidine 300 mg/day (given as 150 mg BID)	MET 250 mg QID	TCN 500 mg QID	BSS 525 QID	10 or 14 days	BSS/MET/TCN combination is available in U.S. as *Helidac*.[15] Ranitidine-based regimen is considered a first-line therapy per 2007 U.S. *H. pylori* treatment guidelines.[2] Give BSS, antibiotics and H_2-blocker together for 14 days. Then give H_2-blocker alone for an additional 14 days. H_2-blocker may be given QD at bedtime OR in two equally divided doses BID. Avoid cimetidine to reduce risk of drug-drug interactions.[15]	71% (PP)[15] 72% (IT)[15]	Yes	No

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PPI or H2-Blocker	**Antibiotic 1**	**Antibiotic 2**	**Bismuth Compound**	**Duration** [2-4]	**Comments**	**Efficacy**[a,b]	**FDA-Approved (U.S.)**	**TPD-Approved (Canada)**
Other Oral Regimens								
RAB 20 mg BID (Days 1-10)	AMOX 1 gm BID (Days 1-5)			10 days	Sequential therapy for total of 10 days. Start with RAB + AMOX for 5 days followed by RAB+ CLAR+ TIN for another 5 days.[16] Recommended as a first-line therapy per 2007 Sanford Guide to antimicrobial therapy.[16] The 2007 U.S. *H. pylori* guideline states that such regimen requires efficacy validation in the North American population before it can be accepted as first-line therapy.[2] May use PPIs other than RAB per 2007 U.S. *H. Pylori* treatment guidelines.[2]	92% (PP)[17] 90% (IT)[17] (in European population)	No	No
	CLAR 500 mg BID (Days 6-10)	TIN 500 mg BID (Days 6-10)						
LANS 30 mg TID	AMOX 1 gm TID			14 days	Use only in clarithromycin allergy/intolerance or in known/suspected clarithromycin resistance.[7]	77% (PP)[7] 70% (IT)[7]	Yes	No

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PPI or H2-Blocker	Antibiotic 1	Antibiotic 2	Bismuth Compound	Duration [2-4]	Comments	Efficacy[a,b]	FDA-Approved (U.S.)	TPD-Approved (Canada)
Other Oral Regimens Con't								
OMP 20 mg BID	CLAR 250 mg BID	MET 500 mg BID		7 days	Available as *Losec 1-2-3 M* in Canada.	91-94% (PP)[11] 87-95% (IT)[11]	No	Yes
OMP 20 mg BID	BIS 140 mg MET 125 mg TCN 125 mg **(*Pylera*)** 3 capsules QID			10 days	Each *Pylera* capsule contains BIS 140 mg, MET 125 mg and TCN 125 mg.	93% (PP)[19] 88% (IT)[19]	Yes	Yes (as *Helizide*, but not marketed)
OMP 40 mg QD	CLAR 500 mg TID			14 days	Give CLAR and OMP together for 14 days. Then give only OMP 20 mg daily for an additional 14 days for ulcer healing and symptom relief.[10, 18]	64-74% (IT)[10,18]	Yes	No

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PPI or H2-Blocker	Antibiotic 1	Antibiotic 2	Bismuth Compound	Duration [2-4]	Comments	Efficacy[a,b]	FDA-Approved (U.S.)	TPD-Approved (Canada)
Other Oral Regimens Con't								
ESOMP 20 mg BID **or** LANS 30 mg BID **or** OMP 20 mg BID **or** PANT 40 mg BID **or** RAB 20 mg BID	RIF 150 mg BID	AMOX 1 gm BID		10 or 14 days	Reserve as salvage therapy for patients who have failed two different first-line therapies.	70-85% (IT)[17]	No	No
ESOMP 20 mg BID **or** LANS 30 mg BID **or** OMP 20 mg BID **or** PANT 40 mg BID **or** RAB 20 mg BID	LEV 500 mg QD	AMOX 1 gm BID		10 days	May be considered as salvage therapy for patients with persist *H. pylori* who have failed other treatment regimens.[2] The 2007 U.S. *H. pylori* guideline states that such regimen requires efficacy validation in the North American population before it can be accepted as first-line therapy.[2]	63-94% (not specified PP or ITT)[2*]	No	No

a. Efficacy reported as cure rate by *intention-to-treat* (IT) analysis or by *per-protocol* (PP) analysis. IT means that outcomes were analyzed for all patients, based on the treatment to which they were randomized, regardless of whether they dropped out. PP means that outcomes were analyzed for all patients who completed the study and complied with protocol. Based on the American College of Gastroenterology and Canadian Helicobacter Study Group Consensus criteria, the range for the 95% confidence interval should remain above 80% (IT) and above 90% (PP) for an effective regimen. **Any regimen with a range that drops below 80% (IT) or 90% (PP) should not be recommended.[2,4]**

b. *H. pylori* resistance to clarithromycin is on the rise. Recent data suggest that cure rates for first-line triple therapy (PPI+CLAR+AMOX [or MET]) fall below 80%.[17]

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H. Pylori Treatment Regimens

Helicobacter pylori infection plays a major role in the pathogenesis of peptic ulcer disease, chronic active gastritis, lymphoid tissue lymphoma, and gastric cancer.[17] Recent data suggest *H. pylori* resistance to current recommended first-line triple therapy regimen is on the rise with up to 20% treatment failure observed.[2,17] In light of the increased resistance rate, researchers are investigating new treatment regimens for *H. pylori* eradication. This document includes a chart comparing the efficacy of the 2007 American College of Gastroenterology (ACG) and Canadian Helicobacter Study Group (2004) and Dyspepsia Working Group (2005) recommended *H. pylori* treatment regimens and other new treatment regimens.

Both U.S. and Canadian treatment guidelines recommend PPI-based triple therapy (standard PPI dose BID + clarithromyicn 500 mg BID + amoxicillin 1000 mg BID [**or** metronidazole 500 mg BID if penicillin allergic]) as first-line treatment of *H. pylori* infection [Evidence level A, high quality RCTs].[2-4] The ACG recommends 14 days of treatment duration whereas the Canadian guidelines recommend at least seven days of treatment.[2-4] Several studies and meta-analyses have shown that triple therapy works better if the PPI is dosed twice daily and when clarithromycin 500 mg rather than 250 mg BID is used.[17] All different PPIs seem to have similar efficacy. Although recommended as an alternative to patients who are penicillin allergic, the combination of metronidazole and clarithromycin should be discouraged as there is currently no effective salvage therapy if such combination failed.[17]

An alternative to the triple therapy treatment regimen is the quadruple combination of a PPI, bismuth, tetracycline, and metronidazole for ten to 14 days.[2,3] Quadruple therapy was previously considered a rescue regimen rather than first-line treatment regimen due to the perception that the dosing was too complex and less well-tolerated than PPI triple therapies.[4] However, a recent meta-analysis concluded that the efficacy and tolerability of PPI triple therapies and quadruple therapy were similar [Evidence level A, high quality meta-analysis].[4] The ACG recommends quadruple therapy as a first-line treatment option or as a salvage therapy in those who have failed clarithromycin-based triple therapy.[2]

The U.S. FDA recently approved the first three-in-one capsule (*Pylera*) for use in combination with a PPI for the treatment of *H. pylori.* Each *Pylera* capsule contains bismuth subcitrate potassium 140 mg, metronidazole 125 mg, and tetracycline 125 mg. Because of *Pylera's* different bismuth salt, its use is not a concern in people with aspirin allergy.[22] The recommended dosing regimen is standard PPI dose BID + three *Pylera* capsules QID.[19] In clinical trials, omeprazole 20 mg BID + *Pylera* three capsules QID was found to be at least as effective as the widely used triple therapy of omeprazole 20 mg BID + amoxicillin 1000 mg BID + clarithromycin 500 mg BID (intent-to-treat eradication rates were 88% and 83%, respectively).[19] The AWP for a 10-day course of *Pylera* treatment is $266.61 plus the cost of PPI.[20]

Another currently available bismuth based regimen combination in the U.S. is *Helidac*. *Helidac* contains 14 prepackaged dosing blister cards. Each dose contains four pills: two bismuth subsalicylate 262 mg chewable tablets, one metronidazole 250 mg tablet, and one tetracycline 500 mg capsule. The dosage is one dose (all four pills) QID plus either an H2-blocker or a PPI BID.[1-4,15] Compared to *Pylera*, *Helidac* dosing may be more complicated, requiring the patient to take more tablets. A 14-day course of *Helidac* treatment is $294.48 plus the cost of PPI.[21]

In light of the increased resistance rate to the current recommended PPI-based triple therapies, researchers are investigating other treatment regimens. A 10-day sequential therapy combining a 5-day course of PPI BID with amoxicillin 1000 mg BID immediately followed by a second course of clarithromycin 500 mg BID, tinidazole BID, and a PPI BID for five additional days is one of the promising new regimens[16,17] Cure rates of such sequential therapy has been shown to be as high as 92% in Europe [Evidence level A; high quality RCTs].[16,17] The 2007 Sanford Guide to Antimicorbial Therapy recommends such sequential treatment regimen as a first-line treatment for *H. pylori* infection along with the standard PPI-based triple therapies.[16] While sequencial therapy has been shown to be effective in the European

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population, some clinicians feel more experience with a North American population is needed before recommending it as a treatment option. The ACG states that sequential therapy cannot be widely accepted as first-line therapy in the U.S. until efficacy has been validated in the North American population.[2]

For salvage therapy, an option besides quadruple therapy is the levofloxacin-based triple therapy, which shows eradication rates ranging from 63% to 94% in Asian and European populations. A recent meta-analysis including four randomized controlled trials showed that a 10-day levofloxacin-based triple therapy regimen had a superior eradication rate and was associated with fewer side effects compared to a 7-day course of bismuth-based quadruple therapy.[2] However, these results require validation in the North American population.

Although double therapy (e.g., PPI+AMOX) for ten to 14 days is an FDA-approved regimen, such regimens should not be recommended since the eradication rate falls <80%.[9,23]

In treating *H. pylori* infection, it is important to achieve a high eradication rate in order to reduce symptoms and complications of the infection.[23] The eradication rate of *H. pylori* is highly dependent on patient compliance to the treatment regimen. An ideal treatment regimen should be simple, well-tolerated, cost-effective, encourage patient compliance, and provide a bacterial eradication rate of >80%.[23]

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Levels of Evidence

In accordance with the trend towards Evidence-Based Medicine, we are citing the **LEVEL OF EVIDENCE** for the statements we publish.

Level	Definition
A	High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)
B	Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study
C	Consensus Expert opinion
D	Anecdotal evidence In vitro or animal study

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