H. pylori Eradication Regimens

1-2-3 Cured

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Highlights

- *H. pylori* eradication drastically reduces ulcer recurrence in patients with duodenal or gastric ulcers.
- **7-day** triple therapies with a proton pump inhibitor (PPI) + two antibiotics given BID are currently recommended ***first-line*** for *H. pylori* eradication e.g. lansoprazole (or alternate PPI) + clarithromycin + either metronidazole or amoxicillin (see **Table 3**)
- A dose of clarithromycin **250mg** po BID is preferred when using in combination with a PPI and metronidazole; however, the 500mg po BID dose is recommended in combination with a PPI + amoxicillin.
- Maintenance acid suppression therapy is not necessary following *H. pylori* eradication except in high-risk patients (e.g. severe GI bleed; refractory ulcer disease).
- Ranitidine Bismuth Citrate or ***RBC*** **(Pylorid®)** is a new agent useful in *H. pylori* eradication regimens.

Background

Helicobacter pylori is an important cause of duodenal and gastric ulcers. Greater than 90% of duodenal ulcers and 70% of gastric ulcers are associated with *H. pylori*.[1] Eradication of *H. pylori* is effective in healing ulcers and drastically reducing the ulcer recurrence, eliminating the need for maintenance therapy.[2]

H. pylori is a gram negative bacillus which colonizes in the gastric mucosa and causes an increase in gastrin release. *H. pylori* stimulates an inflammatory response involving the release of chemotactic cytokines such as interleukin-8.[1]

Besides being a major etiological factor in peptic ulcer disease (PUD), there is some evidence that it may also be associated with other gastric diseases.[3] *H. pylori* is not easy to eradicate. Factors such as the bacterial resistance and difficulty achieving bactericidal concentrations in the gastric mucosa contribute to the variable response to antibiotic therapy. As a result, triple and quadruple pharmacotherapy regimens are now used to ensure high eradication rates.

Indications for *H. pylori* eradication

The most recent Canadian *H. pylori* Consensus Conference recommends that "all *H. pylori*-positive patients with an unequivocal duodenal or gastric ulcer, whether active or inactive, should receive eradication treatment. Even if NSAIDs are the suspected etiological agent, eradication of documented *H. pylori* infection is appropriate".[4] The Consensus Conference discussed various other indications for *H. pylori* eradication therapy and the reader is referred to the document for a complete discussion of this area.

H. pylori - Treatment Options

First-line **eradication regimens** achieve high rates of both eradication and patient compliance. Two triple therapy - 7 day regimens are currently accepted as *first-line* therapy (**see Table 3**).[4] They combine a proton pump inhibitor (PPI) with either metronidazole and clarithromycin (Biaxin®), or amoxicillin and clarithromycin. These regimens generally achieve eradication rates of >80% on an intention-to-treat analysis (ITT) and >90% on a per-protocol analysis (PP). Since non-compliance can drastically reduce eradication rates, twice daily administration schedules are recommended. The approach is sometimes referred to as **'*1,2,3*'** - *one week, twice a day, with three medications.*

Second-line **eradication regimens** include quadruple therapy with bismuth, metronidazole, and tetracycline plus either a PPI or an H_2 receptor antagonist (H_2RA) (**see Table 3**).[4] If a PPI is chosen, the regimen can be given for 7 days; however, if an H_2RA is used, 14 days are recommended. Quadruple therapies are considered *second-line* because the regimens require a more complex administration schedule (e.g. QID) and may be less well tolerated. Quadruple therapies are therefore usually reserved for patients who have failed one or more courses of triple therapy.[4,5] Some quadruple therapies are less costly and appropriate for patients in whom cost is a significant factor.

Pylorid® is a new drug which consists of **ranitidine bismuth citrate (RBC)** 400mg. It may be useful in second-line triple therapy regimens when combined with two antibiotics (see Table 1). RBC was not included in recommendations from the last Canadian Consensus Conference as it was not yet on the market. It has shown similar efficacy to PPI's in 7 day - triple therapy regimens (see also **Table 1**). Further studies are awaited to verify efficacy compared to PPI-triple therapy regimens.

Considerations in Choosing a Regimen

•If the patient has a **penicillin allergy**, amoxicillin-containing regimens must be avoided. Amoxicillin regimens may also be less effective in patients pretreated with PPI's.[1]

•If the patient has previously been on **metronidazole**, or is not willing to give up **alcohol** for the 7 day therapy, a non-metronidazole regimen may be preferred.

•If **cost** is a significant concern, a low-cost regimen such as RBC (Pylorid®) + metronidazole + tetracycline appears to offer eradication rates similar to first-line PPI triple therapy at a cost of ~ $45 for 7-day therapy. (Although *H. pylori* eradication is expensive, it consistently results in lower costs and better outcomes than H_2RA maintenance therapy.[6,7])

•If **compliance** is a major concern, the *HP-Pack* (see Table 3) offers the advantage of a convenient blister card. Each card provides one day's therapy, with morning and evening dosing clearly indicated.

•If a patient is on **phenytoin**, **diazepam**, **warfarin**, **theophylline** or other drugs metabolized by **CYP-2C9** or **CYP-2D6**, pantoprazole (Pantoloc®) may be the preferred PPI. Omeprazole is thought to be most likely, and pantoprazole least likely, to have CYP_{450} related drug interactions, although the significance appears to be minimal.[8] Clarithromycin has more significant potential for drug interactions with various agents as listed in Table 2.

Follow Up Acid Suppression

Recurrence of ulcers following *H. pylori* eradication are uncommon. One prospective study which followed 141 duodenal ulcer and 45 gastric ulcer patients for 9.8 years found no ulcer recurrence after *H. pylori* eradication in patients not taking ASA or NSAIDs.[9] **Thus, most patients do not require further acid suppression treatment following *H. pylori* eradication**. Additional short term acid suppression with PPI's or H_2RA's may be indicated in symptomatic patients.[5] Complicated patients with large, or refractory ulcers, should receive acid suppression treatment until ulcer healing and *H. pylori* eradication can be documented.[2] In the case of gastric ulceration, follow-up is important in ensuring complete ulcer healing, and excluding the possibility of malignancy. Upon eradication of *H. pylori* and completion of ulcer healing, maintenance therapy is only indicated in patients at high risk for recurrence of bleeding (e.g. need for continued ASA/NSAID therapy; high acid-secretory condition).

Related Questions

What do we know about the relative efficacies of the various eradication regimens?

•It is difficult to compare eradication rates reported from different studies. There are many variables that can affect these rates. It has been suggested that the intention-to-treat (ITT) rather than the per-protocol (PP) analysis should be used as the primary end-point.[10] Few definitive head to head studies have been performed, and given the relatively high eradication rates currently achieved with triple therapies, studies showing significant differences are unlikely.

What are the rates of *H. pylori* resistance in Canada?

•*H. pylori* resistance to metronidazole ranges from 11% to 38%. However, when metronidazole is used in regimens with bismuth subsalicylate (BSS) or clarithromycin, they are often still highly effective even if *H. pylori* appears to be metronidazole resistant.[11]

•Primary resistance of *H. pylori* to clarithromycin is low generally less than 2%.[11,12] Acquired resistance can approach 6%, reinforcing the recommendation to use triple rather than dual therapy.

Is clarithromycin 250mg as good as 500mg in the PPI-triple based regimens?

•When used in combination with a PPI and metronidazole, clarithromycin should be given as **250mg** po BID.[13] This is supported by the MACH I Study which found that eradication rates were higher with the 250mg dose of clarithromycin than they were with the 500mg dose (90% versus 84% respectively).[14] The lower dose is also better tolerated and less costly.

•When given with a PPI and amoxicillin, the current recommendations are to use **500mg** clarithromycin po BID. Whether this dose offers additional benefit is uncertain. In the MACH I study, the higher clarithromycin dose was superior to the low dose[14]; however, several studies have used doses of clarithromycin 250mg po BID while maintaining eradication rates >85% ITT.[15,16,17] Unless patient tolerance or cost are significant concerns, the 500mg mg dose of clarithromycin is recommended for PPI triple therapy with amoxicillin.

Is there any rational for selecting one PPI over another?

•Studies to date suggest that omeprazole 20mg BID, lansoprazole 30mg BID, and pantoprazole 40mg BID have comparable efficacy in *H. pylori* eradication.[2,16,18,19] Most controlled studies have used either omeprazole or lansoprazole. Currently, lansoprazole may be preferred. It has shown more potent inhibition of *H. pylori* urease activity,[20] is generally less costly, and has less potential for drug interactions than omeprazole.

What if a triple therapy fails?

•Although routine documentation of *H. pylori* eradication is not recommended in uncomplicated ulcer patients, a recurrence of ulcer symptoms warrants a reassessment of *H. pylori* status.[2] Endoscopy and biopsy or a urea breath test may be performed at least four weeks after eradication, and seven days after stopping acid suppressive therapy.[4] Serologic assays are inappropriate as they remain high for several months following successful eradication.

•Retreatment should usually be attempted with different antibiotics than were originally used.[4] Resistance is especially a concern with metronidazole and rarely with clarithromycin. Alternative therapy with a quadruple regimen (e.g. PPI, BSS, metronidazole, and tetracycline) [11] or a triple regimen with RBC (Pylorid®) may be considered **(see Table 3)**.

Is classical triple therapy with bismuth, metronidazole and tetracycline still an option?

• This triple regimen was not recommended by the Canadian Consensus Conference because a meta-analysis showed that on an ITT analysis, it had an eradication rate of ~78%, below the arbitrary 80% cut-off rate.[2]

References available on request

The Rx Files: *H. pylori* Eradication
Supplementary Tables

Table 1

Ranitidine bismuth citrate (RBC) (Pylorid®)

Description:

- A salt complex resulting from a direct reaction between ranitidine and bismuth citrate. Each 400mg tablet contains 162mg of ranitidine base, 128mg trivalent bismuth, and 110mg of citrate.[21]
- Effective in the treatment of H. pylori when used in combination with antibiotics.

RBC (Pylorid®) Combination Regimens:

- Pylorid® 400mg po BID + tetracyline 500mg po QID + metronidazole 500mg po TID x 7 days[22] Eradication rates: 86% (ITT)
- Pylorid® 400mg + clarithromycin 500mg + amoxicillin 1000mg po BID x 7 days[22] Eradication rates: 92% (ITT)
- Pylorid® 400mg + clarithromycin (Biaxin®) 500mg po BID x 14 days[22,21] Eradication rates: 82-95% (ITT)

Adverse Effects & Drug Interactions[23]

- Diarrhea, the only adverse effect seen in >1% of patients. When used in combination with clarithromycin, diarrhea (6%), headache (4%), and taste disturbance (6%) may occur. Other *side effects* include temporary and harmless darkening of the stool and/or tongue.
- Ranitidine concentrations may be increased by ~57% when given with clarithromycin. No other significant *drug interactions* have been observed although ranitidine may exert a minor effect on the CYP_{450} enzyme system.

Contraindications[23]

- Hypersensitivity; Porphyria: The combination of RBC and clarithromycin is contraindicated in patients with a history of porphyia.
- Renal dysfunction: avoid if a CrCl <25ml/min.

Precautions

- Pregnancy/Lactation: Pregnancy Category C (no adequate controlled studies in women; no evidence of harm in animal studies). Not recommended in nursing mothers due to lack of data.

Place in H. pylori eradication (See also Table 3)[2]

- **RBC + tetracycline + metronidazole x7 days** offers an effective low cost alternative to currently accepted first line triple therapies. It has the disadvantages of requiring QID dosing (which may have a negative impact on compliance) and it has not been as well studied.
- **RBC + clarithromycin + amoxicillin x7 days** does not offer any significant advantages over currently accepted first line triple therapies with a PPI and two antibiotics.
- **RBC + clarithromycin x 14 days** is a second line option in patients who are not able to tolerate amoxicillin or metronidazole in PPI triple therapy regimens. Regimen is simple (2 tablets twice daily) and well tolerated, but requires 14 days of therapy. Resistance is a concern with a single antibiotic regimen.

Table 2

Anti-*H. pylori* Agents[24,25]

Amoxicillin

- good MIC's; resistance uncommon; (ampicillin NOT effective as not actively secreted into gastric juice)
- coadministration with a PPI or H_2RA increases efficacy
- contraindications: penicillin allergy
- side effects: diarrhea, PMC, candidiasis

Bismuth subsalicylate (BSS) (Peptol Bismol®)

- topically active - cytoprotective and antimicrobial effects; accumulates in bacterial membranes causing structural degeneration; blocks *H. pylori* adhesion to glycerol lipid receptors and inhibits urease activity
- tablets or suspension available; must use **suspension** if regimen includes tetracycline (BSS tablets contain Ca^{++})
- DI's: may ↑ warfarin effect; ↓ tetra/doxy-cycline absorp.
- side effects: tongue and stool may turn black; tinnitus

Clarithromycin (Biaxin®)

- most effective anti-*H. pylori* in vivo; most expensive
- cautions: DI's with cyclosporin, theophylline, cisapride, terfenadine, astemizole, and warfarin
- side effects: taste disturbance

Metronidazole

- regional variation in resistance rates (11-38%)
- combination use with bismuth decreases resistance
- smoking reduces efficacy
- contraindications: avoid alcohol (disulfiram-like reaction)
- side effects: furry coated tongue, metallic taste, diarrhea, dyspepsia, nausea, neuropathies (rare with short-term admin)

Tetracycline

- good MIC's; resistance uncommon
- requires frequent (QID ac) dosing
- Ca^{++}, Mg^{++}, Al^{++} containing food/products (e.g. dairy products, antacids) interfere with efficacy; Space by >1hr
- may ↓ effectiveness of oral contraceptives
- contraindications: pregnant women and children
- side effects: tinnitus

Proton Pump Inhibitors (PPI's)

- inhibit *H. pylori* growth by unknown mechanism; also enhance antimicrobial activity certain antibiotics
- omeprazole (Losec®), lansoprazole (Prevacid®), and pantoprazole (Pantoloc®) have shown comparable efficacy in *H. pylori* eradication. Only omeprazole & lansoprazole are approved for this indication in Canada.

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Table 3: *H. pylori* Eradication - 7 Day Regimens with >80% eradication rates (ITT) Prepared by Loren Regier BA, BSP - ***The Rx Files*** **- AUG/2000**

	Regimens	Days	Cost	CCC[4]	Comments
First-Line **Triple Therapy** **(PPI + 2 antibiotics)**	**lansoprazole** (*Prevacid*®) ✎ 30mg po BID **metronidazole** (*Flagyl*®) 500mg po BID **clarithromycin** (*Biaxin*®) **250**mg po BID	**X7d**	**$ 80**	✔	• **250mg dose of clarithromycin** preferred as better tolerated, equal or better efficacy (MACH I study[26]), and less costly than 500mg dose in PPI+metronidazole regimen • lansoprazole regimen may be preferred as less costly & less DI's than omeprazole in the *Losec 1-2-3-M*® regimen • avoid alcohol! (DI: metronidazole ➔ disulfiram rx.) • SE's: taste disturb. (~14%), diarrhea (~13%), headache (~6%); Also (less common): neuropathy, coated tongue
	Losec 1-2-3-M®: omeprazole (Losec®)20mg po BID ✎ metronidazole 500mg po BID clarithromycin **250**mg po BID	**X7d**	$ 84	✔	
	Hp-PAC® ✎ **:** lansoprazole ✎ 30mg po BID amoxicillin 1000mg po BID clarithromycin **500**mg po BID	**X7d**	**$ 94**	✔	• **Hp-PAC**® contains the triple combination in a convenient 7 day blister pack; may be preferred as more convenient, less expensive and possibly less DI's than *Losec 1-2-3-A*® regimen • lower dose of clarithromycin (250mg) was effective in some studies but not currently recommended • SE's: diarrhea (~28%), taste disturbance (~15%) • MCI's: avoid if penicillin allergy
	Losec 1-2-3-A®: omeprazole ✎ 20mg po BID amoxicillin 1000mg po BID clarithromycin **500**mg po BID	**X7d**	$ 113	✔	
Alternative ***Second-Line*** **Triple Therapy** **RBC (Pylorid®) + 2 antibiotics)**	RBC (*Pylorid*®) ✎ 400mg po BID metronidazole 500mg po TID tetracycline 500mg po QID	**X7d**	**$ 46**	-	• advantage: **low cost option**; disadvantage: QID dosing • SE's: temporary darkening of stool and tongue, diarrhea • MCI's: porphyria, renal dysfx (CrCl <25ml/min), pregnancy, children; avoid alcohol
	RBC (*Pylorid*®) ✎ 400mg po BID metronidazole 500mg po BID clarithromycin 250mg po BID	**X7d**	$ 69	-	• SE's: temporary darkening of stool and tongue, diarrhea, headache, taste disturbance • avoid alcohol • MCI's: porphyria, renal dysfx (CrCl <25ml/min)
	RBC (*Pylorid*®) ✎ 400mg po BID amoxicillin 1000mg po BID clarithromycin 500mg po BID	**X7d**	$ 98	-	• SE's: temporary darkening of stool and tongue, diarrhea, headache, taste disturbance • MCI's: porphyria, renal dysfx (CrCl <25ml/min); pen allergy
Alternative ***Second-Line*** **Quadruple Regimens** **(PPI + bismuth + 2 antibiotics)**	lansoprazole ✎ 30mg po BID bismuth subsalicylate (*Peptol Bismol*®) 30mls po QID metronidazole 250mg po QID tetracycline 500mg po QID ac	**X7d**	$ 75	✔	• Quadruple therapy may be indicated in cases of treatment failure requiring retreatment • Peptol Bismol® **suspension preferred** to tablets to avoid drug interaction with tetracycline (Peptol Bismol® tablets contain calcium carbonate which can interfere with tetracycline) • SE's: temporary darkening of stool and tongue, diarrhea • MCI's: porphyria, renal dysfx (CrCl <25ml/min), pregnancy, children; avoid alcohol
	omeprazole ✎ 20mg po BID bismuth subsalicylate (*Peptol Bismol*®) 30mls po QID metronidazole 250mg po QID tetracycline 500mg po QID ac	**X7d**	$ 79	✔	

CCC = Canadian (*H. pylori*) Consensus Conference approved; **DI** = Drug interactions (see Table 2); **SE's** = Side Effects; **MCI's** = major contraindications; **Cost** = retail cost to consumer in SK per 7 day therapy - includes markup and dispensing fee(s); ✎ **= EDS**; **PPI** = Proton pump inhibitors; **RBC** = ranitidine bismuth citrate; **ITT =** intention to treat analysis. **Other Comments**: Pantoprazole (Pantoloc®) - not officially indicated for H. pylori however appears to be as effective as other PPIs (less well studied); Compliance is likely the most important factor in achieving eradication; Resistance is variable to metronidazole and may affect eradication rates; Bismuth/metronidazole combinations appear to be effective even in areas of higher metronidazole resistance; Follow-up acid suppression (with PPI or H2 receptor antagonist) not generally indicated once *H. pylori* eradicated except for acute ulcer healing, symptomatic, and complicated/high risk patients. Other regimens in the literature: 1. Classic triple therapy (bismuth 30ml po QID + metronidazole 250mg po QID + tetracycline 500mg po QID x14days; ER~78%); 2. Quadruple 14 day therapy (ranitidine 300mg po BID + bismuth 30ml po QID +metronidazole 250mg po QID + tetracycline 500mg po QID; ER >80%); 3. Four-day triple & quadruple therapies have also been recently studied with ER's >85%.[27,28] Comment on RBC: Eradication rate data for RBC awaits verification in further studies in order to fully evaluate its potential role compared to well established PPI-triple therapy regimens.

The Rx Files - H. pylori Eradication - March/1999
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