NAVIGATING ACID SUPPRESSION OPTIONS

Considerations for Optimal PPI Therapy

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Objective comparisons for optimal drug therapy

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Key Messages, Tips and Pearls

1. There are no clinically important differences among standard doses of PPIs in the initial treatment of most gastrointestinal conditions.
2. Double dose PPI is generally no more efficacious than standard dose as initial therapy for most GI conditions (e.g. GERD, dyspepsia, NSAID ulcer treatment & prophylaxis).
3. Assess need for ongoing therapy beyond the initial course of 4-8 weeks. Some GERD patients, especially those with erosive esophagitis (EE) will require regular PPI.
   {Also consider lifestyle measures, e.g. stop smoking; weight loss}
4. Periodically reassess PPI therapy. Those on high / double dose PPIs may benefit from reassessing dosage; use the lowest effective dose when maintenance therapy is required.
5. Histamine 2 receptor blockers (H2RAs) are an option for some patients with mild GERD, step-down /maintenance therapy, endoscopic negative reflux disease (ENRD), functional dyspepsia and PRN for dietary indiscretion.
6. Recent safety concerns have been raised regarding PPI use. Although PPIs are quite safe, patients should use only for the duration indicated and at the lowest effective dose.
7. For patients at high risk of NSAID induced ulcers, standard dose H2RAs are NOT effective. Use a standard dose PPI.

Are there any differences in efficacy between PPIs? [1,2]

- PPIs appear more similar than different. They share a similar mechanism of action, decreasing acid secreted from the "proton pump" at the parietal cell. Systematic reviews support clinical outcome equivalency for PPIs when equivalent doses are used in the treatment of GERD[2,3,4], NSAID ulcer prophylaxis/healing and *H. pylori* eradication[5].
- There are minor variations in pharmacokinetic profiles and drug interactions[6]; these are seldom of clinical significance. (See Acid Suppression Drug Comparison Chart.) Variation in patient response may be seen, and is unpredictable.
- Controversy in this area surrounds **esomeprazole dosing**. Most literature supports that a **20mg** dose is equivalent to standard doses of other PPIs; however, the **40mg** dose is more commonly used. Some 40mg trials in more severe EE have shown small incremental benefit in healing.[2] The marginal difference is insufficient to recommend its use over other PPIs. {Some would consider esomeprazole 40mg to be a cost-effective higher-dose PPI option.}

What constitutes a "standard dose" of a PPI?

Rabeprazole	PARIET, generic	**20mg daily**	$41 /mo	**Best given ~ 30 minutes pre-meal** {e.g. before breakfast}
Omeprazole*	LOSEC Cap $46, generic	**20mg daily**	$52 /mo	
Pantoprazole	PANTOLOC	**40mg daily**	$75 /mo	
Lansoprazole	PREVACID	**30mg daily**	$79 /mo	
Esomeprazole	NEXIUM**	**20mg daily**	$82 /mo	

* Jan/08 price in flux; Losec caps now lower than generic, due to generic rabeprazole

** 20mg is representative of equivalent Nexium dose [1,2] and recommended dosage CPS for most indications except *H pylori* eradication (20mg BID) and reflux esophagitis (initial); however, the most commonly used strength is 40mg (40mg daily, $82).

GERD: Initial Approach Considerations

- Standard dose PPI therapy is a treatment option and more efficacious than H2RAs for initial therapy of GERD.[1]
- Double dose PPI is generally no more efficacious than standard dose PPI as initial therapy for GERD (including EE).[1] One review [2007 Cochrane] noted that any benefit is very modest (NNT=25).[2] Some suggest that patients with a higher severity of GERD may benefit from double dose although this is unclear.
- The initial GERD duration of treatment should be at least 4 weeks for PPIs to ensure healing. After 4-8 weeks, therapy should be discontinued. Patients whose symptoms reoccur can be initiated on regular, intermittent or on-demand therapy. Long-term PPI should be limited to those who demonstrate a need for maintenance therapy.
- Regular daily dosing in patients with EE is usually required.

When should higher PPI doses be used?

- Double dose PPI therapy may be considered if standard doses are not effective (e.g. after 2-4 weeks of therapy).[2,7] Double dose PPI should be reassessed after 4-8 weeks of therapy.[2]
- Lack of response to standard dose PPI warrants reassessment of the diagnosis and whether patient taking the PPI appropriately.
  "The best predictor of those not likely to respond to a twice daily PPI is lack of response to a daily PPI." *Specialist comment*
- Higher dose PPI therapy is indicated in hypersecretory conditions (e.g. Zollinger-Ellison syndrome), *H. pylori* eradication regimens and select patients post-GI bleed [(4 weeks)].
- Hospital patients discharged on PPIs should be assessed for possible dosage reduction or discontinuation.

What is the role for "On Demand" PPIs in GERD?

- "On demand" use involves starting therapy after symptoms reoccur, and discontinuing when symptoms resolve.
- Patients who relapse after initial therapy will require some form of maintenance. The lowest dose and frequency required to achieve symptom control should be used.[8] 20% of patients with uninvestigated GERD will not require maintenance with a PPI.[9]
- On demand therapy or low dose PPIs may be suitable options for ENRD. It can be considered after a successful 4-8 week initial course. Of interest, patients with ENRD who respond to initial PPI therapy require on average 0.3 doses per day.[10,11]

What about recent safety concerns with PPIs?

- PPIs have an excellent safety profile and few side effects.
  {Common SE [1-8%]: headache, diarrhea, rash; Rare SE: allergy, nephritis}
- Observational data has raised concern regarding the following:
  - Fracture risk (???; with higher doses & long-term use)
  - *C. difficile* associated diarrhea (conflicting data)
  - Pneumonia (associated with recent initiation)
  - Low vitamin B12, iron and magnesium levels {routine monitoring not recommended}
- **Summary**: Given uncertainties and potential risks with long term PPI use, patients should use the lowest effective dose and only for the duration indicated. "Reassess periodically!"
  {See Table 3 – PPI Safety Concerns – Supplementary Data}

How effective are H2RA's relative to PPIs?

- Standard dose PPIs for up to four weeks are more efficacious than H2RAs for improvement of reflux symptoms in the initial treatment of uninvestigated GERD. A review of 5 RCTs[1] found symptom relief at 4-8weeks was as follows:
  - PPI 55-75% {NNT = 4-6 at 4-8 weeks}
  - H2RAs 27-58%
- PPIs have somewhat higher efficacy for those patients with uninvestigated GERD requiring maintenance therapy.[12]
  Complete symptom control at 12 months:
  - Pantoprozole 20mg/d 77%
  - Ranitidine 150mg bid **59%**

  {NNT = 6 CI=4-13; no difference in relapse}
- In ENRD, PPIs offer only a slight advantage over H2RAs (improvement in 53% vs 42% at standard dose; 50% vs 44% at half-dose PPI). There was no difference in quality of life.[1,13]
- PPIs are more effective than H2RAs in the treatment and maintenance of patients with erosive esophagitis.[1,14]

Which patients can be trialed on an H2RA?

- H2RAs may be an effective option for the following patients:
  - mild-moderate GERD, ENRD, uninvestigated GERD
  - infrequent dietary indiscretion (H2RAs may work faster than PPIs)
  - step-down therapy following PPIs in non-erosive GERD {can be successful without affecting quality of life; reduces cost}
  - functional dyspepsia (both H2RAs and PPIs marginally effective)[1]

Is it reasonable to add a nighttime H2RA for a patient having nocturnal GERD symptoms?

- H2RAs are known to provide nocturnal acid suppression. One study suggests that nighttime use in addition to a daytime PPI is useful in patients with nocturnal symptoms.[15] Recent guidelines suggest this is not usually recommended. They cite the lack of evidence and the potential for tachyphylaxis to develop to H2RAs after 7 days of therapy. In such cases adding a 2nd PPI dose is likely to be more effective than a nighttime H2RA.[8]

PPI cost-considerations?

- Cost differences for acid suppression regimens provide an opportunity for cost savings. A cost comparison for the PPIs is shown below in Table 1.
- Two strategies to address **cost** and **safety** concerns include:
  - initiating PPI therapy at standard dose
  - reassess use/dose with long-term use
- PPIs are a 1.2 billion dollar market in Canada [2004], and 12 billion worldwide [2007]. Strategies to use low cost PPIs, lowest effective dose and periodically reassess need for therapy could save > $150 million/year in Canada.[16]

Table 1: Acid Suppression Cost Considerations

	Low Cost / $ Month	High Cost / $ Month
H2RA (excluding cimetidine [$15])	Ranitidine gen ZANTAC 150mg po BID $27	Nizatidine AXID 150mg BID $45
½ Dose PPI	Rabeprazole gen PARIET 10mg po daily ac $24 Or: omeprazole 20mg every other day ($28)	Lansoprazole PREVACID 15mg po daily ac $79
Standard Dose PPI Jan/08 Losec cap 20mg daily ($46)	Omeprazole generic 20mg po daily ac $52 Rabeprazole gen PARIET 20mg po daily ac $41	Esomeprazole NEXIUM 20mg po daily ac $82 {Common high dose used 40mg po daily ac} $82

- see also RxFiles Drug Comparison Chart for more complete listing

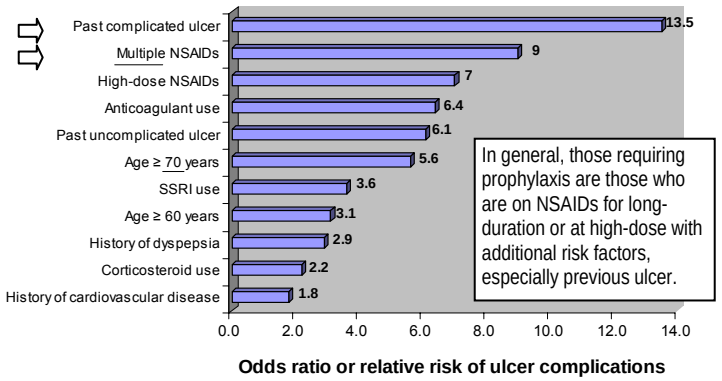
A note on the PPI Scientific Report – March 2007. In 2005 COMPUS set up a national Expert Review Panel on PPIs. This extensive report was published in March 2007 and is available online. Panel members included: Dr. Alan B.R. Thomson (Gastroent), Dr. Sander V. van Zanten (Gastroent), Dr. John K. Marshall (Gastroent), Dr. Laura Targownik (Gastroent), Dr. Anne Holbrook (Clin Pharmacol), Dr. Melissa C. Brouwers (Methodologist), Dr. Marilyn Caughlin (FP), Mr. Ron Goeree (Health Economist), Dr. Malcolm Man-Son-Hing (Geriatrician) , Ms. Pam McLean-Veysey (Pharmacist), Dr. John A. Rideout (FP), Dr. Brenda G. Schuster (Pharmacist).

Prevention of Drug Induced GI Bleeds

Who's at risk of NSAID associated ulcers?

- Patients who are at high risk for ulcer complications should be considered for prophylaxis if NSAID treatment is necessary (including those on low-dose ASA).
- Those NSAID patients at especially high risk include those with a history of complicated ulcer, on anticoagulants, those who are ≥70 years old and those with multiple risk factors (Figure 1). Combinations of antithrombotic agents also greatly increase bleeding risk (e.g. ASA/NSAID, with either warfarin or clopidogrel). [17]

Figure 1: Who's at Risk for NSAID Ulcer Complications [18]



Which agents help prevent NSAID associated ulcers?

- The following agents help prevent NSAID associated ulcers:
  - PPIs at standard dose (e.g. omeprazole 20mg/day ac)
  - misoprostol CYTOTEC 400-800mcg/day.[1,19,20] (≥ 600mcg better; use limited by diarrhea & abdominal pain; avoid in pregnancy!)
- Usual doses of H2RAs are not effective.
- There is no difference in ulcer recurrence and bleeding between a coxib and the combination of PPI + conventional NSAID (e.g. celecoxib versus lansoprazole + naproxen) in patients with previous NSAID-associated bleeds.[1,21] Of note, any GI advantage for coxibs may be lost if ASA is given concomitantly.[22,23]

Managing NSAID patients post-GI bleed

- Stop NSAID and treat with standard dose PPI for 4-8 weeks.
- Avoid NSAIDs where possible. Patients are at very high risk to re-bleed (5% over 6 months). Alternatives therapy options may include acetaminophen, opioids and non-drug measures.
- If an NSAID or coxib must be used, add a PPI.
- Whether use of a coxib+PPI offers an advantage over a NSAID+PPI combination has not been studied.
  {One recent trial evaluated patients post hospital admission for GI bleed. Patients were assigned to celecoxib 200mg bid with or without esomeprazole 20mg bid.[24] Combination treatment was more effective in preventing upper GI bleeding over 13 months. However, the trial did not address the issue of coxib+PPI versus conventional NSAID+PPI or cardiac concerns.}

Testing for H. pylori in new NSAID or ASA patients?

- Testing for *H. pylori* in patients starting long-term ASA or NSAID therapy has been proposed, but is not routinely recommended.[25,26,27] It may be useful in high risk patients.

In an ASA related GI bleed, is it safer to use Clopidogrel?

- No. In *H. pylori*-negative patients who have a history of ulcer bleeding on low-dose ASA, the combination of low-dose ASA and a PPI esomeprazole 20mg od-bid is associated with a lower risk of recurrence of ulcer complications as compared to clopidogrel alone.[28,29] {0.7% vs 8.6%; ARR=7.9; CI: 3.4-12.4; NNT=13}

A Tool for Dyspepsia Management

- Figure 2 displays a clinical tool for dyspepsia management
- The tool suggests a systematic assessment approach. Following confirmation of upper GI symptoms (e.g. to rule out cardiac cause), it is important to note whether patient's age or presence of alarm symptoms suggest the need for referral or more thorough investigation.
- If alarm symptoms are ruled out, one can then go on to consider NSAIDS/other drug causes, reflux disease and finally, *H. pylori*. {See Table 2 for list of other drug/herb causes.}
- Further discussion is beyond the scope of this newsletter.

Figure 2: Dyspepsia Clinical Management Tool [CanDys 25]

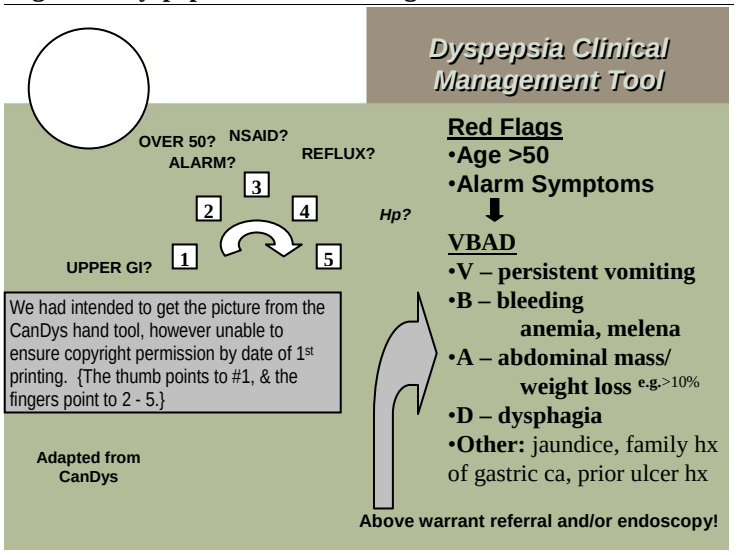


Table 2: Medications & Herbs associated with GERD

↓lower esophageal sphincter pressure		Direct mucosal irritants /Med Induced Esophagitis
Anticholinergics	Opioids	Alendronate, ASA (Aspirin),
β-agonists; Barbiturates	Nicotine	Clindamycin, Iron
Caffeine	Phentolamine	NSAIDs, Quinidine,
CCBs: nifedipine, felodipine, amlodipine	Progesterone	Potassium chloride,
Estrogen, Ethanol	Theophylline	Tetracycline, White willow

Table 3: PPI Safety Concerns – Supplementary Data {Observational data: limited & potential confounders}

- **Fracture risk**: case control studies suggest PPIs increase the risk of hip fractures.[30,31] The absolute risk was small with 4/1000 person-years for PPI users compared to 1.8/1000 person-years [crude rate] for acid suppression non-users. The risk is associated with duration.
  - 1 year [Adjusted]: OR 1.22 (CI = 1.15-1.30)
  - 2 year [Adjusted]: OR 1.41 (CI = 1.28-1.56)
  - 4 year [Adjusted]: OR 1.59 (CI = 1.39-1.80)

  This risk is also associated with higher doses.
  - ≤ 1.75 doses/day [>1yr]: OR 1.40 (CI = 1.26-1.54)
  - > 1.75 doses/day [>1yr]: OR 2.65 (CI = 1.80-3.90)
- **Risk of *C. difficile* associated diarrhea** (CDAD) and other enteric infection appears to be increased in patients on PPIs.[32,33,34] {observational trials; CDAD: OR 1.96 (CI=1.28-3.00)}[35] One Canadian study did not find an association between PPIs and hospitalization with CDAD in community elderly.[36]
- **Community acquired pneumonia** risk may be increased with PPIs.
  - One case control study found an increase in risk of 1.73 (OR: CI = 1.33-2.25).[37] This risk was greater at higher doses.
    - <1 dose/day: OR 1.23 (CI =0.78-1.93)
    - >1 dose/day: OR 2.28 (CI =1.26-4.10)
  - Authors estimate NNH=226; On average, 1 of every 226 patients treated with PPI for 5 months would develop pneumonia.
  - A more recent case control study also found an increase risk (OR=1.5; CI:1.3-1.7) but did not find a dose relationship.[38] They did find that recent initiation within the last 7 days had a stronger association (OR=5.0; CI=2.1-11.7).
- **Other reported adverse reactions** include low vitamin B12, iron levels and hypomagnesemic hypoparathyroidism.[39] Health Canada is reviewing two European studies regarding increased cardiovascular events with omeprazole and esomeprazole. Preliminary analysis is inconclusive.[40]

CI=confidence ration; OR=odds ratio; NNH=number needed to harm

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References

[1] CADTH - COMPUS Scientific Report: Evidence for PPI in gastroesophagearl reflux disease, dyspepsia and peptic ulcer disease [Scientific Report], March 2007. Accessible online at: http://www.cadth.ca/media/compus/reports/compus_Scientific_Report_final.pdf {Related COMPUS reports/tools available at: http://www.cadth.ca/index.php/en/compus/current-topics/ppis }
[2] Khan M, Santana J, Donnellan C, Preston C, Moayyedi P. Medical treatments in the short term management of reflux oesophagitis. Cochrane Database Syst Rev. 2007 Apr 18;(2):CD003244.:CD003244.
[3] van Pinxteren, B, Numans, ME, Lau, J, de Wit, NJ, Hungin, APS, Bonis, PAL. Short term treatment of gastroesophageal reflux disease: A systematic review and meta-analysis of the effect of acid-suppressant drugs in empirical treatment and in endoscopy-negative patients. *J Gen Intern Med* 2003;18:755-763.
[4] Blackhouse G, Lal A, Rajbhandary S, Belanger D, et al. Economic evaluation of alternative strategies for the management of patients with heartburn predominant GERD symptoms in Canada. Ottawa:The Agency; 2007 Mar.
[5] a) McDonagh MS, Carson S. Drug class review on proton pump inhibitors: final report update 3. Portland(OR): Oregon Health & Science University; 2005.
b) Gisbert JP, Pajares JM. Esomeprazole-based therapy in Helicobacter pylori eradication: a meta-analysis. Dig Liver Dis. 2004 Apr;36(4):253-9.
c) Gisbert JP, Khorrami S, Calvet X, Pajares JM. Systematic review: Rabeprazole-based therapies in Helicobacter pylori eradication. Aliment Pharmacol Ther. 2003 Mar 15;17(6):751-64.
d) Gisbert JP, Khorrami S, Calvet X, Pajares JM. Pantoprazole based therapies in Helicobacter pylori eradication: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2004 Jan;16(1):89-99.
e) Vergara M, Vallve M, Gisbert JP, Calvet X. Meta-analysis: comparative efficacy of different proton-pump inhibitors in triple therapy for Helicobacter pylori eradication. Aliment Pharmacol Ther. 2003 Sep 15;18(6):647-54.
[6] Martin de Argila C. Safety of potent gastric acid inhibition. Drugs. 2005;65 Suppl 1:97-104.
[7] DeVault KR, Castell DO; American College of Gastroenterology. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Am J Gastroenterol. 2005 Jan;100(1):190-200.
[8] Armstrong D, Marshall JK, Chiba N, Enns R, Fallone CA, Fass R, et al. Canadian consensus conference on the management of gastroesophageal reflux disease in adults: update 2004. *Can J Gastroenterol* 2005;19(1):15-35.
[9] Armstrong D, Veldhuyzen van Zanten SJ, Barkun AN,et al; The CADET-HR Study Group. Heartburn-dominant, uninvestigated dyspepsia: a comparison of 'PPI-start' and 'H2-RA-start' management strategies in primary care--the CADET-HR Study. Aliment Pharmacol Ther. 2005 May 15;21(10):1189-202.
[10] Metz DC, Inadomi JM, Howden CW, van Zanten SJ, Bytzer P. On demand therapy of gastroesophageal reflux disease. *Am J Gastoenterol* 2007;102:642-653.
[11] Goh KL. "On demand" therapy for gastroesophageal reflux disease: are current proton pump inhibitors good candidates? *J Gastroenterol Hepatol* 2006;21:S115-118.
[12] Talley NJ, Moore MG, Sprogis A, Katelaris P. Randomised controlled trial of pantoprazole versus ranitidine for the treatment of uninvestigated heartburn in primary care. Med J Aust. 2002 Oct 21;177(8):423-7.
[13] van Pinxteren B, Numans ME, Bonis PA, Lau J. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Database Syst Rev. 2006 Jul 19;3.
[14] Chiba N, De Gara CJ, Wilkinson JM, Hunt RH. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. Gastroenterology. 1997 Jun;112(6):1798-810.
[15] Peghini PL, Katz PO, Castell DO. Ranitidine controls nocturnal acid breakthrough on omeprazole: a controlled study in normal subjects. Gastroenterology 1998;115:1335-9.
[16] Estimate: {Financial data: 1) Worldwide annual sales ($ billion) based on 2nd quarter 2007: Nexium $5, Pantoloc $2.5, Prevacid $2.3, Pariet $1.3, Losec $1.2, generics ?. Canadian # Rx's: Pantoloc>Pariet >Nexium>Losec >Prevacid>Apo-omeprazole. Canadian 2004 IMS data: PPI sales = $ 1.2 billion; 30% of SK Rx's were for Nexium, Pantoloc, Prevacid, Losec.} {Based on ½ of the 12.4 million scripts/yr, with average savings of $25 per script; conservative estimate.}
[17] Delaney JA, Opatrny L, Brophy JM, Suissa S. Drug drug interactions between antithrombotic medications and the risk of gastrointestinal bleeding. CMAJ. 2007 Aug 14;177(4):347-51.
[18] Hunt RH, Barkun AN, Baron D, Bombardier C, et al. Recommendations for the appropriate use of anti-inflammatory drugs in the era of the coxibs: defining the role of gastroprotective agents. Can J Gastroenterol. 2002 Apr;16(4):231-40.
[19] Hawkey CJ, Karrasch JA, Szczepanski L, Walker DG, Barkun A, Swannell AJ, Yeomans ND. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. Omeprazole versus Misoprostol for NSAID-induced Ulcer Management (OMNIUM) Study Group. N Engl J Med. 1998 Mar 12;338(11):727-34.
[20] Silverstein FE, Graham DY, Senior JR, Davies HW, Struthers BJ, Bittman RM, Geis GS. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 1995 Aug 15;123(4):241-9.
[21] Lai KC, Chu KM, Hui WM, Wong BC, et al. Celecoxib (200mg/d) compared with lansoprazole (30mg/d) and naproxen (750mg/d) to prevent gastrointestinal ulcer complications. Am J Med. 2005 Nov;118(11):1271-8.
[22] FDA Docket – CLASS data submitted: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_01_searle.pdf & http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_03_med.pdf
[23] BMJ 2002;324:1287-1288. Accessed at:) http://www.bmj.com/cgi/reprint/324/7349/1287?ijkey=ea97b0ee3555a38b3c0826a6e4fddab7225d2669
[24] Chan FK, Wong VW, Suen BY, Wu JC, et al. Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial. Lancet. 2007 May 12;369(9573):1621-6. {Celecoxib 200mg BID; Esomeprazole 20mg BID; n=441}
[25] Van Zanten VSJ, Flook N, Chiba N, Armstrong D, Barkun A, Bradette M, et al. An evidence-based approach to the management of uninvestigated dyspepsia in the era of Helicobacter pylori. Canadian Dyspepsia Working Group. *CMAJ* 2000;162(12 Suppl):S3-S23. Available: http://www.cmaj.ca/cgi/content/full/162/12_suppl/s3 (accessed 2007 Mar 8).
[26] Hunt RH, Fallone CA, Van Zanten VSJ, Sherman P, Smaill F, Flook N, Thomson ABR. Canadian Helicobacter Study Group Consensus Conference: Update on the management of *Helicobacter pylori* – An evidence-based evaluation of six topics relevant to clinical outcomes in patients evaluated for *H pylori* infection. Can J Gastroenterol 2004;18(9): 547-554
[27] Chey WD, Wong BC; Practice Parameters Committee. American College of Gastroenterology guideline on the management of Helicobacter pylori infection. Am J Gastroenterol. 2007 Aug;102(8):1808-25.
[28] Chan FK, Ching JY, Hung LC, Wong VW, et al. Clopidogrel versus aspirin and esomeprazole 20mg bid to prevent recurrent ulcer bleeding. N Engl J Med. 2005 Jan 20;352(3):238-44. {n=320}
[29] Lai KC, Chu KM, Hui WM, Wong BC, et al. Esomeprazole 20mg/d with aspirin versus clopidogrel for prevention of recurrent gastrointestinal ulcer complications. Clin Gastroenterol Hepatol. 2006;4(7):860-5. Epub 22Jun06. {n=170}
[30] Yang YX, Lewis JD, Epstein S, Metz DC Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA. 2006 Dec 27;296(24):2947-53.
[31] Vestergard P, Rejnmark L, Mosekilde L. Proton pump inhibitors, histamine H_2 receptor antagonists and other antacid medications and the risk of fracture. *Calcif Tissue Int* 2006;79:76-83.
[32] Yearsley KA, Gilby LJ, Ramadas AV, Kubiak EM, Fone DL, Allison MC. Proton pump inhibitor therapy is a risk factor for Clostridium difficile-associated diarrhoea. Aliment Pharmacol Ther. 2006 Aug 15;24(4):613-9.
[33] Dial S, Delaney JA, Schneider V, Suissa S. Proton pump inhibitor use & risk of community-acquired Clostridium difficile-associated disease defined by prescription for oral vancomycin therapy. CMAJ 2006,26;175:745-8.
[34] Dial S, Alrasadi K, Manoukian C, Huang A, Menzies D. Risk of Clostridium difficile diarrhea among hospital inpatients prescribed proton pump inhibitors: cohort and case-control studies. CMAJ. 2004 Jul 6;171(1):33-8.
[35] Leonard J, Marshall JK, Moayyedi P. Systematic Review of the Risk of Enteric Infection in Patients Taking Acid Suppression. Am J Gastroenterol. 2007 May 17; [Epub ahead of print]
[36] Lowe DO, Mamdani MM, Kopp A, Low DE, Juurlink DN. Proton pump inhibitors and hospitalization for Clostridium difficile-associated disease: a population-based study. Clin Infect Dis. 2006 Nov 15;43(10):1272-6. Epub 2006 Oct 13.
[37] Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. JAMA. 2004 Oct 27;292(16):1955-60.
[38] Gulmez SE, Holm A, Frederiksen H, Jensen TG, Pedersen C, Hallas J. Use of PPIs and the risk of community-acquired pneumonia: a population-based case-control study. Arch Intern Med. 2007;167(9):950-5.
[39] Epstein M, McGrath S, Law F. Proton-pump inhibitors and hypomagnesemic hypoparathyroidism. N Engl J Med. 2006 Oct 26;355(17):1834-6.
[40] Health Canada reviewing new safety information on cardiac events in patients taking Losec (omeprazole) or Nexium (esomeprazole). Online 09Aug07. http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2007/2007_95_e.html

GASTROINTESTINAL - ACID SUPPRESSION DRUGS: EVIDENCE, TIPS AND PEARLS

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Five Key Decision Points in the Approach to Patients with Uninvestigated Dyspepsia (pain or discomfort in upper abdomen) [3]

1. Are there other possible causes for the symptoms? Consider cardiac, hepatobiliary, medication-induced, lifestyle or dietary indiscretion
2. Is the patient **>50yrs**, or does the patient have alarm symptoms? Alarm features and increased age identify patients at higher risk of organic causes, including cancer and ulcers.
   Alarm symptoms - ***VBAD*⇨** (**V**omiting, **B**leeding/anemia, **A**bdominal mass/uninvestigated wt loss, **D**ysphagia) ⇨ warrant prompt investigation
3. Is the patient regularly using conventional NSAIDs (including ASA)? Stop therapy if possible
4. Is the dominant symptom heartburn or acid regurgitation, or both? If yes, these are reliable indicators of GERD (gastroesophageal reflux disease)
5. Is the patient infected with *Helicobacter pylori*? Considering this question last will assist in legitimate indications for *H.pylori* testing

GERD

- symptomatic response to antisecretory therapy with proton pump inhibitor (**PPI**) or H2 antagonist (**H2RA**) is generally considered to support the presumptive diagnosis of GERD.
- mild symptomatic GERD <3x/week,↓ duration& intensity can often be managed with lifestyle & dietary changes along with OTC antacid or H2RA

PHARMACOLOGICAL CONSIDERATIONS

Initial therapy

- Standard dose PPI is more efficacious than H2RA[1]; double dose PPI is generally no more efficacious than standard dose for initial therapy in erosive esophagitis [1]

Reassess therapy at 4-8 wks

- if symptoms respond to 4-8weeks of therapy STOP therapy, if symptoms recur repeat original therapy
- if symptoms not resolved,
  →if not on a PPI, switch to a PPI x 4-8 weeks
  →if on a PPI give bid x 4-8 weeks or consider investigation;
  {Ensure PPI taken ~30 minutes before am meal, or pm meal if primarily nocturnal symptoms}

Long-term therapy

- REASSESS NEED FOR THERAPY following initial therapy & periodically thereafter.
- Tailor the dose and frequency to control symptoms. Patients should be maintained on the lowest dose of therapy that was adequate to provide symptom relief.

On-Demand PPI after response to initial PPI

- patients who respond to initial PPI therapy, subsequent "on-demand" PPI is more efficacious than continuous H2RA, but less efficacious than standard dose PPI {in uninvestigated GERD}[1]

STANDARD DOSES OF PPIs

There are no clinically important differences among standard doses of PPIs in treatment of symptomatic GERD, ENRD and esophagitis [1] **Patient variation in response may be seen.**

{Standard dose: Omeprazole, rabeprazole & esomeprazole 20mg od; lansoprazole 30mg od; pantoprazole 40mg od}.

PPIs are **not efficacious** in **asthma** associated with GERD, in improving **laryngeal** symptoms associated with reflux or improving **chronic cough** with or without GERD[1]

PUD & *H.pylori* (Non-NSAID PUD)

- ≈90% of DU & 70% of GU may be *H.pylori* positive
- the standard of care for all patients with GU/DU is *H. pylori* testing & treating if positive (~**30%** of Canadians are infected ↑ with age)
- smoking cessation improves ulcer healing rates and reduces ulcers not related to *H.pylori* infection

H.pylori TESTING – Noninvasive

- diagnostic testing for *H. pylori* should only be performed in pts suspected of having *H pylori*-related conditions such as PUD and if treatment is intended. (test and treat strategy)

Urea Breath Test (UBT)

- should be used for routine diagnosis, unless endoscopy is indicated for another reason
- excellent sensitivity, specificity and ease of use
- to prevent false –'ve results Hefikit, patients should **stop** for: antibiotics 4 weeks, bismuth 2 weeks, PPIs 3 days & H2RA 1 day
  (prn use of antacids can be used for Sx while awaiting tests)

Serology:

- appropriate if no access to UBT or endoscopy, higher rate of false positives results (≈20%)

Repeat H.pylori testing after *H.pylori* eradication

- confirmation of *H.pylori* eradication is not required unless symptoms persist, pt with bleeding or perforated ulcers, MALT lymphoma or gastric cancer do 4weeks after tx
- serology cannot be used to determine cure from infections (IgG antibodies still detectable 6-12 months after eradication)

H. pylori Regimens (see *H.pylori* Chart; all PPIs equally effective)

- *H. pylori* regimens 1-2-3 =**1** week, **2** times a day, **3** drugs commonly used, but quadruple regimens also an option
- single and two drug regimens not recommended
- 7 & 10 regimens equally effective, but 14 day regimens more efficacious than 7 day regimens [1,(American ACG recommends 10-14days) 9]
- consider the following when selecting regimen: allergy history, recent antibiotic metronidazole/clarithromycin or EtOH use (avoid metronidazole), potential compliance issues (1-2-3 regimens, Hp-PAC®), DIs
  [See also RxFiles H. Pylori Eradication chart http://www.rxfiles.ca/acrobat/CHT-Hpylori.pdf]

PPI treatment after *H. pylori* eradication

- for uncomplicated duodenal ulcer, once HP has been eradicated, continued PPI use does not produce higher ulcer healing rates and is generally not indicated [1]
  {Note: PPI may be indicated for acute healing of gastric ulcer}

PUD & NSAIDs - Prevention

- NSAIDS are responsible for the majority of HP negative PUD
- routine concomitant antiulcer prophylaxis is not warranted for all pts taking NSAIDs; assess patient risk

Preventing NSAID Induced Ulcer in High Risk Patients

High Risk: especially if hx of ulcers/UGIB. See note at bottom.*
Those with several risk factors are at highest risk for NSAID-induced GI toxicity (up to 9% at 6 months)

- avoid NSAID if possible (use alternatives e.g. acetaminophen)
- if NSAID must be used, use lowest dose & shortest duration
- **GI Ulcer Prophylaxis**
  →standard dose PPI (all PPIs, similar efficacy) [1]
  →misoprostol 200ug tid-qid $38-49 (SE: GI upset & diarrhea)
  {H2RAs are **not** recommended for GI prophylaxis in NSAID pts}

HP Eradication and NSAID Use

- *H.pylori* & NSAID additive on the risk of PUD/UGIB
- Testing for H. pylori in patients starting long-term ASA or NSAID therapy has been proposed, but is not routinely recommended.[9] Those at greatest risk (hx of peptic ulcers, dyspepsia, steroids, and/or warfarin) most likely to benefit.

COXIBs:

- The GI sparing effect of COXIBs is compromised when used concurrently with low dose ASA, therefore the GI advantage of a COXIB especially at high-dose is lost. When a COXIB is used with warfarin concurrently, the risk is similar to NSAIDS.
- COXIB risks {e.g. cardiac, renal, gastric} are dose dependent
- COXIB vs {NSAID + PPI} appear to have similar efficacy in prevention and recurrence of ulcer/bleeding in patients with previous NSAID associated UGIB[1]

TREATMENT OF NSAID INDUCED ULCER

- Discontinue NSAID, *H.pylori* test & treat if positive, treat like a non-NSAID ulcer {e.g. PPI or H2RA (x4wk in DU); (x8wk in GU)}
- Healing rates: standard dose PPI x4-8weeks is more efficacious than H2RA or misoprostol [1]

If NSAID MUST BE CONTINUED

- PPI more effective than H2RA, but similar efficacy to misoprostol 400-800ug/day endoscopic evidence 1
- *H. pylori* –'ve pts (ulcer bleeding history) on **low dose ASA+PPI** have lower risk of ulcer complications vs clopidogrel alone[1] (Chan'05 & Lai'06)

COXIBs= Selective cyclooxygenase 2 inhibitors **DI**=drug interactions **DU**=duodenal ulcer **ENRD**=endoscopic negative reflux disease **EtOH**=alcohol **GERD**=gastroesophageal reflux disease **GI**=gastrointestinal **GU**=gastric ulcer ***H.pylori***=*helicobacter pylori*
H2RAs=H2-receptor antagonist **NSAIDS**=nonsteroidal anti-inflammatory drugs **OTC**=over the counter **PPI**=proton pump inhibitor **PUD**=peptic ulcer disease **UBT**=urea breath test **UGIB**=upper GI bleed. [**See also** http://www.rxfiles.ca/acrobat/CHT-AcidSuppression.pdf]

References

1. CADTH. Scientific Report: Evidence for PPIs use in Gastroesophageal Reflux Disease, Dyspepsia and Peptic Ulcer Disease (Mar 2007) www.cadth.ca
2. 2006 UpToDate® • www.uptodate.com [See also RxFiles NSAID/COXIB chart: http://www.rxfiles.ca/acrobat/CHT-NSAID-Cox2.pdf]
3. Veldhuyzen van Zanten SJ, Flook N, Chiba N, Armstrong D, Barkun A, Bradette M, et al. An evidence-based approach to the management of uninvestigated dyspepsia in the era of Helicobacter pylori. Canadian Dyspepsia Working Group. CMAJ 2000;162(12 Suppl):S3-S23.
4. e-therapeutics www.e-therapeutics.ca
5. Preventing NSAID-Induced Ulcers.. Pharmacist's Letter/Prescriber's Letter 2002; 18(3):180306.
6. Armstrong A, et al. Canadian Consensus Conference on the management of GERD in adults – update 2004. Can J Gastroenterol 2005;19(1):15-35.
7. Hunt RH, et al. Canadian Helicobacter Study Group. Consensus Conference Update: Infections in Adults. Can J Gastroenterol 1999;13(3): 213-217.
8. Hunt R, Thomson ABR. Canadian Helicobacter pylori Consensus Conference. Can J. Gasteroenterol 1998;12(1):31-41.
9. Chey et al; Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of Helicobacter pylori infection. Am J Gastroenterol. 2007 Aug;102(8):1808-25. Epub 2007 Jun 29.

* **NSAID Ulcer Complication Risk Factors** (**x=↑ odds ratio**): ●hx complicated ulcer x13.5 ●multiple NSAID x9 ●high dose NSAID x7 ●concomitant anticoagulant use x6.4 ●age≥70 x5.6 ●SSRI use 3.6 ●age ≥60 x3.1 ●concomitant steroids x2.2 ●heart disease x1.8

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