PHYSICIANS' INTERACTIVE EDUCATION CASE STUDIES

Unless otherwise indicated, clinical and price information in this document is taken from:

Canadian Agency for Drugs and Technologies in Health. Evidence for PPI use in gastroesophageal reflux disease, dyspepsia, and peptic ulcer disease: scientific report. *Optimal Therapy Report – COMPUS* 2007;1(2). Available: http://www.cadth.ca/index.php/en/compus/current-topics/ppis (accessed 2007 March 28).

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The Role of PPI Therapy in Management of Gastroesophageal Reflux Disease (GERD)

History:

- 49-year-old male, otherwise healthy
- Presenting complaint is retrosternal burning
- Symptoms have been ongoing for approximately six months
- At onset, retrosternal burning was occurring one to two times per week, mainly after meals
- Symptoms do not worsen with activity or inspiration, but often worse when bending over or reclining
- Burning occasionally accompanied by acidic taste in mouth
- Over the last month, symptoms have been occurring on a daily basis, with the patient occasionally awakening at night with similar symptoms which disturb sleep
- Patient has been using TUMS® and Maalox®, finds they work, but only relieve symptoms temporarily
- Patient has never seen a physician for similar symptoms or used prescription medication
- Patient does not report any dysphagia, nausea, vomiting, other abdominal pain, change in bowel habits, melena, bright red blood with stooling, or weight loss
- Non-smoker; low alcohol consumption (average two beers per week)

Current Medications Including Over-the-counter and Herbal Medications: None

Physical Exam:

- Patient appears generally well nourished
- BP 132/70, pulse 84 bpm, afebrile
- Current weight 102 kg; height 178 cm
- No conjunctival pallor, no scleral icterus
- Oral cavity normal, normal dentition
- Save for central obesity, remainder of physical exam within normal limits

Questions:

1) **Which investigations would you order at this time?**
2) **What would you use for initial management?**
3) **If you do initiate therapy with a proton pump inhibitor (PPI):**
    a. **which PPI would you use?**
    b. **what dose would you recommend?**

Teaching Point #1

Patients with symptoms strongly suggestive of gastroesophageal reflux disease and no signs or symptoms of complications do not require confirmatory investigations.

The presence of either heartburn or acid regurgitation is very specific for the presence of acid-reflux.[1] Therefore, patients with predominant symptoms of heartburn or acid regurgitation can be assumed to have GERD, and do not need testing (either through endoscopy, barium series, or 24h pH testing) to confirm the diagnosis.

The presence of alarm signs – specifically significant weight loss, dysphagia, hematemesis, or melena – is an indication for endoscopic evaluation to rule out esophageal strictures or malignancy.

Teaching Point #2

Either Histamine$_2$-receptor antagonists (H_2RAs) or PPIs can be used for initial treatment of GERD. H_2RAs are more effective than placebo, and PPIs are more effective than H_2RAs.

According to the Canadian Agency for Drugs and Technologies in Health (CADTH) scientific report on PPIs, PPIs are more effective than H_2RAs in the initial management of GERD.[2] However, there are no studies specifically comparing PPIs and H_2RAs in patients with mild GERD symptoms. It is these subjects in whom H_2RAs may be more likely to provide adequate symptomatic relief.[1] In the comparative trials, most patients had at least moderate heartburn at baseline. Symptom relief with initial therapy (four to eight weeks) was 55% to 75% with PPIs and 27% to 58% with H_2RAs (95% CI 3-15).[2]

The CADET-HR trial, which compared a "PPI-start" strategy (i.e., omeprazole 20 mg daily) to an "H_2RA-start" strategy (i.e., ranitidine 150 mg twice daily), found that patients in the "PPI-start" group had more rapid relief of symptoms at four weeks (55% versus 27% relief, respectively, $p<0.001$) and a lower likelihood of requiring step-up therapy for relief.[3] Moreover, a recent cost-effectiveness analysis of treatment strategies for moderate to severe heartburn commissioned by COMPUS concluded that initial therapy with one of the less expensive PPIs (e.g., generic omeprazole) appears to be cost-effective compared to initial therapy with H_2RAs.[4]

Therefore, it is reasonable to initiate therapy with a PPI in the initial management of GERD symptoms. However, initial therapy with an H_2RA is also acceptable.

Teaching Point #3

All PPIs have similar efficacy, and have a similar side-effect profile. The decision on the initial choice of a PPI should be based solely on price.

There is no role for double-dose PPIs in the initial management of GERD.

The CADTH scientific report determined that there are few clinically significant benefits in choosing one PPI over any other. Esomeprazole (Nexium™) 40 mg is marginally superior to standard doses of other PPIs in the healing of erosive esophagitis, although the absolute difference is marginal and insufficient to justify its routine use in place of other PPIs.[2] Esomeprazole is not superior to other PPIs for symptom relief in patients with non-erosive reflux disease.[5-8]

Furthermore, there are no studies which have demonstrated that any one PPI has a more favourable safety profile than any other PPI. Although, theoretically, rabeprazole and pantoprazole may have a lower risk of drug-drug interaction due to differences in how they are metabolized,[9-11] there are no studies which have demonstrated an increased risk of clinically significant drug-drug interactions with any specific PPI versus any other PPI.

Therefore, the only consideration that should be used in determining the initial choice of PPI is price.

Follow-up Presentation #1:

You prescribe generic omeprazole at a dose of 20 mg per day, and arrange for a follow-up visit in four weeks' time.

At four weeks, Mr. T. returns and reports complete relief of symptoms. He does not report any side effects related to the medication.

His physical exam is unchanged from the previous visit.

Question:

4. Do you make any changes to the patient's medical management?

Teaching Point #4

In subjects who attain complete relief of GERD symptoms with a PPI:

- continuation of daily PPIs is superior to on-demand PPIs and step-down to H_2RAs
- use of on-demand PPIs is superior to stepping down to continuous H_2RAs
- up to 20% of subjects may remain symptom-free long-term upon discontinuation of all active medication.

There is no clear consensus on what constitutes optimal maintenance therapy for subjects who attain symptomatic relief with PPIs. Continuation of daily PPI therapy, switching to on-demand PPI use, stepping-down to H_2RAs, or a trial of medication discontinuation are all reasonable options, and the treatment decision should be individualized, based on discussions between the patient and the physician.

Follow-up Presentation #2:

You decide to continue therapy with omeprazole 20 mg once daily. Four months later, Mr. T. returns to your clinic complaining of worsening heartburn over the past month. He claims to have been compliant with medical therapy as prescribed. He still does not report any alarm symptoms.

His physical examination remains unchanged.

Question:

5. **Would you recommend any changes to his management at this time?**

Teaching Point #5

For patients who remain symptomatic on a standard dose of PPIs, options include:

- increasing the dose of the PPI
- switching to a different PPI maintaining the status quo.

There is a single study in which persons with GERD symptoms who did not respond to a standard dose of PPI (omeprazole 20 mg daily) after four weeks of therapy were randomized to either continuing omeprazole 20 mg daily or increasing to 40 mg of omeprazole daily. This study demonstrated a statistically significant benefit to the increased PPI dose regarding healing of esophagitis (64% versus 45%, p=0.02), and heartburn relief (72% versus 60%, p<0.002).[12]

There has been a single study where patients who remained symptomatic on a standard dose of PPI (lansoprazole 30 mg) either had the dose of lansoprazole doubled to 60 mg daily or were switched to a different double-dose PPI (omeprazole 40 mg daily). This study showed no significant difference in symptom relief between the two double-dose regimens.[13] However, there are no published studies where switching to a different PPI (at either standard or double dose) has been compared to maintaining the status quo in patients with persistent symptoms following a trial of initial standard-dose PPI therapy.

In this situation, there is relatively limited evidence regarding the optimal strategy for Mr. T. Either doubling the dose of omeprazole to 40 mg daily or switching to another standard dose of a PPI could be tried. As switching to a standard dose of another PPI is generally less expensive than doubling the dose of the original PPI, this would be the preferred option if cost was a primary consideration.

Prevention and Treatment of Peptic Ulcer Disease

History:

- 57-year-old female
- Presents with three-month history of difficult ambulating secondary-to-left knee pain
- Pain worsens with activity, improves with rest
- Had been using extra-strength acetaminophen (500 mg tablets) with minimal relief
- You had seen her in the clinic two months ago, where you performed the following investigations:
    - CBC, chemistry panel, renal function, ESR: all normal
    - X-ray left knee:
        - asymetrical joint-space narrowing, subchondral osteosclerosis
        - consistent with osteoarthritis
- At that time, you had recommended using acetaminophen 1g four times daily, and scheduled a follow-up for today
- Today, she reports only minimal improvement in pain and mobility
- Aside from her knee symptoms, she has no other complaints
- No history of reflux or ulcers
- Non-smoker; no alcohol

Current Medications, Including Over-the-counter and Herbal Medications:

- Acetaminophen 1g four times daily

Physical Exam:

- Patient appears generally well
- BP 118/64 pulse 72
- No conjunctival pallor
- Cardiorespiratory and abdominal exam normal
- Left knee:
    - No evidence of effusion, no redness/warmth
    - Decreased active and passive ROM in flexion secondary to pain
    - No obvious deformity
- Remainder of exam unremarkable

You have decided to initiate therapy with daily non-steroidal anti-inflammatory drug (NSAID).

Questions:

1) **Does this person require gastroprotection? If yes, which agent would you recommend?**

Teaching Point #1

Patients requiring NSAID therapy who do not have risk factors for gastrointestinal complications of NSAID therapy do not require supplemental gastroprotection (with a PPI, COX-2 inhibitor, or misoprostol).

Having a history of a previous ulcer or previous upper gastrointestinal ulcer complication (bleeding, perforation, obstruction) are the most important risk factors for development of a future NSAID-related complication.

Other risk factors for NSAID-induced gastrointestinal complications include:[14]

- high-dose NSAIDs
- concomitant therapy with:
  - systemic corticosteroids
  - anticoagulants (warfarin, heparin)
- increased age (>60 years)
- severe medical co-morbidity.

There are no clear recommendations on whether or not patients should be assessed for *Helicobacter pylori (H. pilori)* and treated if present in low-risk asymptomatic patients about to initiate chronic NSAID therapy.

The annual incidence of gastrointestinal complications in NSAID users is 1% to 4%,[15] although the probability of such complications is quite low (~1%) in patients without risk factors.[16] It has been repeatedly demonstrated that the routine use of gastroprotective strategies (including co-prescription of misoprostol, or the use of a COX-2 selective NSAID) in this subset of patients is not cost-effective, and thus should not be routinely recommended.[16-18]

In patients who are asymptomatic and have no previous history of dyspepsia or peptic ulcer disease, testing and treatment of *H. pylori* is not recommended prior to initiation of NSAID therapy. While treatment of *H. pylori* has been shown to prevent the formation of asymptomatic ulcers in NSAID users (5.8% in placebo arm versus 1.2% in patients treated with *H. pylori* eradication therapy, $p<0.05$),[19] there are no data to show it is effective in preventing NSAID-induced complications in patients without a previous history of ulcers. In the absence of definitive data to support pre-emptive eradication, and the low likelihood of NSAID-related complications in persons without other risk factors, routine testing and treating prior to NSAID therapy is not required.

Follow-up Presentation #1:

Two years later, Mrs. W. has been admitted to hospital with an acute, upper gastrointestinal bleed, and you are her admitting physician. She had been using naproxen 500 mg twice daily, chronically over the past two years, with adequate control of her symptoms of osteoarthritis. She was not using any other medications on presentation, and has not developed any other medical illnesses since you last evaluated her in the clinic.

She has already been in the hospital for three days, and the bleeding has ceased. A gastroscopy performed on admission revealed the presence of a duodenal ulcer with a non-bleeding visible vessel. It was treated endoscopically with placement of a hemostatic clip.

Since the endoscopy, Mrs. W. has been using intravenous pantoprazole (80 mg bolus, then 8 mg per hour for the next 72 hours). She has had no evidence of recurrent bleeding, and is tolerating oral feeds. Her pantoprazole infusion is now complete.

A biopsy taken by the gastroenterologist from the gastric antrum does not reveal the presence of *H. pylori.*

Question:

2) **What would you recommend for continued therapy of the ulcer?**

Teaching Point #2

An eight-week course of PPI therapy is more effective in the healing of NSAID-induced peptic ulcers than are H_2-receptor antagonists and misoprostol, even if NSAIDs are continued.

There is no difference in the healing rate of ulcer disease between the different PPIs.

Double-dose PPIs are no more effective than standard doses of PPIs for healing peptic ulcers.

In this situation, one should use a standard dose of the lowest-cost PPI to promote healing of the established duodenal ulcer.

There is evidence that PPIs are more effective than both standard doses of H_2RAs and misoprostol 800 µg/d in healing NSAID-induced peptic ulcers, and are standard therapy for patients with documented peptic ulcer disease.[20,21]

According to the recent CADTH report, there are no significant differences among the PPIs in the healing rates of peptic ulcer disease, although there have been no direct comparisons between PPIs.[2] Therefore, the decision to use a PPI in the healing of peptic ulcer disease should be based primarily on price.

Also, double doses of PPIs are not more effective than standard doses of PPIs in healing peptic ulcers in large randomized clinical trials.[20-24] In the absence of evidence, the use of double dose PPIs for the healing of established peptic ulcer disease is not recommended.

Follow-up Presentation #2:

You are now seeing Ms. W. in the clinic, eight weeks following her discharge from hospital. She has had no symptoms or signs of recurrent gastrointestinal bleeding, and does not have any ongoing gastrointestinal symptoms. She continues to use omeprazole 20 mg per day.

Since her admission, she has abstained from using NSAIDs, but has again developed severe left-knee pain and decreased mobility. She has been using acetaminophen 1g four times daily, but does not find that this adequately relieves her symptoms.

Question:

3) **Can this patient be prescribed an NSAID again?**

Teaching Point #3

The risk of recurrent gastrointestinal complications with NSAID therapy in a person with a history of gastrointestinal bleeding is very high (15% to 20% per year).[25]

Both COX-2 inhibitors and co-prescription of a standard-dose PPI may reduce the risk of recurrent NSAID-related gastrointestinal complications, but the risk of recurrent complications is still significantly elevated (3% to 6% per year).[26,27]

There is some evidence that the combination of COX-2 inhibitors and PPIs is superior to COX-2 therapy alone, but it is insufficient to make this recommendation routinely.[28]

Overall, NSAID use should be avoided in any subject with a history of NSAID-related gastrointestinal complications, and other pharmacologic, non-pharmacologic, and surgical analgesic options should be considered. If an NSAID must be used, the combination of PPIs and a COX-2 inhibitor is preferred.

If NSAID therapy is not re-initiated, there is no further need for PPI therapy following an eight-week course of PPIs, and it may be safely discontinued.

In patients with a recent history of gastrointestinal bleeding who continued NSAID therapy and were also *H. pylori* positive, PPI therapy without *H. pylori* eradication was superior to *H. pylori* eradication alone (recurrent bleeding at six months: 4.4% versus 18.8%, p=0.005).[25]

In two studies of *H. pylori*-negative subjects with a recent NSAID- related upper gastrointestinal bleed, there was no difference between use of a traditional NSAID with a PPI and the use of a COX-2 inhibitor, with recurrent bleeding rates varying from 3% to 6%.[26,27]

There is a single randomized trial comparing therapy with a COX-2 inhibitor alone, and a COX-2 inhibitor and PPI in combination in which no subject who received both a COX-2 inhibitor and a PPI developed recurrent bleeding at one year. In contrast, 8.9% of those using the COX-2 inhibitor alone had recurrent bleeding.[28]

Management of Dyspepsia

History:

- 26-year-old female with past history of depression
- Complains of intermittent pain in the upper abdomen, which has been occurring over the last six months
- Pain generally occurs two to three times per week after eating
- Pain occasionally radiates to the sides, lasts 30 to 60 minutes, then eases off gradually
- Pain is not associated with activity, body position, time of day, or menstrual cycle
- Patient cannot describe any exacerbating or mitigating factors
- Occasional nausea, no vomiting, no heartburn
- No alteration in bowel habits, no melena or hematochezia
- Has gained approximately 10 lbs in the last six months
- Review of systems otherwise normal
- Non-smoker; no alcohol

Current Medications, Including Over-the-counter and Herbal Medications:

- Alesse 21 (for three years), citalopram 20 mg daily (for three years)

Physical Exam:

- BP 126/80, pulse 92 bpm, weight 87.0 kg
- No conjunctival pallor, normal thyroid, no cervical lymphadenopathy
- Cardiorespiratory exam N
- Moderate tenderness to palpation in the epigastrium, no masses, no palpable organomegaly
- Remainder of exam within normal limits

Investigations:

- CBC normal; chemistry panel, liver enzymes, renal function normal
- Celiac antibody panel (anti-endomysial antibody/tissue transglutaminase antibody) negative

Questions:

1) **Are any further investigations required at this time?**
2) **What are the treatment options?**

Teaching Point #1

Patients with dyspepsia under age 50 and without "alarm" signs (evidence of GI bleeding, iron deficiency, family history of gastric cancer, weight loss, or intractable vomiting) do not require any further diagnostic testing, including endoscopic procedures or radiographic imaging.[29]

Management strategy based on initial (prompt) endoscopy does not produce better outcomes (e.g., improvement of symptoms, failure of treatment strategy, quality of life) than empirical PPI therapy in patients with uninvestigated dyspepsia.

If NSAID therapy is not re-initiated, there is no further need for PPI therapy following an eight-week course of PPIs, and it may be safely discontinued.

The overwhelming majority of subjects with chronic dyspepsia will have one of three diagnoses: peptic ulcer disease, gastroesophageal reflux disease, or functional (non-ulcer) dyspepsia.[30,31] The rate of malignancy in a person under the age of 45 without alarm symptoms is approximately 0.1% – a rate sufficiently low to justify not routinely ordering diagnostic evaluation.[32]

There is also evidence from a single trial where early endoscopy did not lead to improved symptoms and quality of life in patients with dyspepsia.[33]

Other diagnostic possibilities include biliary pain, chronic pancreatitis, and abdominal wall or myofascial pain. A diagnostic abdominal ultrasound should be considered in a patient with classical biliary colic, but is otherwise not necessary.[34]

Teaching Point #2

Treatment options for a patient with uninvestigated dyspepsia in the non-NSAID user include:

- testing for *H. pylori* and treating, if positive ("test and treat")
- a trial of H_2-receptor antagonists
- a trial of PPIs.

There is no clear consensus on the optimal initial management of patients with non-heartburn dominant, uninvestigated dyspepsia. "Test-and-treat" tends to be favoured as the first approach in most circumstances because it has definitive circumscribed treatment for persons with peptic ulcer disease and may eliminate symptoms in a small proportion of subjects with functional dyspepsia. This is supported by the CADET-HP trial in which *H. pylori*-positive subjects with uninvestigated dyspepsia treated with eradication therapy had an absolute increase of 14% in the rate of successful treatment as compared to those *H. pylori*-positive subjects with uninvestigated dyspepsia treated empirically with a PPI.[35] Presumably, this effect was due to the healing of underlying peptic ulcer disease. However, if a patient is diagnosed with functional dyspepsia on the basis of a normal upper endoscopy, the value of *H. pylori* eradication is lessened. In a meta-analysis of subjects with functional dyspepsia, eradication of *H. pylori* was associated with a 7% increase in the absolute likelihood of developing symptom relief when compared to placebo.[36]

If the patient tests negative for *H. pylori* or does not have improvement of symptoms with documented eradication of *H. pylori,* one can consider a four- to eight-week course of medical therapy. There is evidence that PPIs and H_2-receptor antagonists are both superior to placebo in relieving symptoms of dyspepsia.[37,38] However, there are few well-performed direct comparisons between the different pharmacologic management strategies. Furthermore, subjects with dyspepsia tend to be less responsive to medical therapy in general than subjects with heartburn-predominant symptoms, with the therapeutic gain over placebo being 15% to 20% when comparing PPIs to placebo.[37,39]

According to the CADTH report, one study (the CADET-HP trial) demonstrated that PPIs were superior to H_2RAs at four weeks in relieving dyspeptic symptoms (51% versus 36% with no or minimal pain at four weeks, p=0.01). However, when patients with accompanying heartburn were excluded, there was no significant difference between the treatment arms.[39]

In this case, Ms. D. can be tested for *H. pylori* infection and treated if positive. If she is *H. pylori*-negative, or symptoms persist after eradication of the infection, initiation of therapy with the least expensive therapy (i.e., H_2-receptor antagonists) would be a reasonable option given the lack of definitive evidence of superiority between the pharmacologic strategies. Step-up to PPIs could be considered if there was inadequate relief of symptoms on H_2RAs.

Management of ASA-related Gastrointestinal Bleeding

History:

- 61-year-old male, past history of:
  - myocardial infarction in 2004, followed by triple coronary artery bypass graft (CABG)
  - hypertension
  - type 2 diabetes
  - hypercholesterolemia
- Medications include:
  - ASA 81mg daily
  - metoprolol 50 mg twice daily
  - atorvastatin 40 mg daily
  - ramipril 10 mg daily
- Patient is currently in hospital, he presented to hospital three days ago with a one day history of melena
- On presentation:
  - patient is alert and not distressed
  - BP 134/63 HR 95
  - abdominal exam unremarkable
  - digital rectal exam: no masses, +++melena
- Labs:
  - Hgb 112 MCV 86.3
  - INR 1.1, platelets 384
  - Electrolytes, renal function, liver enzymes all normal
- Upper endoscopy revealed multiple, clean-based duodenal ulcers
- Rapid urease testing of gastric biopsies for *H. pylori* are negative
- ASA is being held
- Started on rabeprazole 20 mg by mouth daily

Questions:

Assuming Mr. R. requires ongoing anti-platelet therapy for secondary prophylaxis of cardiovascular disease:

1. **Should clopidogrel be used in place of aspirin?**
2. **If he were *H. pylori* positive, would *H. pylori* be sufficient to prevent recurrent gastrointestinal bleeding?**

Teaching Point #1

In patients with a recent history of upper gastrointestinal bleeding, the combination of low-dose aspirin and a PPI is superior to clopidogrel in preventing recurrent upper gastrointestinal bleeding.

Until recently, clopidogrel was often recommended as a substitute for aspirin in persons who developed upper gastrointestinal bleeding while using aspirin for prevention of cardiovascular disease and its complications. However, two recently performed comparisons of clopidogrel and the combination of low-dose aspirin and a PPI proved that the ASA/PPI combination was more efficacious in preventing recurrent gastrointestinal bleeding (8.6% versus 0.7% in clopidogrel versus ASA/esomeprazole-treated subjects at 12 months in one study,[40] and 13.6% versus 0% with the same treatments at 52 weeks in another).[41] Therefore, the substitution of clopidogrel for aspirin in this setting is not recommended.

There are currently no direct comparisons of low-dose aspirin + PPI and clopidogrel + PPI.

Teaching Point #2:

Data regarding the role of *H. pylori* eradication in the prevention of ASA-related gastrointestinal bleeding are conflicting. Co-prescription of a PPI is at least as good as, and possibly superior to, one-time *H. pylori* eradication in patients requiring ongoing aspirin therapy following an upper gastrointestinal bleeding event.

There have been two similar trials in the medical literature assessing the efficacy of *H. pylori* eradication and continuous PPI therapy in patients with a history of ASA-related upper gastrointestinal bleeding requiring ongoing ASA use.

In one trial, there was not a statistically significant difference in the rate of recurrent bleeding at six months between *H. pylori*-positive subjects given *H. pylori* eradication therapy alone, or continuous PPI therapy alone (bleeding rates were 1.9% versus 0.9%, respectively).[25] However, a similar trial comparing continuous PPI therapy versus placebo in *H. pylori*-positive subjects successfully treated for the infection reported a dramatically different rate of recurrent hemorrhage in the arm treated with *H. pylori* eradication alone (14.8%).[42] There is no clear explanation as to why these trials reached such drastically different conclusions. Given these results, it is likely preferable to co-prescribe PPIs in patients requiring ongoing ASA therapy following an ASA-related gastrointestinal bleeding episode, regardless of whether or not *H. pylori* is eradicated.

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