# Peptic Ulcer Disease: Pharmacotherapy for Prevention & Treatment

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Version 2.2, Apr 2017 updates at *www.peterloewen.com*

**PUD Causes:**
H.pylori ("type B" chronic gastritis) or NSAIDs (90-95%)
Zollinger Ellison Ellison syndrome (<1%)

## Primary Prevention
which of these risk factors are present?

**Chronic NSAID therapy (non-ASA)**

**Chronic ASA therapy**
at ≤325mg/d excess Any GI bleed risk 0.21%/year (NNH=476 x 1y) ;
Major GI bleed risk 0.11%/year (NNH=1000 x 1y) [Lanas 2011]

**Zollinger Ellison Syndrome**
(gastrin-secreting neuroendocrine tumors. 2/3 are malignant and 1/3 have metastasized by dx. 30% 10y survival.)

PPI 40-120 mg/d

**Additional Risk Factors**
[Wolfe et al. NEJM 1999;320:1888-98]
**alcoholism, serious systemic illness (CHF, RA, CAD, others), age>60, smoking, concurrent systemic glucocorticoid therapy**

No primary PUD prevention indicated. None of these is an indication for gastroprotective therapy in the absence of NSAID/ASA:

-minimize ASA dose? Probably no safer than 325mg/d. [Derry&Loke], but conflicting evidence [Serebruany. Am J Cardiol 2005;95:1218–22]
-enteric coating/buffering has no effect on PUD risk
-add PPI? No primary prevention trials available.
-eradicate Hp? Best evidence: Annual ulcer bleeding risk (cohort study): just starting ASA with no PUD hx: 0.5%; ASA with prior PUD+Hp eradication: 1.1%; ASA with prior PUD but Hp(-) 4.6%. [Chan. Gastroenterol 2005;128:A133.] ACCF/AHA recommends Hp eradication if prior PUD & starting ASA. ACG says eradication "could be considered" in all pts.

**Estimating Annual Risk of Clinical UGI Event with NSAID** in an Individual Pt
[El-Serag HB, et al. Arch Int Med 2002;162:2105-10]
(A) Baseline w/NSAID 2.5 (1.5-4.5)
(B) Fold Increase (Range) [These are additive]
Age >65 yrs: 2.5 (1.5-5.5)
Use of Anticoag: 2.5 (2.0-3.0)
Use of Steroids: 2.0 (1.0-3.0)
Hx PUD: 5.0 (2.0-12.0)
Presence H pylori: 1.5 (1.0-3.0)
(C) Risk Reduction: %
PPI cotherapy: 50
Coxib: 50
H pylori Tx inf person: 50
200mcg tid misoprostol: 40
**Total Risk (%/year) = (A)x(B)x(C)**

Newly initiated NSAID?
no → NSAID already chronic. Hp eradication not effective. [Hawkey. Lancet 1998;352:1016-21].
yes → **Eradicate Hp**. 6-month complicated ulcer rate: placebo 27.1% vs. eradicated 4.2% [Chan. Lancet 2002;359:9-13]

Proceed to "Risk Minimization"

## Suspected Peptic Ulcer/UGIB

**acute upper GI bleeding, presumed non-variceal**
5-15% case-fatality. S&Sx: dizziness, coffee ground / bloody emesis, melena stool

OR

**PUD symptoms with no "alarm signs"** (acute bleeding, weight loss, vomiting, severe sx)

Glasgow-Blatchford Score (GBS)>1?
GBS outperforms full or admission Rockall score, PNED, AIMS65 to predict transfusion, endoscopic treatment, interventional radiology, surgery, or 30 day mortality [Stanley et al. BMJ 2017; 356: i6432]
no → GBS≤1: Manage as outpatient/non-emergently. GBS ≤1 is optimum threshold to predict survival without intervention (sensitivity 98.6%, specicity 34.6%)
yes ↓

ABCs + **Pantoprazole 80mg IV bolus + 8 mg/h infusion x 72h**. ↓ 72h rebleeding (OR 0.46; NNT 12), surgery (OR 0.59; NNT 20), not mortality. [BMJ 2005;330(7491):568] **OR intermittent bolus PPI** if endoscopic therapy being performed (non-inferior to bolus+infusion when endoscopic therapy performed [JAMA Intern Med 2014;174:1755-62, ArchInternMed 2010;170:751-8]. e.g. Omep 40 IV or PO daily, panto 80 IV then 40 IV daily, eso 40 po bid, rabep 20 po bid. Starting PPI before endoscopy no more effective (rebleed, surgery, death) than afterward [CDSR CD005415], but 2010 AGIB guidelines recommend as it may "downstage" the lesion and reduce need for endoscopic therapy (OR 0.68). Interrupt NSAID/ASA therapy for several days.

Endoscopic investigation +/- endoscopic therapy + Hp test. PPI effective with or without endoscopic therapy [CDSR 2006;1:CD002094, Can J Gastro 2009;23(4):287-99.].

**Forest PUD Endoscopic Classification**
[Lancet 1974;17:394-397]
Forrest class - type of lesion (risk of 72h rebleeding if untreated)
IA - Arterial spurting bleeding (100%)
IB - Arterial oozing bleeding (55%)
IIA - Visible vessel (43%)
IIB - Sentinel clot (22%)
IIC - Hematin covered flat spot (10%)
III - No stigmata of hemorrhage (5%)

Forest class I, IIA, IIB lesion: continue PPI infusion x 72h, then choose secondary prevention strategy
Forest class IIC lesion: D/C PPI infusion and choose secondary prevention strategy
Forest class III: suspect lower GI or esophageal source of bleeding, or alternate diagnosis

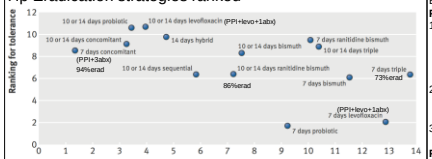
Assess probability of PUD based on risk factors. Differentiate from non-ulcer ("functional") dyspepsia and gastric cancer.

**Strategies for "uninvestigated dyspepsia":**
(+modification of risk factors where possible)
1. Trial of H2RA or PPI x 2-4 weeks.
2. **Test & Treat for Hp**. Recommended approach by Canadian guidelines. ACG Guidelines say it "is a consideration". Some conflicting evidence of cost-effectiveness and dependence on Hp prevalence. Tx success (asymptomatic) @ 12mos: 50% vs. 36%, fewer lab tests and endoscopies. [Chiba N, BMJ; 2002;324(7344):1012]
3. Endoscopy

If PUD diagnosed or presumed

**Hp Testing** [all positive tests must be treated!]
**Biopsy-based:** (Rapid urease, histology, culture, PCR): requires mucosal biopsy. Gold standard.
**Urea Breath**: excellent PPV/NPV. Always useful. Sn 96%/Sp 98%. LR(+)48;LR(-)0.04. Hold H2RA/PPI x 1-2 weeks before.
**Fecal Antigen**: Requires stool. Sn 96%/Sp 93%. LR(+) 14;LR(-)0.04. Always useful.
**Serology (antibody)**: requires blood. Sn 85-93%/Sp 79-90%. LR(+)9;LR(-)0.38. Qualitative method not useful to verify eradication. Quantitative ELISA method can be used 1, 3, & mos after treatment to document eradication through titre drop.

**Hp Eradication strategies ranked**



Li B-Z, et al. BMJ 2015;351:h4052. 143 studies network meta-analysis.

**Hp Eradication** [2017ACG Guidelines, 2012 European guidelines]
**First-Line Recommended**
1. "*Clarithromycin triple therapy*": PPI bid*+clarithromycin 500 bid+(amoxicillin 1000 bid OR metronidazole 500 bid) x 10-14d. 73% eradication. [Hp-PAC=blister-packed lansop+amox+clarithro x7d]
2. "*Bismuth quadruple therapy*": BSS 525 qid+metro 250 qid+tetra 500 qid+(ranit 150 bid OR PPI qd or bid) x 10-14d. 85% eradication.
3. "*Concomitant therapy*": PPI + clarithromycin + amoxicillin + metro x 10-14d

**First-Line Suggested**
1. "*Sequential therapy*": PPI +amox 1000 bid x 5-7d, then PPI+clarithro 500 bid+metro/tinidzaole 500 bid x 5-7d. 87% eradication. Consider especially in areas where triple-therapy eradication rates are <80%. [Gisbert JP. J Clin Gastroenterol. 2010;44:1]
2. "*Hybrid therapy*" PPI+amoxicillin x7d then PPI + amoxicillin + clarithromycin + metro x7d.
3. "*Levofloxacin triple therapy*": PPI + levofloxacin + amoxicillin x 10-14d.
4. "*Fluoroquinolone sequential therapy*": PPI + amoxicillin x5–7d , then PPI + fluoroquinolone + metro x5–7d.

**NOTES**: Canadian (2004) & European (2012) guidelines support 7-day duration. Clarithro XL 500 QD (with metro) or 1000 QD (with amox) may be used. Failure of first-line therapy should prompt susceptibility testing. 20% metro, 8% clarithro resistance in Canada.

**Salvage (ACG 2017):**
*Bismuth quadruple therapy* x14d OR *Levofloxacin triple therapy* x 14d OR *Concomitant therapy* x 14d

*PPI: lans 30, omep 20, pant 40, rabep 20, eso 40. eso is QD. "High dose" PPI increases cure rate by 6-10% in *relative* terms [Villoria et al. Aliment. Pharmacol. Ther. 2008;]: eso 40 bid, rabep 40 bid.

**Hp Test for Cure** ACG 2017 : "*Whenever H. pylori infection is identified and treated, testing to prove eradication should be performed using a UBT, FAT or biopsy-based testing at least 4 weeks after the completion of antibiotic therapy and after PPI therapy has been withheld for 1–2 weeks.*"

## Secondary Prevention
which of these risk factors are present?

ongoing NSAID (non-ASA)
Initial event while on NSAID (non-ASA?)
yes → Consider patient "high risk" (prior non-NSAID/ASA-associated PUD event), presume they're Hp(+), and evaluate per PRIMARY prevention above.
no → Consider patient "high risk" (prior non-NSAID/ASA-associated PUD event), presume they're Hp(+), and evaluate per PRIMARY prevention above.

Ongoing ASA therapy
Initial event while on ASA?
no → Consider patient "high risk" (prior non-NSAID/ASA-associated PUD event), presume they're Hp(+), and evaluate per PRIMARY prevention above.
yes →
- Hp eradication similar to chronic PPI therapy. rebleeding @ 6mos: eradication 1.9% vs. omeprazole 20mg/d 0.9%. [Chan. NEJM 2001;344:967-73]. ACCF/ACG/AHA recommends Hp eradication.
- add PPI: recurrent adverse GI events OR 0.34. NNTx1y=34 [Lanas 2011].
- Hp eradication+chronic PPI better than Hp eradication alone: 14.8% vs. 1.6% ulcer complications @ 12 months with lansoprazole 30mg/d vs. placebo [Lai et al. NEJM 2002;346:2033-8.]
- Interrupt aspirin for 8 weeks while ulcer healing? 30-day rebleeding (5.4% placebo vs. 10.3% aspirin, NS), but higher 8-week MORTALITY (12.9 vs. 1.3%). [Ann Intern Med. 2010;152:1-9]. Restart aspirin within a few days post-AGIB.
- Switch to clopidogrel safer than ASA alone? [CAPRIE: GI bleeding 2.66% ASA vs. 1.99% clopidogrel over 1.91y. NNT=150 x 1.9y]
- Switch to clopidogrel inferior to ASA+PPI: clopidogrel 8.6% vs. ASA 80mg/d+esomeprazole 20mg/d 0.7% rebleeding @ 12mos. [Chan. NEJM 2005;352:238-44]
- ASA+hi-dose H2RA inferior to ASA+PPI: famotidine 40 bid vs. panto 20 daily - 7.7% vs. 0% recurrent bleeding @ 48 weeks [Gastroenterol 2010;138:82-8]
- Minimize ASA dose? See above under "Primary Prevention". ≤81mg/d probably indicated for secondary prevention
- combination of ASA with clopidogrel increases major GI bleeding risk (CURE, MATCH, CHARISMA) over either alone: OR 1.86, NNHx1y=125 [Lanas 2011].

Hp initially negative and NSAID/ASA stopped
Heal ulcer: PPI x 4-6 wks for duodenal; 6-8 wks for gastric ulcer.

H.pylori positive
**Eradicate Hp.** Rebleeding OR 0.10-0.17 vs. no therapy. OR 0.14-0.24 vs. long-term antisecretory therapy. Duodenal ulcer recurrence: RR 0.2. 14% vs. 64% over 5y. Gastric ulcer recurrence: RR 0.29. 14% vs. 58% over 5y [CDSR CD004062.]

Then evaluate for the other risk factors in this category. Ongoing gastroprotection following eradication usually not necessary if no other risk factors present.

Hp initially negative AND ulcer not NSAID/ASA associated
**Idiopathic UGIB.**
Heal ulcer: PPI x 4-6 wks for duodenal; 6-8 wks for gastric ulcer.
Lifelong gastroprotective therapy (PPI or H2RA) probably indicated unless other risk factor(s) are reversible.

**NSAID PUD RISK MINIMIZATION OPTIONS, CONSIDERATIONS, EVIDENCE**
1. a**void** NSAID
2. choose **safest** NSAID (celecoxib [see #6], ibuprofen, naproxen) [Henry et al. BMJ 1996;312:1563-1566]
3. use NSAID **intermittently**, PRN, "intelligent noncompliance"
4. use smallest possible **dose** (consider co-analgesia)
5. avoid **multiple** NSAIDs (including combination with ASA)
6. use **celecoxib** instead: *Primary prevention*: CONDOR (n=4484 RCT): celecox 200 bid vs. diclofenac 75 bid+omeprazole20 in high-risk OA/RA pts clinically significant GI events: 0.9 vs. 3.8%/6-months [RR 0.25 (0.15-0.40)] [Lancet 2010;274:173-9]. *Secondary prevention*: equivalent rebleeding to NSAID+PPI, ~10%/y (Chan. NEJM 2002;347:2104-10), possibly more cost-effective than NSAID+PPI. **No safer than NSAID if on concurrent ASA**. [CLASS, TARGET, EDGE] **or warfarin** [Battistella et al. Arch Intern Med 2005;165:189-92]
7. add **PPI:** recurrent adverse GI events OR 0.34. NNTx1y=34 [Lanas A, Clin Gastro Hepatol 2011;9:762-8]. Endoscopic ulcers vs. placebo 3-12 mos: OR 0.23 [CDSR CD002296] (eg. ASTRONAUT, OMNIUM). Vimovo®[naproxen+esomeprazole]: don't use prn.
8. add **H2RA** (inferior to PPI - ASTRONAUT: endoscopic recurrence (72% vs. 59% @ 6mos). Must be used at "double-dose" to prevent endoscopic duodenal & gastric ulcers. Regular doses prevent only duodenal. [CDSR CD002296]
9. add **misoprostol**: only agent proven to prevent clinical ulcers in NSAID users: OR 0.49 with 800 mcg/d. [CDSR CD002296] MUCOSA: 200 mcg qid NNT x 6mos to prevent 1 serious GI event=263 (0.56% vs. 0.95%). - 20% d/c d/t diarrhea within 1 month. Inferior to PPI (OMNIUM) w.r.t. endoscopic recurrence (61% vs. 48% @ 6mos).
10. use **celecoxib+PPI** instead - most effective and expensive 2ndary prevention regimen possible. 0% vs. 8.9% 13-month rebleeding [Lancet 2007; 369:1621–26]
11. **Hp eradication** *Primary prevention*: Recommended per above when initiating long-term NSAID. *Secondary prevention*: inferior to chronic PPI if prior PUD on NSAID: rebleeding @ 6mos: eradication 18.8% vs. omeprazole 20mg/d 4.4%. [Chan. NEJM 2001;344:967-73].

**SELECTED REFERENCES**

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