

# Peptic Ulcer Disease: Pharmacotherapy for Prevention & Treatment

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

**Estimating Annual Risk of Clinical UGI Event with NSAID in an Individual Pt**  
[E-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  
200mg tid Misoprostil: 40

Total Risk (%/year) = (A)x(B)x(C)

## Primary Prevention

which of the following risk factors are present?

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

Newly initiated NSAID?

no

yes

NSAID already chronic. Hp eradication not effective. [Hawkey. Lancet 1998;352:1016-21].

**Eradicate Hp.** 6-month complicated ulcer rate: placebo 27.1% vs. eradicated 4.2% [Chan. Lancet 2002;359:9-13]

**Chronic ASA therapy**  
at  $\leq 325$ mg/d excess GI bleed risk  $\sim 0.5\%$ /year (NNH=200 x 1y) [Derry&Loke, Hernandez-Diaz]

-minimize ASA dose? Probably no safer than 325mg/d. [Derry&Loke], but conflicting evidence (e.g. Serebruany. Am J Cardiol 2005;95:1218-22)  
-enteric coating/buffering has no effect on PUD risk  
-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/ACG/AHA recommends Hp eradication if prior PUD & starting ASA.

**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(24):1888-1898]  
No particular primary PUD prevention indicated. None of these is an indication for gastroprotective therapy in the absence of NSAID/ASA.  
-alcoholism  
-serious systemic illness (CHF, RA, CAD, others)  
-age>60  
-smoking  
-concurrent systemic glucocorticoid therapy

**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%. LRI(+)/LRI(-):0.04. Hold H2RA/PPI x 1-2 weeks before.  
**Fecal Antigen:** Requires stool. Sn 96%/Sp 93%. LRs ? Always useful.  
**Serology (antibody):** requires blood. Sn 85-93%/Sp 79-90%. LRI(+)/LRI(-):0.08. 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** [2008 ACG Guidelines]  
**First-Line**  
1. PPI bid+clarithromycin 500 bid+(amoxicillin 1000 bid OR metronidazole 500 bid) x 10-14d. 70-85% efficacy.  
2. BSS 525 qid+metro 250 qid+itra 500 qid+(ranit 150 bid OR PPI qd or bid) x 10-14d. 75-90% efficacy.  
3. PPI +amox 1000 bid x 5 days, then PPI+clarithro 500 bid+trindaazole 500 bid x 5d. >90% efficacy.  
**NOTES:** Canadian (2004) 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:**  
H2 above x 7d (68% efficacy). OR PPI+amox+levofloxacin 500 qd x 10d. (87% efficacy)  
\*PPI: lans 30, omepr 20, pant 40, rabepr 20, eso 40, eso is QD.

**Hp Test for Cure** (UBT or FAT [LRI]:0.1 @ 2 weeks-post)  
On the basis of consensus, ACG recommends in any patient with Hp-associated ulcer persistent dyspepsia despite attempted eradication pts with Hp-associated MALT lymphoma pts with gastric cancer resection

**REFERENCES**  
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## Acute Treatment of Peptic Ulcer

**acute upper GI bleeding, presumed non-variceal**  
5-10% case-fatality. S&S: dizziness, coffee ground / bloody emesis, melena stool

Glasgow-Blatchford Score (GBS)>0?  
GBS outperforms full or admission Rockall score. Lancet 2009;373: 42-7.

no  
GBS=0: Manage as outpatient/non-emergently.

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

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

**Strategies:** (including modification of risk factors where possible)  
1. Trial of H2RA or PPI x 2-4 weeks.  
2. Test & Treat for Hp. ("uninvestigated dyspepsia") Recommended approach by Canadian guidelines, despite conflicting evidence of cost-effectiveness and dependence on Hp prevalence.  
3. Endoscopy

**ABCs + Pantoprazole 80mg IV bolus + 8 mg/h infusion x 72h.** 1. 72h rebleeding (OR .46 NNT 12), surgery (OR 0.59 NNT 20), not mortality. [BMJ 2005;330(7491):568] Lower-dose regimens (eg. Omepr40 PO q12h, Pant40 IV q12h, Pant80 PO q12h) are non-inferior [ArchInternMed 2010;170:751-8]. 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**  
Forrest JA, et al. 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

## Secondary Prevention

which of the following risk factors are present?

ongoing NSAID (non-ASA)

Ongoing ASA therapy

Hp initially negative and NSAID/ASA stopped

H.pylori positive

Hp initially negative AND ulcer not NSAID/ASA associated

Initial event while on NSAID (non-ASA)?

yes

no

Initial event while on ASA?

yes

no

Heal ulcer: PPI x 4-6 wks for duodenal; 6-8 wks for gastric ulcer.

**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.

**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.

Consider patient "high risk" (prior non-NSAID/ASA-associated PUD event), presume they're Hp(+), and evaluate per PRIMARY prevention above.

-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.  
-Hp eradication+chronic PPI better than Hp eradication alone: 14.8% vs. 1.6% ulcer complications @ 12 months with lansoprazole 30mg/d vs. placebo [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% clopidogrel vs. 1.99% aspirin 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".  $\leq 81$ mg/d probably indicated for secondary prevention  
-combination of ASA with clopidogrel increases GI bleeding risk (CURE, MATCH, CHARISMA) over either alone

## NSAID PUD RISK MINIMIZATION OPTIONS, CONSIDERATIONS, EVIDENCE

-avoid NSAID  
-choose **safest** NSAID (probably ibuprofen, naproxen) [Henry et al. BMJ 1996;312:1563-1566]  
-use NSAID **intermittently**, PRN, "intelligent noncompliance"  
-use smallest possible **dose** (consider coanalgesia)  
-avoid **multiple** NSAIDs (including combination with ASA)  
-use **celecoxib** instead: **Primary prevention:** CONDOR (n=4484 RCT): celecoxib 200bid vs. diclofenac 75bid+omeprazole 20 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,  $\sim 10\%/y$  [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]  
-add **PPI:** Endoscopic ulcers vs. placebo 3-12 mos: OR 0.23 [CDSR CD002296] (eg. ASTRONAUT, OMNIUM). No direct evidence of clinical event reduction.  
-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]  
-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).  
-use **celecoxib+PPI** instead - most effective and expensive 2ndary prevention regimen possible. 0% vs. 8.9% 13-month rebleeding [Lancet 2007; 369: 1621-26]  
-**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].