Criteria for Use of Intravenous Pantoprazole

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

These criteria were based on the best clinical evidence currently available. The recommendations in this document are dynamic, and will be revised as new clinical information becomes available. This guidance is intended to assist practitioners in providing consistent, high quality, cost effective drug therapy. These criteria are not intended to interfere with clinical judgment; the clinician must ultimately decide the course of therapy based on individual patient situations.

A summary of the literature review used to support the criteria for use of pantoprazole is available at http://www.pbm.va.gov.

Background

Pantoprazole is the first proton pump inhibitor (PPI) available in an intravenous formulation (pantoprazole for injection) in the U.S. It is FDA-approved for the short-term treatment of gastroesophageal reflux disease associated with a history of erosive esophagitis and for pathological hypersecretion associated with Zollinger-Ellison syndrome.

Intravenous pantoprazole has also been used off label for short-term management of nonvariceal acute upper gastrointestinal bleeding (NVAUGIB). Most of the data supporting the use of PPIs for NVAUGIB have involved omeprazole, which is not available in an intravenous formulation in the U.S. For peptic ulcer bleeding (PUB), high-dose, continuous intravenous infusions of PPIs have been recommended, mainly based on pH studies rather than clinical outcomes. Until two years ago, a high-dose continuous infusion of omeprazole was also the only regimen evaluated and found to be efficacious for PUB in placebo-controlled trials in patients who had received endoscopic therapy. There is now evidence that high oral doses of PPIs may reduce re-bleeding rates after endoscopic hemostasis of PUB.

Although acid-suppressive agents are often used in the management of PUB, there is an insufficient number of well-designed trials to make definite conclusions about the role of PPIs either before or after endoscopic therapy. Their use should be tempered with the understanding that the potential benefits and risks of such treatment are uncertain.

VA Criteria for Use

1. Patient must be NPO

AND

2. ONE OF THE FOLLOWING CONDITIONS MUST BE MET:

   Clinical signs of significant upper gastrointestinal bleeding before urgent endoscopy in patients with high risk for peptic ulcers

   Confirmed active or recent peptic ulcer bleeding associated with endoscopic stigmata suggestive of high risk for re-bleeding (active acute hemorrhage, nonbleeding visible vessel (NBVV), or lesion with sentinel clot)

   Bleeding or severe erosive esophagitis

   Pathologic hypersecretion associated with Zollinger-Ellison syndrome

   Contraindication to using histamine$_2$-receptor antagonists (H_2RAs) (e.g., H_2RA-related thrombocytopenia) for stress ulcer prophylaxis (SUP)

In studies that demonstrated efficacy of intravenous PPIs for high-risk PUB, the drug was administered *after* endoscopic diagnosis and hemostasis.[1,2] There is a lack of clinical outcome evidence to support the use of intravenous PPIs in unselected patients with upper gastrointestinal bleeding. The recommendation that intravenous pantoprazole may be used for clinical signs of significant upper gastrointestinal bleeding *before* urgent endoscopy in patients with high risk for peptic ulcers is intended as temporary management in situations where endoscopy cannot be performed in a timely manner.

Inappropriate Indications for Use

1. **Patient is not NPO.** In the absence of clinical outcome studies comparing oral with intravenous PPIs in PUB, these criteria recommend oral or nasogastric administration of PPIs for patients who are not NPO. Oral quadruple doses of omeprazole (80 mg per day in 2 or 4 divided doses) have been shown to reduce rates of re-bleeding following endoscopic hemostasis of PUB.[3, 4] In healthy volunteers, oral and intravenous doses of pantoprazole produce similar effects on intragastric pH,[5] and nasogastric lansoprazole is at least as effective as intravenous pantoprazole in controlling intragastric pH.[6, 7] Once patients are no longer NPO, intravenous pantoprazole should be discontinued and PPI therapy continued orally or nasogastrically.
2. **Stress ulcer prophylaxis.** There is limited published evidence to support the routine use of intravenous PPIs over H_2RAs for stress ulcer prophylaxis. Intravenously administered pantoprazole should not be used for SUP in the presence of thrombocytopenia that is not temporally or causally related to H_2RA use. Intravenously administered H_2RAs should be used in such cases.
3. **Temporary conversion of an oral PPI in a patient who is made NPO, but who does not have an upper GI bleed or a contraindication to H_2RAs.** This includes temporary, short-term use in intensive care patients for uncomplicated gastroesophageal reflux disease or other indications unrelated to critical care illness. Intravenous H_2RAs should be used in these situations if continued acid-suppressive therapy is determined to be clinically appropriate.

Contraindications

Documented hypersensitivity to pantoprazole

Dosage

Peptic ulcer bleeding	40 mg i.v. bolus then 6.7 mg/h continuous infusion x 72 h (160 mg/d after bolus) OR 80 mg i.v. bolus then 8 mg/h continuous infusion x 72 h (192 mg/d after bolus)
Bleeding or severe erosive esophagitis	40 mg i.v. once daily for 7 to 10 days
Pathologic hypersecretion/Zollinger-Ellison syndrome	80 mg i.v. every 12 hours; may increase to 80 mg every 8 hours if needed; may titrate to higher doses depending on acid output
Stress ulcer prophylaxis	80 mg i.v. every 12 h for 24 h followed by 40 mg every 12 h

For PUB, high-dose continuous intravenous infusions of pantoprazole that provide a total of 160 mg per day after a 40-mg bolus[8] or 192 mg per day after an 80-mg bolus[1, 2] may be used, as there is insufficient evidence and no consensus on the optimal dose. A quadruple-dose regimen of pantoprazole (160 mg i.v. per day in 2 or 4 divided doses) can be derived from results with orally administered omeprazole[3, 4]; however, these intravenous intermittent dosage regimens have not been studied in patients with PUB.

If PUB is not confirmed on urgent endoscopy, intravenous doses of pantoprazole should be discontinued. If PUB at high risk for re-bleeding is found on endoscopy, pantoprazole may be continued for 72 hours after hemostasis is achieved with endoscopic therapy. After 72 hours, the intravenous infusion of pantoprazole should be discontinued and oral PPI therapy at standard doses should be started.

If the patient must remain NPO after 72 hours, pantoprazole should be given as intermittent intravenous doses of 40 mg once daily until the patient can be converted to oral PPI therapy. Since intravenous and oral doses of pantoprazole have been shown to be equivalent in terms of pH control,[5] this recommended intravenous dose of pantoprazole is the same as the off-label oral doses used for healing and maintenance of peptic ulcers.[9-17]

When intravenous pantoprazole is used for clinical signs of significant upper gastrointestinal bleeding before urgent endoscopy in patients with high risk for peptic ulcers, it should be continued for up to 72 hours or until endoscopy is performed. Therapy should then follow the recommendations above based on the endoscopic findings and patient's NPO status.

For oral administration, quadruple doses of a PPI (e.g., omeprazole 80 mg, rabeprazole 80 mg, or lansoprazole 120 mg daily, each given in 2 or 4 divided doses for 5 days), are suggested for PUB. For nasogastric administration for PUB, the same dose of omeprazole may be given as a Simplified Omeprazole Suspension[a] or lansoprazole may be administered as a mixture of the enteric-coated granules in apple juice, or a Simplified Lansoprazole Suspension.[a]

Dosing in Special Patient Populations

At standard doses, no dosage adjustment is necessary in elderly patients, patients with renal impairment, patients with hepatic impairment, or patients on hemodialysis. Higher than standard intravenous doses of pantoprazole have not been studied in these patient populations and therefore no recommendation can be made.

Administration

Intravenous boluses of pantoprazole should be given over 2 to 5 minutes.

Sodium chloride 0.9% solution is recommended for reconstituting and diluting pantoprazole for injection. Admixtures of pantoprazole for injection must be administered intravenously through a dedicated line, **using the in-line filter provided**. The filter removes precipitate that forms when the reconstituted drug is mixed with intravenous solutions and does not affect drug concentration. If a Y-site is used, then the in-line filter should be positioned below the Y-site that is closest to the patient. No other drugs should be concomitantly administered through the dedicated line.

The venous line should be flushed before and after administration of pantoprazole for injection with dextrose 5%, sodium chloride 0.9%, or lactated ringer's solution for injection. Pantoprazole for injection should not be simultaneously administered through the same line with other intravenous solutions.

Admixtures of pantoprazole for injection are stable at room temperature for 12 hours.

Table 1 shows the method that is being used to prepare pantoprazole infusions in the manufacturer's study investigating the use of pantoprazole for injection in the prevention of re-bleeding after endoscopic treatment of PUB (data on file, Wyeth Pharmaceuticals).

Table 1 Administration method for high-dose infusion of pantoprazole (80 mg + 8 mg/h)

Loading dose: 80 mg over 5 min
– Reconstitute 2 vials of pantoprazole (40 mg/vial) by injecting 10 ml of NS into each vial. This will provide a total of 80 mg per 20 ml.
– Remove and discard 35 ml from a 50-ml minibag of NS for injection. Inject the contents of the two reconstituted vials of pantoprazole (20 ml) to the solution remaining in the NS minibag (15 ml). This will result in a final concentration of 2.3 mg/ml in a final volume of 35 ml.
– In order to infuse the required loading dose of 80 mg over 5 minutes, infuse at the rate of 420 ml/h (7 ml/min = 35 ml/5 min).
Continuous infusion: 8 mg/h for 72 h
– Since admixtures should not be administered beyond 12 h from the time of admixture, bags were changed every 8 h.
– For each 8-h period, reconstitute 2 vials of pantoprazole (40 mg/vial) by injecting 10 ml of NS into each vial. This will provide a total of 80 mg per 20 ml.
– Add the 2 reconstituted vials of pantoprazole (20 ml) to a 400-ml bag of NS. This will provide a final concentration of 80 mg/520 ml (0.154 mg/ml). In order to infuse the required dose of 8 mg/h, infuse at a rate of 52 ml/h for 72 h.

Drug Costs

The intravenous doses of pantoprazole suggested by this guidance are 6 to 7 times more expensive than quadruple oral doses of rabeprazole or lansoprazole.

[a] Simplified Omeprazole Suspension: 2 mg/ml 8.4% sodium bicarbonate; stable for 1 week at room temperature or 24 weeks frozen (non-oral syringe); protect from light. 18. Phillips JO, Metzler MH, Johnson M. The stability of simplified omeprazole suspension (SOS) (abstract). *Critical Care Medicine* 1998;28:A221. Simplified Lansoprazole Suspension (SLS): 3 mg/ml 8.4% sodium bicarbonate; stable for 14 days at room temperature or 28 days refrigerated (non-oral syringe).[29]

Daily drug acquisition costs

Pantoprazole i.v.		Rabeprazole p.o.	Lansoprazole p.o.
6.7 mg/h (40-mg bolus)	**8 mg/h (80-mg bolus)**	**80 mg/d**	**120 mg/d**
$15.28 ($3.82)	$18.34 ($7.64)	$2.60	$2.60

FSS prices, April 2003. Prices for pantoprazole i.v. do not include intravenous minibags or infusion tubing.

Evidence Table

Strength of Recommendation and Evidence Rating	References	Quality of Evidence	Overall Quality
Grade A (always indicated and acceptable):			
No studies			
Grade B (may be useful/ effective):			
Quadruple-dose, orally administered PPI (omeprazole 20 mg every 6 h or 40 mg every 12 h) for prevention of re-bleeding of high-risk PUB after endoscopic hemostasis	Kaviani (2003)[3] Javid (2001)[4]	I I	Good
High-dose intravenously administered PPI (omeprazole 80 mg then 8 mg/h or doses shown to maintain intragastric pH > 6.0) for prevention of re-bleeding or surgery in high-risk PUB after endoscopic hemostasis	Lau (2000)[1] Sharma (2001)[2]	I III (abstract)	Fair
Prefer high-dose, intravenously administered PPI (omeprazole 40-mg bolus then 6.7 mg/h infusion) over H_2RA for high-risk PUB with non-bleeding visible vessel	Lin (1998)[8]	I	Fair
Prefer nasogastrically administered PPI (omeprazole) over H_2RAs for stress ulcer prophylaxis	Levy (1997)[19] Phillips (1998)[20]	I III (abstract)	Fair
Grade C (may be considered):			
Prefer intravenously administered pantoprazole (40 mg i.v. x 3 over 72 h) over H_2RAs for prevention of re-bleeding or surgery in high-risk PUB	Duvnjak (2001)[21] Fried (1999)[22]	III (abstract) III (abstract)	Poor
Intravenously administered H_2RAs for stress ulcer prophylaxis	Cook (1996)[23] Messori (2000)[24] Hanisch (1998)[25] Metz (1993)[26]	I I I I	Good
Prefer intravenously administered PPI (pantoprazole) over H_2RAs for stress ulcer prophylaxis	Morris (2002)[27]	III (summary)	Poor
Grade D (may not be useful/ effective; possibly harmful):			
Prefer high-dose, intravenously administered PPI (omeprazole) over H_2RAs for active PUB (Forrest Ia or Ib, spurting or oozing)	Lin (1998)[8] Villanueva (1995)[28]	I I	Good
Grade I (insufficient evidence to recommend for or against):			
Optimal intravenous dosing regimen of PPI	Insufficient evidence	—	—

Evidence rating scheme based on the methods used by the third U.S. Preventive Services Task Force[29]

Key to Quality of Evidence rating: I = At least one properly done randomized controlled trial; III = Opinion of respected authorities, case reports, expert committees

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Summary of Literature Review: Criteria for Non-formulary Use of Intravenous Pantoprazole for Upper Gastrointestinal Bleeding

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Background

The literature review was directed toward answering 12 questions concerning the use of acid-suppressive agents for nonvariceal acute upper gastrointestinal bleeding (NVAUGIB) or stress ulcer prophylaxis (SUP). The search strategy focused on randomized, controlled clinical trials and was limited to English-language studies retrieved from the MEDLINE/PubMed database (1966 to February 2003). Additional articles were obtained from a review of reference lists in study reports and the manufacturer of pantoprazole (Wyeth Pharmaceuticals). Clinical outcomes of interest for NVAUGIB were rebleeding, surgery, and mortality. For SUP, the outcomes of interest were clinically significant gastrointestinal bleeding (GIB) (i.e., hemodynamic instability, severe anemia), pneumonia, and mortality. Precedence was given to studies in which patients received drug therapy after endoscopic therapy. A total of 41 RCTs were relevant to this review. The quality of clinical trial reports was rated using a validated scoring system by Jadad.[1] Virtually all NVAUGIB studies included only patients with peptic ulcer bleeding (PUB).

Abbreviations: **GIB** Gastrointestinal bleeding; **H_2RA** Histamine$_2$ receptor antagonist; **NBVV** Nonbleeding visible vessel; **NVAUGIB** Nonvariceal acute upper gastrointestinal bleeding; **PPI** Proton pump inhibitor; **PUB** Peptic ulcer bleeding; **RCT** Randomized controlled trial

1. Does medical therapy provide additional benefit over endoscopic therapy for NVAUGIB?

2. Are there treatment differences between placebo and either H_2RAs or PPIs for NVAUGIB?

For relevance to clinical use, only studies in which all patients received endoscopic therapy are discussed.

H_2RAs vs. placebo. The literature search found no RCTs that compared H_2RAs with placebo in a population of patients who had received endoscopic therapy. Therefore, there is a lack of evidence demonstrating the efficacy of H_2RAs for PUB after endoscopic hemostasis.

PPIs vs. placebo. The results of three studies and one meta-analysis in patients with peptic ulcer hemorrhage at high risk for recurrence (spurting, oozing, NBVV, or adherent clot) support the use of either quadruple-dose oral PPI (omeprazole 80 mg daily in 2 or 4 divided doses) or high-dose intravenous PPI therapy (omeprazole 80-mg bolus then continuous infusion at 8 mg per hour or 192 mg/d) as an adjunct to endoscopic therapy in preventing re-bleeding (Table 1).[2-5]

Two of the three studies used oral PPI therapy. The first study was a well-designed, excellent-quality, placebo-controlled, double-blind RCT comparing omeprazole (20 mg p.o. every 6 hours) in 160 Iranian patients with high-risk PUB (spurting, oozing, or NBVV).[2] The analysis was performed on data for 149 patients after excluding 11 patients (9 from the omeprazole group and 2 from the placebo group) who had received H_2RA therapy (and therefore met exclusion criteria) after randomization. Omeprazole was superior to placebo in reducing the rate of re-bleeding, shortening hospital stay, and reducing the amount of blood transfused.

The second study was a well-designed, excellent-quality, placebo-controlled, double-blind RCT evaluating omeprazole (40 mg p.o. every 12 hours) in 166 Indian patients with high-risk PUB (spurting, oozing, NBVV, or adherent clot).[3] The intent-to-treat analysis showed that omeprazole was superior to placebo in reducing the rate of re-bleeding, the proportion of patients requiring blood transfusion, and duration of hospital stay. There is potential for bias because adherent clots (seen in 37% of patients) were only gently washed and therefore, some of these patients may actually have had a NBVV. The inclusion of patients with adherent clots makes the patient population of this study different from studies that included only patients with spurting, oozing, or NBVV.

The third study used intravenous PPI therapy. It was a well-designed, good-quality, placebo-controlled, double-blind RCT in Chinese patients. It found a high-dose, continuous infusion of omeprazole (80 mg then 8 mg/hour) to be superior to placebo in terms of re-bleeding rates, blood transfusion requirements, and duration of hospital stay.[4] The external validity of the study results are questionable, however, because the parietal cell mass of Chinese has been found to be smaller than that of Caucasians.[6]

There was no difference between treatments in terms of surgical and death rates in each of the three RCTs. The studies included Iranian,[2] Indian,[3] or Chinese patients.[4] The results of these studies may not be applicable to other ethnic groups.

There is also some evidence from the subgroup analysis of a meta-analysis (published as an abstract) which suggests that medical therapy provides additional benefit over endoscopic therapy alone (with placebo control) in terms of preventing re-bleeding or need for surgery.[5]

In contrast, one good-quality, open-label RCT found injection endoscopic therapy plus intravenous boluses of omeprazole to be no different from injection therapy alone (without placebo dummy) in preventing re-bleeding, need for surgery, or death.[7]

No study found a benefit with PPIs over placebo in reducing deaths.

In summary, there is good-to-excellent–quality evidence that high doses of either orally or intravenously administered omeprazole provide additional benefit over endoscopic hemostasis in preventing re-bleeding of high-risk PUB in Iranian, Indian, and Chinese patients. It is expected that similar benefits would be obtained with other PPIs (see Question 9). Further studies are needed to determine whether the same doses of PPI are effective in other races.

3. Are there treatment differences between i.v. H_2RAs and i.v. PPIs for NVAUGIB?

4. Which subsets of patients with AUGIB are most likely to benefit?

For relevance to clinical use, only studies in which all patients received endoscopic therapy are discussed.

Two good-quality, open-label RCTs and two poor-quality RCTs (abstracts) have compared i.v. H_2RAs and PPIs in patients with PUB (Table 2). The first good-quality RCT included 100 Taiwanese patients with high-risk PUB.[8] Omeprazole (40 mg i.v. followed by 6.7 mg/hour for 72 hours) was superior to cimetidine (300 mg i.v. followed by 300 mg i.v. every 6 hour for 72 hours) in preventing re-bleeding at day 3 overall and in a subgroup of patients with NBVV. There was no treatment difference in reducing re-bleeding in the subgroup of patients with spurting or oozing bleeds, or in decreasing surgery or deaths in the entire cohort.

In the second good-quality trial, 96 very high-risk patients with active peptic ulcer bleeding (spurting or oozing) were randomized to either omeprazole (80 mg i.v. then 40 mg i.v. every

8 hours) or ranitidine (50 mg i.v. every 6 hours for 12 to 24 hours then 150 mg p.o. every 12 hours).[9] This trial found no difference between omeprazole and ranitidine in preventing re-bleeding, surgery, or death in patients with spurting or oozing bleeds, similar to the findings of the subgroup analysis in the previous study,[8] which found no reduction in re-bleeding rates among patients with active bleeding.

In the two poor-quality RCTs (abstracts), pantoprazole was compared with ranitidine in patients with high-risk PUB following endoscopic hemostasis. In the first trial, 62 patients with endoscopically treated Forrest Ia, Ib, IIa, or IIb PUB (oozing, spurting, NBVV, or sentinel clot) were randomized to pantoprazole (4 doses of 40 mg i.v. during 72 hours) or ranitidine (4 doses of 150 mg i.v. during 72 hours).[10] The number of patients in each treatment group was not stated. The rate of re-bleeding during 72 hours was 3.2% with pantoprazole and 12.9% with ranitidine (statistics not reported). Forrest III classification (no stigmata of hemorrhage), which was defined as a successful outcome, was obtained with 25 ulcers in the pantoprazole group and 19 ulcers in the ranitidine group. The authors concluded that intravenous pantoprazole was superior to intravenous ranitidine in the prevention of re-bleeding from PUB after initial endoscopic therapy.

In the second poor-quality trial, 133 patients with Forrest Ia to IIb PUB were randomized to open-label treatment with either pantoprazole (40- mg bolus then 8 mg/hour i.v.; N = 66) or ranitidine (50-mg bolus then 12.5 mg/hour i.v.; N = 67) for 2 days.[11] There was no difference between pantoprazole and ranitidine in terms of re-bleeding (6/61, 10% vs. 10/58, 17% at 48 hours; Cochran-Mantel-Haenszel test not significant). Deaths occurred in 1.5% of patients in each group.

Therefore, there is good-quality evidence that, after endoscopic treatment, there is a benefit of omeprazole over H_2RAs in a subgroup of patients with NBVV. The two drugs are similar in efficacy for active PUB. For pantoprazole, the available evidence is preliminary, poor quality, and conflicting. At relatively low doses in a small population (N = 62), pantoprazole seems to be better than ranitidine in preventing re-bleeding. At higher doses, no difference could be demonstrated despite a larger study population (N = 133). The doses of pantoprazole that were studied were less than 192 mg/d or lacked an 80-mg bolus; however, the rationale for such high doses is based on pH studies, not clinical outcomes (see Question 10).

5. For SUP, are there treatment differences between H_2RAs and placebo,

6. PPIs and placebo, or

7. H_2RAs and PPIs?

H_2RAs vs. placebo. Two meta-analyses and two RCTs have compared H_2RAs with placebo (Table 3). The results of the first meta-analysis by Cook, et al. (N = 7218, 57 RCTs) showed that H_2RAs were better than placebo and no treatment as a combined group in preventing clinically important bleeding.[12] Clinically important bleeding was defined as overt bleeding accompanied by (a) a decrease in blood pressure of 20 mm Hg within 24 hours of bleeding, (b) a decrease in blood pressure of 10 mm Hg and an increase in heart rate of 20 beats per minute on orthostatic change, or (c) a decrease in hemoglobin of 20 g/L and transfusion of 2 U of blood within 24 hours; or as gastric bleeding requiring surgery). Overt bleeding was defined as hematemesis, bloody gastric aspirate, melena, or hematochezia. Different trial standards were applied, in that the analysis mixed trials with untreated controls and trials with active controls, and combined the results of placebo and untreated control groups.

The other meta-analysis, using the same definition of clinically important bleeding as Cook, et al (1996) found no difference between ranitidine and placebo (N = 398, 5 RCTs) in preventing clinically important bleeding related to stress ulcers.[13] It also found no treatment difference in the rate of pneumonia.

The two RCTs, which used different efficacy end points, obtained different results. One study found no difference between ranitidine and placebo in reducing clinically *relevant* bleeding or in development of pneumonia.[14] Mortality rates were also similar. Unlike other studies that used specific criteria for clinically *important* bleeding, this study used a nonstandardized definition of clinically relevant bleeding.

The other RCT found ranitidine to be superior to placebo in reducing the rate of stress-related upper GIB (3/86, 3% vs. 15/81, 19%; p = 0.002), but the rates of pneumonia were similar (14% vs. 19%).[15] Stress-related upper GIB was mainly defined by the presence of overt bleeding and therefore the results may have overestimated the efficacy of ranitidine.

Therefore, one meta-analysis and one RCT found H_2RAs to be superior to placebo while the other meta-analysis and RCT found no treatment difference.

PPIs vs. placebo. No published RCTs comparing PPIs and placebo were found by the literature search.

H_2RAs vs. PPIs. Three RCTs compared H_2RAs and PPIs in the prophylaxis of stress ulcers (Table 4). The first study was a good-quality, single-center, open-label RCT by Levy, et al.[16] Intensive care patients (N = 70) with at least 1 of 9 risk factors regarded as strong indications for SUP were randomized to either omeprazole capsules given orally or water-based omeprazole suspension given nasogastrically (40 mg daily) or ranitidine administered intravenously (50 mg then 150 mg/d as a continuous infusion or 50 mg every 8 hours). Omeprazole was superior to ranitidine in terms of reducing "clinically important bleeding" (nonstandardized definition) and preventing major surgery, and in terms of the number of samples with intragastric pH > 4. There were no treatment differences in the rate of nosocomial pneumonia or deaths, or in the mean intragastric pH.

The second study was a multicenter RCT that was published as an abstract (poor quality; blinding not stated).[17] Eligible patients had to be critically ill, have 2 or more risk factors for stress ulcers, and have a baseline intragastric pH of 4 or less. Based on data from 58 analyzed patients, simplified omeprazole solution (bicarbonate based) given nasogastrically was superior to ranitidine given intravenously in reducing clinically significant bleeding, decreasing the rate of two consecutive intragastric pH $\leq$ 3.5, and increasing the change in pH after starting treatment. The results of this study were consistent with those found by Levy, et al. in the first RCT.

The third RCT was a multicenter, open-label pilot study that was reported only as a summary of a presentation (poor quality). It compared five doses of intravenous pantoprazole (ranging from 40 mg every 24 hours to 80 mg every 8 hours) and intravenous cimetidine (300 mg then 50 mg/hour) over a period of 2 to 7 days in 112 intensive care patients.[18] The patients were stratified based on the likelihood of receiving enteral feeding after remaining NPO for 24 hours. The primary efficacy variable was intragastric pH. Both agents were able to achieve intragastric pH $\geq$ 4 within hours of initiating therapy; however, subsequently, the pH progressively increased with pantoprazole while the effect of cimetidine waned by day 2. There were similar rates of undefined bleeding (1 of 90, 1.1% for pantoprazole vs. 0 of 22, 0% for cimetidine) and pneumonia (2 of 90, 3.3% vs. 1 of 22, 4.5%; statistics not performed).

In summary, two of the three available studies provide limited evidence which suggests that PPIs administered orally or intragastrically may be superior to H_2RAs given intravenously in preventing clinically important bleeding in critically ill patients at risk for stress ulcers. Double-blind RCTs comparing H_2RAs and PPIs are needed before PPIs can be recommended over H_2RAs for SUP.

8. What is the optimal dose of PPIs for NVAUGIB?

High-dose PPI given as a continuous infusion (e.g., omeprazole 80 mg bolus followed by an infusion of 8 mg per hour) is often recommended for treatment of PUB. In healthy volunteers, a regimen consisting of an 80-mg bolus of pantoprazole followed by a continuous infusion of 8 mg per hour achieved the best pH control, maintaining intragastric pH > 4.0 for a median of 99% of a 24-hour period.[19] Intragastric pH was maintained above 4.0 for 82% of the 24-hour period using a regimen with a slower bolus (40 mg/hour for 2 hours then 8 mg/hour); and, in separate evaluations, 54% of Day 1 and 85% of Day 2 using a 40-mg bolus then 4 mg/hour infusion and 20% of Day 1 and 47% of Day 2 using intermittent doses of 40 mg every 8 hours. It has also been shown in patients with Forrest Ia, Ib, or IIa PUB (spurting, oozing, or NBVV) to maintain intragastric pH > 4 to > 6 for 58.4% to 99.6% of the time.[20] This dosing approach is the only *intravenous* regimen used with omeprazole that was demonstrated to be superior to placebo in reducing re-bleeding or surgery in double-blind studies (three RCTs).[4,21,22]. Only one of these studies was performed in patients who had all undergone EGD therapy[4]; the other two included some patients who had not received EGD therapy.[21,22]

High-dose, continuous infusions, however, have not been demonstrated to be superior to lower doses given as intermittent boluses in comparative trials (Table 5). One study was a poor-quality trial (abstract) in which 168 patients received endoscopic therapy then were randomized to either high-dose pantoprazole (40-mg i.v. bolus then an infusion of 8 mg per hour) or low-dose pantoprazole (40 mg i.v. daily).[23] Study treatment was continued for 72 hours. There was no significant difference between higher and lower doses of PPI in preventing re-bleeding. The rates of surgery, death, and blood transfusions were similar in the two treatment groups.

Notably, in one good-quality, double-blind RCT, in which 102 (72%) of 142 analyzed patients with high-risk PUB (oozing, spurting, NBVV, sentinel clot, or hematin-covered lesion) underwent endoscopic therapy, a regular dose of intravenous omeprazole (20 mg once daily) was demonstrated to be statistically *equivalent* to high-dose omeprazole (80-mg bolus followed by 8-mg per hour continuous infusion) in preventing re-bleeding, surgery, and death.[24]

In contradiction to the belief that high-dose continuous infusions are necessary, there is excellent-quality evidence that even oral omeprazole (80 mg daily in divided doses) is efficacious in preventing re-bleeding, reducing transfusions, and shortening hospital stay in patients with peptic ulcer bleeding initially controlled with endoscopic therapy (see Questions 1 and2).[2,3] There is also a lack of evidence that better pH control is associated with better clinical outcomes (see Question 10).[25-28]

Although there is excellent-quality evidence supporting the efficacy of quadruple oral doses of PPIs and good-quality evidence supporting high-dose continuous infusions of PPIs, there is insufficient evidence to establish the optimal dose of PPIs for preventing complications related to PUB.

9. Can the results for omeprazole be extrapolated to pantoprazole? Is there a class effect?

Most clinical trials evaluating continuous PPI infusions have used omeprazole. The question of whether equivalent doses of pantoprazole would produce similar responses still remains, as there are no published trials directly comparing intravenous omeprazole and pantoprazole for NVAUGIB.

There seems to be a class effect based on indirect evidence. Noncomparative studies of pantoprazole continous infusions (doses up to 80-mg bolus then 8 mg/hour) have found pH responses similar to those produced by the same dosage regimen of omeprazole in other studies.[19,20] In *Helicobacter pylori*–negative healthy volunteers, a double-blind RCT showed that a standard dose of pantoprazole (40 mg p.o. daily) was at least as efficacious as a standard dose of omeprazole (20 mg p.o. daily) in reducing meal-stimulated gastric acid secretion during certain periods on days 1 and 3 of therapy and in time to onset.[29] Two other double-blind RCTs in healthy volunteers found standard-dose pantoprazole to be similar to or better than standard-dose omeprazole in terms of median 24-hour pH.[30,31] In healthy volunteers, two open-label RCTs found that a standard dose of lansoprazole given nasogastrically (30 mg once daily) is at least as efficacious as intravenous pantoprazole (40 or 80 mg daily) in terms of pH control.[32,33] Finally, a double-blind RCT demonstrated that rabeprazole (20 mg daily) was better than omeprazole (20 mg daily) in reducing 24-hour acidity on day 1 but not day 8, and increasing median 24-hour intragastric pH and percentage of time that intragastric pH was > 3 and > 4 on days 1 and 8.[34] Therefore, according to pH response, all available PPIs at their standard doses are similar.

10. Is there clinical evidence for the target pH values in NVAUGIB?

The rationale for using acid suppressive agents in the management of upper gastrointestinal bleeding is based on in vitro evidence that low intragastric pH inhibits hemostasis and induces fibrinolysis.[36-38] The antiplatelet and fibrinolytic effects seem to be primarily mediated not directly by acid but by pepsin, which is highly sensitive to changes in pH.

Thresholds for hemostasis (in vitro):

pH < 4.0	Fibrinolysis
pH < 5.4	No platelet aggregation and plasma coagulation
pH < 6.0	Platelet disaggregation
pH < 6.8	Abnormal platelet aggregation and plasma coagulation

Based on in vitro findings, a target pH > 6.0 has been recommended. In order to maintain such high pH levels, high doses of PPIs must be given by continuous infusion. Omeprazole (80 mg then 8 mg/hour) has been shown to maintain intragastric pH > 6.0 for 84% to 100% of a 24-hour period.[19,28] PPIs not only achieve and maintain higher intragastric pH levels for a longer duration than H_2RAs, they have also not been associated with development of tolerance (tachyphylaxis), which has been observed with H_2RAs.[28,39,40]

However, RCTs that have assessed intragastric pH as well as clinically meaningful outcomes (e.g., re-bleeding, surgery, or death) in patients with PUB have not consistently confirmed a relationship between better pH control with PPIs and lower risk of complications. In four small trials (N = 40 to 60), of which two were good-quality[25,28] and two poor-quality,[26,27] a difference between PPI and H_2RA in pH control was observed but there was no difference in re-bleeding, surgery, or death (Table 6). These trials may have lacked sufficient power to detect a treatment difference if a true difference existed (Type II error).

A single study by Lin et al. (1998) has been able to demonstrate improved clinical outcomes in conjunction with better pH control (Table 6). This good-quality RCT (N = 100) found a continuous infusion of omeprazole (40 mg then 6.7 mg/hour i.v.) to be superior to cimetidine (300 mg i.v. every 6 hour) for rebleeding and pH control. Measurements for pH and clinical outcomes, however, were taken over different periods (1 day vs. 3 and 14 days).[8]

Of the five studies, one used a high-dose continuous infusion of omeprazole (80 mg then 8 mg/hour i.v.)[28] This small study consisted of two 24-hour, parallel trials in patients with duodenal or gastric ulcers (N = 20 each; 40 total). Endoscopic therapy was performed in 24 patients with Forrest I or IIa (active bleeding or NBVV). It found omeprazole to be superior to ranitidine (50 mg then 0.25 mg/kg/hour i.v.) in mean intragastic pH after 12 hours and percentage of time above hemostatic pH thresholds (see tables below).

IG pH during 13th to 24th hour

	OME N = 10	RTD N = 10
DU		
pH (mean)	6.75	6.22
95% CL	6.47, 6.97	5.44, 6.47
P-value	0.01	
GU		
pH (mean)	6.65	5.66
95% CL	6.07, 7.08	4.92, 6.32
P-value	0.03	

Source: Labenz (1997)[28]
DU = Duodenal ulcer; GU = Gastric ulcer
OME = Omeprazole 80 mg then 8 mg/h i.v.
RTD = Ranitidine 50 mg then 0.25 mg/kg/h i.v.

Holding time (%) for hemostatic pH thresholds

DU Study				GU Study			
	OME	RTD			OME	RTD	
pH	N = 10	N = 10		pH	N = 10	N = 10	
2–12 h				**2–12 h**			
4.0	100	100		4.0	100	100	
5.4	100	98		5.4	100	94	
6.0	98	96		6.0	100	88	
6.8	38	38		6.8	52	51	
13–24 h				**13–24 h**			
4.0	100	97	*	4.0	100	87	*
5.4	100	87	*	5.4	100	75	*
6.0	100	80	*	6.0	100	55	*
6.8	48	27		6.8	27	26	

Values estimated from Labenz (1997),[28] Figure 2. * P<0.003
DU = Duodenal ulcer; GU = Gastric ulcer; OME = Omeprazole 80 mg then 8 mg/h i.v.; RTD = Ranitidine 50 mg then 0.25 mg/kg/h i.v.

Clinical outcomes between groups were similar, however, in terms of re-bleeding (no clinical re-bleeding in either group), surgery (1 gastric ulcer patient, treatment group not stated), and death (1 duodenal ulcer patient, treatment group not stated).[28] As noted above, the small sample size may have been inadequate to show a treatment difference in clinical outcomes (Type II error).

In summary, four of five trials have not been able to demonstrate that better pH control is associated with improvement in re-bleeding, surgery, or mortality rates. One trial has shown better pH control and lower rates of re-bleeding. There have been no double-blind studies, and only two studies used continuous infusions of a PPI.[8,28] Although the results of in vitro studies convincingly show that intragastric hemostasis is highly pH-dependent, there is insufficient evidence demonstrating that achievement of a target pH > 4.0 or > 6.0 translates to improved clinical outcomes.

11. Are there treatment differences between i.v. boluses and continuous infusions of either PPIs or H_2RAs?

No studies compared intravenous boluses and continuous infusions of the same daily dose of either PPIs or H_2RAs in patients with NVAUGIB or SUP.

12. Are there treatment differences between oral and parenteral PPIs for NVAUGIB or SUP?

The literature search found no RCTs that compared orally and parenterally administered PPIs in patients with NVAUGIB or SUP. Three studies, all poor-quality, single-center, open-label, crossover RCTs, have been conducted in healthy volunteers using intragastric pH control as the basis for comparison (Table 7). One of the three trials compared oral and intravenous doses of the same PPI (pantoprazole 40 mg for 5 days) and found the two routes to be equivalent (mean % time pH $\geq$ 4: 42% vs. 38%; mean difference: 4.4; 90% CI: 0.6 to 8.3).[35] The other two trials demonstrated that nasogastrically administered lansoprazole (30 mg daily) for 5 days was superior to intravenously administered pantoprazole (40 or 80 mg daily) in terms of the mean 24-hour intragastric pH.[32,33]

Therefore, based on pH studies, the oral or nasogastric route seems to be at least as efficacious as the intravenous route of PPI administration. RCTs that compare intravenous and oral doses of PPIs for PUB in terms of clinical outcomes are lacking.

Table 1 Randomized controlled trials comparing PPIs and placebo in peptic ulcer bleeding after endoscopic hemostasis

			Re-bleeding				Surgery			
Reference / Design	**Treatment**		**Results**	**RRR**	**ARR**	**NNT**	**Results**	**RRR**	**ARR**	**NNT**
Quality of Report	**Dose (mg), Duration**	**$N_{R/A}$**	**(PPI vs. PLAC)**	**(95% CI)**	**(95% CI)**	**(95% CI)**	**(PPI vs. PLAC)**	**(95% CI)**	**(95% CI)**	**(95% CI)**
RCTs										
Oral PPI vs. PBO										
Kaviani (2003){Kaviani, 2003 #3149 R DB 2-center PP Iranian pts with Forrest Ia to IIa PUB *Jadad score: Excellent (5)*	OME 20 p.o. q6h PBO x 5 d	160 / 149	**OME > PBO** 12/71, 17% (95% CI: 12.7 to 39.0) vs. 26/78, 33% (95% CI: 29.6 to 57.6); p = 0.022; RR=0.51 (95% CI: 0.28 to 0.93)	49.3% (7.3% to 72.3%)	16.4% (2.8% to 30.0%)	6 (3 to 36)	**OME ~ PBO** 1/71, 1.4% vs. 1/78, 1.3%	—	—	—
Javid (2001)[3] R DB SC ITT Indian pts with Forrest Ia to IIb PUB *Jadad score: Excellent (5)*	OME 40 p.o. q12h PBO x 5 d	166 / 166	**OME > PBO** 6/82, 7% vs. 18/84, 21%; p=0.02; RR=3.5 (95% CI: 1.3 to 9.2)	65.9% (18.3% to 85.7%)	14.1% (3.7% to 24.5%)	7 (4 to 27)	**OME = PBO** 2/82, 2% vs. 7/84, 9%; p=0.17; RR=3.6 (95% CI: 0.7 to 18.0)	—	—	—
Intravenous PPI vs. PBO										
Lau (2000)[4] R DB SC ITT Chinese pts with Forrest Ia to IIa PUB *Jadad score: Good (4)*	OME 80 i.v.b. + 8/h PBO x 3 d	240 / 240	**OME > PBO** 5/120, 4% vs. 24/120, 20% (day 3); p<0.001	79.2% (47.2% to 91.8%)	15.8% (7.8 to 23.8)	7 (4 to 13)	**OME = PBO** 3/120, 2.5% vs. 9/120, 7.5%; p=0.14	—	—	—
Meta-analysis										
PPI vs. PBO										
Sharma (2001)[5] Meta-analysis RCTs using PPI doses shown to maintain intragastric pH > 6.0 *Jadad score: N/A*	8 RCTs with and 10 RCTs without prior EGD tx 17 RCTs used OME i.v. 1 RCT used PAN i.v.	NR	With EGD tx, subanalysis: **PPI > PBO** RRR 42%; ARR 9.2%; 95% CI: 5.3 to 13.1; NNT 11	42%	9.2% (5.3 to 13.1)	11	With EGD tx, subanalysis: **PPI > PBO** RRR 46%; ARR 4.4%; 95% CI: 1.5 to 7.3; NNT 23	46%	4.4% (1.5 to 7.3)	23

All except one RCT by Hasselgren (1997)[21] found no statistically significant treatment difference in terms of rate of deaths. Hasselgren, et al. found no treatment difference in deaths at day 3 (1/159, 0.6% vs. 1/163, 0.6%), but a significantly lower rate of deaths in the placebo group compared with the OME group at day 21 (1/159, 0.6% vs 11/163, 6.9%; p<0.012). Of the 11 OME patients, 10 (91%) died of cardiovascular causes between days 3 and 21 after bleeding. Deaths were uniformly distributed over the follow-up period, suggesting that factors for unfavorable outcome other than high age, shock, rebleeding, and endoscopic stigmata determine long-term outcome.

† NNT calculated using reported OR and control event ratios of 0.20 for re-bleeding (OR 0.513, 95% CI: 0.377 to 0.699) and 0.075 to 0.111 for surgery (OR 0.583, 95% CI: 0.408 to 0.833); the range of control event ratios for surgery was obtained from the double-blind RCTs by Lau (2000), Hasselgren (1997), and Schaffalitzky (1997)

Table 2 Randomized controlled trials comparing PPIs and H_2RAs in peptic ulcer bleeding after endoscopic hemostasis

Reference / Design *Quality of Report*	Treatment Groups (doses in mg)	$N_{R/A}$	Results > means *statistically superior to* = means *not statistically different from ($p \geq 0.05$)* Rebleeding	Surgery	Death	Other
Lin (1998)[8] R OL Taiwan Forrest Ia, Ib, IIa PUB: 21 (21%) spurting; 13 (13%) oozing; 66 (66%) NBVV *Jadad score: Good (3)*	OME 40 i.v.b. + 6.7/h x 72 h + 20 p.o. q.d. x 2 mo (N=50) CTD 300 i.v.b. + 300 i.v.b. q6h x 72 h + 400 p.o. b.i.d. x 2 mo (N=50)	100 / 100	Overall (PEV): **OME b.c.i. > CTD i.b.** at day 3 (0/50, 0% vs. 8/50, 16%; p=0.003) and day 14 (2/50, 4% vs. 12/50, 24%; p=0.004) [day 3 p=0.015; RRR 0.941; 95% CI: 0.007 to 0.997; ARR 0.157; 0.051 to 0.263; NNT 6.375; 4 to 20] Spurting or oozing: **OME b.c.i. = CTD i.b.** for both types of active bleeding (0/9, 0% vs. 2/12, 17% and 1/4, 25% vs. 1/9, 11%, respectively) NBVV: **OME b.c.i. > CTD i.b.** (21/37, 3% vs. 9/29, 31%; p<0.05)	**OME b.c.i. = CTD i.b.** (0/50, 0% vs. 0/50, 0%)	**OME b.c.i. = CTD i.b.** (0/50, 0% vs. 2/50, 4%; p>0.05)	Median volume of blood transfused: **OME b.c.i. = CTD i.b.** (0, range: 0–2500, vs. 0, range: 0–5000; p=0.05) Days in hospital: **OME b.c.i. = CTD i.b.** (7 vs. 6 days; p>0.05) Mean IG pH from 1 to 24 h after start of infusion: **OME b.c.i. vs. CTD i.b.**, 6.0 vs. 4.0 to 5.5 % of time pH>6: **OME b.c.i. > CTD i.b.** (84.4% vs. 53.5%; p<0.001)
Villanueva (1995)[9] R OL Very high-risk pts with active PUB (Forrest Ia or Ib): 8 (10%) spurting; 73 (90%) oozing *Jadad score: Good (3)*	OME 80 i.v. bolus + 40 i.v. q8h x 4 d + 20 p.o. q.d. (N=45) RTD 50 i.v. q6h x 12–24 h + 150 p.o. q12h (N=41)	96 / 86	Spurting or oozing (combined results): **OME i.b. = RTD i.b.** (11/43, 26% vs. 9/38, 24%; 95% CI for difference: –17% to 20%; p = 0.8) NBVV: Not included in study	**OME i.b. = RTD i.b.** (9/45, 20%, 95% CI: 9% to 35% vs. 9/41, 22%, 95% CI: 10% to 38%; 95% CI for difference: –19% to 15%; p = 0.8)	**OME i.b. = RTD i.b.** (3/45, 7% vs. 1/41, 2%; p ≥ 0.05)	Blood transfusion (units. mean): **OME = RTD** (2.2 vs. 2.4; 95% CI for difference: –0.7 to 1.1; p = 0.6) Length of hospital stay: **OME = RTD** (14.1 vs. 15.3 d; 95% CI for difference: –7.5 to 5.1; p = 0.7)
Duvnjak (2001, abstract)[10] R Forrest Ia to IIb PUB (spurting, oozing, NBVV, sentinel clot) *Jadad score: Poor (1)*	PAN 40 i.v.b. then 40 x 3 doses over 72 h RTD 150 x 4 doses over 72 h	62 / 62	**PAN i.b. > RTD i.b.** (1/31, 3.2% vs. 4/31, 12.9% during 72 h)	—	—	*Successful outcome (Forrest III after 72 h)*: **PAN i.b. > RTD i.b.** (25/31, 81% vs. 19/31, 61%) *Blood transfusions*: **PAN i.b. ~ RTD i.b.**

Reference / Design ***Quality of Report***	**Treatment Groups (doses in mg)**	**$N_{R/A}$**	**Results** **> means *statistically superior to*** **= means *not statistically different from (p ≥ 0.05)***			
			Rebleeding	**Surgery**	**Death**	**Other**
Fried (1999, abstract)[11] R OL MC PP Forrest **I**a to **II**b PUB (spurting, oozing, NBVV, sentinel clot) *Jadad score: Poor (1)*	PAN 40 i.v.b. then 8/h (N=66) RTD 50 i.v.b. then 12.5/h (N=67) x 2 d	133 / 119	**PAN b.c.i. = RTD b.c.i.** (6/61, 10% vs. 10/58, 17% at 48 h; Cochran-Mantel-Haenszel test not significant)	—	**PAN b.c.i. = RTD b.c.i.** (1 case [1.5%] in both groups at 10 d)	

Meta-analysis by Zed et al. was excluded (compared PPIs with combined H_2RA and placebo results).

Table 3 Are there treatment differences between placebo and H_2RAs for SUP?

Reference / Design *Quality of Report*	Treatment Groups (doses in mg)	$N_{R/A}$	Results > means *statistically superior to* = means *not statistically different from ($p \geq 0.05$)* Bleeding	Pneumonia	Death
Cook (1996)[12] Meta-analysis, RCTs Non-English and English 56 articles of 57 studies 22 assessed SUB and pneumonia 36 assessed SUB, not pneumonia 5 assessed pneumonia, not SUB *Jadad score: N/A*	AA H_2RA SUC PBO Untreated Control	— / 7218	Clinically important bleeding† **AA = PBO / Control** (3 Trials) (0.35; 0.09 to 1.41) **H_2RA > PBO / Control** (10 Trials) (common OR, 0.44; 95% CI, 0.22 to 0.88) **H_2RA = AA** (10 Trials) (0.86; 0.46 to 1.59) **SUC = PBO / Control** (1 RCT) (1.26; 0.12 to 12.87) **SUC = AAs** (5 Trials) (1.49; 0.42 to 5.27) **SUC = H_2RA** (4 Trials) (1.28; 0.27 to 6.11)	Pneumonia: **H_2RA = PBO /Control** (8 RCTs) (common OR, 1.25; 95% CI, 0.78 to 2.00) **H_2RA = AA** (3 RCTs) (1.01; 0.65 to 1.57) **SUC = PBO / Control** (2 RCTs) (2.11; 0.82 to 5.44) **SUC = AA** (6 RCTs) (common OR, 0.80; 95% CI, 0.56 to 1.15) **SUC = H_2RA** (common OR, 0.78; 95% CI, 0.60 to 1.01)	Mortality: **AA = PBO /Control** (4 RCTs) (1.42; 0.82 to 2.47) **H_2RA = PBO / Control** (15 RCTs) (1.15; 0.86 to 1.53) **H_2RA = AA (14 RCTs)** (0.89; 0.66 to 1.21) **SUC = PBO /Control** (4 RCTs) (1.06; 0.67 to 1.67) **SUC > AA** (11 RCTs) (common OR, 0.73; 95% CI, 0.54 to 0.97) **SUC = H_2RAs** (11 RCTs) (common OR, 0.83; 95% CI, 0.62 to 1.09)
Messori (2000)[13] Meta-analysis, RCTs *Jadad score: N/A*	RTD (various b.c.i., c.i., or i.v.b. regimens) SUC (4 to 6 g/d p.o. or n.g. in 3 to 6 divided doses) PBO	398 (5 RCTs): RTD vs PBO , efficacy 54 (1 RCT): SUC vs. PBO , efficacy 311 (3 RCTs): RTD vs. PBO , pneumonia 226 (2 RCTs): SUC vs. PBO , pneumonia 1825 (8 RCTs): RTD vs. SUC	Clinically important bleeding† **RTD = PBO** (summary OR 0.72; 95% CI: 0.30 to 1.70; p=0.46 for fixed effect model) **SUC = PBO** (1.26; 0.12 to 12.9; p = 0.70)	Pneumonia: **RTD = PBO** (0.98, 0.56 to 1.72; p = 0.94) **SUC = PBO** (2.21; 0.86 to 5.65; p = 0.10) **SUC > RTD** (greater risk with RTD vs. SUC; 1.35; 1.07 to 1.70; p = 0.012)	—
Hanisch (1998)[14] R DB SC Germany ICU pts *Jadad score: Excellent (5)*	RTD 50 i.v. t.i.d. (N=57) Pirenzepine 10 i.v. t.i.d. (N=44) PBO (N=57)	1568 entered 827 / 158	Clinically relevant bleeding‡: **RTD = PIR = PBO** (3/57, 5.3% vs. 3/44, 6.8% vs. 2/57, 3.5%; p=0.41)	Pneumonia among pts mechanically ventilated ≥ 48 h (PEV): **RTD = PIR = PBO** (10/57, 17.5% vs. 10/44, 22.7% vs. 12/57, 21.1%; p=0.17)	**Mortality:** **RTD ~ PIR ~ PBO** (7/57, 12.3% vs. 12/44, 27.3% vs. 12/57, 21.1%)
Metz (1993)[15] R DB MC ITT ICU pts with severe head injury (Glasgow coma score ≤ 10) *Jadad score: Good (4)*	RTD 6.25 mg/h i.v. (N=86) PBO (N=81) x max. 5 d	167 / 167	Stress-related upper gastrointestinal bleeding§: **RTD > PBO** (3/86, 3% vs. 15/81, 19%; p = 0.002) None of the individual risk factors had a significant effect on bleeding frequency.	Pneumonia: **RTD ~ PBO** (14% vs. 19%)	—

† Clinically important bleeding = Overt bleeding accompanied by (a) a decrease in blood pressure of 20 mm Hg within 24 hours of bleeding, (b) a decrease in blood pressure of 10 mm Hg and an increase in heart rate of 20 beats per minute on orthostatic change, or (c) a decrease in hemoglobin of 20 g/L and transfusion of 2 U of blood within 24 hours; or as gastric bleeding requiring surgery); Overt bleeding = hematemesis, bloody gastric aspirate, melena, or hematochezia.

‡ Clinically relevant bleeding: Bright red blood via gastric tube or melena combined with hemodynamic changes [SBP < 100 mm Hg, tachycardia > 100 bpm] and rquirement of blood transfusion [fall in Hg > 2 g/dl within 24 h] and EGD identification of bleeding site and activity.

§ Stress-related upper gastrointestinal bleeding: Gastroccult-positive NGT drainage; BRBPNGT; hematemesis, Hemoccult-positive stool; melena, or hematochezia AND (a) Was gastric drainage occult blood positive and were "coffee grounds" present for the previous 8 h; (b) Was there a minimum of 50 ml of BRBPNGT? (c) Did the patient experience hematemesis in the last 8 h? (d) Was there EGD or surgical confirmation of an upper gastrointestinal source of bleeding?

Table 4 Are there treatment differences between i.v. H_2RAs and i.v. PPIs for SUP?

Reference / Design *Quality of Report*	Treatment Groups (doses in mg)	$N_{R/A}$	Results > means *statistically superior to* = means *not statistically different from (p≥0.05)* **Bleeding**	**Pneumonia**	**Death**	**Other**
Levy (1997)[16] R OL SC ICU pts with at least 1 of 9 risk factors regarded as strong indications for SUP *Jadad score: Good (3)*	OME 40 p.o. q.d. or WOS 40 n.g. q.d. (N=35) RTD 50 i.v.b. then 150/d c.i. OR 50 i.v. q8h (N=35)	70 / 67	"Clinically important bleeding"†: **OME p.o./n.g. > RTD c.i./i.b.** (2/32, 6% vs. 11/35, 31%; p=0.013) Regardless of treatment, the risk of clinical important bleeding was related to the number of baseline risk factors for stress ulceration [Calculated ARR = 25%; NNT = 4]	Nosocomial pneumonia: **OME p.o./n.g. = RTD c.i./i.b.** (1, 3% vs. 5, 14%; p>0.05)	Deaths: **OME p.o./n.g. = RTD c.i./i.b.** (11, 34% vs. 12, 34%); related to increased APACHE scores	Of 27 pts who underwent endoscopy, 25 had stress ulcers (11/12 OME, 14/15 RTD) Underwent major surgery: **OME p.o./n.g. > RTD c.i./i.b.** (6/32, 18.8% vs. 13/35, 37.1%; p=NR) Mean IG pH (n=7 OME, 8 RTD): **OME p.o./n.g. = RTD c.i./i.b.** (5.8 vs. 5.2; p>0.05) No. of samples with pH > 4: **OME p.o./n.g. > RTD c.i./i.b.** (results expressed as pH ≤ 4: **OME p.o./n.g.** 10/86, 11.6% vs. **RTD c.i./i.b.** 44/157, 28.0%; p<0.05)
Phillips (1998, abstract)[17] R MC Critically ill pts with ≥2 risk factors and baseline gastric pH ≤ 4 *Jadad score: Poor (1)*	OME susp (SOS) 40 n.g. x 2 on day 1, then 20 q.d. (N=NR) RTD c.i.: 50 i.v.b. + 150–200/24 h (N=13 for 150, N=12 for 200)	— / 58 No. R for SOS: NR	Clinically significant bleeding (not defined in abstract): **SOS > RTD c.i.** (1/33, 3% vs. 4/25, 16%; p < 0.05)	**SOS = RTD c.i.** (18% vs. 16%; p > 0.05)		[Lower rate of] two consecutive IG pH ≤ 3.5 (4 h apart): **SOS > RTD c.i.** (5/33, 15% vs. 13/25, 52%; p<0.05) [Greater change in] gastric pH after starting treatment: **SOS > RTD c.i.** (4.0 ± 1.6 vs. 2.2 ± 1.4; p < 0.05) SAEs: **SOS ~ RTD c.i.** (0/33, 0% vs. 3/25, 12%)

Reference / Design ***Quality of Report***	**Treatment Groups (doses in mg)**	**$N_{R/A}$**	**Results** **> means *statistically superior to*** **= means *not statistically different from (p≥0.05)***			
			Bleeding	**Pneumonia**	**Death**	**Other**
Morris (2002)[18] R OL MC pilot ICU pts, stratified based on the likelihood to receive enteral feeding after remaining NPO for 24 h *Jaded score:* — *(summary of abstract)*	PAN 80 i.v. q8h (n=17) PAN 80 i.v. q12h (n=22) PAN 80 i.v. q24h (n=12) PAN 40 i.v. q12h (n=22) PAN 40 i.v. q24h (n=17) CTD 300 i.v.b. then 50/h c.i. (n=22) x 2 to 7 d	112 / 112	**PAN i.b. ~ CTD b.c.i.** (1/90, 1.1% vs. 0/22, 0%) Bleeding event was secondary to n.g. tube irritation of distal esophagus within the 2-d observational period	**PAN i.b. ~ CTD b.c.i.** (2/90, 3.3% vs. 1/22, 4.5%)	—	IG pH (PEV): Median time to pH≥4 after 1st dose: **Treatment (mg) — h** PAN 80 q8h — 2.5 PAN 80 q12h — 3.4 PAN 80 q24h — 2.0 PAN 40 q12h — 3.2 PAN 40 q24h — 2.0 CTD 300 then 50/h — 2.5 % of time pH≥4 on 1st day **Treatment (mg) — %** PAN 80 q8h — 72 PAN 80 q12h — 69 PAN 80 q24h — 55 PAN 40 q12h — 53 PAN 40 q24h — 42 CTD 300 then 50/h — 77 % of time pH≥4 on 2nd day **Treatment (mg) — %** PAN 80 q8h — 82 PAN 80 q12h — 82 PAN 80 q24h — 62 PAN 40 q12h — 74 PAN 40 q24h — 54 CTD 300 then 50/h — 66 % change between day 1 and 2 **Treatment (mg) — %** PAN 80 q8h — +10 PAN 80 q12h — +13 PAN 80 q24h — +7 PAN 40 q12h — +21 PAN 40 q24h — +12 CTD 300 then 50/h — –11

† Hemodynamic instability resulting from gross bleeding as manifest by hematemesis, aspiration of coffee ground material from the NG tube, or melena; also defined as a decrease in Hg of more than 2 g/dl complicated by either the need for transfusion or hemodynamic instability.

Table 5 What is the optimal dose of PPIs?

Design	Treatment Groups (doses in mg)	$N_{R/A}$	Results > means *statistically superior to* = means *not statistically different from* ≡ means *equivalent to* Re-bleeding	Surgery	Death	Other
All patients received EGD tx						
Schönekas (1999, abstract)[23] R OL pilot PUB, active bleeding or NBVV, Forrest Ia, Ib, or IIa EGD tx PP *Jadad score: — (abstract)*	Low-dose PAN 40 i.v. q.d. (N=82) High-dose PAN 40 i.v. then 8/h b.c.i. (N=86) x 72 h All pts received EGD tx)	168 / 150	**Low-dose PAN i.b. = High-dose PAN b.c.i.** (9/74, 12% vs. 10/76, 13% at 72 h)	**Low-dose PAN i.b. ~ High-dose PAN b.c.i.**	**Low-dose PAN i.b. ~ High-dose PAN b.c.i.** (2/78, 2.5% vs. 2/80, 2.4% at 14 d)	*Blood transfusion*: **Low-dose PAN i.b. ~ High-dose PAN b.c.i.**
Some patients received EGD tx						
Udd (2001)[24] R DB 2-ctr Forrest Ia to IIc PUB PP, one-sided equivalence test *Jadad score: Good (4)*	102 (71.8%) pts underwent EGD tx as decided by endoscopist (50/73, 68.5% of regular-dose gp and 52/69, 75.4% of high-dose gp) Regular-dose OME 20 i.v. q.d. x 3 d (60 over 72 h) (N=73) High-dose OME 80 + 8/h i.v. x 3 d (652 over 72 h) (N=69)	168 /142	Overall: **Regular-dose OME ≡ High-dose OME** (6/73, 8.2% vs. 8/69, 11.6%; p=0.58) Difference in proportions: –3.4% (95% exact CI: -20.6% to 9.7%) Exact upper 90% CL for one-sided equivalence: 7.8% (within ± 15% TL); p=0.002 for equivalence NBVV: **Regular-dose OME ≡ High-dose OME** Difference in proportions: -2.9% (95% exact CI –20.8% to 10.0%) Exact upper 90% CL for one-sided equivalence: 8.1% (within ± 15% TL); p=0.003 for equivalence	**Regular-dose OME ~ High-dose OME** (3/73, 4.1% vs. 5/69, 7.2%; p=0.49) Difference in proportions: -3.1% (95% exact CI: -19.4% to 8.3%)	**Regular-dose OME ~ High-dose OME** (4/73, 5.5% vs. 2/69, 2.9%; p=0.68) Difference in proportions: 2.6% (95% exact CI: -7.9% to 17.7%) Cause of death (Regular-dose vs. High-dose OME): Rebleed 1 vs. 1 Post-op 0 vs. 1 Other 3 vs. 0	

Table 6 Is there clinical evidence for the target pH values in NVAUGIB?

Reference / Design *Quality of Report*	Treatment Groups (doses in mg)	$N_{R/A}$	Results > means *statistically superior to* = means *not statistically different from* Re-bleeding	Surgery	Death	Other
All patients underwent initial EGD therapy						
Tseng (1999)[25] R OL PUB (spurting, oozing, and NBVV: N=6, 4, and 10, respectively) Taiwan *Jadad score: Good (3)*	All pts underwent EGD tx OME 20 i.v.b. q3h (N=20) OME 40 i.v.b. q6h (N+20) OME 80 i.v.b. q12h (N=20)	60 / 60	OME**20 = OME40 = OME80 (4/20, 4/20, 5/20)**	OME**20 = OME40 = OME80 (1/20 in each group)**	OME**20 = OME40 = OME80 (0/20, 1/20, 0/20)**	IG pH: **OME40 > OME20 and OME80 (p<0.0001)** **OME / Mean / 95% CL** **20 / 6.1 / 6.0, 6.2** **40 / 6.4 / 6.2, 6.5** **80 / 5.8 / 5.7, 5.9** Duration of IG pH>6.0 (%): **OME20 ~ OME40 ~ OME80** **OME / Mean / 95% CL** **20** / 70.9 / 57.3, 84.4 **40** / 83.1 / 73.1, 93.1 **80** / 66 / 51.5, 80.4 Volume of blood transfusion (ml): OME**20 = OME40 = OME80 (500, 1000, 500)**
Lin (1998)[8] R OL UGIB: 21 (21%) spurting; 13 (13%) oozing; 66 (66%) NBVV (information solicited by different authors) *Jadad score: Good (3)*	OME 40 i.v.b. + 6.7/h x 72 h + 20 p.o. q.d. x 2 mo (N=50) CTD 300 i.v.b. + 300 i.v.b. q6h x 72 h + 400 p.o. b.i.d. x 2 mo (N=50) (after HPT or MPEC EGD tx)	100 / 100	Overall: **OME b.c.i. > CTD b.c.i.** at day 3 (0/50, 0% vs. 8/50, 16%; p=0.003) and day 14 (2/50, 4% vs. 12/50, 24%; p=0.004) Spurting or oozing: **OME b.c.i. = CTD b.c.i.** for both types of active bleeding (0/9, 0% vs. 2/12, 17% and 1/4, 25% vs. 1/9, 11%, respectively) NBVV: **OME b.c.i. > CTD b.c.i.** (21/37, 3% vs. 9/29, 31%; p<0.05)	**OME b.c.i. = CTD b.c.i.** (0/50, 0% vs. 0/50, 0%)	**OME b.c.i. = CTD b.c.i.** (0/50, 0% vs. 2/50, 4%; p>0.05) Deaths in CTD group: (1) cholangiocarcinoma with metastasis; died of bleeding after second administration of MPEC + OME; (2) Renal cell carcinoma with metastasis; died of sepsis after receiving EGD tx 3 times.	Median volume of blood transfused: **OME b.c.i. = CTD b.c.i.** (0, range: 0–2500, vs. 0, range: 0–5000; p=0.05) Days in hospital: **OME b.c.i. = CTD b.c.i.** (7 vs. 6 days; p>0.05) Mean IG pH from 1 to 24 h after start of infusion: OME b.c.i. vs. CTD b.c.i., 6.0 vs. 4.0 to 5.5 % of time pH>6: **OME b.c.i. > CTD b.c.i.** (84.4% vs. 53.5%; p<0.001)

Reference / Design *Quality of Report*	Treatment Groups (doses in mg)	$N_{R/A}$	Results > means *statistically superior to* = means *not statistically different from* Re-bleeding	Surgery	Death	Other
Some patients underwent initial EGD therapy						
Labenz (1997)[28] R OL Two parallel studies (DU and GU) Forrest **I** and **II** *Jadad score: Good (3)*	Forrest **I** and **IIa** underwent EGD tx with Epi + FTG (N=8 with active bleeding; N=16 with NBVV) OME 80 i.v.b. + 8/h (N=10 per study; 20 total) RTD 50 i.v.b. + 0.25/kg/h (N=10 per study; 20 total) x 24 h	40 (20 per study)	Clinical rebleeding: **OME b.c.i. ~ RTD b.c.i.** (0 in both groups) EGD rebleeding: **OME b.c.i. ~ RTD b.c.i.** (2/20, 10% vs. 3/20, 15%).	1 pt with GU (tx group not stated)	1 pt with DU died of massive rebleeding on day 2 (tx group not stated)	Median time to reach pH>6: **OME b.c.i. = RTD b.c.i.** (36 vs. 60 min.; p=0.42) Mean **I**G pH during 2nd to 12th hour: **OME b.c.i. = RTD b.c.i.** DU: pH 6.61 vs. 6.52; 95% CL 5.96, 6.79 vs. 5.75, 6.86; P-value 0.80 GU: pH 6.72 vs. 6.68; 95% CL 6.10, 7.09 vs. 5.28, 7.13; P-value 0.68 Mean **I**G pH during 13th to 24th hour: **OME b.c.i. ≥ RTD b.c.i.** (see text table, page 7) *Median* **I**G pH values during the first and second halves of the study period: not statistically significant. DU. Holding time (%) for hemostatic pH thresholds: **OME b.c.i. > RTD b.c.i. from 13 to 24 h** (see text table, page 7)**.** GU. Holding time (%) for hemostatic pH thresholds: **OME b.c.i. > RTD b.c.i. from 13 to 24 h (**see text table, page 7)**.** The only independent variable related to the pH response (% of time pH>6 during the second half of treatment) was the type of antisecretory drug given (OME vs. RTD; p<0.0001, multiple regression analysis).

Reference / Design *Quality of Report*	Treatment Groups (doses in mg)	$N_{R/A}$	Results > means *statistically superior to* = means *not statistically different from* Re-bleeding	Surgery	Death	Other
Lin (1997)[26] R OL, preliminary PUB with NBVV *Jadad score: Poor (2)*	OME 40 i.v.b. + 40 i.v.b. q.d. (N=13) OME 40 iv.b. + 40 i.v.b. q12h (N=13) CTD 300 i.v.b. + 300 i.v.b. q6h (N=13) HPT + CTD in doses given above (N=13) x 2 d CTD 400 b.i.d. after discharge EGD tx given only in HPT + CTD group	52 / —	**OME q.d. = OME q12h = CTD = HPT + CTD** (2, 2, 5, 2)			Volume of blood transfusion: **OME q.d. = OME q12h = CTD = HPT + CTD** (ml, mean: 230, 923, 596, and 519) Hospital stay: **OME q.d. = OME q12h = CTD = HPT + CTD** (d, mean: 4.3, 4.6, 5.5, 4.7. Mean 24-h IG pH: **OME q.d. and OME q12h > CTD and HPT + CTD** (mean: 5.8, 6.4, 4.3, and 4.9; p<0.05) % of time IG pH > 6.0: **OME q.d. and OME q12h > CTD and HPT + CTD** (mean: 70.9%, 87.1%, 39.2%, and 39.4%; p<0.05)
No patient underwent initial EGD therapy						
Lanas (1995)[27] R, OL PUB with EGD predictors of rebleeding *Jadad score: Poor (2)*	OME 80 i.v.b. + 40 i.v.b. q12h RTD 50 i.v.b. q4h No EGD tx at time of diagnosis, but EGD tx given for rebleeding (0 OME vs. 1 RTD)	51 / 51 20 under-went pH monitoring (10 OME, 10 RTD)	**OME i.v.b. = RTD i.v.b.** (6/28, 21.4% vs. 9/23, 39.1%; p=0.1)	**OME i.v.b. = RTD i.v.b.** (1/28, 3.8% vs. 5/23, 22.7%; p=0.05)	**OME i.v.b. = RTD i.v.b.** (2/28, 7.1% vs. 2/23, 8.7%) Deaths occurred only in old patients (80.5 yr) with multiple concomitant severe diseases 1 death related to PUB	Blood transfusion units, length of hospitalization, lowest Hct: **OME i.v.b. = RTD i.v.b.** % of time pH < 6: **OME i.v.b. > RTD i.v.b.** (15.3% vs. 61.8%, p < 0.0001). Subgroup analyses: rebleeding and need for surgery were reduced in the same subgroup

Table 7 Are there treatment differences between oral and parenteral PPIs for NVAUGIB or SUP?

Reference / Design ***Quality of Report***	**Treatment Groups** **(doses in mg)**	**$N_{R/A}$**	**Results** **> means *statistically superior to (p < 0.05)*** **= means *not statistically different from (p ≥ 0.05)*** **~ means *similar to***
NVAUGIB or SUP			
No studies found			
Healthy volunteers			
Hartmann (1998)[35] R OL CO SC Healthy volunteers, 2- to 3-wk washout, PP *Jadad score: Poor (2)*	PAN 40 mg i.v. q.d. PAN 40 mg p.o. q.d. x 5 d	21 / 20	*Mean % time pH ≥ 4 (PEV for "equivalence" analysis)*: **PAN i.v. ≡ p.o.** 42% vs. 38% Mean difference: 4.4 (90% CI: 0.6 to 8.3) *Median 24-h pH:* **PAN i.v. ≡ p.o.** 3.3 vs. 3.1 Mean difference: 0.2 (90% CI: -0.03 to 0.44)
Freston (2001)[32] R OL CO SC Healthy volunteers (7 *Helicobacter pylori*-positive), 2-wk washout PP *Jadad score: Poor (2)*	LAN 30 n.g. q.a.m. (in apple juice) PAN 40 i.v. q.a.m. x 5 d	36 / 33	Mean 24-h intragastric pH: **LAN n.g. > PAN i.v.** Day 1: 3.05 vs. 2.76 (p<0002) Day 5: 3.65 vs. 3.45 (p<0.024) Mean % of time pH > 3, 4, 5, or 6 Day 1: **LAN n.g. > PAN i.v. for pH > 3 to 5** (p < 0.001) **LAN n.g. = PAN i.v. for pH > 6** Day 5: **LAN n.g. > PAN i.v. for pH > 3** (p < 0.05) **LAN n.g. = PAN i.v. for pH > 4, 5, or 6** pH: 3 / 4 / 5 / 6 Day 1: LAN n.g. 37% / 27% / 15% / ~7% PAN i.v. 28% / 19% / 10% / ~5% Day 5: LAN n.g. 54% / ~40% / ~20% / ~10% PAN i.v. 49% / ~38% / ~19% / ~10% Mean Cp-time profiles: **LAN n.g. ~ PAN i.v.** on days 1 and 5 Rate of adverse events: **LAN n.g. ~ PAN i.v.** 23% vs. 21% (no SAEs)
Taubel (2001)[33] R OL CO SC Ph. I, Healthy volunteers, 2-wk washout, PP *Jadad score: Poor (2)*	SLS 30 n.g. q.d. PAN 80 i.v. q.d. x 5 d	36 (E, R) 34 (C, A)	***Mean 24-h IG pH (PEV)*:** **SLS n.g. > PAN i.v.** Day 1: 3.13 vs. 2.67 Day 5: 3.95 vs. 3.61 p<0.001 for both analyses ***Point estimates for AUC_{24}*:** increased by 7% for SLS and decreased by 3.5% for PAN between Days 1 and 5. No tx comparisons.

Table Abbreviations:

AA = Antacid; b.c.i. = Bolus plus continuous infusion (intravenous); c.i. = Continuous infusion (intravenous); CI = Confidence interval; CL = Confidence limit; CTD = Cimetidine; DB = Double-blind; Epi = Epinephrine; FTG = Fibrin tissue glue; HPT = Heater probe thermocoagulation; H_2RA = Histamine$_2$-receptor antagonist; i.b. = Intermittent bolus (intravenous); ID = Insufficient data; IG = Intragastric; i.v.b. = Intravenous bolus; ITT = Intent-to-treat; MPEC = Multipolar electrocoagulation; NBVV = Non-bleeding visible vessel; $N_{R/A}$ refers to number of patients randomized / analyzed; NSD = No (statistically) significant difference; NVAUGIB = Nonvariceal acute upper gastrointestinal bleeding; OL = Open-label; OME = Omeprazole; PAN = Pantoprazole; PBO = Placebo; PIR = Pirenzepine; PP = Per protocol; PUB = Peptic ulcer bleeding; R = Randomized; RTD = Ranitidine; SC = Single-center; SAEs = Serious adverse events; SLS = Simplified Lansoprazole Solution; SOS = Simplified Omeprazole Solution; SUC = Sucralfate; SUP = Stress ulcer prophylaxis; TL = Tolerance limit

Forrest Classification of upper gastrointestinal bleeding: Ia = Arterial spurting hemorrhage; Ib = Oozing hemorrhage; IIa = Non-bleeding visible vessel (NBVV); IIb = Lesion with sentinel clot; IIc = Lesion covered with hematin; III = No stigmata of hemorrhage

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