

## EDITORIALS

### Management of Ulcers With Adherent Clots

See article on page 407.

Peptic ulcers are still the most common cause of hospitalization for upper gastrointestinal (GI) bleeding in the United States, accounting for approximately 140,000 hospitalizations annually and representing almost 45% of admissions for upper GI hemorrhage.<sup>1</sup> At presentation, independent predictors of outcome in patients with upper GI bleeding are hemodynamic instability, concurrent illness, and age.<sup>2</sup> The appearance of an ulcer at endoscopy, however, provides important additional prognostic information. Data from older studies in which patients received no endoscopic therapy indicate that surgery for further bleeding was required in 0.5% of patients with clean-based ulcers, 6% of those with flat pigmented spots, 10% of those with clots in the ulcer base, 34% of those with nonbleeding visible vessels, and 35% of those with active bleeding.<sup>3</sup>

The endoscopic features of an ulcer are therefore key in assessing risk and guiding subsequent management in patients who present with ulcer bleeding. Patients with clean-based ulcers who are stabilized, have no other important medical problems, and have adequate home support may be discharged after their endoscopic examination, thereby decreasing costs.<sup>4-6</sup> On the other hand, patients with actively bleeding ulcers or ulcers with nonbleeding visible vessels clearly benefit from endoscopic therapy, with (1) decreased rates of further bleeding, surgery, and death; (2) shorter hospital stays; (3) less blood transfused; and (4) lower costs.<sup>7-9</sup>

#### Variability in Studies of Ulcers With Nonbleeding Clots

The role of endoscopic therapy in patients with nonbleeding clots in an ulcer base has been controversial. Reported prevalences of clots in patients with bleeding ulcers are widely variable, ranging from 0 to 50%,<sup>3</sup> whereas rebleeding rates also vary markedly, from 8% to 36%.<sup>3,10-12</sup> To determine the appropriate management for patients with adherent clots, we first must try to understand the marked variability between studies of clots.

One possible explanation is that different endoscopists have different definitions of a clot. We and others have shown that there is relatively poor agreement among endoscopists (even among international experts) when labeling stigmata of hemorrhage such as clots or visible vessels.<sup>13,14</sup> This agreement can be improved somewhat by teaching sessions,<sup>13</sup> and the trial from Jensen et al. in this issue of *GASTROENTEROLOGY*<sup>11</sup> did attempt to improve uniformity of diagnosis with a pre-study meeting of investigators.

Another important potential confounding factor is the degree of vigor with which clots are irrigated. Some studies perform little or no irrigation, whereas others wash the ulcer base vigorously with water pumps. Minimal or gentle irrigation with a syringe may fail to expose the underlying stigmata, and more vigorous irrigation will allow separation into categories of low-risk and high-risk stigmata. Presumably, most cases of rebleeding in patients with clots occur because of the presence of higher-risk stigmata beneath the clot.

We prospectively studied this hypothesis, irrigating ulcers with clots in 46 patients using the 3.2-mm bipolar probe for up to 5 minutes.<sup>13</sup> We found that the clot remained adherent in 57% of patients, and the rebleeding rate without endoscopic therapy was only 8% in this group (endoscopic therapy at the time of rebleeding successfully prevented further bleeding in these patients). The clot was washed away in the remaining patients, exposing low-risk stigmata in 13%, and high-risk stigmata necessitating endoscopic therapy in 30%.

Another prospective study of irrigation and subsequent rebleeding in patients with adherent clots was performed in Taiwan.<sup>15</sup> Irrigation using a syringe removed clots in only 9% of 165 patients, whereas just 10 seconds of WaterPik (Teledyne, Fort Collins, CO) irrigation removed clots in another 26% of the remaining patients. Fifteen percent of 101 patients with adherent clots rebled within the next 3 days. Shock, initial hemoglobin  $\leq 10$  g/dL, and comorbid illness were the independent predictors of rebleeding.

Based on the above results, we have recommended that vigorous irrigation for up to several minutes be used in an attempt to determine if high-risk stigmata lurk beneath the clot, and that patients whose clots remain

adherent despite vigorous irrigation do not require endoscopic therapy.

### **Prior Studies of Endoscopic Therapy for Adherent Clots**

Published randomized controlled trials of endoscopic therapy vs. no endoscopic therapy have reported their results on the subgroup of patients with clots,<sup>16-19</sup> and none documented a benefit with endoscopic therapy. However, these studies were not designed specifically to look at patients with clots; they included patients with a variety of stigmata and provided subgroup analysis of patients with clots at the conclusion of the study. Also, the number of patients with nonbleeding clots in each study was generally small (5-28 patients per study). Meta-analysis, however, noted that endoscopic therapy provided significant benefit only in patients with active bleeding or nonbleeding visible vessels, whereas rebleeding was not reduced in patients with ulcers containing flat spots or adherent clots.<sup>7</sup>

Two randomized trials of endoscopic therapy in patients with clots were published in abstract form, in 1993 and 1997, but have not subsequently been published as full manuscripts. The first abstract, by Jensen et al., found no significant benefit of endoscopic therapy (epinephrine and alcohol in 6, heater probe in 7) compared with medical therapy (N = 7): 46% rebled in the endoscopic group vs. 29% in the medical arm.<sup>20</sup> The second abstract, a study of 56 patients at 7 centers, did find a significant benefit with endoscopic therapy (epinephrine plus heater probe) compared with medical therapy: rebleeding rates were 5% and 34%.<sup>12</sup>

### **Current Study of Endoscopic Therapy for Adherent Clots**

The article by Jensen et al. in this issue of *GASTROENTEROLOGY* is the first published randomized trial designed to evaluate endoscopic therapy in patients with clots.<sup>11</sup> Jensen et al. are to be congratulated on their examination of a difficult issue of interest and importance to endoscopists. However, any new study should be carefully evaluated in a systematic fashion before its conclusions are accepted and a new therapy is applied to patients. Several aspects of this trial limit our ability to conclude that endoscopic therapy is indicated in the treatment of patients with adherent clots, and the authors themselves are appropriately circumspect in their Discussion.

### **Unequal distribution of confounding factors.**

Even when studies have appropriate randomization, it is important to determine whether randomization worked (i.e., were potentially confounding patient characteristics equally distributed in the 2 study groups?). Unequal distribution of an important clinical feature will favor one treatment over the other. A marked imbalance was present between the medical and endoscopic arms in the number of patients who developed bleeding while already hospitalized for another medical problem (53% vs. 20%). Concurrent illness and bleeding when already hospitalized are well documented to be extremely important predictors of poor outcome, as reconfirmed by Jensen et al. Thus, this unequal distribution led to a bias in favor of endoscopic therapy.

**“Outlier” results.** When results of a therapy are much better or worse than typically reported, we need to be cautious in our interpretation. The results of endoscopic therapy in this study are better than generally expected: a 0% rebleeding rate. This is especially important in a study of small sample size. If only one of the patients treated endoscopically had rebled (a 7% rebleeding rate) instead of zero, the difference in rebleeding between endoscopic and medical therapies would not have been significant.

**Endpoints.** The primary endpoint of this and most endoscopic studies is rebleeding. Nevertheless, rebleeding is a somewhat subjective outcome, an especially important issue when investigators are unblinded and sample sizes are small. Although the aim of endoscopic therapy is to prevent further bleeding, our major goal in practice is to improve clinically meaningful outcomes such as transfusions, length of hospitalization, repeat endoscopy, surgery, and death. When a new therapy fails to demonstrate a benefit in any of these important clinical outcomes, we must be cautious in embracing it. Only larger trials allow us to determine if the lack of differences is “real” or caused by inadequate sample size.

**Small sample size and premature discontinuation of a study.** When studies are planned, the sample size is determined based on assumptions about outcomes of the primary endpoint (rebleeding in this case) in the treatment and control groups, with the goal of demonstrating a *P* value <0.05 on comparison of the 2 study arms. This assumes a single comparison when the planned number of patients is enrolled. Still, a “significant” difference will be seen by chance 1 out of 20 times. If comparisons are done repeatedly, even a greater chance of finding a “significant” difference by chance exists, and

so adjustments need to be made in the *P* value that is considered significant at the end of the study.

In some studies, interim analyses are done before the planned number of patients is enrolled. This may be especially important when there is strong potential for harm from a treatment or lack of treatment, or the baseline assumptions regarding outcome were uncertain. The *P* values for stopping the study at the interim analyses are determined before the start of the study. In addition, the *P* value used at the end of the study is lower than the standard 0.05. A variety of interim analysis strategies have been suggested, but the method of O'Brien and Fleming, cited by Jensen et al., is among the most frequently used. In this case, the *P* value for significance used at the interim analysis is small (e.g., 0.005) and the *P* value used at the end of the study is slightly less than the standard 0.05 (e.g., 0.047).<sup>21</sup> When 2 interim analyses are planned during a trial, *P* values for study termination are prespecified for both the first (e.g., 0.0006) and second (e.g., 0.015) interim analysis.<sup>21</sup> Use of such small *P* values at the interim analyses avoids stopping a study when the results provide only borderline support for the new therapy; the study will only be terminated at a smaller-than-planned sample size if the difference is clear-cut and convincing (e.g., *P* = 0.005) at the interim analysis.

The current study was stopped early at a smaller-than-planned sample size, after an interim analysis was performed with rebleeding rates of 4 of 15 patients in the medical group and 0 of 16 in the endoscopic therapy group. The *P* value for this comparison is 0.043 (by the Fisher exact test), much larger than *P* values such as 0.005 that typically would have been used to stop the study at the interim analysis, and larger than the early termination *P* value of 0.02 chosen by Jensen et al. A subsequent statistical comparison was then performed after 2 more patients were enrolled, without any adjustment of the significance level for this additional unplanned comparison. Therefore, confidence that the 2 treatments are truly different is limited. As mentioned, if only 1 patient in the endoscopic therapy arm had rebled, the difference between treatments would not have been significant.

### **Practical Issues of Endoscopic Therapy in Patients With Clots**

Some may ask why debate the issue? Why not just treat everyone who has a clot with endoscopic therapy, even without clear-cut demonstration of benefit? First, use of endoscopic therapy substantially increases the

professional fee and facility fee, so an unnecessary increase in cost may occur. Second, application of endoscopic therapy commonly induces bleeding in nonbleeding lesions. This induced bleeding usually can be controlled with further endoscopic therapy, but uncommonly it requires other intervention such as surgery. Finally, perforation rarely may occur with endoscopic treatment of ulcers.

When endoscopic treatment of adherent clots is performed, the proper technique is uncertain. The authors were successful with guillotining the clot off after epinephrine injection. However, some have expressed concern about induction of bleeding when the clot is shaved down, and no study has compared the safety and efficacy of guillotining vs. other techniques, such as burrowing in beneath the clot with a thermal probe. Furthermore, although epinephrine injection before manipulation with a thermal probe is intuitively attractive, documentation that this combined therapy is better than monotherapy with a thermal probe alone is lacking.

### **Proton Pump Inhibitor Therapy**

Standard practice frequently changes between the time a study is initiated and the time it is completed, and the use of proton pump inhibitor (PPI) therapy in patients with adherent clots also must now be considered. The proposed mechanism of benefit with PPI therapy is to promote clot formation and stability by sustaining intragastric pH at 6–7.

A double-blind, placebo-controlled trial documented that twice daily oral omeprazole (40 mg) significantly decreased rebleeding (0 vs. 21%) and surgery (0 vs. 10%) in 125 patients with adherent clots who did not receive endoscopic therapy.<sup>22</sup> A subsequent double-blind study of oral omeprazole after endoscopic therapy from the same investigators revealed a significant benefit with PPI therapy in rebleeding (0% vs. 13%; *P* = 0.049) but not surgery (0% in each arm) in 62 patients with clots.<sup>23</sup> These studies were performed in Kashmir, India, where twice daily oral PPI therapy reportedly sustained intragastric pH >6.8 throughout a 24-hour period.<sup>22</sup> In contrast, patients in the United States and Europe do not have a sustained pH >6 with oral PPIs; even high-dose PPI therapy given 3 times a day leads to an intragastric pH below 6 for a majority of the day.<sup>24</sup> This may explain why most prior studies of intermittent antisecretory therapy failed to document benefit in patients with upper GI bleeding.

However, several studies have recently documented that constant intravenous infusion of high-dose omepra-

zole, which does maintain intragastric pH >6 for much of a 24-hour period, decreases further bleeding in high-risk patients.<sup>25–28</sup> Constant PPI infusion is clearly beneficial in patients with active bleeding and nonbleeding visible vessels,<sup>28</sup> but information documenting benefit specifically in the patients with clots has not been presented. Whether constant infusion of a PPI should be used, alone or together with endoscopic therapy, in patients with adherent clots is uncertain based on available literature. The study of Khuroo et al.<sup>22</sup> suggests that PPI therapy alone may achieve rebleeding rates as low as endoscopic therapy or combined therapy.

## Conclusions

Patients who present with upper GI bleeding and are found to have a nonbleeding adherent clot in an ulcer at endoscopy have widely variable rates of rebleeding. Studies from tertiary care centers, where patients have numerous other comorbidities and may have developed bleeding while already hospitalized for another medical problem, seem to have higher rates of rebleeding. In contrast, studies from nonreferral centers, in which patients are younger, have fewer concurrent illnesses, and are admitted for upper GI bleeding, have much lower rates of rebleeding. Vigorous irrigation also may expose underlying high-risk stigmata in perhaps a third of patients with clots, resulting in low rebleeding rates in the remaining patients whose clots were resistant to washing.

Trials in patients with active bleeding and nonbleeding visible vessels clearly document that endoscopic therapy benefits patients at high-risk for rebleeding. Therefore, in hospitals where the rate of rebleeding with adherent clots even after vigorous irrigation is high, endoscopic therapy seems likely to decrease rebleeding rates and can be used. In contrast, in centers such as mine, in which rates of rebleeding with adherent clots are low, no significant benefit will be gained with the use of endoscopic therapy.

Constant intravenous infusion of a PPI (80 mg bolus followed by 8 mg/h infusion for omeprazole or pantoprazole) also may be reasonable in patients with adherent clots at high-risk for recurrent bleeding. However, the expense of both endoscopic treatment and PPIs might not be justified in patients with clots because either therapy alone has been reported to decrease rebleeding rates toward zero in this population.

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## References

1. Agency for Healthcare Research and Quality. HCUP Nationwide Inpatient Sample. Rockville, MD, 1997.
2. Rockall TA, Logan RF, Devlin HB, Northfield TC. Risk assessment after acute upper gastrointestinal haemorrhage. *Gut* 1996;38:316–321.
3. Laine L, Peterson WL. Bleeding peptic ulcer. *N Engl J Med* 1994;331:717.
4. Lai KC, Hui WM, Wong BCY, Ching CK, Lam SK. A retrospective and prospective study on the safety of discharging selected patients with duodenal ulcer bleeding on the same day as endoscopy. *Gastrointest Endosc* 1997;45:26–30.
5. Cipolletta L, Bianco MA, Rotondano G, Marmo R, Piscopo R. Outpatient management for low-risk nonvariceal upper GI bleeding: a randomized controlled trial. *Gastrointest Endosc* 2002;55:1–5.
6. Lee JG, Turnipseed S, Romano PS, Vigil H, Azari R, Melnikoff N, Hsu R, Dirk D, Sokolove P, Leung JW. Endoscopy-based triage significantly reduces hospitalization rates and costs of treating upper GI bleeding: a randomized controlled trial. *Gastrointest Endosc* 1999;50:755–761.
7. Cook DJ, Salena B, Guyatt GH, Laine L. Endoscopic therapy for acute non-variceal upper gastrointestinal hemorrhage: a meta-analysis. *Gastroenterology* 1992;102:139–148.
8. Laine L. Multipolar electrocoagulation in the treatment of active upper gastrointestinal tract hemorrhage: a prospective controlled trial. *N Engl J Med* 1987;326:1613–1617.
9. Laine L. Multipolar electrocoagulation in the treatment of peptic ulcers with non-bleeding visible vessels: A prospective, controlled trial. *Ann Intern Med* 1989;110:510–514.
10. Laine L, Stein C, Sharma V. A prospective outcome of patients with clot in an ulcer and the effect of irrigation. *Gastrointest Endosc* 1996;43:107–110.
11. Jensen DM, Kovacs TOG, Jutabha R, Machicado GA, Gralnek I, Savides TJ, Smith J, Jensen ME, Alofaituli G, Gornbein J. Randomized, trial of medical or endoscopic therapy to prevent recurrent ulcer hemorrhage in patients with adherent clots. *Gastroenterology* 2002;123:407–413.
12. Bleau BL, Gostout CJ, Shaw MJ, Keate SRF, Harford WV, Bracy W Jr, Magee DE, Fleischer DE. Final results: rebleeding from peptic ulcers associated with adherent clots: a prospective randomized controlled study comparing endoscopic therapy with medical therapy (abstr). *Gastrointest Endosc* 1997;45:AB87.
13. Laine L, Freeman M, Cohen H. Lack of uniformity in diagnosis of endoscopic prognostic features of bleeding ulcers. *Gastrointest Endosc* 1994;40:411–417.
14. Lau JYW, Sung JY, Chan ACW, Lai GWY, Lau JTF, Ng EKW, Chung SCS, Li AKC. Stigmata of hemorrhage in bleeding peptic ulcers: an interobserver agreement study among international experts. *Gastrointest Endosc* 1997;46:33–36.
15. Lin HJ, Wang K, Perng CL, Lee FY, Lee CH, Lee SD. Natural history of bleeding peptic ulcers with a tightly adherent blood clot: a prospective observation. *Gastrointest Endosc* 1996;43:470–473.
16. Swain CP, Bown SG, Storey DW, Kirkham JS, Northfield TC, Salmon PR. Controlled trial of argon laser photocoagulation in bleeding peptic ulcers. *Lancet* 1981;2:1313–1316.
17. Swain CP, Kirkham JS, Salmon PR, Bown SG, Northfield TC. Controlled trial of Nd-YAG laser photocoagulation in bleeding peptic ulcers. *Lancet* 1986;1:1113–1117.
18. Balanzo J, Azinz S, Such J, Espinos JC, Guarner C, Cusso X, Mones J, Vilardell F. Endoscopic hemostasis by local injection of

- epinephrine and polidocanol in bleeding ulcer: a prospective randomized trial. *Endoscopy* 1988;20:289–291.
19. Matthewson K, Swain CP, Bland M, Kirkham JS, Bown SG, Northfield TC. Randomized comparison of Nd YAG laser, heater probe, and no endoscopic therapy for bleeding peptic ulcers. *Gastroenterology* 1990;98:1239–1244.
  20. Jensen DM, Kovacs TOG, Randall GM, Machicado GA, Sue M, Freeman M, Jensen ME, You S, Pelayo E. Initial results of a randomized controlled study of non-bleeding adherent clots in patients with severe ulcer hemorrhage (abstr). *Gastrointest Endosc* 1993;39:279.
  21. Skovlund E. Interim analyses of survival data in cancer clinical trials. *Acta Oncologica* 1998;37:645–650.
  22. Khuroo MS, Yattoo GN, Javid G, Khan BA, Shah AA, Gulzar GM, Sodi JS. A comparison of omeprazole and placebo for bleeding peptic ulcer. *N Engl J Med* 1997;336:1054–1058.
  23. Javid G, Masoodi I, Zargar SA, Khan B, Yattoo GN, Shah AH, Gulzar GM, Sodhi JS. Omeprazole as adjuvant therapy to endoscopic combination injection sclerotherapy for treating bleeding peptic ulcer. *Am J Med* 2001;111:280–284.
  24. Blum RA, Hung RH, Kidd SL, Shi H, Jennings DE, Greski-Rose PA. Dose-response relationship of lansoprazole to gastric acid antisecretory effects. *Aliment Pharmacol Ther* 1998;12:321–327.
  25. Schaffalitzky de Muckadell OB, Havelund T, Harling H, Boesby S, Snel P, Vreeburg EM, Eriksson S, Fernstrom P, Hasselgren G. Effect of omeprazole on the outcome of endoscopically treated bleeding peptic ulcers: randomized double-blind placebo-controlled multicentre study. *Scand J Gastroenterol* 1997;32:320–327.
  26. Hasselgren G, Lind T, Lundell L, Aadland E, Efskind P, Falk A, Hyltander A, Soderlund C, Eriksson S, Fernstrom P. Continuous intravenous infusion of omeprazole in elderly patients with peptic ulcer bleeding. *Scand J Gastroenterol* 1997;32:328–333.
  27. Lin HJ, Lo WC, Lee FY, Perng CL, Tseng GY. A prospective randomized comparative trial showing that omeprazole prevents rebleeding in patients with bleeding peptic ulcer after successful endoscopic therapy. *Arch Intern Med* 1998;158:54–58.
  28. Lau JYW, Sung JY, Lee KKC, Yung MY, Wong SKH, Wu JCY, Chan FKL, Ng EKW, You JHS, Lee CW, Chan ACW, Chung SCS. Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. *N Engl J Med* 2000;343:310–316.

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## Is There a “Barrett’s Iceberg?”

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Barrett’s esophagus (BE), a metaplastic change of the lining of the esophagus with replacement of the normal squamous epithelium by intestinalized columnar epithelium, is associated with an increased risk of adenocarcinoma of the esophagus.<sup>1,2</sup> Because of the association with cancer, clinicians use the presence of BE to stratify cancer risk among those with chronic reflux disease.<sup>3</sup> Those patients who possess BE are believed to be at increased risk of cancer, and are usually offered entry into endoscopic surveillance programs to monitor them for the development of adenocarcinoma.<sup>4</sup>

### Metaplasia-Dysplasia-Carcinoma Sequence

The rationale of surveillance programs in BE depends on a conceptual pathogenic sequence of the development of esophageal cancer,<sup>5</sup> as follows: chronic gastroesophageal reflux disease (GERD) leads to both the symptoms of heartburn, as well damage to the squamous mucosa. Acid and other ill-defined host-specific factors

combine to cause the regeneration of specialized columnar, as opposed to squamous, epithelium, in the damaged areas. In a small number of subjects, still other factors cause progression of the metaplastic columnar cells through stages of dysplasia and on to cancer. Intervention in the late stages of dysplasia or in early carcinoma leads to improved survival.

Although all of these suppositions seem reasonable, there are large gaps in our knowledge. We note the association of BE and adenocarcinoma, but have little proof of causality. We hope that surveillance endoscopy allows for detection of earlier and more curable neoplasia, but data supporting this contention are lacking.

The success of endoscopic screening and surveillance programs for BE depends on our ability to locate those with BE before the development of incurable cancer. Currently, it appears that we are doing a poor job of this, as the majority of those developing esophageal adenocarcinoma are not known to have BE before the development of cancer.<sup>6,7</sup> If we assume that cancer arises from Barrett’s, the poor rate of detection of BE before cancer may be caused by 1 of 2 reasons: either endoscopic screening/surveillance programs are insufficiently popu-