The continuing story of peptic ulcer bleeding
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Citation for published version (APA):
Chapter 3

Management in peptic ulcer bleeding;
A Dutch national inquiry

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Endoscopy 2000; 32 (12): 935-942
Abstract

**Background and study aim:** There is no consensus which endoscopic hemostatic therapy and pharmacotherapy should be used in peptic ulcer bleeding. We conducted a mail survey to investigate current management of ulcer bleeding in the Netherlands.

**Methods:** A questionnaire was sent to gastroenterologists or, if not present, to internists, performing endoscopies, in every hospital in the Netherlands (N=123). Endoscopic hemostatic therapy, pharmacotherapy, endoscopic re-intervention and management of Helicobacter pylori infection were evaluated.

**Results:** 90 123 (73%) questionnaires were returned. Endoscopic hemostatic therapy is given in ulcers classified as Forrest Ia Ib Ila Ilb IIc by respectively 89%, 93%, 83%, 47% and 19% of respondents. Gastroenterologists perform more often endoscopic therapy in Forrest Ib (p=0.03), Ila (p=0.002) and Ilb (p=0.001) ulcers compared with internists. As first modality, endoscopic injection therapy is used by 93%. Adrenaline combined with polidocanol is most commonly used (60%). Pharmacotherapy is given by 97%. Seventy-one percent use proton pump inhibitors, 26% use H₂-receptor-antagonists, both mainly initially given intravenously. In case of suspected rebleeding, endoscopic re-intervention is performed by 76%, among whom significantly more gastroenterologists (89% of gastroenterologists vs 60% of internists, p=0.005), whereas the others refer the patient directly for surgery. Almost all responders perform detection of H. pylori infection. Eradication is confirmed by only 64% (80% of gastroenterologists vs. 50% of internists, p=0.004).

**Conclusions:** There are important differences in management of peptic ulcer bleeding between gastroenterologists and internists in the Netherlands. Management is only partly conform evidence-based medicine.
Introduction

Acute upper gastrointestinal bleeding is a common medical emergency situation with an incidence of 62 per 100,000 persons per year in the Amsterdam area. Peptic ulcer bleeding (PUB) is responsible for almost half of all cases. Despite advances in diagnosis and treatment in the past years, rebleeding occurs in about 10-30% after initial hemostasis and mortality is still around 6-14%. Especially rebleeding, one of the risk factors that might be influenced, is a strong risk factor for mortality.

There is no up to date consensus about which endoscopic treatment modality and pharmacotherapy should be used in PUB. Bipolar electrocoagulation, heater probe coagulation and endoscopic injection therapy are all similarly effective at improving the outcome. Controversies also still exist with respect to acid suppressant therapy. With this background we conducted a national mail survey to investigate the daily routine therapeutic strategies in the management of PUB.

Methods

Questionnaire
A questionnaire was developed for data collection. The questionnaire consisted of 21 multiple-choice questions. The first part included questions about demographic information, the second part requested specific information relating to the practice of acute gastroduodenal ulcer bleeding (table 1).

In every hospital in the Netherlands (N=123) one gastroenterologist, or, if not present, an internist, being member of the Dutch Society of Gastroenterology and performing endoscopies, was randomly selected. In the Netherlands, both gastroenterologists and internists do perform endoscopies. Gastroenterologists have had gastroenterology training for 3 years. Internists are physicians who have completed training in internal medicine and are allowed to perform endoscopies, usually upper intestinal endoscopy and sigmoidoscopy, when they have followed at least a six-month gastroenterology-training course. In the 123 hospitals in the Netherlands, 49 hospitals do have one or more gastroenterologists.
### Table 1. Questionnaire: Therapy in Peptic Ulcer Bleeding

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you a gastroenterologist/internist?</td>
<td>[ ] Yes</td>
</tr>
<tr>
<td>How long ago did you finish your endoscopic training?</td>
<td>[ ] Less than 5 years ago</td>
</tr>
<tr>
<td>How many cases with acute upper gastrointestinal bleeding do you see?</td>
<td>[ ] Less than 100 cases</td>
</tr>
<tr>
<td>How often do you give endoscopic hemostatic therapy?</td>
<td>[ ] Less than once/month</td>
</tr>
<tr>
<td>Do you use a scoring system for patients with acute ulcer bleeding?</td>
<td>[ ] Yes</td>
</tr>
<tr>
<td>Which ulcers do you treat?</td>
<td>[ ] Yes</td>
</tr>
<tr>
<td>Do you remove an adherent clot?</td>
<td>[ ] Yes</td>
</tr>
</tbody>
</table>

A 45-year-old man presents at the emergency room with hematemesis and signs of shock. On EGD an oozing ulcer with a diameter of 0.5 cm in the lesser curve of the stomach is found.

**What is your treatment modality of first choice?**
- [ ] injection therapy
- [ ] heater probe
- [ ] laser photocoagulation
- [ ] bipolar coagulation
- [ ] hemoclip
- [ ] argon plasma coagulation
- [ ] combination
- [ ] direct surgery

**When no hemostasis is achieved what do you use next?**
- [ ] injection therapy
- [ ] heater probe
- [ ] laser photocoagulation
- [ ] bipolar coagulation
- [ ] hemoclip
- [ ] argon plasma coagulation
- [ ] combination
- [ ] direct surgery

**If you use injection therapy, what agent do you use and how much do you use?**
- [ ] adrenaline
- [ ] polidocanol
- [ ] ethanol
- [ ] fibrin glue
- [ ] histoacryl
- [ ] other
- [ ] amount: ml

**Where do you administer injection therapy?**
- [ ] in the visible vessel
- [ ] in the ulcer base
- [ ] at the edge of the ulcer

**Do you perform a second-look endoscopy?**
- [ ] No
- [ ] Yes

**Do you give supportive medical therapy?**
- [ ] No
- [ ] H2RA
- [ ] PPI
- [ ] sucralfate
- [ ] oral
- [ ] dose: mg

After one day the patient has signs of rebleeding with hematemesis and an unstable circulation.

**What do you do?**
- [ ] Endoscopic re-intervention
- [ ] refer the patient directly for surgery

**Do you routinely test for H. pylori?**
- [ ] No
- [ ] Yes

**Do you treat H. pylori?**
- [ ] No
- [ ] Yes

**Do you confirm eradication of H. pylori?**
- [ ] No
- [ ] Yes

After one day the patient has signs of rebleeding with hematemesis and an unstable circulation.
In the 74 hospitals left, there is no gastroenterologist and internists perform endoscopies. To increase the response rate, a duplicate questionnaire was mailed 6 weeks after the initial mailing.

Statistical analysis
Data were analysed using the statistical package SPSS 8.0 for Windows. Descriptive statistics were used to analyse and report the data. Fisher’s exact test, Chi-square test and Chi-square test for trends were used to determine differences between internists and gastroenterologists.

Results

A total of 90 evaluable questionnaires were returned, which gave a response rate of 73% (90% of the gastroenterologists and 60% of the internists). Gastroenterologists reported significantly more cases of upper gastro-intestinal bleeding per month (p < 0.001) and performed significantly more often endoscopic hemostatic therapy (p < 0.001) (table 2).

Table 2. Demographic characteristics of respondents

<table>
<thead>
<tr>
<th>Years since training:</th>
<th>Gastroenterologists (N=44), No. (n%)</th>
<th>Internists (N=45), No. (n%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-5 (16)</td>
<td>2 (4)</td>
</tr>
<tr>
<td></td>
<td>6-10 (14)</td>
<td>7 (16)</td>
</tr>
<tr>
<td></td>
<td>11-15 (23)</td>
<td>12 (27)</td>
</tr>
<tr>
<td></td>
<td>16-20 (23)</td>
<td>13 (29)</td>
</tr>
<tr>
<td></td>
<td>&gt;20 (25)</td>
<td>11 (24)</td>
</tr>
<tr>
<td>Number of UGIB month</td>
<td>0-5 (27)</td>
<td>27 (60)*</td>
</tr>
<tr>
<td></td>
<td>6-10 (50)</td>
<td>17 (38)</td>
</tr>
<tr>
<td></td>
<td>&gt;10 (24)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Number of ET month</td>
<td>0-5 (60)</td>
<td>44 (98)**</td>
</tr>
<tr>
<td></td>
<td>&gt;5 (40)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

UGIB: upper gastrointestinal bleeding. ET: endoscopic therapy. * data about specialization was missing in one questionnaire. * p < 0.001 (Chi-square test for trend). ** p < 0.001 (Fisher’s exact test).
Classification of the ulcer

Of the respondents, 66% perform an esophagastroduodenoscopy (EGD) within 12 hours and all within 24 hours. The Forrest classification\textsuperscript{17} for stigmata of recent hemorrhage is used by 61%, significantly more often by gastroenterologists (p=0.001). Two percent use a personal descriptive classification (no further details were given about this classification) and 36% use no specific classification. Sixty-nine percent of the internists indicate no attempt to remove an adherent clot compared with 32% of the gastroenterologists (p=0.001).

Endoscopic hemostatic therapy

Endoscopic hemostatic therapy is given in ulcers with spurtin g bleeding (Forrest Ia), oozing bleeding (Ib), nonbleeding visible vessel (IIa), adherent clot (IIb), and black hematin covered ulcer base (IIIc) by respectively 89%, 93%, 83%, 47% and 19% of respondents. Gastroenterologists perform significantly more often endoscopic therapy in Forrest Ib (p = 0.03), IIa (p = 0.002) and IIb (p = 0.001) ulcers compared with internists (figure 1).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{fig1.png}
\caption{Endoscopic therapy given in ulcers classified according to the Forrest classification.\textsuperscript{15} Ia: spurtin g bleeding, Ib; oozin g bleeding, IIa; nonbleeding visible vessel, IIb; nonbleedin g ulcer with adherent clot, IIIc; ulcer with hematin-covered base. III: clean ulcer base. * P < 0.01 (Chi-square test).}
\end{figure}

Treatment modality

Endoscopic injection therapy is performed by 93% as first treatment. Two physicians use adrenaline combined with hemoclip, 1 uses argon plasma coagulation, 1 uses adrenaline combined with heater probe and 3 do not give endoscopic therapy. When no hemostasis is achieved after the first attempt, repeated endoscopic injection therapy in the same session is
given by 23\% of respondents, hemoclip by 14\%, bipolar electro-coagulation by 8\% of respondents, the heater probe by 7\%, argon plasma coagulation by 4\% and laser photoagulation by 2\% of respondents. The agents used for endoscopic injection therapy are a combination of adrenaline and polidocanol (60\%), adrenaline and histoacryl-thrombin-fibrin-alcohol (7\%, 4\%, 1\% and 1\%, respectively), adrenaline alone (14\%) and polidocanol alone (6\%). The mean maximum amount of adrenaline given is 9.8 ml (SD 7.3); the mean maximum amount of polidocanol given is 5.6 ml (SD 4.1).

**Site of application**
Adrenaline injection therapy is applied in the ulcer base around the supposed visible vessel (56\%), submucosal at the edge of the ulcer (28\%) or ‘in’ the supposed visible vessel combined with injection in either the ulcer base or at the edge of the ulcer (11\%). A sclerosant is injected ‘in’ the supposed visible vessel (60\%), in the ulcer base (28\%) or in the edge of the ulcer (6\%). Six percent of respondents inject the sclerosant both in the ulcer base and supposed visible vessel.

**Acid suppressant therapy**
Almost all responders (97\%) give acid suppressant therapy. Proton pump inhibitors (PPIs) are most frequently given (71\%), of which 80\% is administered intravenously. The mean intravenous dosage given is 164.2 mg (SD 95.7) per 24 hours. Twenty-six percent of the responders give H₂-receptor antagonists (H₂-RA), of which 92\% is administered intravenously.

**Second look re-intervention**
Twenty-nine percent of the physicians routinely perform a second look endoscopy within 24 hours. In case of repeat hematemesis or signs of circulatory instability, 76\% perform endoscopic re-intervention (89\% gastroenterologists vs. 60\% internists, p=0.005), while the others (24\%) refer the patient directly for surgery. Risk factors, most commonly identified as reasons for referral to the surgeon, were the first or second rebleeding, location of the ulcer (especially the posterior wall of the duodenum) and age of the patient. Ulcer size was only reported in 12\% as a main reason for referral.
Detection of *H. pylori*

Detection of *H. pylori* is performed in 90% of cases. Histology is most often used, in 29% as single detection method and in 42% combined with either the rapid urease test, culture, or both or combined with serology. The rapid urease test as single detection method is used by 18% of responders. For *H. pylori* eradication, PPI triple therapy with amoxicillin and clarithromycin or metronidazole is most frequently used (84%) and 64% of the physicians confirm eradication (80% gastroenterologists vs. 50% internists, p=0.004). Confirmation is most often done by histology combined with culture (20%), histology alone (14%), urea breath test (14%), rapid urease test combined with histology and/or culture (20%), serology (7%) and other combinations of above-mentioned methods (25%).

**Discussion**

This survey illustrates the current endoscopic and pharmacological management of peptic ulcer bleeding in the Netherlands. Endoscopic injection therapy is well established and acid suppressant therapy is common. There is not a standard treatment regimen in the Netherlands concerning the treatment of PUB and there are important differences in management between gastroenterologists and internists.

A total of 66% of respondents perform endoscopy for acute upper gastrointestinal bleeding within 12 hours and 100% within 24 hours. Ideally, emergency endoscopy should be performed as soon as safely possible in patients at high risk for further bleeding. In the routine daily practice however logistic aspects also play a role, for example the availability of resources and staff, as well as the availability of a 24-hour endoscopy team, especially in regional/community-based hospitals. Cooper et al evaluated early endoscopy, defined as endoscopy within 24 hours, in patients with upper gastrointestinal bleeding. Endoscopy early in the clinical course of patients was associated with reduction in length of stay and, possible, the risk of recurrent bleeding and surgery compared to endoscopy at any point during hospitalization. So, in general, the advise should be to perform endoscopy as soon as safely possible but at least within 24 hours.

**Classification of the ulcer**

The NIH Consensus Conference recommends standardization of terminology of stigmata of recent hemorrhage (SRH), quantitation of rebleeding risk and the development of a scoring...
system to predict risk of persistent or recurrent bleeding. A number of composite scoring systems have been developed including the Baylor Score and the Rockall risk scoring system, but the usefulness of a scoring system has yet to be proven. In this study, 63% of responders use a classification, mainly the Forrest classification. During routine daily practice the clinical parameters are always taken into account when making a decision about management of an individual patient, but scoring systems as the Baylor or Rockall score are not used in routine daily practice. The Forrest classification, which only classifies the stigmata of recent hemorrhage, is one of the most frequently used classifications systems, although there is important inter-observer variability, even among experienced gastroenterologists.

In order to get a proper classification of the ulcer base one should gently try to wash away the adherent clot for better assessment. Whether to further try to remove the adherent clot, when it is not removed by only gently washing, remains controversial. This inquiry shows that 51% do not try to remove an adherent clot.

Using a Doppler probe to assess the feeding vessel in an ulcer base might overcome the variation in classification of ulcer type and might help in determining the optimal management and thus influencing the outcome of the patient. In a randomized trial Kohler et al treated patients with peptic ulcer bleeding based on the Forrest classification of the ulcer in one group and based on the Doppler signal of the ulcer in the other group. In the group with Doppler-based local endoscopic treatment, rebleeding occurred significantly less frequent than in the Forrest group (2% vs 14%, p<0.03). Further studies are being awaited for, before the doppler-guided assessment of the ulcer-base can be recommended as routine diagnostic tool.

Endoscopic therapy

It is striking that ulcers with spurting or oozing bleeding, visible vessel or adherent clot are not always treated endoscopically, although these ulcers are at risk for persistent or recurrent bleeding. There has been some discussion about the need for endoscopic therapy for ulcers with adherent clots, but several studies do advice endoscopic therapy for such lesions. All Forrest Ia-IIb should be treated endoscopically.
According to the NIH Consensus Conference, bipolar electro-coagulation and heater probe coagulation are the most promising modalities for endoscopic hemostatic therapy. In the Netherlands endoscopic injection therapy is by far the most popular treatment modality for achieving hemostase. Endoscopic injection therapy is effective, simple, cheap, and easy to perform and in controlled trials, injection therapy is at least as effective as thermo-coagulation or laserphacoagulation. In several studies addition of a sclerosant has been reported to be highly effective for endoscopic hemostasis in gastroduodenal ulcer bleeding, but trials have not shown superiority over adrenaline injection alone. Yet, 60% of responders do routinely add sclerosant to adrenaline injections. Adrenaline, even in a larger volume, is considered to be safe, whereas sclerosants can cause extensive tissue necrosis and further ulceration in a dose-dependent manner. It is striking that the mean maximum amount of polidocanol used is 5.6 ml, with a reported upper range as high as 20 ml, which might cause extensive tissue injury. Sclerosants should be used with caution, and if used, only in a limited amount. Repeat injection therapy with fibrin glue or injection therapy with adrenaline plus human thrombin might reduce recurrent bleeding. Further studies with fibrin glue and thrombin are being awaited for before general guidelines for the use of these agents can be given.

Combination therapy with injection therapy and a thermal device is not routinely applied in the Netherlands. Only one responder uses adrenaline combined with the heater probe as first line therapy. A recent study from Lin et al showed a beneficial effect of the use of combined adrenaline injection and gold probe compared with adrenaline injections alone and gold probe alone, in preventing rebleeding and decreasing the need for blood transfusion. In this study however, the reported incidence of rebleeding in the adrenaline group and in the gold probe group was high (35.5% and 30% respectively). Chung et al only found an additional advantage of adrenaline injections combined with heater probe compared with adrenaline alone in ulcers with spurting bleeding. In this group the relative risk for surgery was lower in the group with combination therapy (RR 0.17; 0.03-0.87) and length of hospital stay was significantly shorter. Rebleeding and mortality did not differ significantly. Two randomized studies compared adrenaline injection plus bipolar coagulation with bipolar coagulation alone for actively bleeding ulcers and for non-bleeding visible vessels. In both studies there was
no significant difference between the rebleeding and mortality rate. Primary hemostasis was significantly higher with combination therapy for actively bleeding ulcers. It is apparent from the literature that clinicians are increasingly resorting to the use of combination therapy: adrenaline injection and a second modality, especially thermo-coagulation, to target the vessel, although results of randomized controlled trials do not give convincing evidence for this management. It remains uncertain what the best current regimen is.

Site of application
The site of application of injection therapy was highly variable. The general idea is to administer diluted adrenaline in four quadrants around and into the visible vessel, while others inject submucosally in the edge of small ulcers or into the ulcer base and directly besides the visible vessel in large ulcers. The sclerosant is usually injected into the visible vessel. Our results show that a sclerosant is applied into the visible vessel, but also besides the visible vessel in the ulcer base and even in the edge of the ulcer. There are no precise guidelines where a sclerosant should be applied.

Acid suppressant therapy
Several in vivo studies have shown that hemostatic mechanisms are highly pH-dependent and that coagulation and stable platelet aggregation do not occur at pH levels below 6. A profound reduction of gastric acidity so that the pH maintains approximately above 6, could stabilize the clot over an ulcer and stop bleeding or prevent rebleeding. In order to create and maintain a high intragastric pH for a sufficient period of time, continuous intravenous infusion of high dose PPI (e.g. Omeprazole 80-mg bolus, followed by 8 mg/h) is needed. A lower dose of PPI or H2RA do not consistently maintain gastric pH above 4.0 for long periods. In randomized trials, however, the role of PPI in preventing rebleeding in patients with PUB has been controversial. Some recent studies have shown a significantly improved overall outcome in patients with ulcer bleeding receiving high dose intravenous Omeprazole compared to placebo and compared to H2RA, although mortality was not influenced. Other studies could not find any benefit of the use of proton pump inhibition. Kharoo et al. found that even orally administered Omeprazole 40 mg twice daily was effective in reducing rebleeding and emergency surgery in patients with nonbleeding visible vessels or adherent clots, but not in those with arterial spurting or oozing ulcers. In this study no
endoscopic injection therapy was given. Based on the literature the use of acid suppression is inconclusive, further studies are needed before general guidelines can be given.

Second look endoscopy

Elective second look is discussed in the literature but there is no clear consensus reached about its value. Some studies showed significantly less rebleeding after second look endoscopy\textsuperscript{64,65}, whereas others showed no benefit.\textsuperscript{66,67} Second look endoscopy may be beneficial in some high-risk patients.

Endoscopic re-intervention

Whether one should perform a re-endoscopy in case of rebleeding should probably be individualized. In a recent study the outcome of 100 patients with PUB and rebleeding, after initial control of the bleeding, was evaluated, comparing endoscopic re-treatment with surgical intervention.\textsuperscript{68} Endoscopic re-treatment reduced the need for surgery without increasing the risk of death and was associated with fewer complications than surgery. The success rate of endoscopic re-treatment was high in patients with smaller ulcers (< 2-cm) and relatively stable hemodynamic parameters. It is difficult to extrapolate these results to standard daily practice, because the endoscopic therapeutic effect and the outcome of surgery are influenced by the local expertise and clinical condition of the individual patient. Endoscopy in a bleeding patient generally requires a higher level of skill and is technically more demanding. For experienced physicians, endoscopic re-intervention should be the first option in patients with smaller ulcers and relatively stable hemodynamic parameters, whereas for less experienced physicians, decision about further management should be carried out at discretion of the physician and in co-ordination with surgical consultation.

H. pylori detection

Investigation for H. pylori should be performed in all patients. Confirmation of H. pylori eradication is important in patients with PUB\textsuperscript{69}, but only 64\% of respondents confirm eradication.

The data presented are from the Dutch perspective. In the Netherlands gastroenterologists and internists both perform endoscopies. Each of these groups has a different endoscopy training.
which might explain the differences in management. Part of the variability in practice reflects the controversies in management strategies to the challenging clinical problem of upper gastrointestinal bleeding. However, the approach of management of bleeding ulcers is not always consistent with current knowledge and emphasizes the need for further training, especially in the group with internists.

The results of this questionnaire must be interpreted in consideration of typical study limitations, e.g. self-reported data. In addition, the sample was limited to one physician per hospital which may not be reflective of all practitioners in emergency endoscopy, but will at least give a general impression about management of PUB in the Netherlands. Nevertheless, results from more than 70% respondents accentuate the need for, and acting upon, guidelines on issues regarding management in PUB.

In summary, there are important differences in management between gastroenterologists and internists. Management is only partly conform evidence-based medicine. This study shows the need for further research and for evidence-based protocols, but especially the need for continuous education and sticking to protocols, to improve the quality of care received by patients with PUB.
References


52. Jensen DM, Kovacs TO, Jutabha R, Gralnek IM, Machicado GA, Sasides TJ et al. Randomized, Prospective Study of Bipolar Coagulation Alone Compared to Combination Epinephrine Injection and Bipolar Coagulation for Prevention of Rebleeding from Ulcers with Non-Bleeding Visible Vessels [abstract]. Gastrointest Endosc 2000; 51: AB130.


