The continuing story of peptic ulcer bleeding
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Summary
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Peptic ulcer bleeding (PUB) is still an important emergency situation and rebleeding and mortality are substantial. In this thesis several aspects of PUB are discussed.

Chapter 2 gives a general overview and describes the epidemiological data regarding PUB. Risk factors for ulcer disease are discussed and the, probably, independent etiological role for NSAID aspirin use and Helicobacter pylori is explained. Furthermore, data about management of PUB, including endoscopic therapy and acid suppressive therapy, as well as diagnostic tests for H. pylori and surgical management of PUB are reviewed. We finish this chapter by focusing on prevention of PUB.

Because there is no consensus in The Netherlands regarding endoscopic and pharmacological therapy for PUB we conducted a national mail survey among gastroenterologists and internists performing endoscopies. Chapter 3 describes the results of the inquiry. In total 90 123 questionnaires were returned. Gastroenterologists did perform significantly more often endoscopic therapy in high-risk ulcers for rebleeding than internists. Endoscopic injection therapy was often used (93%). Commonly, injection therapy was performed using adrenaline combined with polidocanol (60%). However, controlled trials have not shown a beneficial effect of the use of sclerosant agents like polidocanol. Proton pump inhibitors (PPIs) were administered by 71%, H2-receptor-antagonists by 26%. In case of suspected rebleeding, endoscopic re-intervention was performed by only 76%. Almost all responders performed detection of H. pylori. Eradication was confirmed by 64%, instead of a 100%. This study showed that there were important differences in management between gastroenterologists and internists. Management was only partly based on the results of recent trials. Further research for evidence-based protocols is necessary, but especially the need for continuous education and sticking to protocols, to improve the quality of care received by patients with PUB is important.

In chapter 4 data of two epidemiological cohorts are presented. Data from all patients presenting with upper gastrointestinal bleeding in the period 1993-94 and 2000 were prospectively collected in a defined geographical area (greater Amsterdam area). Overall
incidence of acute upper gastrointestinal bleeding significantly decreased from 61.7 \(10^5\) person year in 1993 to 47.7 \(10^5\) person year in 2000. Incidence was especially high among patients with higher age. Rebleeding (16\% vs 15\%) and mortality (14 vs 13\%) did not differ between the two time periods.

The incidence of ulcer bleeding remained stable and ulcer bleeding remained responsible for almost half of all cases of bleeding. Almost 50\% of all patients presenting with PUB was using aspirin and/or NSAIDs. In 2000 still only a minority (12\%) of patients with a history of ulcer disease and concomitant aspirin and/or NSAID use was prophylactically using a proton pump inhibitor. Attention should be given to prevention of PUB.

Also among patients with ulcer bleeding, rebleeding (22\% vs 20\%) and mortality (15\% vs 14\%) did not differ between the two time periods. Age, severe and life-threatening co-morbidity and rebleeding were predictive factors for mortality. We should try to prevent recurrent ulcer bleeding by a more aggressive approach (including early endoscopy, endoscopic therapy and high dose i.v. PPI for all ulcers at risk for rebleeding), in order to reduce mortality.

Invasive diagnostic tests for H. pylori infection are less sensitive in the acute phase of PUB. Urea breath test might be a good alternative, but this test is less sensitive when patients are using acid suppressants. For this reason we investigated a new non-invasive H. pylori stool immunoassay (HpSA-test) in 36 patients with PUB. Results of this test are presented in Chapter 5. Using either culture or rapid urea test and histology as the “gold standard”, the sensitivity and specificity of the HpSA test was 100\% and 52\%, respectively.

To evaluate cross-reaction with blood constituents, blood samples from 10 healthy volunteers were assessed by the HpSA test. Four of these gave a positive test result, suggesting cross-reaction with blood constituents. The HpSA test gave a high number of false positive results in patients with PUB, probably due to blood constituents cross reacting in the enzyme immunoassay. In contrast to the advice for patients with peptic ulcer disease, the use of the HpSA for the assessment of \textit{H. pylori} infection in patients with peptic ulcer bleeding cannot be recommended.
The introduction of endoscopic hemostatic techniques, the introduction of PPIs and eradication of H. pylori did result in a negative patient selection for those who require emergency surgery. Chapter 6 describes the outcome of a retrospective study evaluating emergency surgery for PUB, which could not be controlled by endoscopic therapy, between 1988-2001. In total 63 patients underwent surgery, 51 for duodenal, 11 for gastric and 1 for an anastomotic ulcer. Surgery was performed for the initial bleeding in 33% of patients and because of rebleeding in 65% of patients. One patient had semi-elective surgery. Rebleeding occurred in almost one third (27%) of patients after surgical intervention. Mortality rate was substantial. Twenty-three patients (37%) died in hospital. Comorbidity and spurting bleeding at initial endoscopy were found to be predictive for mortality. Further research should be done to evaluate alternative techniques for hemostasis, for example transcatheter arterial embolization.

Stigmata of recent hemorrhage in peptic ulcer bleeding are an important prognostic factor. In chapter 7, we evaluated interobserver agreement in Forrest classification among endoscopists using video recordings from emergency endoscopies. Furthermore, differences between Forrest classification and endoscopic Doppler assessment were evaluated. Forrest classifications of 19 video-fragments of ulcers were obtained from 56 endoscopists. There was a high variation in classification of stigmata of recent hemorrhage in peptic ulcers. Agreement was fair among gastroenterologists and poor among internists. There was lack of agreement between the visual interpretation and the endoscopic Doppler assessment of the ulcer base. Out of 14 ulcers with a positive endoscopic Doppler signal (suggesting a superficial vessel), which theoretically need endoscopic treatment, a mean of 25% would not have been treated based on the Forrest classification. The Doppler investigation might be an objective diagnostic tool to assess the risk of rebleeding and to make decisions about endoscopic therapy and early discharge. The value of Doppler assessment in clinical practice should be evaluated.

In a prospective study we evaluated the diagnostic value of Doppler assessment in PUB. The results of this study are presented in chapter 8. In total 80 patients were analyzed. No difference was found in primary outcome (rebleeding, mortality and surgery within 96 hours) between ulcers with or without a superficial Doppler flow signal. Three out of 23 patients
without a superficial Doppler signal (one with a Forrest IIa (visible vessel), one with a Forrest IIb (adherent clot) and one with a Forrest III (clean base) ulcer) did have recurrent bleeding. There was only a trend towards lower rebleeding rate in ulcers where the Doppler signal was abolished after endoscopic therapy compared to the ulcers where the Doppler signal remained positive. In contrast to earlier studies, Doppler assessment of the ulcer base did not provide additional information when added to the Forrest classification in our study. Unfortunately, we are still searching for an objective tool to predict the clinical outcome of the patient.

In chapter 9, results of this thesis are placed in perspective with the international literature. Prevention of PUB should get high priority. Furthermore, factors applicable for improving the outcome of PUB are mentioned and an aggressive approach of patients at risk for recurrent bleeding is advocated. Recommendations and suggestions for further research are given. The story of PUB continues.