

Material and methods.

A decision analytic model was used to compare the monetary cost and health care benefits of each strategy.

Patient population

Hospitalized patients with an initial upper gastrointestinal haemorrhage due to peptic ulcer disease were the population of interest. Patients with variceal bleeding or bleeding from gastric or duodenal erosions were not considered.

Non-steroidal anti-inflammatory drug (NSAID) use represents a wide spectrum of risk of bleeding, depending on the drug and the dose employed and the characteristics of the patient. Taking this into account, and to avoid complicating the analysis, patients on acetylsalicylic acid (ASA) were considered as part of the range of patients on NSAID therapy, ranging from low risk (low-dose ASA alone) to high risk (ASA and NSAID cotherapy), and were not analysed separately.

Perspectives and time horizon

The perspectives were those of a third part payer – the National Health Service in the case of Catalonia (Spain), and a health insurer in the case of the US. The time horizon was 2 years. As the time horizon was short, no discount rate was applied either to the costs or to benefits. When the costs obtained from the

literature referred to previous years, values were corrected assuming a fixed annual inflation rate of 3%.

Decision model

Analysis was performed by using a decision tree (figure 1), which seemed the best approach for a point decision. Four initial strategies were analysed: 1) Test for *Helicobacter pylori* (*Hp*) and treatment if positive, 2) Proton pump inhibitor (PPI) maintenance, 3) No preventive treatment and 4) Empirical *Hp* eradication immediately after bleeding. NSAID co-therapy and losses to follow-up were considered in all strategies. The decision tree included the major choices to be taken, chance events that may occur during follow-up and secondary strategies for management of chronic NSAID therapy, failures of *Helicobacter pylori* treatment and its combinations. In the four strategies patients underwent emergency endoscopy in order to evaluate the initial bleeding episode.

In the first strategy (“test for *Hp* and treatment if positive”), currently in use at most centres, *Helicobacter pylori* infection was investigated by histology (1). Patients were discharged after resolution of the bleeding episode and attended on an outpatient basis. Those with a histology showing *Helicobacter pylori* infection were prescribed triple therapy (omeprazole 20 mg, clarithromycin 500 mg, and amoxicillin 1000 mg all twice a day) for seven days (2-5). A negative initial histology result was interpreted as a probable false negative test (6) and was followed by a ¹³C-urea breath test (UBT). If this test was positive, triple therapy was indicated. A patient was considered not infected when both initial histology and subsequent UBT were negative; in this case, maintenance

therapy with a PPI was indicated. Diagnosis of *Helicobacter pylori* after triple therapy was performed systematically at least two months after treatment with a UBT in duodenal ulcers and with endoscopy plus histology in gastric ulcers requiring biopsies to rule out malignancy. A positive test was followed by a second antibiotic treatment with quadruple therapy (7,8) omeprazole 20 mg twice a day, bismuth subcitrate 120 mg four times a day, tetracycline 500 mg four times a day and metronidazole 500 mg three times a day for 7 days. After this, a new UBT was performed. In the very small proportion of patients in whom a second *Helicobacter pylori* treatment was unsuccessful, maintenance PPI treatment was recommended. Discontinuation of NSAID therapy was attempted in all patients. Long-term prophylaxis with a PPI was also recommended in patients requiring continued NSAID. Losses to follow-up 20% (range 10-40%) were considered in this strategy. Mean number of clinical visits was 2.8 per patient and 9 patients needed re-treatment therapy for *Hp* eradication (quadruple therapy). Diagnostic tests used in this strategy were: 84 patients were administered UBT (19 as a second diagnostic *Hp* test after a negative result for initial histology, 56 for diagnosis of *Hp* after triple therapy and 9 for diagnosis of *Hp* after quadruple therapy); 12 patients with gastric ulcer underwent endoscopy plus histology in order to confirm ulcer healing and rule out malignancy.

In strategy 2 (proton pump inhibitor maintenance), healing therapy for peptic ulcer with standard dose of PPI once daily for 4 weeks was prescribed. After this, only patients with gastric ulcer underwent endoscopy. No testing for *Hp* or eradication treatment was performed. All patients were prescribed long-term

maintenance PPI to prevent rebleeding. In this strategy we assume that the probability of discontinuing PPI treatment was 30% (range 20-40%) The patients who stopped PPI maintenance treatment were exposed to a very high risk of re-bleeding. The mean number of clinical visits in this strategy was 0.9 per patient and no tests were performed.

In strategy 3 (no preventive treatment) healing therapy for peptic ulcer with standard dose of PPI once daily for 4 weeks was prescribed, only patients with gastric ulcer underwent endoscopy, no testing for *Hp* or eradication treatment was performed and patients did not receive further treatment (PPI). The mean number of clinical visits was 1.3 per patient and no tests were performed.

Finally, in strategy 4 (empirical *Hp* eradication immediately after bleeding) no test for *Hp* was performed after initial endoscopy. First line triple therapy for *Hp* eradication was initiated before discharge, as soon as the patient tolerated oral intake. Subsequent follow-up was similar to those of the patients in strategy 1 (“test for *Hp* and treatment if positive”). Losses to follow-up in this strategy were assumed to be about 10% (range 2-15%). Therefore, many patients lost to follow-up had already received triple therapy for *Hp* eradication; this was the main difference between strategies 1 and 4. The mean number of clinical visits was 2.4 per patient; 12 patients need re-treatment therapy for *Hp* eradication (quadruple therapy). Eighty-six UBT were performed (74 for diagnosis of *Hp* after triple therapy and 12 for diagnosis of *Hp* after quadruple therapy) and 16 patients with gastric ulcers underwent endoscopy plus histology in order to confirm healing and rule out malignancy.

Discontinuation of NSAID therapy was attempted in all groups and long-term prophylaxis with a PPI was also performed in patients requiring continued NSAID.

Probabilities and costs

Probability values and ranges used in the sensitivity analysis were taken from the medical literature. Assumed baseline probabilities are shown in Table 1. Histology was selected as the first test for diagnosis of *Helicobacter pylori* infection, since it has better sensitivity than UBT for diagnosis *Hp* infection in patients with bleeding – 77.2% vs. 45.5% respectively (1). Triple therapy was selected as first line therapy, as it is the most widely used in our area. Its reported cure rates for 7 days of therapy range around 85% (3-5,8,9). In addition, triple therapy has demonstrated a high efficacy in patients with *Helicobacter pylori* infection and bleeding peptic ulcer (4). Second line treatment was quadruple therapy with omeprazole 20 mg twice a day, bismuth subcitrate 120 mg four times a day, tetracycline 500 mg four times a day and metronidazole 500 mg third times a day for 7 days. This is one of the most widely recommended rescue treatments; it has also demonstrated a high efficacy as second line treatment after failed triple therapy (7,8). Post-treatment follow up was performed by a UBT. This technique is non-invasive and highly reliable, and has been widely recommended for follow-up after therapy (8). The risk of recurrent bleeding after eradication, in patients with and without PPI

maintenance and in those receiving NSAID treatment, was extracted from a meta-analysis (10) and from many clinical trials (11-17).

Costs were estimated for two different settings: i) a low-cost-for-care area and ii) a high-cost-for-care area. For the low cost area we obtained data from Catalanian Public Health Service (18) and from an article published in Spain which evaluated costs of NSAID associated with gastrointestinal side effects (19). Costs were expressed in Euros (€). For the high cost area US dollars were used as a monetary unit (1.4\$ = 1€, approximately). US costs were obtained from a previous paper on the topic (20,21). Cost values and their confidence intervals are shown in table 2. A fixed inflation rate of 3% per year since the year of estimation of the cost was used to correct cost values.

Due to the lack of primary and secondary information, indirect costs were not included. As indirect costs increase in parallel with the number of clinical visits and procedures, it was assumed that their effect on the analysis would be similar to that of increasing the costs of clinical visits in the sensitivity analysis.

Analysis

The primary evaluation variable was the risk of recurrent bleeding. The incremental cost-effectiveness ratio (ICER) for upper gastrointestinal haemorrhage avoided was calculated. Mortality was calculated as a secondary variable. The cost per patient was calculated by assigning probabilities and cost

values to each branch of the decision tree. Costs were weighted by their probabilities and added to obtain the total direct cost for each branch. All calculations were performed using conventional software (Microsoft Excel XP). Sensitivity analysis was performed to evaluate the stability of the model in the context of regional differences and possible market changes. One-way sensitivity analyses were performed by applying a wide range of values for each probability and costs in order to evaluate their effect.

Finally, multiple way probabilistic sensitivity analyses were performed using a Monte Carlo simulation for Microsoft Excel XP on the most clinically significant influential variables: *Hp* prevalence, eradication rate for *Hp* triple therapy, the proportion of patients lost to follow-up in strategies 1 and 4 and the probability of discontinuing PPI in strategy 3. No monetary variables had a significant influence on the one way sensitivity analysis and so none were included in the Monte Carlo simulation. Variables included in the Monte Carlo simulation were tested both using normal distribution and gamma distributions. No differences were found between the two distributions, thus confirming the robustness of the results. The proportion of patients lost to follow-up in strategies 1 and 4 and the probability of discontinuing PPI in strategy 3 were tested with a correlation coefficient between the three proportions of 0.9.

Table 1. Parameters used in the analysis (probabilities and ranges).

Value of the parameters used in the model	Baseline (%)	Range (%)
Hp eradication with triple therapy (3-5,9)	86	70-95
Hp eradication with quadruple therapy (7)	87	65-90
Recurrent UGIH Hp positive, no PPI maintenance (10,22)	24	15-50
Recurrent UGIH Hp negative, no PPI maintenance (10,13,23)	2	0-5
Recurrent UGIH Hp positive with PPI maintenance (16)	6	2-15
Recurrent UGIH Hp negative with PPI maintenance (10,13)	0.5	0-5
Recurrent UGIH Hp + taking NSAID plus a PPI (24)	15	4-25
Recurrent UGIH Hp - taking NSAID plus a PPI (25,26)	4.5	2-10
UGIH mortality (21,27,28)	10	4-20
Probability of NSAID discontinuation (21)	20	10-60
Sensitivity histology after UGIH (1)	90	77-95
Prevalence duodenal ulcer in UGIH (6,29)	82	72-94
Prevalence of Hp only in UGIH (30)	56	35-60
Prevalence of NSAID treatment only in UGIH (30)	11	7-25
Prevalence of NSAID treatment + Hp positive in UGIH (30)	29	16-58
Losses to follow-up for empirical eradication (estimated)	10	2-25
Losses to follow-up for “test and treat” strategy (31,32)	20	10-40

Hp: *Helicobacter pylori*; PPI: proton pump inhibitor; UGIH: upper gastrointestinal haemorrhage; NSAID: non-steroidal anti-inflammatory drugs.

Table 2. Costs of diagnostic and therapeutic procedures.

Cost		SPAIN (€)(18,19)	USA (\$) (20,21)
Upper gastrointestinal haemorrhage			
	Baseline	2025	6282
	Highest	3075	9500
	Lowest	984	3167
¹³C-urea breath test			
	Baseline	49	132
	Highest	155	253
	Lowest	24	57
PPI treatment per day			
	Baseline	1.03	4.67
	Highest	1.96	5.8
	Lowest	0.44	2.5
Specialist visit			
	Baseline	74	180
	Highest	111	380
	Lowest	34	95
Upper endoscopy with biopsy and histology			
	Baseline	103	382
	Highest	264	650
	Lowest	39	316
Triple therapy for Hp infection			
	Baseline	70	319
	Highest	87	600
	Lowest	54	158
Quadruple therapy for Hp infection			
	Baseline	72.7	156
	Highest	82.2	325
	Lowest	60	63
Managing upper gastrointestinal haemorrhage with ultimately fatal outcome			
	Baseline	20256	63338
	Highest	30747	95000
	Lowest	9839	31669

Hp: *Helicobacter pylori*; PPI: Proton pump inhibitor

Figure 1. Detailed decision tree.

(see pdf file: Figure 1. Appendix)

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