The search for optimal Helicobacter pylori eradication regimen : a mid 1997 update

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Eradication therapy for HP-related disorders is obviously a difficult problem : in a recent extensive review, Penston and Mc Coll (1) reported up to 536 different treatment schemes in 352 studies. For the present updating review of eradication therapies, the following multiple-step methodology was used :

1. Retrieval of published papers and abstracts by EMBASE (Excerpta Medica) from 1987 to mid 1997 and abstracts from UEGW, DDW and EHPSG workshops.
2. Exclusion of duplicate publications, papers with inadequate eradication assessment, or without data allowing a true ITT-based analysis (the ratio : n successful eradication's/n HP positive patients for whom eradication therapy is prescribed).
3. Exclusion of papers dealing with standard Oral triple therapy (OTT) and PPI-based dual therapies, which have been previously reviewed (2).
4. Pooling of ITT eradication rates (ER) for the different regimens.
5. Validation by comparison with the most recent review (1), when feasible.

Available drugs

Proton pump inhibitors (*PPI*) are frequently used in HP eradication schemes : through pH effect and decrease of gastric secretion, they increased both concentration and bactericidal effects of antibiotics, they possibly reduce the degradation of natural antibodies and Omeprazole was shown to have its own bactericidal property (3). There is a pharmacological synergy between Omeprazole and Clarithromycin (4) but, on the other hand, Omeprazole was shown to decrease gastric juice Metronidazole concentration, probably because of a shift to non-ionized form of Metronidazole due to pH increase (5).

Amoxycillin is locally active after oral administration and low concentrations are detected in gastric juice after intravenous dosing (5). *Macrolides* (Clarithromycin and Azithromycin) are stable in acidic environment and Azithromycin might take advantage from a long-term tissular accumulation (6). *Imidazoles compounds* are actively secreted in gastric juice (5). *Ranitidine Bismuth Citrate* (*RBC*), soluble at pH 4.6, was shown to inhibit pepsin isoenzymes and to have a better antibacterial activity than Ranitidine plus Bismuth salt (6).

Obsolete treatment schemes

We know for a while that monotherapies are not efficient, as well as the dual therapy Amoxycillin-Imidazole without acid inhibitors, mainly because of primary resistance to Imidazole-compounds (3).

The two-week Oral Triple Therapy (the "classic" OTT), using Colloidal Bismuth Subcitrate 120 mg qid, Metronidazole 500 mg tid or qid, Amoxycillin 500-750 mg or Tetracyclin 500 mg tid or qid) provides ER from 72% to 96% (mean 85.8% in 517 patients) in per protocol analysis (3) but the mean ITT eradication rate is 77% of 6677 patients (1) and the rate of side effects is very high : 34% in a previous analysis of 983 patients with 4% of serious adverse events (7).

The two-week, PPI-based, dual therapies are not superior. The eradication rate with 14 days of Amoxycillin 1000 mg bid plus Omeprazole 20-120 (!) mg ranged from 0% to 82% (3), 47% in ITT analysis in our own experience (8). Out of 4139 patients, the ITT ER is 59% and side effects are present in 14% of 3640 patients, with 2% of serious adverse events (1).

Omeprazole 20 bid plus Clarithromycin 500-mg tid (two weeks) gave an ITT eradication ER of respectively 72% and 65% in two large multicentre studies (9,10). In the review by Chiba *et al.* (11) the ITT eradication rate was 73.7% from 494 patients and 68% from 1265 cases in the review by Penston and Mc Coll (1). In Belgium, we observed an even lower rate : 71% by per protocol analysis (8). Side effects are observed in 26% (1) and up to 37% (7) with 3% of serious complications.

The two-week Ranitidine Bismuth Citrate-Clarithromycin dual therapy has been reviewed through 8 studies (only one published as a full paper and one accepted for publication) with a total of 990 patients (12-19). Mean ITT eradication rate is 78.5% (777/990). To note, most patients (707/990) received RBC 400 bid for 4

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weeks and Clarithromycin in 500 bid for the first two weeks.

Bazzoli, Bazzoli-like and "Bordeaux" recipe

The Bazzoli one-week, low-dose triple therapy (20) and Bazzoli-like schemes give conflicting results : from 91 to 95% of ITT eradication rate for the 167 first published patients but around 70% in other studies including our early trial (8). In a four-arm, randomized study in 160 patients (21), we compared Lansoprazole uid versus Omeprazole uid plus Clarithromycin 250-mg bid and either Tinidazole 500-mg bid or Amoxycillin 1000-mg bid. We obtained a very low eradication both in per protocol analysis (65%) and ITT (54%) and these results has been confirmed by other centers in Brussels (2) : the mean ITT eradication rate was 59% in a total of 259 patients in four centers. The optimistic conclusion of Penston and Mc Coll (1) about the effectiveness, safety and low-cost of Bazzoli therapy cannot be applied in Belgium.

The three candidates deserving careful attention

1. PPI one dose bid plus two antibiotics (Amoxycillin, Macrolide, or Imidazole) bid for 7 days as recommended by the European Consensus (22).
2. RBC 400 bid plus two antibiotics (like above) bid for 7 days.
3. De Boer's quadruple therapy (QT) : PPI bid for 7 days plus Tetracyclin 500 qid, CBS 120 qid and Metronidazole 500 qid for the last 4 days (23).

The results of one-week triple therapies using either RBC bid or PPI bid plus two antibiotics have been reviewed according to the methods described in the introduction. An exhaustive listing of PPI-based clinical trial may be found in the reviews from Penston and Mc Coll (1) and the more recent analysis by Unge (24). Eight studies using either RBC-Clarithromycin 500 or 250-Imidazole twice a day or RBC-Clarithromycin 500-Amoxycillin twice a day with a total of 710 patients have been reviewed (15,17,19,25-29). One-week triple treatment schemes with ITT eradication rate above 75% are reported in Table I.

First of all, it must be stressed that the association PPI-Amoxycillin-Metronidazole consistently gave a lower ITT eradication rate (around 75%).

Omeprazole has been tested in 4991 patients, Lansoprazole in 1268, Pantoprazole in 968 and RBC in 710. Clarithromycin was part of the game in 7929 patients, roughly 50% of the reviewed cases. The most consistent results are obtained with PPI-Clarithromycin-Amoxycillin recipe. OCT and LCM are the most effective with a contrasting situation of a lesser effectiveness of OCM and LCT, perhaps because of synergistic phenomenon's. Smoking and pre-treatment with PPI reduce ER by 12 and 18% respectively (1).

Table I. — **Eradication rates with one-week full-dose triple therapies**

Regimen	N patients	N Eradicated	ITT Eradication Rate (%)
OCA	2509	2111	84%
LCA	696	542	82%
PCA	450	350	78%
RBC CA*	308	258	84%
OCM	1379	1142	83%
LCM	334	289	87%
PCM	510	435	85%
RBC CM	402	333	83%
OCT	1103	955	87%
LCT	238	186	78%

O : Omeprazole 20 mg bid ; C : Clarithromycin 500 mg bid ; A : Amoxycillin 100 mg bid : L : Lansoprazole 30 mg bid ; P : Pantoprazole 40 mg bid ; RBC : Ranitidine Bismuth 400 mg bid ; M : Metronidazole 500 mg bid ; T : Tinidazole 500 mg bid. *53 patients were given RBC 400 bid for more than 7 days (14 or 28 days).

To note, in case of Imidazole primary resistance, the ER is consistently reduced by 30% in all Imidazole-containing regimens (1). The overall ITT ER for RBC-based short triple is 83.2% (710 patients) versus 84.5% (8945 patients) for PPI-based short triple, a figure very close to the 86% previously reported (1). There is no significant difference either between different PPI's nor between PPI- and RBC-based short triple's, in three randomized comparative studies with a total of 251 patients (28,29,30).

In a review of 9 studies (567 patients-11), quadruple therapy was successful in 94.8% of patients by All Patients Treated (APT) analysis but according to Penston and Mc Coll's paper (1), the ITT eradication rate is 83%. To note, quadruple therapy can be prescribed in patients with penicillin allergy, (or intolerance for macrolides) and might overcome primary resistance to Imidazoles. Finally, Azithromycin has been used in various PPI-based one- or two-week triple therapies, at the dose of 500-mg uid for the first 3 days.

Table II. — **Incidence of side effects with HP eradicating therapies**

Regimen	Overall side effects	Serious
Ome Amox 2 w	14%	2%
Ome Clari 2 w	26%	3%
OTT 2 w	40%	4%
Quadruple 1 w	40%	4%
OCT (Bazzoli) 1 w	7%	< 1%
OAMtz 1 w	39%	2%
OAC (500 bid)	22%	1%
RBC triple 1 w*	24%	?

* Data available in 567 patients out of 766.

In 6 studies (329 patients), the mean ITT ER was 79.6%. The occurrence of side effects for different schemes in 148 studies (1) is reported in table II. Few data are available for RBC-based schemes mainly reported in oral communications or abstracts. Never-

theless, available data suggest a similar occurrence of side effects in PPI-based and RBC-based triple therapies. In quadruple therapy, side effects are more frequent and they are minimal with Bazzoli scheme, unfortunately poorly effective in Belgium.

There are few data about the fate of patients who need re-treatment because of eradication failure. The choice for re-treatment obviously depends of previous therapy but should be, in most cases, based on culture and strain's sensitivity testing. In any cases, if the patient previously received a treatment containing either Imidazole and/or Clarithromycin, the quadruple therapy might be the best empiric bet.

Conclusions

1. One week treatment schemes, PPI- or RBC-based triple therapies and quadruple therapy reach an ITT eradication rate around 85% and seem equivalent.
2. PPI-based regimens are the best documented. In Belgium, because of a high rate of Imidazole-resistance and poor results of Bazzoli-like regimens, the association PPI-Clarithromycin 500-Amoxycillin 1000 twice a day is the best choice with the lowest rate of side effects and the most consistent eradication rate in the literature. In 71 consecutive patients we observed ITT eradication rate of 82% and APT eradication rate in 85% (unpublished data).
3. Quadruple therapy is an excellent alternative despite suspected difficulties for full compliance and a reported 40% of adverse events. It is indicated for patients with penicillin allergy (5% in our experience) and overcomes Imidazole-resistance and Macrolide-resistance, a disquieting and growing problem in our country.
4. RBC-based triple therapies are also effective and deserve validation in Belgium.
5. Azithromycin-containing therapies still need further studies to confirm promising results and should not be recommended in routine practice to day.
6. Rapid symptomatic relief, a key factor for compliance, must be assessed by double blind, randomized studies comparing PPI- and RBC-based treatments.

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