The eradication treatments of *Helicobacter pylori*

• Joël Wermeille, Georges Zelger and Michael Cunningham

Introduction

Since its discovery in 1982 by Marshall and Warren [1], the small curved bacterium successively named *Campylobacter pyloridis*, then *Campylobacter pylori* and finally *Helicobacter pylori*, has given rise to an abundance of literature (150 publications in 1988, 1000 in 1990, several thousand at present), and the number of works establishing a correlation between this bacterium and different gastric and duodenal ailments has not stopped growing.

But despite the explosion of fundamental and clinical research in the area of *H. pylori*, tending to present the gastric and duodenal ulcer for consideration as an infectious disease, numerous questions remain concerning the clinical importance of this bacterium and the indications of the treatments for its elimination.

Whilst it is true that a close association exists between peptic ulcers and infection by *H. pylori* (95% of patients with a duodenal ulcer and 80% of patients with a gastric ulcer are infected by this microorganism), there remains a very large prevalence of gastric infestation by the bacterium in subjects with no history of an ulcer (33% in the adult European population, 50% in the population of those over 50 years old in developed countries, 70-90% in the adult population in developing countries) [2-7]. It remains equally difficult to explain the extreme rarity of conjugal ulcers, as 68% of the wives of male subjects who are *H. pylori* positive are themselves infected by the bacterium [8].
The principal benefit expected from eradication of *H. pylori* is the spectacular decrease in ulcer recurrence, dropping from about 70% to less than 10% in the following year [7 9-11]. This is certainly a major benefit but other treatment modalities can achieve similar results. Selective vagotomy and chronic antisecretory treatment (H_2-receptor antagonist or proton pump inhibitors) are also accompanied by a low rate of relapse (about 2% per year for the former and 10-30% for the latter) [10 12 13]. The eradication of *H. pylori* is however the most cost effective treatment if one considers that a patient can 'recover' from his peptic ulcer disease in 7 to 14 days with adequate antibiotic treatment, rather than undergo surgery or several years of anti-secretory treatment [10 20 21].
Though *H. pylori* infection represents only one factor of aggression among others (hydrochloric acid, proteolytic enzymes, bile salts, NSAIDs, etc.), in ulcer disease it continues to be a key element, as its elimination alone serves to accelerate the healing of peptic ulcer and considerably reduces the risk of recurrences, including that of complicated ulcers, notably hemorrhagic [10 11 16-22].

At present, for a very large majority of specialists, the eradication of *H. pylori* represents the basis for treatment of gastric or duodenal peptic ulcers in infected patients [11 16 17 23 24]. It seems in all likelihood to be sufficient to heal duodenal and gastric ulcers [25-30]. The anti-infectious treatment can be combined with antisecretory symptomatic treatment [25 30].

Finally, various studies present the eradication

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Abstract
The eradication of *Helicobacter pylori* is at present widely recognized as the adequate therapeutic approach for gastric and duodenal ulcers in infected patients. In those with dyspepsia but no ulcer as well as in those with type B chronic gastritis, eradication remains controversial.
It is difficult to have a clear opinion on the advantages and disadvantages of the numerous existing therapies. Therefore, a systematic review of published treatments has been made by the authors. Ideally, the eradication treatment of *H. pylori* should have the following advantages: 1. eradication superior to 90%, 2. simplicity, 3. short duration, 4. safety, 5. low cost, 6. reproducibility of results.
Dual therapies (2 antibiotics or a proton pump inhibitor in combination with an antibiotic) rarely allow an eradication greater than 90% and the results have poor reproductibility. Consequently, they do not represent an ideal anti-*H. pylori* treatment.
Triple therapies come closer to the requirements for an ideal treatment, with eradication rates generally close to 90%, varying little between studies and the countries in which they were performed. The triple therapy *bismuth-imidazole-tetracycline (or amoxicillin)* still represents for many authors the standard reference therapy. It has the advantage of low cost, high efficacy and widespread use. It is the therapy that has been the most studied. However, the increasing emergence of strains resistant to imidazoles, the complexity of the treatment (10 to 12 tablets per day), the numerous adverse effects and the lack of availability of bismuth salts in certain countries has led to the elaboration of therapeutic schemes combining an antisecretory drug with 2 antibiotics. Among these, the combination *PPI-clarithromycine-imidazole* during 7 days represents the most studied *triple therapy of short duration.* For some authors, it already represents a new standard. However, the efficacy of this therapy seems dependent on the sensitivity of the bacteria to imidazoles. Consequently, this combination cannot be considered as the ideal anti-*H. pylori* treatment in the areas where the prevalence of strains resistant to imidazoles is high. The association *PPI-clarithromycine-amoxicillin* appears on the contrary to be very effective against strains resistant to metronidazole and therefore could constitute the treatment of choice in population with high prevalence of such strains. Great hope is currently surrounding the finalization of a vaccine directed against the urease of the bacteria. This approach would allow both the treatment and the prevention of *Helicobacter pylori* infection on a large scale.

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treatment of *H. pylori* as the most economical method of controlling peptic ulcer [14 15 31], while others clearly point to an improvement of the quality of life for ulcer patients after the elimination of the bacterium [31 32].

Indications for eradication treatment of *Helicobacter pylori*

The wide prevalence of infection by this bacterium in the general population makes it difficult to envisage, with our present knowledge, antibiotic treatment of all infected patients. The eradication of *H. pylori* is consequently limited to a group of persons presenting the most serious symptomatology.

In 1994, a consensus conference was held in the United States under the aegis of the National Institutes of Health (NIH) in order to define the indications of the treatment of *H. pylori* infection [23].

The conclusions of this conference are supported by numerous authors of review articles from various countries around the world and by another consensus conference held by the French National Society for Gastroenterology [7 16 24 33-35].

Gastric or duodenal ulcers

At the end of the above-mentioned conference, the consensus panel of experts estimated that a sufficient amount of data existed to recommend eradication in all patients presenting a gastric or duodenal ulcer associated with *H. pylori* infection in the case of a first occurrence, a recurrence or a peptic ulcer associated with the taking of NSAIDs.

It was also recommended that patients benefitting from a chronic gastric antisecretory treatment (H_2-receptor antagonist or proton pump inhibitor) for the prevention of simple or complicated (hemorraghic) ulcer recurrences should be treated as well, if they were infected. At the same time, the maintenance of preventive antisecretory treatment, along with the eradication of *H. pylori*, remains, until proven otherwise, necessary in cases involving prevention of serious complications of peptic ulcer disease.

Gastritis and dyspepsia without ulcerative lesions, gastric cancers

The consensus panel of the conference held by the NIH (1994) [23] estimated that it was not justified, with our present knowledge, to treat a patient infected by *H. pylori*, presenting gastritis without ulcerative lesions, with or without dyspepsia. It also concluded that a relationship between the bacterium and the development of a gastric cancer, having not been sufficiently studied to date, a systematic eradication of the micro-organism as a preventive measure could not be recommended.

However, despite these recommendations and the still uncertain and contradictory data on the cause-effect relationship between infection by *H. pylori* and non-ulcer dyspepsia [36], some specialists propose eradication (around 50% of the dyspeptic patients are infected) in cases where symptomatic treatments (reputed as being effective) have failed. In some dyspeptic patients the result of eradication is spectacular, whilst in others it is without effect [33 37-39]. The vast majority of studies that have examined the effect of *H. pylori* eradication on symptoms in non-ulcer dyspepsia have only a short follow-up period, usually 1-3 months [36 38]. However, the physiologic anomalies (hypergastrinaemia, hyperacidity, delayed gastric emptying) take much longer to resolve [38 40]. Therefore it is important in such studies to have longer observation periods. In recent studies in which patients have been followed for 12 months, there was a clear advantage of eradication [38 40].

As regards chronic gastritis of patients infected by *H. pylori* without ulcerative lesions, the benefit that eradication could bring is still widely debated. It is presently admitted that chronic gastritis is a factor predisposing to the development of cancer, as it can evolve towards atrophy, metaplasia and dysplasia [41-44]. *H. pylori* is recognized as the causal agent of chronic active gastritis type B (70% to 90% of chronic active gastritis) [36 45-47] thus, it represents one co-factor of gastric carcinogenesis. Consequently, some specialists propose an eradication treatment of the bacterium in infected patients with gastritis and severe symptoms or intense inflammatory reactions, or in individuals from families with a history of cancer and those in whom evidence of atrophy, metaplasia or dysplasia are found early in life [33 35].

If it is true that a cause-effect relationship exists between *H. pylori* and the gastric cancers (grade 1 carcinogens) [41-44 48 49], the value of eradication with the goal of cancer prevention has still not been scientifically proven in the general population and among dyspeptics. The number of patients susceptible to developing an adenocarcinoma or a gastric lymphoma is minimal in proportion to the population infected.

Though the importance of eradication of *H. pylori* is not yet clearly demonstrated in gastric adenocarcinoma, the importance of the elimination of this germ in the control of gastric lymphoma of type low-grade MALT (mucosa-associated lymphoma tissue) is, on the other hand, becoming increasingly recognized. In certain studies a recovery from the lymphoma after eradication of the bacterium was obtained in more than 2/3 of the cases [43 50 51 52].

In Ménétrier's hypertrophic gastritis, it is admittedly beneficial to eradicate the germ because of possible regression of lesions known to be at high risk of cancers [53].

Eradication treatments of *Helicobacter pylori*

The present review was based on a MEDLINE search of literature from 1988 to 1996 and on abstracts presented at gastroenterology meetings. Articles and abstracts were reviewed regardless of study design. For each evaluated therapy regime, only studies that used optimal and comparable dosage and duration of treatment were included in the compilation of the combined eradication rates presented.

H. Pylori is a bacterium with a slow growth rate, and its eradication generally necessitates polytherapy. The antimicrobial drugs used for its elimination are divided into two categories: those having topical activity and those having systemic activity. In fact, only the bismuth salts have an activity which is uniquely topical. The antibiotics used for the treatment all have activity which is both topical and systemic.

Table 1 **In vitro *antibacterial activity and clinical efficacy of antimicrobial and anti-ulcer agents against* Helicobacter pylori *infection [54-59]***

Class	Agent	MIC_{90} [µg/ml]	% Eradication
ß-Lactams	Amoxicillin	0.02	0-30
	Penicillin	0.03	0
	Ampicillin	0.2	-
	Cefaclor	1	-
	Cefotaxime	1	-
	Imipenem	<2	-
Macrolides	Clarithromycin	0.03	36-42
	Erythromycin	0.25	5-7
	Azithromycin	0.25	-
Tetracyclines	Tetracycline	1.2	0
	Doxycycline	2.4	0
Nitroimidazoles	Metronidazole	1	5-30
	Tinidazole	4	5
Others antibiotics	Ciprofloxacin	0.25	0
	Ofloxacin	1	0-5
	Clindamycin	8	0-10
	Furazolidone	2.4	0-44
	Rifampicin	1	0
	Sulfonamides	>500	-
	Vancomycin	>500	-
Bismuth salts	Bismuth subcitrate	5-25	0-30
	Bismuth subsalicylate	5-25	0-30
Anti-ulcerants	Cimetidine	>500	0
	Ranitidine	>500	0
	Sucralfate	>500	-
	$Al(OH)_3$	>3200	-
	Omeprazole	20-25	0-14
	Lansoprazole	6	0-10

MIC90: concentration of drug (µg/ml) required to inhibit 90% of strains of *Helicobacter pylori*.
% Eradication: number of patients successfully treated / number of patients treated

Ideally, the eradication treatment of *H. pylori* should have the following features:
- efficacy (rate of eradication of the bacterium nearly 100%)
- simplicity (small daily doses and short duration of treatment in order to obtain the best possible adherence to the treatment)
- safety
- good tolerance
- low cost

It is important to differentiate between the clearance and the eradication of *H. pylori*. The former corresponds to the absence of evidence of the bacterium at the end of a therapeutic period, which can be obtained with the aid of any treatment acting on the growth of the micro-organism. The eradication by contrast implies the absence of evidence of the bacterium at least four weeks after the end of the treatment. This alone corresponds to a true cure of the infection.

Single therapies

Despite high sensitivity of *H. pylori* to a large number of antibiotics *in vitro*, the first therapeutic tests *in vivo* using single-drug therapy were disappointing, the rates of eradication obtained rarely surpassing 20 % (Table 1).

Bismuth

Bismuth subcitrate and subsalicylate are the two salts most often used for the treatment of *H. pylori* infections. They are not commercialized in all European countries because of the possible risk of encephalopathy observed during prolonged treatment in patients presenting severe renal insufficiency, or during the administration of other, more soluble, salts of bismuth. The systematic absorption rate of these two salts being very low, side effects are extremely rare [60]. Bismuth subnitrate is also used in some countries [30]. All these salts are topically ulcer-healing drugs as effective as the H_2-receptor antagonists; they stimulate the synthesis of the gastric prostaglandins and, in an acid environment, form a protective layer covering the ulcer crater. Furthermore, they have an antibacteriuml effect on *H. pylori*. They disturb the integrity of the bacterium cell wall, the adhesion of

Table 2 *Prevalence rates of metronidazole resistance in various countries [68 69]*

Countries	*Prevalence*
Spain	6%
Sweden	10%
Ireland	7-20%
Portugal	23%
Italy	23%
Netherlands	6-41%
France	25%
United Kingdom	19-33%
Belgium	24-29%
Switzerland	30%
Finland	27-36%
Greece	45%
Australia	17%
Canada	35%
Zaire	84%

micro-organism to the gastric epithelium and enzymatic functions of the bacterium [61]. It is still not known whether their ulcer-healing activity is due to their antibacterium or cytoprotective properties.

In single therapy, the rates of eradication obtained with these bismuth salts are low (20%), but they are still useful when combined with two antibiotics in triple therapy. These are the first antiulcer drugs to have been studied in *H. pylori* infections. In fact, it was long ago observed that recurrences one year after the cure of a peptic ulcer were less frequent after treatment with bismuth than after treatment using a H_2-receptor antagonist [62 63].

Dosages used: subcitrate of bismuth : 480 mg/d; subsalicylate of bismuth: 1200-1800 mg/d.

Amoxicillin

Even though *H. pylori* is very sensitive *in vitro* to Amoxicillin, the rates of eradication obtained in single therapy are around 20%. This antibiotic represents one of the basic molecules for the eradication treatment of the bacterium, by reason of the absence of resistance observed up to now and its strong secretion at the gastric level [55 64]. Even though this penicillin is relatively stable in an acid environment, it reaches its maximum activity at a pH of near neutrality, which explains the important increase of activity in combination with a gastric antisecretory drug [65] (Table 3).

Dosage used: 1500-2000 mg/d.

Tetracycline

In vitro, *H. pylori* is also very sensitive to tetracycline, an antibiotic which, like amoxicillin, does not seem to lead to resistance and with effectiveness little influenced by gastric acidity [55]. A strain of *H. pylori* resistant to tetracycline has however already been described [66], contrary to amoxicillin. The low rates of eradication obtained *in vivo* in single therapy, however, confines its use to triple therapy.

Dosages used: 1500-2000 mg/d.

Metronidazole

This molecule is highly active against *H. pylori*. It is strongly secreted at the gastric level [67], and has little sensitivity to gastric pH [55]. Its use however is partially limited by frequent resistance of the bacterium to this antibiotic (Table 2). Its combination with a salt of bismuth and another antibiotic increases its efficacy [68]. Tinidazole has properties equivalent to those of metronidazole.

Dosage used: 1000-1500 mg/d.

Macrolides and azilide

These antibiotics are very effective *in vitro* on *H. pylori*, the MIC_{90} situated between 0.03-0.25 µg/ml. *In vivo*, only azithromycine and roxithromycine in a limited number of studies [70-75] and especially clarithromycine have shown an interesting activity in dual and triple therapy. The poor results obtained with the other macrolides seem principally related to their instability in acid environments [76].

Clarithromycine has shown excellent results, mainly in dual and triple therapy, but also in single therapy with 36-42% eradication of the bacterium, which for single therapy is exceptional. Despite its high cost and the emergence of resistances (1-12% in developed countries) [69 77-85], it represents, at present, one of the basic molecules for the eradication treatment of *H. pylori*.

Dosage used: 500-1500 mg/d.

Other antibiotics

In spite of a strong activity *in vitro*, quinolones, clindamycin and rifampicin have not shown sufficient efficacy *in vivo* for use in *H. pylori* infections.

Ulcer-healing drugs

The antacids appear less active *in vitro* (MIC_{90} 40 to >3200 µg/ml) and *in vivo* against *H. pylori*, despite the partially contradictory results reported by some studies [56 86-88].

H_2-receptor antagonists seem inactive *in vitro* and i*n vivo* [87 88] against the bacterium, but they maintain an important place in eradication treatment because in raising the gastric pH, they potentiate the activity of certain antibiotics.

According to research, the observed activity of sucralfate against the bacterium is quite variable [89 90]. However, one recent study has demonstrated that sucralfate can potentiate the action of different antibiotics (amoxicillin, tetracycline, metronidazole and erythromycine) against *H. pylori*, as effectively as omeprazole [91]. Furthermore, a recent review of reports found an average eradication rate of 80% for triple therapy combining sucralfate with two antibiotics [92]. But the position of sucralfate remains to be clarified.

The proton pump inhibitors (PPIs) have a known activity *in vitro* and *in vivo* against *H. pylori*, with MIC_{90} close to those of bismuth salts and imidazoles with which these molecules have certain structural similarities [54]. *In vivo*, the rates of eradication obtained with omeprazole and lansoprazole in single therapy according to studies vary between 0% and 14% [57 58]. The importance that these molecules have in the eradication treatment of *H. pylori* is related to their strong capacity for raising the gastric pH, thus allowing potentiation of the effects of certain antibiotics [57 58 65].

Table 3 *Dual therapy regimens in the eradication of* **Helicobacter pylori**

Drugs used	*Dosage*	*Duration*	*# Eradicated/# Treated* ***% Eradication***	*Authors (references)*	
Bismuth: SCBC or SSB	480mg/d 1800-2000mg/d	14-42 days	86/197		
+ Amoxicillin	1500-2000mg/d	7-28 days	**43.7%** (from 28 to 60%)	Chiba (1992)	[59]
Bismuth: SCBC or SSB	480mg/d 2080mg/d	7-28 days	65/118 **55.1%**	Chiba (1992)	[59]
+ Metronidazole	1000-1500mg/d	7-14 days	(from 38 to 79%)		
Bismuth: SCBC + Clarithromycin	480mg/d 1000mg/d	14 days 14 days	33/48 **68.8%**	Noach (1994)	[57]
Metronidazole or Tinidazole	1200mg/d 1000-2000mg/d	7 days 4-8 days	98/170 **57.6%**	Rauws (1992) Chiba (1992)	[96] [59]
+ Amoxicillin	1500-2000mg/d	4-8 days	(from 52 to 69%)		
Amoxicillin + Omeprazole or Lansoprazole	2000-3000mg/d 40-80mg/d 60mg/d	14 days 14 days 14 days	671/1015 **66.1%** (from 28 to 92%)	Adamek (1992) Labenz (1992) Logan (1992) Wagner (1992) Labenz (1993) Rokkas (1993) Atherton (1994) Goh (1994) Labenz (1994) Labenz (1994) Labenz (1994) Logan (1994) Tyszkiewicz (1994) Al-Assi (1995) Cayla (1995) Graham (1995) Jaspersen (1995) Jaspersen (1995) Laine (1995) Parente (1995) Saberi-F (1995) Soulé (1995) Meining (1996) Sung (1996) Vanderhulst (1996)	[97] [98] [99] [100] [93] [101] [102] [103] [104] [105] [106] [107] [108] [109] [110] [111] [20] [21] [112] [113] [114] [115] [116] [27] [117]
Clarithromycin + Omeprazole or Lansoprazole	1000-1500mg/d 40-80mg/d 60mg/d	14 days 14 days 14 days	401/545 **73.6%** (from 55 to 83%)	Burette (1993) Neri (1993) Greaves (1994) Gurbuz (1994) Logan (1994) Logan (1994) Neri (1994) Harris (1995) Hunt (1995) Katelaris (1995) Logan (1995) O'Morain (1995) Takimoto (1995)	[118] [119] [120] [121] [107] [122] [123] [124] [125] [126] [127] [128] [129]

SCBC = bismuth subcitrate colloidal
SSB = bismuth subsalycilate
 # Treated = cumulated number of patients treated in the reviewed clinical studies
 # Eradicated = cumulated number of patients successfully treated in the reviewed clinical studies
% Eradicated = overall eradication rate

Table 4 *Triple therapy regimens in the eradication of* **Helicobacter pylori**

Drugs used	*Dosage*	*Duration*	*# Eradicated/# treated* ***% Eradication***	*Authors (references)*
Bismuth: SCBC or SSB + Tetracycline + Metronidazole	480mg/d 1000-2000mg/d 1250-2000mg/d 800-1200mg/d	14 days 14 days 14 days	491/563 **87.2%** (from 65 to 94%)	Rodionoff (1990) [134] Bell (1992) [135] Daskalopoul. (1992) [136] Graham (1992) [137] Labenz (1992) [138] Sobala (1992) [139] Balatsos (1993) [140] Culter (1993) [141] Thijs (1993) [142] Iser (1994) [143]
Bismuth: SCBC or SSB + Tetracycline + Metronidazole	480mg/d 1000-2000mg/d 1500-2000mg/d 800-1200mg/d	7 days 7 days 7 days	338/404 **83.7%** (from 65 to 94%)	Rodionoff (1990) [134] Daskalopoul. (1992) [136] Hosking (19940 [25] Noach (1994) [57] De Boer (1995) [144] Phull (1995) [145] Sung (1995) [26] Sung (1996) [27]
Bismuth: SCBC or SSB + Amoxicillin + Metronidazole	480mg/d 1000-2000mg/d 1500-3000mg/d 800-1500mg/d	14 days 14 days 14 days	223/261 **85.4%** (from 81 to 100%)	Börsch (1989) [146] Rautelin (1992) [147] Seppala (1992) [148] Tucci (1994) [149] Chen (1995) [150]
Bismuth: SCBC or SSB + Amoxicillin + Metronidazole	480mg/d 1000-2000mg/d 1500-3000mg/d 800-1500mg/d	7-14 days 7 days 7 days	121/162 **74.7%** (from 50 to 90%)	Börsch (1989) [146] Lambert (1990) [151] Rauws (1990) [152] Lambert (1994) [153] Chen (1995) [150]
Ranitidine + Clarithromycin + Metronidazole or Tinidazole	300-600mg/d 400-500mg/d 500-1000mg/d	35-42 days 7-14 days 7-14 days	79/93 **84.9%** (from 78 to 93%)	Kihira (1996) [156] Spadaccini (1996) [157] Yousfi (1996) [158]
Ranitidine + Clarithromycin + Amoxicillin	300mg/d 1500mg/d 2250mg/d	42 days 10 days 10 days	25/29 **86.2%**	Al-Assi (1994) [159]
Ranitidine + Amoxicillin + Metronidazole or Tinidazole	300mg/d 1500-2250mg/d 1000-1500mg/d	42 days 12-15 days 10-14 days	114/137 **83.2%** (from 75 to 89%)	Lamouliatte (1992) [160] Hentschel (1993) [11] Powell (1994) [161] Lahaie (1995) [162]

Dual therapy

Different treatments combining a bismuth salt and an antibiotic, two antibiotics, or an antisecretory drug and an antibiotic, have been tested with the aim of improving rates of eradication obtained in single therapy or of diminishing the side-effects associated with bismuth-metronidazole-tetracycline triple therapy [93] (Table 3).

Only the antisecretory/antibiotic combination has given good results with rates of eradication capable of surpassing 80%. The two most-studied dual therapies are those combining a proton pump inhibitor (PPI) and amoxicillin or clarithromycin.

Some researchers have studied the *H_2-receptor antagonist/clarithromycin* and *H_2-receptor antagonist/amoxicillin* combinations with a high dose of an

Table 4 *Continued*

Drugs used	*Dosage*	*Duration*	*# Eradicated/# treated* ***% Eradication***	*Authors (references)*	
IPP: Omeprazole	20-40mg/d			Bazzoli (1994)	[164]
or Lansoprazole	30-60mg/d	7 days	895/990	Moayyedi (1994)	[165]
or Pantoprazole	80mg/d			Moayyedi (1994)	[166]
+			**90.4%**	Jaup (1995)	[167]
Clarithromycin	500mg/d	7 days	(from 69 to 96%)	Buckley (1995)	[168]
+				Grasso (1995)	[169]
Metronidazole	800-1000mg/d	7 days		Jaup (1995)	[170]
or Tinidazole				Labenz (1995)	[171]
				Labenz (1995)	[172]
				Labenz (1995)	[173]
				Lind (1995)	[174]
				Deltenre (1996)	[175]
				Misiewicz (1996)	[176]
				Peitz (1996)	[77]
				Pryce (1996)	[81]
				Sito (1996)	[177]
IPP: Omeprazole	40-80mg/d				
or Lansoprazole	60mg/d	7 days	239/254	Lind (1995)	[174]
+				Schütze (1995)	[179]
Amoxicillin	2000mg/d	7 days	**94.1%**	Laine (1996)	[180]
+				Monès (1996)	[181]
Clarithromycin	1000mg/d	7 days	(from 77 to 98%)	Peitz (1996)	[182]
IPP: Omeprazole	40mg/d				
or Lansoprazole	60mg/d	7 days	273/317	Lind (1995)	[174]
+				Labenz (1996)	[183]
Amoxicillin	2000mg/d	7 days	**86.1%**	Misiewicz (1996)	[176]
+				Yousfi (1996)	[184]
Clarithromycin	500mg/d	7 days	(from 77 to 98%)		
IPP: Omeprazole	40mg/d				
or Lansoprazole	30-60mg/d	7 days	434/539	Lind (1995)	[174]
+				Bell (1995)	[185]
Amoxicillin	1500-2000mg/d	7 days	**80.5%**	Labenz (1996)	[183]
+				Misiewicz (1996)	[176]
Metronidazole	800-1200mg/d	7 days	(from 73 to 91%)	Sito (1996)	[177]
or Tinidazole					

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 # Treated = cumulated number of patients treated in the reviewed clinical studies
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antisecretory drug (1200 mg ranitidine). The rates of eradication were close to those obtained with a PPI (84% for the *ranitidine/clarithromycin* combination and 69% for the *ranitidine/amoxicillin* combination) but they have not been confirmed [94 95].

PPI-amoxicillin

In spite of the very promising results of the first studies citing eradication rates of greater than 80% [97 98 100], the efficacy of this therapy seems to vary considerably (28% to 92% eradication of *H. pylori*) depending on the study and the place in which it was performed, with no clear explanation of the differences. In studies done in Germany, eradication rates near 80% were observed [20 21 93 97 98 104-106], while studies made in other countries (USA, France, Italy, Great Britain, etc.) frequently showed rates of elimination less than 60% [99 109-115]. This therapeutic schema, however, is the only one to have exhibited an efficacy through intravenous methods [64]. In 1993, Axon (VIth Workshop on Gastroduodenal Pathology and *Helicobacter pylori*. Brussels, 1993) defined the optimal conditions for use of this dual therapy based on a review of articles on 14 studies (essentially German). According to the author, it is the therapy using omeprazole 2 x 20 mg/d (or lansoprazole 2 x 30 mg/d) and amoxicillin 2 x 1000 mg/d for 14 days which allows the best rates of eradication to be obtained. Though the duration of the treatment and the daily doses of the PPI and the antibiotic are also considered optimal by other authors, the division of the doses of the PPI (2 x 20 mg of omeprazole/d as opposed to 1 x 40 mg/d) by contrast is not unanimously considered to be a determin-

Table 5 *One, two and four day treatments*

Drugs used	*Dosage*	*Duration*	*# Eradicated/# treated* **% Eradication**	*Authors (references)*	
Bismuth: SCBC	4 x 240mg	1 day			
+					
Amoxicillin	4 x 2000mg	1 day	23/32	Tucci (1993)	[187]
+			**71.8%**		
Metronidazole	4 x 500mg	1 day			
+					
Omeprazole	1 x 40mg	1 day			
Bismuth: SCBC	4 x 300mg	1 day			
+					
Amoxicillin	4 x 2000mg	1 day	19/26	Dobrucali (1993)	[188]
+			**73.1%**		
Metronidazole	4 x 500mg	1 day			
+					
Omeprazole	1 x 40mg	1 day			
Bismuth: SCBC	4 x 240mg	1 day			
+					
Amoxicillin/acid clav.	4 x 500/250mg	1 day	18/23	Takats (1994)	[189]
+			**78.3%**		
Metronidazole	4 x 500mg	1 day			
+					
Omeprazole	1 x 20mg/d (1st day: 40mg)	28 days			
Bismuth: SCBC	4 x 240mg/d	1 day			
+				Wermeille (1998)	[193]
Amoxicillin	4 x 2000mg/d	1 day	3/15	Cunningham	[193]
+			**20%**		
Clarithromycin	4 x 500mg/d	1 day			
+					
Lansoprazole	3 x 30mg/d	1 day			
Bismuth: SCBC	4 x 240mg/d	2 days			
+					
Amoxicillin	4 x 1000mg/d	2 days	27/30	Tucci (1995)	[190]
+			**90.0% (*)**		
Tinidazole	4 x 500mg/d	2 days			
+					
Omeprazole	1 x 40mg/d	7 days			
Bismuth: SCBC	4 x 240mg/d	2 days			
+					
Tetracycline	4 x 500mg/d	2 days	20/26	Kung (1996)	[191]
+			**76.9%**		
Metronidazole	4 x 400mg/d	2 days			
+					
Omeprazole	2 x 20mg/d	7 days			
Bismuth: SCBC	4 x 120mg/d	4 days			
+					
Tetracycline	4 x 500mg/d	4 days	49/54	De Boer (1995)	[192]
+			**90.7%**		
Metronidazole	3 x 500mg/d	4 days			
+					
Omeprazole	2 x 20mg/d	7 days			

SCBC = bismuth subcitrate colloidal
SSB = bismuth subsalycilate
 # Treated = cumulated number of patients treated in the reviewed clinical studies
 # Eradicated = cumulated number of patients successfully treated in the reviewed clinical studies
% Eradicated = overall eradication rate
(*) : In this study, one inclusion criterion was: 'susceptibility of the isolated strains of *H. pylori* to both amoxicillin and tinidazole'.

ing element [101 107 111 130 131].

Dosages and duration of this therapy are summarized in Table 3.

PPI-clarithromycin

Numerous studies of this combination have been made showing eradication rates varying between 55% and 83%, in which omeprazole and clarithromycin were administered at doses equal to or higher than 40 mg and 1000 mg per day, respectively, for 14 days (Table 3). The reasons for this dispersion of results in different studies remains unexplained. The emergence of *H. pylori* strains resistant to clarithromycin could be a possible explanation. It is presently established that the doses of omeprazole and of clarithromycin proposed below correspond to the minimum necessary for obtaining a good response with this dual therapy [132]:

Dosages and duration of this therapy are summarized in Table 3.

Triple therapies

Triple drug therapy constitute presently the most certain means of obtaining an efficacy equal or superior to 90%. Furthermore, they seem to have the advantage that they can be administered for a shorter duration (7 days), when compared to dual therapy, with a superior rate of eradication (Table 4).

Bismuth-tetracycline (or amoxicillin)-metronidazole

This treatment is internationally recognized, notably by the consensus specialists of the conference held in 1994, under the aegis of the National Institutes of Health (NIH) [23] and by a group of experts which met during the 1990 world Congress of gastroenterology in Sydney.

This is the first combination to allow a rate of eradication higher than 90%. The results obtained by Borody et al. (94% eradication) [133] with this type of treatment were later confirmed by numerous other studies carried out in different countries, where metronidazole was sometimes replaced by tinidazole and tetracycline by amoxicillin. The combinations with the latter antibiotic seem nevertheless to be slightly less effective [57] (Table 4). Thousands of patients throughout the world have been treated with the aid of these triple therapies, that have the advantage of high efficacy and low cost. Disadvantages comprise, on one hand, frequent adverse effects (observed in 20% to 60% of patients), in general in the digestive tract, and on the other hand the large number of tablets (10 to 12 per day) patients have to take. These are two important factors compromising therapeutic compliance. Further, a diminution of efficacy of the combinations is observed in patients carrying strains resistant to imidazoles (6% to 45% of strains resistant to metronidazole in Europe) (Table 2). Though these triple therapies are in general very effective (eradication rate greater than 90%) for patients carrying strains sensitive to imidazoles, they allow an eradication of the bacterium in only 30% to 70% of patients infected by a strain resistant to this family of antibiotics [135 139 147 154]. The usual duration of these triple therapies (and the most studied) is 14 to 15 days, but it seems that a treatment of 7 days has comparable efficacy [34 57 59 134 136 150 155] (Table 4). Strictly concerning eradication of the bacterium with *bismuth-tetracycline-metronidazole* therapy, the benefit of adding a gastric antisecretory (H_2-receptor antagonist or PPI) remains highly disputed and differs depending on the study [25 30 144 145]. However, some benefit can be expected for the symptomatic treatment of peptic ulcers.

For this review, we only take into consideration triple therapies without addition of an antisecretory agent. The most of the published studies on *Bismuth triple therapies* use a H_2-receptor antagonist, and are consequently quadruple therapies.

Dosages and duration of this therapy are summarized in Table 4.

H_2-receptor antagonist-2 antibiotics

This type of combination has shown good results in some studies, with eradication rates between 78% and 93%, depending on the particular combination used [11 156-162] (Table 4).

H_2-receptor antagonist being inactive against *H. pylori* (MIC>500), the results obtained with these therapies suggest that the inhibition of acid secretion plays a predominant role in the efficacy of treatments combining a gastric antisecretory and 2 antibiotics, compared to the direct effect on the bacterium that is observed with the proton pump inhibitors.

Dosages and duration of this therapy are summarized in Table 4.

Proton pump inhibitors (PPI)-2 antibiotics

This type of triple therapy has acquired a wide popularity by reason of its high efficacy (eradication rates generally superior to 90%), its low number of adverse effects and its short duration of treatment (7 days), which facilitates compliance, an important factor in success of the treatment [163].

PPI-clarithromycin-imidazoles

It was Bazzoli et al. who first proposed in 1993 a short triple therapy with reduced doses combining 20 mg/d of omeprazole, 2 x 250 mg/d of clarithromycin and 2 x 500 mg/d of tinidazole for 36 patients, with 100% elimination of the infection [163]. This result has since been supported by a number of other studies [77 81 164-168 170 171 173 174 176 177] which have further demonstrated that substitution of tinidazole by metronidazole did not influence efficacy. Efficacy does seem however to diminish in cases of resistance of the bacterium to one of the two antibiotics [78 80 81]. The eradication of *H. pylori* appears similar if the antisecretory is used in single doses (20 mg/d of omeprazole or 30 mg/d of lansoprazole) or double doses [166]. The administration of clarithromycin in small doses (250 mg/d) offers the double advantage of a diminution of the frequency of the adverse effects and of the cost of the treatment. This combination currently represents, for some authors, a standard to which new therapies should be compared [191].

Dosages and duration of this therapy are summarized in Table 4.

PPI-clarithromycin-amoxicillin

This combination also allows excellent results to be obtained (in general > 90% eradication), particularly in studies where clarithromycin was administered in

doses of 2 x 500 mg/d [174 179-182]. It offers an interesting alternative of short triple therapy in countries where the resistance to imidazoles is high. The use of clarithromycin in doses of 2 x 500 mg/d seems more effective than its administration in weaker doses (2 x 250 mg/d), but this remains to be verified [174] (Tables 4). This type of treatment represents the most onerous 7-day triple therapy. The impact of resistance of *H. pylori* to clarithromycin on the efficacy of the treatment is not well documented, by reason of the infrequency of strains resistant to macrolides. Presently the optimal dose of the PPI is not clearly defined. A daily dose of 20 mg omeprazole or of 30 mg lansoprazole is probably sufficient, but the studies carried out to date almost all used a double dose of antisecretory.

Dosages and duration of this therapy are summarized in Table 4.

PPI-amoxicillin-metronidazole

This combination seems somewhat less effective than the two preceding combinations [34 174 176] (Table 4), but it represents an interesting alternative in cases of resistance or of contraindication of the clarithromycin.

Dosages and duration of this therapy are summarized in Table 4.

Two vast multicentric tests have been carried out in order to make a comparison between the different 7-day triple therapies combining a PPI and two antibiotics. The largest of these, the MACH 1 study [174], was carried out on 787 patients (of which 684 could be evaluated) in 5 countries (Germany, Canada, Ireland, the United Kingdom and Sweden). It allowed the comparison of 5 different combinations. The second study [176], more recent, was carried out on 496 patients (of which 465 could be evaluated) in 4 centers of the United Kingdom. It allowed the comparison of 4 different combinations. These two multicentric studies have confirmed the high efficacy of the triple therapies *PPI-clarithromycin-amoxicillin* and *PPI-clarithromycin-metronidazole*.

Other therapies and experimental therapies

Triple therapies comprising sucralfate or a zinc salt and two antibiotics

As cited above, a recent review of articles has found an average eradication rate of 80% (59% to 100% depending on the study) with the combination sucrasulfate + 2 antibiotics [92].

A triple therapy combining a zinc salt, metronidazole and amoxicillin has shown an efficacy of 100% in a study carried out on 26 patients [186].

These two substances thus appear promising, but their place in the eradication treatment of *H. pylori* still remains to be confirmed by other studies.

Treatments of 1, 2 and 4 days

The search for a treatment of very short duration with the goal of improving compliance to reduce treatment failure has led some researchers to experiment with quadruple therapies (bismuth-PPI-amoxicillin (or tetracycline)-imidazole) of 1, 2 and 4 days duration with eradication rates that are quite acceptable (72, 73 and 77% for treatment of one day, 77 and 90% for treatments of 2 days and 91% for a treatment of 4 days)[187-192] (Table 5). These results, obtained with a relatively moderate number of patients, still require confirmation. But these treatments appear to be very promising, particularly in geriatrics where compliance is often very poor for reasons of the polypharmacy which applies principally to that age group. However, the authors of this review have evaluted in a randomized clinical study the efficacy of a 'one-day-quadruple-therapy' containing amoxicillin, clarithromycin, bismuth subcitrate and lansoprazole (Table 5). An eradication rate of only 20% was obtained. It was interesting to note that 90% of the patients who failed with the 'one-day-quadruple-therapy' were healed of their infection after 7 days of triple therapy consisting of amoxicillin, clarithromycin and lansoprazole [193].

Ranitidine bismuth citrate

The efficacy of this molecule (combination of two antiulcer drugs) in healing the infection of *H. Pylori* and of peptic ulcers has been demonstrated in several studies. The eradication rates obtained with this molecule are low and correspond to those observed with only bismuth (0-20%). By contrast, in combination with an antibiotic, the rates of elimination of the bacterium vary between 48% and 94% depending on the dose administered and the antibiotic used [194-199]. The best results (82-94% eradication) have been obtained with 800 mg/d of *ranitidine-bismuth-citrate* for 4 weeks combined with 1000-1500 mg/d of clarithromycin for 14 days [194-197]. This treatment appears to be well tolerated and very effective, but the results, obtained with a relatively moderate number of patients (17-58 persons per group of patients treated), requires confirmation. The principal disadvantage of this dual therapy is its duration (4 weeks).

Eradication treatment of H. pylori *by topical administration of anti-infectious agents*

A topical treatment of one hour has shown an efficacy of 96% in a study carried out on 25 patients [200]. The patients were pretreated for two days with the aid of lansoprazole and pronase, before receiving, by means of a nasogastric probe directly in the stomach, a solution containing subnitrate of bismuth, amoxicillin, metronidazole and pronase. The solution was removed by aspiration one hour after its introduction.

Vaccine

The large prevalence of the *H. pylori* infection in the general population and the inherent difficulties with its elimination by antibiotics has lead to the development of a vaccinal approach and to the search for vaccine with preventative and therapeutic properties. Various teams are currently working to finalize a vaccine against bacterial urease. The results obtained in animal experiments [201 202] and in the first clinical test on humans allows hope for a vaccine against *H. pylori* to be on the market within the next years.

Control of the efficacy of the treatment and reinfection

The success of the eradication treatment of *H. pylori* is defined arbitrarily as the absence of evidence of the bacterium at least 4 weeks after the end of the thera-

py [203]. The evaluation of the efficacy of a treatment is made ideally with the *Carbon-13 Breath Urea Test*, which is reliable and non invasive (specificity and sensitivity superior to 90%) [204]. This test relies on the enzymatic hydrolysis of ingested urea (labeled with carbon-13 (^{13}C), a stable isotope) by urease, an enzyme present in high concentration in *H. pylori* infection. Urea labeled with ^{13}C is ingested by the patient and hydrolysed in the stomach by the urease of the bacterium into ammonia (NH_3) and carbon dioxide ($^{13}CO_2$). The $^{13}CO_2$ passes into the blood and is eliminated by the lungs into the air expired where the proportion of $^{13}CO_2$ is measured.

Culture, which requires endoscopic biopsy, nonetheless remains the method of reference.

Because today's treatments have a high efficacy (rate of eradication close to 90%), as a general rule, verification of the elimination of the bacterium is not performed except in cases of complicated, refractory and relapsing ulcers.

In developed countries, the rate of reinfection is understood to be between 0.5 and 1% per year [205 206].

Adverse effects

Adverse effects appear in 10% to 60% of patients depending on the treatment used. They consist most frequently of minor incidents (nausea, loose stool, diarrhea, changes in taste, dizziness, headaches), which rarely necessitate cessation of treatment (2 to 5% depending of the treatment studied).

The dual therapy *PPI-amoxicillin* seems to be the treatment that presents the lowest amount of adverse effects (0-20% depending on the study), while the triple therapies Bismuth-biantibiotics (comprising more than 1000 mg/d of metronidazole), may be the ones that present the most (20-60% depending on the study) [154]. In a recent review of articles, Penston [207] found an average frequency of side effects of 11% (n = 84/737) for the dual therapy *PPI-amoxicillin.* The same author reported 32% of adverse effects (n = 474/1492), for triple therapy combining bismuth and 2 antibiotics. The side effects requiring a cessation of treatment were 2% for dual therapy and 4% for triple therapy. These results are supported by various reviews and studies which directly compared these 2 treatments in the same group of patients [27 93] and by the studies cited in Tables 3 and 4.

The dual therapy *PPI-clarithromycin* shows (depending on the study) 20-50% adverse effects, of which the most frequent is a metallic taste, directly related to the doses of clarithromycin administered.

During the 7-day triple therapies combining a PPI and 2 antibiotics, one generally observes 15 to 30% undesirable effects. In the majority of cases these comprise diarrhea, most frequent in cases where amoxicillin is used, or alteration of taste, most frequent in patients consuming 2 x 500 mg/d of clarithromycin. The *short-duration-triple-therapy* proposed by Bazzoli et al. (PPI + 2 x 250mg of clarithromycin + 2 x 500 mg of tinidazole or metronidazole) [164] appears to be the best tolerated [131 174 208] (studies cited in Tables 3 and 4).

Factors contributing to the failure of treatments

Bacterium resistance to antibiotics

This represents a major factor in the failure of a treatment. Among the antibiotics used for the elimination of this bacterium, only amoxicillin and tetracycline do not appear to induce resistant strains. To date, resistance to amoxicillin has never been recorded, and very rarely to tetracycline [66]. Resistance concerns principally the imidazoles (metronidazole and tinidazole) with rates of 6-45% in Europe [68]. The resistance of *H. pylori* to the macrolides is less well documented, because of its low prevalence. It seems more common in France and Belgium (5-12% of resistant strains) [79 83-85], compared to other industrialized countries, where the primary rate of resistance is generally less than 5% [69 77 80-82].

It appears that the development of the resistance to nitroimidazoles and to macrolides is strongly related to their prior use in the treatment of other infections (parasitic, gynecological, lung or ORL infections) and the therapeutic failures after dual or triple therapy [78-80]. The largest prevalence of resistant strains is observed in countries where these antibiotics are the most widely used. Metronidazole is frequently used in Zaïre for different parasitoses. In this country, there is a rate of resistance to imidazoles greater than 80% [68]. In France and Belgium, where macrolides are frequently used as a primary intention for various benign infectious ailments (ORL), the rate of resistance varies between 5 and 10%.

With regard to the standard triple therapies combining bismuth, tetracycline (or amoxicillin) and metronidazole, the impact of the resistance of *H. pylori* to imidazoles is relatively well documented. In general an eradication rate above 90% is found in patients carrying strains sensitive to metronidazole, and 30 to 70% in cases of resistant strains [135 139 147 154].

The influence of the sensitivity of strains to imidazole and to macrolides on the eradication rates obtained with triple therapies of short duration combining a PPI and 2 antibiotics is very poorly documented. Nevertheless it seems that the combination PPI-clarithromycin-imidazole is very effective only on strains sensitive to both the antibiotics (eradication rate near 100%). In cases of resistance to imidazoles, the eradication rate drops to 52-88% and to 0% in cases of resistance to 2 antibiotics [77-81 166]. The rate of eradication obtained with the triple therapy PPI-amoxicillin-clarithromycin and the triple therapy PPI-amoxicillin-metronidazole also appears to lower in cases of resistance to clarithromycin for the former and to imidazoles for the latter [161 209-211]. The results obtained to date with the combination PPI-amoxicillin-clarithromycine on the strains resistant to metronidazole are excellent (eradication rates on the order of 90%) [211-213].

Therapeutic compliance

For some authors, this represents the most important factor in determining success of the treatment [214]. It depends on factors which are subjective (personality of the patient, symptom of the illness, etc.) as well as objective, such as the number of daily dosages, the appearance of adverse effects, the duration and the complexity of the treatment. With triple therapy com-

bining bismuth, tetracycline and metronidazole, Graham et al. have observed an eradication rate of 69% in the group of patients having taken less than 60% of the prescibed drugs and an eradication rate of 96% in the group of patients having taken more than 60% of the treatment [137]. Similar results have been observed for the dual therapy *omeprazole-amoxicillin* and the triple therapy *omeprazole-amoxicillin-metronidazole* [102 141 215 216].

Other factors

The activity of certain antibiotics on *H. pylori* strongly depends on pH. This is the case notably for amoxicillin and the macrolides (in a small way for clarithromycin, azithromycin and roxithromycin), which exert their maximum activity at a neutral pH. Only the imidazoles, the tetracyclines and the bismuth salts are not affected by gastric acidity. This may explain the low efficacy of the triple therapy *bismuth-amoxicillin-metronidazole* compared to the triple therapy *bismuth-tetracycline-metronidazole*. Similarly a low gastric pH over the course of the therapy *PPI-amoxicillin* could explain partly the failures observed with this treatment [214].

The consumption of tobacco appears to diminish the efficacy of certain eradication treatments of *H. pylori*. It seems to have no effect on the dual therapy *PPI-clarithromycin*, but could diminish the eradication rates obtained with the dual therapy *PPI-amoxicillin* and the triple therapy *PPI-clarithromycin-metronidazole* [214 217 218].

Discussion and conclusion

Eradication is at present clearly indicated in *H. pylori* gastric and duodenal ulcers. In patients with dyspepsia but no ulcer as well as in those with type B chronic gastritis, eradication remains controversial and is not widely accepted in these settings.

It is difficult to have a clear opinion on the advantages and disadvantages of the numerous therapies cited in this article, as there are presently no large studies which compare the efficacy, adverse effects, compliance and the eradication rates obtained in relation to sensitivity to antibiotics of the different treatments. According to Axon [219] and Lamouliatte [209], the criteria for an ideal eradication treatment of *H. pylori* are the following: 1. eradication superior to 90%, 2. simplicity, 3. short duration, 4. safety, 5. low cost, 6. reproductibility of results.

Dual therapies rarely allow an eradication rate greater than 90% (Table 3: 64% on the average for the combination *PPI-amoxicillin*, 74% for the combination *PPI-clarithromycin*), and the results have poor reproductibility (eradication rates varying between 28 and 92% for the combination *PPI-amoxicillin*, and between 55 and 84% for the combination *PPI-clarithromycine*). Consequently, they do not represent an ideal anti-*H. pylori* treatment, despite the good tolerance of the *PPI-amoxicillin* therapy.

Triple therapies come closer than the dual therapies to the requirements for an ideal treatment of the infection, with eradication rates generally close to 90%, varying little between the studies and the countries in which they were performed. The triple therapy *bismuth-imidazole-tetracycline (or amoxicillin)* still represents for many authors the standard reference treatment [23 154 220]. It has the advantage of low cost, high efficacy and widespread use. It is therapy that has been the most studied and documented. However, the increasing emergence of strains resistant to imidazoles, the complexity of the treatment (10 to 12 tablets per day), the frequency of adverse effects and the lack of availability of bismuth salts in certain countries has led to the elaboration of therapeutic schemes combining an antisecretory drug with 2 antibiotics. Among these, the combination PPI-clarithromycine (2 x 250 mg/d)-imidazole (2 x 500 mg/d) represents the most studied *triple therapy of short duration.* It is very effective (eradication rates superior to 90%), requires relatively few dosages (5 to 6 per day), is of short duration (7 days) and seems to be better tolerated than other triple therapies. For some authors, it already represents a new standard [178]. However, the efficacy of this therapy seems to be dependent on the sensitivity of the bacterium to imidazoles. Consequently, this combination cannot be considered as the ideal anti-*H. pylori* treatment in the areas where there is a high prevalence of strains resistant to imidazoles. The association *PPI-clarithromycin-amoxicillin* appears on the contrary to be very effective against strains resistant to metronidazole [211-213], and could therefore constitute the treatment of choice in populations with high prevalence of such strains.

Clarithromycin has numerous interactions with different drugs metabolized by cytochrome P450 (cisapride, terfenadine, astemizole, theophylline, carbamazepine). The triple therapy standard (bismuth-biantibiotics) and the combination PPI-amoxicillin-metronidazole are consequently of particular interest for patients requiring doses of one of these medicines. The efficacy of therapies combining an H_2-receptor antagonist and 2 antibiotics is presently well demonstrated. However, studies are still too few and the data allowing a comparison of these treatments with those comprising a PPI are still insufficient and disputed [156 157 160-162 221]. A comparative study carried out on a large collective of patients will be necessary for determining the place of the H_2-receptor antagonist in the treatment of *H. pylori*.

The treatments based on sucralfate, zinc sulfate, ranitidine bismuth citrate, the topical treatments, and the therapies of very short duration (1-2 days), could all present certain advantages, but an insufficient number of studies is available.

Great hope is currently surrounding the finalization of a vaccine directed against the urease of the bacterium. This approach would simultaneously allow both the treatment and the prevention of *H. pylori* infection on a large scale.

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