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A systematic review of Helicobacter pylori *eradication therapy—the impact of antimicrobial resistance on eradication rates*

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SUMMARY

Background: We systematically reviewed all available data in the literature to determine the overall eradication rates of currently advised *Helicobacter pylori* eradication regimens and to resolve conflicting evidence on the impact of antimicrobial resistance on the eradication rates.

Methods: A comprehensive search of all published trials on *H. pylori* eradication therapy was carried out via an electronic database search, hand-searching and checking reference lists of pharmaceutical companies and other reviews. Full papers and abstracts in the English language which study currently advised eradication regimes were included.

Results: 770 study-arms were analysed. Mean eradication rates for bismuth based triple, proton pump inhibitor triple, quadruple and ranitidine bismuth citrate combination therapies vary from 65 to 92%. In case of nitroimidazole resistance, a drop in efficacy of up to 50% was found for bismuth-based triple and proton pump inhibitor-based triple therapies. For quadruple therapy, a significant difference in efficacy was found in the equal-effects analysis; however, this could not be confirmed in the random-effects analysis. In case of clarithromycin resistance, a mean drop in efficacy of 56% was found for one- and two-week clarithromycin containing proton pump inhibitor-triple therapies and of 58% for two-week ranitidine bismuth citrate combined with clarithromycin therapies. For ranitidine bismuth citrate combined with clarithromycin and nitroimidazole, no difference in efficacy was found in case of nitroimidazole or clarithromycin resistance, but data are still scarce.

Conclusions: The cure rate with most regimens dropped significantly, in case of nitroimidazole-resistant strains, compared to nitroimidazole-susceptible strains. In case of clarithromycin resistance, the efficacy of most regimens is also decreased; however, data are still scarce. These data should allow physicians to make a better choice of an appropriate therapy for their patients.

INTRODUCTION

Helicobacter pylori were first isolated in 1983 by Warren and Marshal.[1] Since then, an enormous amount of studies has been performed regarding this bacterium. We now know that it is the main cause of peptic ulcer disease and also plays a role in gastric lymphoma and gastric carcinoma.[2–4]

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Over time, different combinations of bismuth, acid inhibitors and antimicrobial agents have become increasingly effective in eradicating the *H. pylori*; however, in 10–30% of cases, currently advised therapies still fail to eradicate *H. pylori.*[5] Despite the abundance of data on treatment of *H. pylori* infection, there is still controversy regarding the eradication regimen of choice, and confusion persists regarding which factors may lead to therapy failure.

In infectious diseases, antimicrobial resistance is, in general, an important factor leading to therapy failure. In *H. pylori* this is not always evident and Megraud already stated that 'there is no situation where the clinical relevance of antimicrobial resistance detected *in-vitro* is more controversial than *H. pylori* resistance to nitroimidazole compounds'.[6]

There are several problems regarding *in vitro* assessment of antimicrobial resistance, especially in the case of nitroimidazole resistance. Nitroimidazole resistance does not show a bimodal distribution but rather shows a continuous spectrum of minimal inhibitory concentrations (MICs). This pattern suggests that there may be many different pathways responsible for this resistance.[7] Considerable care is required for routine isolation to be successful, as well as the need for rapid transport and use of appropriate transport media before culture.[8] There is currently no standardized method available for testing susceptibility of *H. pylori* and there is also a relative lack of reproducibility for a given method.[9] Besides, nitroimidazole resistance appears to be unstable and dependent on the redox potential.[10, 11] The redox potential level at which the test should be carried out has not been determined and at the level of the gastric mucosa probably varies from one patient to another and from one moment to another.[9] Heterogeneity of *H. pylori* is also a factor that must be considered. In the human stomach one may find different *H. pylori* strains, and some institutions test multiple *H. pylori* strains, while other centres test only one strain. It is obvious that when testing multiple strains the chance of finding a resistant strain is higher.[12]

The goal of culturing *H. pylori* is to detect clinically relevant antimicrobial resistance. That means that, via an *in vitro* assay, one hopes to predict the likelihood of successfully treating the infection with a particular antimicrobial regimen. Therefore we use a clinical definition of antimicrobial resistance, i.e. a strain is resistant if the likelihood of eradication by a given treatment is low.

Neither *in vitro* data, nor animal studies can predict the clinical efficacy of anti-*H. pylori* regimens in man. Therefore, clinical studies are essential to compare the eradication rates with the MIC of the antibiotic. Because current eradication regimes have become very effective with eradication rates in excess of 90%, it becomes very difficult, if not impossible, to conduct trials that are large enough to identify factors that influence the cure rates.

We systematically reviewed all published data to determine the effectiveness of currently advised eradication regimens in patients harbouring resistant or susceptible *H. pylori* strains. We focused on nitroimidazole and clarithromycin, since these antibiotics are widely used to eradicate *H. pylori* and resistance is common and rapidly increasing.[9] Resistance of *H. pylori* to penicillin, tetracycline and fluoroquinolones is seldom described.

METHODS

Location and selection of studies

We aimed to locate studies in which *H. pylori*-eradication was reported, published as abstract or full paper. These studies were included in this review when the treatment consisted of triple or quadruple eradication therapies, combining at least three of the following: proton pump inhibitors, H2-receptor antagonists, bismuth or antibiotics. Mono-and dual-therapy trials were not included, except for dual therapy trials with ranitidine bismuth citrate. Studies were excluded when the different medications given to eradicate *H. pylori* were not clearly stated or when the duration of therapy was not known. Studies were also excluded when the number of treated and cured patients could not be extracted.

A comprehensive search of the literature was conducted, starting in 1984 and ending in October 1998, after including the abstracts presented at the European *Helicobacter Pylori* Study Group meeting and the World Congress of Gastroenterology. An electronic database search was performed with a broad search strategy in medline, embase and the 'Cochrane Controlled Trials Register'. The search was limited to publications in the English language. Studies were also identified through hand-searching the annual meetings of the Digestive Disease Week, European Helicobacter Pylori Study Group meetings, United European Gastroenterology Week and the World Congress of Gastroenterology of

Table 1. Treatment groups

Code	Medication
BAM1	Bismuth/amoxycillin/nitroimidazole 1 week
BAM2	Bismuth/amoxycillin/nitroimidazole 2 weeks
BTM1	Bismuth/tetracyclin/nitroimidazole 1 week
BTM2	Bismuth/tetracyclin/nitroimidazole 2 weeks
PPI-AC1	Proton pump inhibitor/amoxycillin/clarithromycin 1 week
PPI-AC2	Proton pump inhibitor/amoxycillin/clarithromycin 2 weeks
PPI-AM1	Proton pump inhibitor/amoxycillin/nitroimidazole 1 week
PPI-AM2	Proton pump inhibitor/amoxycillin/nitroimidazole 2 weeks
PPI-CM1	Proton pump inhibitor/clarithromycin/nitroimidazole 1 week
PPI-CM2	Proton pump inhibitor/clarithromycin/nitroimidazole 2 weeks
PPI-BTM1	Proton pump inhibitor/bismuth/tetracyclin/nitroimidazole 1 week
PPI-BTM2	Proton pump inhibitor/bismuth/tetracyclin/nitroimidazole 2 weeks
RBC-C1	Ranitidine bismuth citrate/clarithromycin 1 week
RBC-C2	Ranitidine bismuth citrate/clarithromycin 2 weeks
RBC-CM1	Ranitidine bismuth citrate/clarithromycin/nitroimidazole 1 week
RBC-CM2	Ranitidine bismuth citrate/clarithromycin/nitroimidazole 2 weeks

B = bismuth subcitrate and bismuth subsalicylate; PPI = all proton pump inhibitors; M = Nitroimidazole = metronidazole or tinidazole.
One-week therapy is defined as the regimen as a whole being given from 4 to 9 days. Two-week therapy is defined as the regimen being given for more than 9 days.

1994–98. Finally, reference lists of published reviews on *H. pylori* eradication therapy and reference lists from the pharmaceutical companies ASTRA and GLAXO Wellcome were checked to identify studies for possible inclusion in this review.

Publications identified as duplicates were excluded. In case of suspected duplicate patient material, the authors were contacted.

One investigator carried out the assessment of each article for inclusion in this review.

Data collection and definitions

Different eradication regimens were pooled into 1- and 2-week regimens. One-week therapy is defined as the regimen as a whole being given from 4 to 9 days. Two-week therapy was defined as the regimen being given for more than 9 days. Intention-to-treat (ITT) analysis includes all patients that were randomized or started with therapy. All patients who had no follow up are considered not eradicated (worst-case scenario). Per protocol (PP) analysis is defined as all treated patients who complied with the study protocol, had complete follow up and took at least 70% of the prescribed medication. Wherever possible, eradication rates were recalculated to this definition. Where no intention-to-treat nor per protocol analysis could be given, a so-called 'all-patients-treated' eradication rate was calculated, that is in general somewhere in between the intention-to-treat analysis and per protocol analysis. In retrospective studies only the all-patients-treated analysis was given. The total number and the eradicated number of patients harbouring nitroimidazole and/or clarithromycin-resistant and -susceptible strains were collected. In these sub-groups the intention-to-treat analysis was used wherever possible. A selection of currently used eradication regimens was made (Table 1). For this review, all proton pump inhibitors (e.g. omeprazole, lansoprazole, pantoprazole) were pooled together, as well as bismuth preparations (bismuth subcitrate, bismuth subnitrate and bismuth subsalicilate) and nitroimidazoles (metronidazole and tinidazole).

Each study was assigned a unique study number. Two different reviewers independently analysed each study-arm and recorded the data on a form. Both forms were compared and one form was used to correct errors and disagreements. The final version was entered in an ACCESS database. This database has multiple automated error-control functions and was also checked by hand for errors.

Data analysis and statistical methods

Statistical computer programs SPSS and SAS were used to analyse and summarize the data. The data were analysed by two different methods. First, we analysed

Table 2. Overall efficacy analysis of all studies

		Intention-to-treat			Per protocol		
Therapy-code	No. arms	*n*	Cure-rate (%)	95% CI	*n*	Cure-rate (%)	95% CI
BAM1	40	978	66	63–69	295	64	59–70
BAM2	89	3322	74	73–76	1120	79	76–81
BTM1	32	1571	79	77–81	815	80	78–83
BTM2	94	5358	80	78–81	2843	85	84–87
PPI–AC1	113	6839	81	81–82	2735	84	82–85
PPI–AC2	59	2823	85	84–86	897	91	89–93
PPI–AM1	42	2446	74	73–76	1113	84	82–86
PPI–AM2	71	2986	80	79–81	839	83	80–85
PPI-CM1	119	6990	86	85–87	3215	90	88–91
PPI–CM2	23	872	83	81–86	484	90	87–93
PPI-BTM1	29	1458	87	86–89	896	92	91–94
PPI–BTM2	13	534	72	68–75	288	90	86–93
RBC–C1	3	171	77	70–83	51	80	69–92
RBC–C2	28	2249	76	75–78	1021	87	85–89
RBC–CM1	12	839	87	84–89	293	92	89–95
RBC–CM2	3	178	75	69–82	42	86	75–97

No. arms = number of study-arms; *n* = total number of treated patients; 95% CI = 95% confidence interval.

the data with the equal effects analysis. The mean eradication rate in this model is weighted by the number of patients ('N-weighted'). This equal effects model assumes that every study population has the same outcome, in this case the mean eradication rate, for a given therapy. In reality, however, there is a considerable heterogeneity among all studies, caused by differences in population and protocol. Therefore, we also performed a random-effects analysis where a different weighting factor is used, consisting of the inverse of the sum of the within-study variance and the between-study variance.[9]

RESULTS

A total of 1091 study-arms from 718 studies were analysed. For this review we selected only currently advised eradication regimens that were reported in 770 study-arms from 561 studies, involving 39 614 patients according to the ITT analysis and 16 947 patients according to the PP analysis. A total of 3848 patients were classified as 'all-patients-treated' and were not included in this review.

Of the 770 study-arms, 348 were published as full papers and 422 as abstracts only. A total of 369 randomized study-arms were analysed and 71 were double-blind, 39 single blind and 660 were open-labelled studies. Six studies were performed in Africa, 32 in Australia, 108 in Asia, 551 in Europe, 50 in North America, and eight in South America. Fifteen studies were coded as being performed on more than one continent.

Pooled eradication rates

Pooled N-weighted ITT and PP eradication rates are listed in Table 2.

The results from the equal-and random-effects analysis of eradication rates in patients harbouring nitroimidazole or clarithromycin-resistant or -susceptible *H. pylori* strains are listed in Tables 3 and 4, respectively.

DISCUSSION

This study is the largest database of pooled results of *H. pylori* eradication trials published to date and the first meta analysis on the effect of antimicrobial resistance in *H. pylori* eradication therapy. It presents the mean N-weighted ITT and PP eradication rates of currently used regimens with their 95% confidence intervals (Table 2). We also present the eradication rates for patients harbouring nitroimidazole- or clarithromycin-resistant or -susceptible strains. These data indicate that detecting metronidazole or clarithromycin resistance *in vitro* does indeed predict a drop in eradication rate with most regimens in *H. pylori* infections (Tables 3 and 4).

Table 3. Efficacy analysis of patients with nitroimidazole-resistant or -susceptible strains

Therapy code	No. arms	Nitroimidazole-resistant			Nitroimidazole-susceptible			Analysis					
								Equal			Random		
		n	Cure-rate (%)	95% CI	*n*	Cure-rate (%)	95% CI	Delta cure rate	95% CI	*P*-value	Delta cure rate	95% CI	*P*-value
BAM1	**4**	70	16	0–24	111	64	55–73	48	36–61	< 0.00001	55	30–83	< 0.00001
BAM2	5	96	63	53–72	213	90	86–94	27	17–38	< 0.00001	32	20–44	< 0.00001
BTM1	**6**	218	69	63–75	357	90	86–93	21	14–28	< 0.00001	42	21–64	< 0.00001
BTM2	19	570	78	75–81	762	91	89–93	13	9–17	< 0.00001	33	18–48	< 0.00001
PPI-AM1	**7**	123	54	46–63	317	92	89–95	38	29–48	< 0.00001	39	19–60	< 0.00001
PPI-AM2	12	169	72	65–79	252	88	84–92	16	8–24	< 0.00001	34	18–50	< 0.00001
PPI-CM1	15	358	73	69–78	433	94	91–96	21	16–26	< 0.00001	22	11–32	< 0.00001
PPI-CM2	4	52	83	72–93	175	90	85–94	7	– 4–19	0.13	3	– 8–14	0.57
PPI-BTM1	12	161	83	77–89	287	94	92–97	11	4–17	0.0002	6	– 3–15	0.19
PPI-BTM2	**4**	60	77	66–88	137	95	91–99	18	7–30	0.0002	25	– 5–54	0.10
RBC-CM1	1	22	95	86–100	62	97	92–100	2	– 8–11	0.77	2	– 6–10	0.62

No. arms = number of study-arms. *n* = total number of treated patients. 95% CI: 95% confidence interval. Delta cure rate = difference in eradication rate (this is not necessarily the same in the random-effects analysis as in equal-effects analysis due to the different weighing factors of the two statistical methods).

Table 4. Efficacy analysis of patients with clarithromycin-resistant or susceptible strains

Therapy code	No. arms	Clarithromycin-resistant			Clarithromycin-susceptible			Analysis					
								Equal			Random		
		n	Cure-rate (%)	95% CI	*n*	Cure-rate (%)	95% CI	Delta cure rate	95% CI	*P*-value	Delta cure rate	95% CI	*P*-value
PPI-AC1	**6**	21	48	24–71	146	81	74–87	33	11–56	0.0007	2	– 6,7–71	0.96
PPI-AC2	10	6	0	0–46	275	95	92–97	95	77–100	< 0.0001	95	70–100	< 0.00001
PPI-CM1	10	21	24	0–44	447	84	81–88	60	42–79	< 0.0001	61	38–54	< 0.00001
PPI-CM2	2	3	33	0–100	98	94	89–99	61	7–100	= 0.0001	*		
RBC-C2	5	51	29	16–42	387	87	84–90	58	45–71	< 0.0001	43	3–82	0.035
RBC-CM1	1	4	100	40–100	80	96	92–100	– 4	– 22–15	0.69	*		

No. arms = number of study-arms. *n* = total number of treated patients. 95% CI: 95% confidence interval. Delta cure rate = difference in eradication rate (this is not necessarily the same in the random-effects analysis as in equal-effects analysis due to the different weighing factors of the two statistical methods).
* Random-effects analysis cannot be applied due to low number of study-arms.

This review has been designed and conducted with the utmost attention to exclude all possible bias. The search through the literature has been extensive. Data were extracted independently by two different reviewers and discussed in case of differences. Duplicate studies were excluded and the computer input was checked extensively. Because different studies have used different definitions for the ITT and PP eradication rate, we recalculated eradication rates to the definition as stated under Methods.

Since different studies have been performed in different regions of the world, with different populations and using different protocols, an equal effects analysis might not be appropriate to summarize the data. Therefore, we also used a random-effects model to account for possible differences between trials.[9] In case substantial heterogeneity exists between trials, a random effect analysis will give more conservative estimates compared with an equal effects analyses. This phenomenon can be observed in Table 3, where the equal effects analyses of the proton pump inhibitor-BTM1 and proton pump inhibitor-BTM2 was highly significant, but the random effects analysis not. In such cases the estimate from the random effects model would be preferred because it reflects the uncertainty about the true difference in eradication rate.

Treatment allocation among the different regimens was not randomized. Therefore, unequal distribution of prognostic factors may have led to incomparable populations at baseline. It is likely that this phenomenon caused the discrepancy in efficacy between the 1-week proton pump inhibitor-BTM and the 2-week proton pump inhibitor-BTM. For example, it is possible that the 2-week quadruple therapies were given to patients who were more likely to be noncompliant or former treatment failures. Since these factors are often not reported in trials, we cannot establish the exact reason for this discrepancy in efficacy.

Impact of nitroimidazole resistance

The reported prevalence of nitroimidazole resistance is highly variable and has increased over time. In developing countries resistance rates are reported to be 80–90%, while in most western countries resistance rates vary from 10 to 56%.[13–15]

There are essentially two nitroimidazole compounds used to treat *H. pylori*: metronidazole and tinidazole; these were pooled together in this review. There is cross-resistance between these two drugs.

There are many conflicting results among studies regarding the clinical relevance of nitroimidazole resistance. The reasons for these discrepancies are unclear, but may be explained by the variability in susceptibility testing, variability in defining the MIC cut-off value, differences in dosage or duration of therapy, or differences in patient populations.

Detailed information regarding the method of nitroimidazole resistance testing was given in only 100 study-arms: agar dilution was used in seven study-arms, *E*-test in 60 study-arms and disc diffusion in 33 study-arms. All of these methods showed the same trend to a lower efficacy with most pooled regimens in the case of nitroimidazole resistance. The MIC cut-off value varied between 4 and 32 between the different studies. In this study, data were pooled, irrespective of the MIC cut-off value and the method of susceptibility testing.

At this point in time, the clinical relevance of measuring nitroimidazole resistance *in vitro* is still unclear. In dual-therapy and bismuth based triple therapy it has become accepted that *in vitro* measurement of nitroimidazole resistance does indeed predict a drop in eradication rate.[16, 17] We did not study dual therapies, but for bismuth-based triple therapies we confirm a highly significant drop in efficacy in the case of nitroimidazole resistance ($P < 0.0001$; Table 3).

Evidence accumulates that eradication rates with a proton pump inhibitor, nitroimidazole and amoxycillin decrease in the presence of metronidazole-resistant *H. pylori* strains,[17] as was confirmed in this review ($P < 0.0001$; Table 3). The clinical relevance of metronidazole resistance for *H. pylori* eradication rates in patients treated with a proton pump inhibitor, nitroimidazole and clarithromycin is still controversial. A few studies to date have found a significant drop in efficacy with this regimen,[18–24] while several others were unable to detect a difference in efficacy.[25–32] We found a significant drop in eradication rates for nitroimidazole-resistant, compared to nitroimidazole-susceptible strains for 1-week proton pump inhibitor/clarithromycin/nitroimidazole therapy ($P < 0.0001$; Table 3). The mean ITT eradication rate with the 2-week proton pump inhibitor/clarithromycin/nitroimidazole therapy was lower in patients harbouring nitroimidazole-resistant strains; however, this was not significant.

In 1- and 2-week quadruple therapy the equal-effects analysis yields a significant difference in efficacy between nitroimidazole-susceptible and -resistant organisms. However, when the random-effects analysis was applied, this could not be confirmed (Table 3), probably as a result of the several small studies that carry a relatively large weight in the random-effects analysis. Five studies to date have found a drop in efficacy in nitroimidazole-resistant strains with these regimens;[33–37] however, this was only significant in the largest published series by Van der Hulst *et al.*[33] All other studies, in which mostly only a few patients with nitroimidazole-resistant strains were treated with quadruple therapy, have not found a drop in efficacy in case of nitroimidazole-resistance.[38–47] The reason for these discrepant results is not clear. More data are needed to definitely establish the clinical relevance of detecting nitroimidazole resistance *in vitro* in quadruple therapy.

Data on the effect of nitroimidazole resistance with ranitidine bismuth citrate combined with clarithromycin and nitroimidazole are still scarce, with only one published patient-group,[48] yielding large, overlapping 95% confidence intervals. Therefore we need more data to determine whether there is a clinical relevance in measuring nitroimidazole resistance in ranitidine bismuth citrate-based therapies.

Since studies from different regions of the world sometimes report different eradication rates, and different mechanisms of antimicrobial resistance may occur in different parts of the world,[7] we also studied the data per continent. It appeared that all pooled regimens yielded a lower eradication rate in patients with nitroimidazole-resistant strains, compared to patients with nitroimidazole-susceptible strains. However, this was not always significant, probably due to the smaller patient numbers. Most data came from Europe, where all pooled regimens reported in this review showed a significantly lower eradication rate in patients with nitroimidazole-resistant strains, according to the equal effect analysis.

Many studies have been published without data on antimicrobial resistance, which showed high overall eradication rates. Since nitroimidazole-resistant strains still have a considerable chance of eradication, the overall effectiveness of an eradication regimen is only jeopardized when the prevalence of resistance is high. Besides, the effect of nitroimidazole resistance is not absolute and can at least be partly overcome.[30, 49] It seems logical that, when the MIC is higher, the chance of eradication decreases, as was reported for proton pump inhibitor-triple therapy by Kist *et al.*[21]

Impact of clarithromycin resistance

The prevalence of clarithromycin resistance varies from country to country; the highest reported prevalence comes from the south of Europe and is now almost 15%.[15] In most countries it is still below 5%, but will rise over the next years as a result of the increasing use of macrolides. A mutation on the 23 S rRNA gene, causing diminished binding of the antibiotic to the ribosome, seems the most significant mechanism of macrolide-resistance. This appears to be a stable phenomenon with cross-resistance to other macrolides. There is a clear bimodal distribution between clarithromycin-susceptible and -resistant *H. pylori* strains; therefore the method of measuring clarithromycin resistance is not crucial. Since the prevalence of clarithromycin resistance is low, only a small number of patients have been studied. A significant drop in efficacy in the case of clarithromycin resistance was found in the equal-effects analysis with 1- and 2-week proton pump inhibitor/amoxycillin/clarithromycin and proton pump inhibitor/clarithromycin/nitroimidazole regimens and with 2-week ranitidine bismuth citrate–clarithromycin. This could be confirmed in the random-effects analysis for proton pump inhibitor/amoxycillin/clarithromycin 2 weeks, proton pump inhibitor/clarithromycin/nitroimidazole 1 week and ranitidine bismuth citrate/clarithromycin 2 weeks, but not for proton pump inhibitor/amoxycillin/clarithromycin 1 week, probably due to the fact that only three studies reported patients with nitroimidazole-resistant strains. For ranitidine bismuth citrate/clarithromycin/nitroimidazole 1 week no drop in efficacy was found in case of clarithromycin-resistant strains, but data are too scarce to draw conclusions. For proton pump inhibitor/clarithromycin/nitroimidazole 2 weeks and ranitidine bismuth citrate/clarithromycin/nitroimidazole 1 week the random-effects analysis could not be applied due to low number of study-arms (Table 4).

RECOMMENDATIONS

These data show that the cure rate with most regimens in patients with nitroimidazole-resistant strains is decreased up to almost 50%, compared to patients harbouring metronidazole-susceptible strains. In case of clarithromycin resistance, the efficacy of most regimens

is also lowered; however, data are still scarce. Routine pre-treatment testing seems currently not necessary; however, the rise in antibiotic resistance emphasizes the need for surveillance of *H. pylori* sensitivity at a national, or rather regional level. In the case of therapy failure, we recommend culturing *H. pylori* with resistance testing on an individual basis. It is important that resistance-testing methods are standardized and validated to allow comparisons to be made between different studies and to monitor the clinical impact of antimicrobial resistance. In addition, for future therapies we need to know the effectiveness of different regimens separately for susceptible and resistant *H. pylori,* and this information should be required of all treatment trials.

Clinicians should choose first-choice treatment regimens primarily based on effectiveness, since efficacy has been shown to be the single most important determinant of cost-effectiveness.[50] The most effective regimen will also minimize development of secondary resistance that may occur for nitroimidazole and clarithromycin in over 50% of cases.[18, 21] Together with knowledge of local epidemiology and trends of drug resistance in *H. pylori,* these data should help the clinician to define rational treatment strategies.

The exact search-strategy list is available upon request.

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