Treatment after failure: the problem of "non-responders"

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Summary
Although the currently most effective treatment regimens cure about 90% of infections, 10% of patients remain *Helicobacter pylori* positive. Several factors contribute to treatment failure. These include patient compliance, bacterial resistance to antibiotics, and treatment related issues. Treatment failure leads to the development of bacterial resistance to metronidazole and clarithromycin. Retreatment can be undertaken after considering several different strategies: to repeat the same regimen with full doses of medications and a longer treatment duration, or to choose different regimens to avoid the antibiotic previously used, or to switch to proton pump inhibitor (PPI) based quadruple therapy or ranitidine bismuth citrate (RBC) based triple therapy. In principle, full doses and longer treatment durations are advisable. As retreatment is always difficult, choosing the best available first line treatment regimen is still the best "rescue" treatment.

Introduction

It has been over 12 years since the first randomised, placebo controlled clinical trial for the eradication of *H pylori* infection was published.[1] Treatment to eradicate the infection has evolved from single agents to multiple combination treatments consisting of an antisecretory agent and one or more antibiotics.[2 3] Treatments that achieve an eradication rate of greater than 80%, on an intent to treat basis, have been recommended by most consensus conferences and authorities.[4–7] These now include bismuth based triple therapy, triple therapy involving a PPI and two antibiotics, quadruple therapy, or more recently combinations with RBC and two antibiotics. Although these combination treatments are very effective for eradicating *H pylori* infection in most patients, a significant proportion of patients fail these treatments for a variety of different reasons such as bacterial resistance, poor compliance, or treatment related factors.[8 9] Retreatment of these non-responders remains a challenging issue as some patients may need more than two attempts for eradication of the infection. This paper reviews the current literature on the possible causes for *H pylori* treatment failure, discusses several approaches to retreatment, and gives suggestions for future studies.

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Table 1 H pylori eradication: pooled success and failure rates with the most commonly used regimens

	Success (ITT)			*Failure (%)*		
*Regimen**	*n*	*%*	*95% CI*	*Mean*	*Range*	*Reference*
PAC500	514	90	86–94	10	6–14	Huang and colleagues[10]
PMC500	253	91	81–100	9	0–19	Huang and colleagues[10]
PBMT	611	90	86–94	10	6–14	Huang and colleagues[10]
RCA	521	82	79–85	18	15–21	Pipkin and colleagues[11]
RMC	791	89	87–91	11	9–13	Pipkin and colleagues[11]

*See text for definitions.
CI, confidence interval; ITT, intent to treat; n, total number of patients.

How serious is the problem of treatment failure?

To answer this question, we need to assess the efficacy of the currently most recommended treatment regimens. In a comprehensive meta-analysis involving 294 treatment arms and 15 971 patients, we found that the most effective treatment regimens reported up to 1997 were seven day triple therapy consisting of a PPI, clarithromycin (C) 500 mg twice daily, and amoxcillin (A) or metronidazole (M), or quaduple therapy with a PPI and bismuth (B), metronidazole (M), and tetracycline (T).[10] These regimens achieve a pooled eradication rate of at least 90% by intent to treat analysis. However, a large variation in efficacy exists between studies in these treatment regimens, with 95% confidence intervals (CI) ranging from 81% to 100%. This means that up to 19% of patients will fail these treatments and remain *H pylori* positive (table 1). In a recent review of RBC based triple therapy, Pipkin *et* al showed that the pooled eradication rate for seven day RBC, clarithromycin, and metronidazole was 89% (95% CI 87 to 91%) by intent to treat analysis and 82% (95% CI 79 to 85%) for RBC, clarithromycin, and amoxicillin, respectively.[11] This suggests that up to 21% of patients will fail RBC based triple therapy and require retreatment for the infection.

Factors leading to treatment failure

PATIENT RELATED FACTORS

Poor compliance

Poor compliance has been considered a major factor for treatment failure. In a stepwise regression analysis of factors influencing the effectiveness of bismuth based triple therapy, Graham *et al* have shown that patient compliance was the most important factor predicting treatment success.[9] The *H pylori* cure rate was 96% for patients who took more than 60% of the prescribed medications and only 69% for those who took less (p=0.001). In a recent study of treatment failure of *H pylori* infection in an ambulatory population, 30 *H pylori* infected patients were treated with lansoprazole (L) 30 mg twice daily, amoxicillin 1000 mg twice daily, and clarithromycin 500 mg twice

Abbreviations used in this paper: PPI, proton pump inhibitor; RBC, ranitidine bismuth citrate; PUD, peptic ulcer disease; NUD, non-ulcer dyspepsia.

daily for seven days.[12] Patient compliance was assessed by the Medication Event Monitoring System (MEMS) containers, which contained a concealed electronic device recording the time of opening. The overall eradication rate was 63%. In patients who took more than 60% of the stipulated medications, the cure rate was 72% (18/25), whereas the eradication rate was only 20% (1/5) in those who took less than 60% of the prescribed pills (p=0.028).[12] These results confirm that patient compliance plays an important role in the success of *H pylori* eradication treatment. However, a significant proportion of the treatment failures in this study cannot be explained by the poor compliance as the eradication rate was only 72% in patients who had taken more than 60% of the prescribed medications.

Bacterial resistance

Bacterial resistance to metronidazole or clarithromycin is an important factor leading to treatment failure. There is a good correlation between bacterial resistance to clarithromycin and eradication failure; however, the clinical relevance of *H pylori* resistance to nitroimidazoles detected in vitro has been controversial. Some studies suggest that triple therapy consisting of a PPI, clarithromycin, and a nitroimidazole are effective at eradicating *H pylori* infection in patients harbouring metronidazole resistant strains[13–15]; others show that the efficacy is significantly decreased when metronidazole resistance is present.[16–19] Several factors might have contributed to these differences, including different methods used for diagnosing metronidazole resistance,[20 21] different cut off values for determining the minimum inhibitory concentrations,[22 23] and probably different locations where biopsy samples were taken.[24] In patients who harbour metronidazole resistant strains, the eradication rate is about 30% lower than in those infected with metronidazole sensitive strains, when treated with bismuth, metronidazole, and tetracycline or amoxicillin triple therapy.[8] Although a PPI can overcome partially the impact of metronidazole resistance on *H pylori* eradication,[25] the eradication rate achieved with PAM in patients infected with metronidazole resistant strains is about 30% lower than in those who are infected with metronidazole sensitive strains.[8 23 26 27] A similar difference is also seen when patients are treated with the PMC combination.[8 28]

The prevalence of *H pylori* resistance to clarithromycin is generally much lower than that to metronidazole worldwide.[8] However, the resistance of *H pylori* to clarithromycin has a significant impact on treatment success for regimens containing this drug. The presence of primary bacterial resistance to clarithromycin is almost 100% predictive of treatment failure with dual therapy consisting of omeprazole and clarithromycin.[29] Hence dual therapy should not be used. In studies with PAC combinations given for 10–14 days, *H pylori* eradication rates ranged from 83% to 98% in patients infected with clarithromycin sensitive strains, whereas only 25–50% of infections were eradicated in those who harboured strains resistant to clarithromycin.[8]

The secondary bacterial resistance to metronidazole or clarithromycin increases significantly in patients who have failed previous eradication treatments. Buckley *et al* reported that, of 87 patients treated with seven day PMC (omeprazole 20 mg was given once daily), 31 patients (35.6%) were infected with metronidazole resistant strains and three (3.4%) were infected with strains resistant to both antibiotics.[16] Secondary bacterial resistance to clarithromycin developed in seven (58.3%) of the 12 patients with metronidazole resistant strains who failed treatment.[16] In another study, metronidazole resistance was detected in 28% of patients (7/25) before eradication treatment but increased to 66.7% (12/18) after unsuccessful treatment with metronidazole containing regimens.[30] Clarithromycin resistant strains also increased from 32% before treatment to 70.6% after unsuccessful treatment.[30] This suggests that previous treatment failure is a significant contributing factor to acquired bacterial resistance to both metronidazole and clarithromycin.

H pylori strains

The results from recent studies also indicate that the cagA$^-$ status of bacterial strains is also a risk factor for treatment failure. In a multicentre study, Marais *et al* have shown that *H pylori* eradication was achieved in 87% of patients (54/62) infected with cagA$^+$ strains, when treated with seven day PPI based triple therapy compared with 69% (47/68) of those harbouring cagA$^-$ strains.[31] This observation may explain, at least in part, the difference in *H pylori* eradication rates, which are reported between patients with peptic ulcer disease (PUD) and those with non-ulcer dyspepsia (NUD), when patients are treated with the same regimens.[32] Virulent strains of *H pylori* infection are more prevalent in patients with PUD than in those with NUD.[33] This might have contributed to the higher eradication rates achieved in patients with PUD compared with NUD in some studies.[34 35] However, as discussed before, patient compliance plays an important role in determining the success of treatment. In comparison with patients with PUD, those with NUD may tolerate eradication treatment less well due to the refractoriness and diverse nature of symptoms. Indeed, when patient compliance is greater than 90%, eradication can be achieved in over 90% of NUD patients treated with a PPI, clarithromycin, and amoxicillin or nitroimidazole.[36 37]

TREATMENT RELATED FACTORS

Components of a regimen

The components of a treatment regimen also play an important role in *H pylori* eradication, such as which drugs are selected, the number and doses of medications used in a combination, dosing frequency, and treatment duration. PPI based triple therapy is significantly more effective for *H pylori* eradication than dual therapy consisting of two antibiotics or a PPI plus an antibiotic.[2 28] PPI given twice daily is

significantly more effective than once daily in combination with clarithromycin and amoxicillin or nitroimidazole.[11 38] PPI based triple therapy may eradicate more *H pylori* infections when given for 10–14 days than for seven days.[39] Therefore, a good combination therapy should include full doses of medications, optimal dosing frequency, and adequate treatment duration.

Strategies for rescue treatment after failure

Several steps can be taken in the management of patients with treatment failure. These include the determination of the status of bacterial resistance to metronidazole, and/or clarithromycin (or less likely to amoxicillin), and patient compliance with the previous treatment regimen. This information is helpful for selecting a proper rescue therapy as to whether retreatment should be given with full doses of the medications and for longer with the same combination, or with different combinations to avoid the antibiotic previously used when bacterial resistance to the antibiotic is suspected.

Ricci *et al* reported a study of 123 *H pylori* infected patients who were treated with a PPI 20 mg twice daily, amoxicillin 1 g twice daily, and clarithromycin 250 mg twice daily for seven days.[40] *H pylori* eradication was achieved in 85% of the 123 patients. Fifteen patients failed the therapy and remained *H pylori* positive four weeks after treatment. These patients underwent a second course of eradication treatment with full dose clarithromycin 500 mg twice daily and 10 days' treatment. *H pylori* infection was cured in 67% (6/9) of the evaluable patients.[40] This result suggests that retreatment of *H pylori* infection with the same combination is still a choice when the status of bacterial resistance to antibiotics is not known. However, full doses and a longer treatment duration must be used. If patients are treated with the same combination and for the same treatment duration, a poor eradication rate is usually reported.[41]

As acquired bacterial resistance to metronidazole or clarithromycin results primarily from the previous treatment failure, rescue therapies generally should avoid these antibiotics and use different combinations in order to achieve a high eradication rate. PPI based triple therapy is generally very effective for treating patients who have failed PPI based dual therapy.[42 43] In the event of PPI based triple therapy failure such as seven days' omeprazole (O), amoxicillin (A), and metronidazole (M), retreatment with seven days' omeprazole 20 mg twice daily, amoxicillin 1 g twice daily, and clarithromycin (C) 500 mg twice daily has proved to be very effective with a success rate of 85%.[44] When metronidazole and/or clarithromycin resistance is present, retreatment with seven days OMC has been shown, in a randomised controlled study by Houben *et al*,[41] to be ineffective in salvaging therapeutic failure, when compared to seven days' quadruple therapy consisting of bismuth (B), metronidazole (M), tetracycline (T), and omeprazole. *H pylori* eradication was achieved in 100% (11/11) of the patients treated with OBMT, including eight patients infected with metronidazole resistant and/or clarithromycin resistant *H pylori* strains, whereas the success rate was only 25% (2/8) in patients given OMC. None of the patients who was infected with metronidazole resistant and/or clarithromycin resistant strains responded to OMC.[41]

More recent data suggest that RBC based triple therapy may overcome the impact of metronidazole resistant and clarithromycin resistant strains on *H pylori* eradication treatment. In a study reported by Wouden *et al*, 111 patients infected with *H pylori* were treated with RBC 400 mg twice daily, clarithromycin 500 mg twice daily, and metronidazole 500 mg twice daily for seven days. The overall success rate was 96% by intent to treat analysis. The infection was cured in 95% (20/21) of the patients harbouring metronidazole resistant strains, and in 100% (4/4) of those who were infected with clarithromycin resistant strains or with metronidazole resistant and clarithromycin resistant strains.[45] As the number of patients included in this study was small, these promising results need to be confirmed by future studies. One recent anecdotal report has also suggested that furazolidone can be used to replace either clarithromycin or metronidazole in PPI based triple therapy for *H pylori* treatment.[46] In this small study of 12 patients infected with metronidazole sensitive and clarithromycin sensitive strains of *H pylori*, Graham *et al* reported that triple therapy, consisting of furazolidone 100 mg three times daily, omeprazole 20 mg four times daily, and metronidazole 500 mg three times daily or clarithromycin 500 mg three times daily given for 14 days, successfully eradicated all infections.[46] This promising result also needs to be confirmed in larger, randomised studies.

Recommendations from major consensus conferences

Recommendations for retreatment of *H pylori* infection have been made in several major consensus conferences worldwide.[4–7] The European *Helicobacter pylori* Study Group recommended that, in the case of treatment failure, a retreatment regimen should be selected after consideration of previous treatment or microbial sensitivities, or both. PPI based quadruple therapy can be used in the event of failure of triple therapy.[6] In the Asian-Pacific Consensus, it is suggested that, following treatment failure with PCA or RBC based clarithromycin and amoxicillin combination, the same regimen may be repeated.[7] Following one treatment failure with a regimen containing metronidazole, treatment may be repeated, substituting amoxicillin for metronidazole. Seven days PPI based quadruple therapy was also recommended as a back up treatment by the panel.[7] In the United States, treatment duration is longer than that recommended in Europe, the Asia-Pacific region, and Canada.[4] Two weeks' treatment is recommended by the US consensus meeting.[4] The extended treatment duration is important in the management of treatment

failure, which can increase the success rate of retreatment.[40]

What is the best "rescue" strategy?

As previous treatment failure leads to the development of secondary bacterial resistance to both metronidazole and clarithromycin[30] and the efficacy of retreatment is also significantly decreased by the number of previous treatments,[47] it is understandable that the higher success rate with the first line treatment, the lower will be the treatment failure. Thus, choosing the best available first line treatment regimen should be considered to be the best approach to "rescue" treatment. In areas where the prevalence of metronidazole resistance in the general population is high, seven days' triple therapy including a PPI at the recommended doses, clarithromycin 500 mg twice daily, and amoxicillin 1 g twice daily should be used if the bacterial sensitivity is not known. In the event of clarithromycin resistance, a seven day PPI based quadruple therapy or 14 day H_2 receptor antagonist based quadruple therapy should be considered.[5] The PPI and H_2 receptor antagonist should be given at the recommended doses. Colloidal bismuth salicylate is given as 120 mg four times daily, metronidazole as 250 mg four times daily, and tetracycline as 500 mg four times daily.[5] RBC 400 mg twice daily given with clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily for seven days may also be considered as an alternative first line treatment regimen.

Conclusion

In conclusion, the information on treatment failure of *H pylori* infection in the current literature is scarce. Many reports are published only in abstract form and are limited by the small number of patients and study design. However, even with the current most effective treatment regimens, about 10% of patients will fail a variety of treatments and remain *H pylori* positive. Patient compliance, bacterial resistance to antibiotics, and the components of the regimen should be assessed when retreatment is considered. Full doses of all components of the combination should be used and treatment given for two weeks. As acquired bacterial resistance mainly results from previous treatment failure, the most effective first line treatment regimen should be regarded as the best "rescue" treatment strategy.

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