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High-dose rabeprazole–amoxicillin dual therapy and rabeprazole triple therapy with amoxicillin and levofloxacin for 2 weeks as first and second line rescue therapies for *Helicobacter pylori* treatment failures

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SUMMARY

Background
H. pylori eradication failures are difficult to treat and rescue therapies often consist of complex treatment regimens.

Aim
To determine an effective and practical rescue therapeutic strategy for *H. pylori* treatment failures using two consecutive regimens: *first rescue therapy* - rabeprazole 20 mg t.d.s. and amoxicillin 1 g t.d.s. for 2 weeks and for failures a further *second rescue therapy* - rabeprazole 20 mg b.d., levofloxacin 500 mg b.d., amoxicillin 1 g b.d. for a further 2 weeks.

Methods
Consecutive patients who failed the proton pump inhibitor (PPI) 1-week triple therapy were recruited for the study. *H. pylori* status was determined by a C^{13} urea breath test.

Results
One hundred and forty-nine patients received the *first rescue therapy*. Seven were not compliant to medication/defaulted follow-up. Eradication success-*first rescue therapy*: per protocol (PP) analysis-107/142 (75.4%) (95% CI (68.3–82.4%) and intention to treat (ITT) analysis-107/149 (71.8%) 95% CI (64.6–79.0%). Thirty-one of 35 patients who failed the *first rescue therapy* received the *second rescue therapy*. All were compliant with medications. Eradication success- PP and ITT was 28/31 (90.3%) 95% CI (74.2–98.0%). The cumulative eradication rate using both rescue therapies: PP analysis- 135/138 (97.8%) 95% CI: (93.8–99.6%), ITT analysis- 135/149 (90.6%) 95% CI: (84.7–94.8%).

Conclusions
A 2-week high dose PPI-amoxicillin dual therapy followed by a PPI-amoxicillin-levofloxacin triple therapy were highly successful in achieving eradication in *H. pylori* treatment failures.

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INTRODUCTION

With the widespread treatment of *H. pylori* infection, eradication failures are now frequently encountered in clinical practice. Eradication failures are difficult to treat as the bacterium has often acquired resistance to the commonly used antibiotics: clarithromycin and metronidazole.[1] The difficulty of achieving successful eradication increases with each successive failure. It is therefore crucially important that rescue therapies are carefully chosen to take into account not just the background antibiotic resistance patterns but tolerability of the drugs used, to ensure a high compliance to medications by patients. The availability of the drugs used should also be an important consideration.

Rescue therapies often consist of complex treatment regimens with drugs that are not commonly used in clinical practice such as bismuth compounds and rifabutin. The Maastricht 3 and the Asian Pacific consensus meetings for example, have both recommended the use of bismuth-based quadruple therapy as rescue therapy.[2, 3] Bismuth compounds, however, are not easily available in Malaysia and in many countries in Asia.

In planning therapy for treatment failures, we have chosen amoxicillin as a key antibiotic. Amoxicillin is a robust antibiotic for the treatment of *H. pylori* with virtually no bacterial resistance reported.[1] Levofloxacin has been shown to have a low MIC to *H. pylori*[4] and has good bioavailability with rapid gastrointestinal absorption which is unaffected by co-ingestion of food. It has only recently been introduced into Malaysia and with no primary bacterial resistance reported as yet.[5]

The objective of the study was to determine the overall success at eradication of treatment failures with two planned consecutive rescue therapies: the *first rescue therapy* – proton pump inhibitor (PPI) high dose dual therapy with rabeprazole and amoxicillin for 2 weeks and a *second rescue therapy* – PPI triple therapy with rabeprazole, amoxicillin and levofloxacin for 2 weeks.

METHODS

This was a single-centre prospective, open-labelled study conducted over a 3 year period from 2006–2009.

Patients

Consecutive patients with documented treatment failure following treatment with a 1 week PPI–clarithromycin containing triple therapy were recruited for the study. These patients were recruited from our own clinical service at the University of Malaya Medical Centre as well as referrals from general practitioners. Patients were confirmed to have *H. pylori* infection by a C^{13} urea breath test (UBT) before the start of therapy. Patients under the age of 18 years, those with clinically significant medical conditions (cardiorespiratory, liver or renal diseases, insulin-dependent diabetes mellitus, neoplastic diseases, or coagulopathy), previous gastric surgery or allergy to any of the drugs used were excluded from this study. Pregnant or lactating mothers were also not included into the study.

Treatment schedule

Patients were prescribed a 2 weeks course of rabeprazole 20 mg t.d.s. (Pariet, Eisai HHC, Tokyo, Japan) and amoxicillin 1 g t.d.s. (Ospamox, Biochemie, Kundl, Austria). This treatment was labelled as the *first rescue therapy*. Testing for eradication success was carried out 4 weeks after completion of therapy using the C^{13} UBT. Before testing it was confirmed that patients were not on any antibiotics, bismuth compounds or PPIs for at least 2 weeks for any other indication. The C^{13} UBT was carried out using an infrared spectrometer (IRIS, Wagner Analysen-Technik GmbH, Bremen, Germany). Breath samples were taken at 4 time points: at baseline, 10, 20 and 30 min. ^{13}C is measured as a ratio of ^{13}C to ^{12}C with cutoff of delta over baseline of 4 per mil was considered positive.

Patients who continued to have a positive C^{13} UBT were then offered a *second rescue therapy* which consisted of rabeprazole 20 mg b.d., levofloxacin 500 mg b.d. (Cravit, Dai-Ichi, Tokyo, Japan) and amoxicillin 1 g b.d. for a further 2 weeks. Treatment success was again assessed at least 4 weeks after completion of therapy using the C^{13} UBT. Rabeprazole was prescribed to be taken before breakfast and amoxicillin and levofloxacin prescribed to be taken after meals.

All subjects were informed about the potential side effects of medications and the importance of completing the entire course of treatment. They were asked to return after 2 weeks to check for compliance to medications (defined as completing at least 90% of prescribed medications) and to report on any side effects of treatment experienced.

The study protocol, patient information sheet and consent form were approved by the University of Malaya Medical Centre Ethics Committee and performed according to GCP-ICHC guidelines.

Statistical analysis

We planned to collect a minimum of 140 patients based on an estimated eradication rate with the first rescue therapy of 80% giving a narrow 95% confidence interval

of 73.4–86.6%. All data were entered into SPSS (Statistical Packages for the Social Sciences, version 15, Chicago, IL, USA) program for analysis. Eradication rates were calculated as for intention-to-treat (ITT) analysis and per-protocol (PP) analysis with 95% confidence intervals. Fisher's exact tests and Chi square tests were used to compare categorical data. A two-tailed test was used in all analyses and *P*-value of <0.05 was considered statistically significant.

RESULTS

One hundred and forty-nine patients were recruited for the study and received the *first rescue therapy*. 142 patients were compliant with medications and returned for the scheduled follow-up. Three patients were not compliant with medications defined as ingestion of less than 90% of the prescribed medications and 4 defaulted follow-up. (Figure 1). These patients were not considered for the subsequent treatment. The treatment success was: PP analysis – 107/142 (75.4%) (95% CI (68.3–82.4%) and intention to treat (ITT) analysis – 107/149 (71.8%) 95% CI (64.6–79.0%) (Table 1).

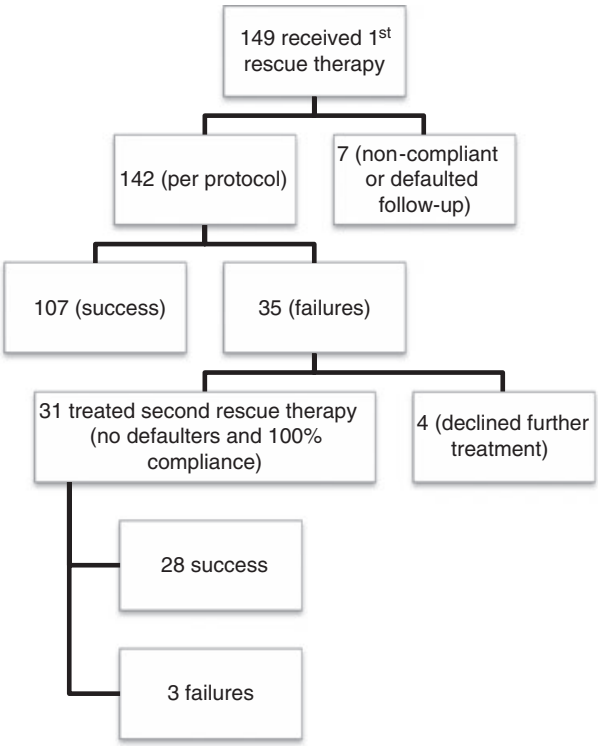

Figure 1 | Treatment flow of patients.

Of the 35 patients who failed the first rescue therapy, 31 agreed to undergo treatment with the second rescue therapy. Four declined further treatment for their *H. pylori* infection (Figure 1). All 31 patients were fully compliant with medications and returned for follow-up. Twenty-eight had successful eradication of H. pylori and the PP and ITT success rate was 28/31 (90.3%) 95% CI (74.2–98.0%) (Table 1).

Overall the cumulative success rate using both rescue therapies was: PP analysis – 135/138 (97.8%) 95% CI: (93.8–99.6%) and ITT analysis – 135/149 (90.6%) 95% CI: (84.7–94.8%) (Table 1).

The *first rescue therapy* was highly tolerable: eight patients (5.6%) complained of mild diarrhoea during treatment. 1(0.7%) complained of a skin rash which subsided with discontinuation of the medications. Overall, 139 (97.9%) patients took the full course of medications. 3 (2.1%) patients missed a few doses but cumulatively took >90% of the medications.

The *second rescue therapy* was also highly tolerable. 2 (6.5%) – anorexia, 1 (3.2%) – diarrhoea, 1 (3.2%) headaches and 1 (3.2%) dizziness. All patients took 100% of the prescribed medications.

DISCUSSION

As with other parts of the world, the 1 week PPI-clarithromycin containing triple therapies have been the mainstay of treatment for *H. pylori* in Malaysia since 1998. Earlier studies have shown a high eradication success with these therapies [6–8] and it has been recommended by the Malaysian Working Party on *Helicobacter pylori* infection in 1998.[9] However, a recent in-clinical practice study showed an eradication rate of only 70% on intention-to-treat analysis for primary treatment of the infection.[10]

Table 1 | Treatment success of consecutive rescue therapies: intention-to treat and per protocol analyses

	First rescue therapy high dose dual therapy (RA)	*Second rescue therapy* Levofloxacin triple therapy (RAL)	Overall (cumulative success)
Per protocol analysis	107/142 (75.4%) (95% CI (68.3–82.4%)	28/31 (90.3%) 95% CI (74.2–98.0%)	135/138 (97.8%) 95% CI: (93.8–99.6%)
Intention-to-treat analysis	107/149 (71.8%) 95% CI (64.6–79.0%)	28/31 (90.3%) 95% CI (74.2–98.0%)	135/149 (90.6%) 95% CI: (84.7–94.8%)

The two main reasons for treatment failure in clinical practice are poor compliance to medications and bacterial resistance to antibiotics. The key antibiotics that have been used in treatment of *H. pylori* have been clarithromycin, amoxicillin and metronidazole.

Even though the background resistance to clarithromycin has been shown consistently to be very low in Malaysia,[5–7, 11–13] emergence of resistance is well known to occur quickly in treatment failures [14, 15] The primary resistance to metronidazole on the other hand, has been shown to be high and which has essentially negated its usefulness in *H. pylori* eradication.[5–7, 11, 12, 16] No bacterial resistance to amoxicillin has been shown in our local strains.[5] With little emergence of resistance following treatment failures,[1] amoxicillin is therefore a key antibiotic in our choice of any 'rescue' therapies.

We chose as first rescue therapy the high dose dual therapy with rabeprazole and amoxicillin. The high dose PPI dual therapy with amoxicillin is an 'old' therapy which had been used in the early years of *H. pylori* treatment. Bayerdoffer *et al.* were the first to publish on their results of high dose PPI-amoxicillin in t.d.s. dosing for 2 weeks as first line treatment, achieving an eradication rate in excess of 90%.[17, 18] However later studies have shown that it was less than a robust therapy [19–22] and it was then largely superseded by the 1 week PPI, clarithromycin based triple therapies.

Miehlke *et al.* [23] and then Furuta *et al.* [24] emphasised the critical role of increased PPI dosing in the success of the dual therapy and commented that the inconsistent results achieved by other groups were due to the relatively lower doses of PPIs used. Furuta *et al.* also used the PPI, rabeprazole which is not metabolised by the CYP2C19 pathway and therefore not affected by the polymorphisms of this enzyme.[25] This had also influenced our choice of rabeprazole as the PPI used in our rescue therapy regimens. Rabeprazole has also been shown to be a potent acid suppressing agent with a rapid onset of action.[26] A steady level of acid inhibition has been shown to be crucial in optimising the effects of antibiotics such as amoxicillin which is acid-labile, thus our choice of a more frequent dosing of PPI.[27, 28]

In more recent years, high dose dual therapy has been used as second line therapy for treatment failures with good success by the groups of Furuta *et al.* [24, 29, 30] and Miehlke *et al.*[31] In a more recent study by Zullo *et al.*, perhaps out of 'desperation', high dose dual therapy was used successfully in patients who had failed treatment with three preceding therapies.[32]

Our eradication success of 75% on PP analysis with the high dose rabeprazole–amoxicillin dual therapy can be considered reasonably good for a rescue therapy. It was a highly tolerable treatment with good compliance to medications. Both drugs were easily available and patients did not find the three times a day dosing inconvenient.

Levofloxacin is a newly introduced antibiotic in Malaysia although it has been widely used for treatment of *H. pylori* since 2000. It has a very low MIC to *H. pylori* and its usefulness for treatment failures has also been well documented.[33, 34] Although in our local Malaysian setting, no resistance to levofloxacin has been documented in our local strains isolated,[5] there have been reports of rapid emergence of resistance elsewhere.[35–37] This has prompted us to be judicious in its use and we have therefore reserved it for a second line rescue therapy.

In our second rescue therapy, there is a possibility of selection bias for highly motivated patients. This notwithstanding, we have achieved a high eradication rate with this therapy considering that the group of patients can be considered truly refractory having failed two courses of eradication therapy.

Cumulatively utilising these two rescue therapies, we achieved a very high rate of success of over 90% on PP and ITT analysis which reaffirms the utility of such a planned treatment approach for dealing with *H. pylori* treatment failures. The usefulness of a consecutive therapy has been previously shown by Rokkas *et al.* who used the Maastricht 1st and 2nd line recommended therapies and as a second rescue therapy a similar PPI, amoxicillin and levofloxacin triple therapy for 10 days.[38]

Our treatment approach is simple, logical and practical. The first-line rescue therapy is easily available and inexpensive in our local setting. As has been shown in our study the compliance to medications was good and side effects minimal and tolerable. This is crucial, bearing in mind that many treatment failures in the first instance would have been due to poor compliance. While the bacterial resistance to levofloxacin remains low, it is clearly a good antibiotic for the treatment of *H. pylori*. However it is relatively expensive, as such we have reserved it as second-line rescue therapy. The issue of emergence of resistance to levofloxacin is also a cause for concern and undoubtedly there should be continued careful use of this antibiotic in clinical practice.

Other treatment regimens have been recommended and used as rescue therapy. Repeating 1 week-PPI based standard triple therapy or extending it to 10–14 days has been common in clinical practice. But given the low eradication rates nowadays of this regimen as first line therapy,[39] its

use as first line rescue therapy and even more so, as rescue therapy may now well be construed as unacceptable and even unethical.[40, 41] The Maastricht guidelines recommend the bismuth–PPI quadruple therapy. Bismuth is not widely available in Malaysia as with many other countries and this will preclude against its routine use in rescue therapies. Other antibiotics such as furazolidine and rifabutin have also been used in rescue therapies. In clinical practice we have found these antibiotics to be generally intolerable with fairly severe side-effects.

CONCLUSION

A treatment strategy with two consecutive rescue therapies: a *first rescue therapy* with high-dose PPI–amoxicillin dual therapy and a *second rescue therapy* with PPI triple therapy with amoxicillin and levofloxacin was highly effective in the treatment of refractory *H. pylori* infection. Treatment was easily available and was well tolerated by our patients.

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