Clinical audit of current Helicobacter pylori treatment outcomes in Singapore

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Abstract

Introduction: H. pylori eradication reduces the risk of gastric malignancies and peptic ulcer disease. First-line therapies include 14-day PAC (proton pump inhibitor [PPI], amoxicillin, clarithromycin) and PBMT (PPI, bismuth, metronidazole, tetracycline). Second-line therapies include 14-day PBMT and PAL (PPI, amoxicillin, levofloxacin). This clinical audit examined current treatment outcomes in Singapore.

Methods: Clinical data of H. pylori-positive patients who underwent empirical first- and second-line eradication therapies from 1 January 2017 to 31 December 2018 were reviewed. Treatment success was determined by 13C urea breath test performed at least 4 weeks after treatment and 2 weeks off PPI.

Results: A total of 963 patients (862 PAC, 36 PMC [PPI, metronidazole, clarithromycin], 18 PBMT, 13 PBAC [PAC with bismuth], 34 others) and 98 patients (62 PMBT, 15 PAL, 21 others) received first- and second-line therapies respectively. A 14-day treatment duration was appropriately prescribed for first- and second-line therapies in 65.2% and 82.7% of patients, respectively. First-line treatment success rates were noted for PAC (seven-day: 76.9%, ten-day: 88.3%, 14-day: 92.0%), PMC (seven-day: 0, ten-day: 75.0%, 14-day: 69.8%), PBMT (ten-day: 100%, 14-day: 100%). 14-day treatment was superior to seven-day treatment (90.8% vs. 71.4%; P = 0.028). PAC was superior to PMC (P < 0.001) but similar to PBMT (P = 0.518) and PBAC (P = 0.288) in 14-day therapies. 14-day second-line PAL and PBMT had similar efficacy (90.9% vs. 82.4%; P = 0.674).

Conclusion: First-line empirical treatment using PAC, PBMT and PBAC for 14 days had similar efficacy. Success rates for second-line PBMT and PAL were similar.

Keywords: First-line treatment, Helicobacter pylori, second-line treatment

INTRODUCTION

Helicobacter pylori (H. pylori) infection is a common infection globally.[1] It is a major risk factor for gastric malignancies and peptic ulcer disease and its eradication has been shown to reduce the risk of disease occurrence.[2,3] Eradication is recommended for all infected patients.[4] In the 1990s, seven-day triple therapy using twice-daily proton pump inhibitor (PPI), clarithromycin and amoxicillin (PAC) achieved eradication rates of around 90% and was accepted as the standard empirical first-line therapy globally, especially since it was less complicated and better tolerated than bismuth-based quadruple therapy, which comprised PPI, bismuth, metronidazole and tetracycline (PBMT).[5] Treatment outcomes are affected by local patterns of antibiotic susceptibility, making local validation relevant, and the success of this regimen was confirmed in Singapore in 2000.[6] Since then, it was further established that 14-day treatment was superior to seven-day treatment, and this is now the recommended treatment duration.[7]

H. pylori eradication outcomes have been graded as follows: F or unacceptable (≤80%), D or poor (81%–84%),
C or fair (85%–89%), B or good (90%–95%), and A or excellent (95%–100%). The ideal is to use therapies that score 'excellent' (A grade). Regimens that score as B or 'good' can be used if 'excellent' results are not obtainable. Globally, the success of PAC has declined due to increasing clarithromycin resistance, such that treatment success rate fell lower than 80%, although there are regions where it remains effective. This led to guidelines suggesting that PAC be abandoned as empirical first-line therapy, unless it can be shown that local treatment success rates can achieve the required acceptable thresholds. Currently, 14-day PAC remains a first-line treatment option in Singapore. A randomised study in Singapore in 2015 that compared PAC with two non-bismuth-based quadruple therapies (sequential and concomitant therapies) demonstrated that PAC was effective with a modified intention-to-treat success rate of 92.1%, comparable to the quadruple therapies. A 15-year retrospective study from Singapore reported that while amoxicillin resistance rates remained low, there was a temporal increase in clarithromycin resistance rates, increasing from 7.9% in 2000–2002 to 17.1% in 2012–2014. A clarithromycin resistance rate of 15%–20% in the population is generally regarded as indication of low treatment success rate with empirical PAC and should prompt reconsideration of the use of PAC as empirical first-line therapy. It is crucial to objectively examine whether the success rate of PAC remains acceptable. In the context of failure of first-line therapy, empirical second-line therapies using 14-day PBMT and PAL (PPI, amoxicillin, levofloxacin) are commonly utilised. An earlier small retrospective study (n = 53) from Singapore reported an eradication rate of 82.2% when using seven-day PBMT. H. pylori culture and antibiotic susceptibility testing is not routinely performed, due to the past high efficacy of empirical first-line treatment, the issue of added costs and the practical issue of non-availability of this test. However, guidelines now recommend the use of antibiotic susceptibility data whenever available.

Therefore, it was timely to review our empirical first-line H. pylori treatment in order to ascertain if treatment success rates remain acceptable. This is important to guide treatment in Singapore. This clinical audit examined the efficacy of current empirical first- and second-line H. pylori eradication therapies from a tertiary referral centre in Singapore.

METHODS

This was a retrospective clinical audit of the efficacy of empirical first- and second-line H. pylori eradication therapies in Changi General Hospital, Singapore. Formal institutional board review and approval were therefore not required.

The study period was from 1 January 2017 to 31 December 2018. A list of patients who underwent 13C urea breath test (CUBT) assessment during the period of January 2017 to March 2019 was generated by electronic search. This list included patients who underwent testing for both the initial diagnosis and post-treatment assessment. Patients who were included had been diagnosed with H. pylori infection (including patients diagnosed through CUBT or who received a diagnosis during prior upper gastrointestinal endoscopy and underwent post-treatment CUBT assessment) during the study period and had undergone empirical first- and second-line H. pylori eradication therapies. Patients were excluded if the infection was diagnosed outside the study period or if no post-treatment assessment of H. pylori status was available due to default from follow-up. Patient demographics, type of treatment regimen, duration of treatment and post-treatment H. pylori status were recorded.

Post-treatment outcome was determined by CUBT duration of treatment and post-treatment H. pylori status was assessed. Patients were deemed to be eradicated if the CUBT test was negative or if the patient had no symptoms or any evidence of infection by the end of the treatment course. The prescribed treatment duration was appropriate. The minimum duration recommended for PBMT is eight days, and for PAL it is ten days. The recommended treatment duration based on guidelines was 14 days. Acceptable empirical first-line treatment regimens were PAC, PBMT and PAC (PAC with bismuth). Acceptable empiric second-line therapies were PBMT and PAL.

The primary outcome measures of this study were success rates of currently recommended empirical first- and second-line H. pylori eradication therapies in Singapore. The secondary outcome measures were adherence to current treatment guidelines in terms of choice of treatment regimen and treatment duration, the impact of clinical variables on success rate of treatment, and the difference between empirical H. pylori therapies. Statistical analysis was performed using IBM SPSS Statistics version 20.0 (IBM Corp, Armonk, NY, USA). Continuous variables were analysed using t-test, and categorical variables were analysed using Chi-square and Fisher’s exact tests as appropriate. A P value < 0.05 was considered as statistically significant.

RESULTS

During the two-year period from 2017 to 2018, a total of 963 patients were newly diagnosed with H. pylori infection and underwent empirical first-line treatment. The mean age (standard deviation) was 54.4 ± 14.8 years. 56.0% of patients were male, and 83.2% were Singaporean.

Details of the prescribed first-line treatments are summarised in Table 1. The prescribed treatment duration was appropriate at 14 days in 65.2% (n = 628) of patients, and suboptimal at ten days in 33.3% (n = 321) and seven days in 1.5% (n = 14) of patients. Two patients with PPI allergy were prescribed famotidine 40 mg twice daily for acid suppression. PMC (PPI, metronidazole, clarithromycin) was prescribed to 36 patients due to penicillin allergy and PAM (PPI, amoxicillin, metronidazole) to nine patients due to clarithromycin allergy, although the recommended treatment regimen in such cases with allergies should have been PBMT instead. Appropriate
empirical first-line treatment regimen was prescribed in 92.7% (893/963; 862 PAC, 18 PBMT, 13 PBAC) of cases. The clinical success rates of first-line treatment with PAC, PMC, PBMT and PBAC are summarised in Table 2. The treatment success rate of 14-day PAC was significantly higher than that of 14-day PMC (92.0% vs. 69.6%; \( P < 0.001 \)) but similar to 14-day PMBT (92.0% vs. 87.5%; \( P = 0.518 \)) and 14-day PBAC (92.0% vs. 100.0%; \( P = 0.288 \)). There was a trend of greater efficacy with longer treatment duration for PAC (14-day: 92.0% vs. ten-day: 88.3% vs. seven-day: 76.9%; \( P = 0.054 \)).

Overall, in terms of variables affecting treatment success rate, a longer treatment duration of 14 days was associated with a significantly higher treatment success rate (14-day: 90.8% vs. ten-day: 87.5% vs. seven-day: 71.4%; \( P = 0.028 \)). Other factors such as gender and nationality did not show any impact on treatment outcome.

A total of 98 patients received empirical second-line treatment. The prescribed treatment duration was appropriate at 14 days in 82.7% (\( n = 81 \)) of them, and suboptimal at ten days in 15.3% (\( n = 15 \)) and seven days in 2.0% (\( n = 2 \)) of patients. The majority (71.4%) were appropriately treated with PAL and PBMT [Table 3]. Treatment success rates with 14-day PAL and PBMT were similar (90.9% vs. 82.4%, \( P = 0.674 \)) [Table 2].

**DISCUSSION**

Knowledge of local antibiotic resistance rates is important to guide empiric therapy. Only one study has examined the *H. pylori* antibiotic resistance profile in Singapore. It reported a significant increase in resistance rates for metronidazole (2000–2002: 24.8%, 2012–2014: 48.2%; \( P < 0.001 \)), clarithromycin (2000–2002: 7.9%, 2012–2014: 17.1%; \( P = 0.022 \)) and levofloxacin (2000–2002: 5%, 2012–2014: 14.7%; \( P = 0.007 \)). The resistance rates for tetracycline (2000–2002: 5%, 2012–2014: 7.6%) and amoxicillin (2000–2002: 3%, 2012–2014: 4.4%) remained stable.\([16]\) The combination of PAC remained the most commonly prescribed empirical first-line treatment in this clinical audit, although other recommended alternatives such as PBMT and PBAC are also being prescribed, possibly due to concerns about potential for decline in PAC efficacy based on overseas reports.\([9]\) In reality, our treatment success rate of 92.0% with 14-day PAC is similar to past data, which was 87% (intention-to-treat analysis) and 94% (per-protocol analysis) in 2000,\([13]\) and 92.1% (modified intention-to-treat analysis) in 2015.\([14]\) One can therefore conclude that over the last 20 years in Singapore, the treatment success with PAC has been maintained at an acceptable B or good (90–95% success) level. This data is graphically summarised in Figure 1. It must also be noted that treatment duration has increased, from seven days\([15]\) to ten days\([14]\) and now 14 days. This may explain its continued efficacy despite the rise in clarithromycin resistance rates. The data on clarithromycin and amoxicillin resistance rates (derived from Ang et al.)\([16]\) is shown in Figure 2. It must be highlighted that no strains of *H. pylori* with dual resistance to both clarithromycin and amoxicillin were isolated in that study. PBMT and PAL were appropriately utilised as empirical

**Table 1. Spectrum of prescribed empirical first-line *H. pylori* therapy.**

| Treatment regimen | No. based on treatment duration | Total no. (\( n = 963 \)) |
|-------------------|---------------------------------|--------------------------|
|                   | 7-day                           | 10-day                   | 14-day                   |
| PPI, amoxicillin, clarithromycin | 13 | 300 | 549 | 862 |
| PPI, metronidazole, clarithromycin | 1 | 12 | 23 | 36 |
| PPI, bismuth, metronidazole, tetracycline | 0 | 2 | 16 | 18 |
| PPI, bismuth, amoxicillin, clarithromycin | 0 | 0 | 13 | 13 |
| PPI, amoxicillin, metronidazole | 0 | 1 | 8 | 9 |
| PPI, clarithromycin, levofloxacin | 0 | 1 | 3 | 4 |
| PPI, metronidazole, levofloxacin | 0 | 0 | 3 | 3 |
| PPI, amoxicillin, levofloxacin | 0 | 2 | 0 | 2 |
| PPI, amoxicillin, clarithromycin, tetracycline | 0 | 0 | 2 | 2 |
| PPI, amoxicillin, clarithromycin, metronidazole | 0 | 0 | 2 | 2 |
| PPI, bismuth, amoxicillin, metronidazole | 0 | 1 | 1 | 2 |
| PPI, bismuth, metronidazole, clarithromycin | 0 | 0 | 2 | 2 |
| PPI, bismuth, metronidazole, levofloxacin | 0 | 0 | 2 | 2 |
| PPI, levofloxacin, tetracycline | 0 | 0 | 1 | 1 |
| PPI, metronidazole, tetracycline | 0 | 0 | 1 | 1 |
| PPI, bismuth, amoxicillin, levofloxacin | 0 | 1 | 0 | 1 |
| PPI, metronidazole, levofloxacin, tetracycline | 0 | 1 | 0 | 1 |
| Famotidine, amoxicillin, clarithromycin | 0 | 0 | 1 | 1 |
| Famotidine, bismuth, metronidazole, tetracycline | 0 | 0 | 1 | 1 |

PPI: proton pump inhibitors
second-line treatment in most cases, but treatment success remained fair between 82.7% and 85.7%.

What is of concern from our audit is that there are instances where recommendations from guidelines such as treatment duration of 14 days, or appropriate type of treatment regimens, were not followed, with a risk of subsequent treatment failure, either for first- or second-line empirical therapy. For instance, in patients with penicillin or clarithromycin allergy, some prescribers utilised PMC (PPI, metronidazole, clarithromycin) and PAM (PPI, amoxicillin, metronidazole) as alternatives, respectively. If we truly appreciated the current pattern of antibiotic resistance that recognises the high rates of metronidazole resistance, a more logical option would have been to substitute PAC with PBMT in the context of penicillin allergy, and PAC with PBMT or PAL in the context of clarithromycin allergy. The only scenario in which metronidazole resistance is less relevant in \( H. pylori \) treatment is when it is used in PBMT, due to the bactericidal effect of bismuth. \( H. pylori \) treatment is prescribed by doctors with different levels of experience. Even with formal guidelines, it is evident that there are knowledge gaps that should be addressed.

Despite the continued efficacy of PAC as empirical first-line treatment, we should examine whether we can further improve our \( H. pylori \) treatment such that it achieves the A or excellent grade, with treatment efficacy reaching 95–100%. This is because when salvage therapy is needed, the success rate of such second-line treatment tends to be lower. Antibiotic susceptibility and adequacy of acid suppression are two important factors and will be discussed further in this paper. Other factors include patient compliance to treatment and adherence to 14-day treatment duration. The previous study by Ang et al. demonstrated that non-bismuth quadruple therapies such as concomitant and sequential therapies did not perform as well as triple therapy.
not confer additional advantage while making the treatment more complicated. Alternative strategies are needed. These may include routine pre-treatment antibiotic susceptibility testing, adding bismuth to PAC, and attempting to further suppress gastric acid production by changing from standard PPI to vonoprazan, a newly available potassium-competitive acid blocker.

Knowledge of updated local patterns of antibiotic susceptibility is crucial for the success of empirical therapies, in view of the concern over rising rates of antibiotic resistance. Routine pre-treatment culture and antibiotic susceptibility testing is currently not part of the initial management of H.pylori infection. H.pylori infection is not an emergency that requires urgent treatment, and thus it would seem logical to adopt culture-guided therapy. Conventionally, this involved culture and antibiotic susceptibility testing of H.pylori isolates obtained from gastric biopsies. Lately, a polymerase chain reaction-based approach, which assesses point mutations responsible for antibiotic resistance from gastric biopsy samples, has emerged as an alternative option. However, this is only applicable to antibiotic resistance to clarithromycin, fluoroquinolone and tetracycline that occurs as a result of specific mutations in a small region of the responsible gene.

Stool-based molecular testing on susceptibility has been developed as a non-invasive technique with promising results, and a meta-analysis by López-Góngora et al. demonstrated that susceptibility-guided therapy was superior to empirical therapy. In the past, susceptibility testing of H.pylori infection was limited by availability, but it has become more affordable and is available in most public hospitals in Singapore at present. If the test was only performed after failure of empirical treatment, the patient would require repeat endoscopy and incur additional costs and procedural risks. Studies have shown that culture-directed treatment can be cost-effective. In the local setting, we will need to balance the cost of additional testing with the failure rate of empirical therapy; this approach will be more important when resistance rates increase further.

Bismuth-based quadruple therapy has been recommended as first-line empirical H.pylori eradication therapy in areas with high clarithromycin resistance rate (more than 15%). Studies have shown that bismuth-containing regimens were superior to non-bismuth regimens in regions with high clarithromycin resistance. Apart from a primary therapeutic effect, bismuth has synergistic activity with antibiotics to overcome antibiotic resistance. Addition of bismuth to PAC has been shown to increase the eradication rate. H.pylori resistance rates towards clarithromycin in Singapore from 2012 to 2014 were reported as 17.1%. The Toronto Consensus Report, which included outcome data, recommended the use of clarithromycintriple therapy in regions where the clarithromycin resistance rate was less than 15% or those with high local eradication rates exceeding 85%. The clinical success rate of 14-day PAC in our audit was 92%. Hence, one may continue using PAC as empirical first-line therapy, but it must be for 14 days. The addition of bismuth to PAC can also be considered. However, more data is needed to establish its incremental value in our local setting even though it appears promising.

Potent acid suppression is crucial for H.pylori eradication when using acid-sensitive antibiotics such as clarithromycin and amoxicillin. Vonoprazan was approved by the Health Sciences Authority, Singapore, in July 2018 for treatment of H.pylori infection. Vonoprazan can achieve greater acid suppression than current PPIs. Studies conducted in Japan demonstrated a superior eradication rate compared to PPI-based triple therapy. However, the dose of antibiotics (amoxicillin 750 mg, clarithromycin 200 mg or 400 mg twice daily) and treatment duration (one week instead of two weeks) used in Japan are different from those in other guidelines. A recent study reported that vonoprazan-based triple therapy was non-inferior to susceptibility-guided PPI-based triple therapy. The incremental value of vonoprazan and the efficacy of one-week treatment remain to be objectively validated in our setting. To answer this question, we have initiated a randomised controlled trial comparing two-week PPI and one-week vonoprazan-based triple therapy (reference no. NCT03908619).

Our study had intrinsic limitations. This was a retrospective clinical audit rather than a randomised controlled trial. Data such as degree of treatment compliance and adverse events related to treatment, as well as antibiotic susceptibility data, was also not available. Nonetheless, with the relatively large sample size for first-line empirical treatment, it provides important real-world data and is a very important snapshot of current empirical first-line treatment efficacy in Singapore.

To conclude, the efficacy of PAC as empirical first-line therapy has remained constant over the last two decades, exceeding 90%. The outcome of empirical second-line treatment using PBMT or PAL has remained fair, greater than the minimum threshold of 80% but less than 90%. It is crucial to ensure
compliance to treatment guidelines and to understand the rationale behind treatment combinations to optimise treatment success. Continual efforts are required to optimise the empirical treatment success rate to reach the ideal range of 95% to 100%.

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Ang TL is a member of the SMJ Editorial Board, and was thus not involved in the peer review and publication decisions of this article.

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