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Treatment of *Helicobacter pylori* in the Arab world: a systematic review and network meta-analysis

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Abstract

Purpose: We conducted a systematic review and network meta-analysis (NMA) to estimate the efficacy of *Helicobacter pylori (H. pylori)* treatment strategies in Arab countries.

Methods: We searched electronic databases from inception to July 18, 2020, using boolean operators. Search terms were (*Helicobacter pylori* R *H. pylori* OR *pylori* OR *helicobacter*). The risk of bias was assessed using Cochrane risk of bias tool. Retrieved articles were screened, and relevant data were extracted. We used R programming software to analyze extracted data.

Results: Fifty-four articles (n= 7829 patients) were included in the NMA. Pooled analysis demonstrated that adjuvant therapy (standard triple or sequential therapy plus another adjuvant drug) was the best treatment with higher odds of eradication rate [OR= 6.42, 95% CI (1.37: 30.05), P-score= 0.21]. In naïve population, quinolones-based therapy (QBT) and sequential therapy (SQT) were associated with higher eradication rates than other regimens [OR= 1.94, 95% CI (1.19: 3.16), P score=0.19] and [OR= 1.66, 95% CI (1.10: 2.50), P score=0.33]. In experienced population, all medication showed a non-significant difference in eradication rates when compared to triple therapy (TT); QBT (OR= 1.86, 95% CI, [0.15, 22.88], p=0.44) and SQT (OR= 1.49, 95% CI, [0.13, 17.59], p=0.52).

Conclusion: Our findings suggested that QBT and SQT therapies were the most effective regimens for eradicating *H. pylori* in naïve patients in the Arab countries. In experienced patients, all medication showed a non-significant difference in eradication rates.

Keywords: *Helicobacter pylori; Eradication, Regimen, Anti-Bacterial Agents; Arab; Network meta-analysis; Quinolones, bismuth, resistance*

Introduction

Helicobacter pylori (H. pylori) infection affects more than 50% of the world population 1. The infection is higher in developing countries (70.1% in Africa and 69.4% in South America) than in developed countries (34.3% in Western Europe and 37.1% in North America) 1. H. pylori infection is highly prevalent in the Middle East and North Africa (MENA) region 2. It may cause chronic gastritis, peptic ulcer disease, atrophic gastritis, and intestinal metaplasia that predispose to gastric cancer3-5. H. pylori may contribute to the pathogenesis of autoimmune and hematologic diseases; whether H. pylori can contribute to insulin resistance and metabolic syndrome is still controversial 6-8. H. pylori was classified as a class I human carcinogen9. H. pylori eradication can reduce gastric inflammation and mucosal damage, improve gastric acid secretion, return the microbiome to normal, and suppress further H pylori-induced DNA damage10.

Several treatment strategies have been proposed, including triple therapy for 14 days and bismuth or non-bismuth quadruple therapies 11-14. Several studies showed that concomitant therapy, which is composed of proton pump inhibitor (PPI), amoxicillin, clarithromycin, and metronidazole or tinidazole, was more effective than triple therapy given for 7 or 10 days 15-18. In Egypt, the preferred first-line treatment strategy for H. pylori eradication is Clarithromycin-based therapy. Furthermore, a concomitant quadruple non-Bismuth regimen or a Levofloxacin-based triple therapy are offered for the patients who are failing the first-line regimen. Currently, sequential and hybrid treatments are not endorsed since they have demonstrated little incremental advantage over the recommended regimens 19. A Lebanese study showed an 80% eradication rate with 14-day sequential therapy versus 50% with bismuth-containing quadruple therapy. However, the number of patients included in the study was very small 20. A study on Saudi children showed no difference between sequential and standard therapy 21. A multicenter study in Egypt and Saudi Arabia compared seven days levofloxacin-based regimen versus standard triple therapy (clarithromycin, amoxicillin, and esomeprazole) showed an eradication rate of 90.6% for levofloxacin-based regimen and 78.6% for standard triple therapy 22. We conducted this systematic review and meta-analysis in Arab patients as they share the same culture and the same habits of antibiotic use, however there are no systematic reviews describing the rates of eradication of different used regimens. So, we aimed to conduct a systematic review and network meta-analysis (NMA) to estimate the efficacy of different Helicobacter pylori (H. pylori) treatment strategies in Arab countries.

Methods

During the preparation of this review, the Cochrane Handbook guidelines of Systematic Reviews and Meta-analysis and the Preferred Reporting Items of Systematic Reviews and Meta-analysis (PRISMA) were followed [23, 24].

Eligibility Criteria

We included all studies that met our eligibility criteria: (1) studies that were conducted in Arab countries and included patients who were diagnosed with H.pylori infection; (2) studies that assessed the efficacy of different H.pylori regimens; (3) studies that compare between H.pylori regimens and placebo or other regimens; (4) studies that reported data regarding eradication rate of H.pylori, which defined as negative H.pylori stool antigen test or urea breath test 4-6 weeks after treatment; (5) studies that were experimental in design (RCT, controlled trials, or Quasi-experimental) or observational (Cohort, case-control, cross-sectional, self-controlled). We excluded narrative reviews, animal studies, conference abstracts, and non-English language studies. Used treatment regimens and their description are presented in **Table 1**.

Information Source and Literature Search

We systematically searched the electronic databases PubMed, Scopus, Web of Science (WOS), EBSCO, and EMBASE from inception to July 18, 2020, using boolean operators. We used the following search terms: (Helicobacter pylori OR *H. pylori* OR pylori OR helicobacter) AND (Jordan OR United Arab Emirates OR UAE OR Bahrain OR Tunisia OR Algeria OR Djibouti OR Saudi Arabia OR Sudan OR Syria OR Somalia OR Iraq OR Oman OR Palestine OR Qatar OR Comoros OR Kuwait OR Lebanon OR Libya OR Egypt OR Morocco OR Mauritania OR Yemen). Hand-searching of the Bibliographies of the included studies was also performed.

Study Selection

The screening process was performed in two steps; 1) title and abstract screening and 2) full-text screening. Both steps were conducted using an offline 2016 Microsoft Excel sheet by four independent reviewers (SA, IB, MA, and MZ), who assessed the retrieved articles' eligibility. Any disagreement between both reviewers was resolved by a third reviewer (MA).

Extraction of relevant data

We extracted the following domains using an offline data extraction sheet: (1) study ID, (2) study year, (3) design, (4) population characteristics, (5) sample size, (6) available data of outcome measures, and (7) quality assessment domains.

Risk of bias

We assessed the risk of bias using the Cochrane risk of bias tool (ROB) [25]. Seven domains were evaluated during this step: 1) random sequence generation (selection bias), 2) allocation sequence concealment (selection bias), 3) blinding of participants and personnel (performance bias), 4) blinding of outcome assessment (detection bias), 5) incomplete outcome data (attrition bias), 6) selective outcome reporting (reporting bias) and 7) other potential sources of bias. The final judgment of the authors was categorized as low, unclear, or high risk of bias.

Table 1: Used regimens and their description

Abbreviation	Regimen	Characteristics
TT7	Standard triple therapy for 7 days	PPI twice, clarithromycin 500 twice plus either Amoxicillin 1gm twice or metronidazole 500 twice
TT14	Standard triple therapy for 10-14 days or more	PPI twice, clarithromycin 500 twice plus either Amoxicillin 1gm twice or metronidazole 500 twice
SQT	Sequential therapy	PPI twice plus amoxicillin 1 gm twice for 5-7 days then PPI twice, clarithromycin 500 twice plus metronidazole 500mg or tinidazole 500 mg twice for 5-7 days.
CC	Concomitant therapy	Concomitant administration of PPI plus Amoxicillin 1gm twice plus Clarithromycin 500 mg twice plus either metronidazole 500 mg or tinidazole 500 twice all drugs given for 7-10 days
BBT	Bismuth based therapy	Bithmus based quadrable therapy: Bisthmus 140, tetracycline 125, metronidazole 125 four times daily plus Omeprazole 20 twice. Or Bithmus based triple therapy: bismuth subcitrate 120 mg p o, q.i.d tetracycline 500 mg p.o, q.i.d and metronidazole 500 p.o, t.i.d
QBT	Quinolones based regimens	1- Quinolones based triple therapy: quinolones, Amoxycillin, and PPI Or Quinolones + Nitazoxznide 500 mg twice + PPI 2- Quinolones based sequential therapy: PPI twice daily + Amoxicillin 1 g twice daily for 5 days followed by PPI twice daily + quinolones ± metronidazole 500 twice daily 3- Quinolone based quadrable therapy: Nitazoxanide (500mg bid), levofloxacin (500mg once daily), omeprazole (40mg bid), and doxycyclin (100mg twice daily)
AdjT	Adjuvant therapy	Standard triple therapy or sequential therapy plus either Simvastatin, Probiotic, Vitamin C, folic acid or vitamin B complex.
Others	Miscellaneous	1- Omeprazole 20 mg, tinidazole 500 mg, doxycycline 50 mg b.i.d 2- Lansoprazole 30 mg daily for four weeks, and clarithromycin 500 mg twice daily for one week. 3- I.V Ranitidine 150 mg bid, I.V ampicillin 1000 mg bid, rectal metronidazole 500 mg bid, 4- Omeprazole alone (20mg bid) 5- lansoprazole plus clarithromycin only 6- Nitazoxanide 500 mg b.i.d., clarithromycin 500 mg b.i.d., and omeprazole 40 mg b.i.d.

The Newcastle-Ottawa Scale (NOS) for observational studies (Case-control and Cohort studies) was used [26]. The NOS uses a star system (with a maximum of 9 stars) to evaluate a study in 3 domains: the selection of participants (4 items; Representativeness of the sample, Selection of the Non-Exposed, Ascertainment of Exposure, Non-respondents); comparability of study groups (2 items; Control for Confounders); and the ascertainment of outcomes of interest (3 items; Assessment of outcome, Was Follow-Up Long Enough for Outcomes to Occur, Adequacy of Follow-Up of Cohorts). We interpreted the score as follows: Very good studies (9 points), Good studies (7-8 points), satisfactory studies (5-6 points), unsatisfactory studies (0-4 points).

Assessment of Heterogeneity

To assess heterogeneity, we used two methods: 1) visual inspection of the forest plots and 2) using the I-square (I^2) and Chi-square (Chi^2) tests. According to the Cochrane handbook, the interpretation of the I^2 test should be based on the following cutoff points: minimal (0% to 30%), moderate (30% to 60%), and high (60% to 100%).

Data Synthesis and Statistical Analysis

Data were calculated and presented as odds ratio (OR) and confidence interval (CI) for the eradication rate. In the case of heterogeneity, we used the random-effects model instead of the fixed-model for calculating weighted ORs and 95% CIs in meta-analysis. I^2 test was used to assess the heterogeneity between trials. Besides, we used the random-effect consistency model of NMA by integrating direct and indirect comparisons from various trials. The disagreement between the direct and indirect estimates was identified using the global inconsistency test and the fitting design-by-treatment model. The frequentist methodology for rating therapies in the "netrank" feature of the NMA was used to rank different treatments (the smaller the P-score, the better the intervention). In addition, the "netsplit" function of NMA was used to generate the split direct and indirect forest plots. We have generated funnel plots to assess the publication bias. The analyses were all done using the "netmeta" and "meta" packages for NMA with RStudio version 1.2.5019 (©2009-2019 RStudio, Inc.)[27]. We classified used regimens into 8 regimens: standard triple therapy for 7 days (STT7), standard triple therapy for 10 to 14 days (STT14), sequential therapy (SQT), concomitant therapy (CC), Bismuth based therapy (BBT), quinolnes based therapy (QBT), standard triple therapy or sequential therapy plus adjuvant/s (AdjT). Details of used regimens are present in Table 1.

Results

Study Selection:

The electronic search of the aforementioned databases yielded 3,047 unique citations. About 363 full-text papers have been retrieved and screened for eligibility following the title and abstract screening. We excluded 309 articles and included 54 articles (n= 7829 patients) in the final analysis, **Figure 1. Supplementary Material table 1** includes descriptions of the included studies and the specific characteristics of their populations. The bias risk graph is shown **in Figure 2.**

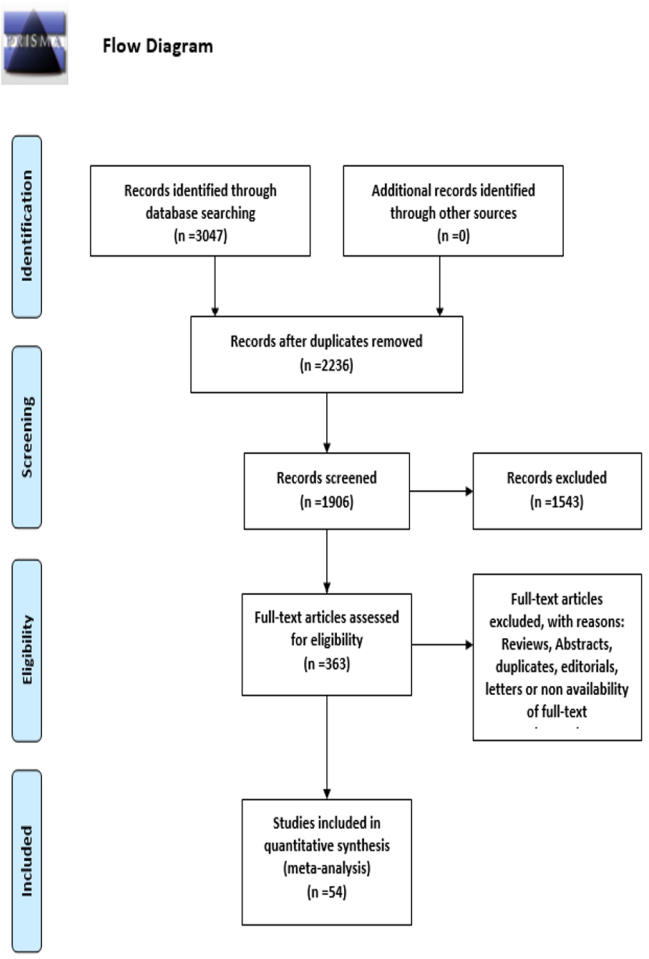

Figure 1: PRISMA Flow diagram

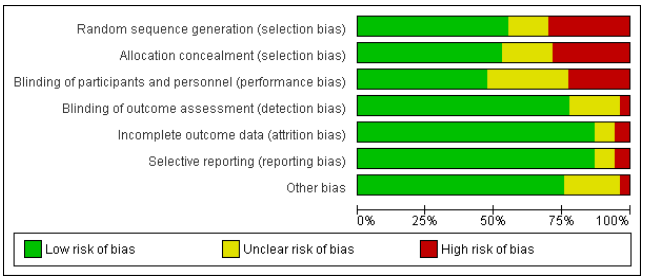

Figure 2: Risk of bias graph

Patients and Study Characteristics

Our sample consisted of a total of 7,829 patients, including both genders aged between 2 and 75 years. Studies from Egypt (n=18)[28-45], Saudi Arabia (n=8)[46-53], Lebanon (n=6)[54-59], UAE (n=5)[60-64], Iraq (n=3)[65-67], Qatar (n=3)[68-70], Algeria (n=2)[71, 72], Palestine (n=1)[73], Morocco (n=1)[74], Syria (n=1)[75], Yemen (n=1)[76] Tunisia (n=1)[77], Jordon (n=1)[54], Sudan (n=1)[78], and Bahrain (n=1)[79], were included in addition to a multinational study [80].

Eradication rate in all patients:

Overall effect estimates showed that adjuvant therapy was ranked as the best treatment with higher odds of eradication rate [OR= 6.42, 95% CI (1.37: 30.05), P-score= 0.21]. Moreover, in all included patients (experienced and naïve), Sequential therapy (SQT) and Quinolones based regimens (QBT) were associated with higher eradication rate compared to other regimens [OR= 4.83, 95% CI (1.49: 15.64), P-score= 0.30] and [OR= 4.32, 95% CI (1.15: 16.16), P-score= 0.36], respectively. Because of the significant variation within the groups and analyzed regimens, the pooled analysis was heterogeneous (Q=120.56; I^2=84.2%; P<0.0001) **Figure 3A**.

According to the Egger test, there was no observed publication bias (p=0.937), **Figure 4A**. The split analysis demonstrated that SQT therapy has a higher eradication rate [OR= 2.07, 95% CI (1.01: 4.27)] compared to triple therapy for 14 days, Supplementary Material Figure 1. The network ranking graph presents the rank of regimens, **Figure 5A**. League table was presented in Supplementary Material Table 2.

Eradication rate in adults:

Interestingly, in the adult population, the efficacy of QBT was dramatically increased to reach the first rank as the best treatment for the eradication of *H. pylori* [OR= 2.00, 95% CI (1.09, 3.69), P score= 0.19]. On the other hand, adjuvant therapy showed non-significant eradication than the SQT [OR= 1.26, 95% CI (0.70: 2.26), P score=0.62] Supplementary Table 3. Pooled analysis was homogenous (Q=2.87; I^2=0%; P=0.41), Figure 3B. The split analysis demonstrated that there was no significant difference between SQT vs. adjuvant or Triple therapy vs. adjuvant, Supplementary Material Figure 2. The network ranking graph showed the rank of studied regimens, Figure 5B. League table was presented in Supplementary Material Table 3.

Eradication rate in naïve patients:

In this subgroup, QBT and SQT showed a significant increase in the eradication rate [OR= 1.94, 95% CI (1.19: 3.16), P score=0.19] and [OR= 1.66, 95% CI (1.10: 2.50), P score=0.33], respectively. On the other hand, other regimens, including lansoprazole, tinidazole, and doxycycline, were observed to reduce the eradication rate in this specific group [OR= 0.07, 95% CI (0.03, 0.17), P score=1.00]. Pooled analysis was moderately heterogeneous (Q=40.14; I^2=50.2%; P=0.004) due to the significant variation among the analyzed regimens, Figure 3C. Publication bias analysis showed that there was no detected bias according to the Egger test (p=0.86), Figure 4B. The split analysis demonstrated that compared to triple therapy, SQT increased the eradication rate [OR= 1.66, 95% CI (1.10, 2.50)], Supplementary Material Figure 3. The network ranking graph showed the rank of studied regimens in the naïve group, Figure 5C. The League table was presented in Supplementary Material Table 4.

Eradication rate in the experienced patients:

All medication showed a non-significant eradication when compared to TT; QBT (OR= 1.86, 95% CI, [0.15, 22.88], p=0.44) and SQT (OR= 1.49, 95% CI, [0.13, 17.59], p=0.52). Pooled analysis was heterogeneous (Q=26.44; I^2=92.4%; P<0.0001) due to the significant variation among the analyzed regimens, Figure 3D. The split analysis demonstrated that there was no significant difference between analyzed regimens, Supplementary Material **Figure 4**. The network ranking graph showed the pooled analysis of the eradication rate of experienced patients, Figure 5D. League table was presented in Supplementary Material Tables 5.

***Figure* 3**

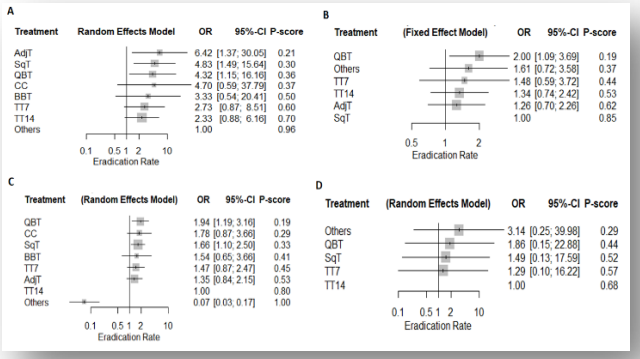

Figure 3: *Forest plots of network meta-analysis; A) Forest plot of pooled data regarding the efficacy of studied treatment strategies in all patients; B) Forest plot of pooled data regarding the efficacy of studied treatment strategies in adults; C) Forest plot of pooled data regarding the efficacy of studied treatment strategies in naïve patients; D) Forest plot of pooled data regarding the efficacy of studied treatment strategies in experienced patients*

Figure 4

Figure 4: *Funnel plot; A) funnel plot of publication bias of the analysis of all patients; B) funnel plot of publication bias of the analysis of naïve patients*

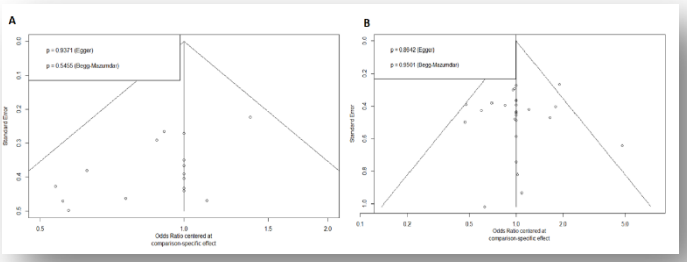

Figure 5

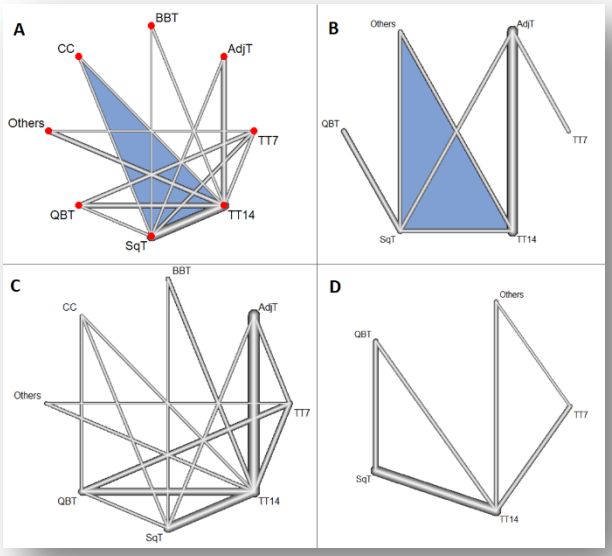

Figure 5: *Network graph A) All patients; B) Adult population; C) Naïve patients; D) Experienced patients*

Discussion

The current guidelines recommend that all patients positive for *H. pylori* infection should be offered treatment [81]. Meanwhile, achieving eradication is not always feasible due to multiple factors related to inherent drug resistance, microbial virulence, or the patient's compliance and tolerability of drugs. The first line therapy varies depending on the patient's known hypersensitivity to penicillin or previous exposure to macrolides. In patients with penicillin allergy and no previous history of macrolide exposure, clarithromycin triple therapy (TT) with metronidazole or bismuth quadruple therapy (BBT) are recommended as first-line therapies. In the absence of penicillin hypersensitivity, either concomitant (CC), sequential therapy (SQT) with clarithromycin, Hybrid therapy, levofloxacin triple therapy, or fluoroquinolone sequential therapy (QBT) could be initiated [81].

In this NMA, we showed that adjuvant therapy was ranked as the best treatment with a higher odds of eradication rate when all trials were analyzed. Moreover, SQT and QBT were associated with a higher eradication rate compared to other regimens. However, there was significant heterogeneity among these trials. The split analysis demonstrated that SQT therapy has a higher eradication rate compared to triple therapy for 14 days. A recent meta-analysis for concomitant therapy vs. triple therapy as the first-line treatment of *helicobacter pylori* infection showed that concomitant therapy given for 5 or 10 days was superior to 5- or 7-, or 10-day triple therapy but was not superior to 14-day triple therapy [82]. Also, we showed in the split analysis that there was no significant difference between SQT vs. adjuvant or Triple therapy vs. adjuvant; this could be attributed to the difference in clarithromycin resistance in the Arab population from other parts of the world that needs to be explicitly studied [83, 84]. Moreover, few included studies provided data on the prevalence of clarithromycin and metronidazole resistance. Subgroup analysis showed that in the adult population, the efficacy of QBT was dramatically increased to reach the first rank as the best treatment for the eradication of *H. pylori*. Subgroup analysis of those previously failed eradication showed a non-significant difference in eradication rates when comparing TT, QBT, and SQT. While Marin et al., in their meta-analysis of QBT rescue therapies after failure of non-bismuth quadruple therapies, demonstrated that QBT had a low eradication rate (≤80%), they found that levofloxacin/bismuth-containing quadruple therapies (LBQ) therapies had an encouraging rate of eradication despite the low strength of evidence. They recommend further evaluation of LBQ, especially in areas with moderate to high bacterial resistances [85].

The large sample size of included studies and the subgroup analysis were the main strength points of this NMA. To the best of our knowledge, this is the first NMA of current regimens in the Arab world. However, we acknowledge that our study has some limitations including, the limited data regarding the efficacy of studied treatment in children, susceptibility testing was done in a small number of these trials, and the frequency of adverse effects was not evaluated in our study. Further longitudinal studies are needed to evaluate the efficacy of these treatments in symptomatic children in high endemicity localities.

In conclusion, the current evidence suggests that QBT and SQT therapies were the most effective regimens for eradicating *H. pylori* in naïve patients in the Arab countries. In experienced patients, all medication showed a non-significant difference in eradication rates. Further randomized controlled studies are essential to compare the efficacy, side effects, antimicrobial resistance, and compliance to different regimens.

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