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Review Article: Classic Bismuth Quadruple Therapy for *Helicobacter pylori* Infection—Questions Focused on Clinical Practice

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ABSTRACT

Background: Classic bismuth quadruple therapy (BQT)—the combination of a proton pump inhibitor, bismuth, tetracycline, and metronidazole—is a standard regimen for treating *Helicobacter pylori* infection.

Aims: This review addresses practical questions regarding its current role in managing the infection.

Methods: A comprehensive bibliographic search was conducted to identify studies evaluating the efficacy, safety and optimization of BQT in different clinical contexts.

Results: BQT is a cornerstone of *H. pylori* eradication, combining agents with complementary mechanisms of action and maintaining high efficacy even in the presence of antibiotic resistance. Optimal acid suppression with a double proton pump inhibitor dose twice daily maximises therapeutic success. When tetracycline is unavailable, minocycline may serve as an alternative, whereas doxycycline is not recommended due to lower efficacy. Ten-day regimens achieve eradication rates comparable to 14-day courses, with similar or better tolerability. The three-in-one single-capsule formulation simplifies administration, enhances adherence, and maintains high efficacy (> 90%). BQT is endorsed as first-line therapy in most international guidelines, particularly in regions with clarithromycin resistance exceeding 15%, and remains the most reliable rescue option after failure of clarithromycin- or fluoroquinolone-based regimens. It is also the treatment of choice for patients with penicillin allergy. The regimen is generally well tolerated, with mostly mild, transient and gastrointestinal adverse events.

Conclusions: BQT remains the most effective, safe, and practical regimen for *H. pylori* eradication, ensuring high cure rates across diverse resistance patterns and clinical settings. Simplified formulations further improve convenience and adherence, reinforcing its role as a globally applicable therapy.

1 | Introduction

Helicobacter pylori infection is the most prevalent worldwide and is the leading cause of highly common and clinically significant

conditions such as chronic gastritis, peptic ulcer disease and gastric cancer [1, 2]. Strikingly, despite more than 30 years of experience, the optimal treatment for this infection has not yet been definitively established. The primary objective of antimicrobial

Abbreviations: AE, Adverse event; BQT, bismuth quadruple therapy; CI, confidence interval; *H. pylori*, *Helicobacter pylori*; Hp-EuReg, European Registry on *Helicobacter pylori* Management; ITT, intention-to-treat; NBQCT, non-bismuth quadruple concomitant therapy; PPI, proton pump inhibitor; RCT, randomised controlled trial; RR, relative risk.

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therapy is to achieve reliable eradication of *H. pylori* infection in the majority of treated patients [3]. Thus, current guidelines emphasise that a regimen should not be considered acceptable unless it consistently attains eradication rates above 90% [4].

Bismuth salts act as topical antimicrobials which, although seldom curative when used alone, substantially reduce *H. pylori* bacterial load and exert synergistic effects with other antibiotics [5]. The first consistently effective antimicrobial regimen for *H. pylori* infection was a multidrug combination of bismuth, metronidazole and tetracycline [6, 7]. However, its efficacy was soon found to be compromised in the presence of metronidazole resistance. Subsequently, in 1995 it was demonstrated that adding a proton pump inhibitor (PPI) to this bismuth-based triple therapy—leading to the so-called “classic bismuth quadruple therapy” (BQT)—improved treatment efficacy [8, 9].

Although BQT was largely neglected for many years (remaining primarily a rescue therapy), mainly due to the advent of simpler regimens such as clarithromycin-based triple therapy, it has recently experienced a resurgence, primarily driven by the marked increase in *H. pylori* antibiotic resistance (primarily to clarithromycin). In this regard, one of the main advantages of BQT is that this therapy is not affected by macrolide resistance and overcomes metronidazole resistance [10]. Furthermore, bismuth is one of the few antimicrobials that do not induce resistance, making it a valuable component for the treatment of *H. pylori* infection, particularly in regions with high levels of antimicrobial resistance [11–13].

In summary, in the context of increasing antibiotic resistance, BQT presents notable advantages by combining agents with distinct mechanisms of action: (a) bismuth, acting primarily as an antiseptic with no reported resistance; (b) tetracycline, associated with very low resistance rates; and (c) metronidazole, which shows high in vitro resistance globally but retains clinical efficacy since resistance can often be overcome by increasing dosage and treatment duration and through synergistic effects when combined with bismuth [14, 15].

Accordingly, BQT has been progressively adopted as a first-line treatment in most national and international guidelines [16]. However, in clinical practice, several highly relevant questions arise regarding the day-to-day management of patients with *H. pylori* infection. These questions have not been thoroughly addressed in the existing literature. Therefore, this narrative review aims to raise a series of practical questions on the role of BQT (i.e., the combination of a PPI, bismuth, tetracycline and metronidazole) in the management of *H. pylori* infection and to provide clear and concise answers.

2 | Approach to the Literature

A bibliographic search was designed to identify studies assessing the role of BQT in the management of *H. pylori* infection. An electronic search was performed in PubMed up to August 2025 using the following algorithm: *pylori*[TI] AND *bismuth*[TI]. In addition, the reference lists of the selected articles were reviewed to identify additional studies of potential interest. Only articles available in full-text format (as complete articles) were included. Articles published in any language were included. If

a study was duplicated, the most recent one fulfilling the inclusion criteria was included. Up to August 2025, 635 articles were retrieved with this search strategy.

3 | Questions Focused on Clinical Practice

3.1 | What Are the Components of BQT and Their Dosing Regimen?

BQT is composed of a PPI, bismuth, tetracycline, and metronidazole. In this section, the most appropriate formulation and dosage of each of these components are reviewed.

3.1.1 | PPI

It is well established that the efficacy of certain *H. pylori* eradication regimens improves with maximised gastric acid suppression through high-dose PPI administration. Thus, in the context of standard triple therapy, PPIs are generally recommended at a dosage of omeprazole 40 mg (or equivalent)—that is, double dose—every 12 h [3]. While the beneficial effect of this dosage is clearly demonstrated for triple therapy [17–19], its impact on BQT remains less well defined. Pabon-Carrasco et al. assessed the impact of PPI dosage on the effectiveness of *H. pylori* eradication regimens using data from the European Registry on *Helicobacter pylori* Management (Hp-EuReg) [20], and concluded that standard-dose PPIs (i.e., 40 mg of omeprazole or equivalent twice daily) appear sufficient in 10-day BQT [21]. In line with this, the study by Olmedo et al., also based on data from the Hp-EuReg, found that none of the BQT regimens achieved effectiveness above 90% when combined with a low-dose PPI (i.e., only 20 mg of omeprazole or equivalent twice daily) [22]. Rather, this study supports that the minimum PPI dose required for optimal BQT outcomes is 40 mg of omeprazole or equivalent administered twice daily [22, 23]. However, higher doses than these do not appear to provide any additional benefit in BQT therapy. This is supported by a prospective, open-label, randomised controlled trial (RCT), which compared the efficacy of BQT with esomeprazole 20 or 40 mg, both administered twice daily, and found that eradication rates did not differ significantly between the two groups, suggesting that the potency of acid suppression may not be critical beyond a certain threshold [24]. In summary, when prescribing BQT, the PPI dose should probably be omeprazole 40 mg (or equivalent) twice daily.

3.1.2 | Bismuth

Bismuth salts exert a short-term topical effect, with a mechanism of action that remains incompletely understood but is thought to resemble that of an antiseptic rather than an antibiotic, and no resistance has been documented. The main commercially available formulations are those that have demonstrated greater effectiveness in terms of eradication rates, bismuth subcitrate and bismuth subsalicylate [25], although no head-to-head trials have directly compared their efficacy. These compounds are marketed in different forms—as solid salts or as colloidal suspensions—and the actual amount of elemental bismuth they contain varies between formulations, which can make direct dose comparisons difficult. The optimal bismuth dosage has

not been clearly established; most clinical studies have administered 120–240 mg of bismuth subcitrate per dose, typically as 120 mg every 6 h or 240 mg every 12 h.

3.1.3 | Tetracycline

In the context of BQT, tetracycline is generally administered as 500 mg every 6 h. In a pioneering study conducted in 1999 by Roghani et al., patients with *H. pylori* infection were randomised to receive bismuth triple therapy (without a PPI) with varying doses of tetracycline [26]. When metronidazole was given at the lower dose, reducing tetracycline from 1500 mg/day to 750 mg/day did not further reduce efficacy; however, the study did not assess whether this lower tetracycline dose would be equally effective when combined with high-dose metronidazole. Overall, these findings support maintaining standard tetracycline dosing (1500 mg/day) [27]. Nevertheless, further studies are warranted to evaluate the efficacy and safety of BQT regimens using reduced tetracycline doses.

3.1.4 | Metronidazole

Metronidazole resistance is highly prevalent in vitro worldwide, yet its clinical impact appears limited and can often be overcome by increasing both the dose and duration of therapy. In BQT, metronidazole is typically administered at 400–500 mg every 8 h. However, evidence from an RCT, in which patients with *H. pylori* infection received bismuth triple therapy (without a PPI) with varying metronidazole doses, demonstrated that increasing the dose from 375 mg/day to 750 mg/day significantly improved eradication rates (77% vs. 50%) [26]. These results support the use of high-dose metronidazole (750 mg/day) to optimise bismuth triple therapy (without a PPI). However, it remains unknown whether these results can be extrapolated to BQT (i.e., when a full quadruple regimen including a PPI is administered).

3.2 | Could BQT With All Its Components Be Administered Every 12h?

Currently, BQT is most often prescribed as a PPI twice daily, bismuth salts two to four times daily, tetracycline 500 mg four times daily, and metronidazole 500 mg three times daily. However, several studies have investigated the possibility of reducing BQT administration to twice-daily dosing, suggesting that simplified regimens may achieve comparable efficacy to conventional schedules [28–32]. For example, Kim et al. compared a twice-daily regimen (tetracycline 1 g, metronidazole 750 mg, bismuth subcitrate 300 mg, and pantoprazole 20 mg per dose for 1 week) with the conventional four-times-daily regimen in 198 patients who had failed first-line therapy [31]. Eradication rates were similar (94% vs. 93%), but gastrointestinal adverse events (AEs) such as abdominal pain, discomfort, and distension were significantly less frequent with the simplified schedule, supporting the potential benefit of twice-daily administration.

However, Graham et al. evaluated a 10-day twice-daily BQT regimen and showed an overall cure rate of only 70% [33]. Stratification by antimicrobial resistance demonstrated high

efficacy in metronidazole-sensitive strains (90%) but markedly reduced success in metronidazole-resistant isolates (41%). These findings suggest that twice-daily BQT may be suitable in regions with low baseline metronidazole resistance, but its utility may be limited where resistance to this antibiotic is common.

In summary, the components of BQT (excluding the PPI) are usually administered every 8 h, or even every 6 h for some agents such as tetracycline. However, no universally optimal dosing scheme has been established. Emerging evidence indicates that modifications in dosing intervals may yield regimens with both high eradication rates and improved patient adherence. Simplification of BQT, such as administering all their components twice daily, has been proposed. Nevertheless, BQT has yet to be fully optimised [34], and further RCTs and exploratory studies are needed to validate regimen adjustments aimed at enhancing convenience and tolerability without compromising therapeutic success (i.e., eradication $\geq 90\%$).

3.3 | When Prescribing BQT, Is It Better to Use Vonoprazan Instead of PPIs?

Some RCTs have compared PPIs versus vonoprazan in BQT [35–38], and some systematic reviews and meta-analyses have synthesised their results. In the meta-analysis by Benito et al., no significant differences were observed between vonoprazan- and PPI-based quadruple regimens, which in most studies included amoxicillin and bismuth salts in combination with furazolidone or clarithromycin [13]. These results may be explained by the incorporation in quadruple therapies of bismuth and antibiotics such as furazolidone, whose bactericidal activity is not directly dependent on gastric pH, thus allowing these regimens to circumvent bacterial antibiotic resistance [13]. Consequently, the potential superiority of vonoprazan-based over PPI-based triple regimens may be diminished when BQT therapy is employed. Nevertheless, these findings contrast with those of a recent meta-analysis by Yang et al., which reported significantly higher eradication rates with vonoprazan compared with PPI (90% vs. 84%) in the context of BQT [39]. Additionally, in the meta-analysis by Cheng et al., the vonoprazan-based BQT was significantly more effective than PPI-based BQT (89% vs. 84%), while both had a similar compliance and safety profile [40].

Consistent results were observed in the network meta-analysis conducted by Li et al., which indicated that the regimen combining vonoprazan, bismuth, and two antibiotics achieved the highest ranking in comparative efficacy analyses and was not inferior to esomeprazole-based BQT [41]. Finally, a recent systematic review performed by Taufiqurrachman in 2025 showed the potassium-competitive acid blockers-based BQT had slightly higher efficacy than PPI-based BQT in the meta-analysis [42]; however, the network meta-analysis revealed that vonoprazan-based BQT did not show superiority over esomeprazole-based BQT [42].

In summary, current evidence from RCTs and meta-analyses suggests that vonoprazan-based BQT achieves eradication rates comparable to, and in some analyses slightly higher than, PPI-based regimens. However, the magnitude and consistency of this potential benefit remain uncertain, likely due to regional variability in antibiotic resistance and methodological heterogeneity

among studies. Given that all available data derive from East Asian populations, additional large-scale, well-designed trials in diverse geographic settings are required to confirm whether vonoprazan offers a clinically meaningful advantage over traditional PPI-based BQT.

3.4 | What Should Be the Duration of BQT?

BQT treatment duration remains a matter of debate [13]. The Maastricht VI guidelines recommend a 14-day course, unless highly effective 10-day regimens are available [3]. Early evidence from a meta-analysis published in 2007 demonstrated that BQT regimens administered for 1–7 days had significantly lower eradication rates compared with those lasting 10–14 days [43]. A subsequent Cochrane systematic review published in 2013, which included 75 studies, assessed the optimal length of eradication therapy [44]. Only six studies (1157 patients) evaluated PPI-BQT with different antibiotic combinations (tetracycline plus metronidazole, furazolidone plus amoxicillin and clarithromycin plus amoxicillin). Comparisons between 7-, 10- and 14-day regimens did not reveal clear superiority of longer therapy, but the limited number and heterogeneity of trials/regimens precluded firm conclusions [44].

More recent data have refined this evidence. A meta-analysis published in 2023, including four RCTs, confirmed that 10-day bismuth-based quadruple regimens (not always including BQT, e.g., with metronidazole and tetracycline) had similar efficacy and fewer AEs compared with 14-day regimens [45]. Similarly, a more recent meta-analysis including 15 trials and 4505 patients found that, although shorter regimens (7 or 10 days) had lower overall eradication rates than 14-day BQT (relative risk [RR] 0.96, 95% confidence interval [CI] 0.93–0.99), 10-day regimens in particular achieved outcomes comparable to 14-day courses (RR 0.98, 95% CI 0.95–1.00) [46]; while AEs and compliance rates were similar across durations. Finally, a very recent meta-analysis published in 2025, including seven RCTs and 2424 patients, found no significant differences between the 10-day and 14-day bismuth-based quadruple regimens, either in the intention-to-treat (ITT) (RR 0.97; 95% CI 0.94–1.01) or in the per-protocol analysis (RR 0.96; 95% CI 0.93–1.00) [47]; AEs and compliance were also similar between the two regimens [47]. Likewise, subgroup analyses restricted to BQT regimens (PPI, bismuth, metronidazole, tetracycline) showed no differences [30, 48, 49].

Resistance patterns could play a critical role in the decision of choosing a longer or shorter treatment duration. Metronidazole resistance rates vary from 20% to 40% in the United States/Europe to 50%–80% in developing countries [50]. It has been suggested that in regions with high resistance, prolonging therapy to 14 days may still improve efficacy, as shorter courses could be inadequate when resistance reaches 40% or higher [11]. Nevertheless, accumulating data indicate that 10-day regimens can achieve $\geq 90\%$ eradication rates across multiple settings, including those with significant antimicrobial (metronidazole) resistance [45].

On the other hand, in recent years, excellent results have been achieved with the three-in-one single-capsule formulation of BQT (Pylera), which is commercially designed for a 10-day course. A recent meta-analysis including 30 studies and more

than 6000 patients treated with Pylera for 10 days reported an efficacy (by ITT) of 90% in first-line therapy [51]. In eight studies, the proportion of patients with clarithromycin or metronidazole resistance could be estimated, and Pylera remained highly effective despite the presence of such resistances [51]. Furthermore, more recently, large-scale registry data from Hp-EuReg (including more than 5000 patients) demonstrated that 10-day single-capsule BQT achieved cure rates of $\geq 90\%$ [23, 51, 52].

In summary, while earlier data and some consensus guidelines favoured 14-day BQT, recent high-quality evidence indicates that 10-day regimens—particularly with the single-capsule formulation—achieve eradication rates comparable to 14-day regimens, with similar or fewer AEs. Importantly, treatment duration should be tailored according to local effectiveness results. Thus, a 10-day course appears sufficient in most settings, although 14 days may still be advisable in areas of very high resistance.

3.5 | Is It Possible to Use Doxycycline or Minocycline Instead of Tetracycline in BQT?

3.5.1 | Doxycycline

In many regions, tetracycline is no longer available, leading many pharmacies to substitute it with doxycycline, a tetracycline analogue [53]. The initial experience with doxycycline in the treatment of *H. pylori* infection concluded that it could not effectively replace tetracycline in bismuth triple therapy [54]. In that study, patients were randomised to receive either doxycycline or tetracycline, combined with bismuth and metronidazole (but without a PPI). Eradication was achieved in only 65% of patients receiving doxycycline, compared with approximately 80% of those treated with tetracycline [54].

A meta-analysis of six case–control studies by Niv et al. [55] found no significant difference in eradication rates between doxycycline- and tetracycline-containing regimens. However, none of these studies were randomised, and most did not directly compare tetracycline versus doxycycline-containing BQT in particular. Only two studies performed such direct comparisons—one favouring tetracycline and the other showing no difference—but in both cases, the overall effectiveness of doxycycline-containing BQT was suboptimal [56].

More recently, a meta-analysis assessed the efficacy and safety of semisynthetic tetracycline regimens—including doxycycline—in *H. pylori* treatment [57]. In the first-line and second-line quadruple regimens with doxycycline (including BQT and other antibiotic combinations), the pooled eradication rates were 84% and 87%, respectively, in the ITT analysis [57].

Finally, a sub-analysis of the Hp-EuReg evaluated third-line *H. pylori* eradication with a PPI, bismuth, metronidazole, and either tetracycline, doxycycline, or the single-capsule formulation after failure of clarithromycin- and levofloxacin-containing regimens [58]. Among 454 patients, eradication rates were 88% for BQT single-capsule, 76% for BQT with tetracycline, and 65% for BQT with doxycycline, confirming the inferiority of the latter regimen. Therefore, it was concluded that doxycycline-based BQT was less effective than tetracycline-based regimens and

should not be recommended for third-line therapy [58]. On the other hand, it has been suggested that doxycycline may be better tolerated than tetracycline [58]; however, other authors have reported opposite findings [54].

In summary, the use of doxycycline instead of tetracycline in the context of a BQT should not be recommended.

3.5.2 | Minocycline

Minocycline, a semisynthetic derivative of tetracycline, possesses several pharmacological advantages that make it an attractive candidate for *H. pylori* eradication therapy. Compared with tetracycline, it exhibits superior bactericidal potency, broader antimicrobial activity, higher oral absorption, greater lipid solubility, and fewer food-drug interactions [59–61]. Its longer elimination half-life allows once- or twice-daily dosing, a feature that may improve patient adherence [60, 61]. Importantly, resistance of *H. pylori* to minocycline remains uncommon (as it is the case also for tetracycline) [62]. Despite these advantages, it is still uncertain whether minocycline can replace tetracycline in *H. pylori* eradication regimens.

Evidence from systematic reviews and meta-analyses provides further insight. A meta-analysis of semisynthetic tetracycline regimens, including minocycline, reported pooled eradication rates of approximately 83% [57]. Another meta-analysis, which included five RCTs with 2004 patients, found that minocycline-based BQT achieved an eradication rate of 84%. When compared directly with tetracycline-containing regimens, eradication rates were identical (85% in both groups), with no significant differences in the incidence of AEs [60, 63–67]. More recently, a comprehensive review including 22 studies assessed minocycline-containing regimens and reported an overall eradication rate of 82% by ITT analysis [61]. Safety and compliance were generally favourable, with most AEs being mild to moderate. Dizziness, however, appeared relatively frequently (16%).

The optimal dosing strategy for minocycline remains undefined. A recent trial compared four minocycline-metronidazole regimens with classic BQT in the setting of rescue *H. pylori* therapy [68]. A novel BQT with a reduced minocycline dose (100 mg/day) achieved efficacy comparable to classic BQT (with tetracycline) (≈90%), while demonstrating a lower incidence of AEs and improved adherence [68].

In summary, available evidence suggests that minocycline-based BQT is a promising alternative to conventional BQT with tetracycline. Given its favourable pharmacological properties and comparable efficacy and safety, minocycline may be particularly useful when tetracycline is unavailable. Nonetheless, further high-quality RCTs directly comparing minocycline with tetracycline are required to better define its role.

3.6 | In Which Countries Is BQT Recommended as First-Line Treatment?

The efficacy of BQT as a first-line treatment is well established. The increased reliance on BQT is closely linked to the growing

prevalence of clarithromycin resistance worldwide, which has substantially reduced the efficacy of clarithromycin-based triple therapy [50, 69–75]. Thus, this decline has reinforced the role of BQT as a robust alternative. In this context, the efficacy and safety of BQT have been documented across diverse geographic regions.

As it is summarised in Table 1, BQT is recommended by most national and international guidelines as an alternative first-line regimen to standard triple therapy in regions with low clarithromycin resistance rates [3, 76–90]. Moreover, it is endorsed as the preferred first-line option in areas where the prevalence of clarithromycin resistance exceeds 15% or remains unknown (Table 1). Taken together, these data confirm the central role of BQT in contemporary *H. pylori* management. Its growing use across many countries worldwide, together with its sustained efficacy even in high-resistance settings, underscores its value as a reliable first-line therapeutic option.

In Europe in particular, the efficacy of BQT has been confirmed in several countries participating in the Hp-EuReg registry, including Spain [91], Slovenia [92], Serbia [93], Ireland [94], and many other countries. In this respect, a recent Hp-EuReg-based global analysis assessed temporal trends in the use and outcomes of BQT in Europe [22]. Among approximately 50,000 patients recorded between 2013 and 2021, 15,582 (31%) received BQT. Its use increased markedly during this period, rising from 8.6% of all regimens in 2013 to 39% in 2021. Regimens achieving >90% eradication included both the 10-day single-capsule BQT and the 14-day conventional BQT.

In summary, these data collectively reinforce the pivotal role of BQT in current *H. pylori* management worldwide. Its increasing adoption across many countries and its consistent efficacy even in high-resistance contexts highlight its value as a reliable first-line treatment option.

3.7 | What Is the Efficacy of BQT as a Second-Line Rescue Treatment?

After failure of a clarithromycin-containing therapy, it is reasonable to assume that *H. pylori* was already resistant to this antibiotic (primary resistance) or that it developed resistance (secondary resistance) following the unsuccessful eradication treatment; therefore, clarithromycin should be avoided in subsequent regimens. In this regard, a pooled analysis of eight studies reported a very low eradication rate (46%) when a clarithromycin-containing treatment was repeated [95].

When standard triple therapy (PPI, clarithromycin, and amoxicillin) has failed, the traditional rescue option has been BQT. According to a meta-analysis already published in 2013, BQT provided a mean eradication rate of 78% [95]. More recently, a meta-analysis of nine studies using BQT reported similar results (76%) [86]. In recent years, increasing experience has been gained with the use of single-capsule BQT as a rescue treatment. An updated meta-analysis concluded that this regimen achieves an efficacy (by ITT) of 89% as a second-line therapy, with a favourable safety profile [51]. Similarly, the experience from the

TABLE 1 | First-line recommended *H. pylori* eradication treatments in different guidelines/consensus worldwide.

Geographic area (reference)	Year of publication	Development organization	Recommended regimen
Belgium [76]	2023	Belgian <i>Helicobacter pylori</i> and Microbiota Study Group	Empirical treatment: BQT or NBQCT If C has been excluded: CTT
Brazil [77]	2018	Núcleo Brasileiro para Estudo do <i>Helicobacter pylori</i> e Microbiota	First-line: CTT Alternatives: BQT, NBQCT
Canada [78]	2016	Canadian Association of Gastroenterology	In areas of high (> 15%) C resistance: BQT or NBQCT In areas of low (< 15%) C resistance: CTT
China [79]	2022	<i>Helicobacter Pylori</i> Study Group of Chinese Society of Gastroenterology	BQT or HDDT
Europe (Maastricht VI/Florence) [3]	2022	European Helicobacter and Microbiota Study Group	In areas of high (> 15%) or unknown C resistance: BQT (if unavailable: NBQCT) In areas of low (< 15%) C resistance: BQT or CTT
Germany [80]	2024	German Society of Gastroenterology, Digestive and Metabolic Diseases	BQT
Hong Kong [81]	2023	The Hong Kong Society of Gastroenterology	CTT or BQT
India [82]	2022	Indian Society of Gastroenterology	In areas of high C resistance: BQT In areas of low C resistance: CTT
Indonesia [83]	2023	Directorate of Research and Community Service, Deputy for Strengthening Research and Development Ministry of Research and Technology/Research Agency and National Innovation	CTT; this therapy should be implemented with caution in some regions in Indonesia with high (> 10%) C resistance Alternatives: BQT and NBQCT
Ireland [84]	2024	The Irish <i>Helicobacter pylori</i> Working Group	BQT (first-line treatment in the absence of C susceptibility testing or where C resistance has been confirmed) CTT (only if C susceptibility has been confirmed)
Italy [85]	2022	Italian Working Group	BQT, CTT or SEQ CTT only considered in areas of low (< 15%) C resistance
Korea [86]	2021	Korean Society of Clinical Microbiology, the Korean Society of Pathologists, and the Korean Society of Gastroenterology	CTT, BQT, NBQCT or SEQ
Poland [87]	2023	Polish Society of Gastroenterology	BQT or NBQCT
Saudi Arabia [82]	2022	The Saudi <i>H. pylori</i> Working Group	BQT Alternatives: NBQCT, SEQ with quinolones, hybrid therapy, HDDT, vonoprazan triple therapy
Spain [88]	2022	Spanish Association of Gastroenterology and Spanish Society of Digestive Pathology	BQT or NBQCT
USA [89]	2024	American College of Gastroenterology	BQT when antibiotic susceptibility is unknown Rifabutin triple therapy or potassium-competitive acid blocker dual therapy is a suitable empiric alternative

(Continues)

TABLE 1 | (Continued)

Geographic area (reference)	Year of publication	Development organization	Recommended regimen
Vietnam [82]	2022	Vietnam Association of Gastroenterology	BQT Alternative: PPI-amoxicillin-levofloxacin-bismuth
WGO [90]	2023	World Gastroenterology Organization	In areas of high C resistance: BQT (or PPI-bismuth-amoxicillin-metronidazole) In areas of low C resistance: CTT

Note: Only those guidelines published in English are included. Guidelines exclusively focused on children were excluded. In case there are multiple publications, only the most updated one has been included.
Abbreviations: BQT, classic bismuth quadruple therapy (PPI, bismuth, tetracycline, metronidazole); C, clarithromycin; CTT, clarithromycin triple therapy (PPI, clarithromycin, amoxicillin); HDDT, high-dose dual therapy (PPI, amoxicillin); NBQCT, non-bismuth quadruple concomitant therapy (PPI, clarithromycin, amoxicillin, metronidazole); PPI, proton pump inhibitor; SEQ, sequential therapy (PPI plus amoxicillin for 5–7 days followed by PPI plus clarithromycin and metronidazole for another 5–7 days).

Hp-EuReg has also been encouraging, confirming the results of the aforementioned meta-analysis by reporting eradication rates of approximately 90% (by ITT) after failure of a first eradication attempt [52, 91, 96]. As an example, Nyssen et al. evaluated the effectiveness and safety of empiric second-line treatments in Europe in a total of 5055 patients, and found that regimens such as 14-day classic BQT and 10-day single-capsule BQT achieved optimal effectiveness [96].

Accordingly, the Maastricht VI guidelines state that ‘after failure of PPI-clarithromycin-amoxicillin triple therapy, a BQT, a fluoroquinolone-containing quadruple (or triple) therapy, or a PPI-amoxicillin high-dose dual therapy are recommended as a second-line treatment’ [3]. In addition, after failure of a quadruple therapy with clarithromycin, the same regimens are recommended [3].

In summary, after failure of a clarithromycin-containing regimen, BQT represents probably the most reliable and effective second-line option, consistently achieving high eradication rates and maintaining a favourable safety profile.

3.8 | What Is the Efficacy of BQT as a Third-Line Rescue Treatment?

BQT is unaffected by clarithromycin or fluoroquinolone resistance and can therefore serve as an effective third-line eradication therapy. In fact, BQT provides an effective rescue option following failure of clarithromycin-containing first-line therapy and levofloxacin-containing second-line therapy [51, 52, 58, 97–101]. Accordingly, the Maastricht VI guidelines state that ‘after failure of the first-line treatment with clarithromycin-containing triple or non-bismuth quadruple therapies, and second-line treatment with fluoroquinolone-containing therapy, it is recommended to use the BQT’ [3].

Some comparative studies between BQT and other therapeutic options provide relevant information. Thus, salvage therapy with BQT has been demonstrated to be superior to triple therapies and effective as an empirical option from the second through the fifth line of treatment [102]. An RCT compared rifabutin-containing triple therapy with BQT for rescue treatment in patients with at least two prior eradication failures [103]. Among 364 subjects, ITT eradication rates were similar

(89% vs. 90%) with the two regimens, but AEs were significantly less frequent with rifabutin triple therapy (26% vs. 54%). In contrast, a trial compared rifabutin-based triple therapy with BQT (single-capsule) as a salvage therapy from second through sixth line treatment among 423 patients and reported a higher eradication rate with the BQT regimen (88% vs. 62%) [104]. Rifabutin efficacy declined with increasing number of prior failures, whereas BQT maintained effectiveness even as fourth-line therapy. These results highlight the consistent performance of BQT in rescue settings [104].

The Hp-EuReg evaluated empirical rescue therapies beyond the second-line for *H. pylori* infection [105]. Among a wide range of regimens used, BQT was the most frequently prescribed, and acceptable outcomes were achieved only with this regimen [105]. Again based on data from the Hp-EuReg, real-world clinical experience showed a pooled third- to sixth-line effectiveness of BQT as high as 92% [52]. Finally, a meta-analysis of studies evaluating the efficacy of BQT reported a mean third-line eradication rate of 82% [51].

In summary, BQT remains the most reliable and effective empirical option for rescue therapy after multiple eradication failures, maintaining high efficacy even beyond the third-line setting.

3.9 | What Is the Experience With the Three-In-One Single-Capsule BQT Formulation (Pylera)?

A recognised limitation of BQT is the need to administer four distinct agents within a complex dosing schedule. A novel formulation, including a single three-in-one capsule incorporating bismuth, metronidazole and tetracycline, was initially developed in the early 2000s, with the potential to streamline treatment administration and thereby enhance its feasibility and acceptability [106–108]. Subsequently, the single-capsule presentation most widely used today, known as Pylera (a three-in-one capsule containing 140 mg bismuth subcitrate, 125 mg tetracycline, and 125 mg metronidazole), was developed [10].

Table 2 summarises the studies that have evaluated the efficacy of single-capsule BQT [97–100, 104, 109–136]. Based on the 34

TABLE 2 | Studies evaluating the efficacy and safety of three-in-one single-capsule bismuth quadruple therapy (Pylera).

Author	Publication year	Country	Treatment line	Efficacy by ITT (%)	Incidence of AEs (%)
Laine [109]	2003	USA	Naïve	121/138 (88)	86/147 (59)
O'Morain [110]	2003	Australia, Canada, Ireland, the Netherlands and USA	Naïve	158/170 (93)	130/177 (73)
Malfertheiner [111]	2011	France, Germany, Ireland, Italy, Poland, Spain and UK	Naïve	174/178 (98)	101/216 (47)
Salazar [112]	2012	USA	Naïve	40/47 (85)	35/47 (75)
Delchier [98]	2014	France, Germany, Italy and Spain	Second	44/47 (94)	33/49 (67)
Muller [99]	2016	France	Overall, second (NR), third (NR) and fourth (NR)	85/103 (82)	56/103 (54)
Di Ciaula [113]	2017	Italy	Overall Naïve Second Third Fourth Fifth	220/227 (97) 85/85 (100) 116/118 (98) 12/13 (92) 5/9 (56) 2/2 (100)	NR
Fiorini [114]	2017	Italy	Overall Second Third Fourth ≥Fifth	94/116 (81) 39/45 (87) 23/29 (79) 18/21 (86) 14/21 (66)	71/116 (61)
Gómez-Rodríguez [115]	2017	Spain	Overall Naïve Second	54/58 (93) 40/41 (98) 14/17 (82)	28/58 (48)
Miehlke [116]	2017	Germany	Overall Naïve Second Third	266/322 (83) 197/238 (83) 47/54 (87) 22/30 (73)	NR
Rodríguez de Santiago [100]	2017	Spain	Third	81/101 (80)	68/101 (67)
Tursi [117]	2017	Italy	Overall Naïve Second	316/349 (90.5) 136/149 (91) 180/200 (90)	55/339 (16)
Zullo [97]	2017	Italy	Overall Second Third Fourth Fifth	180/208 (86.5) 74/87 (85) 79/88 (90) 21/24 (87.5) 6/9 (67)	97/208 (47)

(Continues)

TABLE 2 | (Continued)

Author	Publication year	Country	Treatment line	Efficacy by ITT (%)	Incidence of AEs (%)
Agudo-Fernández [118]	2018	Spain	Naïve Second Third Fourth Fifth	84/107 (78) 35/41 (85) 19/31 (61) 5/5 (100) 1/1 (100)	9/185 (4.9%)
De Francesco [119]	2018	Italy	Naïve	52/61 (85)	15/61 (25)
Fiorini [120]	2018	Italy	Naïve	223/245 (91)	131/230 (57)
Pérez-Arellano [121]	2018	Spain	Overall Naïve Second	88/100 (88) 68/75 (91) 20/25 (80)	18/100 (18)
Tarhini [122]	2018	Lebanon	Naïve	15/30 (50)	NR
Xie [123]	2018	China	Naïve	166/192 (86)	76/186 (41)
Zagari [124]	2018	Italy	Overall Naïve Second Third Fourth Fifth	339/376 (90) 202/221 (91) 112/128 (87.5) 22/24 (92) 2/2 (100) 1/1 (100)	122/376 (32)
Castro Fernandez [125]	2019	Spain	Naïve	183/200 (91)	57/200 (28)
Ciccaglione [126]	2019	Italy	Naïve	30/32 (94)	15/32 (47)
Dore [127]	2019	Italy	Overall Naïve Second	44/50 (88) 25/25 (100) 19/21 (90)	NR
Macías-García [128]	2019	Spain	Naïve	51/54 (94)	25/54 (46)
Alcedo [129]	2020	Spain	Naïve	187/212 (88)	188/212 (89)
Saracino [104]	2020	Italy	Overall Second Third Fourth Fifth	128/153 (84) 37/42 (88) 42/48 (87) 26/31 (84) 23/32 (72)	95/145 (65)
Nyssen [52]	2021	Spain	Overall Naïve Second Third to sixth	1724/2023 (85) 1135/1288 (88) 361/443 (81) 228/268 (85)	570/1979 (29)
Gravina [130]	2021	Italy	Naïve	227/250 (91)	67/250 (27)
Arino Perez [131]	2022	Spain	Naïve	71/87 (82)	NR
Losurdo [132]	2022	Italy	Second	62/73 (85)	14/73 (19)
Marinelli [133]	2022	Italy	Naïve	70/85 (82)	60/85 (71)
Moreno Márquez [134]	2022	Spain	Naïve	36/40 (90)	NR
Correia [135]	2023	Portugal	Second and rescue therapy	100/151 (90)	63/151 (42)
Oueslati [136]	2025	Tunisia	Naïve	87/100 (87)	62/100 (62)

Abbreviations: AE, Adverse events; ITT, intention-to-treat; NR, not reported.

studies included, encompassing a total of 4085 patients, the mean *H. pylori* eradication rate was 87% (95% confidence interval: 86%–88%). When only treatment-naïve patients were considered (4350 patients), the mean efficacy was 89%; in second-line therapy (1492 patients), 85%; in third-line (619 patients), 83%; in fourth-line (96 patients), 88%; and in fifth-line therapy (75 patients), 69%.

Data from the Hp-EuReg have confirmed these excellent results in Europe in the largest cohort analysed to date, showing eradication rates exceeding 90% [52]. A total of more than 2000 patients were prescribed single-capsule BQT, of whom the majority were treatment-naïve. The overall modified ITT effectiveness was 92%. The eradication rate achieved 95% in first-line therapy, and remained high when used as rescue therapy, both in second-line treatment (89%) and in subsequent lines (third to sixth, 92%) [52]. In a subsequent update of the Hp-EuReg focused on the outcomes of bismuth-containing quadruple therapies, single-capsule BQT emerged as the most frequently prescribed regimen (43%) and the only one that consistently achieved cure rates above 90% across all geographical regions [22].

A meta-analysis including 30 studies and 6482 patients evaluated Pylera plus a PPI for *H. pylori* eradication [51]. The ITT eradication rates were 90% in first-line, 89% in second-line, and 82% in third-line therapy, irrespective of PPI type or dosage. In metronidazole-resistant infections, first-line efficacy reached 93%, and in second-line regimens following clarithromycin failure, 90%. Thus, it was concluded that a 10-day single-capsule BQT regimen achieved consistent eradication rates of around 90% in both first- and second-line settings; and that this applies also to patients with clarithromycin- or metronidazole-resistant strains, and to those previously treated with clarithromycin [51]. However, although the results of the single-capsule formulation are clearly favourable, the lack of head-to-head RCTs precludes any firm conclusion regarding its superiority over classical BQT.

Regarding the safety of the single-capsule formulation, in the aforementioned meta-analysis evaluating Pylera AEs occurred in 43% of patients, were generally mild, and led to treatment discontinuation in only approximately 3% of cases [51]. Analysis of the studies included in Table 2 (covering 6701 patients) showed a mean AE incidence of 39% (95% confidence interval: 38%–40%). Although this rate is relatively high, most of these AEs were mild. The safety profile was comparable to that of quadruple eradication regimens containing three antibiotics [51, 137].

Finally, data from the largest series to date—encompassing approximately 2000 patients from the Hp-EuReg—reported an AE incidence of 29% [52]. The most frequent were nausea (9.5%) and diarrhoea (8%). The mean duration of AEs was quite limited, ranging from 4.8 to 8.4 days. Most were mild (99%) and transient; however, 17% of patients with fatigue, 14% with anorexia, and 10% with heartburn rated them as severe. Overall, AEs had a limited impact on adherence (3.3% of patients), leading to treatment discontinuation in only 1.7% of the cases. Serious AEs requiring hospitalisation occurred in fewer than 1% of patients [52].

In summary, the three-in-one single-capsule BQT formulation has simplified treatment administration (although it still

involves taking 14 tablets and capsules per day: 12 Pylera and two PPI doses), while maintaining high efficacy and good tolerability. Across clinical trials and large real-world studies, eradication rates consistently approach or exceed 90%, even in rescue settings and in the presence of antibiotic resistance. Although mild AEs are relatively frequent, discontinuations are rare, confirming its favourable safety and adherence profile.

3.10 | Can the Three-In-One Single-Capsule BQT Formulation (Pylera) be Administered Every 8h Instead of Every 6h?

The conventional administration of single-capsule BQT involves three capsules taken four times daily, together with a PPI twice daily. While this schedule is supported by regulatory approval, its complexity represents a major drawback, often raising concerns regarding patient adherence. Simplifying the regimen without compromising efficacy would therefore be of clear clinical relevance.

Data from the Hp-EuReg have recently addressed this question by evaluating an alternative three-times-daily regimen, in which four capsules are administered three times daily for 10 days [23]. This adjustment maintains the total daily dose while reducing the number of intakes. The study included 3712 patients, of whom 2516 received the traditional schedule and 1196 the three-times-daily regimen. The findings indicate that the modified regimen not only preserves but may even improve eradication outcomes compared with the standard schedule (94% vs. 91%). Importantly, this advantage was most evident in treatment-naïve patients, where cure rates reached 96% vs. 93%, respectively. In any case, it should be taken into consideration that the differences, although statistically significant, are of limited clinical relevance; moreover, they derive from an observational study, and to date no RCT has compared the two therapeutic regimens. Adherence and safety profiles were similar across both regimens, with AEs being predominantly mild and serious events remaining uncommon.

These results have important implications for clinical practice. A regimen based on three daily intakes aligns better with patients' daily routines, likely facilitating adherence outside of controlled trial conditions. Moreover, the comparable safety profile reinforces its acceptability in routine care. Nevertheless, evidence is still largely derived from observational data, and confirmation in RCT settings and across different geographic regions would strengthen the case for wider adoption.

In summary, administration of three-in-one single-capsule BQT (Pylera) every 8h appears feasible and potentially associated with higher eradication rates compared with the currently approved 6-hourly regimen, without an apparent compromise in safety or adherence; however, confirmation in randomised controlled trials and diverse populations is warranted, and it should be noted that the approved prescribing information for single-capsule BQT specifies administration as three capsules taken four times daily.

3.11 | How Does *H. pylori* Antibiotic Resistance Affect the Efficacy of BQT?

The most frequent reason for the failure of otherwise reliable or highly effective *H. pylori* eradication regimens is, aside from poor patient adherence, the presence of strains resistant to one or more of the antibiotics used [75]. Resistance rates vary significantly across different geographical regions [90, 138], making it necessary to adjust treatment regimens based on local resistance patterns. Notably, several recent reviews have documented a global increase in clarithromycin resistance across multiple regions [50, 71–75, 138]. An advantage of BQT is that it is not influenced by macrolide resistance. On the other hand, metronidazole resistance is of lesser concern, as its resistance can often be overcome by BQT [10, 12, 139–141].

In Korea, a prospective study evaluated changes in BQT effectiveness as a second-line therapy over 15 years [142]. The trial included 452 patients who had failed first-line treatment and received a 14-day BQT regimen. Despite a high prevalence of metronidazole resistance (45%), eradication rates remained stable over time, with no significant annual decline observed throughout the study period [142].

In a recent study based on data from the Hp-EuReg, a total of 2852 naïve patients with culture results were analysed [75]. Resistance to clarithromycin, metronidazole, and quinolones was 22%, 27% and 18%, respectively. The most effective treatment, regardless of resistance, was the single-capsule BQT (91% eradication rate), offering optimal cure rates even in the presence of bacterial resistance to clarithromycin or metronidazole. A total of 1118 non-naïve patients were also analysed, and resistance to clarithromycin, metronidazole, and quinolones was 49%, 41% and 24%, respectively. Again, the single-capsule BQT was the most effective regimen, achieving 87% cure rate [75].

In summary, in regions where the *H. pylori* antibiotic resistance rate—mainly clarithromycin—is high, eradication treatment with BQT is probably the best option.

3.12 | What Is the Rationale for Using BQT Instead of Clarithromycin Triple Therapy?

Currently, the efficacy of clarithromycin-based triple therapy is seriously compromised in many regions worldwide, with eradication rates having declined to unacceptably low levels, primarily due to the emergence of clarithromycin-resistant *H. pylori* strains. In Europe, the overall clarithromycin resistance rate rose from 9% in 1998 [143] to over 20% in recent years [50]. Thus, clarithromycin resistance has risen across most European countries, with prevalence rates now exceeding 20% in central, western, and southern Europe—levels that classify these regions as high-resistance zones [144] (a threshold of 15%–20% has been proposed to distinguish between areas of low and high clarithromycin resistance [3, 16]). Finally, very recently, an international survey on antibiotic resistance conducted in 31 countries on 6 continents demonstrated a marked increase in antibiotic resistance worldwide [138].

Pooled data from 20 studies involving almost 2000 patients treated with standard triple therapy demonstrated an eradication rate of 88% in clarithromycin-susceptible strains, compared to only 18% in resistant strains [145]. Additionally, the potential for both direct and ecological increases in antibiotic resistance—affecting *H. pylori* and other bacterial species—must be carefully considered before implementing eradication programs [3].

Three meta-analyses conducted over the last decade suggested that BQT (with a mean efficacy between 77% and 81%) offered no advantage over triple therapy [146–148]. However, in the studies on which these meta-analyses were based, BQT was administered for only 7 days, and they were published a decade or more ago, when clarithromycin resistance rates (which markedly reduce the efficacy of triple therapy) were considerably lower.

In summary, the empirical use of clarithromycin-containing triple therapy is no longer appropriate in most parts of the world. Thus, if individual susceptibility testing is not available, the recommended first-line treatment in areas of high (>15%) or unknown clarithromycin resistance is BQT [3]. However, in the rare settings where clarithromycin resistance remains below 15% and where local data confirm eradication rates of at least 90% with the standard PPI-clarithromycin regimen, this combination may still be considered as a first-line option—although BQT remains an equally valid alternative [3].

3.13 | What Is the Rationale for Using BQT Instead of Non-Bismuth Quadruple Concomitant Therapy?

Non-bismuth quadruple concomitant therapy (NBQCT), consisting of a PPI, clarithromycin, amoxicillin, and a nitroimidazole (usually metronidazole) administered simultaneously [149], has shown high efficacy in numerous trials [150]. In fact, NBQCT and BQT were the only regimens to consistently achieve $\geq 90\%$ eradication rates across all European regions in the Hp-EuReg [52, 151].

However, the main limitation of NBQCT is its vulnerability to dual clarithromycin-metronidazole resistance. While resistance to a single antibiotic usually does not compromise efficacy, eradication rates fall clearly below 90% once dual resistance prevalence exceeds 15% [149]. Moreover, NBQCT exposes all patients to at least one unnecessary antibiotic, which may contribute to antimicrobial resistance, particularly as clarithromycin or metronidazole are redundant in resistant infections. Consequently, the Maastricht VI Consensus and other guidelines recommend NBQCT only when BQT or other effective alternatives are unavailable [3].

Several systematic reviews and meta-analyses have directly compared BQT and NBQCT. An initial meta-analysis by Guo et al. reported comparable eradication rates and similar AE frequencies between both regimens [152]. Likewise, a more recent meta-analysis by Zagari et al., including six studies [119, 153–157] with 1810 patients, also found similar ITT eradication rates of 87% for BQT and 85% for NBQCT, with no significant differences in safety [158]. Similarly, in the most recent meta-analysis by Parra et al., BQT achieved eradication rates equivalent to NBQCT, both in efficacy and in safety outcomes [150]. In this

last meta-analysis, when only RCTs were included [119, 153–157, 159–161], encompassing more than 3000 patients, no significant differences were observed in ITT eradication rates between the two regimens (85% for BQT and 86% for NBQCT); moreover, sensitivity analyses confirmed comparable results when adjusting for treatment duration [150].

However, recent evidence from large real-world data sets suggests a modest advantage for BQT over NBQCT. Thus, in Spain, analysis of nearly 14,000 patients from the Hp-EuReg showed that 10-day single-capsule BQT achieved slightly (but statistically significant) higher eradication rates than 14-day NBQCT (94% vs. 91%; $p < 0.001$) [162].

Adherence may be another differentiating factor between these two regimens. Although NBQCT is theoretically simpler, being administered every 12 h, real-world adherence has been lower than with single-capsule BQT. Hp-EuReg data indicate that NBQCT ranks among regimens with the poorest adherence, while BQT benefits from a simplified single-capsule formulation, minimising pill burden [23, 162, 163]. Such simplification may enhance adherence and, consequently, therapeutic efficacy, particularly when the single-capsule BQT is administered three times daily instead of the conventional four-times-daily regimen, as suggested by a recent study [23].

Regarding safety, single-capsule BQT has demonstrated a slightly more favourable tolerability profile compared with NBQCT, although differences are minor and both regimens have a favourable safety profile [162].

Cost considerations vary by country. In Spain, NBQCT and single-capsule BQT are similarly priced ($\approx$ €60 with standard-dose PPI) (<https://www.sanidad.gob.es/profesionales/nomenclator.do>), whereas in the United States single-capsule BQT is substantially more expensive (\$300–1100) (www.drugs.com) [162].

Regarding accessibility, NBQCT demonstrates greater worldwide availability, since single-capsule BQT and its components—bismuth and tetracycline—remain less accessible in many regions.

With respect to β -lactam allergy, BQT is also recommended as a first-line option for patients with penicillin allergy [101]. This distinction is clinically relevant, as BQT can therefore be administered to nearly all patients, whereas NBQCT has more limited applicability.

Finally, from an antibiotic stewardship perspective, BQT is better aligned with rational prescribing principles. NBQCT combines three antibiotics—clarithromycin, amoxicillin, and metronidazole—commonly used in other infections, raising concerns about resistance selection in gastrointestinal and systemic microbiota. In contrast, BQT includes tetracycline, an antibiotic with limited current indications beyond *H. pylori*, thereby posing a lower ecological risk. This stewardship-oriented profile supports BQT as a more sustainable option for first-line therapy [162].

In summary, both BQT and NBQCT are highly effective and safe first-line regimens, achieving eradication rates of $\approx$ 90% in

many settings. While meta-analyses show comparable efficacy, recent large real-world data suggest a slight advantage for BQT in terms of effectiveness, adherence and antibiotic stewardship. However, differences remain modest, and local availability, resistance patterns and cost should ultimately guide regimen selection.

3.14 | How Does BQT Compare With High-Dose Dual (PPI and Amoxicillin) Therapy?

In regions with high ($>15\%$) dual—clarithromycin and metronidazole—resistance rates, high-dose PPI-amoxicillin dual therapy may represent a viable alternative, as it circumvents resistance to both antibiotics, particularly in settings where bismuth, tetracycline, or the single-capsule BQT are unavailable [164]. The dosing frequency is a critical determinant of efficacy in high-dose dual therapy, given the time-dependent bactericidal activity of amoxicillin. A meta-analysis of 15 RCTs reported that administering PPI-amoxicillin four times daily achieved significantly higher eradication rates compared with lower dosing regimens [165].

Several meta-analyses have shown that high-dose dual therapy can yield cure rates approaching 90%, with efficacy comparable (or even higher) to that of BQT, and a lower incidence of AEs and similar or better compliance [165–171]. The most recent meta-analysis included 20 RCTs, encompassing 7891 patients, and compared high-dose dual therapy with BQT [171]. ITT analysis showed no significant difference in eradication rates between both regimens (86% vs. 85%). However, AEs were significantly less frequent with high-dose dual therapy [171]. Finally, in a network meta-analysis, high-dose dual therapy for 14 days appeared to be the optimal primary therapy for *H. pylori* among Asian populations, with efficacy and compliance comparable to BQT, while causing fewer AEs [167].

As it is the case for PPI-amoxicillin dual therapy, current evidence indicates that vonoprazan-amoxicillin dual therapy has an efficacy comparable (or even higher) to that of BQT, and a lower incidence of AEs and similar or better compliance [172, 173] (however, to date, no comparative studies have been conducted between BQT and dual therapy with a potassium-competitive acid blocker other than vonoprazan). In the most updated meta-analysis comparing both regimens, vonoprazan-amoxicillin dual therapy achieved higher eradication rates than BQT (87% vs. 80% by ITT), with significantly better compliance and fewer AEs (11% vs. 27%).

However, it should be noted that almost all studies evaluating high-dose PPI- or vonoprazan-amoxicillin dual therapy have been conducted in Asia, and the limited experience in other regions has generally been disappointing. For instance, in Europe, this combination has been associated with eradication rates below 80% [174, 175].

In summary, high-dose PPI- or vonoprazan-amoxicillin dual therapy offers an effective and well-tolerated alternative to BQT, achieving comparable eradication rates with fewer AEs and better adherence. These regimens are particularly valuable in regions with high dual antibiotic resistance or limited access to

bismuth-containing therapies. However, it should be borne in mind that treatment outcomes may differ across geographical areas (due, among other factors, to varying resistance rates); in this regard, as the most favourable results derive from studies in Asian populations and have not been consistently replicated in Western settings, their widespread adoption should await further confirmatory evidence from diverse geographic regions [3, 174, 175].

3.15 | Is the Addition of Probiotics Beneficial in BQT?

The potential role of probiotics as an adjuvant to BQT for *H. pylori* eradication has been broadly investigated, with heterogeneous results. Some studies have suggested that probiotic supplementation may enhance eradication efficacy [176, 177], whereas others have found no significant benefit [133, 134, 178].

Regarding tolerability, evidence is somewhat more consistent. Most trials have reported a reduction in AEs when probiotics were combined with BQT [134, 176–178], whereas only one study failed to demonstrate any benefit [133]. Probiotic strains investigated include *Lactobacillus rhamnosus* [133], *Saccharomyces boulardii* [177], and *Lactobacillus reuteri* [134, 178].

A meta-analysis by Yao et al. synthesised data from ten studies to evaluate whether probiotics improve BQT outcomes [179]. The pooled results showed a modest but statistically significant increase in eradication rates in the probiotic group compared to controls (RR 1.07, 95% CI 1.02–1.11). In addition, probiotics significantly reduced the overall incidence of AEs (RR 0.58, 95% CI 0.37–0.91), particularly diarrhoea and bitter taste. However, it is noteworthy that this meta-analysis did not restrict antibiotic selection within BQT regimens (including metronidazole and tetracycline), thereby including also modified bismuth quadruple schemes (with other antibiotics). In fact, only two of the included studies specifically evaluated standard/classic BQT [134, 180].

In summary, current evidence suggests that probiotics may improve tolerability and, in some cases, efficacy when added to BQT. Nevertheless, the heterogeneity of probiotic strains studied and the limited number of trials focusing exclusively on classic BQT highlight the need for further high-quality, regimen-specific RCTs.

3.16 | What Is the Safety of BQT?

Systematic reviews and meta-analyses assessing the overall safety of eradication regimens support that BQT is generally safe and well tolerated. A systematic review of 35 RCTs involving 4763 patients found no serious AEs related to bismuth and no significant differences in the incidence of total AEs compared with placebo or antibiotic regimens without bismuth [181]. Similarly, other pooled analyses have reported comparable tolerability between BQT and triple or non-bismuth quadruple therapies [147, 148, 182, 183]. Table 2 summarises the studies that have evaluated the safety of single-capsule BQT [52, 97–100, 104, 109–112, 114, 115, 117–121, 123–126, 128–130, 132, 133, 135, 136]. In a total of 5980 patients included, the mean incidence rate of AEs was 39%, and most of them were mild.

In a study from the Hp-EuReg, which included more than 22,000 patients, BQT showed the highest incidence of AEs among commonly prescribed regimens, affecting 37% of patients [184]. Metallic taste (16%), diarrhoea (12%), and nausea (20%) were the most frequently reported. This relatively high proportion of AEs (compared with other regimens) may be partly attributable to the extended treatment duration (14 days) used in a large proportion of patients in the Hp-EuReg [184]. Consistently, a recent meta-analysis found that prolonging therapy from 7 to 14 days was associated with an increased incidence of AEs [44]. Finally, the single-capsule BQT was associated with a lower incidence of AEs (28%) compared with the classic BQT, possibly due to the lower tetracycline dose in the single-capsule formulation.

Taken together, BQT is associated with a relatively high frequency of mild gastrointestinal AEs, particularly when administered for 14 days, but serious AEs are exceptional. Its safety profile is broadly comparable to that of other eradication regimens, and simplified formulations such as single-capsule BQT may improve tolerability. From a clinical perspective, comprehensive patient counselling, provision of written treatment instructions, and clear communication regarding the expected transient and benign nature of most AEs are critical to ensure adherence and maximise the effectiveness of the therapy [183, 184].

In summary, BQT is generally safe and well tolerated, with mostly mild and transient gastrointestinal AEs. Although their overall incidence is relatively high—especially with 14-day regimens—serious events are rare, and treatment discontinuations remain uncommon. The single-capsule formulation appears to further improve tolerability through optimised dosing.

3.17 | How Does BQT Affect the Intestinal Microbiota?

Several studies have shown that BQT leads to a transient imbalance in the intestinal microbiota, which gradually recovers within one year [159, 185–191]. In the most recently published study, an RCT comparing the effects of BQT and other quadruple therapy on the gut microbiota, the transient increases in antibiotic resistance and in the gut microbiota resistome, along with the perturbations of the gut microbiota observed shortly after eradication therapy, were largely reversible, returning to baseline levels within 2 months to 1 year after treatment [191]. The impact on the gut microbiota appears to be comparable between BQT and non-bismuth quadruple therapies [186, 188]. However, compared to BQT, regimens such as high-dose dual PPI-amoxicillin therapy and levofloxacin quadruple therapy had a milder impact on gut microbiota [191, 192]. In summary, these findings collectively indicate that *H. pylori* eradication therapy in general, and BQT in particular, is safe in the long term with respect to its impact on the gut microbiota.

3.18 | Tailored *H. pylori* Treatment or Empirical BQT?

As previously discussed, antibiotic resistance to *H. pylori* has reached alarming levels worldwide, making the selection of an

appropriate eradication regimen increasingly challenging [193]. Regional surveillance of antimicrobial resistance is therefore essential to guide the choice of the most effective empirical therapies for each specific area. In principle, the treatment of any bacterial infection should rely on antibiotic susceptibility testing; however, this approach is particularly complex in *H. pylori* infection. Although pretreatment susceptibility testing enables personalised therapy, it traditionally requires an invasive procedure—gastroscopy for bacterial culture—which is impractical for large-scale eradication programs, such as those intended for gastric cancer prevention in the general population [194].

Recently, genotypic testing for clarithromycin resistance using stool samples has emerged as a non-invasive and accurate alternative, allowing for more rational antibiotic selection [195–197]. Despite its promise, the technique still faces important limitations: the number of studies remains small, their accuracy results are heterogeneous, and commercial availability of diagnostic kits is limited across healthcare systems [3]. Consequently, whether all patients should undergo systematic molecular testing (either stool- or biopsy-based) prior to initiating eradication therapy remains controversial in clinical practice [3]. Nevertheless, in settings where biopsy-based PCR testing is routinely available, clarithromycin triple therapy remains a highly effective, simple, and well-tolerated first-line option for patients with clarithromycin-susceptible strains.

While some early meta-analyses suggested that susceptibility-guided therapy achieves higher eradication rates than empirical treatment, more recent and comprehensive analyses indicate that susceptibility-based regimens do not confer a significant advantage when the empirical therapy uses modern optimised quadruple regimens [194, 198, 199]. In particular, when BQT is employed empirically as a first-line regimen and achieves high local eradication rates, the added value of pretreatment susceptibility testing becomes minimal. This observation aligns with the well-established high efficacy of BQT, even against clarithromycin- or metronidazole-resistant strains, while tetracycline resistance is exceedingly rare. For instance, eradication rates achieved with empirical BQT and susceptibility-based therapy were 96% and 96%, respectively, in the study by Choi et al. [200]; 88% and 80% in the study by Cha et al. [201]; and 92% and 88% in the study by Chang et al. [202].

Finally, in addition to its robust efficacy, empirical BQT has been shown to be more cost-effective than susceptibility-guided therapy, as demonstrated by Chang et al. [202].

In summary, current evidence supports the use of empirical BQT as a highly effective and practical first-line strategy, achieving eradication rates comparable to those of susceptibility-guided therapy while offering greater feasibility and lower cost. Given its robust activity against resistant *H. pylori* strains and its independence from clarithromycin susceptibility, routine pretreatment antimicrobial testing appears unnecessary when BQT is employed.

3.19 | What Are the Main Limitations of BQT?

The primary limitation of BQT lies in its complex dosing schedule, as it requires the administration of four different drugs, and

some components are generally prescribed four times daily. This complexity poses a significant challenge to patient adherence, underscoring the need for clinical trials aimed at simplifying the regimen to enhance compliance. To address this limitation, a simplified formulation consisting of a single three-in-one capsule—combining bismuth, metronidazole, and tetracycline—has been developed, significantly reducing the pill burden and improving patient adherence to therapy [51]. However, this formulation remains unavailable in many countries worldwide.

Another important limitation of BQT is the limited global availability of bismuth salts, coupled with a growing shortage of tetracycline in many countries. In addition, as previously mentioned, the three-in-one capsule formulation is currently available in only a small number of countries worldwide. In regions where commercially available BQT formulations are not accessible, several pragmatic alternatives may be considered in clinical practice. These include prescribing the individual components of BQT separately when bismuth salts, tetracycline, and metronidazole are available through standard or hospital-based pharmacies, as well as the use of locally compounded formulations prepared by specialised pharmacies. In some countries, regulatory pathways for restricted-access or orphan drugs, compassionate-use programmes, or special procurement schemes may also allow access to bismuth-containing compounds.

Regarding cost, due to the low price of its components (bismuth, tetracycline, and metronidazole), BQT is often the preferred option in settings where treatment affordability is a primary concern. As previously noted, in some European countries (such as Spain), NBQCT and single-capsule BQT are similarly priced, whereas in other European countries or in the United States, single-capsule BQT is substantially more expensive [162].

In summary, the main limitations of BQT include its complex dosing, which may hinder adherence, and the limited global availability of bismuth and tetracycline. Although the single-capsule form improves convenience, its restricted access and higher cost in some regions remain major challenges. Broader access to bismuth formulations and optimised dosing are needed to enhance BQT's global applicability.

4 | Conclusions

BQT—a combination of a PPI, bismuth, tetracycline, and metronidazole—remains the cornerstone of *H. pylori* eradication worldwide. By integrating agents with complementary mechanisms of action, BQT maintains consistently high efficacy, safety, and reliability, even in the presence of antimicrobial (particularly clarithromycin, but also metronidazole) resistance. Therefore, it is the preferred empirical option for both first-line and rescue therapy and the regimen of choice for patients with penicillin allergy. In this respect, empirical BQT achieves eradication rates comparable to susceptibility-guided therapy, with superior feasibility and cost-effectiveness, making routine susceptibility testing unnecessary in most regions. Furthermore, BQT is safe and well tolerated, with mostly mild, transient gastrointestinal AEs. It transiently alters the gut microbiota, which normalises within months after therapy.

Although traditional regimens require multiple drugs administered up to four times daily, simplification strategies—such as twice-daily dosing or the development of a single three-in-one capsule—have demonstrated comparable eradication rates with improved convenience. The single-capsule formulation, in particular, has reduced pill burden and enhanced adherence while maintaining a favourable safety profile. Doxycycline should not replace tetracycline due to reduced efficacy, whereas minocycline may serve as a viable alternative when tetracycline is unavailable. The PPI dose should probably be 40 mg of omeprazole (or equivalent) twice daily to ensure adequate acid suppression. Vonoprazan-based BQT achieves similar or slightly higher eradication rates than PPI-based regimens, though the clinical advantage remains uncertain outside Asia. Shortening treatment duration to 10 days appears sufficient in most circumstances, particularly with optimised and single-capsule formulations, though longer courses (14 days) may still be advisable in areas of very high metronidazole resistance. The addition of probiotics may further enhance tolerability and, in some cases, efficacy, although the evidence remains heterogeneous.

Despite these strengths, BQT still faces practical limitations, notably its complex dosing schedule and the limited availability of bismuth and tetracycline in many regions. The high cost and limited availability of the single-capsule formulation—particularly in certain regions—remains barriers to its global implementation.

In summary, BQT is widely endorsed as a first-line regimen in most international guidelines—particularly in regions with high clarithromycin resistance—and remains the most reliable second- and third-line rescue therapy after failure of clarithromycin- or fluoroquinolone-based regimens. It continues to represent the most effective, evidence-based, and broadly applicable option for *H. pylori* eradication, combining robust efficacy across resistance patterns with good safety and increasing practicality through simplified formulations.

Author Contributions

Javier P. Gisbert wrote the first draft of the manuscript and critically reviewed the final version. Pablo Parra and Olga P. Nyssen complemented draft sections and critically reviewed the final version.

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Conflicts of Interest

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Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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