ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Mini Review

Common Errors in *H. Pylori* Management - Recommendations for an Improved Practice

Rabbia Tariq, Sarush Ahmed Siddiqui*, Ariba Moin, Hiba Ahmed, Maheen Tariq, Alina Moin, Imad Uddin Sawal, Muhammad Faizan Yousuf, Fahad Hassan Shaikh and Shajie UR Rehman Usmani

Department of Internal Medicine, Dow University of Health Sciences, Pakistan

***Corresponding Author:** Sarush Ahmed Siddiqui, Department of Internal Medicine, Dow University of Health Sciences, Pakistan.

Received: April 26, 2022; **Published:** May 24, 2022

Abstract

Helicobacter pylori (*H pylori*) infection affects half of the world's population and accounts for 90% of all gastric cancers. This alarming situation is a byproduct of increasing antibiotic resistance due to which many previously successful therapies have been rendered ineffective. A major challenge that stands in the way of *H pylori* eradication is the inept and delayed implementation of clinical guidelines, creating a gap between scientific recommendations and actual clinical practice. This review highlights the discrepancies in guideline implementation and common errors that are made by practitioners while prescribing therapy. These errors include prescribing triple therapy instead of quadruple regimen as first-line therapy, repeating antibiotics in subsequent therapies, prescribing therapy for 7 - 10 days instead of 14 days, prescribing a low-dose of proton pump inhibitors (PPIs), not checking eradication success and failing to consider the importance of treatment compliance. This review also outlines some recommendations for the practitioners to overcome these prevailing errors in treatment, as well as some suggestions for the healthcare authorities to actively disseminate the clinical guidelines and ensure that they are meticulously implemented.

Keywords: *Helicobacter pylori*; *Antibiotic Resistance; Holistic Therapy; Treatment Compliance*

Introduction

Helicobacter pylori (*H pylori*) infection poses a significant global health challenge, as it accounts for approximately 90% of all gastric cancers, and is a causative agent in various gastrointestinal disorders, including chronic gastritis, peptic ulcer disease and gastric adenocarcinoma [1]. The World Health Organization categorized it as a group 1 carcinogen in 1994[2] while the more recent Kyoto Global Consensus Report from 2015 established *H. pylori* gastritis as an infectious disease regardless of symptoms and complications [1]. Although commendable efforts have been made so far to curb the prevalence of *H pylori* infection, half the world's population remains affected by it with its prevalence increasing to 90% in developing nations [3]. Furthermore, the dangerously increasing antibiotic resistance to previously efficacious antibiotics and resultant absence of a gold standard treatment for *H pylori* has led to a decline in its eradication rate in recent years [4]. Despite that, a myriad of therapeutic options are continuously explored and culminated into clinical guidelines, the latest of which include the IV Spanish Consensus Report [5], the Maastricht V/Florence Consensus Report [6], and the American College

of Gastroenterology (ACG) Clinical Guidelines [7]. However, translating these recommendations into clinical practice remains a serious challenge, with several mistakes being made while prescribing therapy. In this review, we aim to identify the gap in knowledge by discussing the common mistakes made in clinical practice while managing *H pylori* infection, thereby raising awareness amongst practitioners so that these prevailing errors are rectified and standard of care is elevated. We also review certain recommendations to medical practitioners, healthcare authorities, and researchers, in an attempt to encourage a meticulous implementation of clinical guidelines and aid in the management of *H pylori* infection which, despite more than three decades of experimentation, has remained at the cusp of skepticism.

Common mistakes in management

Physician adherence to *H pylori* clinical guidelines has remained suboptimal. A survey in Spanish physicians revealed that only 40% had read at least one Maastricht consensus, 34% attended a course about *H pylori*, and only 20% adhered to treatment recommendations [8]. In another study, only 50% of physicians reported using professional guidelines for *H pylori* management [9]. Similarly, a Chinese survey showed that up to 40% of physicians do not follow recommendations for *H pylori* diagnosis [10].

The frequent discrepancies in *H pylori* management might be attributed to the barriers that stand in the way of physician adherence. These include personal barriers such as disagreement or lack of familiarity with the guidelines, inability to comprehend the guidelines, difficulty in overcome the inertia of previous practice; or external barriers such as organizational constraints, lack of a reminder system or counseling materials, insufficient consultant support, heavy workload, increased practice costs, poor primary-secondary care dialogue and access restrictions on diagnostic facilities for primary care doctors [11-13]. The subpar compliance to guidelines has left room for mistakes made by physicians in treating *H pylori* infections, six of which are highlighted in this review.

Prescribing triple therapy as primary regimen in areas of high clarithromycin resistance and in patients who are allergic to penicillin

According to Maastricht V[6] and ACG[7] guidelines, quadruple regimen (bismuth in combination with a PPI and two antibiotics) is recommended as first-line therapy for *H pylori* eradication as bismuth has long been known to have an antibacterial activity and most importantly, has no prior resistance reported to *H. pylori* [14]. Standard triple therapy (PPI, clarithromycin, and amoxicillin), which was previously considered as the ideal regimen, is no longer recommended as first-line treatment, primarily due to an increase in *H. pylori* resistance to clarithromycin as a consequence of which the triple therapy fails in 20 - 30% of patients [6,15]. In a meta-analysis by Venerito., *et al,* quadruple regimen was superior to triple therapy in the presence of simultaneous metronidazole and clarithromycin resistance [16]. In another study, the eradication rate was 64.7% with triple therapy whereas for quadruple regimen it was more than 93% [17]. The resistance rate to clarithromycin shows regional differences, for example, 30% in Austria and around 10% in Germany [1]. Nonetheless, it is well-established that when the local clarithromycin resistance rate increases beyond 15 - 20%, quadruple therapy should be preferred as the first line of treatment [18].

Penicillin allergy is another contraindication for the prescription of triple therapy, apart from high local clarithromycin resistance rate. Opting for a combination of PPI-clarithromycin-metronidazole in case of amoxicillin allergy does not yield encouraging results, precisely due to the burgeoning problem of resistance to both clarithromycin and metronidazole; hence a bismuth-based quadruple regimen should be administered in such patients, as substantiated by literature [19].

Contrary to guidelines, physicians are less likely to consider clarithromycin resistance while prescribing therapy. As per the European Registry for *H pylori* management, 46% of patients are prescribed with triple therapy [20]. This is further corroborated by various surveys conducted in different countries showing high percentages of physicians; 56.4% in Spain [8], 93.0% in Israel [21], 66.3% in Croatia [22],

81.4% in Asia-Pacific [23], 88% in Korea [24] and 83% in the USA [25], who continue to prescribe standard triple therapy for 7 - 14 days as the primary regimen. Furthermore, in patients allergic to penicillin (primarily amoxicillin), many physicians continue to prescribe triple therapy with clarithromycin and metronidazole, as observed in 38% of patients with penicillin allergy in Europe [20]. In Germany, 81% of physicians prescribe triple therapy to patients who are allergic to penicillin and only 19% correctly prescribe bismuth quadruple therapy [26]. Therefore, despite evidences, practitioners continue to deviate from practice guidelines. Some explanations for this discrepancy might include the unavailability of bismuth in many countries [27] or the large pill burden of bismuth quadruple therapy resulting in less compliance [28].

Repeating antibiotics in subsequent therapies

In case of failure of first-line treatment, second-line treatment and subsequent treatments should avoid already used antibiotics, as validated by a recently conducted study which demonstrated that repeating metronidazole in successive therapy had a cure rate of as low as 37% [29]. While the resistance to amoxicillin, tetracycline and rifabutin is rare due to which they can be repeated in subsequent therapies, secondary resistance to clarithromycin, levofloxacin or metronidazole occurs in almost all cases [30]. Thus, these antibiotics should not be repeated after eradication failure.

However, previously administered antibiotics are still repeated in more than 15 - 30% of the cases in Europe [20]. Likewise, as per a Korean observational study, a large proportion (40.7%) of primary care physicians reused the same regimen after eradication failure [24]. In another study, only 2.8% of primary care physicians in Croatia correctly recommended first and second line of treatment for H. pylori infection [22].

Prescribing therapy for 7 - 10 days instead of 14 days

Although the duration of therapy has been under constant debate, a Cochrane systematic review [31] clearly establishes that increasing the length of triple therapy from 7 to 14 days increases cure rate, while the same is elucidated for quadruple therapy in a clinical trial [32]. Accordingly, a 14-day therapy is the duration recommended by relevant consensus reports as well, including Maastricht V guidelines[6] as many suspect that antibiotic resistance could be overcome with longer duration therapy [16].

Regardless, a lot of practitioners make the error of prescribing short duration courses. In 69% of triple therapy cases and 58% of quadruple therapy cases in Europe, the prescribed duration of therapy is 7 or 10 days instead of 14 days [20]. Spanish primary care survey reports that 43.0% of treatments are prescribed for 10 days and 46.0% for 14 days [8]. Among practitioners from Israel who favor triple therapy, 77% recommended that treatment be continued for less than 14 days [21]. In a Korean survey, majority of physicians responded that they prescribe medication for 7 days (65.7%) [24] where as a Mexican survey reports that 12% of physicians prescribe therapy for 7 - 10 days [33]. Therefore, many practitioners opt for a 7 - 10day prescription instead of 14 days, possibly due to shorter duration courses resulting in greater patient compliance or due to risk of adverse events such as diarrhea, anorexia, bitter taste and abdominal fullness, being associated with the prescription [32].

Prescribing a low-dose of proton pump inhibitors (PPIs)

Evidence suggests that a high-dose of PPI increases the cure rate of triple therapy by 6% - 10% [34]. This is because PPIs have an antibacterial effect and also reduce the acid-related degradation of antibiotics due to acid inhibition [30]. In a clinical trial, high-dose rabeprazole had an eradication rate of 96.3% and was more effective than its low-dose equivalent which had an eradication rate of 84.9% [35]. Another study showed that treatment eradication was higher (100%) among patients who received high dose PPI compared to those treated with low dose PPI (81.5%) [36]. The effectiveness of double dose PPI compared to its single dose was further emphasized

by more studies [37,38], and accordingly the Maastricht V consensus report also stated that the use of high-dose PPI twice a day increases the efficacy of eradication therapy [6].

Nonetheless, some practitioners continue to prescribe low-dose PPIs. An underlying cause of this might be independent patient requests due to the risks that accompany the repeated exposure to high-dose acid suppression, such as liver and kidney problems, osteoporosis-related fractures, micronutrient deficiency and dementia, particularly in vulnerable populations such as the elderly [39-41]. In spite of the general recommendation of prescribing high dose PPIs, 48% of triple therapies prescribed in Europe include low-dose PPIs [20]. Fortunately, this percentage has decreased over time, from 67% in 2013 to 20% in 2019 but the problem still persists.

Not checking eradication success

Taking into account the globally declining eradication rates, emerging antimicrobial resistance, the risk of disease recurrence (e.g. peptic ulcer disease), the risk of disease persistence (e.g. superficial low-grade mucosa-associated lymphoid tissue lymphoma) and the possibility of developing future complications (e.g. gastric cancer), confirmatory testing is the practice recommended by all major clinical guidelines [2]. The updated ACG guidelines suggest that testing, using urea breath test, fecal antigen testing, or biopsy-based testing, should be performed at least four weeks after completion of antibiotic therapy and after PPI therapy has been withheld for one to two weeks [42].

Emphasis is placed on checking the success of *H pylori* eradication after treatment, yet 6% of patients in Europe do not undergo confirmatory testing [20]. Unfortunately, as per other previously conducted studies, retesting rates are even lower, ranging from 30% to 70% [2]. In a Chinese physicians' survey, about 20% of the respondents did not pay attention to confirmatory testing [10]. Likewise, surveys conducted in various other countries are also testament to poor confirmatory testing, with retesting rates as low as 43.6% in Israel [21], 14% in USA [43], 9.3% in Korea [24], and 50% in Peru [44]. These low rates might be attributed to the cost associated with retesting or lack of wide availability of diagnostic facilities, as demonstrated by a Spanish survey in which 16% of practitioners reported no direct access to any validated diagnostic method, only 44% to urea breath test, and 33% did not systematically refer to eradication confirmation test [8]. Another reason for these low rates might be the advance planning involved, as the confirmatory test requires a mandatory minimum waiting time of 4 weeks following antibiotic therapy and 1 - 2 weeks off acid-suppressive therapy, which might make follow up cumbersome for physicians and patients [2].

Failing to consider the importance of treatment compliance

Treatment compliance is one of the most important factors that determine cure rates, as validated by one study in which 40% of treatment failures were attributed to poor compliance to therapy [45]. In one study, eradication levels of 96% were observed for patients who took 60% or more of medications, compared to 69% for those taking less than that [46]. The issue of patient non-compliance to treatment due to reasons other than the occurrence of an adverse event, although seen in only 2% of patients in Europe [20], is much more prevalent in clinical practice. Previous literature suggests that 10% of patients who are prescribed *H pylori* eradication therapy fail to take even 60% of their medication [47].

Non-compliance can be attributed to barriers that may be patient-related; such as forgetfulness, physical intolerance of medication, too much pill burden, low health literacy, inability to comprehend the complexity of the regimen and receiving conflicting information from physicians, media and the internet. There might also be some system-related barriers including high prices and low accessibility to medicine or tests, as well as provider-related barriers such as the physician feeling time pressured, burdened or lacking motivation to communicate critical details with the patient and assess medication adherence [48,49].

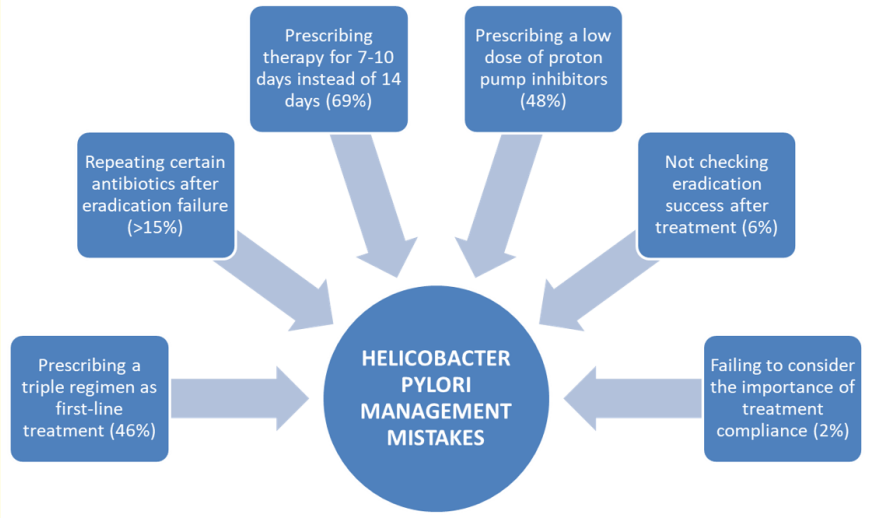

Figure 1: *H pylori management mistakes with their frequency in Europe.*

Future recommendations

Role of healthcare professionals

In order to overcome the mistakes highlighted in this review and to usher the declining eradication rates to an ascending path, consistent efforts from healthcare professionals are of utmost importance. As per the recent AGA Clinical Practice Update, medical practitioners should carefully weigh the potential benefits of *H pylori* treatment against the prospect of adverse events associated with longer exposure to antibiotics and higher dose of PPIs; and on the other hand practitioners should also consider conducting penicillin allergy testing in patients who are labeled as being allergic but have no prior anaphylaxis history, so as to enable the use of amoxicillin in such patients [50]. Patients should be asked about previous antibiotic exposure to help guide the treatment regimen and avoid failures because of resistance [7]. A US survey reported that only 38% of participating providers asked patients about prior antibiotic exposure [25]; thus, there is a lot more that has to be done in this regards. In addition to that, practitioners should consider *H pylori* treatment holistically as one continuous 'test, treat, retest' episode and should make use of advance planning and improved communication channels to increase confirmatory retesting rates. Electronic health record alerts and reminders to both patients and physicians can augment the retesting process and another effective strategy might be a rank priority order of retesting; being mindful of those scenarios where retesting is neither sensible (e.g. advanced gastric cancer) nor necessary (e.g. advanced age, multiple comorbidities) [2].

Ensuring patient adherence to medical treatment is a major challenge for clinicians, therefore employing pragmatic strategies such as the use of pillboxes, medication calendars, text-based reminders and follow-up telephone calls might be useful to boost compliance. This was verified in a clinical trial in which employing these strategies led to a significant increase in the numbers of patients taking more than 90% of medications [47]. Another clinical trial shows that counseling patients regarding the importance of completing the prescribed regimen, giving them clear dosing instructions and notifying them about the possible side-effects, might also break the barriers to adherence [51]. Other beneficial interventions include polypills, combined blister packs, adjuvant therapies and modified release compounds [48].

Role of healthcare authorities

The concrete evidence provided by clinical guidelines does not yield substantial clinical output unless their implementation is facilitated. Although progressively greater compliance with current guidelines is seen [20], the penetration of updated recommendations is still inadequate. Healthcare authorities are the main stakeholders of public health and should be in charge of ensuring that the gap between scientific recommendations and clinical practice is effectively bridged. The first step should be to actively disseminate the guidelines by translating them, officially endorsing them and by making them the basis of postgraduate educational programs [13]. Furthermore, active educational interventions such as workshops, outreaches and seminars for practitioners can also prove to be an effective tool for changing practice. These may consist of presentations describing the guidelines, in-depth discussions about new practices, along with reinforcement visits after a few months [52]. Most guidelines for the management of H. pylori infection have been criticized for their failure to address the issues that are pertinent to primary care [53]. Therefore, recommendations on H. pylori infection should be adaptable to local factors and health care traditions relevant to primary care, and it is also worth consideration to involve clinicians in formulating guidelines because internally developed guidelines are usually more successful than externally developed ones [54]. Additionally, evaluation programs to gauge the extent of guideline adherence among practitioners might also be useful.

Along with ascertaining the implementation of clinical guidelines, the healthcare authorities should develop facilities for urea breath test in countries with access restrictions and should also facilitate the inclusion of *H pylori* treatment in the primary care budget [13], thereby reducing the costs associated with diagnostic tests and medications, particularly in low-income countries where *H pylori* incidence is very high. Furthermore, authorities can develop surveillance registries and national centers of excellence to monitor and maintain up-to-date data on local antibiotic resistance patterns which can assist practitioners in taking informed decisions regarding regimen prescriptions and can also act as focal points for research collaborations [55]. Many of the drawbacks of pharmaceutical therapy could be overcome if an effective vaccine is developed [48]. Hence, investment to invigorate *H pylori* research and development should be of high-priority. Adding on to that, more research needs to be done on the cost-effectiveness of confirmatory retesting as well as on the most cost-effective way to diagnose *H pylori* in primary care setting, as there is a paucity of scientific evidence regarding this [13]. With prompt steps taken in the right direction, the healthcare community can successfully overcome the mistakes outlined in this review.

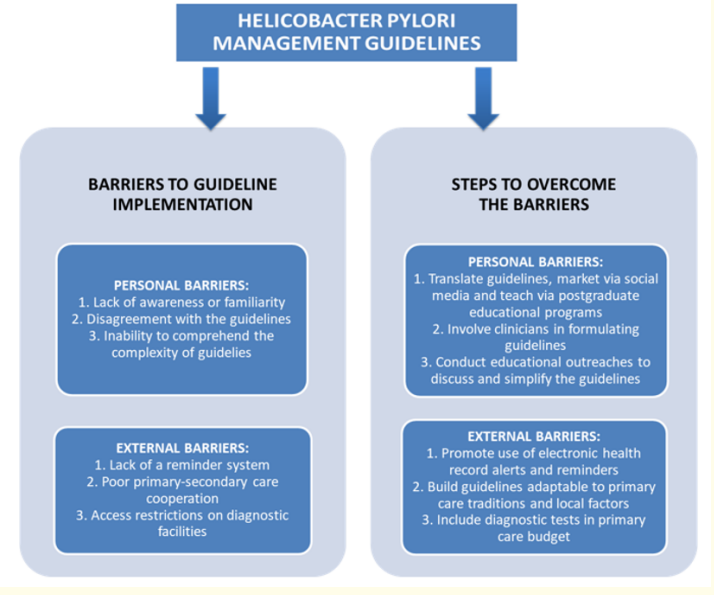

Figure 2: *The Major Personal and External Barriers to Guideline Implementation and Steps to Overcome Them.*

Conclusion

Studies suggest that *H pylori* management continues to be disrupted by common mistakes that are made by gastroenterologists, indicating the presence of a knowledge gap between clinical guidelines and actual clinical practice. The type, duration and compliance with therapy, the prescribed dose of PPIs, the consideration of penicillin allergy and antibiotic resistance, as well as the significance of confirmatory retesting, all of these are imperative elements of a successful eradication regime and should be the subject of careful decision making by practitioners. However, due to inefficient implementation of clinical recommendations, the eradication of *H pylori* is currently bereft of any major successes and half of the world continues to battle with it. This article also highlights the primary challenges that lie behind effective incorporation of evidence-based guidelines into medical practice, along with future recommendations that can be integrated into the healthcare system for closing the clinical gap. The responsibility lies on medical authorities to disseminate these guidelines efficiently, on practitioners to adhere to these guidelines meticulously, as well as on the researchers to continuously modify the guidelines based on changing health patterns. Hence, all constituents of the healthcare system should stand at the forefront to win the fight against *Helicobacter pylori* in this age of increasing antibiotic resistance.

Acknowledgements

None to declare.

Conflict of Interest

None to declare.

Bibliography

1. Selgrad M and Malfertheiner P. "Management of Helicobacter pylori infection: what should the surgeon know". *Visceral Medicine* 33.3 (2017): 216-219.
2. Sharara AI. "Confirmatory Testing for Eradication of Helicobacter pylori: Challenges and Opportunities". *Clinical Gastroenterology and Hepatology* 19.2 (2020): 232-234.
3. Flores-Treviño S., *et al*. "Helicobacter pylori drug resistance: therapy changes and challenges". *Expert Review of Gastroenterology and Hepatology* 12.8 (2018): 819-827.
4. Zou Y., *et al*. "The effect of antibiotic resistance on Helicobacter pylori eradication efficacy: A systematic review and meta-analysis". *Helicobacter* 25.4 (2020): e12714.
5. Gisbert JP., *et al*. "IV Spanish Consensus Conference on Helicobacter pylori infection treatment". *Gastroenterología y Hepatología* 39.10 (2016): 697-721.
6. Malfertheiner P., *et al*. "Management of Helicobacter pylori infection-the Maastricht V/Florence consensus report". *Gut* 66.1 (2017): 6-30.
7. Chey WD., *et al*. "ACG clinical guideline: treatment of Helicobacter pylori infection". *Official Journal of the American College of Gastroenterology| ACG* 112.2 (2017): 212-239.
8. McNicholl AG., *et al*. "Spanish Primary Care Societies SEMFyC, SEMERGEN and SEMG, the Spanish Association of Gastroenterology and OPTICARE Long-Term Educational Project, 2019. Spanish primary care survey on the management of Helicobacter pylori infection and dyspepsia: Information, attitudes, and decisions". *Helicobacter* 24.4 (2019): e12593.

9. Na'amnih W., *et al*. "Physicians' adherence to management guidelines for H. pylori infection and gastroesophageal reflux disease: a cross-sectional study". *Israel Journal of Health Policy Research* 9.1 (2020): 1-7.

10. Song C., *et al*. "Management of Helicobacter pylori infection by clinicians: a nationwide survey in a developing country". *Helicobacter* 24.6 (2019): e12656.

11. Cabana MD., *et al*. "Why don't physicians follow clinical practice guidelines?: A framework for improvement". *The Journal of the American Medical Association* 282.15 (1999): 1458-1465.

12. Fischer F., *et al*. "Barriers and strategies in guideline implementation-a scoping review". *InHealthcare Multidisciplinary Digital Publishing Institute* 4.3 (2016): 36.

13. De Wit NJ., *et al*. "Guidelines on the management of H. pylori in primary care: development of an implementation strategy". *Family Practice* 17.2 (2000): S27-s32.

14. Poonyam P., *et al*. "High effective of 14-day high-dose PPI-Bismuth-containing quadruple therapy with probiotics supplement for Helicobacter pylori eradication: a double blinded-randomized placebo-controlled study". *Asian Pacific Journal of Cancer Prevention: APJCP* 20.9 (2019): 2859.

15. Gisbert JP and Calvet X. "Review article: the effectiveness of standard triple therapy for Helicobacter pylori has not changed over the last decade, but it is not good enough". *Alimentary Pharmacology and Therapeutics* 34.11-12 (2011): 1255-1268.

16. Venerito M., *et al*. "Meta-analysis of bismuth quadruple therapy versus clarithromycin triple therapy for empiric primary treatment of Helicobacter pylori infection". *Digestion* 88.1 (2013): 33-45.

17. Kekilli M., *et al*. "Inefficacy of triple therapy and comparison of two different bismuth-containing quadruple regimens as a firstline treatment option for helicobacter pylori". *Saudi Journal of Gastroenterology: Official Journal of the Saudi Gastroenterology Association* 22.5 (2016): 366.

18. Malfertheiner P., *et al*. "Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report". *Gut* 56.6 (2007): 772-781.

19. Gisbert JP., *et al*. "Helicobacter pylori first-line and rescue treatments in the presence of penicillin allergy". *Digestive Diseases and Sciences* 60.2 (2015): 458-464.

20. Nyssen OP., *et al*. "Room for Improvement in the Treatment of Helicobacter pylori Infection: Lessons from the European Registry on H. pylori Management (Hp-EuReg)". *Journal of Clinical Gastroenterology* (2021).

21. Boltin D., *et al*. "Attitudes and practice related to Helicobacter pylori infection among primary care physicians". *European Journal of Gastroenterology and Hepatology* 28.9 (2016): 1035-1040.

22. Jukic I., *et al*. "Adherence to Maastricht V/Florence consensus report for the management of Helicobacter pylori infection among primary care physicians and medical students in Croatia: A cross-sectional study". *Helicobacter* 23 (2020): e12775.

23. Chuah YY., *et al*. "Real-world practice and Expectation of Asia-Pacific physicians and patients in Helicobacter Pylori eradication (REAP-HP Survey)". *Helicobacter* 22.3 (2017): e12380.

24. Kim BG., *et al*. "Discrepancies between primary physician practice and treatment guidelines for Helicobacter pylori infection in Korea". *World Journal of Gastroenterology: WJG* 12.1 (2006): 66.

25. Murakami TT., *et al*. "Management of Helicobacter Pylori in the United States: results from a national survey of gastroenterology physicians". *Preventive Medicine* 100 (2017): 216-222.

26. Miehlke S., *et al*. "Diagnostic and therapeutic management of Helicobacter pylori infection: a survey among resident gastroenterologists in Germany". *Zeitschrift für Gastroenterologie* 54.10 (2016): 1130-1137.

27. Jheng GH., *et al*. "Comparison of second-line quadruple therapies with or without bismuth for Helicobacter pylori infection". *BioMed Research International* (2015).

28. Chen YI and Fallone CA. "A 14-day course of triple therapy is superior to a 10-day course for the eradication of Helicobacter pylori: a Canadian study conducted in a 'real world'setting". *Canadian Journal of Gastroenterology and Hepatology* 29.8 (2015): e7-10.

29. Puig I., *et al*. "Fourteen-day high-dose esomeprazole, amoxicillin and metronidazole as third-line treatment for Helicobacter pylori infection". *International Journal of Clinical Practice* 71.9 (2017): e13004.

30. Calvet X. "Dealing with uncertainty in the treatment of Helicobacter pylori". *Therapeutic Advances in Chronic Disease* 9.4 (2018): 93-102.

31. Yuan Y., *et al*. "Optimum duration of regimens for Helicobacter pylori eradication". *Cochrane Database of Systematic Reviews* 12 (2013).

32. Kim TH., *et al*. "Comparison of 7-and 14-day eradication therapy for Helicobacter pylori with first-and second-line regimen: randomized clinical trial". *Journal of Korean Medical Science* 35.5 (2020).

33. Cano-Contreras AD., *et al*. "The approach, attitudes and knowledge about Helicobacter pylori in general practitioners is deficient. There is much to improve". *Revista de Gastroenterología de México* 83.1 (2018): 16-24.

34. Villoria A., *et al*. "Meta-analysis: high-dose proton pump inhibitors vs. standard dose in triple therapy for Helicobacter pylori eradication". *Alimentary Pharmacology and Therapeutics* 28.7 (2008): 868-877.

35. Kositchaiwat C., *et al*. "Low and high doses of rabeprazole vs. omeprazole for cure of Helicobacter pylori infection". *Alimentary Pharmacology and Therapeutics* 18.10 (2003): 1017-1021.

36. Boltin D., *et al*. "European Registry on Helicobacter pylori management (Hp-EuReg): First-line Therapy in Israel". *The Israel Medical Association Journal: IMAJ* 23.1 (2021): 38-42.

37. Lamouliatte H., *et al*. "Double vs single dose of pantoprazole in combination with clarithromycin and amoxycillin for 7 days, in eradication of Helicobacter pylori in patients with non-ulcer dyspepsia". *Alimentary Pharmacology and Therapeutics* 13 (1999): 1523-1530.

38. Vallve M., *et al*. "Single vs. double dose of a proton pump inhibitor in triple therapy for Helicobacter pylori eradication: a meta-analysis". *Alimentary Pharmacology and Therapeutics* 16.6 (2002): 1149-1156.

39. Fossmark R., *et al*. "Adverse effects of proton pump inhibitors-Evidence and plausibility". *International Journal of Molecular Sciences* 20.20 (2019): 5203.

40. Nehra AK., *et al*. "Proton pump inhibitors: review of emerging concerns". *In Mayo Clinic Proceedings* 93.2 (2018): 240-246.

41. Yang Y., *et al*. "Proton-pump inhibitors use, and risk of acute kidney injury: a meta-analysis of observational studies". *Drug Design, Development and Therapy* 11 (2017): 1291.

42. Randel A. "H. pylori infection: ACG updates treatment recommendations". *American family physician* 97.2 (2018): 135-137.

43. Howden CW., *et al*. "Practice patterns for managing Helicobacter pylori infection and upper gastrointestinal symptoms". *American Journal of Managed Care 13*.1 (2007): 37.

44. AY EP and AE JC. "How do gastroenterologists in Peru deal with Helicobacter pylori infection? Study based on a survey conducted in 2014". *Revista de gastroenterologia del Peru: organo oficial de la Sociedad de Gastroenterologia del Peru* 35.4 (2015): 295-305.

45. Wermeille J., *et al*. "Failure of Helicobacter pylori eradication: is poor compliance the main cause?" *Gastroentérologie Clinique et Biologique* 26.3 (2002): 216-219.

46. Graham DY., *et al*. "Factors influencing the eradication of Helicobacter pylori with triple therapy". *Gastroenterology* 102.2 (1992): 493-496.

47. Lee M., *et al*. "A randomized controlled trial of an enhanced patient compliance program for Helicobacter pylori therapy". *Archives of Internal Medicine* 159.19 (1999): 2312-2316.

48. O'Connor JP., *et al*. "Improving compliance with Helicobacter pylori eradication therapy: when and how?" *Therapeutic Advances in Gastroenterology* 2.5 (2009): 273-279.

49. Brown MT., *et al*. "Medication adherence: truth and consequences". *The American Journal of the Medical Sciences* 351.4 (2016): 387-399.

50. Shah SC., *et al*. "AGA Clinical Practice Update on The Management of Refractory Helicobacter pylori Infection: Expert Review". *Gastroenterology* (2021).

51. Al-Eidan FA., *et al*. "Management of Helicobacter pylori eradication–the influence of structured counselling and follow-up". *British Journal of Clinical Pharmacology* 53.2 (2002): 163-171.

52. Banait G., *et al*. "Modifying dyspepsia management in primary care: a cluster randomised controlled trial of educational outreach compared with passive guideline dissemination". *British Journal of General Practice* 53.487 (2003): 94-100.

53. Noya H., *et al*. "Do urea breath test (UBT) referrals for Helicobacter pylori testing match the clinical guidelines in primary care practice? A prospective observational study". *Journal of Evaluation in Clinical Practice* 14.5 (2008): 799-802.

54. O'Connor HJ. "Helicobacter pylori and dyspepsia: physicians' attitudes, clinical practice, and prescribing habits". *Alimentary Pharmacology and Therapeutics* 16.3 (2002): 487-496.

55. O'Connor A and O'Moráin C. "Mistakes in the management of Helicobacter pylori infection and how to avoid them". Mistakes in…. (2017): 17.

Volume 9 Issue 6 June 2022