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Helicobacter pylori **retreatment: When clinical guidelines meet patient reality**

H. pylori retreatment and follow-up gap

Abstract

There is growing concern over *Helicobacter pylori* how to eradicate which is important to prevent peptic ulcer disease and gastric cancer. Nevertheless, routine practice remains inconsistent in managing patients after documented treatment failure. Recent data from a European registry showed that 14% of patients with confirmed eradication failure did not receive further treatment, drawing attention to a clinically important gap in post-failure care. Antimicrobial resistance cannot explain this gap alone. Previous treatment intolerance, poor adherence, multiple prior failures, inadequate risk communication, and limited access to susceptibility testing may all influence the decision to proceed with rescue therapy. In this Opinion Review, we summarize recent advances in rescue treatment such as optimized bismuth quadruple therapy, rifabutin-containing regimens, vonoprazan-based therapy, and susceptibility-guided strategies. We also discuss some unresolved post-failure issues including which patients should undergo retreatment, when tailored therapy should take precedence over empirical therapy, how age and comorbidity should be incorporated into decision-making, and how quality of care should be assessed after treatment failure. We propose that rescue therapy should be considered within a structured post-failure care pathway rather than as a prescribing decision alone. In future studies, it would be important to think about assessing patient-reported reasons for refusal of retreatment, prospective evaluation of care bundles after failure, and development of new longitudinal quality indicators of the whole process, from diagnosis to treatment failure and rescue therapy and confirmation of eradication.

Key Words: *Helicobacter pylori;* Eradication failure; Rescue therapy; Retreatment; Adherence; Shared decision-making

Core Tip: Recent registry data show that a substantial proportion of patients with confirmed *Helicobacter pylori* eradication failure do not receive rescue therapy. The post-failure treatment gap is a reflection of not only antimicrobial resistance but also prior treatment-related adverse events, poor adherence, repeated treatment failure, and

inadequate risk communication. Consequently, while improving rescue regimens is indispensable and not adequate, structured reassessment after failure, individualized counseling, and clearly defined follow-up pathways are also essential.

INTRODUCTION

Infection by *Helicobacter pylori* (*H. pylori*) is one of the world's most common chronic bacterial infections. It continues to play a central role in the pathogenesis of peptic ulcer disease, chronic gastritis, premalignant gastric lesions, and gastric cancer[1,2]. A substantial body of mechanistic and epidemiologic evidence has established persistent *H. pylori* infection as a major driver of gastric carcinogenesis[3–6]. This relationship is now being refined by single-cell evidence showing that *H. pylori*-associated gastric tumorigenesis involves not only epithelial alterations, but also broader remodeling of stromal, myeloid, and intercellular signaling landscapes[7]. In response to this evidence, recent international guidelines have increasingly endorsed eradication of documented infection whenever treatment is appropriate and feasible[8,9]. Meanwhile, large collaborative efforts such as the European Registry on *H. pylori* management (Hp-EuReg) have provided valuable insight into how *H. pylori* infection is managed in routine clinical practice beyond the controlled setting of clinical trials[10,11]. Lately, besides an expansion of therapy indications, the other most important change in everyday practice is greater difficulty being faced in obtaining long-lasting eradication with empirical first-line therapy[12–14]. Antimicrobial resistance and poor adherence are causing traditional regimens to become less reliable in today's practice[15,16].

THE POST-FAILURE GAP AS A SPECIFIC CLINICAL ISSUE

The Majority of *H. pylori* management focuses on selection of first line regimen, confirmation of eradication, slowly becoming more focused on antimicrobial resistance. However, the recent Hp-EuReg analysis by *Cantú-Germano et al* redirects attention to a later and far less examined stage of care: The management of patients after eradication

failure has already been confirmed. Of 6904 documented treatment failure European patient, 14% failed to receive re-treatment, about half of this was attributed to patients and slightly more than two-fifths to physicians[17]. The results indicate a gap after failure that is clinically relevant, not a simple matter of prescription choice. The relationship between failure to confirm eradication and failure to proceed with rescue therapy is not a matter of definition. The former embodies post-treatment assessment that is incomplete, while the latter represents a decision-making malfunction for an established persistent infection. The clinical significance of the differentiation is that dealing with the disease is now considered not just symptomatic control but also a way of long term gastric cancer prevention[18,19]. Such a rationale of prevention has been reaffirmed by data from randomized trials and population-based studies[20–23].

RECENT PROGRESS IN RESCUE THERAPY

Rescue therapy for *H. pylori* infection has evolved considerably over the past decade. The optimized bismuth quadruple therapy is an essential option, especially when susceptibility testing is unavailable. Also, when prior use of an antibiotic does not negate a reasonable chance of benefit[8,9,13,24]. Rifabutin-containing regimens have also regained attention in refractory settings, largely because rifabutin resistance remains uncommon and their efficacy in later-line treatment appears acceptable in appropriately selected patients[25–28]. These developments are also complemented by innovations in acid suppression. Randomized trials and pooled analyses show that using either a vonoprazan-based dual regimen or a vonoprazan-based triple regimen can lead to high eradication rates and a relatively simple treatment structure[29–31]. Early real-world data likewise suggest that vonoprazan-based rescue strategies may retain clinical value even in patients with previous eradication failure[32,33]. An increased emphasis on susceptibility-guided and genotype-guided retreatment is another development. Comparative studies and meta-analyses are increasingly supporting tailored therapy after treatment failure, especially in patients with high previous antibiotic exposure[34–36]. Nevertheless, translating this approach into practice is

difficult. The availability of culture-based testing, molecular resistance assays and timely reporting varies significantly across healthcare systems[8,37,38]. As a result, empirical retreatment continues to predominate in many real-world settings[39–42].

REAL-WORLD DETERMINANTS OF NON-RETREATMENT

The registry analysis provides an important entry point for understanding why rescue therapy is not consistently undertaken after documented eradication failure. Earlier nonadherence, treatment intolerance in prior courses, older age, and multiple prior failures were all correlated with lower chances for retreatment[17]. According to these findings, the post-failure gap is not due to the antimicrobial resistance. This also determines how the patients experience the initial and subsequent treatment process. Data apart from Hp-EuReg backs this. According to the studies conducted on the real world, a substantial amount of variation in regimen selection, incomplete follow-up and the gap between the ondemand guideline and everyday practice exists[40–43]. Patient understanding is likewise uneven. Several surveys done in various regions reported that there is a lack of knowledge about transmission, cancer risk, reinfection, and purpose of eradication[44–47]. Similar disparities have been seen among physicians, undermining consistent application of recommended care[43,48,49]. Although social-media and short-video platforms may broaden access to *H. pylori*-related information, the variable quality of content and the potential for misinformation limit their reliability as a foundation for clinical decision-making[50–52]. Taken together, these observations suggest that non-retreatment is best viewed not as an isolated event after treatment failure, but as the downstream consequence of broader shortcomings in implementation, communication, and follow-up.

MAJOR CONTROVERSIES IN POST-FAILURE MANAGEMENT

One of the major controversies related to post-failure management is whether every recorded eradication failure must always be followed by another treatment. The present recommendations continue to favour eradication, as far as feasible, in principle[8,9,25].

According to meta-analyses and data from long-term randomized clinical trials, successful eradication lowers gastric cancer risk[18,21]. Community-based screening and mass-eradication programs support a treatment based on prevention, not just the development of symptoms[20,23]. The benefit-burden ratio is not similar across patients in clinical practice. A person with a peptic ulcer disease, premalignant gastric lesions or at an increased risk of gastric cancer is a different clinical character than a frail elderly patient who has already been subjected to multiple treatment attempts without success and is unwilling to continue. A related area of debate concerns the place of empirical rescue therapy in relation to susceptibility-guided treatment. Current evidence strongly supports the rationale for personalized treatment after treatment failure[8,9,25,53]. Even so, a universal insistence on resistance testing may be inappropriate in settings where such testing is inaccessible, prohibitively expensive, or too slow to inform the next therapeutic decision. In routine clinical practice, the more clinically relevant question is therefore not whether susceptibility-guided therapy is preferable in principle, but under which circumstances its added value justifies the delay it may introduce. The influence of age and comorbidity on retreatment decisions remains similarly unsettled. In Hp-EuReg, older age was associated with physician-driven non-retreatment[17]. While that would make sense, chronological age alone is not a sufficient measure of treatment. Data from elderly cohorts and the geriatric prescribing literature indicate that eradication therapy remains feasible and generally well tolerated in selected older adults, provided that frailty, polypharmacy, drug-drug interactions, life expectancy, and individual goals of care are assessed explicitly[54–56].

A recurring question is whether repeated treatment failure should be viewed primarily as a microbiological issue or as one of the care delivery process. In actual operations, they often overlap. The antimicrobial resistance is still a main reason for failure, and current evidence still confirms the importance of resistance patterns and adequate acid suppression[9,25]. This clinical concern is further reflected in disease-specific settings such as gastrointestinal lymphomas, where a recent meta-analysis linked *H. pylori* antibiotic resistance to poorer treatment outcomes[57]. Research into the

mechanisms also suggested that the efflux pump activity most likely interact with the resistance-associated gene mutations, and therefore, refractory infection is more likely a more dynamic process of resistance acquisition and maintenance rather than standalone point mutations only[58]. Newer salvage options, including rifabutin- and vonoprazan-based regimens, address part of this biological challenge[26,28,29,32,33,59]. At the same time, repeated failure is also shaped by events surrounding the prescription itself. Real-world studies and adherence-focused interventions suggest that regimen complexity, poor understanding of treatment, adverse events, and fragmented follow-up can all reduce the likelihood that rescue therapy will be initiated, completed, or formally confirmed[16,17,44]. Digital reminders and structured educational support may help reduce some of these barriers[60–62]. Refractory infection should therefore not be interpreted solely through the lens of antibiotic resistance. The measure of quality after treatment failure is also disputed. Traditionally, the quality of *H. pylori* care has been judged by eradication rates and, more recently, by completion of post-treatment test-of-cure; both remain essential measures[9]. However, real-world data suggest that these endpoints alone are insufficient, because some patients with likely persistent infection may not proceed to further treatment after first-line therapy. In a large US cohort, only 11.1% of patients who received first-line therapy went on to second-line therapy, and the authors suggested that not all patients with eradication failure received subsequent treatment[63]. Similarly, European registry data showed that up to 14% of patients with confirmed eradication failure were not retreated[17]. A more informative quality framework should therefore evaluate the entire post-failure pathway, including the initiation of rescue, the completion of treatment, and confirmatory testing after rescue, rather than stopping at completion of first-line therapy[64].

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ADHERENCE, TOLERABILITY, AND RISK COMMUNICATION

An enduring theme of recent research has been that adherence is not fixed and can be improved. Evidence supports that clearer instructions, structured patient education, and communication support enhance completion rates of treatment and may enhance

eradication[65–68]. Digital reminders and education delivered through new media are also of interest, particularly when integrated into routine follow-up rather than offered as one-off interventions[60,66]. Adherence support, therefore, should not be viewed as an optional adjunct after treatment failure, but as an integral component of regimen planning from the outset. The patient perspective remains insufficiently captured in *H. pylori* research. In the study by *Cantú-Germano et al*, approximately half of the decisions not to proceed with retreatment were classified as patient-driven, yet the underlying reasons were not recorded[17]. This is a meaningful gap. Survey data from the United States, China, Japan, and Jordan suggest substantial variation in public understanding of *H. pylori* infection, gastric cancer risk, and the rationale for eradication[44–47]. The quality of online health information, health literacy, risk perception, personal beliefs and worries, and practical barriers to access and complete follow-up influence further communication and decision-making[46,50,69,70]. Without accounting for these factors, the label "patient refusal" is too imprecise to inform clinical decision-making **(Table 1)**.

PERSPECTIVE ON RESCUE THERAPY AS A STRUCTURED CARE PATHWAY

We propose that the management of rescue therapy should take the form of a pathway (*i.e.*, a planned sequence of steps) that should be considered after confirmed treatment failure, rather than being limited to the choice of another regimen only. Once failure of eradication is established, an initial treatment course should be systematically reviewed, including the regimen used, treatment duration, pill burden, dosing complexity, interruptions, tolerability and timing of confirmatory testing. That said, the most likely driver of failure should be assessed as primarily biological, behavioural or systems-related with an understanding that they often overlap. Only then should the selection of the next rescue regimen be made. The management plan should include measures that support therapy completion, including anticipatory counselling, simple instructions, adverse-event planning and a pre-arranged confirmatory test **(Table 2)**. Although not overly idealistic, this framework highlights the main lesson from registry-based evidence: Eradication failure is not purely a microbiological event. Patient experience

and the delivery of care are also part of the shaping process. More effective rescue regimens are certainly important but they alone are unlikely to close a retreatment gap that is partly the result of prior intolerance, incomplete understanding and diminished confidence to further therapy. Post-failure management should therefore be seen as a care process that patients can realistically accomplish, rather than as a single prescribing decision.

POSSIBLE FUTURE DIRECTION

The next phase of research has several priorities based on current evidence. Registry-based research needs to go beyond whether rescue therapy was prescribed to also beginning to capture why it was declined, including patient-reported reasons and standardised measures of treatment burden[17,71,72]. Despite existing surveys finding important gaps in knowledge, they do not explain how this knowledge ultimately influences decisions taken after confirmed eradication failure[47,50]. Meanwhile, implementation research is needed to test structured post-failure care bundles in prospective settings, linking regimen selection with adherence support, adverse-event counselling and prearranged follow up[61,62,65–68]. Comparative studies should also define more clearly which patients and practice environments derive meaningful benefit from tailored therapy beyond eradication rates alone, especially in healthcare systems where access to susceptibility testing remains constrained[37,73,74]. More broadly, prevention-oriented programmes should not be judged solely by first-line eradication success. Their evaluation should extend across the full care pathway, incorporating indicators for confirmatory testing after treatment, follow-up after documented persistence, uptake of second-line or rescue therapy, and final eradication outcomes[75].

LIMITATIONS OF CURRENT EVIDENCE

Current evidence base subject several important limitations. Registry studies can contribute to defining actual practice but they are limited to causally distinguishing the

relationship of events from patterns that arise from clinical selection. Patients who do not receive retreatment might differ systematically in ways not captured in existing data, including reasons related to socioeconomic disadvantage, medication costs and transportation difficulties, competing medical conditions, and quality of previous counselling. The data that's available also provides little insight into clinician decision-making and rarely includes validated patient-reported outcomes. These limitations do not undermine the significance of the signal identified by Hp-EuReg. However, they do argue against turning the observed correlations into causal conclusions. Another limitation is a relative lack of implementation-focused research. Many comparative studies still focus on which regimen produces the highest eradication rate. But far fewer compare how patients are counselled, followed, re-engaged in care after treatment failure. Consequently, it appears that the literature is much further advanced in pharmacologic optimization than with respect to care delivery science. In the context of post-failure management, this imbalance is no longer trivial: A field that continues to refine rescue regimens while paying insufficient attention to the clinical pathway surrounding them may improve efficacy in theory more readily than effectiveness in routine practice.

CONCLUSION

The management of *H. pylori* infection has progressed considerably, yet care after eradication failure remains far less standardized than first-line treatment. The retreatment gap highlighted by *Cantú-Germano* et al is clinically important because it exposes a critical disconnect between guideline recommendations and real-world practice[17]. While antimicrobial resistance remains a key focus, it does not account for post-failure management. The delivery of rescue therapy in patients is influenced by treatment burden, prior negative experiences, the quality of doctor-patient communication, and the ability of the health system to re-engage patients in follow-up. The necessity of improved rescue regimens is thus clear, but it will not be sufficient

unless retreatment is incorporated into a structured post-failure pathway that patients can realistically complete.