European Registry on *Helicobacter pylori* management shows that gastroenterology has largely failed in its efforts to guide practitioners

David Y Graham [1], Hashem B El-Serag[2]

COMMENTARY

The authors report the results of a 5-year (2013–2018) audit of the effectiveness of *Helicobacter pylori* therapy in clinical practice in several regions of Europe.[1] The study provides a contemporary prospective regarding empirical *H. pylori* treatment. Importantly, there was little centralised influence on choice of therapy apart from sending periodic updates, presenting updates at the meeting of the European *H. pylori* study group and including local feedback in the form of post-treatment testing for cure. The strengths of the report include the large sample size, representative population, and high level of complete data on treatment type, duration and follow-up. Overall, 30 394 patients from 27 European countries provided data on 21 533 first-line empirical *H. pylori* treatments using more than 100 different schemes. Antibiotic susceptibility data were obtained from 11% (2.7% to 16.7% in different regions). In that small sample, the prevalence of *H. pylori* resistance to clarithromycin and metronidazole was high (ie, 23% and 32%, respectively). Clarithromycin triple therapy was most commonly used but use declined over time from >50% in 2013–2015 to 32% in 2017–2018. The use of bismuth quadruple therapy was uncommon and varied markedly between regions but also tended to increase over time. They concluded that the management of *H. pylori* infection by European gastroenterologists was heterogeneous, suboptimal and discrepant with current recommendations.

There seems to be an ongoing slow paradigm shift from therapies identified by trial and error to therapies based on the principles of antimicrobial stewardship. This shift is also between two schools, which we call the What and the Why Schools of thought regarding planning and analysis of clinical trials. The What School's primary approach uses comparisons between regimens often relying on meta-analysis to ask whether treatment A or B is superior irrespective of why or whether either reliably achieves a high cure rate. This has often led to recommendations to use A rather than B, when both produce poor results.[2] The Why School focuses on attainment of a prespecified cure rate (eg, >95%); comparisons are rare, and are generally limited to head-to-head comparisons of proven highly reliable optimised regimens and use non-inferiority methods with both regimens expected to achieve high cure rates.[3] This shift needs to be recognised, encouraged and expedited.

The authors also presented some comparative effectiveness data that involved comparisons of treatments between different populations but lacked both susceptibility data and randomisation. This approach is less powerful than clinical trials for making valid inferences. However, they report that concomitant therapy and bismuth quadruple therapy were generally more effective, but neither regimen reliably achieved cure rates expected of typical infectious disease therapies. The absence of resistance data is important for interpretation of comparisons because in the presence of resistance, the effectiveness with bismuth quadruple therapy depends on metronidazole dosage and especially on duration of therapy.[4] The principles of antimicrobial stewardship also argue against use of concomitant therapy because all recipients receive at least one unnecessary antibiotic.[5]

The two most common causes of failure of previously highly effective therapies are poor adherence and antimicrobial resistance. Worldwide, *H. pylori* resistance to clarithromycin, metronidazole and fluoroquinolones has increased such that it has been recommended that their use in triple therapies be limited to susceptibility-guided therapy or areas of proven local effectiveness.[6] Although susceptibility testing is not widely available, it is important to note that susceptibility patterns can be assessed directly, indirectly or can be implied. Direct assessment uses culture whereas indirect assessment involves molecular methods using DNA obtained from gastric biopsy or stool. Implied susceptibility patterns are based on clinical experience with proven locally highly effective regimens. In this report, the high failure rates and the pattern of failures is consistent with a high prevalence of resistance reported. The study used empirical therapy defined as *H. pylori* treatment prescribed without knowledge of its local effectiveness or susceptibility patterns. The principles of antimicrobial stewardship require empiric therapies to be highly effective, given only to patients likely to benefit and use strategies designed to ensure that the regime remains sustainable. The use of empirical therapies also implies ongoing surveillance (eg, test of cure, susceptibility testing, etc) so that if effectiveness declines, the empirical regimen can be rapidly replaced.

THE FUTURE

The Hp-EuReg produced a landmark study of the current practices that shows that gastroenterology has largely failed in its efforts to guide practitioners to reliably cure this disease. Although neither the patients nor the physicians participating in this audit benefited significantly, the study provides a model to use when more reliable therapies become available. The Hp-EuReg might now refocus on introducing the principles of antimicrobial stewardship to identify therapies that are reliably highly effective. Such studies in China have been able to identify a number of reliably highly effective regimens that can be successfully used empirically.[7] The recent advances in vonoprazan–amoxicillin dual therapy also offer promise of a simple highly effective empirical regimen for patients not allergic to penicillin.[8] Finally, it is important to institute programmes of antimicrobial stewardship for *H. pylori*. The USA may have taken the lead in that the Centers for Medicare and Medicaid Services recently finalised a new regulation requiring all hospitals participating in its programmes to establish antimicrobial stewardship programmes by 30 March 2020.[9] They also suggest using the US Centers for Disease Control documents regarding antimicrobial stewardship in hospitals with limited resources as a guide.[10] These guidelines require creation and promotion of susceptibility-based treatment, tracking of antibiotic dispensing and setting targets

[1]Medicine (111D), Baylor College of Medicine, Houston, Texas, USA
[2]Gastroenterology and Hepatology, Baylor College of Medicine, Houston, Texas, USA

Correspondence to Dr David Y Graham, Medicine (111D), Baylor College of Medicine, Houston, TX 77030, USA; dgraham@bcm.edu

for improvement (ie, monitoring and reporting).

SUMMARY

The Hp-EuReg report highlights practice variability but also marks the slow transition of *H. pylori* therapy to therapies based on the principles of antimicrobial stewardship and reliable high eradication rates. Expediting these changes will require relinquishing cherished practices and ways of thinking about *H. pylori* therapy. Whether antimicrobial stewardship will be embraced by gastroenterology remains to be seen.

Contributors All authors have read and approved the final manuscript and each meets the criteria for authorship established by the International Committee of Medical Journal Editors and verify the validity of the results reported. We confirm that our paper has not been published in its current form or a substantially similar form (in print or electronically, including on a website), that it has not been accepted for publication elsewhere and that it is not under consideration by another publication.

Funding DYG and HE-S are supported in part by the Office of Research and Development Medical Research Service Department of Veterans Affairs, Public Health Service grant DK56338 which funds the Texas Medical Center Digestive Diseases Center.

Competing interests DYG is a consultant for RedHill Biopharma and Phathom Pharmaceuticals regarding novel *Helicobacter pylori* therapies and has received research support for culture of *H. pylori* and is the PI of an international study of the use of antimycobacterial therapy for Crohn's disease. HE-S is a consultant for Phathom Pharmaceuticals regarding novel *H. pylori* therapies.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Graham DY, El-Serag HB. *Gut* 2021;**70**:1–2.

Received 18 July 2020
Accepted 9 August 2020
Published Online First 21 September 2020

Linked

► http://dx.doi.org/10.1136/gutjnl-2020-321372

Gut 2021;**70**:1–2.
doi:10.1136/gutjnl-2020-322385

ORCID iD
David Y Graham http://orcid.org/0000-0002-6908-8317

REFERENCES

1 Olga P, Nyssen OP, Bordin D, *et al*. European Registry on *Helicobacter pylori* management (Hp-EuReg): patterns and trends in first-line empirical eradication prescription and outcomes of 5 years and 21,533 patients. *Gut* 2021;70:40–54.
2 Chey WD, Leontiadis GI, Howden CW, *et al*. ACG clinical guideline: treatment of *Helicobacter pylori* infection. *Am J Gastroenterol* 2017;112:212–39.
3 Riedner G, Rusizoka M, Todd J, *et al*. Single-dose azithromycin versus penicillin G benzathine for the treatment of early syphilis. *N Engl J Med* 2005;353:1236–44.
4 Graham DY, Dore MP, Lu H. Understanding treatment guidelines with bismuth and non-bismuth quadruple *Helicobacter pylori* eradication therapies. *Expert Rev Anti Infect Ther* 2018;16:679–87.
5 Dang BN, Graham DY. *Helicobacter pylori* infection and antibiotic resistance: a WHO high priority? *Nat Rev Gastroenterol Hepatol* 2017;14:383–4.
6 El-Serag HB, Kao JY, Kanwal F, *et al*. Houston Consensus Conference on testing for *Helicobacter pylori* infection in the United States. *Clin Gastroenterol Hepatol* 2018;16:992–1002.
7 Chen Q, Long X, Ji Y, *et al*. Randomised controlled trial: susceptibility-guided therapy versus empiric bismuth quadruple therapy for first-line *Helicobacter pylori* treatment. *Aliment Pharmacol Ther* 2019;49:1385–94.
8 Furuta T, Yamade M, Kagami T, *et al*. Dual therapy with vonoprazan and amoxicillin is as effective as triple therapy with vonoprazan, amoxicillin and clarithromycin for eradication of *Helicobacter pylori*. *Digestion* 2019:1–9.
9 Core elements of antibiotic stewardship, 2019. Available: https://www.cdc.gov/antibiotic-use/core-elements/resource-limited.html [Accessed 15 Jul 2020].
10 A Rule by the Centers for Medicare & Medicaid Services, 2019. Available: https:/ / federal register.gov/ d/ 2019-20736