Letters to the Editors

Triple vs. quadruple therapy for treating *Helicobacter pylori* infection: an updated meta-analysis

SIRS, Since we submitted our paper, 'Triple vs. quadruple therapy for treating *Helicobacter pylori* infection: a meta-analysis', for publication in *Alimentary Pharmacology and Therapeutics*,[1] a new study comparing triple with quadruple therapy has been published.[2] Full-text reports of two of the studies included in the meta-analysis in abstract form have also been published.[3, 4] The objective of this letter is to update the meta-analysis using these new results.

The report of Mantzaris *et al.* compares triple with quadruple therapy for *H. pylori* infection in patients with duodenal ulcer.[2] The authors obtained better eradication rates with triple than with quadruple therapy. However, the differences did not reach statistical significance. The results of the report by Katelaris *et al.* are identical to those published in abstract form,[3] whereas there are small differences between the abstract and full-text form of the paper by Laine *et al.*[4]

The results of our meta-analysis did not change after introducing these modifications (Figure 1). In the intention-to-treat analysis, eradication was achieved in 449 of 559 patients with quadruple therapy [80%; 95% confidence interval (CI), 77–84%] and in 451 of 569 patients with triple therapy (79%; 95% CI, 74–81%). The odds ratio (Figure 1) was 1.00 (95% CI, 0.64–1.57; $P = 1$). In the per protocol analysis, eradication was achieved in 421 of 486 patients with quadruple therapy (87%; 95% CI, 84.1–90.5%) and in 435 of 509 patients with triple therapy (85%; 95% CI, 81.4–88.3%). The odds ratio was 0.95 (95% CI, 0.58–1.57; $P = 0.9$).

In conclusion, the update of our meta-analysis suggests that the conclusions of the previous report can be maintained, and that the effectiveness of quadruple and triple therapy is very similar for the initial treatment of *H. pylori* infection.

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REFERENCES

1 Gené E, Calvet X, Azagra R, Gisbert JP. Triple vs. quadruple therapy for treating *Helicobacter pylori* infection: a meta-analysis. Aliment Pharmacol Ther 2003; 17: 1137–43.
2 Mantzaris G, Petraki K, Archavlis E, *et al.* Omeprazole triple therapy versus omeprazole quadruple therapy for healing duodenal ulcer and eradication of *Helicobacter pylori* infection: a 24-month follow-up study. Eur J Gastroenterol Hepatol 2002; 14: 1237–43.
3 Katelaris PH, Crotty B, Reiner R, *et al.* A randomized comparison of quadruple and triple therapies for *Helicobacter pylori*

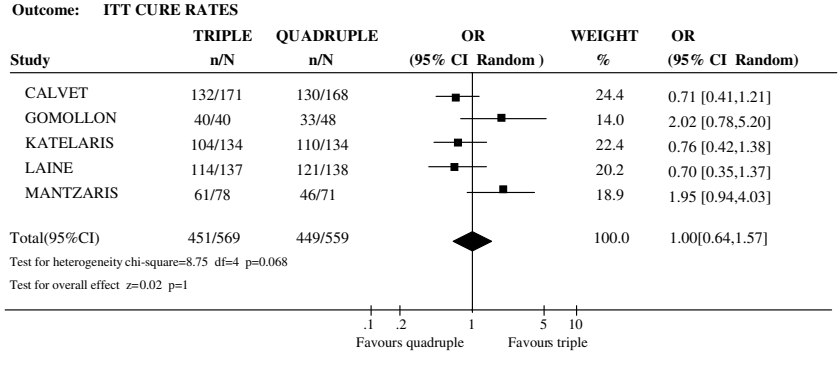

Figure 1. Triple vs. quadruple therapy. Intention-to-treat (ITT) analysis. CI, confidence interval; OR, odds ratio.

eradication: the QUADRATE study. Gastroenterology 2002; 123: 1763–9.
4 Laine L, Hunt RH, El Zimaity HMT, Nguyen B, Osato MS, Spenard J. Bismuth-based quadruple therapy using a single capsule of bismuth biskalcitrate, metronidazole, and tetracycline given with omeprazole versus omeprazole, amoxicillin and clarithromycin for eradication of *Helicobacter pylori* in duodenal ulcer patients: a prospective randomized multicenter, North American trial. Am J Gastroenterol 2003; 98: 562–7.

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Practice makes imperfect

SIRS, In a recent issue of *Alimentary Pharmacology and Therapeutics*, Quan *et al*. described the development of the Diabetes Bowel Symptom Questionnaire (DBSQ).[1] We understand that stomach complaints are a significant problem in patients with diabetes mellitus, and we congratulate the authors on their efforts to develop a validated symptom measure for use in this population. However, we feel that there are certain issues with regard to the design of this study.

Practice effects are recognized as a potential source of bias in measurement studies.[2] The repeated administration of a single questionnaire presents opportunities for subjects to recall their earlier responses, and this can enhance estimates of reliability and validity. Researchers attempt to control for practice effects through careful selection of the test–re-test interval (i.e. this must be long enough to minimize the risk of practice effects, yet short enough to ensure that the same recall period is assessed over successive administrations) and by minimization of the number of administrations of the questionnaire. In the latter case, studies are often designed so that reliability is assessed in one-half of the sample, whilst validity is assessed in the other. This ensures that subjects have minimal exposure to the measure and minimal opportunities to 'memorize' earlier responses.

In the study by Quan *et al*.,[1] test–re-test reliability was assessed in the sample that took part in the validation study. In essence, the subjects had two exposures to the questionnaire prior to the collection of validity data and, consequently, two opportunities to rehearse their responses. Whilst validation was performed against external criteria, the opportunity to practice twice may have influenced the estimates of validity in this study. We also note that 30% of the sample was drawn from an established cohort, which had participated in earlier gastrointestinal research. The authors did not describe the instruments that were used to assess this cohort in earlier studies, and we view this as a significant omission. We understand that there is an earlier version of the DBSQ, which shows considerable content overlap with the current instrument.[3] Earlier exposures to the content of the DBSQ may have increased the risk of practice effects in the study by Quan *et al*.

We suggest that potential practice effects should be carefully evaluated before instruments are presented as reliable and valid measures.

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REFERENCES

1 Quan C, Talley NJ, Cross S, *et al*. Development and validation of the diabetes bowel symptom questionnaire. Aliment Pharmacol Ther 2003; 17: 1179–87.
2 Anastasi A. Psychological Testing, 5th edn. New York: MacMillan Publishing, 1982: 110–1.
3 Talley NJ, Hammer J, Giles N, Jones MP, Horowitz M. Measuring gastrointestinal symptoms in diabetes: development and validation of the diabetes bowel symptom questionnaire. Gastroenterology 2001; 120: A232(Abstract).

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Eradication of *Helicobacter pylori* infection in patients with intractable gastric ulcer

SIRS, We read the article by Higuchi *et al*., 'Is eradication sufficient to heal gastric ulcers in patients infected with *Helicobacter pylori*? A randomized, controlled, prospective study', with interest.[1] They reported that triple therapy against *Helicobacter pylori* was able to induce healing of small ulcers (0.5 to < 1.0 cm in diameter) without follow-up therapy using proton pump inhibitors or H2-receptor antagonists to suppress acid secretion, but that 1-week triple therapy including proton pump inhibitors was not sufficient for the healing of larger ulcers (> 1.5 cm in diameter).

Sung *et al.* reported that the healing rates of gastric ulcers in patients undergoing treatment with antibacterial drugs alone for 1 week were 84% at 5 weeks and 96% at 9 weeks after treatment, although they did not mention the size of the gastric ulcers.[2] Gastric ulcers in patients treated only with placebo may heal spontaneously and the natural healing rate has been reported to be 40–50% at the 8-week evaluation.[3]

In the study by Higuchi *et al.*, the healing rate of gastric ulcers of > 1.5 cm in diameter in patients undergoing triple therapy was low at the 8-week evaluation (5%).[1] We have observed that some patients with intractable gastric ulcers require long-term administration of acid suppressive treatment. Such patients typically have a deep excavated ulcer, marked deformity of the stomach with a shortened lesser curvature due to recurrence, a repeated recurrence and an angular location.[4] We assume that the large ulcers in the patients in the 1-week triple therapy group of the study by Higuchi *et al.* predominantly included so-called intractable ulcers.

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REFERENCES

1 Higuchi K, Fujiwara Y, Tominaga K, *et al.* Is eradication sufficient to heal gastric ulcers in patients infected with *Helicobacter pylori*? A randomized, controlled, prospective study. Aliment Pharmacol Ther 2003; 11: 113–7.
2 Sung JJY, Chung SCS, Thomas KW, *et al.* Antibacterial treatment of gastric ulcer associated with *H. pylori*. N Engl J Med 1995; 332: 139–42.
3 Hansky J. The impact of medical therapy on the natural history of ulcer disease. In: Advances in ulcer disease. Oxford: Elsevier, 1981: 449–59.
4 Okada M, Yao T, Imamura K, *et al.* Factors influencing the healing rate of gastric ulcer under treatment with cimetidine. Am J Gastroenterol 1989; 84: 501–5.

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Intragastric acidity in patients with gastro-oesophageal reflux disease

Sirs, I read with great interest the article by Zentilin *et al.*, who showed that the 24-h intragastric pH profile of patients with non-erosive reflux disease (NERD) does not differ from that of patients with oesophagitis and controls.[1] Some years ago, my coworkers and I were the authors of a study on the 24-h pH monitoring of 65 patients with gastro-oesophageal reflux disease (GERD) with (37) and without (28) oesophagitis.[2] Our results were in partial agreement with those of Zentilin *et al.*, in that the mean gastric pH during the day (data not published) and during the night did not vary between NERD patients and healthy controls (31 subjects). In contrast, we found a significantly higher nocturnal acidity (expressed as both the mean gastric pH and percentage of time with gastric pH < 4 and pH < 2) in patients with oesophagitis than in either controls or refluxers without oesophagitis. When subdividing the night into two parts, we found that the lower gastric pH observed in patients with oesophagitis, relative to that in controls or refluxers without oesophageal lesions, occurred entirely during the second part of the night (03.00–07.00 h). From this, we postulated that oesophagitis sufferers had an altered circadian pattern of gastric acidity, with an absence or reduction in the physiological decrease in late nocturnal acid secretion. Similar findings were also observed in patients with duodenal ulcer.[3] Our study focused on the nocturnal period as no dietary restrictions were given to the patients during the day. The daytime gastric pH data, which were not published, did not show any differences between refluxers with or without oesophagitis and controls. In order to assess the pathogenetic relevance of our findings, we calculated the percentage of time with oesophageal pH < 4 and pH < 2 over the same time periods as those considered for gastric pH analysis. No differences were found with the conventional threshold of pH 4; however, when the threshold of pH 2 was chosen, the oesophageal acid exposure was significantly higher in the second part of the night in oesophagitis sufferers than in NERD patients or controls. We speculated that the oesophageal damage could be related more to the level of acidity of the refluxate, which, in turn, depends on the gastric acidity, than on the duration of exposure of the oesophageal mucosa to acid. In this context, it has been reported that exposure of the oesophagus to pH 0–2, even for an extremely low daily percentage of time (1.32%), is strongly associated with the presence of mucosal lesions, whereas, at higher pH values, this association is far less marked.[4]

Both the study by Zentilin *et al.* and ours were based on continuous pH monitoring, which is the only

method capable of describing the circadian pattern of gastric pH under nearly physiological conditions.[5] Therefore, a comparison between our respective data may be more interesting than a comparison with data emerging from conventional secretory studies, which have yielded conflicting results.[6–8] Our data are also partially conflicting with respect to the nocturnal gastric pH in NERD patients and oesophagitis sufferers; however, this may partly be due to the different patient selection criteria (our patients were all refluxers, whereas those in the study by Zentilin *et al.* were selected on a clinical basis) or the different time intervals considered during pH-metry. Nevertheless, in agreement with Zentilin *et al.*, gastric hyperacidity does not appear to be a characteristic feature of patients with NERD, and mechanisms other than acid may be involved in the reduced symptomatic response to proton pump inhibitor therapy in patients with NERD relative to those with erosive oesophagitis.

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REFERENCES

1 Zentilin P, Dulbecco P, Bilardi C, *et al.* Circadian pattern of intragastric acidity in patients with non-erosive reflux disease (NERD). Aliment Pharmacol Ther 2003; 17: 353–9.
2 Sozzi M, Valentini M, Poletti M, *et al.* Nocturnal gastric acidity pattern in gastro-oesophageal reflux disease with or without oesophagitis. Ital J Gastroenterol 1995; 27: 413–8.
3 Savarino V, Mela GS, Scalabrini P, *et al.* 24-hour study of intragastric acidity in duodenal ulcer patients and normal subjects using continuous intraluminal pH-metry. Dig Dis Sci 1988; 33: 1077–80.
4 Bremner RM, Crookes PF, DeMeester TR, *et al.* Concentration of refluxed acid and oesophageal mucosal injury. Am J Surg 1992; 164: 522–6.
5 Fimmel CJ, Etienne A, Cilluffo T, *et al.* Long-term ambulatory gastric pH monitoring: validation of a new method and effect of H2 antagonists. Gastroenterology 1985; 88: 1842–51.
6 Mulholland MW, Reid BJ, Levine DS, *et al.* Elevated gastric acid secretion in patients with Barrett's metaplastic epithelium. Dig Dis Sci 1989; 34: 1329–35.
7 Collen MJ, Johnson DA, Sheridan MJ. Basal acid output and gastric acid hypersecretion in gastroesophageal reflux disease. Correlation with ranitidine therapy. Dig Dis Sci 1994; 39: 410–7.
8 Hirschowitz BI. A critical analysis, with appropriate controls, of gastric acid and pepsin secretion in clinical esophagitis. Gastroenterology 1991; 101: 1149–58.

10.1046/j.0269-2813.2003.01704.x

Helicobacter DNA in bile: correlation with hepato-biliary diseases

Sirs, We read with interest the study by Fallone *et al.*, reporting that they did not detect the DNA of the *Helicobacter* genus in the bile from Canadian patients with biliary diseases.[1] These results are in disagreement with others that have identified *Helicobacter* DNA in the bile or gall-bladder tissue of patients with or without biliary diseases.[2, 3] In a similar study, we evaluated the presence of *Helicobacter* DNA in gall-bladder tissues and bile samples from 64 Brazilian patients, and found that it was more frequently seen in those with cholelithiasis/cholecystitis.[4] The sequences of the amplified products of the 16S rRNA gene were more than 99.3% similar to that of *H. pylori*. These discordant results may be due to regional differences, as pointed out by Fallone *et al.*,[1] especially when it is considered that gastric *H. pylori* infection is much greater in Brazil than in Canada and the micro-organism may gain access to the bile by retrograde transfer from the stomach/duodenum. However, it should be noted that DNA from *H. pylori* has been detected consistently in biliary specimens only when a more sensitive nested polymerase chain reaction (PCR) is used,[3, 4] as was the case in our study. The sensitivity of conventional PCR is quite low, and it is consistently positive only when the micro-organism is present at a level of 10^3 colony-forming units/mL or more in the sample, as confirmed by Fallone *et al.*[1] Indeed, when we tested our samples using the same primers and PCR conditions as used by Fallone *et al.*,[1] our results were similar to theirs. Conversely, intestinal species of *Helicobacter* have been detected in bile by the conventional PCR technique followed or not by hybridization.[3] These findings suggest that different *Helicobacter* species may be present in the human biliary tree. However, as intestinal *Helicobacter* species are resistant to bile, it is reasonable to suppose that they are found in larger numbers than *H. pylori* in the hepato-biliary tract.

Although it has not been clearly demonstrated whether *Helicobacter* species participate or not in the genesis of biliary diseases, there is evidence that both gastric

and intestinal *Helicobacter* at least circulate in human bile. Further studies are needed to elucidate the role of this group of micro-organisms in the pathogenesis of biliary diseases.

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REFERENCES

1 Fallone CA, Tran S, Semret M, Discepola F, Behr M, Barkun N. *Helicobacter* DNA in bile: correlation with hepato-biliary diseases. Aliment Pharmacol Ther 2003; 17: 453–8.
2 Fox JG, Dewhirst FE, Shen Z, *et al*. Hepatic *Helicobacter* species identified in bile and gallbladder tissue from Chileans with chronic cholecystitis. Gastroenterology 1998; 114: 755–63.
3 Bulajic M, Maisonneuve P, Schneider-Barchert W, *et al*. *Helicobacter pylori* and the risk of benign and malignant biliary tract disease. Cancer 2002; 95: 1946–53.
4 Queiroz DMM, Silva CP, Oliveira AG, *et al*. Presence of *Helicobacter* species in bile and gallbladder as a risk factor for cholelithiasis/cholecystitis. Gastroenterology 2003; 124: S1685, A246.