

Figure 1 Treatment algorithm for hepatocellular carcinoma (HCC) (cited with permission from the Group formed to establish “Guidelines for evidence-based clinical practice for the treatment of liver cancer”).
 *The presence of vascular invasion or extrahepatic metastasis is indicated separately. †Selected when the severity of liver damage is moderate and the tumour diameter is ≤ 2 cm. ‡Tumour diameter ≤ 5 cm, when there is only one tumour.

In conclusion, 1 year after its publication, the *JHCC guidelines* have become well disseminated among both specialists and primary care physicians in Japan. As expected, these guidelines have begun to be applied at every level of clinical decision making for HCC.

Acknowledgements

We thank Mr Hiromichi Suzuki and the International Medical Information Center (Tokyo) for their clerical work for the questionnaire survey.

Norihiro Kokudo
 Department of Surgery, Hepato-Biliary-Pancreatic Surgery Division, Artificial Organ and Transplantation Division, University of Tokyo, Tokyo, Japan

Yo Sasaki
 Department of Gastrointestinal Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

Takeo Nakayama
 Department of Health Informatics, Kyoto University School of Public Health, Kyoto, Japan

Masatoshi Makuuchi
 Department of Surgery, Hepato-Biliary-Pancreatic Surgery Division, Artificial Organ and Transplantation Division, University of Tokyo, Tokyo, Japan

Correspondence to: Professor N Kokudo, Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan; kokudo-2su@h.u-tokyo.ac.jp

doi: 10.1136/gut.2007.119362

Competing interests: None declared.

References

- 1 Group formed to establish “Guidelines for evidence-based clinical practice for the treatment of liver cancer”. *Clinical practice guidelines for hepatocellular carcinoma*. Tokyo: Kanehara, 2005 [in Japanese].
- 2 Makuuchi M, Kokudo N. Clinical practice guidelines for hepatocellular carcinoma: the first evidence based guidelines from Japan. *World J Gastroenterol* 2006;12:828–9.

One- or two-week triple therapy for *Helicobacter pylori*: questions of efficacy and inclusion of a dual therapy treatment arm

We read with interest the recent paper comparing 1 and 2 weeks of triple therapy for *Helicobacter pylori* infection in patients with duodenal ulcer disease. (*Gut* 2007;56:475–9) *H pylori* is an infectious disease and the goal of treatment is to cure the infection. In 2007, one would hope to be able to reliably cure $\geq 95\%$ of the treated patients (discussed by Graham *et al*).¹ In 1989, a successful treatment has been defined as one that cures $>80\%$ of the patients.² By 1995, it seemed that 90% was achievable.³ The Maastricht consensus conferences defined a useful therapy as the one with an intention to treat (ITT) cure rate of $>80\%$,

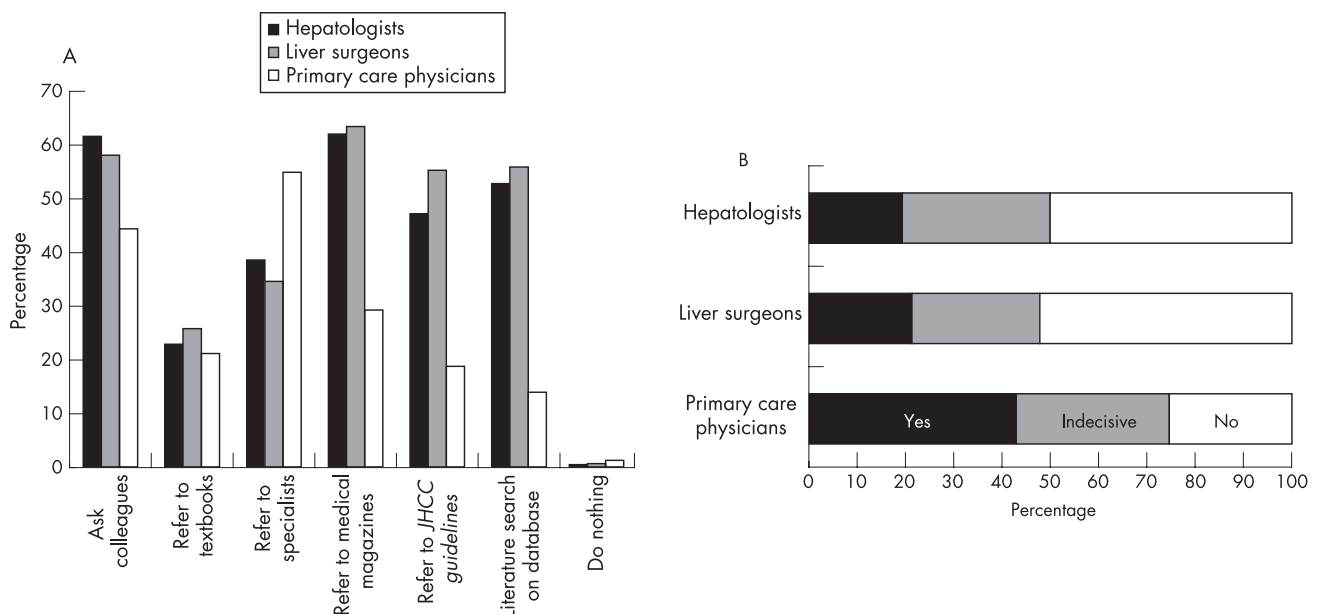


Figure 2 (A) What are your possible actions when you have clinical questions or problems in regard to the management of patients with hepatocellular carcinoma (HCC)? (a multiple-choice question). (B) Have you changed your practice pattern for HCC after reading the *JHCC guidelines*? (Responders who did not acknowledge the guidelines were excluded.)

Table 1 Results of recent large studies with proton-pump inhibitors, clarithromycin and amoxicillin triple therapy in Europe and the US

First author	Total patients (n)	Duration (days)	ITT (95% CI)
Della <i>et al</i> ^f	812	7	72% (69% to 75%)
Bochenek <i>et al</i> ¹⁰	177	7	65% (56% to 73%)
Boixeda <i>et al</i> ¹¹	890	7	77% (74% to 80%)
Calvet <i>et al</i> ⁸	237	7	76% (73% to 80%)
Calvet <i>et al</i> ⁸	210	10	79% (74% to 85%)
De Francesco <i>et al</i> ¹⁰	115	7	71% (63% to 79%)
De Francesco <i>et al</i> ¹²	116	10	80% (72% to 87%)
Fennerty <i>et al</i> ³	123	10	81% (73% to 87%)
Fennerty <i>et al</i> ³	126	14	82% (73% to 88%)
Laine <i>et al</i> ⁴	233	10	77% (71% to 82%)
Scaccianoce <i>et al</i> ⁵	70	7	75% (66% to 86%)
Scaccianoce <i>et al</i> ⁵	71	10	81% (73% to 91%)
Vakil <i>et al</i> ⁶	194	7	77% (71% to 83%)
Vakil <i>et al</i> ⁶	196	10	78% (72% to 84%)
Vakil <i>et al</i> ⁶	206	10	73% (67% to 79%)
Zagari* <i>et al</i>	301	7	79% (74% to 83%)
Zagari* <i>et al</i>	301	14	81% (77% to 85%)
Zullo ¹⁷	527	7	74% (70% to 77%)
Zullo ¹⁷	87	7	80% (72% to 88%)

*ITT Current study being discussed.

which is a relatively low hurdle (ie, those with cure rates of $\leq 80\%$ would be unacceptable).⁴ Although the authors concluded that 7 and 14 days therapy provided essentially equivalent results, the focus should have been on the fact that the cure rates obtained were unacceptably low with either duration (eg, ITT of 79.7 for 7 days and 81.7 for 14 days), especially among patients with duodenal ulcer disease where the cure rates are typically higher than among patients without ulcers.³⁻⁸

Their results are not unexpected as large studies of this legacy triple therapy (proton-pump inhibitor (PPI), amoxicillin and clarithromycin) have recently yielded unacceptably low eradication rates in Europe and the US, and have only infrequently achieved the minimum 80% success rate (table 1).¹⁰⁻¹⁷ Overall, these results suggest that traditional triple therapy should no longer be used in Western populations unless pretreatment susceptibility is confirmed and then it should be used for 14 days.^{18, 19}

H pylori is a serious, chronic, transmissible infectious disease that causes damage to gastric structure and function, and is a major cause of morbidity and mortality worldwide. All the patients in this study had *H pylori*-related ulcer disease, and untreated 10-25% would be expected to develop complications such as haemorrhage. We are concerned about the inclusion of the dual therapy arm of omeprazole and amoxicillin in the trial. The dual therapy at these doses typically yields a cure rate of $\leq 50\%$ and is listed under the category of "not recommended". The manuscript states that the protocol was approved by institutional review boards, and all patients gave informed consent. What was the nature of the informed consent? How was a known ineffective therapy justified to the patients with duodenal ulcer disease and to the review boards? We believe that the information given to patients and the justifications must be described in detail in the publication including what the patients were told, and that they entered the trial knowing that they would have a high chance of treatment failure. Finally, what was done to ensure that the large number of patients with failed treatment subsequently receive appropriate therapy for *H pylori*-related

duodenal ulcer disease? It may also be good time to rethink current approaches to *H pylori* treatment.

Acknowledgements

This material is based upon work supported in part by the Office of Research and Development Medical Research Service Department of Veterans Affairs and by Public Health Service grant DK56338, which funds the Texas Gulf Coast Digestive Diseases Center.

David Y Graham, Yoshio Yamaoka

Department of Medicine, Michael E DeBakey VAMC and Baylor College of Medicine, Houston, Texas, USA

Correspondence to: Dr D Y Graham, Michael E DeBakey Veterans Affairs Medical Center, RM 3A-320 (111D), 2002 Holcombe Boulevard, Houston, TX 77030, USA; dgraham@bcm.tmc.edu

Competing interests: DYG has received small amounts of grant support and/or free drugs or urea breath tests from Meretek, Janssen/Eisai, TAP, and BioHit for investigator initiated and completely investigator controlled research in the area of *H pylori* infections. In addition, DYG is a paid consultant for Otsuka Pharmaceuticals and a member of the Board of Directors of Meretek, Diagnostics, the manufacturer of the ¹³C-urea breath test. He is also a consultant to Novartis with regards to *H pylori* vaccine development and also receives royalties on the Baylor College of Medicine patent covering the serologic test, HM-CAP. YY has no potential conflicts of interest to declare.

References

- Graham DY, Osato MS, Hoffman J, *et al*. Furazolidone combination therapies for *Helicobacter pylori* infection in the United States. *Aliment Pharmacol Ther* 2000;**14**:211-15.
- Graham DY, Klein PD, Opekin AR, *et al*. In vivo susceptibility of *Campylobacter pylori*. *Am J Gastroenterol* 1989;**84**:233-8.
- Graham DY. A reliable cure for *Helicobacter pylori* infection? *Gut* 1995;**37**:154-6.
- European *Helicobacter Pylori* Study Group. Current European concepts in the management of *Helicobacter pylori* infection. The Maastricht Consensus Report. *Gut* 1997;**41**:8-13.
- Broutet N, Tchamgoue S, Pereira E, *et al*. Risk factors for failure of *Helicobacter pylori* therapy—results of an individual data analysis of 2751 patients. *Aliment Pharmacol Ther* 2003;**17**:99-109.

- Broutet N, Marais A, Lamouliatte H, *et al*. *cagA* Status and eradication treatment outcome of anti-*Helicobacter pylori* triple therapies in patients with nonulcer dyspepsia. *J Clin Microbiol*, 2001;**39**:1319-22.
- Wong WM, Xiao SD, Hu PJ, *et al*. Standard treatment for *Helicobacter pylori* infection is suboptimal in non-ulcer dyspepsia compared with duodenal ulcer in Chinese. *Aliment Pharmacol Ther* 2005;**21**:73-81.
- Calvet X, Ducons J, Bujanda L, *et al*. Seven versus ten days of rabeprazole triple therapy for *Helicobacter pylori* eradication: a multicenter randomized trial. *Am J Gastroenterol* 2005;**100**:1696-701.
- Della MP, Lavagna A, Masoero G, *et al*. Effectiveness of *Helicobacter pylori* eradication treatments in a primary care setting in Italy. *Aliment Pharmacol Ther* 2002;**16**:1269-75.
- Bochenek WJ, Peters S, Fraga PD, *et al*. Eradication of *Helicobacter pylori* by 7-day triple-therapy regimens combining pantoprazole with clarithromycin, metronidazole, or amoxicillin in patients with peptic ulcer disease: results of two double-blind, randomized studies. *Helicobacter* 2003;**8**:626-42.
- Boixeda D, Martin dA, Bermejo F, *et al*. Seven-day proton pump inhibitor, amoxicillin and clarithromycin triple therapy. Factors that influence *Helicobacter pylori* eradications success. *Rev Esp Enferm Dig* 2003;**95**:206-5.
- De Francesco V, Zullo A, Hassan C, *et al*. The prolongation of triple therapy for *Helicobacter pylori* does not allow reaching therapeutic outcome of sequential scheme: a prospective, randomised study. *Dig Liver Dis* 2004;**36**:322-6.
- Fennerty MB, Kovacs TO, Krause R, *et al*. A comparison of 10 and 14 days of lansoprazole triple therapy for eradication of *Helicobacter pylori*. *Arch Intern Med* 1998;**158**:1651-6.
- Laine L, Frantz JE, Baker A, *et al*. A United States multicentre trial of dual and proton pump inhibitor-based triple therapies for *Helicobacter pylori*. *Aliment Pharmacol Ther* 1997;**11**:913-17.
- Scaccianoce G, Hassan C, Panarese A, *et al*. *Helicobacter pylori* eradication with either 7-day or 10-day triple therapies, and with a 10-day sequential regimen. *Can J Gastroenterol* 2006;**20**:113-17.
- Vakil N, Lanza F, Schwartz H, *et al*. Seven-day therapy for *Helicobacter pylori* infection in the United States. *Aliment Pharmacol Ther* 2004;**20**:99-107.
- Zullo A, Vaira D, Vakil N, *et al*. High eradication rates of *Helicobacter pylori* with a new sequential treatment. *Aliment Pharmacol Ther* 2003;**17**:919-26.
- Ford A, Moayyedi P. How can the current strategies for *Helicobacter pylori* eradication therapy be improved? *Can J Gastroenterol* 2003;**17**(Suppl B):36B-40.
- Calvet X, Garcia N, Lopez T, *et al*. A meta-analysis of short versus long therapy with a proton pump inhibitor, clarithromycin and either metronidazole or amoxicillin for treating *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2000;**14**:603-9.

Authors' response

We thank Dr Graham and Dr Yamaoka for their interest in our recent publication comparing the efficacy of 1 and 2 weeks of triple therapy for the eradication of *Helicobacter pylori*. They ask about the information given to the patients concerning the dual therapy arm (omeprazole and amoxicillin) with a known low efficacy. As explained in our paper, this arm was included both as a measure of the internal validity of the study and as part of a second long-term follow-up study. Each patient was provided, both verbally and via a written information form, with complete details of the treatments, objectives, possible risks and benefits of the study, and informed consent was obtained from all participants. The full versions of the information form and the informed consent form completed by all