Sequential Therapy for *Helicobacter pylori* Infection: Ethical Considerations Revisited

To the Editor:

We read with interest the recent paper comparing 8 and 10 days sequential therapy with traditional (legacy) triple therapy in a population of Italian patients.[1] In the discussion, the authors note our concern about whether it was "still ethical or not to continue administration of standard triple therapy taking into account that it is now less effective than in the past." The authors misunderstood our concerns. There have been numerous trials of legacy triple therapy in Italy and none has yielded eradication rates in the acceptable range (eg,[2]). By themselves the trials with known inferior therapies or placebos are generally unethical and not needed as we can use a historical untreated control, which is known to estimate 0% eradication.[3–6] One principle of informed consent is that the investigators provide all relevant information, which might affect a subject's willingness to participate in a study. A known inferior therapy cannot be described as "standard" or "approved," and thus would not be an appropriate "control" group to compare investigational *Helicobacter pylori* regimens in Italy. In addition, the investigators, must share the known inferiority of standard triple, with the institutional review board and the patients. Since at least 2004, informed consent would require informing the patients and the institutional review boards that one of the therapies was known to be clearly inferior with an average treatment success of approximately 75% for triple therapy compared with greater than 90% for sequential therapy in Italy. In addition, those who received legacy triple therapy would have an increased risk of developing clarithromycin-resistant organisms, which might prejudice their ability to be subsequently be cured of their infection.[5,6] No additional information was gained by including legacy therapy in the study and doing so only raises ethical questions. Were the patients and the institutional review boards properly informed in this study? Were all treatment failures followed up and *H. pylori* eradication confirmed?

The study is also interesting in that the treatment success was relatively low, only 88% in per protocol and 86% in intention-to-treat analyses for the standard 10-day sequential therapy; efficacy for the 8-day regimen was 90% and 83% for per protocol and intention-to-treat results, respectively. The lack of susceptibility testing precludes testing whether it was because of increasing resistance. Esomeprazole was used, which differs from most other Italian studies. It would be interesting to know if the source or formulation of the other drugs also differed from what had been used in the past.

H. pylori infection, as with any other infectious disease, should be judged compared with the expected outcome (ie, 95% or greater treatment success).[5,7] In Rome, neither 8-day or 10-day sequential therapy seems to be an optimal choice and a different regimen should be offered. The quadruple concomitant therapy containing metronidazole, clarithromycin, amoxicillin, and a proton pump inhibitor may be a better option.

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Conflict of Interest, Disclosure Statement, and the Funding Declaration Statement: This material is based upon work supported in part by the Office of Research and Development Medical Research Service, Department of Veterans Affairs. Dr Graham is supported in part by Public Health Service grant DK56338 which funds the Texas Medical Center, Digestive Diseases Center, and R01 CA116845. The contents are solely the responsibility of the authors and do not necessarily represent the official views of the Veterans Affairs or National Institutes of Health. Dr Graham is an unpaid consultant for Novartis in relation to vaccine development for the treatment or prevention of *Helicobacter pylori* infection. Dr Graham is a also a paid consultant for Otsuka Pharmaceuticals regarding diagnostic testing and until July 2007 was a member of the Board of Directors of Meretek, Diagnostics, the manufacturer of the 13C-urea breath test. Until November 2009, Dr Graham received royalties on the Baylor College of Medicine patent covering materials related to 13C-urea breath test.

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Critically Ill Patients With Cirrhosis and Low Serum Sodium

To the Editor:

We read with interest the paper by Jenq CC et al,[1] recently published in *Journal of Clinical Gastroenterology*, regarding the ability of serum sodium (Na) to predict the survival in critically ill cirrhotic patients admitted to the intensive care unit (ICU). Particularly, low sodium levels were associated with higher complications of cirrhosis, in-hospital mortality, and poor short-term prognosis. To add to their evaluation, we report our experience in 412 patients with cirrhosis (male: 59.2%, mean age: 49.3 ± 12 y, alcohol was the main cause of cirrhosis), who were consecutively admitted to the Royal Free Hospital ICU. At admission, several variables, including demographic and clinical data, and laboratory parameters [including full blood count, lactate, biochemical and

clotting profile, arterial blood gas, and inspiratory concentration of oxygen (FiO_2)] had been prospectively collected for each patient. During the ICU stay, gastrointestinal (G.I.) bleeding episodes, development of aspiration pneumonia and additional use of inotropes, mechanical ventilation or hemofiltration were also recorded. Liver-specific prognostic models [Child-Pugh (CTP) and MELD scores] and general-ICU models (APACHE II and SOFA scores) were evaluated on ICU admission. All data were analyzed using the statistical package SPSS (version 13.0). Chi-square test was used for categorical variables and the Mann-Whitney *U* test was used for quantitative variables in order to compare the patients with hyponatremia ($Na \leq 135$ mmol/L) at admission versus those without hyponatremia ($Na > 135$ mmol/L). The discriminative ability of sodium and prognostic scores at baseline was evaluated by using the area under a receiver operating characteristic (ROC) curve (AUC).

The overall mortality in ICU or 6 months after discharge from ICU was 61.2% mainly owing to multiple organ failure (45.4%), respiratory failure (18.6%), and renal failure (11.9%). The patients with hyponatremia (group 1, n = 118, 28.6%), compared with those with normal sodium (group 2, n = 294, 71.4%), had significantly higher mortality (74% vs. 56%, $P < 0.001$). In addition, group 1 patients, compared with group 2 patients, were more likely to have G.I. bleeding (56% vs. 28%, $P < 0.001$), hepatorenal syndrome (32% vs. 14%, $P < 0.001$), and severe ascites (30% vs. 21%, $P = 0.032$) at admission to ICU, and need for cardiovascular support with inotropes (54% vs. 38%, $P = 0.006$), mechanical ventilation (92% vs. 78%, $P = 0.02$) and hemofiltration support (25% vs. 8%, $P < 0.001$). Interestingly, group 1 patients, compared with group 2 patients, had significantly higher levels of serum bilirubin (11.2 mg/dL vs. 7.8 mg/dL, $P = 0.005$), serum creatinine (2.2 mg/dL vs. 1.4 mg/dL, $P < 0.001$), CTP score (11 vs. 10, $P = 0.041$), and lower pH (7.3 vs. 7.6, $P < 0.001$). However, in the multivariate analysis, FiO_2, serum lactate, bilirubin and renal dysfunction, but not hyponatremia, were the independent factors of mortality. Moreover, based on the area under the ROC curves, the SOFA score had the best discriminative accuracy for mortality (AUC = 0.84) and hyponatremia the worst discrimination value (AUC: 0.62). On the basis of these findings, we believe that although hyponatremia may reflect advanced cirrhosis and it has been suggested for incorporation into the MELD to enhance its prognostic ability,[2] further studies are needed in order to elucidate better its precise impact on mortality in this group of critically ill patients.

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Serum Sodium in Critical Cirrhotic Patients

To the Editor:

We are pleased to have received the expert opinions from Dr Cholngitas et al[1] from Royal Free Hospital, London, UK. The role of hyponatremia in predicting the prognosis of critically ill cirrhotic patients, the main finding of this study, supports the conclusion of the review article by Gines and Guevara.[2] Hyponatremia in liver cirrhosis is the consequence of overactivation of neuroendocrine systems, which results from arterial vasodilatation. It has been considered as a key marker of prognosis in cirrhosis. The development of hyponatremia is associated with an increased risk of developing hepatorenal syndrome and hepatic encephalopathy.[2] Both hepatorenal syndrome and hepatic encephalopathy are poor signs in cirrhotic patients. With regard to different results obtained by this investigation and that of 412 cirrhotic patients carried out by Cholngitas et al,[3] particularly with regard to the role of hyponatremia in outcome prediction in cirrhotic patients, we offer these explanations:

(1) The patient population differs somewhat between the 2 studies. Alcohol is the main cause of cirrhosis (69.4%) in patients surveyed by Cholngitas et al, but accounts for only 21% of the cases of cirrhosis in our study, in which the main cause instead was hepatitis B (41%).
(2) National Health Insurance in Taiwan did not approve terlipressin plus albumin in hepatorenal syndrome until mid 2005. Thus, most of the patients in our study did not receive management for terlipressin plus albumin. In a sense, the clinical course of hyponatremia in our patients was not affected by an effective treatment, such as vasoconstrictor plus albumin, association between hyponatremia and mortality unmodified. We assume that the treatment of terlipressin plus albumin may correct the hyponatremia and improve outcomes, and therefore, impacts the capability of serum sodium level in predicting short-term prognosis of cirrhotic patients.

Finally, given the limitations of this study,[4] we agree that, as mentioned by Dr Cholngitas et al, further studies are required to better elucidate its precise impact on mortality in this group of critically ill patients, especially in the era of vasoconstrictor treatment.

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Funding Sources: None.
Conflict of Interest Disclosure: None.
The authors declare that there is no conflict of interest disclosure and funding declaration about this study.