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Is Furazolidone Therapy for Helicobacter pylori Effective and Safe? Reply

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CORRESPONDENCE

Is Furazolidone Therapy for *Helicobacter pylori* Effective and Safe?

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We have read with great interest the study performed in Pakistan by Abbas et al. [1] on the efficacy and safety of a "rescue" therapy to cure *Helicobacter pylori* infection. Briefly, following a quadruple therapy including high-dose esomeprazole, bismuth salts, amoxicillin-clavulanic acid, and furazolidone, an 81% eradication rate was achieved at ITT analysis, with a side-effects incidence as high as 50%. The authors concluded that "it is reasonably well tolerated and is an effective second-line regimen" and even suggested it could be used as a first-line therapy. We have some concerns about these conclusions. First, following the first-line therapy, *H. pylori* eradication was achieved in 119 (67.6%) out of 176 enrolled patients. Consequently, 57 eradication failure patients were available instead of 52, as was reported. If all these patients received a second-line therapy, then both ITT and PP analysis should be accordingly calculated. Second, the reported side-effects incidence (up to 50%) would appear much higher than that observed following a simpler, 10-day levofloxacin-based second-line triple therapy, which is 18% in near 1,000 patients, with an 81% eradication rate [2]. Third, it has been claimed that drug cost is a cause for concern in developing countries [1]. However, esomeprazole is the most expensive proton pump inhibitor, and the dose used (40 mg b.i.d.) in this study was twice that widely suggested in the literature [3]. This markedly increased the overall therapeutic cost of eradication therapy, contrasting one of the aims of the study. In addition, when bismuth salts are administered with a high-dose of the proton pump inhibitor, bismuth toxicity may also be a cause for concern, since very high blood bismuth concentrations within the Hillemand alarm levels have been found in 9% of patients receiving a quadruple therapy, suggesting there should be more caution in prescribing bismuth salt with proton pump inhibitors [4]. Finally, some relevant ethical concerns arise with the use of furazolidone. This is an antibiotic that was used in the 1980s for parasitic infections, and some studies described its use in human subjects to treat *H. pylori* infection. In the 1990s, studies were published that raised several concerns about this agent and its potential for causing tumors. At the same time, the company that made the agent in the United States (Roberts Pharmaceuticals) was sold to Shire Pharmaceuticals, and the FDA withdrew its approval for furazolidone in March 2005. The drug was ordered removed even from animals as an antibiotic by the FDA in 2002. The FDA has subsequently sued companies that illegally imported the drug from Mexico for use in animals. Simultaneously, the European Medicinal Agency (EMEA; the equivalent of the FDA in the European Union) banned the drug in Europe. Although the drug continues to be available in some developing countries such as Iran, Pakistan, India, Mexico, and Brazil, a number of public and press campaigns from concerned individuals have urged governments to ban the drug in some of those countries. Therefore, can we consider a therapy including furazolidone as the authors declared as "safe"? Although it has been stated that the study was approved by the Ethical Committee, were patients informed of the possible genotoxic and carcinogenetic effects [5, 6] for which furazolidone is not currently approved by the FDA and EMEA?

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Reply

To the Editor,

We would like to thank Dr. Francesco, et al. for critically reading our article and take this opportunity to address their concerns. We felt that we should not include those patients in the analysis who could not be enrolled for the new regimen and did not receive even a single dose. Side-effects reported were mild and no one discontinued the treatment. The cost of esomeprazole is at par with other proton pump inhibitors in our country. We are aware of the concerns about the safety of furazolidone and bismuth compounds. The metabolites of nitrofuran drugs may have some carcinogenic effect in rodents, however, furazolidone has been extensively used and is still being used in humans [7–9] and we find no reports of such side-effects. We find a similar dilemma against nitroimidazoles in literature. In spite of the mutagenic, genotoxic, and carcinogenic activity of metronidazole in animal models [10, 11], the drug is still being used all over the world, not only as an anti-*H. pylori* agent but also for many other indications. There are more than 100 papers related to the use of nitrofuran drugs for *H. pylori* treatment [9]. In fact, the furan compounds are also being researched as anticancer agents [12]. Similarly, bismuth compounds are still a part of the alternate therapies for patients who fail to respond to classical triple therapy and are considered safe and well-tolerated agents [13]. However, we agree that in such trials there is a need to study the long-term safety of the compounds used.

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