

- rifaximin on platelet count. *Am J Gastroenterol* 2010;105:2705–7.
- Afdhal N, McHutchison J, Brown R *et al*. Thrombocytopenia associated with chronic liver disease. *J Hepatol* 2008;48:1000–7.
 - Giannini EG. Review article: thrombocytopenia in chronic liver disease and pharmacologic treatment options. *Aliment Pharmacol Ther* 2006;23:1055–65.
 - Calvet X, Navarro M, Gil M *et al*. Seroprevalence and epidemiology of *Helicobacter pylori* infection in patients with cirrhosis. *J Hepatol* 1997;26:1249–54.
 - Stasi R. Therapeutic strategies for hepatitis- and other infection-related immune thrombocytopenias. *Semin Hematol* 2009;46 (1 Suppl 2): S15–25.
 - Gasbarrini A, Gasbarrini G, Pelosini I *et al*. Eradication of *Helicobacter pylori*: are rifaximin-based regimens effective? *Digestion* 2006;73 (Suppl 1): 129–35.

¹Division of Gastroenterology, Department of Internal Medicine, University of Genoa, Genoa, Italy. Correspondence: Edoardo Savarino, MD, PhD, Di.M.I. Cattedra di Gastroenterologia, Università di Genova, Viale Benedetto XV, 16132 Genova, Italy. E-mail: edoardo.savarino@unige.it

Response to Savarino *et al*.

Georgios Kalambokis, MD¹ and Epameinondas V. Tsianos, MD, PhD¹

This letter underwent AJG editorial review.

doi:10.1038/ajg.2011.109

To the Editor: We appreciate the comments by Savarino *et al*. They suggested that *Helicobacter pylori* infection could be a cause of immune thrombocytopenia in cirrhotic patients and that rifaximin might have improved platelet counts in our study (1) by eradicating this infection (2). Indeed, the response to *H. pylori* infection may generate antibodies that crossreact with platelet antigens (3) and eradication therapy has been shown to increase platelet counts in patients with idiopathic thrombocytopenic purpura (4). However, the possibility that rifaximin treatment could have affected our results through its effects on *H. pylori* infection seems rather unlikely due to several reasons.

First, the prevalence of seropositivity to *H. pylori* infection in cirrhotic patients does not differ from that in the general population (5–7). Considering that only a minority of non-cirrhotic subjects will develop immune-mediated thrombocytopenia due

to *H. pylori* infection, the contribution of *H. pylori* infection to cirrhosis-associated thrombocytopenia is reasonably expected to be limited. By contrast, rifaximin increased platelet counts in 9 of 10 thrombocytopenic cirrhotic patients in our study (1). This suggests that rifaximin improved thrombocytopenia by suppressing other more common mechanisms capable of decreasing platelet counts in the setting of cirrhosis rather than immune mechanisms triggered by *H. pylori* infection. In this regard, the administration of rifaximin in cirrhotic patients has been shown to reduce significantly endotoxemia (8), which, according to our recently reported hypothesis, could negatively affect platelet counts in cirrhosis (9).

Second, thrombocytopenia worsens with progression of cirrhosis (10) whereas the seroprevalence of *H. pylori* infection has been reported to be unrelated to liver disease severity (3) or higher in early than in advanced cirrhosis (6). By contrast, endotoxin concentrations increase proportionally to the severity of cirrhosis (11).

Finally, rifaximin alone has been proved to be effective for *H. pylori* infection, but even the highest dose (1,200 mg/daily) give a cure rate of only 30%. Eradication rates obtained with dual and triple rifaximin-based regimens are still below the standard set by current guidelines (2). Another major drawback of rifaximin could be its inability to reach sufficiently high concentrations in the gastric mucus layer under and within which *H. pylori* is commonly located. This would likely affect eradication rate and particularly in patients with portal hypertension and congestion gastropathy (2).

We conclude therefore that eradication of *H. pylori* infection by rifaximin could not be a major determinant of the beneficial effects of rifaximin on platelet counts in cirrhotic patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- Kalambokis G, Tsianos EV. Thrombocytopenia associated with chronic liver disease: effects of rifaximin on platelet count. *Am J Gastroenterol* 2010;105:2705–7.
- Gasbarrini A, Gasbarrini G, Pelosini I *et al*. Eradication of *Helicobacter pylori*: are rifaximin-based regimens effective? *Digestion* 2006;73 (Suppl 1): 129–35.

- Cines DB, Liebman H, Stasi R. Pathobiology of secondary immune thrombocytopenia. *Semin Hematol* 2009;46:S2–14.
- Franchini M, Cruciani M, Mengoli C *et al*. Effect of *Helicobacter pylori* eradication on platelet count in idiopathic thrombocytopenic purpura: a systematic review and meta-analysis. *J Antimicrob Chemother* 2007;60:237–46.
- Calvet X, Navarro M, Gil M *et al*. Seroprevalence and epidemiology of *Helicobacter pylori* infection in patients with cirrhosis. *J Hepatol* 1997;26:1249–54.
- Schmulson MJ, De León G, Kershenovich A *et al*. *Helicobacter pylori* infection among patients with alcoholic and nonalcoholic cirrhosis. *Helicobacter* 1997;2:149–51.
- Brown LM. *Helicobacter pylori*: epidemiology and routes of transmission. *Epidemiol Rev* 2000;22:283–97.
- Vlachogiannakos J, Saveriadis AS, Viazis N *et al*. Intestinal decontamination improves liver haemodynamics in patients with alcohol-related decompensated cirrhosis. *Aliment Pharmacol Ther* 2009;29:992–9.
- Kalambokis G, Tsianos EV. Endotoxaemia in the pathogenesis of cytopenias in liver cirrhosis. Could simple antibiotics raise blood counts? *Med Hypotheses* 2011;76:105–9.
- Qamar AA, Grace ND, Groszmann RJ *et al*. Incidence, prevalence, and clinical significance of abnormal hematologic indices in compensated cirrhosis. *Clin Gastroenterol Hepatol* 2009;7:689–95.
- Lumsden AB, Henderson JM, Kutner MH. Endotoxin levels measured by a chromogenic assay in portal, hepatic and peripheral blood in patients with cirrhosis. *Hepatology* 1988;8:232–6.

¹First Division of Internal Medicine and Hepato-Gastroenterology Unit, University Hospital, Ioannina, Greece. Correspondence: Epameinondas V. Tsianos, MD, PhD, First Division of Internal Medicine and Hepato-Gastroenterology Unit, Medical School of Ioannina, University Hospital, 45110 Ioannina, Greece. E-mail: etsianos@cc.uoi.gr

High Prevalence of Significant Endoscopic Findings in Patients With Uninvestigated Typical Reflux Symptoms

Amit Kumar Dutta, DM¹, Ashok Chacko, DM¹, Avinash Balekuduru, DM¹, Manoj Kumar Sahu, DM¹ and Sajith Kattiparambil Gangadharan, DM¹

This letter underwent external review.

doi:10.1038/ajg.2011.54

To the Editor: We read with interest the article on prompt upper gastrointestinal endoscopy as an appropriate initial man-

Table 1. Comparison of demographic profile and BMI between the group with and without CSEFs

	CSEFs present (72)	CSEFs absent (494)	Univariate <i>P</i> ^a	Multivariate <i>P</i> ^b
Age >50 years	22 (30.6%)	109 (22.1%)	0.11	0.06
Males	48 (66.7%)	293 (59.3%)	0.23	0.1

BMI, body mass index; CSEFs, clinically significant endoscopic findings.
^aChi-square test.
^bBinary logistic regression.

agement in uninvestigated Chinese patients with reflux symptoms by Peng *et al.* (1) in the September 2010 issue of the *American Journal of Gastroenterology*. The authors reported clinically significant endoscopic findings (CSEFs) in 180 (38.4%) of the 469 patients in the study. The prevalence of CSEFs is surprisingly high, mainly owing to the high prevalence of erosive esophagitis (32.8%) in their patients.

We evaluated the prevalence of CSEFs in Indian patients presenting with reflux symptoms seen at our center during 2008. The patients had heartburn and/or acid regurgitation for more than 6 months, with absence of alarm symptoms. The total number of patients seen was 566 (39.8% female) and their mean age was 41 + 12.3 years. CSEFs were present in 72 (12.7%) patients. In all, 50 (8.8%) patients had erosive esophagitis. The severity according to Los Angeles classification was grade A in 31, B in 12, C in 4, and D in 3. Five patients had Barrett's esophagus. Peptic ulcer disease was present in 16 patients (nine gastric ulcers and seven duodenal ulcers), among whom three also had erosive esophagitis. Malignancy was seen in four, which included carcinoma stomach in three and carcinoma esophagus in one. The distribution of age and sex between patients with CSEFs and those without CSEFs is shown in **Table 1** along with the multivariate analysis. These two factors were not significantly different between the two groups.

Risk factors for CSEFs in Peng *et al.*'s study were age being more than 50 years, being male, obesity, alcohol consumption and *Helicobacter pylori* infestation (1). Older patients and male patients in our study had higher CSEFs, but the difference was not statistically significant. India is in the neighborhood of China and has

a similar *H. pylori* prevalence as Chinese population (2). A recent Chinese population-based study from Shanghai showed the prevalence of erosive esophagitis to be 12.5% in patients with symptomatic reflux (3). Alcohol consumption and obesity were not risk factors for erosive esophagitis in this study (3). Alcohol intake was a significant risk factor for CSEFs in Peng *et al.*'s study (1). However, even if we take off the 64 patients who consumed alcohol, 31.6% (128 out of 405) patients will have CSEFs, which is much higher than the data from the Shanghai study and our data. A previous report on ethnic differences in endoscopic esophagitis showed Indian patients to have higher prevalence of esophagitis than Chinese patients (4). In light of the above arguments, the high prevalence of erosive esophagitis in the Chinese study by Peng *et al.* is difficult to explain and may have population-selection bias. The authors' statement that these CSEF rates are reflective of the clinical practice in China seems inappropriate, as the population-based study from Shanghai significantly differs from their findings (3). Although a comparison of our own data with regard to proton pump inhibitor use, alcohol use, and body mass index could not be done owing to the retrospective nature of our study, the four-times-higher prevalence of erosive esophagitis in Peng *et al.*'s study (32.8%) compared with ours (8.8%) may be too high to be attributable to these factors alone. Therefore, the generalizability of these findings to Asian patients or even the Chinese population should be made with caution.

CONFLICT OF INTEREST

Guarantor of the article: Ashok Chacko, DM.

Specific author contributions: Amit Kumar Dutta was involved in concept of

study/letter, data analysis, and manuscript preparation. Ashok Chacko was involved in data analysis, manuscript preparation, and critical appraisal. Avinash Balekuduru, Manoj Kumar Sahu, and Sajith Kattiparambil Gangadharan were involved in data collection and manuscript preparation.

Financial support: None.

Potential competing interests: None.

REFERENCES

- Peng S, Xiong LS, Xiao YL *et al.* Prompt upper endoscopy is an appropriate initial management in uninvestigated Chinese patients with typical reflux symptoms. *Am J Gastroenterol* 2010;105:1947–52.
- Mishra S, Singh V, Rao G *et al.* Prevalence of *Helicobacter pylori* in asymptomatic subjects—a nested PCR based study. *Infect Genet Evol* 2008;8:815–9.
- Zou D, He J, Ma X *et al.* Epidemiology of symptom-defined gastroesophageal reflux disease and reflux esophagitis: the Systematic Investigation of Gastrointestinal Diseases in China (SILC). *Scand J Gastroenterol* 2010; 46:133–41.
- Rajendra S, Kutty K, Karim N. Ethnic differences in the prevalence of endoscopic esophagitis and Barrett's esophagus: the long and short of it all. *Dig Dis Sci* 2004;49:237–42.

¹Department of Gastrointestinal Sciences, Christian Medical College and Hospital, Vellore, Tamil Nadu, India. Correspondence: Ashok Chacko, DM, Department of Gastrointestinal Sciences, Christian Medical College and Hospital, Vellore, Tamil Nadu 632 004, India. E-mail: gastro@cmcvellore.ac.in

Reply to Dutta *et al.*

Sui Peng, MD¹, Ying-Lian Xiao, MD¹ and Min-Hu Chen, MD¹

This letter underwent AJG editorial review.

doi:10.1038/ajg.2011.57

To the Editor: We would like to thank Amit Kumar Dutta *et al.* (1) for their comments on our article (2). We also read with interest the new data presented by Dutta *et al.* on the prevalence of clinically significant endoscopic findings (CSEFs) in Indian patients presenting with reflux symptoms but without alarm symptoms. In response to their question about the “surprisingly” high prevalence (38.4%) of CSEFs observed in our study, we must first make it clear that the data we presented represent what we observed in our population.

We agree that the high prevalence of CSEF is due mainly to the high prevalence (32.8%) of erosive esophagitis (EE) in our study, and this prevalence is well in line with previously reported data for Chinese patients in Singapore (30.0%) (3) and Hong Kong (58.0%) (4). We agree with Dutta *et al.* that in both India and China there is a high prevalence of *Helicobacter pylori* infection, which has been established as a definite etiological factor for gastric cancer. However, the incidence of gastric cancer is significantly higher in China than in India. In fact, the incidence of gastric cancer varies even within the Chinese population living in different regions. Similarly, it is conceivable that the prevalence of EE also varies among different regions in China. We believe that the difference in the prevalence of EE is due to a combination of factors, including racial preferences for ethnic differences, alternative lifestyles, and ethnic variations in health-seeking behavior, although the population selection bias in the studies, as suggested by Dutta *et al.*, cannot be ruled out.

It is important to note that our study was not intended to determine the prevalence of CSEFs in the general population, as mentioned in the letter (5), but was designed to reflect the daily clinical practice in a tertiary hospital in China. The patients studied in our practice represented a broad mix of patients with upper GI symptoms and conditions and most of them were uninsured or underinsured. We believe that these rates correctly reflect Chinese daily clinical practice because almost all tertiary hospitals in China are open-access settings and provide primary-, secondary-, and tertiary-level care. Of course, this category of clinical practice in China has unique features, which probably make the data difficult to be generalized to other countries. However, Chinese gastroenterologists can use this information to assist in the decision-making process that at present is based largely on conjecture.

Interestingly, Dutta *et al.* also note that CSEFs other than gastroesophageal reflux disease, such as gastroesophageal carcinoma (0.7%) and peptic ulcer disease (2.8%), are present in a considerable proportion of their patients with reflux symptoms but without

alarm features. These observations, echoing our findings, are clinically significant for two reasons: they indicate that the diagnostic accuracy of hallmark symptoms alone is not as high as might be thought and that prompt endoscopy may be an appropriate initial management option in these patients, particularly given its low cost in some countries.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Dutta AK, Chacko A, Balekudur A *et al.* High prevalence of significant endoscopic findings in patients with uninvestigated typical reflux symptoms. *Am J Gastroenterol* 2011;106:1172–3 (this issue).
2. Peng S, Xiong LS, Xiao YL *et al.* Prompt upper endoscopy is an appropriate initial management in uninvestigated Chinese patients with typical reflux symptoms. *Am J Gastroenterol* 2010;105:1947–52.
3. Ho KY, Gwee KA, Khor CJ *et al.* Empirical treatment for the management of patients presenting with uninvestigated reflux symptoms: a prospective study in an Asian primary care population. *Aliment Pharmacol Ther* 2005;21:1313–20.
4. Wu JC, Chan FK, Ching JY *et al.* Empirical treatment based on “typical” reflux symptoms is inappropriate in a population with a high prevalence of *Helicobacter pylori* infection. *Gastrointest Endosc* 2002;55:461–5.
5. Zou D, He J, Ma X *et al.* Epidemiology of symptom-defined gastroesophageal reflux disease and reflux esophagitis: the systematic investigation of gastrointestinal diseases in China (SILC). *Scand J Gastroenterol* 2011;46:133–41.

¹Division of Gastroenterology and Hepatology, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China. Correspondence: Min-Hu Chen, Division of Gastroenterology and Hepatology, The First Affiliated Hospital of Sun Yat-Sen University, 58 Zhongshan Road II, Guangzhou 510080, China. E-mail: chenminhu@vip.163.com

Antibiotics and Oral Contraceptive Efficacy in Inflammatory Bowel Disease

Ann Flynn, MD¹ and Sunanda Kane, MD, MSPH, FACG²

This letter was reviewed externally.

doi:10.1038/ajg.2011.55

To the Editor: Antibiotic therapy is prescribed to patients with Crohn’s disease for

management of conditions including perianal disease, infectious complications such as abscess and perforation, active luminal disease, and small-bowel bacterial overgrowth. When filling prescriptions, female patients may be counseled that the efficacy of their oral contraceptive can be compromised by the antibiotic therapy. It appears to be a commonly asked question at several websites (1). We performed a review of the literature to assess the evidence for this information and formulate a rational guideline for patients with inflammatory bowel disease receiving concomitant oral contraceptives and antibiotic therapy.

The failure rate of oral contraceptives is 0.1% with perfect use. However, a 3% failure rate is estimated with typical use. Concern regarding loss of contraceptive efficacy with antibiotic administration initially arose when a high incidence of unplanned pregnancies was noted among women receiving treatment for tuberculosis. A decrease in plasma hormone levels in women taking oral contraceptives and rifampin was noted, resulting from cytochrome P450 CYP3A induction (2). Decreased contraceptive efficacy was later demonstrated with other cytochrome P450 CYP3A inducers, including anti-convulsants such as carbamazepine.

Excluding rifampin, antibiotics are not known to be inducers of cytochrome P450 CYP3A. However, retrospective survey studies from family planning and abortion clinics have shown that 20–23% of reliable oral contraceptive users seeking care in clinics for unplanned pregnancy report concomitant antibiotic use during the cycle in which they became pregnant (3). These data contrast with retrospective studies performed in outpatient dermatology and obstetrics practices, which identified oral contraceptive failure rates of 1.2–1.6% in patients taking concurrent antibiotic therapy, rates that do not differ significantly from the expected oral contraceptive failure rate with typical use (3). These retrospective studies remain subject to significant recall bias.

Small, prospective studies and systematic reviews have also been completed. Multiple studies have followed steroid levels in patients on oral contraceptives with and without antibiotic therapy. Sig-