A novel hybrid first-line therapy for *H. pylori* eradication: results of a pilot study

To the Editor,

*Helicobacter pylori* (*H. pylori*) eradication remains challenging in clinical practice. Current European guidelines recommend bismuth-based quadruple therapy for 10-14 days in geographic areas with a high prevalence of primary antibiotic resistance (> 20% for clarithromycin, or > 40% for metronidazole, or > 15% for dual resistance), such as Italy [1]. However, a large number of tablets are required for this therapy administered for 10-14 days: indeed, as many as 14 capsules daily are necessary, even if using the Pylera® package (bismuth subcitrate potassium 140 mg, metronidazole 125 mg, and tetracycline 125 mg). Moreover, some trials found that Pylera® causes side-effects leading to an earlier interruption more frequently than other regimens [2-4]. A shorter quadruple regimen might decrease the side-effects, but the efficacy might be reduced. Therefore, by loaning the concept of sequential therapy [5], a short course of amoxicillin-based dual therapy could prevent efficacy reduction of a short course of Pylera® therapy.

Since this is a prospective, open-label, pilot study, a total of 30-40 patients are sufficient [6]. Consecutive adults complaining of dyspeptic symptoms referred for upper endoscopy between February and November 2018 were considered for recruitment into the study. Patients diagnosed for the first time with *H. pylori* infection at the histological assessment of gastric mucosa were invited to participate. A 10-day hybrid therapy with esomeprazole 40 mg and amoxicillin 1 g, both b.i.d, was administered for the first 5 days, followed by esomeprazole 40 mg b.i.d. and Pylera 3 tablets q.i.d (after breakfast, lunch, dinner and before bedtime) for the following 5 days. Patients were instructed that the possible darkness of stools as well as the metallic taste during therapy were clinically irrelevant. At the end of the treatment, patients were invited for a visit to assess the compliance to therapy and the incidence of side-effects by a personal interview. Bacterial eradication was checked 6-8 weeks after treatment by using a $^{13}$C-urea breath test (UBT).

A total of 40 patients (mean age: 57.6 ± 12.1 years; M/F: 20/20; non-ulcer dyspepsia/peptic ulcer: 38/2; smoking/no smoking: 10/30, with mean BMI of 22.2±2.4) not previously treated for the infection were enrolled. One patient was lost to follow-up and was considered as drop-out since no information on therapy was available. The *H. pylori* infection was cured in 39 patients accounting for 97.5% (95% CI = 92.6-100) eradication rate at intention to treat (ITT) and 100% eradication rate at per protocol (PP) analyses. Patient compliance was good (consumption of prescribed drugs >90%) for all but one patient who took therapy for 8 days due to the onset of severe asthenia. The infection was successfully cured also in this case. A total of 5 out of 39 (12.8%) patients complained of side-effects (epigastric pain: 1; abdominal pain: 3; severe asthenia: 1 requiring therapy interruption). Finally, the therapy cost was 48.4 euros/patient.

This study demonstrated that a novel hybrid therapy with a 5-day dual therapy followed by a 5-day Pylera therapy was able to achieve a very high eradication rate as first-line therapy for *H. pylori* infection. This was a relevant result when considering that the cure rate of standard eradication therapies is decreasing worldwide. The high efficacy of this novel therapy regimen may depend on at least three factors. First, amoxicillin administration in the first therapy phase acts on bacterial wall hampering trans-membrane antimicrobial excretion (by efflux pumps, porins etc), as highlighted for standard sequential therapy [7]. Second, this regimen includes amoxicillin and tetracycline, instead of clarithromycin; that is two agents with a very low level of resistance in *H. pylori* strains. Third, it includes a total of four antimicrobial agents (amoxicillin, tetracycline, metronidazole and bismuth salts), instead of three antibiotics, as in either standard sequential or Pylera therapies. Another potential advantage of this therapy could be the safe use of high-dose (40 mg b.i.d.) esomeprazole even in the second therapy phase. Indeed, the very short (5 days) duration of Pylera therapy would prevent the potential...
toxic effect of increased bismuth absorption due to the high-dose esomeprazole [8].

In conclusion, the proposed hybrid first line therapy achieved a very high eradication rate with good patient’s compliance and acceptable costs in this pilot, single center study. Therefore, a larger and multicenter study is urged to confirm these results.

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Ultrasonographic assessment of Crohn’s disease patients: can be easier and more affordable for clinical practice?

To the Editor,

We read with interest the study published by Ilias et al. [1] regarding the impact of fast-track magnetic resonance imaging (MRI) on the management of patients with Crohn’s disease (CD). Their study showed that MRI was useful for a better therapeutical decision (surgery or medical) in patients with active CD, as the MRI findings correlated well with clinical and biomarker activity. Current guidelines recommend cross-sectional imaging (MRI, computer tomography, intestinal ultrasound) and laboratory markers such as C-reactive protein (CRP) besides gold standard endoscopic assessment in managing Crohn’s disease (CD) patients [2]. As opposed to MRI, intestinal ultrasound (IUS) is an inexpensive imaging technique that is becoming increasingly used in managing CD patients. Intestinal ultrasound imaging has proved to have a high sensitivity and specificity in assessing disease activity (92% and 100%, respectively) [3]. A high concordance between IUS and colonoscopy (kappa 0.76 - 0.9) for assessing disease activity and drug response has been proven [4]. Recently, Allocca et al. [3] found also an excellent agreement between IUS and MRI (k=0.84) and significant correlation of disease extension measured by both imaging techniques [3]. Bowel wall thickness (BWT) correlated well with inflammatory syndrome estimated by C reactive protein (CRP) and erythrocyte sedimentation rate (r=0.586 and r=737, respectively, p<0.001) [5].

We would like to present our study conducted in order to evaluate the correlation between IUS luminal activity, measured by BWT, biochemical activity (CRP) and clinical activity (CDAI). Sixty-two patients with confirmed diagnosis of CD (endoscopic and histologic) were ultrasonographically examined by a single operator using a Hitachi Preirus machine and a micro-convex probe (4-8MHz). Intestinal ultrasound evaluated bowel wall thickness and loss of wall structure in the corresponding regions according to endoscopic observations. The cut-off value for normal BWT was considered 3 mm. Data regarding age, disease extension, CRP levels were collected and CDAI was calculated for each patient.

The median age at diagnosis was 34.7 years, with a slight male predominance (54.8%). The majority of patients (27, 43.5%) had an ileo-colonic extension of the disease; 23 (37%) had colonic involvement and 12 (19.3%) had ileal lesions. From the entire cohort, 38 (61.3%) patients had abnormal values of BWT and 18 (29%) had severe alteration of the bowel wall structure. In these patients, 17 (94.4%) had severe disease based on the CDAI score and 15 (8%) had CRP levels higher than 10 mg/dl. Our computed data were similar to those noted by Ilias et al. [1]. Intestinal ultrasound activity correlated with both clinical activity and biomarker positivity (CRP >10mg/L). The correlation with CDAI was moderate with a kappa value 0.679 (p<0.005), similar to that obtained by Ilias et al. The correlation with C-reactive protein was lower (k=0.469, p<0.005). Correlating both CDAI and CRP protein we obtained a kappa value of 0.518, p<0.005). Correlating both CDAI and CRP protein we obtained a kappa value of 0.518, p<0.005.

Considering the advantages of the technique (availability, low cost) together with the presented personal and literature data, we propose IUS to become the technique of choice in evaluating CD patients, prior to other cross-sectional imaging procedures.

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Reply,

To the Editor,

Thank you for your comments on our recently published article: „Optimizing patient management in Crohn’s disease in a tertiary referral center: the impact of fast-track MRI on patient management and outcomes” in Journal of Gastrointestinal and Liver Diseases [1]. We agree with Les et al. comments on the unquestionable advantages of intestinal ultrasound (IUS). Quicker availability of ultrasound helps everyday clinical decisions also in our practice, especially in acute situations.

Regarding ECCO diagnostic guidelines of Crohn’s disease, small bowel imaging should be performed in every newly diagnosed CD patient. Based on local availability and expertise, magnetic resonance (MR) enterography, intestinal ultrasound (IUS) or capsule endoscopy can be chosen [2]. According to a systematic review, published in 2011 by Panes et al. [3] IUS is an accurate, widely available, non-invasive diagnostic technique for suspected CD and for evaluation of disease activity (sensitivity 0.84, specificity 0.92). Magnetic resonance imaging also has a high diagnostic accuracy, better in the imaging of proximal bowel and for evaluation of disease extension and activity (sensitivity 0.93, specificity 0.90) [3]. Another advantage of MR enterography is that it is less operator-dependent and disease location might be better assessed compared to IUS [2].

Intestinal ultrasound can show similar accuracy to MR enterography in detecting small bowel CD, but is less accurate in defining the extent of CD and detection of enteroeiectric fistulas [4]. Good concordance between IUS and MR enterography for disease location has been reported [5]; but some studies’ results suggested false positive results of IUS for abscesses [3]. In patients with severe, complicated CD (e.g. fistulas or perianal involvement) the need of a more detailed imaging evaluation is essential and MR enterography can be more helpful for therapeutical decisions specially in tertiary referral IBD centers as ours.

Moreover, the ECCO-ESGAR diagnostic guideline defines MR enterography as the most accurate imaging modality for perianal CD [2], and in the assessment of response to biological therapy. Different studies that compared MR enterography with endoscopy as a reference standard showed a high accuracy for diagnosis and therapeutic monitoring [7, 8]. Magnetic resonance enterography has a high accuracy for the prediction of endoscopic mucosal healing, and is a reliable indicator to monitor the use of TNF antagonists in patients with CD [6-8].

We believe that MR enterography is more accurate in assessing the extent and severity of lesions, which are important aspects in the long-term management of patients with severe, complicated CD.

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A difficult path in the management of irritable bowel syndrome: from general recommendations to clinical reality

To the Editor,

Irritable bowel syndrome (IBS) has been the subject of interesting articles and debates in your journal [1–3], adding important contributions to the management and treatment of this medical condition. A simplified algorithm for clinical practice of IBS diagnosis and management was published by European experts [4]. In general, medication is targeted towards the patient’s predominant symptoms: constipation, diarrhea, abdominal pain. This approach is physiologically justified, but its efficacy is limited. There are no firm criteria for treatment approach and duration. Although new drugs have entered in the clinical practice such as: chloride channel stimulators (lubiprostone), guanylate cyclase agonists (linaclotide), locally active mixed μ- and κ-opioid receptor agonist and δ-opioid receptor antagonist (eluxadoline), they are not permanently available and their efficacy has not been proved. The cultural role in IBS should not be ignored within the etiology and treatment approaches [5].

The purpose of this letter is to raise awareness for the necessity of a standardized IBS management for Romanian patients elaborated by our National Society of Gastroenterology. This approach is supported by the particularities of the Romanian healthcare system, the availability and the costs of the new treatments, the patient’s preferences and expectations. A customization of the IBS management is required, as there is a category of patients with different perceptions of their health status, which use old folklore remedies, that further affect the natural history of IBS [5].

Most authors recommend therapy towards the dominant bowel symptom [4]. Unfortunately, the large number of IBS mixed cases in the Romanian cohort make this approach unusable. Antispasmodics remain the first-line therapy for abdominal pain in IBS patients. Antispasmodics include several different classes of drugs such as smooth muscle relaxants, anticholinergic agents and calcium channel blockers. One of our previous articles pointed that antispasmodics were suitable for long-term treatment, as well as for short-term and single use. Mebeverine relieved IBS symptoms by reducing the intensity of the abdominal pain, the flatulence and the disturbed bowel movements, thus having a significant improvement in the life quality of the patients [2].

Cognitive behavioral therapy (CBT) is focused on replacing the maladaptive coping strategies by positive ones. Cognitive behavioral therapy has proved to be efficient in reducing the symptoms in IBS, post-treatment and in short-term follow-up [3]. Radu et al. [1] demonstrated that 52% of the overall effect of CBT was mediated by changes in cognition, emotion and behaviour.

An optimal approach for IBS management is to combine interventions adapted to specific patients’ conditions. The evaluation of a patient should detail the risk factors and the cultural background. The patient’s expectations and habits should be respected. The association of the pain treatment (preferably antispasmodics) with CBT must be provided by competent personnel.

This strategy is not opposed to the recommendations resulting from the advancement of the scientific research. It proposes a gradual patient approach adapted to the clinical reality. This patient-oriented management combines quality evidence with the clinical difficulties of IBS treatment.

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Reply,

To the Editor,

We totally agree with the opinions expressed by L. Nedelcu on our paper about CBT in IBS [1]. It is true that progress in the management of IBS is slow and frequently disappointing [2]. Therefore, the use of psychotherapy represents a good
alternative or a complement to pharmacological therapy and lifestyle changes advice [1, 3]. The suggestion to work on a national guideline is welcome. It is true that in this country there is an interest in standardizing therapeutic possibilities for IBS [4], but a national guidelines paper is still due, using the internationally available guidelines as a model and adapting to local conditions [5,6]. We thank L. Nedelcu for his suggestions and look forward to his future contributions to a common nationwide project.

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