Letters to the Editor

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Which severity indices for *Clostridium difficile* infection

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I read with great interest the recently published article by Balihar *et al.* [1] in which the authors aimed to characterize epidemiology and clinical manifestations of *Clostridium difficile* infection (CDI) in a Czech tertiary care center and to identify risk factors of fulminant course. They concluded that severe CDI was identified in 15.8% of patients. Moreover, they identified risk factors for severe CDI including old age, abnormal physical findings on abdominal examination, higher leukocyte count, higher C-reactive protein and creatinine level, and lower level of albumin. However, I think that there are some points that should be emphasized about the study.

C. difficile is the most common cause of hospital-acquired diarrhea, affecting 10% of all hospital admissions [2]. Early identification of potentially severe CDI is important for the assessment of patient management options, both medical and surgical. There are two different severity indices used in Europe and the USA to identify severe cases of CDI. According to the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), severe CDI is defined as an episode of CDI with severe colitis or a complicated course of disease, with significant systemic toxin effects and shock, resulting in need for ICU admission, colectomy, or death. CDI without signs of severe colitis in patients with greater age (≥65 years), serious comorbidity, ICU admission, or immunodeficiency may also be considered at increased risk of severe CDI [3]. In contrast, severe CDI was defined by the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America (SHEA/IDSA) guidelines as an episode of CDI with either a marked leukocytosis or a rise in serum creatinine [4].

In the current article authors used ESCMID definitions to identify severe CDI and severe CDI was identified in 15.8% of patients, with 62% mortality. However, in a retrospective cohort study Starzengruber *et al.* [5] noted that up to 84.5% of CDI cases would have been classified as severe CDI according to ESCMID. If severity was defined according to SHEA/IDSA guidelines only 16.5% could be classified as severe. Moreover, being a severe case according to SHEA/IDSA was significantly associated with a higher probability of death. Identifying severe CDI is critical because use of insufficient clinical prediction scale may led to a bias in patient selection. According to the results of the article it can be said that the SHEA/IDSA definition for severe CDI is more reliable in comparison with the ESCMID definition.

In conclusion, the SHEA/IDSA guidelines should be used to predict severe CDI in critically ill patients. They include a uniform, readily available set of criteria that are easily applicable in the clinical setting and have been supported by previous studies.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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OPEN Accuracy of the GastroPanel test in the detection of atrophic gastritis

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We read with concern the paper of McNicholl *et al.* [1] on the accuracy of GastroPanel (GP) in the diagnosis of

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atrophic gastritis (AG). The major conclusions of the paper are in sharp contrast with the earlier literature [2–6] and the most recent international consensus statements. The skewed GP results reported in the study [1] could be due to any or all of three main reasons: (a) poor laboratory techniques; (b) misclassification bias of the study endpoint (AG); and (c) inadequate statistical power ($n = 85$, 10 with AG).

First of all, it should be noted that the 'Biohit-Deltaclon GastroPanel's Lab' in Spain, where the authors reported their analyses had been carried out [1], has no contract in force with Biohit Oyj (Helsinki, Finland), and accordingly no rights to use either the name Biohit or GastroPanel in this context. It is emphasized that the GP test (Biohit Oyj) is an enzyme-linked immunosorbent assay test and has not been optimized (or even tested) by the manufacturer for use as a chemiluminescent enzyme immunoassay [1]. This type of technical modification inevitably entails that the manufacturer-recommended cutoff values are not valid in the new application. Chemiluminescent assay should have been validated against the reference GP test to confirm the appropriateness of the cutoff values that the authors have used (Figure 1) [1]. Even minor deviations from the appropriately validated cutoff values in a study with a limited number of cases (only 10 with AG) would lead to markedly distorted results.

Plasma pepsinogen I (PGI) levels and severity of AG show a practically linear relationship [2–5]. PGI levels less than 25 μg/l and PGI/PGII ratio less than 3.0 are consistent with moderate or severe AG of the corpus [3]. Therefore, it is surprising that the mean serum level of PGI for patients with AG of the corpus reported in this study is 101 μg/l (Table 1) [1]. On the basis of extensive clinical series, such PGI values are impossible in patients with biopsy-confirmed moderate or severe AG of the corpus [2–6].

The GP test is optimized to be used in context with the Updated Sydney System (USS) for classification of gastritis [2,6]. The five diagnostic categories – (a) normal mucosa, (b) superficial gastritis, (c) atrophic antrum gastritis, (d) atrophic corpus gastritis, and (e) atrophic pangastritis – are common to both the GP test and the USS, which enables direct assessment of their concordance using, for example, weighted κ (intraclass correlation coefficient) testing. When this is done in an adequately powered study based on validated USS classification, an interassay (GP-to-USS) agreement is usually in the range of 0.7 to greater than 0.8 (substantial to almost perfect) [2,6]. This information on the overall test agreement was missing in the present report [1]. The lack of this key information invalidates the correct interpretation of the GP results and also precludes any meaningful calculations on GP performance as an indicator of the AG (study endpoint).

Mild AG of the corpus should never be used as the study endpoint in calculating the performance indicators of the PGI, PGI/PGII, as repeatedly emphasized [2–6]. This fact has been neglected in the present study, in which the GP cutoff values presented in Figure 1 algorithm are indicated for AG in general and not stratified according to the grade of AG [1]. The only appropriate way of calculating the predictive indicators of PGI and PGI/PGII ratio for AG of the corpus is to use the combined moderate/severe AG as the study endpoint. This approach in an adequately powered study with validated USS classification gives receiver operating characteristic (area under the curve) values above 0.970 for PGI and greater than 0.950 for the PGI/PGII ratio [2–6].

Another unique feature of the GP test is the interpretation of the results by specific software (GastroSoft Biohit Oyj, Helsinki, Finland), which is almost mandatory in their correct interpretation. The authors did not report using GastroSoft in their study [1].

The role of the G-17 biomarker is more complex. Low levels of G-17 are not exclusively inherent to antral AG, but may also reflect high gastric acid output, whereas high volumes may result from the use of proton pump inhibitors [2,7,8]. In fact, the use of G-17 is not recommended by the GP manufacturer for the diagnosis of antral AG.

Finally, in a study including only 10 patients with (unclassified) AG in a clinical setting, one cannot draw any conclusions whatsoever on the use of the GP test in a screening setting. Such a setting would necessitate an adequately powered cohort of population-derived (asymptomatic) individuals, all being tested by GP, with all test positives (and random 5% of test negatives) to be confirmed by gastroscopy and validated biopsy classification, and, importantly, all performance indicators being corrected for verification bias by special statistical treatment.

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Conflicts of interest

There are no conflicts of interest.

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Response to: Misleading results in the diagnosis of atrophic gastritis

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We wish to thank Professor Di Mario for his comments [1] on our published work on the accuracy of GastroPanel for the diagnosis of atrophic gastritis [2]. However, we would like to clarify for the readers, with reasoned arguments, some of his comments.

First, we would like to clarify for Professor Di Mario that the 'multicentre' nature of a study, obviously, does not depend on the total number of patients included – much less the number per centre – but on the participation of various centres, as it is the case of our study. As Professor Di Mario seems to indicate in his letter, the sample size of our study is limited and cannot provide a definite answer to the potential usefulness of serology for the diagnosis of gastric atrophy for all settings, but it is enough to fulfil the aim of the study, the validation of GastroPanel in a routine clinical practice setting in Spain. Even Professor Di Mario cites as an acceptable reference the validation study by Rugge *et al.* [3], which included only three patients more than our study.

Professor Di Mario's letter criticizes the lack of evaluation of the severity of histological alterations; however, this is not the case of our study, in which a blinded expert pathologist evaluated the severity of alterations using the modified Sydney system. Concerns are also raised on the proton pump inhibitor treatment; we agree that antisecretory treatment may affect the usefulness of the serologic panel, but as discussed in our article, the usefulness of a method depends on its practicality on clinical routine, in which most upper-gastrointestinal endoscopy patients are under antisecretory treatment. In any case, only 5% of the study patients were under proton pump inhibitor treatment.

It appears that Professor Di Mario's main concern with our study is that our results contradict 'all' previously published literature. However, any updated bibliographic search would show that this debate is not as clear or as finished as some would like us to believe. For example, even Rugge and colleagues, in the study mentioned by Professor Di Mario, only reaches sensitivities of 77 and 85% (with specificities of 67 and 80%), which means that ~20–30% of patients would be misdiagnosed. Masci *et al.* [4] obtained similar results in another study (sensitivity of 83%), which led them to conclude that pepsinogen serology could not reflect the severity of lesions. Zhang *et al.* [5], on evaluating 282 individuals, concluded that the pepsinogen I/pepsinogen II ratio could not distinguish atrophic gastritis from both nonatrophic gastritis and early gastric cancer. Hosseini *et al.* [6], in their study, including 132 patients, obtained areas under the receiver operating characteristic curve below 0.65. Finally, Shafaghi *et al.* [7], evaluating a series of 1390 patients, could not achieve acceptable accuracies (area under the receiver operating characteristic curve < 0.70), and using the best cutoff points, only reached sensitivities of 82% (with an associated specificity of 64%). These are just some of the latest published studies questioning the validity of pepsinogen measurement for the diagnosis of histological alterations that any bibliographic search and critical reading would identify.

In any case, contradiction of the previous literature is not, by itself, a sign of invalidity of results or conclusions; on the contrary, conflicting data and rejection of past theories are the basis of science. Moreover, a major bias in publication could be created if studies contradicting recommendations or previously published data were systematically negatively evaluated. Adding this bias to the already existing (and well demonstrated) bias towards 'positive results publications' would cause an image distortion of the real experience gained by research groups and science worldwide. We expect our study to increase debates on the subject, and allow the final recommendations on this subject to evaluate not only the biased positive results but the full picture.

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Conflicts of interest

There are no conflicts of interest.

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