## The epidemiology of *Clostridium difficile* infection in Romania: what we know, or do not know and why?

**To the Editor,**

We read with interest the recent article by Lupse et al [1] and we would like to make a few comments. The authors evaluated the predictors of a first recurrence in *Clostridium difficile* infection (CDI) and found that 20% of their patients had recurrent infection, and the risk of first recurrence was significantly higher in those older than 70 who also received proton pump inhibitors; these results are in accordance with the literature data. Though we agree with most of the authors' comments, there are some points where we are of a different opinion.

Firstly, the authors stated that their study is "the first on CDI epidemiology in Romania" and that they "observed an increase in CDI cases in Romanian hospitals as well as worldwide". But their study is not an epidemiological one, as they reported the number of patients admitted during 22 months and made no comparison with a similar previous period to see whether CDI incidence really increased, and more important, to what degree. Is CDI more frequent in our country, or just better diagnosed? Do we know the real dimensions of CDI in Romania? As epidemiological studies regarding the incidence of CDI in our country are lacking, we fear that there appears to be more questions than answers.

Secondly, we all know that, over the last decade, CDI has increased worldwide both in incidence and severity, and this is clearly proved by many well performed epidemiological studies [2]. Most likely, the same trend has been present in our country, even if to a lesser extent, but most cases were underdiagnosed, either because of low levels of awareness for CDI among clinicians or misdiagnosed in the absence of sensitive diagnostic tests. Illustratively, in our institution, after the first case diagnosed with pseudomembranous colitis in 2011 [3], number of tests ordered for *C. difficile* by our physicians and, subsequently, patients diagnosed with CDI have significantly increased.

Thirdly, we do not know the real dimension of CDI in Romania, and we will not know it until well-designed epidemiological studies are carried out. With the exception of some case-reports [3, 4], we were unable to find one single epidemiological study concerning CDI. There is, however, one hospital-based survey regarding CDI in Europe, in which 5 Romanian hospitals participated together with 97 hospitals from 34 European countries [5]. Results are certainly not representative for CDI incidence in Romania, but illustrate the lack of awareness; thus, only 3 Romanian patients per 10,000 patient-days were tested as compared with 38 from Hungary, 115 from the UK, or 141 from Finland.

Watery diarrhea is the cardinal symptom in CDI and, therefore, if this symptom is present, especially in relation with the use of antibiotics, CDI must be suspected and any physician should ask a stool test for *C. difficile*. As we already mentioned, there has been a low level of awareness for CDI among our physicians, and this situation could be improved by implementing the recommendations of current guidelines [6]. It should be underlined that other countries too have been confronted in the past with the same low level of suspicion regarding CDI [7, 8]. Thus, in the USA, 69% of internal medicine residents were not aware of the existence of CDI in outpatient settings and would not test for this infection [8].

Finally, we may conclude that fighting this pathogen termed *C. difficile* is difficult, but we can achieve success only by increasing clinical suspicion for CDI in patients with unexplained watery diarrhea, systematically implementing guidelines in our routine clinical practice, as well as supporting education at a wide level.

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## Reply,

We are thankful to Trifan and collaborators for their interest in our recently published study and their comments.

Epidemiology of *C. difficile* infection is a matter of debate everywhere across Europe. Although surveillance of *C. difficile* infection in Europe is now a requirement of the European Commission, reporting it is not standardized or mandatory [1]. *C. difficile* infection is not a reportable condition in Romania and there are no national epidemiological data. Starting with 2013, the National Center for Surveillance and Control of Transmissible Diseases introduced a strategy to reduce the incidence of *C. difficile* infection in Romanian hospitals [2]. Before publication of our study [3], no information regarding the dimension of the problem in Romania was published. The Romanian hospitals referred in the article by Bauer et al were not hospitals of infectious diseases, in contrast with our hospital, so that relevant data for the epidemiology of the disease are lacking [4]. We reported 306 patients treated over 22 months, i.e. an average of 14 patients per month in a population of 691,100 of Cluj County (2011 census), suggesting an incidence of 24.15 per 100,000 population. The study was not intended to be an epidemiological study, but instead to present the characteristics of *C. difficile* infection in Romania concerning gender, age distribution, risk factors, treatment and outcome as well as the factors predicting recurrence of the disease.

As we have been testing for *C. difficile* toxins A and B for more than 5 years, we also observed a significant increase of cases in the last 2 years, related to small outbreaks. Whether the trend in our hospital is representative for Romania is difficult to say but, for sure, as Trifan and colleagues mentioned, the awareness for this disease has increased.

Regarding the clinical presentation of *C. difficile* infection, we should always be aware of the risk factors for the disease. The clinical symptoms and signs of infection with toxin-producing strains of *C. difficile* range from symptomless carriage to mild or moderate diarrhea, and to fulminant and sometimes even fatal pseudomembranous colitis. Expensive laboratory diagnostic tests, longterm antibiotic treatment, high mortality and recurrence rates are responsible for increasing hospital costs. Obviously, more important than diagnosis is the prevention of the disease.

We hope to come forward with more information on the epidemiology of the disease by collaborating with other Romanian hospitals, as we are in total agreement with Trifan and colleagues that implementation of guidelines and an increase of the level of awareness for this disease are mandatory in the clinical practice.

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## Fibrin-glue-sealed liver biopsy: indications, complications and results

**To the Editor,**

Liver biopsy is a key diagnostic tool for many patients with known or suspected liver disease. It is considered a relatively safe procedure, with a complication rate between 0 and 5.3% according to published studies [1]. Mortality is also very low, not exceeding 0.5% in any of the series analyzed [1-3]. Patients at increased risk of developing complications are those with coagulation disorders, platelet dysfunction or ascites. To reduce morbidity and mortality rates in these cases, different strategies have been developed such as transjugular biopsy or biopsies sealed with hemostatic materials [4-9]. The aim of the present study was to analyze our experience with fibrin-glue-sealed liver biopsies (FGSLB) in patients at increased risk of complications.

Our study included 88 FGSLBs performed in 76 patients in a tertiary center from February 1999 to May 2012. We used 14G Tru-Cut needles, and an adhesive material composed of fibrinogen and human thrombin (Tissucol) as a sealing agent. The puncture site was anesthetized using 3% mepivacaine, and biopsies were performed with ultrasound guidance. After performing the sealed biopsy, all patients remained at least 24 hours under hospital observation.

Collected parameters were obtained through ultrasound reports and computerized medical database. The study protocol was approved by the Ethics Committee of Clinical Research and all patients signed an informed consent form prior to biopsy.

Sixty-eight (77.3%) patients were male and the mean age was 49 ±11.7 years. Biopsy indications were graft dysfunction post liver transplantation (61.4%, 54 cases), HBV infection (6.8%), HCV infection (3.4%) and other conditions such as suspected chronic liver disease or abnormal liver function tests (27.3%). Indications for sealing were thrombocytopenia (54.5%), coagulation disorders (20.4%), antiplatelet therapy (10.2%) and other reasons, such as ascites and/or increased bilirubin level (15.9%).

One single pass was needed in 81 patients (92%), and sufficient liver tissue was obtained in 94.3% of cases. The average sample length was 1.4 cm. Complication rate was 7.9% (7 patients). Five were minor complications (5.7%), and two (2.2%) were major: self-limited hemoperitoneum that required transfusion. No deaths occurred.

Despite limitations regarding sample size, the observational design and the lack of a control group (circumstances difficult to overcome due to ethical reasons), these results suggest that FGSLB could be safe and effective for obtaining adequate histological samples. This fact could be particularly important when the biopsy, necessary for the clinical decision, is carried out under unfavorable circumstances.

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## Increased levels of serum amyloid A during the early phase of hepatitis C treatment with interferon are associated with sustained virologic response – a pilot study

**To the Editor,**

Clearance of hepatitis C virus (HCV) infection has been associated with a strong, broadly-targeted T cell response [1, 2]. Activation of T-cells by HCV proteins results in production of soluble cytokines, which in turn induce various acute-phase proteins including serum amyloid A (SAA). It has been shown that SAA inhibits replication of HCV *in vitro* by blocking virus entry into the hepatocytes [3]. We therefore hypothesized that SAA levels measured during the early phases of HCV-therapy might predict the success of antiviral treatment.

We studied 35 consecutive patients with chronic hepatitis C (males/females: 20/15; mean age±SD: 42.0±8.5, range: 23-61 years), who had been treated with peginterferon (pegIFN) plus ribavirin at our centre. HCV genotype (GT)-1 was most prevalent (n=17), followed by GT-3 (n=9), GT-4 (n=7), and GT-2 (n=1); one patient was coinfected with GT-1 and GT-4. All patients received pegIFN α-2a 180μg once weekly plus ribavirin (1000-1200mg daily for GT-1/4 and 800mg daily for GT-2/3). In patients with GT-1 or 4, treatment duration ranged from 24 to 72 weeks and was adapted to the kinetics of HCV-RNA during therapy as described previously [4]. In patients with GT-2 or 3, treatment duration was 24 weeks. Plasma HCV-RNA levels were measured by COBAS TaqMan HCV-RNA assay, version 2.0 (Roche).

Plasma samples that were collected at different time points of treatment were tested for levels of acute-phase reactants including high-sensitivity C-reactive protein (hs-CRP), fibronectin (FNC), human interleukin-6 (IL-6), and SAA as described previously [5].

We observed a sustained virologic response (SVR) in 25 (71%) patients, relapses in 4 (11%), a partial response in 4 (11%), and null responders were 2 (6%). In patients with SVR, SAA-levels increased significantly from 4.8±2.8 mg/l at baseline to a peak concentration of 14.5±21.7 mg/l between

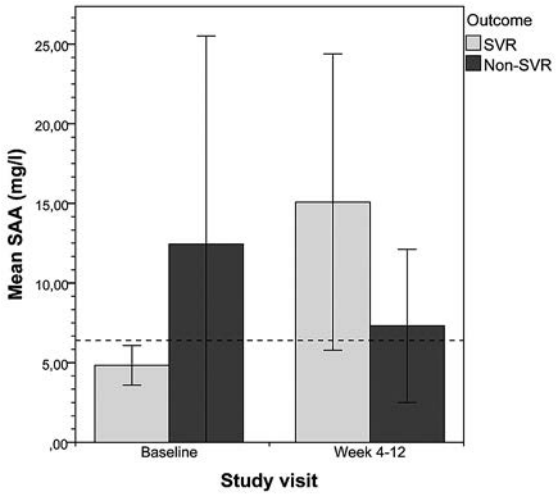


**Fig. 1**. Serum amyloid A level in patients with chronic hepatitis C under treatment with pegIFN/ribavirin. The dashed line indicates the cut-point for defining normal vs increased levels of SAA.

week 4 and week 12 ($p<0.05$, Student's paired t test). In contrast, SAA-levels showed no significant change in patients without SVR (15.1±18.6 mg/l at baseline versus 7.1±5.9 mg/l, week 4-12, Fig. 1). Plasma values of hs-CRP, fibronectin and IL-6 remained within normal limits during the whole treatment period in all patients.

In summary, this pilot study indicates that a significant increase in plasma levels of SAA during the early phase of pegIFN/ribavirin therapy is associated with SVR. In contrast, serum levels of the other acute-phase reactants evaluated were not associated with hepatitis C viral kinetics, a finding in concordance with previous studies [6, 7]. At present, it is unclear whether the observed increase in SAA levels is associated with treatment success because of the antiviral properties of SAA (viral elimination by blocking viral entry into hepatocytes) [8] or it is a surrogate marker for an effective immune response to HCV infection triggered by treatment with interferon. The potential role of SAA as a predictor of SVR in HCV-infected patients should be evaluated in future prospective trials.

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**Conflicts of interest:** None to declare. This study waas supported by a grant of the Austrian Science Fund (grant nr. P25353-B21).

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## Tumor characteristics and surgical therapy influence the outcome of gastrointestinal stromal tumors

**To the Editor,**

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal neoplasms of the gastrointestinal tract. The three main characteristics for predicting how GIST will behave are size, mitotic rate and location [1]. Tumors with low mitotic counts (< 5 / 50 HPFs) and a diameter < 2 cm generally exhibit a benign behavior, while tumors with a diameter > 10 cm and high mitotic counts (> 5 / 50 HPFs) are associated with malignant behavior. Complete surgical resection is the primary treatment modality for GIST. Total excision of the tumor is the most significant factor for a good outcome and can be accomplished in 40 to 60% of all GIST patients [2]. Nevertheless, around 50% of patients tend to develop tumor recurrence and the reported 5-year survival is approximately 50% [3]. The median survival of recurrent GIST after surgical resection is 15 months in the pre-imatinib era [4]. Conventional chemotherapy for the treatment of GIST has a response rate of 5% [5]. Imatinib is a selective inhibitor of specific TK, including KIT, platelet-derived growth factor receptor alpha (PDGFR-a), ARG, c-FMS, ABL and BCR-ABL, and is currently the standard first-line treatment for patients with KIT-positive unresectable or metastatic GIST, or both [2, 6].

In our unit, from January 2002 until February 2009, 33 patients diagnosed with GIST were included in an observational, prospective study. The diagnosis of GIST was based on light microscopy features and membrane positivity for CD117 (cKIT) by immunohistochemistry. The clinical and pathological features of the study group are summarized in Table I. Based on the size of the primary tumor, mitotic index and Fletcher's criteria, the tumors were classified into groups with very low (n=3), low (n=5), intermediate (n=6)

**Table I**. Characteristics of the patients with GISTs

| | |
|---|---|
| Age (years) | |
| Mean (range) | 59.2 (40-81) |
| Gender (n, %) | |
| Male | 15 (46) |
| Female | 18 (54) |
| Location of tumor (n, %) | |
| Stomach | 17 (52) |
| Duodenum | 4 (12) |
| Small bowel | 10 (30) |
| Large bowel | 1 (3) |
| Other | 1 (3) |
| Histopathological subtype (n, %) | |
| Spindle cell | 10 (30) |
| Epithelioid | 4 (12) |
| Mixed | 19 (58) |
| Symptoms (%) | |
| Abdominal pain | 36 |
| Gastrointestinal bleeding | 58 |
| Appetite and weight loss | 43 |
| Abdominal mass | 6 |
| Asthenia | 57 |
| Nausea | 27 |
| Diarrhea | 3 |
| Surgical treatment (n, %) | |
| Complete resection | 29 (88) |
| Enucleation | 4 (13) |

and high (n=7) risk. Progression-free survival (PFS) in the patients with primary gastric GIST was not significantly longer than the PFS in other locations (p=0.28). The PFS differed significantly with the increasing risk as shown by the tumor dimension and mitotic rate (p=0.0001). The patients with an increased risk of tumor recurrence received chemotherapy with Imatinib. Patients treated with Imatinib had a higher PFS and a higher overall survival (OS) compared to patients who had not received chemotherapy (p=0.021 and p=0.005, respectively). The type of surgical intervention did not influence the PFS and OS of patients with GIST (p=0.28).

In conclusion, our data, even on a small number of patients, add to the body of the published literature confirming that survival depends on the location of the tumor, risk of malignancy and type of treatment. The multidisciplinary approach is essential in the assessment of accurate diagnosis of this disease and for the improvement of the therapeutic approach.

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## Is there a role for chromoendoscopy in the diagnosis of coeliac disease?*

**To the Editor,**

Endoscopic markers of villous atrophy have a low sensitivity for the diagnosis of coeliac disease (CD). Small historical studies have suggested that chromoendoscopy can significantly increase their accuracy (Table I). However, these were single endoscopists in a research environment. Modern magnification techniques may enhance detection but this technology is not widely available internationally. For this reason we assessed the role of chromoendoscopy in patients presenting for endoscopy.

Patients undergoing oesogastroduodenoscopy were prospectively recruited from endoscopy department. Patients were divided into two groups: patients with no previous history of CD (Group 1, n=300) and patients with established CD (Group 2, n=45). During the procedure, the endoscopic findings were reported before and after indigo carmine dye spray use in the duodenum. All patients had tissue tranglutaminase antibody (TTG), endomysial antibody (EMA), IgA level and duodenal biopsies (>4) evaluated.

In Group 1, 89/300 (30%) were newly diagnosed CD patients with endoscopic markers identified in 42% (37/89). Chromoendoscopy identified a further 11 patients (48/89, 54%) (P=0.001). Sensitivity, specificity, positive and negative predictive values for standard endoscopy to detect CD were 42%, 98%, 90% and 80%, respectively. For chromoendoscopy they were 54%, 97%, 89% and 83%, respectively. For TTG, 89%, 78%, 63%, 94% and for EMA 78%, 97%, 91% and 91%, respectively. In Group 2, 17/45 (38%) patients had Marsh 3 duodenal changes; chromoendoscopy did not significantly increase detection (P=0.5).

Although chromoendoscopy is inexpensive, easy to use and improves the identification of endoscopic markers, the accuracy for the diagnosis of CD was shown to be poorer than the current serological testing. Therefore, chromoendoscopy cannot be recommended for routine clinical practice.

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**Table I.** Comparison of all published studies utilising chromoendoscopy for the diagnosis of coeliac disease

| Author | Year | Country of Origin | Methodology | Number of Patients | Number of Endoscopists | Comparators | Magnification | Result |
|---|---|---|---|---|---|---|---|---|
| Stevens and McCarthy [1] | 1976 | Ireland | Applied 0.4% **indigo carmine** | 15 (8 with CD) | Not stated | Endoscopic markers | No magnification | No comparison with standard endoscopy Sensitivity and specificity of 100% |
| Siegel et al [2] | 1997 | USA | Applied 0.1% **indigo carmine** | 34 (17 with VA) | Not stated | Endoscopic markers with villous atrophy | Up to x35 | Improved identification of endoscopic markers compared to standard endoscopy Sensitivity and specificity of 94% and 88% respectively |
| Kiesslich et al [3] | 2003 | Germany | Applied 10ml 0.4% **indigo carmine** each to D1 and D2 | 54 (4 with VA) | Not stated | Endoscopic markers | No magnification for 27 patients and up to x105 for the other 27 patients | Endoscopic markers seen before and after dye in all 4 patients with villous atrophy |
| Morishita et al [4] | 2003 | Japan | Applied 0.1% **indigo carmine** | 1 (1 with CD) | 1 | Endoscopic markers | Up to x40 | Endoscopic markers seen before and after dye |
| Iovino et al [5] | 2013 | Italy | Instilled and aspirated 180ml water, followed by 20-30 ml 10% N-acetylcysteine and ~30 ml 0.4% **indigo carmine** | 77 (41 with CD) | 1 | Direct visualisation of mucosal villi with villous atrophy on biopsy | Up to x150 | No comparison with standard endoscopy Endoscopic markers not identified Sensitivity and specificity of 98% and 100%, respectively |
| Niveloni et al [6] | 1998 | Argentina | Applied 5ml 1% **methylene blue** | 167 (80 with VA) | 3 | Endoscopic markers with villous atrophy | No magnification | Endoscopic markers seen before and after dye in all cases Sensitivity and specificity of 94% and 99%, respectively |
| Ravelli et al [7] | 2001 | Italy | Applied 5-10ml 1% **methylene blue** to D2 | 20 | 1 (presence of markers was agreed with one other gastroenterologist) | Endoscopic markers | No magnification | Endoscopic markers seen before and after dye in all cases |

D1 - First part of the duodenum, D2 - Second part of the duodenum, CD - Coeliac Disease, VA - Villous Atrophy

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**Conflicts of interest:** None.

***Previous Presentation:** This study was presented as a poster abstract at the 2013 British Society of Gastroenterology Annual Meeting; June 25, 2013; Glasgow, United Kingdom.

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