LETTERS TO THE EDITOR

Accelerated dose of ustekinumab for acute severe ulcerative colitis

To the Editor,

We read with interest Affendi et al. [1] report about a patient with severe ulcerative colitis who responded to an accelerated dose of ustekinumab. We have the following comments and concerns.

The patient's endoscopic images do not show the typical Mayo score 3 appearances of colitis. Severe ulcerative colitis is characterized by diffuse, circumferentially affected, granular mucosa with superficial ulcerations that may coalesce. Figures from the case show discrete, deep, oval ulcers. Furthermore, it almost has a cobblestone appearance, more specific to Crohn's disease [2].

In addition to colon involvement in Fig. 1A, the small intestinal loops (possible ileal segments) are thickened and edematous in the right lower quadrant, distant from the cecum. There is also the appearance of fat stranding. In ulcerative colitis, involvement of intestinal segments distant from the cecum is not expected, being specific to Crohn's disease [3].

Due to the severity of the disease, a pancolonoscopy could not be performed; therefore, disease extension was described using computed tomography. Not exceeding splenic flexure, it was interpreted as left-sided colitis. According to his medical history, 3 grams of mesalazine was started three weeks prior to his admission. Mesalazine >2.4 g/dL enteral and 1-gram topical forms are recommended by the 2017 ECCO (European Crohn's and Colitis Organisation) guideline for left-sided ulcerative colitis. The remission induction rate at this dose is high when compared to placebo [4]. If the patient has left-sided ulcerative colitis, we anticipate a positive response to a sufficient dose of 5-acetylsalicylic acid preparation.

Finally, the histopathological findings are not mentioned in the article. Although there are no pathognomonic features specific to ulcerative colitis, the presence of granulomas (which can be found in 15-36% of mucosal biopsies) could indicate Crohn's disease [4, 5].

Combined treatment with ustekinumab and parenteral steroids has been found to be successful. The current findings are inconclusive as to whether the underlying disease is ulcerative colitis or ileocolonic Crohn's disease. For both conditions, ustekinumab is recommended for induction of remission [6, 7]. Nevertheless, it is important to clarify the underlying type of inflammatory bowel disease prior to recommending such intervals of doses.

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Reply,

To the Editor,

Thank you for reading and commenting on our previous report [1]; we are very glad that it has stimulated interest and a platform for further discussion [2].

First comment referred to endoscopic images, without a specific aspect of Mayo 3 ulcerative colitis. We agree with your comment that some of the endoscopic features were not typical of ulcerative colitis and might overlap features with Crohn's disease and an undetermined inflammatory bowel disease (IBD) might have been a more encompassing diagnosis. However endoscopically we still feel it favours ulcerative colitis because of the continous circumferential inflammation from the rectum up to the descending colon with sharp demarcation of the affected area and normal mucosa proximally other than a caecal patch which is also well described. It has been well reported in literature that the endoscopic appearance of ulcerative colitis does not always follow the classic appearance in up to 20%.

The second comment argue that in ulcerative colitis the involvement of intestinal segments, distant from the cecum, as depicted on computed tomography, is not expected. However, there was no small interstinal involvement reported. We reviewed the video images from the previous ileocolonoscopy that was performed in referring hospital and the findings were consistent. The edematous small bowel loops is likely to be due to the adjacent colonic inflammation.

Another concern referred to the disease extension, assessed by computed tomography, as pancolonoscopy could not be performed due to the disease extension. It was reported as continuous inflammation from rectum not exceeding splenic flexure and the fat stranding in caecum with minimal peri-colonic fluid suggesting caecal patch.

While we agree that optimal dose of 5-aminosalycilic acid (5-ASA) is 4g/day (this was not started at our centre), this is not relevant as the patient was subsequently admitted for acute severe flare and failed to respond to high dose of intravenous steroids. 5-ASA is effective for mild to moderate colitis but far less so in moderate to severe ulcerative colitis and failure to respond to 5-ASA does not mean that the diagnosis is not ulcerative colitis.

Another criticism was that the histopathological findings were not mentioned in the article. We reviewed the histology report which showed mixed inflammation of the lamina propria, cryptitis, crypt abscesses, and subtle chronicity changes; however, no granulomas were depicted on biopsies at two different occasions. Hence favouring ulcerative colitis over Crohn's disease.

The final remark highlighted the importance to clarify the underlying type of inflammatory bowel disease prior to recommending intervals for ustekinumab doses. We agree that regardless on whether the diagnosis is arbitarily classified as UC, CD or IBD-U, what is undisputed is that the patient met the criteria of acute severe colitis clinically and biochemically and the aim of our case report was to highlight the potential role of ustekinumab in patients who fail to respond to high dose intravenous steroids but with relative contraindications to anti TNF/cyclosporin therapy in this setting.

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Oseltamivir-induced upper gastrointestinal bleeding

To the Editor,

Oseltamivir is an oral neuraminidase inhibitor used to manage acute influenza. The most reported adverse effect of oseltamivir is gastrointestinal discomfort, including nausea and vomiting. The authors describe a rare adverse effect of oral oseltamivir.

An 84-year-old female with a past medical history of hypertension and diabetes was hospitalized with a recent diagnosis of influenza virus and bacterial over infection. She completed a 5-day course of oseltamivir and 7 days of amoxicillin/clavulanic acid without the need for non-steroidal anti-inflammatory drugs, with good clinical and laboratory response. On the 8th day of admission, she presented melena and hypotension, without abdominal pain or other complaints. Laboratory study showed a drop in hemoglobin (7.6 g/dL for a previous of 9.9 g/dL) and an increase in urea levels (81 mg/dL for a previous of 51 mg/dL). The patient was hemodynamically stabilized and transfused with 2 units of blood, with good transfusion results (hemoglobin post transfusion of 10.8 g/dL). On the following day, the patient underwent an emergency

endoscopy that revealed several clean-based ulcers (Forrest III) in the bulb and duodenum up to D2, with a longitudinal extension up to 20 mm, which conditioned bulbar deformation and with surrounding mucosa of congestive, edematous, and granular aspect (Fig. 1). The patient was treated with a proton pump inhibitor with a good clinical and laboratory response, without new episodes of gastrointestinal bleeding.

Oseltamivir is an oral neuraminidase inhibitor widely used to treat acute influenza. Gastrointestinal bleeding is a rare but known adverse effect of this drug; there is scarce published reports of hemorrhagic colitis caused by oseltamivir [1, 2]; but, to the best of the authors knowledge, there is no reports of upper gastrointestinal bleeding.

There are some possible explanations for gastrointestinal bleeding associated to the use of oseltamivir. The evidence suggests that reduction of human endogenous neuraminidase activity by oseltamivir carboxylate (metabolite of orally administered oseltamivir phosphate) may cause delayed type adverse reactions to neuraminidase inhibitors - not only inhibition of antibody and pro-inflammatory cytokine induction but also gastrointestinal bleeding [3]. On the other hand, it is important to mention that the gastrointestinal bleeding reported in association with the use of oseltamivir may be associated with confounding factors such as infection by the influenza virus itself, which enhances coagulation [4, 5].

In conclusion, the gastrointestinal adverse effects of oseltamivir are usually mild, but clinicians and patients should be alerted for rare adverse effects as the one reported.

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Bezafibrate severe late onset drug-induced liver injury in primary biliary cholangitis: case report

To the Editor,

A 65-year-old female was referred to our hepatology clinic due to an elevation of alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT) and aminotransferases. Initial laboratory exams showed: ALP 265 U/L [reference value (RV) < 100], GGT 90 U/L (RV<45), aspartate aminotransferase (AST) 70 U/L (RV<40), alanine aminotransferase (ALT) 65 U/L (RV<40), total serum bilirubin 1.0 mg/dL, immunoglobulin G 1,891 mg/dL (RV<1,600), immunoglobulin M 103 mg/dL, antinuclear antibody 1:160 multiple nuclear dots pattern. Antimitochondrial antibody (AMA), anti-smooth muscle antibody, anti-liver kidney microsomal type 1 antibody and anti-soluble liver antigen antibody (anti-SLA) were negative. There was no serological evidence of viral hepatitis. Magnetic resonance cholangiopancreatography (MRCP) revealed normal intra and extrahepatic bile ducts. Percutaneous liver biopsy showed chronic nonsuppurative cholangitis with florid duct lesion, suggestive of primary biliary cholangitis (PBS), with fibrosis expanding of most portal zones, short fibrous septa and occasional bridging (Metavir F2). The diagnosis of PBC was made and ursodeoxycholic acid (UDCA) 13 mg/kg/day was initiated. After 12 months of treatment, patient was unresponsive to UDCA according to Paris-II biochemical criteria. Furthermore, she developed a moderate pruritus. Add-on therapy with bezafibrate 400 mg/day was then introduced. Within 6 months

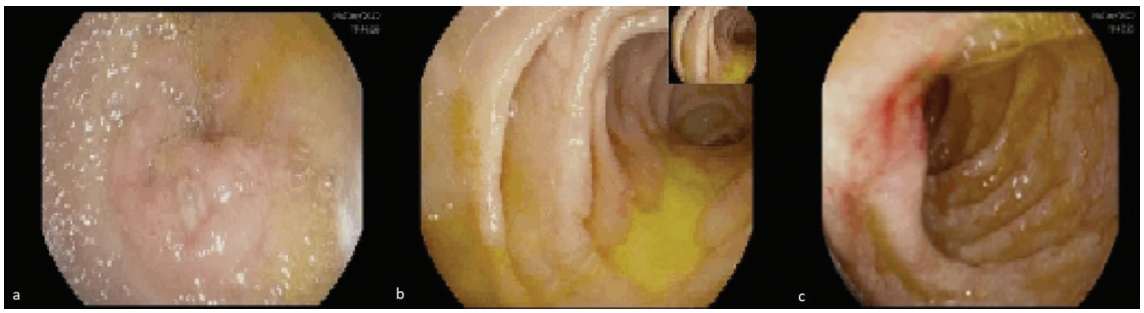

Fig. 1. Urgent endoscopy: several clean-based ulcers (Forrest III) were observed in the bulb (a) and duodenum up to D2, with a longitudinal extension up to 20mm (b), which conditioned bulbar deformation and with surrounding mucosa of congestive, edematous, and granular aspect (c).

of combination therapy, patient evolved with resolution of pruritus and partial reduction of ALP. However, after 52 months, aminotransferases increased to 3 times the upper limit of normal. In this context, the differential diagnosis considered was overlap syndrome with autoimmune hepatitis and late onset bezafibrate hepatotoxicity. Bezafibrate was withdrawn and new exams were collected: anti-SLA antibody was now positive, MRCP persisted unremarkable and liver biopsy showed the same characteristics of PBC, but now with marked bridging fibrosis (F3), associated with moderate interface hepatitis. Prednisone 40mg/day was empirically initiated, but there was no biochemical response after one month: ALP 224U/L, GGT 104U/L, AST 193U/L and ALT 89U/L. Patient evolved with progressive liver disfunction, infectious complications and died after a 58-month follow-up (Table I).

We reported a case of a woman with AMA negative PBC who was unresponsive to UDCA treatment and required add-on therapy with bezafibrate. Although she initially evolved with a decrease of ALP, a late idiosyncratic drug-induced liver injury (DILI) occurred with elevation of aminotransferases and bilirubin. Patient was unresponsive to bezafibrate interruption and prednisone therapy, leading to irreversible liver failure and death.

A recent systematic review that evaluated the use of fibrates for treatment of PBC showed that the most commonly reported adverse events are mild gastrointestinal and musculoskeletal symptoms; however, serious adverse events such as elevation of aminotransferases and serum creatinine can occur [1, 2]. Elevation of aminotransferases has been described in up to 8% of patients using fenofibrate and in 2% treated with bezafibrate [1]. A case series of 7 PBC patients with fenofibrate-DILI showed that the toxicity onset can vary from a short (5-8 weeks) to a very long (18-56 weeks) latency, with the majority of cases presenting with jaundice and hepatocellular, mixed or cholestatic hepatitis [3]. In this case, we show that bezafibrate-DILI can be severe and present a long latency period.

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Acute liver failure: a rare presentation of an adult-onset Still's disease

To the Editor,

A 32-year-old nonalcoholic male presented with one-month history of high-grade episodic fever, chills, arthralgia, generalized weakness, and sore throat. Physical examination revealed a salmon-colored rash on the trunk and extremities, occurring during fever episodes, along with hepato-splenomegaly. Hemogram showed neutrophilic leukocytosis (24.5×10^9/L with 90% neutrophils) and thrombocytosis (540×10^9/L) without atypical cells. Infectious causes of fever were ruled out with negative tests, sterile blood and urine cultures, and normal inflammatory markers. Radiological imaging was unremarkable, and bone marrow biopsy was normal. The notable results were hyperferritinemia (>1,650 ng/mL), mild transaminases, and hyprtriglyceridemia (639 mg/dL). The diagnosis of adult-onset Still's disease (AOSD) was made based on the Yamaguchi criteria [1]. He was started on 1 mg/kg/day prednisolone and discharged in improving condition.

Table I. Laboratory exams evolution during follow-up

	Admission	12 months	16 months	22 months	52 months	53 months
Treatment	–	UDCA	UDCA	UDCA + BF	UDCA + BF	UDCA + PDN
Assessment	UDCA initiation	Pruritus onset	BF initiation	Pruritus resolution	BF suspension and PDN initiation	–
ALP (U/L)	265	242	302	149	236	224
GGT (U/L)	90	45	91	79	153	104
AST (U/L)	70	50	59	70	120	193
ALT (U/L)	65	42	47	41	120	89
Total bilirubin (mg/dL)	1.0	0.6	0.8	1.5	4.0	6.0
IgG (mg/dL)	1861	–	–	–	3176	-

ALP: alkaline phosphatase [reference value (RV)<100 U/L); ALT: aspartate aminotransferase (RV<40 U/L); AST: aspartate aminotransferase (RV<40 U/L); GGT: gammaglutamyl-transferase (RV<45 U/L); IgG: immunoglobulin G (reference value< 1600 mg/dL); IgM: immunoglobulin M; PDN:prednisone; UDCA: ursodeoxycholic acid.

After 4 weeks, he was readmitted with fever, altered sensorium, abdominal pain, and per rectal bleed after discontinuing prednisolone for last 10 days. On examination, he had tachycardia, icterus, and right upper quadrant tenderness. Laboratory investigations revealed leukocytosis (39.7×10^9/L with 90% neutrophils), hemoglobin of 11.5 gm/dL, platelet count of 320×10^9/L, total bilirubin 18 mg/dL, aspartate aminotransferase 1,800U/L, alanin aminotrasferase 2,170U/L, alkaline phosphatase: 201 U/L, gamma-glutamyltransferase 135 U/L, total protein 6 g/dL with albumin: 2.5 g/dL, and international normalized ratio 3.94. Serum ferritin levels were more than 3,000 ng/mL. Toxicology screens were negative, and autoimmune workup yielded no significant findings. Serology for viral hepatitis and leptospira were negative. Abdominal ultrasound showed hepatosplenomegaly with a starry sky pattern of liver echo texture. He was diagnosed with acute liver failure (ALF) secondary to AOSD and prompt initiation of intravenous (i.v.) pulse methylprednisolone (1 g/day for 3 days) along with 6 units of fresh frozen plasma transfusion led to clinical and biochemical improvement. He was discharged after 6 days with near-normal liver function on oral prednisolone which was gradually tapered off to a low dose steroid in next 6 months.

Adult-onset Still disease is a multisystem inflammatory disorder of unknown etiology affecting adults, characterized by quotidian fever, arthritis, evanescent salmon-colored rash, pharyngitis, and lymphadenopathy. Hepatic dysfunction is common, and in rare cases, it can progress to life-threatening ALF. The pathogenesis of AOSD involves various cytokines, including IL-1, IL-6, IL-18, IFN-γ, and TNF-α, with IL-18 playing a crucial role [2].

Yamaguchi criterion [1] is used for diagnosis of AOSD (Table I). It requires the presence of five features, with at least two being major diagnostic criteria. Fautrel et al. [3] proposed a new classification criterion including new biomarker glycosylated ferritin (Table I).

Valluru et al. [4] reviewed seventeen cases of ALF with AOSD of which seven patients had ALF as first presentation of AOSD (7/17 = 41.1%), ten patients (10/17 = 47%) developed ALF during the course of disease (as seen in our patient).

Liver dysfunction in AOSD reflects disease activity, and steroids are commonly used as first-line therapy. In multisystem flares involving vital organs, intravenous methylprednisolone pulse therapy is recommended [5]. Other immunosuppressant drugs like IL-1 antagonists (anakinra), cyclosporine, and methotrexate may also be used. Our case highlights that ALF can be a rare presentation of AOSD, and prompt initiation of high-dose i.v. methylprednisolone pulse therapy can lead to a favorable outcome.

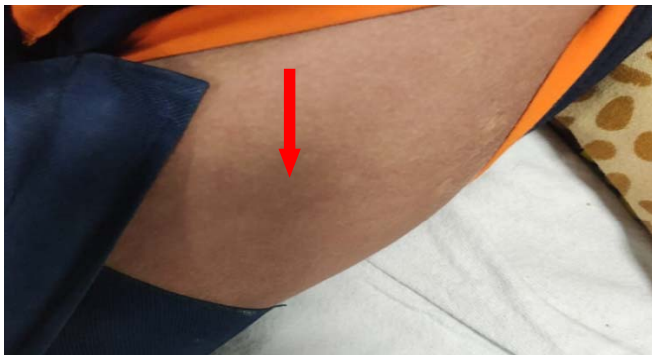

Fig. 1. Classical skin rash of AOSD (Fleeting salmon-colored rash with macular or maculopapular eruption. Occurs with fever, fades when fever subsides. Affects trunk and limbs, not usually itchy.)

We conclude that AOSD should be considered in patients with fulminant hepatic failure without other identifiable causes, and an extensive workup is necessary for diagnosis. Once diagnosed, it can be lifesaving for the patient.

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Table I. Criteria for diagnosis of adult-onset Still's disease (AOSD) [1]

Yamaguchi criteria for AOSD (1992)		
Major criteria	Minor criteria	Exclusion criteria
• Fever (≥39°C), intermittent for ≥ 1 week • Arthralgia of arthritis for ≥ 2 week • Typical skin rash • Leukocytosis ≥ 10,000 / mm³ with PMN dominance (≥ 80%)	• Sore throat • Recent, significant Lymphadenopathy • Hepatomegaly • Splenomegaly • Abnormal LFT • Negative ANA, RF	• Infections • Malignancies • Rheumatic diseases
Fautrel criteria for AOSD (2002) [3]		
Major criteria	Minor criteria	
• Spiking fever (≥ 39°C) • Arthralgia • Transient erythematous rash • Sore throat • PMN ≥ 80% • Glycosylated ferritin ≤ 20%	• Maculo-papular rash • Leukocytosis ≥ 10,000 / mm³	

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A portrait of viral hepatitis in the Roma population highlighting potential disparities

To the Editor,

We read with interest the letter written by Tantau et al. [1] addressing the *Prevalence of hepatitis B and C virus infection in a Roma Population in Cluj County, Romania* published in the last issue of *Journal of Gastrointestinal and Liver Disease*. This is, especially, as for decades, the endemicity of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection in Romania has ranked as the highest in the European region [2, 3].

Assessing 295 Roma subjects from two communities around Cluj-Napoca, Western Romania, the authors have done valuable work, concluding that the prevalence of HBV (4.75%) and HCV (2.03%) infection is higher in the Roma ethnic group as compared to the general population (1.03% and 1.66%, respectively) and emphasizing the importance of screening in this vulnerable population.

However, some challenging points and comments related to this paper may be of benefit from the perspective of a broader screening program aiming to provide high quality and accessible medical services for screening, early detection and linkage-to-care in previously undiagnosed HCV/HBV-infected adults from vulnerable groups, including the Roma ethnic population (the LIVERO2 Program).

Firstly, the sample size is limited to 295 individuals (242 adults and 53 children), selected from 2 Roma communities (295 individuals from the suburban settlement of Cluj-Napoca Pata Rât and 36 from Cojocna commune), with Roma populations from differring backgrounds: the 1,300 Roma in Pata Rât (representing 86.66% of the population) are all from a precarious socio-economic background and their main activities are centered around Cluj-Napoca's garbage dump whereas Cojocna is an up and coming municipality, with salt bath and thermal spa facilities, where Roma population represent 21.36% [4, 5].

Secondly, there is no clear description of the specific methodology applied: how the participants have been selected, have they benefitted from previous education and awareness campaigns, have the community leaders such as representative(s), family physician, priest have been engaged in the process etc. Testing was performed by finger blood rapid diagnostic tests (RDT) for HBsAg and anti-HCV (Abbott Diagnostics) in an adequately equipped mobile unit. There were no eligibility criteria others than Roma ethnicity, signed informed consent and completion of the risk factors questionnaire.

Thirdly, the representativity of the study for Roma population remains limited, this being a local program, with a small number of participants and selection bias that cannot be assumed as informative for Romania.

The ongoing EU-founded (POCU/755/4/9/136208; POCU/755/4/9/136209) (2021-2023) Regional program for the prevention, screening and diagnosis of chronic liver disease following HCV and HBV infections (LIVERO2 South and East) covers 2/3 of Romania (24 counties, 4 developing regions, including the Oltenia, Muntenia, Moldova and Dobrogea historical regions of Romania). The methodology was quite complex consisting of 1) awareness and education campaigns which preceded screening; 2) identification of a NGO partner in charge with the identification, recruitment, access and navigating the eligible subjects, as well as with the recruitment of screening facilitators (affiliated family practitioners); 3) on-site screening in the family practitioner's office by RDT, administration of the risk factor questionnaire, and data introduction into a Electronic Database; 4) linkage-to-care (staging and therapy) for those detected positive in screening. The programmatic targets of LIVERO2 twin programs have been: 240,000 individuals screened, 60% of them (144,000 individuals) recruited from "vulnerable" groups (rural population, poor people, uninsured and homeless individuals, Roma ethnicity, institutionalized individuals, people with disabilities/special needs, people who inject drugs (PWID) and other types of addiction, victims of domestic violence or human trafficking) and 4,800 positive subjects further linked to medical care.

Out of the 315,160 subjects screened between July 2021 – July 2023 in the LIVERO2 Program, with the participation of 871 family practitioners, 8,684 (2.76%) declared to be of Roma ethnicity; this figure is similar with those obtained in the most recent Romanian Census [6]. Regarding the regional distribution of Roma subjects included in the LIVERO2 screening, 63.4% of them reside in South or South-West, Iasi, Dolj and Arges being the counties with the highest proportion of Roma population tested in the LIVERO2 program (p=0.032). Among the 8,684 Roma individuals, 64.54% were women compared to 63.08% in the general population (p=0.51) and the median age was 44.8 years (range18-97) (79% of Roma subjects were younger than 60 years of age) as compared to 54.2 (18-105) in the general population (p=0.001), reflecting a better compliance among women and a shorter lifespan among the Roma population (64 years vs. 74.5 years in general population). Only 17% of Roma individuals screened had a high-level education (college or university), whereas 87.87% of them were inactive or unemployed.

The prevalence of chronic HBV infection among the Roma ethnic group was 2.85% compared to 1.65% in the non-Roma population (p=0.001), slightly higher for men (3.22% vs. 2.52%) (p=0.45) and significantly higher in younger subjects (6.71%, 3.78%, 3.51% in 30-39; 40-49; 50-59 age groups, respectively) (p=0.001). Risk factors significantly associated with HBV infection in Roma population were employment status (p=0.001), education level (p=0.002), family or sexual

contact with a person having HBV infection (p=0.0001), professional exposure (p=0.0001), dental surgical procedures (p=0.015), history of detention (p=0.018), intravenous drug use (IVDU) (p=0.0001), sexually hazardous behaviour (multiple partners, unsafe contact) (p=0.0001), sexual transmisible diseases (p=0.009).

Regarding HCV infection, the prevalence detected among Roma participants in the LIVERO2 screening was 1.28% compared to 1.21% in the non-Roma population (p=0.631); it was significantly higher in Roma female subjects (1.48% vs. 0.91%) (p=0.024) and in subjects older than 60 (p=0.0001). Risk factors associated with HCV infection in Roma population were illiteracy (p=0.0001), low levels of education (p=0.001), family contact with a HCV-infected person (p=0.0001), sexual contact with a HCV-infected person (p=0.001), IVDU (p=0.0001), positive transfusion history (p=0.0001), history of surgery (p=0.007), hemodialysis (p=0.01), history of hospitalization (p=0.0001), dental surgery (p=0.0001), piercing and tatoo (p=0.01), contaminated needle or sharp object exposure p=0.0001), domestic/car/work accidents requiring hospitalization (p=0.006), unsafe/non-prescribed injections (p=0.037), sexually hazardous behaviour (multiple partners, unsafe contact) (p=0.002).

Beyond the criticism, these comments, together with the original authors' paper, draw attention to the fact that viral hepatitis is quitepresent in the western region of Romania, with similar prevalence and common risk factors. While the original paper presents a useful snapshot of screening in western Romania, this process has to be continued in a systemic manner in order to detect all HCV- and HBV-infected subjects and offer them diagnosis, treatment and monitoring. Moreover, elimination strategy has to be centered on vulnerable and hard to reach populations in whom medical measures have to be accompanied by dedicated socio-economic and educational intervention, in order to better integrate these communities, raising their educational level, the level of social and professional integration and, last but not least, medical literacy.

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