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Reply,

To the Editor,

We thank Bancila et al. for their important comments [1]. Their comments emphasize that the data we have so far regarding the progression from one type of achalasia to the other remains contradictory. The „progression” hypothesis states that achalasia is a continuum, starting with type III, followed by type II pattern, with type I pattern as the final stage of the disease, when the esophagus is dilated. A recent study [2] reported histological differences between achalasia subtypes, with more ganglion cell loss in type I achalasia, giving a cellular basis for this hypothesis. In our study [3] we tried to identify clinical and manometric characteristics to support or contradict this idea. Some of our results supported this hypothesis, but others did not. If progression was the case, one would expect type I achalasia patients to be older, with a longer evolution of symptoms and a different pattern of symptoms, such as more regurgitation, heartburn, or cough, given the stasis in the dilated esophagus. As in other studies, including the one of Bancila et al. [1], in our group, patients with type I and type II achalasia were of a similar age, and we did not see a different clinical pattern between achalasia subtypes, nor a longer disease duration in type I compared to type II achalasia. However, more patients with type I achalasia reported that dysphagia worsened in time (patients increased the frequency and the amount of water during meals), compared to type II achalasia patients. In addition, type I patients tended to have a lower body mass index (BMI) compared to type II achalasia patients ($p=0.07$) [3]. Both these two observations could be related with a longer course of the disease in type I achalasia. We didn't have data about weight loss for our entire cohort, therefore these data were not reported in our study. Data from literature [4] and the results of Bancila et al. [1] showed that weight loss is more likely in type II achalasia. These results cannot be really compared with ours, since the authors did not report in their paper the mean BMI of patients with type I or type II achalasia. Among the manometric parameters, such as Bancila et al. [1], we also reported higher 4s-IRP (integrated relaxation pressure) values in type II achalasia, compared to type I achalasia. In addition, in our cohort, lower esophageal sphincter (LES) resting pressure was significantly higher in

type II achalasia [3]. Another study [5] reported higher LES resting pressure values in type II achalasia, but similar IRP values when compared to type I achalasia, possibly due to sampling influence. There is accumulating evidence that with the progression of the disease, there are pressure changes at the level of the LES, but the mechanisms are not completely understood.

In our study, 52.8% of patients had type I achalasia, while type III achalasia was less frequent. The patients with type III achalasia were older [3]. Other studies [5] also reported that type III achalasia was less common, and that patients were older, making less likely the type III pattern as the first stage of the disease. In conclusion, we also believe that so far there are insufficient data to state that achalasia subtypes progress from type III to type I, or even from type II to type I.

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Space organization and personnel psychological support: unmet needs in the endoscopic assessment during pandemic

To the Editor,

During the last year, Gastroenterology and Endoscopy Units have been reorganized worldwide in order to contain the SARS-CoV-2 virus spreading [1, 2]. As outlined in a recent manuscript published in the *Journal of Gastrointestinal and Liver Diseases* [3], novel ways of patients' triage have been applied to identify and then perform only strictly necessary endoscopic examinations in location where the first pandemic

wave had hit hardest. Following a better control of the epidemic and the advent of vaccines, such measures have been further reset to improve productivity with the necessary level of safety for both patients and personnel during the “co-habitation” with SARS-CoV-2. This scenario of “dynamic-risk” first led to a renewed and flexible arrangement of the endoscopic spaces and organization into the Endoscopic Units, and it brought a renewed awareness for the needs of and risks to the endoscopic personnel besides those of our patients.

The mental health of the professionals involved in the aforementioned procedures needs to be taken into particular consideration. In fact, in relation to the mental health of professionals working in COVID-19 care units as both first- and second-line staff, symptoms of burn-out (including mental exhaustion, irritability, detachment from reality, and insomnia) are usually expected as correlations of changed daily routines. In a recent survey involving medical and non-medical healthcare workers, Zhang et al [4] reported a higher prevalence of insomnia, anxiety, depressive, somatoform and obsessive-compulsive symptoms in the mental health of the assessed staff. Moreover, the front-line medical staff operating in close contact with infected patients, including gastroenterologists in endoscopic units, displayed a higher score on the measurement of depressive/anxiety symptoms, with a two-fold risk of developing mental health problems [5]. In some cases, the neglected burden on mental health can contribute to a higher risk of burn-out and suicidal behaviour for healthcare professionals. In light of the above, timely and effective interventions including psychological support, psycho-therapeutic, Eye Movement Desensitization and Reprocessing and neuro-feedback interventions should be made accessible to endoscopists involved in first- and second line COVID-19 units.

The half-life of SARS-CoV-2 in aerosol has been estimated at approximately 1.1 hour (95%CI: 0.64–2.64). To prevent the virus transmission, several aspects should be systematically taken into account. Firstly, overcrowding should be always avoided. Crowding is a result of a mismatch among several independent variables related to either the ambient (e.g., walkable surface, room volume) or the occupants (i.e., patients and healthcare personnel). A systematic review commissioned by the WHO and published in 2018 assessed the certainty of the evidence that reducing crowding would decrease the risk of non-TB respiratory disease as moderate-to-high, depending on the disease (<https://apps.who.int/iris/bitstream/handle/10665/276001/9789241550376-eng.pdf>). Density is an objective measure of crowding and refers to the number of people in any given space - e.g., per square meter. There is no validated threshold for optimal and tolerable crowding index in the endoscopic facilities. Ideally, a value of ≤ 0.14 person per square meter (corresponding to a 7-square meter surface per person) would allow for a potential inter-personal distance of 3 meters. Notably, crowding depends not only on objective parameters such as the density of people sharing the ambient, but even on the people relationships and mobility (<http://condor.stcloud.msus.edu/~jaz/psy373/7.crowding.html>).

The air change per hour (ACH) is another pivotal factor affecting the risk of viral transmission. The ACH is the ratio of the volume of air flowing through a space in a certain period

of time (the airflow rate) to the volume of that space (the room volume) (<https://www.cdc.gov/infectioncontrol/guidelines/environmental/index.html>). ACH depends on several factors (air ventilation, free-space volume, room temperature and shape) whose individual contribution drives the design of modern healthcare buildings. According to the WHO guidelines on the Natural Ventilation for Infection Control in Health-Care Settings advised after the SARS outbreak, patients who require airborne isolation precautions should be placed in an “airborne precaution room” with >12 ACH (e.g., equivalent to >80 l/sec. for a $4 \times 2 \times 3 \text{ m}^3$ room) and controlled airflow direction. In an airborne precaution room for infection control, a pressure > 2.5 Pa (also 10 Pa) is mechanically maintained relative to the corridor. Negative-pressure endoscopic rooms should be preferred, especially for COVID-19 patients, to abolish the contamination of corridors. Alternatively, well-naturally ventilated rooms may be sufficient only when an adequate time interval between examinations is set. Thirty minutes may be a fair amount of time to decrease the airborne viral load, but this largely depends on windows opening and outdoor conditions (e.g., wind speed, wind exposition).

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SARS-CoV-2 infection might cause transient cutaneous lesions in IBD patients under treatment with adalimumab

To the Editor,

The coronavirus 2019 disease (COVID-19) outbreak, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has shown a wide range of clinical manifestations, including dermatological lesions [1]. Recent data found anti-tumor necrosis factor (TNF) α antibodies less dangerous than expected on the outcome of the inflammatory bowel diseases (IBD) patients with COVID-19, and therefore, their during COVID-19 infection is discouraged [2]. Although the clinical picture may be milder in those patients, some unusual features may be detected.

Case 1

A 48-year-old male was admitted to the Ambulatory of Dermatology due to a 5-day history of fever (max 38°C) associated to maculopapular, painful and itching lesion on the scalp and neck, among hair follicle (Fig. 1). He suffered also from ileal Crohn's disease (CD) and had been under treatment with Adalimumab 40 mg subcutaneously e.o.w. for 10 years without any adverse event. He was under sustained remission for 5 years, and no other comorbidities were reported. He denied any drug intake, excepting paracetamol for fever. Rapid serological qualitative testing and nasopharyngeal swab confirmed SARS-CoV-2 infection. The cutaneous lesions were attributed to SARS-CoV-2: he come back in home to quarantine and started immediately therapy with azithromycin 500 mg/day for ten days. Adalimumab injections were not

stopped, and the clinical picture improved rapidly. Fever disappeared within two days, and also dermatological lesions rapidly improved. Pain and itching disappeared within 5 days, and lesions almost disappeared within 10 days. No occurrence of abdominal pain or changes in bowel habits were recorded during the stay home, and also fecal calprotectin assessment was normal (48 mg/kg, normal value <50 mg/kg).

Case 2

A 32-year-old male was admitted to the Ambulatory of Dermatology due to a 3-day history of hitching vesicular eruptions, located in the suprapubic region and on the penis. He suffered also from ileo-colonic CD and was under treatment with Adalimumab 40 mg subcutaneously e.o.w. for 3 years without any adverse event. He was under sustained remission for 2 years, and no other comorbidities were reported. He was affected by asymptomatic SARS-CoV-2 infection by 5 days, and cutaneous lesions occurred 2 days after COVID-19 diagnosis. The lesions were attributed to He come back in home to quarantine, and no treatment was prescribed because he was asymptomatic. The cutaneous lesions rapidly improved: itching disappeared within 2 days, and the lesions disappeared within 7 days. Significantly, also in this case no occurrence of abdominal pain or changes in bowel habits were recorded during his stay at home.

Despite their increasing incidence [3], the mechanisms of COVID-19 cutaneous manifestations are not yet well known. It has been postulated an activation of the immune system as a consequence of the infection, while another hypothesis is that the higher angiotensin-converting enzyme 2 expression in skin tissues [4] could be a target for SARS-CoV-2 and explain therefore the cutaneous lesions during COVID-19.

This mechanism could also explain the finding of our cases. Our patients were suffering from CD, under treatment with adalimumab, an anti-TNF α antibody, and were under remission. We can postulate that adalimumab could control significantly the "cytokine storm", without any recurrence of the intestinal disease and just leading to a milder form of the disease (transient cutaneous lesions) when infected by SARS-CoV-2. This hypothesis seems to be confirmed not only by the lower risk of severe complications both in IBD patients [2] and in psoriasis patients under treatment with biologic therapy and suffering from COVID-19 [5].

In conclusion, these cases not only reported an uncommon single manifestation of COVID-19, but also supported further the hypothesis that anti-TNF α antibodies could be of benefit in reducing the risk of severe disease in patients suffering from COVID-19, sometimes causing just transient cutaneous lesions.

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Fig. 1. Cutaneous lesion of the scalp, behind the right ear, occurring together with fever. It appeared red, painful and hitching, and disappeared within 10 days after first occurrence.