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Lack of complications in patients with eosinophilic gastrointestinal diseases during SARS-CoV-2 outbreak

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Clinical Implications

- In our high-risk area, no cases of coronavirus disease 2019 were reported among patients with eosinophilic gastrointestinal disorders, even though they continued to take proton pump inhibitors and corticosteroids. This suggests that such patients do not require special care regarding isolation, hospitalization, or medication withdrawal.

Eosinophilic gastrointestinal diseases (EGIDs) are chronic immune/antigen-mediated disorders characterized by eosinophilic inflammation. They can affect the esophagus (eosinophilic esophagitis [EoE]), the stomach, and the small bowel (eosinophilic gastroenteritis [EGE]) and the colon (eosinophilic colitis [EC]). Medical therapies consist primarily of proton pump inhibitors (PPIs) or orally administered topical corticosteroids for EoE. Systemic corticosteroids or biologics are used in case of refractory EoE and in case of EGE and EC, despite the well-known adverse events associated with their long-term administration.[1,2]

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for coronavirus disease 2019 (COVID-19), which was declared a pandemic in March 2020, with more than 1,250,000 cases and more than 70,000 fatalities reported worldwide as of April 6, 2020. After the outbreak in China, Northern Italy quickly became one of the areas with the highest incidence of new cases. In particular, mortality appears to be highly influenced by age and concomitant presence of chronic diseases. Currently, no data are available on the potential viral effects in patients with EGIDs. Moreover, it is unknown whether their therapies, including both steroids and PPIs, may represent a risk factor for the development of more severe infectious disease or complications.[3,4]

In this prospective, observational, single-center case-controlled study, we investigated whether patients with EGIDs had an increased risk of beaing infected by COVID-19. Between March 18 and April 6, 2020, we contacted by e-mail or phone all the patients with EGIDs longitudinally followed-up at the University Hospital of Padua and living in the Veneto Region, who had previously provided written informed consent to be included in our EGID registry (CESC 4204/AO/17). For comparison, a group of patients with uncomplicated celiac disease (CeD) diagnosed according to international criteria and routinely followed-up at our center and included in our CeD registry (CESC 4680/AO/19) were asked to complete the same Web-based survey. Patients were asked to complete an ad hoc Web-based COVID-19 survey (see Table E1 in this article's Online Repository at www.jaci-inpractice.org) with questions relating to demographic characteristics, clinical features, type of disease, ongoing therapy, and comorbidities, and information regarding COVID-19.

Of 145 patients with EGIDs who were contacted, 130 returned the questionnaires; the mean age of these participants was 37 years and included 28 females, as described in Table I. The control group was composed of 135 patients with uncomplicated CeD with a mean age of 40.9 years and included 102 females. They were interviewed after following a gluten-free diet for an average of 6.6 years (range, 1-36 years). There were no differences in terms of age ($P = .256$), but the 2 populations differed in terms of sex ($P < .0001$) and PPI use ($P < .0001$).

During the study period, all patients with EGIDs were recommended to continue their treatment regimens (see Table II). Moreover, they declared to have followed the preventive measures suggested by our National Health System and Italian Gastroenterological Societies (100%). Both patients with EGIDs and controls with CeD were in clinical remission. No cases of COVID-19 were reported, and no patient was admitted to hospital with SARS-CoV-2 laboratory-confirmed disease. Similarly, none of the patients with CeD reported SARS-CoV-2 laboratory-confirmed disease (vs EGIDs, $P = 1.0000$). Moreover, 15 patients with EGIDs experienced mild flu-like symptoms, with 3 undergoing nasopharyngeal swabs for SARS-CoV-2 and 15 undergoing serological tests, which provided negative results. In addition, 11 patients with EGIDs reported potential contact with people with COVID-19. Likewise, 19 patients with CeD experienced flu-like symptoms, with 1 of them undergoing nasopharyngeal swab and 6 of them undergoing serological tests, with negative results (vs EGIDs, $P = .7150$). Furthermore, 11 of them reported potential contact with people with COVID-19 (vs EGIDs, $P = 1.0000$). During the same period, 338 patients without any known history of EGIDs were admitted to the University Hospital of Padua because of severe COVID-19 (115 in the non−intensive care unit, 31 in the intensive care unit, 157 discharged, and 35 deceased). Furthermore, for the approximately 4,906,000 inhabitants in the Veneto region, a total of 11,588 cases of SARS-CoV-2 infection were recorded (0.24%; n = 1893 hospitalized; n = 662 deceased).

Chronic conditions, such as diabetes, cardiovascular diseases, and inflammatory bowel diseases, have been associated with increased morbidity and mortality due to COVID-19.[5,6] In contrast, during the peak phase of the SARS-CoV-2 outbreak in Northern Italy, no cases of COVID-19 were reported in our EGID cohort of 135 subjects. Moreover, 15 patients experienced flu-like symptoms, but no complications or development of severe acute respiratory syndrome were seen in them. To note, a similar infection rate and symptom reporting were recorded in our control group of patients with CeD. A potential explanation of these discrepancies is that all our patients with EGIDs were in remission at the time of the COVID-19 peak phase and only a minority of our patients with EGIDs were taking corticosteroids or biologics. In addition, the average age of our cohort was

TABLE I. Demographic and clinical characteristis of patients with EGIDs and controls with CeD included in the study

Characteristic	Patients with EGIDs	Patients with CeD
Number of patients contacted	145	168
Patients who answered the survey, n (%)	100 (69.0)	120 (71.4)
Patients interviewed by phone call or direct contact, n (%)	30 (20.7)	15 (8.9)
Patients who did not answer, n (%)	15 (10.3)	33 (19.6)
Mean age (y) (range)	37.3 (6-79)	40.9 (16-87)
Mean age at diagnosis (y) (range)	33.1 (5-69)	33.8 (10-75)
Sex male/female, n (%)	102/28 (78.4/21.6)	33/102 (24.5/75.5)
BMI (kg/m^2)	23.3(15-42)	22.6 (17-35)
Smoking, n (%)	34 (25.2)	55 (32.7)
Patients with allergic comorbidities, n (%)	93 (71.5)	NA
Disease phenotype		
EoE, n (%)	117 (92.5)	NA
EGE, n (%)	4 (2.5)	NA
EC, n (%)	9 (5.0)	NA
Comorbidities		
None, n (%)	97 (74.6)	83 (61.5)
Diabetes, cardiovascular diseases, hypercholesterolemia, n (%)	10 (7.7)	22 (16.3)
Previous surgery, n (%)	7 (5.4)	12 (8.9)
Previous neoplasia, n (%)	2 (1.5)	6 (4.4)
Klinefelter's syndrome, n (%)	2 (1.5)	0 (0.0)
Others (ulcerative colitis, Crohn disease, autoimmune thyroiditis, rheumatic disorders), n (%)	14 (10.8)	49 (36.3)
Treatments at the time of COVID-19 outbreak		
PPIs, n (%)	88 (67.7)	22 (16.5)
Six Food Elimination Diet, n (%)	9 (7.5)	NA
Gluten-free diet, n (%)	NA	133 (100)
Topical steroids, n (%)	78 (60.0)	NA
Systemic steroids (prednisone, budesonide), n (%)	9 (6.9)	NA
Biologics (ie, vedolizumab, omalizumab), n (%)	Vedolizumab 1 (0.8)	NA
	Omalizumab 1 (0.8)	
Others (leukotriene receptor antagonists, sodium cromoglycate, methotrexate), n (%)	5 (3.8)	NA
Flu vaccination		
No, n (%)	92 (70.8)	110 (81.5)
Yes, n (%)	28 (29.2)	25 (18.5)
Number of patients with confirmed diagnosis of COVID-19 (ie, nasopharyngeal swab or serological tests)	0 (0.0)	0 (0.0)
Number of patients having contact with friends or family members with confirmed diagnosis of COVID-19 (ie, nasopharyngeal swab)?	0 (0.0)	0 (0.0)
Number of patients experiencing flu-like symptoms (malaise, cough, myalgia, arthralgia, fever, dyspnea) suspected for COVID-19	15 (11.1)	19 (13.1)
Number of patients having contact with subjects experiencing flu-like symptoms (malaise, cough, myalgia, arthralgia, fever, dyspnea) suspected for COVID-19?	11 (8.1)	11 (7.5)

BMI, Body mass index; *NA*, not applicable/available.

relatively low. Therefore, we cannot exclude the possibility that some of our patients were indeed infected by COVID-19, but presented poor or no symptoms.

As previously mentioned, at present, there are no data regarding Coronaviridiae infection in patients with EGIDs, especially in those who are taking chronic therapies for their conditions, such as corticosteroids and biologics, which in some cases have been associated with a potential increased risk of infection, including flu.[4,7] Only a minority of our patients were treated with systemic steroids or biologic drugs. However, we did not observe any influence of these treatments on COVID-19 and disease outcomes. Moreover, it is relevant to emphasize that recent uncontrolled observations suggest that immunomodulation could even be helpful in a subgroup of patients with severe COVID-19 with hyperinflammatory features.[8]

PPIs have been associated with increased risk of infection, mainly gastrointestinal infections, although the magnitude of this association varies considerably considering the available literature.[3] Furthermore, a possible association between PPI use and pneumonia has been hypothesized, due to the potential ascending bacterial colonization from the gut as the effect of the high intragastric pH induced by PPIs. This is relevant because recent studies have observed that in more than 20% of patients with SARS-CoV-2, viral RNA remains positive in feces even after negative conversion of viral RNA in the respiratory tract, thus indicating that gastrointestinal viral infection represents a

TABLE II. Medical treatments at the time of COVID-19 peak stratified according to different EGIDs

	Whole EGID population (N = 135)	EoE (N = 117)	EGE (N = 4)	EC (N = 9)
PPIs, n (%)	88 (67.7)	78 (66.7)	3 (75.0)	7 (77.8)
Six Food Elimination Diet, n (%)	9 (7.5)	9 (7.7)	0 (0.0)	0 (0.0)
Topical steroids, n (%)	78 (60.0)	76 (65.0)	2 (50.0)	0 (0.0)
Systemic steroids (prednisone, budesonide), n (%)	9 (6.9)	0 (0.0)	2 (50.0)	7 (77.8)
Biologics (ie, vedolizumab, omalizumab), n (%)	2 (1.6)	0 (0.0)	2 (50.0)	0 (0.0)
Others (leukotriene receptor antagonists, sodium cromoglycate, methotrexate), n (%)	5 (3.8)	1 (0.9)	1 (25.0)	3 (33.3)

potential transmission route for the virus.[9] Nevertheless, despite the remarkable intake of acid-suppressant drugs by our patients with EGIDs (67.7%), we did not observe confirmed cases of COVID-19 in them.

In conclusion, despite the limited sample size of our cohort, particularly considering patients with EGE and EC, and the lack of objective assessment of COVID-19, our data suggest that patients with EGIDs do not appear to have an increased risk of morbidity and mortality for SARS-CoV-2. Moreover, they can be reassured to safely continue their treatments. These preliminary results require further investigation to implement guidelines on the management of patients with EGIDs during the COVID-19 global pandemic.

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ONLINE REPOSITORY

TABLE E1. Questions included in the Web-based COVID-19 survey administered to patients with EGIDs

1.	Please indicate your date of birth (dd/mm/yyyy), age, sex (male/female), height (cm), and weight (kg).
2.	Are you smoking? Yes/No
3.	Are you affected by eosinophilic esophagitis (Yes/No), eosinophilic gastroenteritis (Yes/No), or eosinophilic colitis (Yes/No)? When the diagnosis was achieved (dd/mm/yyyy)?
4.	Are you affected by other allergic comorbidities: rhinitis (Yes/No), conjunctivitis (Yes/No), asthma (Yes/No), atopic dermatitis (Yes/No), others (please, indicate)?
5.	Are you affected by other relevant comorbidities: diabetes (Yes/No), hypertension (Yes/No), hypercholesterolemia (Yes/No), previous surgery (Yes/No), previous neoplasia (Yes/No), ulcerative colitis (Yes/No), Crohn disease (Yes/No), autoimmune thyroiditis (Yes/No), rheumatic disorders (Yes/No), others (please, indicate)?
6.	Which therapy are you taking for your eosinophilic condition: proton pump inhibitors (Yes/No), elimination diet (Yes/No), gluten-free diet (Yes/No), topical steroids such as budesonide spray (Yes/No) or fluticasone spray (Yes/No), systemic steroids such as prednisone (Yes/No) or oral budesonide (Yes/No), biologics such as vedolizumab (Yes/No) or omalizumab (Yes/No), others (please, indicate)?
7.	Are you continuing to take the prescribed therapies for your eosinophilic disorder, as recommended? (Yes/No)
8.	Are you experiencing symptoms potentially related to your eosinophilic condition? (Yes/No). If yes, which symptom? (please, indicate)
9.	Did you undergo seasonal flu vaccination? (Yes/No)
10.	Have you been diagnosed with COVID-19 infection (ie, nasopharyngeal swab)? (Yes/No)
11.	Have you been in contact with someone (friends or family members) diagnosed with COVID-19 (ie, nasopharyngeal swab)? (Yes/No)
12.	Did you experience flu-like symptoms (for instance, malaise, cough, myalgia, arthralgia, fever, dyspnea) suspected for COVID-19 infection? (Yes/No)
13.	Did someone in contact with you experience flu-like symptoms (for instance, malaise, cough, myalgia, arthralgia, fever, dyspnea) suspected for COVID-19 infection? (Yes/No)