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# Digestive and Liver Disease

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## Alimentary Tract

### Impact of COVID-19 pandemic on the management of paediatric inflammatory bowel disease: An Italian multicentre study on behalf of the SIGENP IBD Group



Serena Arrigo<sup>a</sup>, Patrizia Alvisi<sup>b</sup>, Claudia Banzato<sup>c</sup>, Matteo Bramuzzo<sup>d</sup>, Rosaria Celano<sup>e</sup>, Fortunata Civitelli<sup>f</sup>, Giulia D'Arcangelo<sup>g</sup>, Anna Dilillo<sup>h</sup>, Valeria Dipasquale<sup>i</sup>, Enrico Felici<sup>j</sup>, Maurizio Fuoti<sup>k</sup>, Simona Gatti<sup>l</sup>, Daniela Knafelz<sup>m</sup>, Paolo Lionetti<sup>n</sup>, Federica Mario<sup>o</sup>, Antonio Marseglia<sup>p</sup>, Stefano Martellosi<sup>o</sup>, Chiara Moretti<sup>q</sup>, Lorenzo Norsara<sup>r</sup>, Roberto Panceri<sup>s</sup>, Sara Renzo<sup>n</sup>, Claudio Romano<sup>i</sup>, Erminia Romeo<sup>t</sup>, Caterina Strisciuglio<sup>u</sup>, Massimo Martinelli<sup>v,\*</sup>

<sup>a</sup> Pediatric Gastroenterology and Endoscopy Unit, Institute 'Giannina Gaslini', Genoa, Italy

<sup>b</sup> Pediatric Gastroenterology Unit, Maggiore Hospital, Bologna, Italy

<sup>c</sup> Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, Pediatric Division, University of Verona, Verona, Italy

<sup>d</sup> Institute for Maternal and Child Health, IRCCS Burlo Garofalo, Trieste, Italy

<sup>e</sup> Fondazione IRCCS Ca' Grande, Ospedale Maggiore Policlinico, Pediatric Intermediate Care Unit, Milan, Italy

<sup>f</sup> Department of Gender diseases, Child and Adolescent health, Pediatric unit, Sant'Eugenio Hospital, Rome, Italy

<sup>g</sup> Women's and Children's Health Department, Pediatric Gastroenterology and Hepatology Unit, Sapienza University of Rome, Rome, Italy

<sup>h</sup> Pediatric and Neonatology Unit, Sapienza University of Rome, Santa Maria Goretti Hospital, Latina, Italy

<sup>i</sup> Paediatric Gastroenterology and Cystic Fibrosis Unit, Department of Human Pathology in Adult and Developmental Age "Gaetano Barresi", University of Messina, Italy

<sup>j</sup> Pediatric and Pediatric Emergency Unit, "Umberto Bosio" Center for Digestive Diseases, The Children Hospital, AO SS Antonio e Biagio e C. Arrigo, Alessandria, Italy

<sup>k</sup> Pediatric Gastroenterology and GI Endoscopy, University Department of Pediatrics, Children's Hospital, Spedali Civili, Brescia, Italy

<sup>l</sup> Department of Pediatrics, Università Politecnica delle Marche, Ancona, Italy

<sup>m</sup> Hepatology and Gastroenterology Unit, Bambino Gesù Hospital, Rome, Italy

<sup>n</sup> University of Florence-Meyer Hospital, Florence, Italy

<sup>o</sup> Pediatric Unit, Ca' Foncello's Hospital, Treviso, Italy

<sup>p</sup> Fondazione IRCCS Casa Sollievo della Sofferenza, Division of Pediatrics, San Giovanni Rotondo, Italy

<sup>q</sup> Paediatrics Division, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

<sup>r</sup> Paediatric Hepatology Gastroenterology and Transplantation, Papa Giovanni XXIII Hospital, Bergamo, Italy

<sup>s</sup> Department of Pediatrics, University of Milano-Bicocca, Foundation MBBM/San Gerardo Hospital, Monza, Italy

<sup>t</sup> Digestive Surgery and Endoscopy Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

<sup>u</sup> Department of Woman, Child and General and Specialistic Surgery, University of Campania "Luigi Vanvitelli", Naples, Italy

<sup>v</sup> Department of Translational Medical Science, Section of Pediatrics, University of Naples "Federico II", Italy

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## ABSTRACT

**Background:** IBD management has been significantly affected during the COVID-19 lockdown with potential clinical issues.

**Aims:** The aim of this study was to analyse the impact of COVID-19 pandemic on the Italian paediatric IBD cohort.

**Methods:** This was a multicentre, retrospective, cohort investigation including 21 different Italian IBD referral centres. An electronic data collection was performed among the participating centres including: clinical characteristics of IBD patients, number of COVID-19 cases and clinical outcomes, disease management during the lockdown and the previous 9 weeks.

**Results:** 2291 children affected by IBD were enrolled. We experienced a significant reduction of the hospital admissions [604/2291 (26.3%) vs 1281/2291 (55.9%);  $p < 0.001$ ]. More specifically, we observed a

\* Corresponding author.

E-mail address: [massimo.martinelli@unina.it](mailto:massimo.martinelli@unina.it) (M. Martinelli).

duction of hospitalizations for new diagnosis (from  $n=44$  to  $n=27$ ) and endoscopic re-evaluations (from  $n=46$  to  $n=8$ ). Hospitalization for relapses and surgical procedures remained substantially unchanged. Biologic infusions did not significantly vary [393/2291 (17.1%) vs 368/2291 (16%);  $p=0.3$ ]. Telemedicine services for children with IBD were activated in 52.3% of the centres. In 42/2291 (1.8%) children immunosuppressive therapies were adapted due to the concurrent COVID-19 pandemic.

**Conclusion:** Due to the several limitations of the lockdown, cares for children with IBD have been kept to minimal standards, giving priorities to the urgencies and to biologics' infusions and implementing telemedicine services.

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## Introduction

Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has significantly challenged the access to primary hospital cares [1]. Starting from March 2020, Italy has been one of the most affected countries in Europe with up to 10% of the cases requiring admission to intensive care units with over 35,000 deaths up to date [2]. From March 9<sup>th</sup> to May 4<sup>th</sup>, the government established a strict lockdown with significant limitations for the national health system services. All scheduled out and inpatients' visits were postponed and the accesses were limited only for clinical urgencies. As a consequence, the management of chronic inflammatory conditions, such as inflammatory bowel disease (IBD), was significantly affected with potential clinical and psychological issues, including reduced compliance to the immunosuppressants and symptoms denying with reduced disease control [3–5]. Although COVID-19 infection showed less impact on children and adolescents [6,7], it is uncertain whether children with IBD, may be more susceptible to SARS-CoV-2 infection [8,9]. Preliminary reports seem to be encouraging with no or few cases in the most interested areas, as well as a benign course [10–12]. Indeed, despite the potential risks related to immunosuppression, international IBD societies strongly recommended not to suspend treatments in order to reduce the risk of relapses and the need of hospitalization [10,13–16]. Taken into account these considerations, the major concerns were necessarily related to consequence of the lockdown. The aim of this study was to analyse the impact of COVID-19 pandemic related lock-down on the levels of cares offered to paediatric IBD patients all over the

Italian territory, comparing the clinical activities performed before and during the lockdown.

## Methods

This was a multicentre, retrospective, cohort investigation including 21 different IBD referral centres of the Italian Society of Paediatric Gastroenterology, Hepatology and Nutrition (SIGENP). The list of adhering centres is shown in Table 1. In order to determine impact of COVID-19 lockdown on the healthcare system, an electronic data collection through a specifically designed web-based platform was performed among the participating centres. In details, the questionnaire-form included all the following items: demographic and clinical characteristics of IBD patients (age, sex, IBD type), number of patients under immunosuppressive, biologic or combination therapy, number of COVID-19 cases (confirmed with nasopharyngeal swab) and their clinical outcomes. The following data regarding the management of IBD children during the Italian lockdown (from March 9<sup>th</sup> to May 5<sup>th</sup>, 2020) and during the previous 9 weeks were collected: number and reason (clinical relapse, new diagnosis, monitoring) of IBD related hospitalizations and endoscopic investigations, number of outpatient, inpatient, transition and telemedicine visits, number of biologics' infusions, therapy withdrawals, new diagnoses and number of patients put under steroid, immunosuppressive or biologic therapy, or switched from an intravenous to a subcutaneous biologic. The Institutional Review Board of the University of Naples "Federico II" approved the study protocol. Written, informed consent was obtained from all parents and from children, where appropriate.

**Table 1**  
Participating Italian paediatric IBD referral centres.

Centres	N. of IBD children (N = 2291)	Region	N. of COVID19 cases/100000 inhabitants*
University of Naples "Federico II", Naples	183	Campania	78
University of Campania "Luigi Vanvitelli", Naples	13	Campania	-
Maggiore Hospital, Bologna	210	Emilia-Romagna	589
Burlo Garofalo, Trieste	78	Friuli	254
Bambino Gesù Hospital, Rome	376	Lazio	117
University La Sapienza, Rome	207	Lazio	-
Sant'Eugenio Hospital, Rome	2	Lazio	-
Santa Maria Goretti Hospital, Latina	3	Lazio	-
Gaslini Hospital, Genoa	130	Liguria	546
Niguarda Hospital, Milan	35	Lombardia	781
Maggiore Hospital, Milan	35	Lombardia	-
Spedali Civili Hospital, Brescia	72	Lombardia	-
University of Milano-Bicocca, Monza	89	Lombardia	-
Papa Giovanni XXIII Hospital, Bergamo	61	Lombardia	-
Università Politecnica delle Marche, Ancona	42	Marche	419
AO SS Antonio e Biagio e C. Arrigo, Alessandria	63	Piemonte	566
Casa Sollievo della Sofferenza, S. Giovanni Rotondo	105	Puglia	103
University of Messina, Messina	300	Sicilia	65
Meyer Hospital, Florence	227	Toscana	258
Ca' Foncello Hospital, Treviso	42	Veneto	375
University of Verona, Verona	18	Veneto	-

\* Number of COVID-19 cases/100000 inhabitants in each Italian region on May 5<sup>th</sup>, 2020 from Italian Ministry of Health (<http://opendatadpc.maps.arcgis.com/apps/opsdashboard/index.html#/b0c68bce2cce478eaac82fe38d4138b1>) IBD: Inflammatory Bowel Disease

**Table 2**

Clinical characteristics of 2291 Italian children with Inflammatory Bowel disease followed at the referral centres completing the survey at the time of COVID-19 pandemic. Characteristics (n, %)

Mean age ± SD, (years)	14.3 ± 1.6
Gender	
Male	1296 (56.5)
Diagnosis	
Crohn's disease	984 (42.9)
Ulcerative Colitis	1177 (51.3)
IBD-U	130 (5.7)
Immunosuppressive therapy	1717 (74.9)
Immunosuppressants	847 (49.3)
Azathioprine	740 (87.3)
Methotrexate	75 (8.9)
Thalidomide	31 (3.6)
Cyclosporine	1 (0.1)
Biologics	762 (44.4)
Infliximab	372 (48.8)
Adalimumab	332 (43.5)
Vedolizumab	38 (5)
Ustekinumab	16 (2.1)
Risankizumab (clinical trial)	4 (0.6)
Combo therapy	108 (6.3)
IFX+AZA	50 (46.2)
ADA+MTX	21 (19.4)
IFX+MTX	18 (16.6)
ADA+AZA	16 (14.8)
VEDO+MTX	2 (1.8)
VEDO+AZA	1 (0.9)

ADA: Adalimumab; AZA: Azathioprine; CD: Crohn's disease; IFX: Influximab; MTX: Methotrexate; UC: Ulcerative Colitis; VEDO: Vedolizumab

**Statistical analysis**

Variables were screened for their distribution, and appropriate parametric or non-parametric tests were adopted as necessary. Percentages were rounded to the nearest whole numbers. The Student's t-test test for continuous variables and Fisher's exact tests for categorical variables were used where appropriate. Statistical significance was predetermined as  $p < 0.05$ . SPSS version 20 (SPSS Inc, Chicago, Illinois) was used for all the analyses.

**Results**

*Baseline characteristics*

At the time of data collection, 2291 children [Crohn's disease (CD): 984 (42.9%), Ulcerative Colitis (UC): 1177 (51.3%), Inflammatory Bowel Disease Unclassified (IBD-U): 130 (5.7%); mean age ± SD: 14.3 ± 1.6 years; M/F: 1296/995] affected by IBD were regularly followed at the 21 participating referral centres. The clinical characteristics of children affected by IBD are shown in Table 2. Among the study population, 1717 (74.9%) were under immunosuppressive agents, including 847 (49.3%) on conventional IM, 762 (44.4%) practicing biologics and 108 (6.3%) undergoing combined therapy with IM and biologics (Table 2).

**Table 3**

COVID-19 confirmed cases within the study population.

Centre	Age (yrs)	Sex	IBD type	IBD Activity	IBD therapy	COVID-19 symptoms	Hospitalization
Alessandria	11	M	UC	Remission	AZA	Fever, cough	No
Bologna	17	F	CD	Remission	ADA	Fever	No
Florence	15	M	UC	Remission	AZA	Rhinitis	No
Genoa	9	F	UC	Active	Steroids, 5-ASA	None	No
Monza	11	F	CD	Remission	IFX	Fever	No
Rome	18	M	UC	Remission	AZA	Fever, cough Pneumonia	Yes

5-ASA: Mesalazine; AZA: Azathioprine; CD: Crohn's disease; IFX: Influximab; M: male; F: female; UC: Ulcerative Colitis.

*COVID-19 cases*

Only 6 out of 21 (4.7%) participating centres reported children with IBD infected with SARS-CoV-2 with a total of 6 cases out of 2291 (0.2%) being identified. Demographic and clinical characteristics of the infected children are summarized in Table 3. In 5 out of 6 (83.3%) cases, the clinical course of the SARS-CoV-2 infection resulted mild, without the need of hospitalization. Only one 18 years' old girl affected by UC was hospitalized for 1 week due to COVID-19 pneumonia with benign outcomes. The underlying IBD remained generally stable during the infection and the IBD-related medications were not suspended in any of the cases (Table 3).

*Impact of lockdown on IBD management*

During the lockdown phase, we experienced a significant reduction of the overall hospital admissions when compared to the previous 9 weeks [604/2291 (26.3%) vs 1281/2291 (55.9%);  $p < 0.001$ ]. Number and type of hospital admission before and during the COVID-19 lockdown phase are shown in Fig. 1. In details, the number of inpatients with IBD admitted to our hospitals was significantly decreased during the lockdown phase [91/2291 (4%) vs 156/2291 (6.8%);  $p < 0.001$ ], with the mean number of hospitalization per centre reduced from  $6.9 \pm 6.4$  to  $4.1 \pm 6.4$  ( $p = 0.02$ , T-Student test). More specifically, we observed a reduction of hospitalizations for new diagnosis ( $n = 44$  new IBD diagnosis in the 9 weeks preceding the lockdown versus  $n = 27$  during the lockdown) and endoscopic re-evaluation ( $n = 46$  endoscopies performed before the lockdown versus  $n = 8$  during the lockdown). The number of hospitalization for relapse ( $n = 54$  before the lockdown versus  $n = 47$  within the lockdown) and surgical procedure ( $n = 12$  before the lockdown versus  $n = 9$  during the quarantine) remained substantially unchanged. The number and the specific reason of inpatients' visits are summarized in Fig. 2. The overall number of endoscopic procedures performed in IBD children [279/2291 (12.1%) vs 117/2291 (5.1%);  $p < 0.001$ ], as well as the number of outpatients visits [1129/2291 (49.2%) vs 512/2291 (22.3%);  $p < 0.001$ ] were significantly decreased when comparing the period preceding COVID-19 pandemic with the lockdown phase (Fig. 1). Biologics' infusions did not significantly vary [393/2291 (17.1%) vs 368/2291 (16%);  $p = 0.3$ ], while transition visits to adult service were significantly impacted [45/2291 (1.9%) vs 6/2291 (0.2%);  $p < 0.001$ ] (Fig. 1). Seventeen out of 2291 (0.7%) children were addressed to different referral centres as a consequence of the lockdown.

*Telemedicine*

A specific telemedicine service for children with IBD was activated in 11 out of 21 centres (52.3%) with an overall number of 343 telemedicine visits performed. When investigating on how the physician performed the telemedicine visit and which tools were used, we collected the following data: disease activity evaluation [PUCAI, 11/11 (100%); PCDAI, 2/11 (18.1%); weighted PCDAI, 4/11 (36.3%); short-PCDAI 4/11 (36.3%)]; compliance to therapy assess-

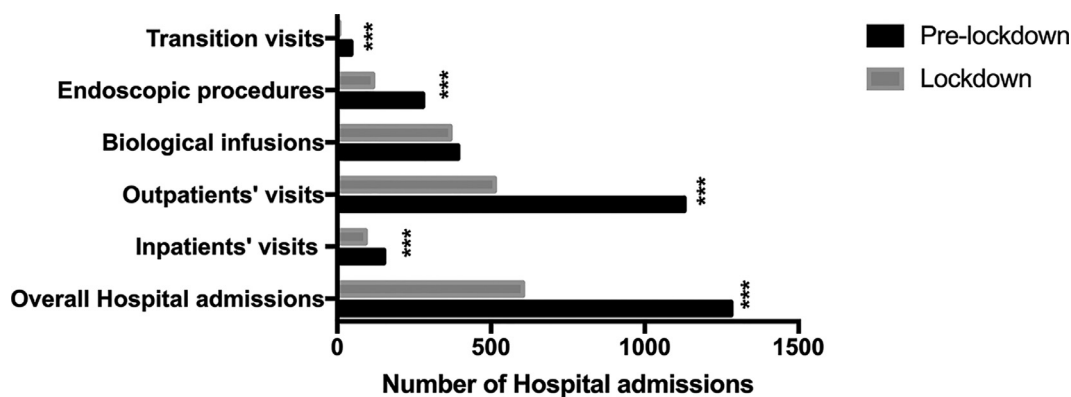


Fig. 1. Number and type of hospital admissions 9 weeks before and during the COVID-19 lockdown phase; Fisher Exact Test (\* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ ).

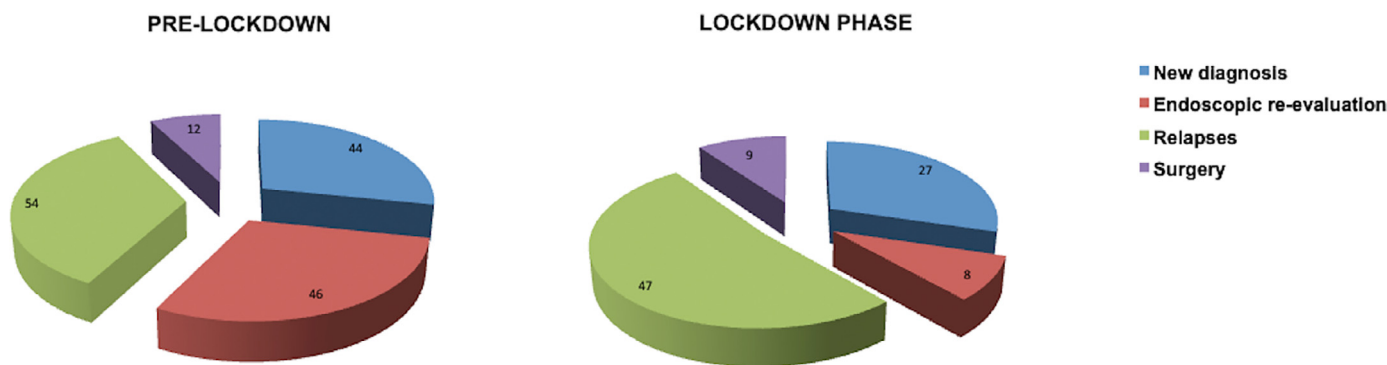


Fig. 2. Number and type of inpatients' visits 9 weeks before and during the COVID-19 lockdown phase.

ment [4/11 (36.3%)]; quality of life evaluation trough IMPACT III [2/11 (18.1%)].

*Management of immunosuppressive therapies during the pandemic*

Four out of 847 (0.5%) children under IM suspended their therapy. Of the 762 children undergoing biologics, 14 (1.8%) postponed their infusion, while in 6 (0.8%) cases a switch to a subcutaneous biologic was performed. Nine out of 108 (8.3%) patients undergoing combined therapy with biologics and conventional IM stopped one of the 2 agents. In 4 out of 27 (14.8%) new diagnoses steroids were not started, while in 5/27 (18.5%) IM or biologics beginning were postponed. Overall, in 42/2291 (1.8%) children the immunosuppressive or biologic therapy was adapted due to the concurrent COVID-19 pandemic. When we looked at the reasons for therapy modifications, we observed that in all the cases the decision was driven by parental refuse to have access to the hospital or to continue the immunosuppressive therapy due to the COVID-19 fear. In 33 children out of 42 (78.5%) these fears were discussed with the caring physician and the therapy adaptations were agreed. Differently, in 9 out of 42 (21.4%) parents decided not to continue the immunosuppressive therapy or not to attend the biologic infusion without medical advice.

**Discussion**

To the best of our knowledge this study includes the largest Italian cohort of children affected by IBD and demonstrates the radical impact of COVID-19 lockdown on its clinical and therapeutic management. As expected, we reported a drastic reduction of overall hospital admissions, with a significant decrease of endoscopic procedures, inpatients' visits, outpatients' and transition visits. As a preliminary consequence, we detected an alarming drop in the

new diagnoses when comparing the lockdown period with the 9 weeks preceding the outbreak. In contrast, despite the large use of immunosuppressants and biologics, in line with previous reports, we confirmed that children with IBD infected with SARS-CoV-2 seem to show an overall benign course.

IBD management in children is notoriously demanding, including endoscopic procedures, medical appraisal to monitor complications and hospital admission in case of severe flares or therapeutic infusions. Therefore, it is not surprising that COVID-19 related lockdown significantly challenged all the paediatric IBD referral centres [16]. The overall hospital admissions rate significantly dropped from 55.9% to 26.3%, with endoscopic procedures and outpatients' visits, including transitioning to the adult service, being the most affected activities. When specifically analysing the reasons for hospitalizations, relapses and surgeries did not vary, demonstrating that paediatric units continued to adequately provide the management of IBD urgent services despite the imposed restrictions. On the other hand elective endoscopic re-evaluations significantly decreased. Our data are in agreement with 2 recent surveys from adult and paediatric gastroenterologists reporting similar approaches in the management of IBD patients during the lockdown [17,18]. These modifications in IBD management are perfectly in line with both the indications of the Italian Health system of postponing non-urgent activities as well as with the recommendations published by International adult and Paediatric IBD Societies [10,13–15]. Despite the compliance to these recommendations, it remains uncertain whether we will register long-term consequences related to the less strict disease monitoring, also taking into account the uncertainty of COVID-19 pandemic evolution [19]. The drop of the new diagnoses during the lockdown represents the only potential alarming finding when comparing the same exact time-frame preceding COVID-19 outbreak. Differently from our data, in a recent paediatric survey conducted

by Ashton and colleagues, the authors did not observe a specific decrease in the new diagnoses compared with usual trends, but reported that in more than 50% of the cases the diagnosis was made without the aid of the histology [18]. Our finding may have different interpretations. While the reduction may simply be justified by physiological variations of the epidemiology, it is not unlikely to hypothesize diagnostic delays related to COVID-19 fear, as already reported for other diseases [20].

This study was also meant to evaluate whether tertiary centres started or implemented specific IBD telemedicine programs. Over the last decade important efforts have been made in order to set-up and implement telemedicine services in IBD patients [21]. Randomized control trials conducted in adult patients confirmed telemedicine as a well-accepted and useful tool for delivering IBD consultation. Together with a great impact on healthcare costs, it has been proven to increase patients' quality of life and to decrease the rates of hospitalization [22,23]. The sudden SARS CoV-2 pandemic represents an obvious opportunity to test and implement telemedicine services for the management of paediatric IBD [24–26]. The results of our study demonstrate that specific telemedicine services for children with IBD were activated in 52.3% of the participating centres with an overall number of 343 visits performed during the lockdown. As expected we demonstrated a huge variations in the tools used during the telephonic interviews. With regards to disease activity indexes, while there was a complete agreement on PUCAI, different scores were used for CD with higher percentages for weighted and short-PCDAI respect to the PCDAI. Additionally only a small percentage of the centres routinely assessed compliance to therapy and quality of life. In a recent British survey, Ashton and colleagues reported a significant increase of telemedicine visits with 100% of centres were able to review patients by telephone and in 65% of them to use a webcam-based review system [18]. Nevertheless, the authors did not mention which tools were used during the interviews [18]. These results confirm the importance and the usefulness of telemedicine particularly during the current pandemic. On the other side we highlight the need for a major standardization of the tools to be provided during the interviews.

Due to the usual aggressive underlying disease and the early immunomodulatory treatments, the risk of opportunistic infections is a well-recognized issue in children affected by IBD [27,28]. As a matter of fact, in our cohort 74.9% of the children were exposed to IM or biologic therapies with 6.3% of the total cases undergoing combined IM plus biologics. Therefore, it is not surprising that paediatric gastroenterology had to face the fear of an increased risk of complicated COVID-19 in children affected by IBD. Nevertheless, as already reported by preliminary studies [10–12], our data confirm that children with IBD do not seem to carry a higher risk of SARS-CoV-2 infection. Overall, only 6 cases out of 2291 (0.2%) were identified and in most of the cases the clinical course of the SARS-CoV-2 infection resulted mild. In addition, IBD-related medications were not suspended in any of the cases. The management of immunosuppressive therapies was indeed one of the main question marks during the COVID-19 lockdown, due both to physicians' and families' worries [5]. Our data demonstrated that Italian paediatric IBD centres did not modify their therapeutic approach in the most of cases, as recommended by the ESPGHAN guidelines [10]. Only in 1.8% of the cohort, therapies were adapted due to the concurrent COVID-19 pandemic, and in all of the cases due to parental fears. These data are in agreement with the recently published worldwide survey in which the rate of treatment suspension resulted very low (9.6%) [17]. Furthermore, the data reported from the SECURE-IBD registry are even more reassuring [29]. The analysis included 525 cases of patients with IBD and COVID-19, of whom 29 were younger than 19 years. None of the children resulted to be affected by severe COVID-19. At the multivariate analysis, nei-

ther biologics nether conventional immunosuppressants were associated with an increase of COVID-19 severe outcomes. Only steroid therapy was significantly associated for the development of severe COVID-19 (*aOR* 6.87, 95% *CI* 2.3–20.5) [27]. Nevertheless, the concerns regarding steroids' use seem not to be perceived in children, as demonstrated by the low 14.5% rate of newly diagnosed children not starting steroid therapy in our cohort.

It is acknowledged that the present study is not without limitations. The main drawback is obviously related to the retrospective nature, which may have resulted in recall biases. Otherwise, the main strength of the study lies in the high number of children well distributed among 21 different IBD tertiary centres on all the Italian territory. This gives us a very well defined picture of paediatric IBD management during the lockdown in one of the most affected countries by the COVID-19 pandemic.

## Conclusions

This study provides data on the impact of COVID-19 related lockdown on the management of paediatric IBD in Italy. In line with the international guidelines, due to the several limitations of the lockdown, cares for children with IBD have been kept to minimal standards, giving priorities to the urgencies, including disease flares and surgeries, and to biologics' infusion programs. The implementation of telemedicine follow-up has started in most of the centres enlarging the possibilities of follow-up for children in remission of disease. In addition, the management of immunosuppressive therapies has been successfully obtained in the majority of the cases due to the apparent mild course of the infection. On the other hand, we reported a potential decrease of the new diagnoses in the lockdown period, which may be partially related to COVID-19 fear. Taking into account the general uncertainty of COVID-19 outbreak evolution and considering the need to minimize the hospital accesses it is strongly recommended to quickly empower and standardize telemedicine strategies. At the same time it is necessary to continue data collection in order to better understand the specific risks of IBD children during COVID-19 pandemic.

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None.

## Declaration of Competing Interest

The authors have no conflict of interests to declare with regards to this manuscript.

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