GE – Portuguese Journal of Gastroenterology

Research Article

GE Port J Gastroenterol
DOI: 10.1159/000522073

Received: September 15, 2021
Accepted: January 5, 2022
Published online: March 9, 2022

Impact of COVID-19 in Pediatric Patients and Young Adults with Inflammatory Bowel Disease

Tiago Magalhães[a, b] Maria Cristina Granado[c] Ana Rute Manuel[d]
Maria do Céu Espinheira[b, e] Eunice Trindade[e]

[a]Pediatrics Department, Centro Hospitalar Universitário São João, Porto, Portugal; [b]Faculty of Medicine of the University of Porto, Porto, Portugal; [c]Pediatrics Department, Hospital Senhora da Oliveira, Guimaraes, Portugal; [d]Pediatrics Department, Hospital Professor Doutor Fernando Fonseca, Lisbon, Portugal; [e]Pediatric Gastroenterology Unit, Pediatrics Department, Centro Hospitalar Universitário São João, Porto, Portugal

Keywords
Crohn's disease · Ulcerative colitis · SARS-CoV-2 · COVID-19 · Pediatrics

Abstract
Introduction: Acute COVID-19 in pediatric and young adult patients tends to be milder in severity compared to adult infection. Recent studies seem to show that inflammatory bowel disease (IBD) patients are at no greater risk than the general population. We aim to describe our experience in the follow-up of pediatric and young adult patients with IBD followed in our center and determine possible risk factors of said population for severe COVID-19. ***Methods:*** We performed a retrospective study of all patients aged under 25 years followed for IBD at the Unit of Pediatric Gastroenterology in a tertiary center between December 2019 and April 2021 evaluating the incidence of COVID-19 and characterization of positive cases. ***Results:*** Of the 268 participants, 24 had COVID-19: the mean age was 19 years old and gender had an equal distribution; 75% (n = 18) had Crohn's disease, whereas only 25% (n = 6) had ulcerative colitis. Most patients were in clinical remission (n = 21). The majority of patients were under treatment with a tumor necrosis factor (TNF) antagonist (58%, n = 14), mainly infliximab, and most had no comorbidities other than IBD (83%). Regarding COVID-19, 17% of the patients were asymptomatic while the rest had only mild symptoms. There were no reported gastrointestinal complaints, no complications nor hospitalizations. Most patients did not require interruption of their IBD treatment. ***Conclusions:*** Our data suggest that pediatric and young adult IBD patients have a low risk for complications and hospitalization, regardless of IBD treatment. We believe that this experience is encouraging and allows for safe counseling regarding treatment options and school attendance in pediatric and young adult IBD patients.

Impacto da COVID-19 em Doentes Pediátricos e Jovens Adultos com Doença Inflamatória Intestinal

Palavras Chave
Doença de Crohn · Colite ulcerosa · SARS-CoV-2 · COVID-19 · Pediatria

Karger@karger.com
www.karger.com/pjg

Correspondence to:
Tiago Magalhães, tiago.magalhaes@chsj.min-saude.pt

Resumo

Introdução: Na população pediátrica e de jovens adultos a gravidade da COVID-19 tende a ser moderada quando comparada com os doentes adultos. Os estudos mais recentes sugerem que os doentes com doença inflamatória intestinal (DII) não têm risco acrescido em relação à população geral. O objetivo do presente estudo é a descrição da nossa experiência no follow-up de crianças e jovens adultos com DII a COVID-19 e determinar a existência de possíveis fatores de risco para doença grave na referida população. ***Métodos:*** Foi realizado um estudo retrospetivo de todos os doentes com idade inferior a 25 anos, seguidos na Unidade de Gastrenterologia Pediátrico de um centro terciário por DII, com avaliação da incidência de COVID-19 entre dezembro de 2019 e abril de 2021, e caracterização dos casos postivos. ***Resultados:*** Entre os 268 participantes, 24 tiveram COVID-19. A idade média foi de 19 anos com uma distribuição por género equiparável. Destes, 75% ($n = 18$) tinham doença de Crohn, enquanto 25% (6) tinham colite ulcerosa. A maior parte dos doentes apresentavam-se em remissão clínica ($n = 21$) e, à data da doença COVID-19. A sua maioria, os doentes encontravam-se sob tratamento com antagonistas do fator de necrose tumoral (58%, $n = 14$), predominantemente o infliximab, e a generalidade dos doentes (83%) não apresentava outras comorbilidades além da DII. Relativamente à COVID-19, 17% eram assintomáticos enquanto os restantes apresentavam apenas sintomas ligeiros. Não houve relato de queixas gastrointestinais, complicações ou necessidade de hospitalização. Na maioria dos casos, não houve necessidade de interromper o tratamento da DII. ***Conclusão:*** Os nossos dados sugerem que doentes pediátricos e jovens adultos com DII apresentam um risco baixo de complicações ou hospitalização associados à COVID-19, independentemente do tratamento em curso para a DII. Este estudo apresenta resultados encorajadores e contribui para o aconselhamento adequado e fundamentado aos doentes e respetivos cuidadores, no que diz respeito às opções terapêuticas e frequência escolar dos doentes pediátricos e jovens adultos com DII.

Introduction

Since its emergence in December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread into a global pandemic of a disease known as COVID-19, with significant public health implications around the globe [1].

The SARS-CoV-2, an enveloped RNA virus, is predominantly transmitted via respiratory droplets [2]. After contact with the virus, it enters the human cells via the angiotensin-converting enzyme 2 (ACE2) receptor using its spike protein S1 subunit. While primarily expressed in the lungs, the ACE2 receptor is also expressed in many extrapulmonary tissues, including the gastrointestinal (GI) tract. High levels of ACE2 receptors were found on the luminal surface of differentiated epithelial cells in the terminal ileum and colon [2–4].

Acute COVID-19 infections in pediatric patients have been milder in severity, with quicker recovery and fewer sequelae compared to adult infection [4, 5]. This difference is believed to be due to multiple factors such as variations in the distribution of ACE2 receptors, T-cell and B-cell responses, and the balance of modulating and pro-inflammatory cytokines [2].

Concerning the pediatric population, as of April 2021, the estimated incidence of COVID-19 in Portugal was almost 15% of all cases [6]. Yet, according to the Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD), only 103 cases were reported [7].

Until the moment, the knowledge concerning the risk of COVID-19 in inflammatory bowel disease (IBD) patients, particularly pediatric IBD patients, is still scarce [8, 9]. Recent studies seem to show that IBD patients are at no greater risk than the general population [9].

This report aims to review the experience of our center and describe the disease course of COVID-19 in our sample of pediatric IBD patients.

Materials and Methods

This retrospective study included all patients under 25 years with IBD infected by SARS-CoV-2 between December 2019 and April 2021 and followed by the Unit of Pediatric Gastroenterology in Centro Hospitalar São João anytime during that period.

Telephone inquiries were performed, in addition to consultation of medical records, and the following variables were collected: demographic data (age, gender), clinical data at the time of COVID-19 (type of IBD, IBD extension according to Paris classification, medication for IBD, disease activity according to the PUCAI and PCDAI scores measured in the last visit previous to infection as well as fecal calprotectin measured within the same timeframe, and presence of comorbidities and COVID-19 data [vaccination status, severity and length of symptoms, presence of GI symptoms, whether medication for IBD was stopped during infection, complications, and need for hospitalization]). COVID-19 severity was determined as stated in the World Health Organization (WHO) definition, being mild when symptoms were present with no evidence of viral pneumonia or hypoxia and moderate when there were clinical signs of non-severe pneumonia [10].

Table 1. Demographics, disease characteristics, and clinical outcomes of pediatric and young adult IBD patients with COVID-19 infection

Characteristic	Pediatric cohort (*N* = 11)	Young adult cohort (*N* = 13)
Median age, years (min–max)	15 (7–18)	20 (18–24)
Female sex, *n* (%)	5 (45.5%)	7 (53%)
Diagnosis, *n* (%)		
Crohn's disease	7 (64%)	11 (85%)
Ulcerative colitis	4 (36%)	2 (15%)
Disease extension (Paris classification), *n* (%)		
Crohn's disease		
L1	1 (14%)	2 (18%)
L1 + L4a	0 (0%)	1 (9%)
L2 + L4a	2 (29%)	1 (9%)
L3	3 (43%)	5 (46%)
L3 + L4a	1 (14%)	1 (9%)
L4b	0 (0%)	1 (9%)
Ulcerative colitis		
E3	4 (100%)	2 (100%)
IBD disease activity (by GPA), *n* (%)		
Remission	8 (73%)	13 (100%)
Mild	1 (9%)	0 (0%)
Moderate	2 (18%)	0 (0%)
Mean fecal calprotectin*	286.2±463.6 µg/g	210.5±186.8 µg/g
Remission	119±133.6 µg/g	210.5±186.8 µg/g
Active disease	730±466 µg/g	N/A
IBD medication, *n* (%)*,#		
Sulfasalazine/mesalamine	5 (45%)	1 (8%)
Steroids (for IBD, not COVID-19)	1 (9%)	0 (0%)
TNF antagonist monotherapy	2 (18%)	5 (38%)
Infliximab	2 (100%)	5 (100%)
TNF antagonist + AZA	2 (18%)	5 (38%)
AZA monotherapy	2 (18%)	2 (15%)
Anti-integrin (vedolizumab)	1 (9%)	0 (0%)
Mean COVID-19 symptoms duration, days	4.1±2.9	6±4.2
Comorbidities, *n* (%)	2 (18%)	1 (9%)
Asthma	0 (0%)	1 (0%)
Hepatitis	1 (9%)	0 (0%)
Cardiac arrhythmia	1 (9%)	0 (0%)

AZA, azathioprine; COVID-19, coronavirus disease 2019; GPA, Global Physician Assessment; IBD, inflammatory bowel disease; MTX, methotrexate; N/A, non-applicable; TNF, tumor necrosis factor. * At the time of COVID-19 infection. # Medication categories are not mutually exclusive unless otherwise noted.

A descriptive analysis was performed. Continuous variables with asymmetrical distribution were presented as a median (minimum–maximum).

The study was approved by the ethical committee of our institution. All information is anonymous and confidential.

Results

Of the 338 patients with IBD included, only 268 were available to answer the telephone inquiry. Of these, 24 participants had COVID-19 (Table 1). Overall, the mean age was 19 years old (minimum seven and maximum 24 years old). Specifically, there were 11 (45%) pediatric patients under 18 years old (mean 15 years) and 13 (55%) young adults (mean 20 years). Both groups had an equal gender distribution (male-to-female ratio of 1:1).

Concerning the IBD classification, 75% (*n* = 18) had Crohn's disease, whereas only 25% (*n* = 6) had ulcerative colitis. Among patients with Crohn's disease, four had ileal disease, three had colonic disease, ten had ileocolonic disease, of which two had concomitant involvement of the distal esophagus, and one patient had exclusive up-

per disease distal to the ligament of Treitz. All patients with ulcerative colitis had extensive disease according to the Paris classification.

Most patients were in clinical remission (n = 21) with only one case of mild disease activity and two cases of moderate disease activity. All three patients with active disease had ileocolic Crohn's disease and a mean disease duration of almost 6 years at the time of COVID-19. Fecal calprotectin had a mean value of 730 ± 493 μg/g in the group of patients with active disease and of 158 ± 213 μg/g in the remission group.

The majority of patients were under treatment with a tumor necrosis factor (TNF) antagonist (58%, n = 14), most commonly infliximab. Of these, 50% were treated with anti-TNF monotherapy and the other 50% with an association of anti-TNF with azathioprine.

Most patients had no comorbidities other than IBD (83%).

Regarding the COVID-19 disease, 17% (n = 4) were asymptomatic, and the remaining patients had mild disease. Average symptom duration was 4 days. In one case, a 19-year-old patient, COVID-19 infection occurred after the first dose of vaccination against COVID-19 (the vaccine used is unknown). There were no reported gastrointestinal complaints. There were no reports of complications or hospitalizations due to COVID-19, and most patients (90%) did not require interruption of their IBD treatment. The three patients who did interrupt their treatment did so for mandatory quarantine, which prevented them from going to the hospital to receive their intravenous treatment.

Discussion/Conclusion

We analyzed a total of 24 patients with IBD, less than 25 years of age, infected with SARS-CoV-2.

Despite being commonly referred to as a respiratory illness, it is now clear that COVID-19 can also affect the GI system, particularly in the pediatric population, as evidenced by a prevalence of 6% of GI symptoms found in a metanalysis of 1,810 healthy pediatric patients [11]. In our study, however, no GI symptoms were observed. This might be explained by the median age in our sample, which was higher than the median age in the metanalysis by Badal et al., even when adjusted to include only the pediatric patients (15 years [7–18] compared to 8 years [6–10]).

We reported no hospitalizations and no complications from COVID-19. These findings are in line with other studies, such as the SECURE-IBD registry that found a rate of 7% hospitalization, a 2% ventilation support requirement, and no deaths in a pool of 209 COVID-19 cases with pediatric IBD [4]. In addition, an observational study of 522 IBD patients, including 59 children in an Italian tertiary referral center, reported no admissions for SARS-CoV-2 infection [12]. Our findings are also identical to reports on young adults who are generally described to have a milder disease with a good prognosis and low hospitalization rates [3]. In fact, our sample results showed a significant overlap between both age groups, which can be explained by the high mean age found in the pediatric group.

The reasons why IBD patients appear to be less affected and develop milder clinical pictures are still unknown. It has been suggested that the lower infection rate may be a consequence of improved adherence to shielding recommendations [13]. Among the possible risk factors for severe COVID-19 described in the literature are IBD treatments such as steroids and thiopurines, whereas the use of TNF-antagonists was reported as protective [4, 14, 15]. Of note, despite concerns shown by the patients and their parents of a higher risk of infection in patients under biologic treatment, it appears that the blockage of the cytokine storm by immunomodulators taken for IBD, which lead to the control of bowel inflammation, may assist in the prevention of COVID-19 severe symptoms [5, 16]. In fact, a study conducted during the first pandemic wave found that up to 23% of pediatric patients who delayed or temporarily discontinued their biologic therapy due to the lockdown experienced a disease exacerbation [17]. Moreover, Turner et al. showed that pediatric patients who interrupted their IBD treatment had a significant rate of developing flairs while those who continued treatment had no complications [18].

The cumulative experience of the last 2 years is in favor of continuing ongoing IBD therapy and not delaying the beginning of conventional immunomodulators or biological therapy because of the pandemic situation, in patients without COVID-19 [19, 20].

An open question is the need for treatment interruption in patients with COVID-19.

The ECCO-COVID Task Force and the IOIBD recommend the interruption of anti-TNF, thiopurines, and corticosteroids in patients with SARS-CoV-2, regardless of symptoms [15, 21, 22].

In our sample, three patients had to delay their intravenous treatment during COVID-19 infection due to mandatory quarantine. The expected half-life of anti-TNF such as infliximab is almost 10 days, but its effect is

largely potentiated by the use of thiopurines like azathioprine whose immunosuppressive effect goes beyond their half-life. Perhaps, while more evidence is awaited, a personalized approach should be considered according to severity and clinical course of the disease.

Additional risk factors found for hospitalization in pediatric IBD patients with COVID-19 included other comorbidities besides IBD, moderate or severe IBD disease activity, and presence of gastrointestinal symptoms [4]. In our sample, comorbidities were found in a rather small number of cases, and only two patients had moderate disease activity. Regardless, no complications nor hospitalizations were reported in this group.

This study has limitations. First, its retrospective nature might have led to the underestimation of the severity and length of the symptoms by the participants. Secondly, no statistical analysis was performed due to the sample size.

In conclusion, we present the reassuring experience of our center in the follow-up of pediatric and young adult patients with IBD who developed COVID-19. Our data suggest that pediatric IBD patients have a low risk for complications and hospitalization, regardless of the IBD treatment. A larger multicentric study with longer follow-up would be required to draw more conclusions, but we believe that this report is encouraging and allows for safe counseling regarding treatment options and school attendance in pediatric and young adult IBD patients.

Statement of Ethics

Informed consent was obtained from participants (or their parent/legal guardian/next of kin) to participate in the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors declare that this work was not supported by research grant or other forms of financial support.

Author Contributions

Tiago Magalhães: conception of the work, analysis and interpretation of data for the work; drafting the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Maria Cristina Granado: conception of the work, acquisition of data for the work; revising the work critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Ana Rute Manuel: conception of the work, acquisition of data for the work; revising the work critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Maria do Céu Espinheira: conception of the work, acquisition of data for the work; revising the work critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Eunice Trindade: conception of the work, acquisition of data for the work; revising the work critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

References

1 Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. 2020 May 1;20(5):533–4.

2 Parsons S, Van Tran L. The trilogy of SARS-CoV-2 in pediatrics (part 1): acute COVID-19 in special populations. J Pediatr Pharmacol Ther. 2021 Mar 1;26(3):220–39.

3 Brenner EJ, Pigneur B, Focht G, Zhang X, Ungaro RC, Colombel JF, et al. Benign evolution of SARS-Cov2 infections in children with inflammatory bowel disease: results from two international databases. Clin Gastroenterol Hepatol. 2021 Feb;19(2):394–6.e5.

4 Puoti MG, Rybak A, Kiparissi F, Gaynor E, Borrelli O. SARS-CoV-2 and the gastrointestinal tract in children. Front Pediatr. 2021;9:617980.

5 Fragoso RP, Rodrigues M. COVID-19 and pediatric inflammatory bowel disease: how to manage it? Clinics. 2020;75:e1962.

6 Direção Geral da Saúde. Ponto de situação atual em Portugal [Internet]. DGS; 2021.

7 Brenner EJ, Ungaro RC, Colommbel JFK. Current summary data. SECURE-IBD database [Internet]. 2020.

8 Moum KM, Moum B, Opheim R. Patients with inflammatory bowel disease on immunosuppressive drugs: perspectives' on COVID-19 and health care service during the pandemic. Scand J Gastroenterol. 2021 Mar 26;56(5):545–51.
9 Chebli JMF, Queiroz NSF, Damião AOMC, Chebli LA, De Magalhães Costa MH, Parra RS. How to manage inflammatory bowel disease during the COVID-19 pandemic: a guide for the practicing clinician. World J Gastroenterol. 2021 Mar 21;27(11):1022–42.
10 Home care for patients with suspected or confirmed COVID-19 and management of their contacts [Internet].
11 Badal S, Thapa Bajgain K, Badal S, Thapa R, Bajgain BB, Santana MJ. Prevalence, clinical characteristics, and outcomes of pediatric COVID-19: a systematic review and meta-analysis. J Clin Virol. 2021 Feb 1;135:104715.
12 Norsa L, Indriolo A, Sansotta N, Cosimo P, Greco S, D'Antiga L. Uneventful course in patients with inflammatory bowel disease during the severe acute respiratory syndrome coronavirus 2 outbreak in Northern Italy. Gastroenterology. 2020 Jul 1;159(1):371–2.
13 Dipasquale V, Passanisi S, Cucinotta U, Cascio A, Romano C. Implications of SARS-COV-2 infection in the diagnosis and management of the pediatric gastrointestinal disease. Ital J Pediatr. 2021 Dec 1;47(1):71.
14 Ungaro RC, Brenner EJ, Gearry RB, Kaplan GG, Kissous-Hunt M, Lewis JD, et al. Effect of IBD medications on COVID-19 outcomes: results from an international registry. Gut. 2021 Apr 1;70(4):725–32.
15 Rubin DT, Abreu MT, Rai V, Siegel CA, Ahuja V, Allez M, et al. Management of patients with Crohn's disease and ulcerative colitis during the coronavirus disease-2019 pandemic: results of an international meeting. Gastroenterology. 2020 Jul 1;159(1):6–13.e6.
16 Dipasquale V, Romano C. Pharmacological treatments and infectious diseases in pediatric inflammatory bowel disease. Expert Rev Gastroenterol Hepatol. 2018 Mar 4;12(3):237–47.
17 Martinelli M, Strisciuglio C, Fedele F, Miele E, Staiano A. Clinical and psychological issues in children with inflammatory bowel disease during COVID-19 pandemic. Inflamm Bowel Dis. 2020 Aug 1;26(9):E95–6.
18 Turner D, Huang Y, Martín-de-Carpi J, Aloi M, Focht G, Kang B, et al. Corona virus disease 2019 and paediatric inflammatory bowel diseases: global experience and provisional guidance (March 2020) from the paediatric IBD Porto Group of European Society of Paediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2020 Jun 1;70(6):727–33.
19 Alrashed F, Battat R, Abdullah I, Charabaty A, Shehab M. Impact of medical therapies for inflammatory bowel disease on the severity of COVID-19: a systematic review and meta-analysis. BMJ Open Gastroenterol. 2021 Oct 1;8(1):e000774.
20 Tripathi K, Brewer GG, Nguyen MT, Singh Y, Ismail MS, Sauk JS, et al. COVID-19 and outcomes in patients with inflammatory bowel disease: systematic review and meta-analysis. Inflamm Bowel Dis. 2021 Oct 27:1–15.
21 Arrigo S, Alvisi P, Banzato C, Bramuzzo M, Civitelli F, Corsello A, et al. Management of paediatric IBD after the peak of COVID-19 pandemic in Italy: a position paper on behalf of the SIGENP IBD working group. Dig Liver Dis. 2021 Feb 1;53(2):183–9.
22 Magro F, Rahier JF, Abreu C, MacMahon E, Hart A, van der Woude CJ, et al. Inflammatory bowel disease management during the COVID-19 outbreak: the ten do's and don'ts from the ECCO-COVID taskforce. J Crohns Colitis. 2020 Oct 1;14(14 Suppl 3):S798–806.