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Benign Evolution of SARS-Cov2 Infections in Children With Inflammatory Bowel Disease: Results From Two International Databases

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The coronavirus disease 2019 (COVID-19) pandemic caused by the highly infectious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) presents most often with mild clinical symptoms, but the severe forms are of major concern.[1] SARS-CoV-2 enters human cells via the angiotensin-converting enzyme 2 receptor, expressed on epithelial and endothelial cells.[2] Because the highest angiotensin-converting enzyme 2 expression is in the terminal ileum and colon, and upregulated further during inflammation, and many COVID-19 patients experience gastrointestinal symptoms, longitudinal data are necessary to determine whether inflammatory bowel disease (IBD) patients are at risk for severe or complicated COVID-19. A recent analysis in IBD patients from the Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD) registry showed older age, steroid medication, and comorbidities as risk factors for severe evolution, and the same study showed that the 29 IBD patients younger than age 20 had only mild disease courses.[3] This report describes the disease course of COVID-19 in an expanded sample of pediatric IBD patients from 2 international databases.

Methods

The SECURE-IBD and the COVID-19 database of the Paediatric IBD Porto group of the European Society for Paediatric Gastroenterology Hepatology and Nutrition were created in March 2020 with the aim to monitor outcomes of COVID-19 occurring in IBD patients.[1,4]

In this analysis, we included all subjects 18 years of age or younger from the SECURE-IBD and the Paediatric IBD Porto Group databases through October 1, 2020. We used descriptive statistics to summarize the demographic and disease characteristics of the study population, both overall and stratified by hospitalization status (hospitalized vs outpatient only), and performed bivariate comparisons (Supplementary Methods).

Results

We included 209 COVID-19 cases in pediatric IBD (PIBD) patients from 23 countries (Table 1). The most common IBD treatment was tumor necrosis factor (TNF) antagonist monotherapy (48%), followed by sulfasalazine/mesalamine (23%). Most patients (86%) had no comorbidities other than IBD. There were no deaths in the study population, and 14 children (7%) were hospitalized, of whom only 2 (1%) required mechanical ventilation.

The 2 children requiring mechanical ventilation were on either sulfasalazine or mesalamine and developed a multisystem inflammatory syndrome and concomitant secondary infection, respectively, with favorable evolution. Characteristics of the 14 hospitalized patients are provided in Supplementary Table 1.

Factors associated with hospitalization included comorbid conditions other than IBD (50% hospitalized vs 12% not hospitalized; $P < .01$), moderate/severe IBD disease activity (64% vs 15%; $P < .01$ overall), gastrointestinal symptoms (71% vs 19%; $P < .01$), sulfasalazine/mesalamine use (57% vs 21%; P .01), and steroid use (29% vs 8%; P .03). TNF antagonist monotherapy was associated with a decreased likelihood of hospitalization (7% vs 51%; $P < .01$) (Table 1). Sulfasalazine/mesalamine

[a]Authors share co-first authorship. [b]Authors share co-senior authorship.

Abbreviations used in this paper: COVID-19, coronavirus disease 2019; IBD, inflammatory bowel disease; PIBD, pediatric inflammatory bowel disease; SECURE-IBD, Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease; TNF, tumor necrosis factor.

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Table 1. Demographics, Disease Characteristics, and Clinical Outcomes of Pediatric IBD Patients Who Developed COVID-19 Infection

Characteristic[a]	Entire cohort (N = 209)	Hospitalized cases (N = 14)	Outpatient cases (N = 195)	*P* value
Age, *y*				.33
Mean (SD)	15 (43)	14 (4)	15 (3)	
Median (IQR)	16 (14–18)	15 (13–17)	16 (14–18)	
Female sex, n (%)	95 (46)	9 (64)	86 (44)	.17
Ethnicity, n (%)				.33
Hispanic/Latino	30 (15)	4 (28)	26 (14)	
Not Hispanic/Latino	152 (72)	9 (64)	143 (77)	
Unknown	18 (13)	1 (7)	17 (9)	
Diagnosis, n (%)				.25
Crohn's disease	138 (66)	7 (50)	131 (67)	
Ulcerative colitis	61 (29)	7 (50)	54 (28)	
IBD unclassified	10 (5)	0 (0)	10 (5)	
IBD disease activity (by PGA), n (%)				<.01
Remission	123 (59)	1 (7)	122 (63)	
Mild	45 (22)	3 (21)	42 (22)	
Moderate	28 (13)	7 (50)	21 (11)	
Severe	10 (5)	2 (14)	8 (4)	
Unknown	3 (1)	1 (7)	2 (1)	
IBD medication,[b] n (%)				
Sulfasalazine/mesalamine	49 (23)	8 (57)	41 (21)	.01
Steroids (started for IBD, not COVID-19)	19 (9)	4 (29)	15 (8)	.03
6MP/azathioprine monotherapy[c]	15 (7)	2 (14)	13 (7)	.27
Methotrexate monotherapy[c]	4 (2)	0 (0)	4 (2)	1.00
TNF antagonist without 6MP/AZA/MTX	100 (48)	1 (7)	99 (51)	<.01
TNF antagonist + 6MP/AZA/MTX	26 (12)	2 (14)	24 (12)	.69
Anti-integrin (vedolizumab)	14 (7)	2 (14)	12 (6)	.24
IL12/23 inhibitor (ustekinumab)	16 (7)	2 (14)	14 (7)	.29
Janus kinase inhibitor (tofacitinib)	3 (1)	0 (0)	3 (2)	1.00
Other IBD medication(s)	6 (3)	1 (7)	5 (3)	.34
No IBD medication	7 (3)	1 (7)	6 (3)	.40
Comorbid condition(s) present, n (%)	30 (14)	7 (50)	23 (12)	<.01
Exposed to tobacco products, n (%)	2 (1)	0 (0)	2 (1)	1.00
Gastrointestinal symptoms, n (%)	47 (23)	10 (71)	37 (19)	<.01
Abdominal pain	28 (13)	9 (64)	19 (10)	<.01
Diarrhea	27 (13)	4 (29)	23 (12)	.09
Nausea	13 (6)	6 (43)	7 (4)	<.01
Vomiting	9 (4)	3 (21)	6 (3)	.02
Other[d]	4 (2)	3 (21)	1 (1)	<.01

NOTE. The study cohort was from the Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease database and from the Paediatric Porto Group database.

AZA, azathioprine; COVID-19, coronavirus disease 2019; IBD, inflammatory bowel disease; IL, interleukin; IQR, interquartile range; MTX, methotrexate; PGA, Physician Global Assessment; 6MP, 6-mercaptopurine; TNF, tumor necrosis factor.

[a]Unless otherwise specified, percentages do not include missing values or unknown values. For all characteristics, less than 4% of data were missing or unknown for each category. Percentages and numbers from each subcategory may not add up to the exact number of total reported cases owing to missing values and/or whole number rounding.

[b]At the time of COVID-19 infection. Medication categories are not mutually exclusive unless otherwise noted.

[c]Monotherapy indicates no TNF antagonist, anti-integrin, IL12/23 inhibitor, or Janus kinase inhibitor.

[d]Other includes blood, abdominal distension, and weight loss.

use remained a risk factor after adjusting for disease activity (adjusted odds ratio, 4.2; 95% CI, 1.3–14.1).

Discussion

We analyzed 209 children and adolescents age 18 years and younger with PIBD who developed COVID-19. The 7% hospitalization rate found here is markedly less than the 33% to 66% hospitalization rate reported in adult IBD patients.[3,5] Our data are in line with other reports indicating that children are at low risk for complicated COVID-19.[6]

Reported cases likely under-represent the actual case burden because most pediatric COVID-19 manifestations

are mild or asymptomatic and SARS-CoV-2 testing is not indicated. A case series of 1213 children found that 55.9% of cases were asymptomatic or mild, and only 5.9% were severe.[6] In addition, mild cases may be under-reported. Thus, the low observed hospitalization rate is likely an overestimation of the true hospitalization rate.

The findings that sulfasalazine/mesalamine and steroid use were associated with increased hospitalization risk and that TNF antagonist monotherapy was associated with decreased risk parallel those reported in adult IBD patients.[3] Other risk factors for hospitalization included other comorbid conditions, moderate/severe IBD disease activity, and gastrointestinal symptoms.

The 6-year-old colitis patient requiring intensive care unit care in this series is in line with recent reports of multisystemic inflammatory (Kawasaki-like) syndrome temporarily related to SARS-CoV-2 infection in children.[7] Our patient had a favorable evolution with steroid medication, whereas a recently reported 14-year-old boy with CD also developing a Kawasaki-like syndrome had an immediate improvement with infliximab medication.[8] The other intensive care unit–level patient developed a secondary infection that required multiple antimicrobial agents.

In conclusion, our data suggest that PIBD patients have a relatively low risk of severe COVID-19, even when receiving biologic and/or other immune-suppressive therapies for their IBD. This finding may reassure parents of children with IBD who are debating the safety of sending their children back to school in the fall. These data support earlier guidance from the Pediatric Porto group to continue maintenance IBD treatment for PIBD throughout the current pandemic.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2020.10.010.

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Conflicts of interest
These authors disclose the following: Bénédicte Pigneur has received lecture fees from AbbVie; Gili Focht has received consultation fees from Eli Lilly and AbbVie; Ryan C. Ungaro is supported by a National Institutes of Health K23 Career Development Award (K23KD111995-01A1), has served as an advisory board member or consultant for Eli Lilly, Janssen, Pfizer, and Takeda, and has received research support from AbbVie, Boehringer Ingelheim, and Pfizer; Jean-Frederic Colombel has received research grants from AbbVie, Janssen Pharmaceuticals, and Takeda, payment for lectures from AbbVie, Amgen, Allergan, Inc, Ferring Pharmaceuticals, Shire, and Takeda, consulting fees from AbbVie, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, Celgene Corporation, Celltrion, Eli Lilly, Enterome, Ferring Pharmaceuticals, Geneva, Genentech, Janssen Pharmaceuticals, Landos, LimmaTech Biologics AG, Ipsen, Imedex, Immunic, Imtbio, Medimmune, Merck, Novartis, O Mass, Ostuka, Pfizer, Shire, Takeda, Tigenix, and Viela bio, and holds stock options in Intestinal Biotech Development and Genfit; Michael D. Kappelman has consulted for AbbVie, Janssen, Pfizer, and Takeda, is a shareholder in Johnson & Johnson, and has received research support from AbbVie and Janssen; Dan Turner has received consultation fees, research grants, royalties, or honorarium from Janssen, Pfizer, Hospital for Sick Children, Ferring, AbbVie, Takeda, Atlantic Health, Shire, Celgene, Lilly, Roche, ThermoFisher, and BMS; and Frank M. Ruemmele has received consultation fees, research grants, or honorarium from Janssen, Pfizer, AbbVie, Takeda, Celgene, Nestlé Health Science, and Nestlé Nutrition Institute. The remaining authors discloses no conflicts.

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Supplementary Methods

Case details were reported directly by providers using case report forms created in Research Electronic Data Capture, a secure, web-based, electronic data capture tool, as has been described previously.[1,2] We removed duplicate reports known to have been entered into both databases. In addition, we double checked for duplicate reports by identifying records with matching age, sex, IBD disease type, and country. Potential duplicates were reviewed manually, and true duplicates were removed. Incomplete reports with missing outcome data were excluded from the analysis.

Disease activity was assessed by Physician Global Assessment, and comorbid conditions were defined as any chronic condition beyond IBD as determined by the reporter. We summarized continuous variables using means and SDs. We expressed categoric variables as the number of participants and proportions. We performed bivariate comparisons by hospitalization status using the Fisher exact test for each categoric variable and the *t* test for continuous variables. We listed demographic and disease characteristics for all cases that required hospitalization.

We performed a post hoc logistic regression evaluating the association between mesalamine/sulfasalazine and hospitalization with adjustment for IBD disease activity by PGA. We reported the adjusted odds ratio and 95% CI.

The databases were constructed and maintained according to the local ethics instructions/committees.

Supplementary References

1. Brenner EJ, Ungaro RC, Gearry RB, et al. Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry. Gastroenterology 2020; 159:481–491.e3.
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Supplementary Table 1. Demographics, Disease Characteristics, and Clinical Outcomes of Pediatric IBD Patients Hospitalized Because of COVID-19 Infection

Case number	Age, *y*	Sex	Country	Hispanic/ Latino ethnicity	Diagnosis disease activity (by PGA)	Medications[a]	Comorbid conditions	Required a ventilator or ICU stay	COVID-19 symptom length, *d*	Additional clinical information
1	15	Female	France	No	Ulcerative colitis, mild	TNF antagonist monotherapy[b]	No	No	N/A	COVID-19 symptoms included cough, dyspnea, fever, abdominal pain, myalgia, and oropharyngeal aphthosis. Patient is s/p ileo-anal pouch anastomosis.
2	13	Male	Italy	No	Ulcerative colitis, mild	Sulfasalazine/ mesalamine, 6-MP/ azathioprine	Yes (Rhett syndrome)	No	6	COVID-19 infection classified as mild. Patient did not receive any medications to treat COVID-19.
3	13	Male	Italy	No	Ulcerative colitis, remission	Sulfasalazine/ mesalamine	Yes (epilepsy)	No	6	No new GI symptoms developed from COVID-19. Patient did not receive any medications to treat COVID-19.
4	14	Male	United States	No	Crohn's disease, moderate	Sulfasalazine/ mesalam ne	No	No	N/A	COVID-19 GI symptoms include abdominal pain, nausea, and vomiting. Patient received hydroxychloroquine and infliximab for COVID-19 treatment.
5	18	Female	United Kingdom	Unknown	Crohn's disease moderate	Steroids (started for IBD care), 6-MP/ azathioprine	No	No	21	Patient was given budesonide and metronidazole for a Crohn's disease flare at the time of COVID-19 infection.

Supplementary Table 1. Continued

Case number	Age, *y*	Sex	Country	Hispanic/ Latino ethnicity	Diagnosis disease activity (by PGA)	Medications[a]	Comorbid conditions	Required a ventilator or ICU stay	COVID-19 symptom length, *d*	Additional clinical information
6	6	Female	United States	Yes	Ulcerative colitis, unknown disease activity	Sulfasalazine/Mesalamine	Yes (asthma)	Yes (both ventilator and ICU stay)	19	Developed postinfectious inflammatory syndrome, coagulopathy, respiratory failure, ascites, secondary infection, and GI bleeding. GI symptoms included abdominal pain, abdominal distension, and vomiting. Received corticosteroids to treat COVID-19 (not for IBD care).
7	11	Female	United States	Yes	Crohn's disease, moderate	Ustekinumab	Yes (obesity, hypertension, diabetes)	No	N/A	Developed abdominal pain, diarrhea, and nausea at the time of COVID-19 infection. The patient did not develop any thrombotic or other COVID-19 complications. Patient did not receive any medications to treat COVID-19.
8	18	Male	United States	No	Crohn's disease, moderate	Ustekinumab, steroids (started for IBD care), sulfasalazine/mesalamine	No	No	14	COVID-19 symptoms included abdominal pain, diarrhea, and nausea. Patient did not receive any medications to treat COVID-19.

Supplementary Table 1. Continued

Case number	Age, *y*	Sex	Country	Hispanic/ Latino ethnicity	Diagnosis disease activity (by PGA)	Medications[a]	Comorbid conditions	Required a ventilator or ICU stay	COVID-19 symptom length, *d*	Additional clinical information
9	16	Female	United States	No	Crohn's disease, moderate	Vedolizumab, sulfasalazine/mesalamine, methotrexate	Yes (Sjögren's syndrome)	No	7	COVID-19 symptoms included abdominal pain and nausea. Patient developed a concomitant secondary infection as a COVID-19 complication. Patient did not receive any medications to treat COVID-19.
10	15	Female	United States	No	Crohn's disease, mild	Infliximab, methotrexate, vancomycin	No	No	4	COVID-19 symptoms included nausea and vomiting. Patient did not receive any medications to treat COVID-19.
11	17	Male	United States	No	Ulcerative colitis, severe	None	No	No	10	COVID-19 symptoms/ complications included GI bleeding, abdominal pain, and diarrhea. Patient did not receive any medications to treat COVID-19.
12	17	Female	Argentina	Yes	Ulcerative colitis, moderate	Infliximab, sulfasalazine/ mesalamine, steroids (started for IBD care), 6-MP/ azathioprine	No	No	4	No new GI symptoms developed resulting from COVID-19. Patient did not receive any medications to treat COVID-19. There were no reported complications from COVID-19.
13	18	Female	United States	No	Crohn's disease, moderate	Vedolizumab, steroids (started for IBD care)	Yes (diabetes, hypertension, chronic renal disease)	N/A	N/A	COVID-19 symptoms included abdominal pain and diarrhea.

Supplementary Table 1. Continued

Case number	Age, *y*	Sex	Country	Hispanic/ Latino ethnicity	Diagnosis disease activity (by PGA)	Medications[a]	Comorbid conditions	Required a ventilator or ICU stay	COVID-19 symptom length, *d*	Additional clinical information
14	7	Female	United States	Yes	Ulcerative colitis, moderate	Sulfasalazine/mesalamine	Yes (asthma)	Yes (both ventilator and ICU stay)	19	Patient developed a concomitant secondary infection as a COVID-19 complication. Patient received methylprednisolone, metronidazole, ceftriaxone, vancomycin, and micafungin during hospitalization.

NOTE. The study cohort was from the Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease database and from the Paediatric IBD Porto Group database.
COVID-19, coronavirus disease 2019; GI, gastrointestinal; IBD, inflammatory bowel disease; ICU, intensive care unit; N/A, not available; PGA, Physician Global Assessment; 6-MP, 6-mercaptopurine; s/p, status-post; TNF, tumor necrosis factor.

[a]At the time of COVID-19 infection. Medication categories are not mutually exclusive unless otherwise noted.

[b]Monotherapy indicates no 6-MP, azathioprine, or methotrexate.