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COVID-19 and paediatric inflammatory bowel diseases: Global Experience and Provisional Guidance (March 2020) from the Paediatric IBD Porto group of ESPGHAN

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ABSTRACT

Introduction: With the current COVID-19 pandemic, concerns have been raised about the risk to children with inflammatory bowel diseases (IBD). We aimed to collate global experience and provide provisional guidance for managing paediatric IBD (PIBD) in the era of COVID-19.

Methods: An electronic reporting system of children with IBD infected with SARS-CoV-2 has been circulated among 102 PIBD centres affiliated with the Porto and Interest-group of ESPGHAN. A survey has been completed by major PIBD centres in China and South-Korea to explore management during the pandemic. A third survey collected current practice of PIBD treatment. Finally guidance points for practice have been formulated and voted upon by 37 PIBD authors and Porto group members.

Results: Eight PIBD children had COVID-19 globally, all with mild infection without needing hospitalization despite treatment with immunomodulators and/or biologics. No cases have been reported in China and South Korea but biologic treatment has been delayed in 79 children, of whom 17 (22%) had exacerbation of their IBD. Among the Porto group members, face-to-face appointments were often replaced by remote consultations but almost all did not change current IBD treatment. Ten guidance points for clinicians caring for PIBD patients in epidemic areas have been endorsed with consensus rate of 92-100%.

Conclusions: Preliminary data for PIBD patients during COVID-19 outbreak are reassuring. Standard IBD treatments including biologics should continue at present through the pandemic, especially in children who generally have more severe IBD course on one hand, and milder SARS-CoV-2 infection on the other.

What is known

- A global pandemic of Coronavirus disease 2019 (COVID-19) is now apparent
- SARS-CoV-2 infection resulting in COVID 19 causes significant pulmonary disease in adults leading Intensive care and sometimes death
- The impact in adults including on mortality is greater in patients with chronic diseases

What is new

- The first PIBD cases to have SARS-CoV-2 infection have been described
- COVID 19 in children, including PIBD, appears to be less severe than in adults
- Standard PIBD treatments should continue as delay e.g. in infusions secondary to the virus in endemic areas in Asia has been associated with disease flare

BACKGROUND

Coronavirus disease 2019 (COVID-19) is caused by the zoonotic coronavirus SARS-CoV-2 and started in China in December 2019 (1). By March 2020 it had been declared by WHO as a global pandemic. It is predominantly spread by airborne droplets but there is also significant viral shedding in stool, giving the potential for faecal-oral transmission (2, 3). In adults, COVID-19 predominantly presents with cough and fever resulting in a proportion of patients developing acute respiratory distress syndrome (ARDS) (4). SARS-CoV-2 infection may also cause gastrointestinal symptoms (5, 6). The disease course of COVID-19 in children is predominantly benign with mild or even no symptoms, and almost no reported mortality (6-8). The severe pulmonary involvement of the virus may be caused also by hyperinflammation and a secondary hemophagocytic-lymphohistiocytosis (HLH)-like picture (9, 10).

SARS-CoV-2 enters cells via the angiotensin-converting enzyme-2 (ACE-2) receptor that is abundantly expressed in cells of the lungs, oral cavity and the gastrointestinal tract. Lymphopenia and elevated CRP, ferritin and lactate dehydrogenase levels are associated with a more severe course (11). Increased levels of cytokines and chemokines, such as interleukin-6 (IL-6), have also been associated with increased disease severity in adults (11) and children (5). It seems that the most severe presentations of COVID-19 result from hyperinflammatory cytokine responses in particularly dysregulated IL-6-dependent acute phase responses associated with a decrease in cytotoxic T cells and NK cells. Those findings explain why in addition to antiviral therapies, immunomodulatory therapies and passive immunisation strategies could potentially be considered to improve outcome in severely affected patients (10). Consistent with this hypothesis is the report that in an endemic area, only 3 children receiving immunosuppressant medication for liver transplantation developed SARS-CoV-2 infection and none were severe (12).

The coronaviruses, SARS-CoV and MERS-CoV, were responsible for previous epidemics. Although clinical and immunological data from these viruses cannot directly be translated to predict interventions in SARS-CoV-2 infections, it is noteworthy that thiopurine metabolites, 6-mercaptopurine and 6-thioguanine, have been shown to have direct antiviral activity by inhibiting the papain-like protease of both viruses (13) as well as host proteins involved in antiviral response (14). Systemic steroids, however, did not confer substantial clinical benefit (15). Indeed, the safety of corticosteroids during COVID-19 is unclear (16), but it seems that if used for short periods and at a low dose they are not related to a worse prognosis, even in patients with COVID-19 pneumonia (17). There are no published data about the safety of monoclonal antibodies during this situation although anti-IL-6 receptor antibody has been used in a few patients with COVID-19 with promising results (18). Nonetheless, current literature related to other viral infections does not indicate stopping these treatments or modifying therapeutic regimes (19). In light of the hyperinflammatory immune response seen in patients with COVID-19 it is highly relevant that blockade of IL-6R with tocilizumab resulted in clinical improvement associated with normalisation of fever, lymphocyte counts and CRP in a retrospective group of 21 adults with severe SARS-CoV-2 infection (20). Locally active medications such as anti-□4□7 (e.g. vedolizumab) or budesonide are unlikely to have a major impact on systemic nor pulmonary SARS-CoV-2 responses.

Despite the above, the IBD-related immunosuppressive treatment has raised concerns regarding the management of COVID-19 with potential implications for treatment, isolation and routine hospital attendance (21, 22). Provisional reports from adult IBD centres in China are reassuring (23), and since some of the pulmonary damage may be caused by autoinflammatory response of the host, immunosuppressive medication have even been proposed to protect from severe disease

(9, 10). Nonetheless, children may have different recommendations than adults given the overall milder course of the infection. On the other hand, IBD in children tends to be more extensive and severe than adults with consistently higher need for immunomodulators and biologics. We thus aimed to collate available data on Paediatric IBD (PIBD) and SARS-CoV-2 globally and to develop consensus statements for the management of PIBD during the COVID-19 pandemic. The consensus process included specialists in paediatric IBD from the Paediatric IBD Porto group of European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).

METHODS

Following an open call to the members of the Paediatric IBD Porto group of ESPGHAN, international experts were selected as the writing group. Besides Porto group members, external paediatric experts from China (YH, YZ) and South Korea (BK), being the first endemic areas, were invited to participate, as well as a representative from the SECURE-IBD registry (MK).

Paediatric Porto Group reporting system

A REDCap reporting system has been constructed to collect all COVID-19 cases among children with IBD in the 102 Porto group-affiliated pediatric IBD centres in Europe (and several beyond). We asked for cases with a virological confirmation of SARS-CoV-2, but to avoid reporting bias of the more severe cases we allowed also highly suspected cases when testing was not available as per local testing policy since several countries permit testing only those with evidence of pneumonia (e.g. France and Spain). Nonetheless, the suspected cases were labelled and justified individually based on both typical symptoms and close contact with a confirmed case. A 7-day follow-up was required to ensure capturing of the disease severity. The registry included demographic questions as well as pre-infection IBD clinical explicit details, treatments and

outcomes. The ethics committee of Shaare Zedek Medical Center, Jerusalem, waived the need for approval given the urgent need for reporting clinical experience and since the report was retrospective, anonymous, and without contacting patients. For the SECURE IBD cases the UNC-Chapel Hill Office for Human Research Ethics has determined that storage and analysis of de-identified data does not constitute human subjects research as defined under federal regulations [45 CFR 46.102 and 21 CFR 56.102] and does not require IRB approval.

Porto Group survey

A survey among members of the Porto Group on changes in common practice in this new situation was launched via online platform in March 22nd, 2020. Investigators working in 32 tertiary centers around Europe, Israel and Canada completed the survey. Different topics related to how the centers have adapted to COVID19 outbreak were collected, both regarding therapeutic strategies and in the logistic organization in the PIBD units.

Chinese survey

A questionnaire was sent on March 20th, 2020 to 19 pediatric gastroenterology centers in China to evaluate the impact of COVID-19 on the prognosis of IBD children. These centers were distributed across 15 cities including Shanghai, Beijing, Guangzhou, Shenzhen, Hangzhou, Chongqing, Chengdu, Wuhan, Changsha, Zhengzhou, Xi'an, Xiamen, Guiyang, Nanjing, and Shenyang, in total care for 1431 children with IBD.

South Korean survey

A short questionnaire was sent on March 19th, 2020 to 4 tertiary centres in the metropolitan city of Daegu and in Gyeonsangbuk-do province where the majority of the total South-Korean

COVID-19 infection cases have been confirmed. Data regarding the changes in medication prescription by physicians, changes in hospital visits, patients' delays in hospital visits and medication administration, and disease exacerbation to the delayed visits were collected since January 20th, 2020, the date of the first COVID-19 occurrence in South Korea.

Statement voting

Based on the above collective data and literature review, the writing group formulated guidance points which were sent to all members of the Porto group of ESPGHAN for comments and electronic voting (Appendix). It has been decided *a-priori* that consensus is reached by at least 80% of voters.

RESULTS

Based on the literature review, the initial global experience described below and the practice surveys 12 statements were formulated and agreed upon by the writing group. Voting by the 37 Porto-group members and the authors retained 10 of which (Table 1), all endorsed with a consensus of at least 92%.

The Chinese experience of PIBD management during COVID-19 outbreak

A total of 917 confirmed and suspected paediatric cases of COVID-19 were reported in the 19 Chinese paediatric gastroenterology centres who participated in the survey (84% from Wuhan), none had a diagnosis of IBD. Between January 20th and March 20th, 233 PIBD children should had received scheduled infliximab infusions, of whom 66 (28%) had their infusions delayed because of the epidemic by 1-8 weeks (average length of delay 19.2±11.5 days) and 2 (0.9%) discontinued infusions temporarily. Among the 66 patients with delayed infusions, 14 (21%)

experienced a disease exacerbation, of whom 10 (15%) required an admission (average length of hospital stay 10.4±6.0 days). In comparison, only 17 children (1.2%) of the 1431 PIBD Chinese children had disease exacerbation during that period due to other causes (including poor compliance to therapy (n=10), uncontrolled primary disease (n=5) and C. *difficile* infection (n=2)).

The South Korean experience of PIBD management during COVID-19 outbreak

Among the 8,413 confirmed infections with SARS-CoV-2 in South Korea as of March 18th, 2020 (24), 87 (1.03%) were between 0-9 years, and 438 patients (5.2%) were in the age group 10-19 years; none died. The proportion of patients ≤19 years with confirmed COVID-19 (6.2%) was much less than the proportion of the country's population ≤19 years as reported by the local statistic bureau (18%; 9,315,774 among 51,629,512).

In the city of Daegu and Gyeonsangbuk-do province, where 87% of the total South Korean COVID-19 infection cases have been confirmed, there are four tertiary centres following in total 272 children with IBD. These centres continued following children with IBD at the outpatient clinics with 297 face-to-face appointments and 52 remote consultations from January 20th to March 18th, 2020. During this two-month period, biologics and immunomodulators have been prescribed without changes in doses or intervals in almost all children (99.3%). No cases of COVID-19 infection have been reported in South Korean children with IBD. Thirteen families (4.8%) have postponed their anti-TNF treatment due to parental anxiety about the virus, of whom 3 (23%) had worsening in their Crohn's disease activity. The median delay in scheduled anti-TNF administration in these patients was 17 days (range 14-22 days).

Porto group of ESPGHAN practice during the COVID-19 outbreak

Of the current 35 members of the Porto group of ESPGHAN, 32 (91%) responded to the survey of their practice during the COVID-19 outbreak, representing 32 PIBD referral centers in Europe, Israel and Canada. Some of the face-to-face visits have been changed to remote visits in 97% of PIBD centers. Thirty centers (94%) try to limit patients attending the hospital if not strictly needed (exceptions are flares, drug collection or infusions). Postponing clinics except those experiencing flares or new diagnosis has been practiced by 40% of centres. Of the 32 centres, 31 (97%) encourage their patients not to make any changes in current treatments in response to COVID-19; drug doses and infusion intervals were not changed and combination therapy was continued. Children requiring infusions (i.e. infliximab, vedolizumab) continued with the same regimen. Twenty-nine centers (91%), including endemic areas in Europe, had no limitations in the administration of parenteral drugs. Other actions implemented in the various centers included facilitating drug administration to the patients (e.g. modifying pharmacy opening hours, and increasing the number of dispensed doses) plus limiting or stopping non-urgent endoscopic procedures.

Paediatric IBD cases with confirmed or highly suspected SARS-CoV-2 infection

Seven children with IBD and COVID-19 have been reported until March 26th, 2020 by the 102 sites affiliated with the Paediatric IBD Porto group of ESPGHAN (Table 2). All cases had a mild infection without the need for admission despite treatment with immunosuppressive medications, steroids and/or biologics. The underlying IBD remained generally stable during the infection and the IBD-related medications were not held in any of the cases.

Experience of COVID-19 and IBD in adults

Surveillance Epidemiology of Coronavirus) Under Research Exclusion (SECURE-IBD) is an international registry to monitor and report on outcomes of COVID-19 occurring in IBD patients. As of March 23, 2020, 40 adults and 1 child with confirmed COVID-19 infection have been reported (22 CD and 19 UC). Eight patients (20%) were reported to have new/worsening GI symptoms. Similar to the Porto group cases, the one paediatric patient had mild course of COVID-19 and did not require hospitalization (known clinical data of this case is added to Table 2). Ten adult patients have been hospitalized. Two patients died (5%) including an 82 years old male with mildly active UC, Alzheimer's disease, and cardiovascular disease on mesalamine and a 25 year old male with moderately active UC on infliximab and methotrexate.

SUMMARY

We provide the first document on the global impact of SARS-CoV-2 infection on pediatric IBD to date, from which we have generated guidance points for pediatric gastroenterologists in the era of this COVID-19 pandemic. The general message of continuing current IBD treatments is supported by the Chinese and South Korean experience reported here of ~20% disease exacerbation in children whose infliximab infusions were delayed.

We provide the first case series of children with IBD who have SARS-CoV-2 infection, all cases were mild despite being treated with immunosuppressive medications. These reassuring cases are supported by the lack of symptomatic disease among children with PIBD cases in China and South Korea. Since SARS-CoV-2 infection is often asymptomatic in children, it is likely that the true mild/minimal infection rate is higher than we identified. Among 171 Chinese children with

COVID-19, nearly a quarter had no symptoms and only one 10 months old infant with intussusception died (8). The reason for the milder infection course in children, resulting in lower hospitalisation rate and mortality, is not yet clear. Our observation of mild or minimal SARS-CoV-2 infection in children with IBD despite treatment with immunosuppressive medications is further supported by observations in children with liver disease on immunosuppression in Northern Italy where only 3/700 were documented to have SARS-CoV-2 infection and none with a severe course (12). The larger case series of adults reported from the SECURE-IBD registry show that current outcomes do not vary substantially from reports from the general population infected with SARS-CoV-2. SECURE-IBD cases may be biased towards more severe cases since only confirmed infections have been reported and in many countries asymptomatic and mild infections are not tested for the virus by local policy. Nonetheless, the mortality case of the 25 year old UC patients is concerning but stands as an outlier to the other currently available evidence outlined here. Careful continuous monitoring of the data is needed to base future possible adjustments to the current guidance.

Based on currently (March 2020) available limited data presented here we suggest the following: IBD children, with and without immunosuppressive and biological therapy, do not seem to carry a higher risk of contracting SARS-CoV-2 infection, compared to the general population. We can cautiously suggest that currently there is no signal indicating worsening the COVID-19 course by IBD-related treatment. On the other hand, the risk of inappropriate management of IBD driven by the fear of the virus may have a significant impact on the health of IBD patients as indicated by increased flares with delayed therapy in China and South Korea. Therefore, there is presently no justification to support adaptation of therapies for children with IBD in the light of the currently ongoing SARS-CoV-2 pandemic, especially in children who have in general a more extensive

and severe IBD on one hand and milder CVID-19 course on the other. Managing disease relapses in this period in epidemic areas can be difficult, thus it is crucial to advise patients to maintain their therapies, particularly when in remission. These interim conclusions may be adjusted in the future based on emerging data on COVID-19 in children with IBD.

QUALIFYING STATEMENT

ESPGHAN is not responsible for the practices of physicians and provides guidelines and position papers as indicators of best practice only. This guidance may be revised as necessary to account for changes in technology, new data, or other aspects of clinical practice. This guidance is intended to be an educational device to provide information that may assist clinicians in providing care to patients. They are not a rule and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment. Clinical decisions in any particular case involve a complex analysis of the patient's condition and available courses of action. Therefore, clinical considerations may require taking a course of action that varies from the suggestions made as part of this guidance.

DISCLAIMER

"ESPGHAN not responsible for the practices of physicians and provides guidelines and position papers as indicators of best practice only. Diagnosis and treatment is at the discretion of physicians".

APPENDICES

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Table 1: Guidance points endorsed by the Paediatric Porto Group of ESPGHAN (37 voting experts)

Statements	Consensus rate
1. IBD *per-se* does not currently seem to be a risk factor for acquiring SARS-CoV-2, nor for a more severe infection.	100%
2. For decreasing the risk of contracting SARS-CoV2 in children with IBD, we recommend using the same measures as in the local population during the pandemic (e.g. good hand hygiene, avoiding contact with anyone with respiratory symptoms and social distancing).	100%
3. When possible by local situation and resources, children should continue follow-up visits to ensure appropriate monitoring of the disease. However, remote telemedicine consultations, along with the use of surrogate markers of inflammation (fecal calprotectin, CRP, patient-reported outcomes) may be an alternative to face-to-face office visits during the epidemic, especially for those in remission. The option of delaying visits should be considered on an individual basis.	97%
4. Active IBD disease should be treated according to the standard guidance PIBD protocols as before the epidemics, since the risk of IBD complications in active IBD outweighs any risk of COVID-19 complications, especially in children.	97%
5. There is currently no concrete evidence that any of the IBD treatments increases the risk for acquiring SARS-CoV-2 or for a more severe infection once infected. Therefore, uninfected children should generally continue their medical treatment, including immunomodulators and biologic therapies, as the risk of a disease flare outweighs any estimated risk of SARS-CoV2 infection. This is especially true in children who have a much milder infection. Specific considerations are listed below.	97%
6. Corticosteroids can be used to treat disease relapses, but as always recommended in children, the drug should be weaned as soon as possible. In Crohn's disease exclusive enteral nutrition should be preferred.	92%
7. The use of anti-TNFs should be continued at the regular intervals and doses. Infusion centers should minimize crowding and implement screening procedures for suspected COVID-19.	97%
8. Switching from infliximab to adalimumab in a stable child should be discouraged unless impossible to provide intravenous infusions, since the risk of disease exacerbation after such a switch has been documented in the clinical trial setting.	97%
9. There is no clear indication to stop IBD treatment during COVID-19 infection, also due to the typical prolonged effect of IBD drugs. Nonetheless, we recommend suspending immunosuppressive treatment during an acute febrile illness until fever subsides and the child returns to normal health, irrespective of the SARS-CoV2 testing status. In case of positive SARS-CoV-2 testing in an asymptomatic child, the decision of therapeutic changes should be individualized. Mesalamine should never be suspended.	100%
10. Elective surgeries and non-urgent endoscopies should be postponed during the epidemic.	97%

Footnotes:

- All statements are limited to children and are based on the emerging but limited data available upon March 2020; it is possible that statements may change as data on PIBD and COVID-19 will accumulate.

The following two statements did not receive consensus of the Porto group and thus were removed: "Up to one-third of patients with COVID-19 may present with gastrointestinal symptoms, mainly diarrhea or nausea. Therefore, these symptoms during an active infection do not necessarily indicate a flare of the underlying IBD" and "In children with suspected symptoms of COVID-19, SARS-CoV2 testing is recommended before any therapeutic change."

Table 2: Cases of children with IBD and COVID-19 infection reported to the Porto group paediatric registry as of March 26th, 2020

CD, Crohn's disease; UC, ulcerative colitis; PGA, physician global assessment; PUCAI, pediatric UC activity index; wPCDAI, weighted paediatric CD activity index;

Comments to the table

1. The two suspected cases: household first-degree relative had concurrent confirmed infection but the child was not tested as per local testing policy since they has only mild presentation
2. None required admission
3. None of the IBD-related medications were stopped due to the SARS-CoV-2 infection
4. No worsening of the IBD has been reported in any of the children
5. Patients #1-7 did not suffered from other chronic disease; patient #8 had cardiovascular disease
6. Cases reported from the Porto group sites in: France, United Kingdom, Italy, Spain, Israel; Case #8 was reported from the SECURE-IBD registry

	Age (yrs), Gender, IBD type	Disease duration (yrs)	Paris classification	PGA of disease activity	Longitudinal PGA of the year prior to infection	PUCAI/ wPCDAI prior to infection	Medications at infection	Past medications	COVID-19 diagnosis	Presenting COVID-19 symptoms	Severity of infection
1	14, F, CD	4.3	A1aL3B2G0	Mild disease activity	Moderate	20	5ASA, thiopurines, adalimumab	Methotrexate, infliximab	Confirmed	Fever, cough	Mild
2	18, M, CD	4.8	A1bL2B1G0	Deep remission	None	0	Infliximab	None	Confirmed	Fatigue, cough	Mild
3	14.8, M, UC	1.2	E3S0	Deep remission	None	0	5ASA, thiopurines	Steroids, 5ASA, thiopurines	Confirmed	Slight rhinitis	Mild
4	16, M, CD	4.6	A1bL3B2G1	Clinical remission	None	10	Adalimumab	None	Suspected	Fatigue, myalgia	Mild
5	14, M, IBD-U	5.9	E2S0	Deep remission	None	0	5ASA, thiopurines	None	Suspected	Fatigue, myalgia	Mild
6	18, F, UC	3.4	E4S0	Deep remission	Mild	0	5ASA, thiopurines, vedolizumab	None	Confirmed	Anosmia, ageusia, mild cough.	Mild
7	18, F, CD	0.2	A2L1B1G0	Moderate disease activity	Moderate	70	Steroids	None	Confirmed	Low grade fever, mild chest pain	Mild
8	17, M, CD	5	Unknown	Unknown	Unknown	Unknown	Infliximab	None	Confirmed	Fever, cough, fatigue	Mild