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Gastroenterology: Inflammatory Bowel Disease

Management and outcomes of histoplasmosis in youth with inflammatory bowel disease in an endemic area

Jonathan C. Wright[1] | **Monica I. Ardura**[2,3] | **Jennifer L. Dotson**[2,4,5] | **Brendan Boyle**[2,4] | **Ross M. Maltz**[2,4] | **Hilary K. Michel**[2,4]

[1]The Ohio State University College of Medicine, Columbus, Ohio, USA

[2]Department of Pediatrics, The Ohio State University College of Medicine, Columbus, Ohio, USA

[3]Section of Infectious Diseases, Host Defense Program, Nationwide Children's Hospital, Columbus, Ohio, USA

[4]Division of Gastroenterology, Hepatology, and Nutrition, Nationwide Children's Hospital, Columbus, Ohio, USA

[5]Center for Child Health Equity and Outcomes Research, The Research Institute, Nationwide Children's Hospital, Columbus, Ohio, USA

Correspondence

Hilary K. Michel, Nationwide Children's Hospital, 700 Children's Dr, Columbus, OH 43205, USA.
Email: hilary.michel@nationwidechildrens.org

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Abstract

Objective: Patients with inflammatory bowel disease (IBD) prescribed immunosuppressive therapies including antitumor necrosis factor (aTNF) therapies are at increased risk of histoplasmosis. We aim to evaluate the presentation, management, and outcomes of youth with IBD and concurrent histoplasmosis.

Methods: Single center, retrospective review of youth with IBD diagnosed with histoplasmosis from January 12, 2007 to January 1, 2022. Management and outcomes were followed for up to 2 years after diagnosis.

Results: Nineteen patients (10 male, median age 16 years, range 8–22) with IBD were diagnosed with histoplasmosis: disseminated ($N = 15/19$; 79%), pulmonary ($N = 3/19$; 16%), lymph node ($N = 1/19$; 5%). At the time of histoplasmosis diagnosis, patients were predominantly receiving aTNF therapy ($N = 17/19$; 89%, median duration 21.9 months (interquartile range 8.5–52.0). Thirteen (13/19, 68%) patients required hospitalization and 2/19 (11%) required intensive care. All achieved antigen clearance with no recurrences. At the time of histoplasmosis diagnosis, aTNF was stopped in 15/17 (88%) patients and the following IBD therapies were initiated: 5-aminosalicylates ($N = 4/19$; 21%), 6-mercaptopurine ($N = 3/19$; 16%), enteral therapy ($N = 2/19$; 11%), and vedolizumab ($N = 2/19$; 11%); 6 of 19 (32%) received no IBD therapy and 2 of 19 (11%) patients continued aTNF. During follow-up, 6 of 19 (32%) patients had an emergency department (ED) visit and/or hospitalization for symptoms attributed to active IBD, all of whom had discontinued aTNF; one patient required colectomy.

Conclusions: Severe histoplasmosis infection in youth with IBD was rare. IBD treatment was modified by reducing immunosuppression. Histoplasmosis outcomes were favorable, but multiple patients required hospitalization or ED visits for IBD symptoms. The optimal approach to managing IBD during histoplasmosis treatment is challenging and requires further study.

KEYWORDS

antitumor necrosis factor (aTNF), Crohn disease, fungal infection, immunosuppression, ulcerative colitis

[Correction added on 27 November 2024, after first online publication: The funding details has been included.]

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1 | INTRODUCTION

Inflammatory bowel disease (IBD) is an immune-mediated condition frequently managed with antitumor necrosis factor inhibitors (aTNF).[1–5] While aTNFs have markedly improved the management of patients with Crohn's disease (CD) and ulcerative colitis (UC), they are associated with an increased risk of infections.[6–10] One pathogen of interest is *Histoplasma capsulatum*, a dimorphic fungi found worldwide but endemic to the Ohio and Mississippi River Valleys.[11,12] *H. capsulatum* is a relatively rare infection typically transmitted through spore inhalation. In immunocompetent hosts, the majority of cases are asymptomatic and clear without treatment, but in immunocompromised hosts, pneumonia or disseminated disease is possible with significant morbidity and mortality.[13] Receipt of aTNF increases *H. capsulatum* infection risk, disease progression, and severity of infection.[14–19] Histoplasmosis is not a nationally reportable infection, thus precise numbers of prevalence and incidence in our location are unavailable. However, a review from 2006 estimated about 4.6 per 1 million children required hospitalization for endemic mycosis per year, most frequently histoplasmosis.[20,21] Evidence-based guidelines recommend histoplasmosis-directed treatment depending on clinical disease manifestation, severity of illness, and in the context of extent of host immune function.[22] Minimization of immunosuppression and antifungal treatment are indicated in individuals with moderate to severe pulmonary histoplasmosis (PH), central nervous system involvement, and disseminated infection, the latter resulting from unchecked, progressive hematogenous dissemination and being fatal if untreated. Duration of antifungal treatment for disseminated histoplasmosis (DH) depends on resolution of clinical symptoms, clearance of serum antigenemia, and is usually at least 1 year to reduce the risk for relapse. The optimal management of IBD while receiving treatment for histoplasmosis remains unclear, especially in pediatrics, where prior research is limited to small case series including a five-patient case series from our center published in 2011.[23] In this study, we aimed to describe the clinical presentation, diagnosis, and outcomes amongst pediatric and young adult patients in an endemic area, highlighting the management of both IBD and histoplasmosis-directed therapies with 12 additional years of data.

What is Known

- Pediatric patients with inflammatory bowel disease (IBD) treated with immunosuppressive therapies such as tumor necrosis factor-alpha inhibitors are at risk for infections like histoplasmosis.
- The diagnosis of histoplasmosis requires a high index of suspicion and is generally managed by reducing immunosuppression and initiating antifungal therapy in moderate to severe disease.

What is New

- While histoplasmosis infection was often severe in pediatric patients with IBD and required prolonged therapy, outcomes were favorable with no mortality or recurrence.
- Optimal management of IBD-directed immunosuppression during histoplasmosis treatment remains unclear; Additional data are needed to propose a standardized IBD-management algorithm.

2 | METHODS

2.1 | Patients and definitions

This was a single-center, retrospective cohort study of youth with IBD (0–22 years of age) between December 2007 and December 2022 at Nationwide Children's Hospital (NCH), a pediatric quaternary care hospital in Columbus, Ohio, a histoplasmosis-endemic area. At the conclusion of this study, our IBD population was approximately 800 children and young adults. This study was approved by the NCH Institutional Review Board.

The cohort was identified by querying an institutional search engine (NCH Enterprise Database Warehouse), including patients with International Classification of Diseases (ICD)-9 or -10 codes for histoplasmosis (115.00–115.99, B39.0–B39.99) or *H. capsulatum*-positive laboratory, microbiology, and histopathology results, and ICD-9/10 codes for IBD (555.00–556.99, K50.00–K51.99). To ensure all patients were identified, our list was cross-referenced with internal databases of patients with IBD and histoplasmosis maintained by NCH's Divisions of Gastroenterology and Infectious Diseases.

Once potential patients were identified, the electronic medical record (EMR) was manually screened to confirm patients met the following inclusion criteria:

1. IBD (CD or UC) diagnosis based on endoscopic, histologic, or imaging findings in accordance with the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) Revised Porto Criteria.[24]
2. Histoplasmosis diagnosis required signs and symptoms consistent with histoplasmosis and at least one of the following positive laboratory

findings: *H. capsulatum* growth on culture (sputum, bronchoalveolar lavage [BAL], blood, or tissue), histopathology (tissue or BAL), serum or urine antigen (MiraVista Diagnostics), or serology (complement fixation titer ≥1:8 or the presence of H or M bands by immunodiffusion ARUP Laboratories), as previously described.[13]

Data extracted from the EMR included demographics, symptoms, diagnostic testing, antifungal and IBD-specific therapies, endoscopic and surgical procedures, and outcome data including IBD disease activity, IBD-related emergency department (ED) visits, hospitalizations, and surgeries, time to histoplasmosis antigen clearance, histoplasmosis recurrence, and mortality. Patient baseline characteristics, IBD diagnosis, and medications were recorded before histoplasmosis diagnosis and outcomes were followed for a minimum of 1 year (±3 months) and maximum of 2 years (±3 months) following histoplasmosis diagnosis. Patients were co-managed by gastroenterology (GI) and infectious disease (ID), and diagnostic tests and imaging studies were performed at the discretion of the treating physician and completed at NCH unless otherwise noted.

IBD phenotype was recorded at the time of histoplasmosis diagnosis per the Paris classification for pediatric IBD.[25] Clinical IBD activity was described via the ImproveCareNow Physician Global Assessment (PGA) and either the short Pediatric Crohn's Disease Activity Index (sPCDAI) or the Pediatric Ulcerative Colitis Activity Index (PUCAI).[26–28] Disease activity scores were collected at four timepoints: the office visit 1–3 months preceding histoplasmosis diagnosis, at the time of histoplasmosis diagnosis, and at 1- and 2-year outpatient visits (±3 months) following histoplasmosis diagnosis. Enteral therapy in this study was defined as 80% of calories from polymeric formula and 20% from regular foods, our local practice pattern. ED visits and hospitalizations were deemed IBD-related if the chief complaint and treatment focused on GI signs and symptoms and no other etiology was identified (i.e., infectious gastroenteritis).

Histoplasmosis infections were classified as proven or probable as previously defined.[29] PH was defined as pulmonary symptoms with corresponding radiographic evidence of pulmonary infiltration, nodules, or lymphadenopathy without other organ involvement. DH was defined as symptoms with positive histoplasmosis-specific diagnostics and at least two or more non-contiguous sites of organ involvement. Liver involvement was defined as alanine transaminase and aspartate aminotransferase greater than twofold the upper limit of normal or abnormal liver imaging. Splenomegaly was based on abdominal imaging. Central nervous system involvement was defined as cerebrospinal fluid with lymphocytic pleocytosis, low glucose, and elevated protein or imaging demonstrating meningitis. Lymph node involvement was defined by histopathology. Histoplasmosis disease severity was classified by type of management: no treatment, outpatient treatment, hospitalization, or intensive care unit (ICU). Acute kidney injury from amphotericin B was defined as a > 2-fold increase in creatinine from baseline and more than twofold the reference range within 2 days of starting amphotericin B and provider documentation of amphotericin discontinuation secondary to creatinine elevation.

2.2 | Statistical analysis

Nonparametric, descriptive statistics were used to summarize demographic data. C-reactive protein (CRP) values with normal reference ranges <0.5 mg/dL and erythrocyte sedimentation rate (ESR) values < 20 mm/h were recorded as zero. *H. capsulatum* antigen values > 19 ng/mL (upper limit of reported quantification; Miravista Diagnostics) were recorded as 19. Time to antigen clearance was calculated as the difference between the date of the initial positive serum antigen to the date of the first of two consecutive negative serum antigen tests.

3 | RESULTS

3.1 | Baseline patient characteristics and IBD therapies

The initial query identified 24 potential patients; three did not meet histoplasmosis diagnostic criteria and two did not have IBD leaving 19 for final analysis. The median age at histoplasmosis diagnosis was 16 years (range 8–22) with a median age at IBD diagnosis 12 years (range 4–19). Nine patients were female (47%) and 100% of the cohort identified as White. Sixteen patients (84%) had CD and three patients (16%) had UC. Seventeen patients (89%) were receiving aTNF therapy for a median duration of 658 days (interquartile range [IQR] 254–1561) before histoplasmosis diagnosis; 13 were receiving combination therapy and four (21%) received systemic corticosteroids in the 30 days preceding histoplasmosis diagnosis. One patient with UC status postcolectomy 2 years before histoplasma diagnosis was not receiving any IBD-directed therapy. An overview of each patient's disease course is illustrated in Table 1.

3.2 | Histoplasmosis presentation, diagnosis, and treatment

The most frequently reported symptoms at histoplasmosis diagnosis were fever, abdominal pain, nausea,

TABLE 1 Summary of immunosuppression management and disease outcomes.

IBD type	Age[a] (years)	IBD therapy at time of histo diagnosis	IBD therapy discontinued at histo diagnosis	IBD therapy during histo treatment	IBD therapy after histo treatment	IBD ED visit?[b]	IBD admission?[b]	Antifungal regimen (duration in days)	Histo type
CD	22	6MP + ADA	All	EEN for 12 months	Monitored w/o therapy	No	No	ITZ (367)	D
CD	18	IFX	All	5ASA immediately	5ASA continued	No	No	A + PSZ (459)	D
CD	17	6MP + IFX	All	5ASA immediately	5ASA continued	No	No	ITZ (803)	D
CD	17	6MP + IFX + Pred	All	Monitored w/o therapy	IFX resumed after 12 months, 6MP resumed after 15 months	Yes (403 days)	Yes (367 days)	ITZ (65)	P
UC	18	None	None	Monitored w/o therapy	Monitored w/o therapy	No	No	None	P
CD	18	MTX + ADA	All	EEN for 9 months	ADA resumed after 9 months, MTX resumed after 12 mo	No	No	A + ITZ (375)	D
CD	17	MTX	All	Monitored w/o therapy	Monitored w/o therapy	No	No	ITZ (113)	D
UC	12	MTX + IFX + Pred	All	5ASA after 2 months	Monitored w/o therapy	No	No	A + ITZ (1048)	D
CD	8	MTX + IFX	All	Monitored w/o therapy	Monitored w/o therapy	Yes (407 days)	No	A + ITZ (487)	D
CD	15	MTX + IFX	All	EEN for 4 months then Vedo	Vedo continued, IFX resumed after 21 months	Yes (135 days)	Yes (337 days)	ITZ (647)	D
CD	16	ADA + 6MP + 5ASA	ADA + 6MP	5ASA continued, ADA resumed after 9 months	ADA continued	No	No	ITZ (204)	D
CD	15	IFX	All	6MP after 2 months	6MP continued	No	Yes (367 days)	A + ITZ (458)	P
UC	9	6MP + IFX	IFX	6MP continued	6MP continued, 5ASA started after 2 months	No	No	ITZ (481)	D
CD	10	IFX	All	6MP after 1 month, IV steroids after 13 months	6MP continued, total colectomy after 2 months	Yes (279 days)	Yes (44 days)	ITZ (57)	D

TABLE 1 (Continued)

IBD type	Age[a] (years)	IBD therapy at time of histo diagnosis	IBD therapy discontinued at histo diagnosis	IBD therapy during histo treatment	IBD therapy after histo treatment	IBD ED visit?[b]	IBD admission?[b]	Antifungal regimen (duration in days)	Histo type
CD	16	IFX + MTX	All	Monitored w/o therapy	ADA started after 17 months	No	No	ITZ (534)	D
CD	15	IFX + MTX	All	Monitored w/o therapy	Monitored w/o therapy	No	No	A + ITZ (540)	D
CD	17	IFX	None	IFX continued	IFX continued	No	No	ITZ (153)	L
CD	16	IFX	All	Vedo after 0.5 month	Vedo continued; IFX resumed after 21 months	No	Yes (16 days)	A + ITZ (371)	D
CD	15	IFX + MTX + 5ASA	All	Resumed all after 1.5 months	Continued all therapy	No	No	A + ITZ (374)	D

Abbreviations: 5ASA, aminosalicylates; 6MP, mercaptopurine; A, patient initially treated with amphotericin; ADA, adalimumab; CD, Crohn's disease; D, disseminated histoplasmosis; EEN, exclusive enteral nutrition; histo, histoplasmosis; IBD, inflammatory bowel disease; IFX, infliximab; ITZ, itraconazole; L, lymphadenitis histoplasma; MTX, methotrexate; P, pulmonary histoplasmosis; PCZ, posaconazole; UC, ulcerative colitis; Vedo, vedolizumab.

[a]Age at time of histoplasmosis diagnosis.

[b]Days since histoplasmosis diagnosis.

fatigue, cough, and vomiting (Table 2). Eleven patients (58%) presented with GI signs and symptoms. Physical examinations were most often nonfocal, but five patients had abdominal tenderness (26%) and two had palpable splenomegaly (11%). Ten patients (53%) had at least one identified potential source exposure to *H. capsulatum* documented (7 (37%) with exposure to a farm, 3 (26%) to soil, 2 (11%) to hay, and 2 (2/19, 11%) to bonfire).

Three of 19 patients (16%) had proven and 16 (84%) had probable histoplasmosis. Most patients presented with DH (15/19, 79%), the remaining had PH (3/19, 16%) or isolated cervical lymphadenitis (1/19, 5%) (Table 2). Specific histoplasmosis laboratory and imaging findings are described in Table 2 and Supporting Information: Table 1. Of note, fecal calprotectin was measured at the time of histoplasmosis diagnosis in nine patients with a median 359 μg/g (IQR 67–1077). Among patients with abdominal imaging (computed tomography, magnetic resonance imaging, or ultrasound; $N = 12$), 50% (6/12) had bowel thickening or inflammation, of whom 50% (3/6) had a PGA indicating active IBD (mild, moderate, or severe disease). Thirteen of 19 patients (68%) patients required hospitalization for management of histoplasmosis, 2 of 19 (11%) required ICU admission, and 4 of 19 (21%) were treated as outpatients. The median duration of hospitalization was 10 days (IQR 6–14).

Histoplasmosis treatment regimens and outcomes are summarized in Table 2. Patients were followed for a median of 24.9 months (range 12.2–29.6) after histoplasmosis diagnosis, and histoplasmosis outcomes were favorable, with no deaths or recurrences. The median time to serum antigen clearance was 13.8 months (IQR 6.4–18.1) with a median duration of serum antigen monitoring of 27.6 months (IQR 12.8–40.5). Eight of 19 patients (42%) received antifungal therapy for ≥12 months, seven due to prolonged antigenemia, one due to continued infliximab during histoplasmosis treatment.

3.3 | Immunosuppression management

Tables 1 and 4 summarize the management of immunosuppression during histoplasmosis therapy. Anti-TNF therapy was discontinued in 88% (15/17) of those receiving it, all of whom had disseminated disease. Amongst all included patients ($N = 19$), three (16%) were prescribed aminosalicylates (one patient with UC, two patients with CD, median time to initiation 26 days), two (11%) were prescribed 6-mercaptopurine (6MP) (median time to initiation 49 days), two (11%) were prescribed enteral therapy (median time to initiation 8 days), and two (11%) were prescribed vedolizumab (median time to initiation 82 days).

Two patients (2/19, 11%) continued their aTNF therapy without delay following histoplasmosis

TABLE 2 Histoplasmosis diagnosis and treatment.

Characteristic[a]	*N* (%)
Presenting symptoms	
Fever	12/19 (63)
Abdominal pain	6/19 (32)
Nausea	6/19 (32)
Fatigue	6/19 (32)
Cough	5/19 (26)
Vomiting	5/19 (26)
Decreased appetite	4/19 (21)
Weight loss	4/19 (21)
Rhinorrhea	4/19 (21)
Headache	4/19 (21)
Night sweats	3/19 (16)
Sore throat	3/19 (16)
Physical examination findings	
Nonfocal	9/19 (47)
Abdominal tenderness	5/19 (26)
Splenomegaly	2/19 (11)
Organ involvement[a]	
Pulmonary	16/19 (84)
Liver	8/19 (42)
Spleen	7/19 (37)
Central nervous system	1/19 (5)
Cervical lymph nodes	1/19 (5)
Chest X-ray	16/19 (84)
Normal	8/16 (50)
Pulmonary infiltrate	5/16 (31)
Nodular density	2/16 (13)
Pleural effusion	2/16 (13)
CT chest	10/19 (53)
Pulmonary infiltrates	6/10 (60)
Nodular density	4/10 (40)
Lymphadenopathy	3/10 (30)
Ground glass opacity	3/10 (30)
Abdominal/pelvic CT/MRI/ultrasound	12/19 (63)
Splenomegaly	6/12 (50)
Bowel thickening/inflammation	6/12 (50)
Ascites	1/12 (8)
Mesenteric lymphadenopathy	1/12 (8)
Histoplasmosis treatment	
Receipt of liposomal amphotericin-B	8/19 (42)
Duration of amphotericin, in days, median (range)	4.5 (1–13)
Dosage of amphotericin, mg/kg/day, median (range)	5.05 (3.17–5.66)
Adverse event reported: acute kidney injury[b]	4/8 (50)
Receipt of itraconazole	18/19 (95)
Duration of itraconazole, days, median (IQR)	375 (143–536)
Therapeutic drug monitoring performed	17/18 (94)
Adverse event reported: rash[b]	3/18 (17)
Second-line antifungal used: posaconazole	1/19 (5)
No antifungal provided[c]	1/19 (5)
Histoplasmosis monitoring and recurrence	
Ag monitoring	16/19 (84)
Both urine and serum antigen	15/16 (94)
Only serum antigen	1/16 (6)
Time to serum histoplasma antigen clearance, in months, median (IQR)	13.8 (6.4–18.1)
Duration of histoplasma Ag monitoring, in months, median (IQR)	27.6 (12.8–40.5)
Recurrence	0/16 (0)

Abbreviations: Ag, antigen; CT, computed tomography; IBD, inflammatory bowel disease; IQR, interquartile range; MRI, magnetic resonance imaging.

[a]Variables are not mutually exclusive.

[b]Only reported adverse reaction to itraconazole was a drug rash. Only reported adverse reaction to amphotericin was acute kidney injury.

[c]Patient with ulcerative colitis status post colectomy, not on IBD therapy.

diagnosis. One patient had localized cervical lymph node disease without detectible antigen and was not treated for histoplasmosis. The other had DH but initial serum histoplasma antigen was low (1.49 ng/mL) and urine antigen undetectable; 1 week after initiating antifungal therapy, serum antigen was <1 ng/mL, and aTNF was administered without interruption.

One patient was prescribed aminosalicylates and another continued 6MP during histoplasmosis treatment. Six patients (6/19, 32%) did not receive any IBD-directed therapies during histoplasmosis treatment.

After completing antifungal treatment, six patients (6/19, 32%) continued the IBD-directed treatment initiated during histoplasmosis treatment, seven (7/19, 37%) received no IBD-directed therapy, and the remaining six (6/19, 32%) either continued ($N = 2$) or restarted ($N = 4$) aTNF therapy (median time to resumption of aTNF 455 days (range 247–700) after histoplasmosis diagnosis).

3.4 | IBD outcomes

At time of histoplasmosis diagnosis, serum ESR, CRP, PGA score, and PUCAI scores were numerically increased when compared to the same assessments 1–3 months before, 1 year (±3 months) after, and 2 years (±3 months) after histoplasmosis diagnosis, while hemoglobin, albumin, and sPCDAI scores remained stable (Table 3). While subsequent outpatient scores reflected stable disease activity, 6/19 patients (32%), all of whom had discontinued aTNF therapy at histoplasmosis diagnosis, required at least one ED visit and/or hospitalization due to increased GI symptoms attributed to IBD activity (median time to first encounter 135 days, range 16–367) (Tables 1 and 4). Management of presumed active IBD included supportive care and initiation of biologic therapy; one patient underwent a total colectomy for refractory UC (Tables 1 and 4).

4 | DISCUSSION

This study describes a cohort of youth with IBD diagnosed with histoplasmosis and summarizes the evaluation and management of these concurrent disorders. Consistent with prior work, nearly all patients were receiving aTNF therapy, either with or without an immunomodulator, at the time of histoplasmosis diagnosis. The majority of patients discontinued antiTNF therapy during histoplasmosis treatment. While histoplasmosis outcomes were excellent, and outpatient IBD disease activity scores and inflammatory markers indicated quiescent disease, approximately one third of patients required an ED visit or hospitalization during the follow-up period for GI symptoms attributed to active IBD. This rate is similar to prior studies examining IBD relapse within 12 months of aTNF withdrawal (19%–52%),[30–32] and highlights the challenge of concurrent IBD and histoplasmosis management and the necessity of close collaboration between ID and GI teams.

While cohort studies have described histoplasmosis in adults with IBD, publications in children are limited.[22,33] To date, the largest study of histoplasmosis in pediatrics was a retrospective review of 73 children, of whom only five had IBD.[13] Vergidis et al. describe 98 patients receiving aTNF diagnosed with histoplasmosis but only a third had IBD and a minority of participants were children. This makes their recommendation for DH treatment—12 months of antifungal therapy while holding immunosuppression—difficult to extrapolate to the pediatric population.[33] In 2011, our center published a case series of five pediatric patients with IBD and histoplasmosis, two of whom are included in this study.[13,23] This study adds an additional 12 years of data to our prior work and highlights practice changes related to newly available therapies.

TABLE 3 IBD outcome measures and labs.

Lab	Reference range and units	Before histoplasmosis diagnosis	At time of histoplasmosis diagnosis	1-Year post-histoplasmosis diagnosis	2-Year posthistoplasmosis diagnosis
Days from histoplasmosis diagnosis,[a] median [IQR]		69 [104–38]	0 [0–12]	378 [341–416]	762 [733–794]
sPCDAI, median [IQR]		0 [0–13]	5 [0–19]	0 [0–10]	5 [0–8]
PUCAI, median [range]		30 [0–55]	65 [20–70]	20 [0–25]	0 [0–10]
PGA, % quiescent		79%	74%	72%	80%
Albumin, median [IQR]	3.4–5.2 g/dL	4.25 [4.1–4.5]	4.1 [3.6–4.4]	4.3 [4.1–4.6]	4.3 [4.0–4.5]
Hemoglobin, median [IQR]	13.5–18.0 g/dL	12.7 [11.7–15.0]	13.3 [11.2–14.8]	12.8 [12.0–14.4]	13.4 [12.4–14.7]
ESR, median [IQR]	<15 mm/h	16 [8.0–28.5]	27 [20–47]	14 [8.3–24]	11 [9–13]
CRP, median [IQR]	<1.0 mg/dL	0.3 [0.0–0.95]	1.0 [0.7–3.3]	0.6 [0.0–1.4]	0.0 [0.0–0.85]

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; IQR, interquartile range; PGA, Physician Global Assessment; PUCAI, Pediatric Ulcerative Colitis Activity Index; sPCDAI, Short Pediatric Crohn's Disease Activity Index.

[a]Days refer to when measurement occurred.

TABLE 4 ED visits and hospitalizations for GI symptoms attributed to IBD.

ED visit without admission						ED visit resulting in admission				
IBD type	Age[a] (years)	Time[b] to ED visit (days)	Chief complaint	IBD therapy at time of ED visit	Management in ED	Time[b] to admission (days)	Chief complaint	Length of stay (days)	Therapy at time of admission	Management while admitted
CD	17	403	Abdominal pain, diarrhea, emesis	IFX and 6MP	Supportive	367	Abdominal pain, weight loss, fever	3	5ASA	Supportive
CD	8	407	Abdominal pain	NT	Supportive	None				
CD	15	135	Melena, emesis	EEN	Supportive	337	Abdominal pain, emesis, melena	5	Vedo	Early vedolizumab infusion
CD	15	None				367	Abdominal pain, diarrhea	5	6MP	Supportive
CD	10	279	Abdominal pain, diarrhea, emesis	6MP	Supportive	44	Abdominal pain, diarrhea, dyspnea	28	MTX	IV steroids, initiate 6MP, total colectomy
CD	16	None				16	Abdominal pain, emesis, diarrhea	12	NT	Initiated vedolizumab

Abbreviations: 5ASA, aminosalicylates; 6MP, mercaptopurine; CD, Crohn's disease; ED, emergency department; EEN, exclusive enteral nutrition; IBD, inflammatory bowel disease; IFX, infliximab; MTX, methotrexate; NT, no treatment; UC, ulcerative colitis; Vedo, vedolizumab.

[a]Age at time of histoplasmosis diagnosis.

[b]Number of days from histoplasmosis diagnosis.

Our patient cohort was typically prescribed aTNF for 2 years before histoplasmosis diagnosis, which is similar to studies analyzing histoplasmosis in adults prescribed aTNF.[6,22,33] Our cohort had similar rates of DH (79%) as adult patients prescribed aTNF (73%–76%).[7,13,22,33] Our rate of amphotericin B use for severe disease was similar to those previously reported (29%–47%),[13,22,33] but median azole duration of 375 days (informed by clearance of antigenemia) was notably longer than the median treatment duration in prior studies: 219 days for DH in adults with IBD and 152 days for DH in children not receiving immunosuppression.[13,22]

The majority (58%) of patients presented with GI signs and symptoms at the time of histoplasmosis diagnosis, a finding rarely reported in the adult IBD study (14%) and not reported in prior pediatric studies.[13,22] In comparison, among adult patients with human immunodeficiency virus (HIV), 70% of DH had a GI presentation.[34] It has been reported that histoplasmosis diagnosis is often delayed by a median of 39.5 days due to nonspecific symptoms.[35] Given this intersection of delayed diagnosis with nonclassic presentation, a high index of suspicion for histoplasmosis is required in patients with IBD presenting with GI symptoms. Further, disease monitoring labs such as ESR, CRP, and fecal calprotectin can be elevated in both active IBD and DH due to involvement of the GI tract, complicating the discernment between histoplasma infection and active IBD.

In this study, we aimed to describe IBD-specific management approaches during histoplasmosis treatment. Most patients (88%) discontinued aTNF at histoplasmosis diagnosis at rates similar to those previously reported (82%–97%); Vergidis et al. report a 97% discontinuation rate with three patients continuing aTNF therapy (two with mild PH and one with cervical lymph node involvement), similar to our two patients who continued aTNF (one with isolated cervical lymph node involvement and another with mild DH and low initial serum antigen that quickly resolved on therapy).[13,22,33]

Subsequent IBD management strategies varied by IBD and histoplasmosis severity and activity over time. At the clinic visit preceding their histoplasmosis diagnosis, 79% (15/19) of patients had quiescent disease by PGA and median lab values (CBC, ESR, and CRP) were normal. Among the patients with mild or moderate PGA activity at histoplasmosis diagnosis ($N = 4$), three had an admission for GI symptoms attributable to active IBD during the follow-up period. However, given the small numbers in this series, we are unable to determine if this association is significant. A third of patients remained asymptomatic following withdrawal of all IBD-direct therapies and continued off therapy, even following completion of antifungal therapy and antigen clearance. Patients with milder IBD symptoms were managed with enteral therapy, aminosalicylates, or 6MP.

At outpatient clinic visits 1 and 2 years after histoplasmosis diagnosis, clinical and serum measures of IBD activity remained low. However, a third required ED visits or hospitalization for GI symptoms attributed to IBD activity during the follow-up period. Amongst patients who required ED visits or hospitalization due to GI symptoms attributed to active IBD, management strategies included supportive care, initiation of vedolizumab, resumption of aTNF, and for one patient, colectomy. Two (11%) of our cohort received vedolizumab (in 2020 and 2022), which was not an option employed in our prior case series. However, it is the most used alternative biologic medication (22.4%) in adult studies due to its gut-specific mechanism of action and low risk of infection.[22] Its use in pediatrics is limited due to lack of FDA approval in this population and therefore it is typically used as a second-line therapy; however, data are growing supporting the safety and efficacy of vedolizumab in pediatric IBD.[36] In our population, both patients who started on vedolizumab achieved clinical remission for a period of time but ultimately resumed aTNF therapy 21 months after histoplasmosis diagnosis due to inadequately controlled disease. Rates of restarting aTNF in our study amongst those who discontinued it (40%) were also similar to those reported in adult studies (25%–34%), with no histoplasmosis recurrence.[22,33]

Our typical approach is as follows: we discontinue aTNF in patients with DH and taper systemic corticosteroids as soon as clinically feasible. Discontinuation of other biologics and small molecules used to treat IBD would require conversation with ID, as guidance does not yet exist for these therapies. Those with active IBD (i.e., clinical symptoms, associated elevations in serum or stool inflammatory markers, or imaging/endoscopy consistent with intestinal inflammation) receive tailored IBD therapy that considers disease type, location, severity, and patient preference. It is also important to consider individual patient risk factors including ongoing histoplasmosis exposure. For individuals with mild IBD disease activity, nutritional therapy or aminosalicylates (for UC) may be considered. For individuals with moderate to severe IBD disease activity, immunomodulators, vedolizumab, or surgery may be considered. For the select patient with localized histoplasmosis and severe IBD, continuation of aTNF could be considered, with close monitoring. Data supporting alternative biologics (i.e., ustekinumab and risankizumab) or small molecules (i.e., tofacitinib, upadacitinib, and ozanimod) in these settings do not yet exist. Antifungal therapy for DH is recommended for 1 year, during which histoplasma antigens are monitored.[21,33] Our local best practice is to resume immunosuppressive therapies, including aTNF, in patients with active IBD who have resolution of histoplasmosis symptoms and in patients with DH, undetectable

antigen levels if indicated. If an immunosuppressive regimen containing aTNF, corticosteroids, or other biologic or small molecule therapies is initiated, we monitor histoplasmosis antigen concentrations for 3 months to 1 year to monitor for recurrence. Individual patient management requires close collaboration between GI and ID to ensure thoughtful consideration of both IBD and histoplasmosis treatment options, weighing risks and benefits, and supporting shared decision making with patients and families.

This study had limitations inherent to a single-center retrospective design which may limit generalizability to centers in other geographic areas. Most patients had two full years of follow-up data, but 3 patients had only 1 year (±3 months) of follow-up, limiting our ability to make conclusions regarding histoplasmosis recurrence, mortality, and IBD disease course. This cohort was homogeneous in regard to race which, while largely reflective of our local patient population, may limit generalizability. Given the small numbers in our cohort, we are unable to comment on whether histoplasmosis or IBD outcomes were different between those on combination versus aTNF monotherapy. aTNF drug levels were also not available in our data set, limiting our ability to comment on any impact drug levels may have had on outcomes. Finally, given the retrospective nature, variables could not be controlled, incomplete data could not be collected, and diagnostic and therapy decisions were at the discretion of the treating physician.

5 | CONCLUSIONS

The management of pediatric IBD and its complications have unique aspects compared with the management of adult IBD. This study provides detailed data regarding the management of pediatric IBD in the setting of concurrent histoplasmosis infection, which generally follows the tenets of minimizing immunosuppression during antifungal therapy. The specific choice of IBD-directed therapy and timing of when to initiate or resume immunosuppression requires close multidisciplinary collaboration. Newer, less immunosuppressive therapies like vedolizumab may provide additional options. Further study is warranted to compare the safety and efficacy of IBD medications during treatment of histoplasmosis, and to establish IBD-specific treatment guidelines to help standardize care for children with these concurrent disorders.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ORCID

Hilary K. Michel https://orcid.org/0000-0002-1742-936X

REFERENCES

1. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002;359(9317):1541-1549. doi:10.1016/s0140-6736(02)08512-4
2. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*. 2007;132(1):52-65. doi:10.1053/j.gastro.2006.11.041
3. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med*. 1999;340(18):1398-1405. doi:10.1056/nejm199905063401804
4. Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut*. 2011;60(6):780-787. doi:10.1136/gut.2010.221127
5. Sandborn WJ, Hanauer SB, Rutgeerts P, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut*. 2007;56(9):1232-1239. doi:10.1136/gut.2006.106781
6. Wallis RS, Broder M, Wong J, Lee A, Hoq L. Reactivation of latent granulomatous infections by infliximab. *Clin Infect Dis*. 2005;41 (suppl 3):194-198. doi:10.1086/429996
7. Cohn HM, Dave M, Loftus EV Jr. Understanding the cautions and contraindications of immunomodulator and biologic therapies for use in inflammatory bowel disease. *Inflamm Bowel Dis*. 2017;23(8):1301-1315. doi:10.1097/mib.0000000000001199
8. Minozzi S, Bonovas S, Lytras T, et al. Risk of infections using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis. *Expert Opin Drug Saf*. 2016;15(suppl 1):11-34. doi:10.1080/14740338.2016.1240783
9. Singh S, Facciorusso A, Dulai PS, Jairath V, Sandborn WJ. Comparative risk of serious infections with biologic and/or immunosuppressive therapy in patients with inflammatory bowel diseases: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2020;18(1):69-81. doi:10.1016/j.cgh.2019.02.044
10. Bonovas S, Fiorino G, Allocca M, et al. Biologic therapies and risk of infection and malignancy in patients with inflammatory bowel disease: a systematic review and network meta-analysis. *Clin Gastroenterol Hepatol*. 2016;14(10):1385-1397. doi:10.1016/j.cgh.2016.04.039
11. Azar MM, Loyd JL, Relich RF, Wheat LJ, Hage CA. Current concepts in the epidemiology, diagnosis, and management of histoplasmosis syndromes. *Semin Respir Crit Care Med*. 2020;41(1):13-30. doi:10.1055/s-0039-1698429
12. Baddley JW, Winthrop KL, Patkar NM, et al. Geographic distribution of endemic fungal infections among older persons, United States. *Emerging Infect Dis*. 2011;17(9):1664-1669. doi:10.3201/eid1709.101987
13. Ouellette CP, Stanek JR, Leber A, Ardura MI. Pediatric histoplasmosis in an area of endemicity: a contemporary analysis. *J Pediatric Infect Dis Soc*. 2019;8(5):400-407. doi:10.1093/jpids/piy073
14. Allendoerfer R, Deepe Jr. GS. Blockade of endogenous TNF-alpha exacerbates primary and secondary pulmonary histoplasmosis by differential mechanisms. *J Immunol*. 1998;160(12):6072-6082.
15. Tsiodras S, Samonis G, Boumpas DT, Kontoyiannis DP. Fungal infections complicating tumor necrosis factor alpha blockade therapy. *Mayo Clin Proc*. 2008;83(2):181-194.

16. Wood KL, Hage CA, Knox KS, et al. Histoplasmosis after treatment with anti-tumor necrosis factor-alpha therapy. *Am J Respir Crit Care Med*. 2003;167(9):1279-1282. doi:10.1164/rccm.200206-563OC
17. Deepe GS Jr. Modulation of infection with histoplasma capsulatum by inhibition of tumor necrosis factor-alpha activity. *Clin Infect Dis*. 2005;41 (suppl 3):204-207. doi:10.1086/429999
18. Furst DE, Wallis R, Broder M, Beenhouwer DO. Tumor necrosis factor antagonists: different kinetics and/or mechanisms of action may explain differences in the risk for developing granulomatous infection. *Semin Arthritis Rheum*. 2006;36(3):159-167. doi:10.1016/j.semarthrit.2006.02.001
19. Hage CA, Bowyer S, Tarvin SE, Helper D, Kleiman MB, Wheat LJ. Recognition, diagnosis, and treatment of histoplasmosis complicating tumor necrosis factor blocker therapy. *Clin Infect Dis*. 2010;50(1):85-92. doi:10.1086/648724
20. Chu JH, Feudtner C, Heydon K, Walsh TJ, Zaoutis TE. Hospitalizations for endemic mycoses: a population-based national study. *Clin Infect Dis*. 2006;42(6):822-825. doi:10.1086/500405
21. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2007;45(7):807-825. doi:10.1086/521259
22. Jansson-Knodell CL, Harris CE, Loftus Jr. EV, Walker RC, Enzler MJ, Virk A. Histoplasmosis in inflammatory bowel disease with tumor necrosis factor-alpha inhibitors: safe to continue biologics? *Dig Dis Sci*. 2021;66(1):190-198. doi:10.1007/s10620-020-06181-x
23. Dotson JL, Crandall W, Mousa H, et al. Presentation and outcome of histoplasmosis in pediatric inflammatory bowel disease patients treated with antitumor necrosis factor alpha therapy: a case series. *Inflamm Bowel Dis*. 2011;17(1):56-61. doi:10.1002/ibd.21378
24. Levine A, Koletzko S, Turner D, et al. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Pediatr Gastroenterol Nutr*. 2014;58(6):795-806. doi:10.1097/mpg.0000000000000239
25. Levine A, Griffiths A, Markowitz J, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. *Inflamm Bowel Dis*. 2011;17(6):1314-1321. doi:10.1002/ibd.21493
26. Kamp KJ, Hawes SE, Tse CS, et al. Concordance and discordance between patient-reported remission, patient-reported outcomes, and physician global assessment. *Inflamm Bowel Dis*. 2022;29(8):1255-1262. doi:10.1093/ibd/izac206
27. Kappelman MD, Crandall WV, Colletti RB, et al. Short pediatric Crohn's disease activity index for quality improvement and observational research. *Inflamm Bowel Dis*. 2011;17(1):112-117. doi:10.1002/ibd.21452
28. Turner D, Hyams J, Markowitz J, et al. Appraisal of the pediatric ulcerative colitis activity index (PUCAI). *Inflamm Bowel Dis*. 2009;15(8):1218-1223. doi:10.1002/ibd.20867
29. Azar MM, Hage CA. Laboratory diagnostics for histoplasmosis. *J Clin Microbiol*. 2017;55(6):1612-1620. doi:10.1128/jcm.02430-16
30. Ben-Horin S, Chowers Y, Ungar B, et al. Undetectable anti-TNF drug levels in patients with long-term remission predict successful drug withdrawal. *Aliment Pharmacol Ther*. 2015;42(3):356-364. doi:10.1111/apt.13268
31. Casanova MJ, Chaparro M, García-Sánchez V, et al. Evolution after anti-TNF discontinuation in patients with inflammatory bowel disease: a multicenter long-term follow-up study. *Am J Gastroenterol*. 2017;112(1):120-131. doi:10.1038/ajg.2016.569
32. Scarallo L, Bolasco G, Barp J, et al. Anti-tumor necrosis factor-alpha withdrawal in children with inflammatory bowel disease in endoscopic and histologic remission. *Inflamm Bowel Dis*. 2022;28(2):183-191. doi:10.1093/ibd/izab046
33. Vergidis P, Avery RK, Wheat LJ, et al. Histoplasmosis complicating tumor necrosis factor-α blocker therapy: a retrospective analysis of 98 cases. *Clin Infect Dis*. 2015;61(3):409-417. doi:10.1093/cid/civ299
34. Nacher M, Valdes A, Adenis A, et al. Gastrointestinal disseminated histoplasmosis in HIV-infected patients: a descriptive and comparative study. *PLoS Neglected Trop Dis*. 2021;15(1):0009050. doi:10.1371/journal.pntd.0009050
35. Miller AC, Arakkal AT, Koeneman SH, et al. Frequency and duration of, and risk factors for, diagnostic delays associated with histoplasmosis. *J Fungi*. 2022;8(5):438. doi:10.3390/jof8050438
36. Atia O, Shavit-Brunschwig Z, Mould DR, et al. Outcomes, dosing, and predictors of vedolizumab treatment in children with inflammatory bowel disease (VEDOKIDS): a prospective, multicentre cohort study. *Lancet: Gastroenterol Hepatol*. 2023;8(1):31-42. doi:10.1016/s2468-1253(22)00307-7

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