patients.³ More recently, a large population based study from Manitoba, Canada, compared 2857 Crohn's disease and 2672 ulcerative colitis patients with age, sex, and geographic location matched controls and reported an almost fourfold increased risk of lymphoma among males with Crohn's disease.⁴ This suggests that disease activity and underlying disease related immune alterations in IBD may be associated with a small but significant inherent risk of lymphoma.

In support of this association, a Swedish nested case control study reported a strong linear association between disease activity in rheumatoid arthritis (RA) patients and risk of developing lymphoma, which was not only independent of immunomodulator treatment but of a larger magnitude than the risks linked to immunomodulator therapy reported in other RA studies.⁵ Compared with RA patients with low inflammatory activity, patients with high and medium inflammatory activity had odds ratios of 25.8 and 5.4, respectively, for the development of lymphoma. This led the authors to recommend "the use of potent immunosuppressive treatment to reduce disease activity, not only to prevent joint damage but possibly also to protect against lymphomas."

The meta-analysis by Kandiel *et al* reported a pooled relative risk of 4.18 for lymphoma risk among IBD patients treated with azathioprine/6-MP. As the authors acknowledge, previously published population based and hospital based cohort studies have presented conflicting results regarding the risk of lymphoma in IBD patients treated with azathioprine and 6-MP. Reasons for these conflicting results may be related to inadequate sample size given the rarity of the outcome of interest as well as a wide range of estimates for the expected number of lymphomas. Discrepancies in the duration and dosage of treatment as well as limited length of follow up have also contributed to the conflicting results. Furthermore, it is well known that cohort studies such as ours⁶ and that reported by Kinlen⁷ which compared hospitalised or referral exposed cohorts to unexposed population based cohorts can result in artificially inflated relative risks as hospitalised or referral centre patients are more likely to have severe disease and multiple illnesses which are not necessarily related (that is, Berkson's bias).⁸ Ultimately, as IBD patients receiving immunomodulators by definition have more severe or refractory disease, it may be difficult to separate whether an increase in lymphoma risk is

related to immunomodulator therapy or the severity of the underlying disease activity.

Unfortunately, as this meta-analysis demonstrates, the actual risk of lymphoma in IBD patients treated remains unknown and our safety data with respect to azathioprine/6-MP and lymphoma, albeit reassuring, remains largely based on observational studies. Thus it is not possible to fully exclude the possibility that an increased risk of lymphoma is associated with disease severity rather than immunomodulator therapy. Larger scale, prospective, population based studies are necessary to define the actual risk of lymphoma in IBD and adequately ascertain the influence of immunomodulators on that risk. Until then, we agree with Kandiel *et al* that the lymphoma risk associated with azathioprine and 6-MP in IBD is likely to be of minimal clinical significance compared with the established and more frequent risks of myelosuppression and infection, and is far outweighed by the benefit of immunosuppression in IBD.

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Acute intermittent porphyria associated with hypoganglionosis in a young adult

We describe for the first time an association between rectal motility disorder and acute intermittent porphyria (AIP) in one patient. Abnormal haeme metabolism appears to play a pivotal role in the pathogenesis of these disorders.

A 20 year old male was admitted urgently with severe abdominal pain of eight days' duration, distension, constipation, faecal vomiting, and general malaise. The attack was preceded by severe upper respiratory infection. His medical history included constipation and encopresis since early childhood. At age 15 years he had been hospitalised for abdominal pain, constipation, and vomiting, and was investigated for the possibility of Hirschsprung's disease (HD) which was excluded after normal rectal mucosal biopsy. Under a diagnosis of habitual constipation, the patient was referred for psychological treatment without improvement over a two year period. Bowel movements occurred once a week, often helped by laxatives. The family history included a sibling with familial Mediterranean fever.

On examination the patient was dehydrated and in severe pain. There was marked abdominal distension with diffuse tenderness but no muscle spasm. Peristalsis was normal. On rectal examination, increased anal tone was noted. The ampoule was loaded with soft faeces. Neurological examination was normal. On plain abdominal x ray, large bowel obstruction was observed. Contrast enema excluded mechanical obstruction. The patient was rehydrated with gastric drainage. Antibiotics and rectal washing with warm saline and paraffin were administered for 3-4 days. Pain and distension gradually subsided. Dark urine was noted in the urinalysis.

Specific porphyria test results, consistent with defective enzyme activity in the liver and normal activity in erythrocytes, are shown in table 1. Anorectal manometry

Table 1 Porphyria test results

	Test I (3rd day of admission)	Test II (after 1 month)	Test III (1 month post op)
(1) Urine samples, 24 h collection			
Ala mg/24 h (n:<5)	17	4.2	7.1
PBG mg/24 h (n:<2)	12.7	2.9	5.3
Porphyrines			
Uroporphyrine (µg/24 h) (n: <30)	90	15	36
Coproporphyrine (1 µg/24 h) (n: <60)	169	40	77
Coproporphyrine (3 µg/24 h) (n: <180)	223	94	192
(2) Stool sample			
Porphyrines	wnl		
(3) Blood sample			
Erythrocyte porphobilinogen deaminase (nmol)	31		38
Uroporphyrine/ml erythrocytes/hr (n: >70% activity)	80%		100%
Plasma spectrum	Normal		Normal

Ala, aminolevulinic acid; PBG, porphobilinogen.

demonstrated no relaxation of the internal anal sphincter. No ganglion cells were detected on frozen sections of full thickness rectal biopsy samples 2 cm above the dentate line. A 6 cm anorectal myectomy followed. Hypoganglionosis was diagnosed on fixed specimens. At follow up after 12 months, the patient is well and has good bowel movements.

AIP is related to marked deficiencies of various enzymatic defects (with variable expression) in the biosynthesis of the metalloporphyrin haeme in the liver.¹ Free haeme exists at the intracellular and extracellular levels. Haeme is degraded by several oxygenases (HO) to CO and bilirubin. Haeme and its metabolites have important intracellular regulatory functions.²⁻⁵

An interaction between CO and nitric oxide in the nonadrenergic, non-cholinergic inhibitory neurotransmission of the internal anal sphincter and rectum has been suggested.⁶ CO has been proposed as a messenger molecule between the gut pacemaker cells of Cajal and smooth muscle cells.⁷

It has been reported that HO-2 is missing in the diseased bowel of patients with Hirschsprung's disease.^{7,8} Furthermore, it has been suggested that motility dysfunction is a result of impaired communication between Cajal cells and smooth muscle cells due to CO deficiency. In this patient, pathogenetic mechanisms operative in the production of intestinal symptoms may have included haeme deficiency in the intrinsic intestinal nervous system, resulting from AIP previously unreported.

Motility problems related to coproporphyria were described in one case report.⁹ Although porphyric constipation may be related to disordered haeme metabolism in the gut intrinsic nervous system, it is generally related to autonomic dysfunction. Early diagnosis of porphyria may help prevent neuroenteric system damage. The wide spectrum of porphyrias and of Hirschsprung's disease necessitates vigorous investigation, particularly in cases of prepubertal and pubertal abdominal pain and constipation. The importance of colonic manometry in the diagnosis and management of defecatory disorders was recently indicated.¹⁰ Full thickness rectal biopsy is necessary in selected cases of early onset constipation or soiling.

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Cytomegalovirus colitis in children with inflammatory bowel disease

The possible association of cytomegalovirus (CMV) infection with a flare up of inflammatory bowel disease (IBD) in adults is known but no case has been reported in children. Many cases were severe, leading to colectomy, and antiviral treatment was not always efficient. Adult CMV colitis in IBD patients produce symptoms, mimicking a flare up of the disease.¹⁻¹⁰

We report the cases of six children followed for IBD who presented with relapse of their disease, a concomitant CMV colitis. Five were steroid resistant and one infliximab resistant. Clinical characteristics of the patients and diagnostic criteria and outcome of CMV coinfection are summarised in table 1.

Their disease was evolving for an average duration of 20 months (0-48). CMV colitis was inducing her ulcerative colitis in one case. After a mean of 18 days (range 7-35) of systemic steroids in five patients and no response to infliximab in one patient, a control endoscopy was performed, showing severe pancolitis and gastritis in two. Mucosal biopsies showed typical intranuclear cytomegalic inclusions, and the presence of CMV was confirmed by immunohistochemistry.

Four patients were treated with ganciclovir (10 mg/kg/day) and one with foscarnet (180 mg/kg/day). Intravenous steroids and immunosuppressors were maintained in all who received them previously. In a few days, rapid improvement occurs, leading to remission and a decrease in steroids. One patient went into remission without CMV treatment. The first two patients treated for only two weeks relapsed one month later due to CMV reactivation. Ganciclovir retreatment for three weeks produced a rapid cure without further relapse (mean follow up 30 months (12-42)).

Our small series of six patients is the first reported of CMV infection in paediatric IBD. Diagnosis of CMV infection was achieved in all patients by colonoscopy and mucosal biopsies because of steroid resistance in five patients and loss of response to infliximab in one. This represent 28% steroid resistant patients in our IBD cohort.

Table 1 Clinical characteristics of inflammatory bowel disease patients and diagnostic criteria and outcome of cytomegalovirus (CMV) infection

Case No/ age/sex	Disease/duration (months)	Disease location	Treatment of flare up/ duration (days)	CMV diagnosis	CMV treatment/ duration (days)	Outcome
1/14 y/F	UC/(24)	Pancolitis	Oral steroids (15), IV steroids (10), aza	Biopsies, CMV Ag+	Ganciclovir (15+21)	CMV relapse at one month; recovery
2/8 y/F	CD/(27)	Gastritis/pancolitis	Oral steroids (10), IV steroids (15), aza	Biopsies, CMV Ag+	Ganciclovir (15+21)	CMV relapse at two months; recovery
3/9 y/M	UC/(8)	Pancolitis	IV steroids (22), 5-ASA	Biopsies, CMV Ag-	None	Recovery
4/14 y/F	UC/(0)	Gastritis/pancolitis	IV steroids (35)	Biopsies, CMV Ag+, CMV IgM+	Ganciclovir (21)	Recovery
5/6 y/F	IC/(12)	Right colon	Oral steroids (8), IV steroids (10), 6MP	Biopsies, CMV Ag+	Foscarnet (21)	Recovery
6/16 y/F	UC/(48)	Pancolitis	5-ASA, infliximab (8 days before)	Biopsies, CMV PCR+, CMV Ag	Ganciclovir (21)	Recovery

IC, indeterminate colitis; UC, ulcerative colitis; CD, Crohn's disease; 6MP, 6 mercaptopurine; aza, azathioprine; 5-AZA, mesalazine.