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.

Four patients were treated with ganciclovir and one with foscarnet, with rapid recovery, despite continuation of immunosuppression and corticosteroids.

Our good therapeutic results with antiviral therapy contrast with previous studies which observed a high rate of mortality (up to 44 %) and surgery (62%). In fact, institution of early antiviral therapy and probably earlier diagnosis of CMV infection in corticosteroid resistant IBD strongly improved the prognosis, as suggested in more recent publications.¹⁻¹⁰

In our series, CMV infection was always diagnosed on mucosal biopsies showing inclusion bodies, and confirmed by immunohistochemistry and positive CMV polymerase chain reaction (PCR) on biopsies in our last patient (not done in the other cases). The actual goal standard for CMV infection complicating IBD is CMV PCR positive on biopsies with or without the presence of CMV IgM antibodies and/or CMV antigenaemia in blood. Inclusion bodies on haematoxylin-eosin staining of biopsies seems to be less sensitive.^{1,2}

In conclusion, CMV infection in children with IBD can occur with severe pancolitis, usually resistant to steroids or infliximab. Systematic early detection and treatment seem to improve the prognosis and could avoid surgery.

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Reflux associated cough is usually not associated with reflux: role of reduced cough threshold

We read with great interest the article by Sifrim and colleagues (*Gut* 2005;**54**:449-54) addressing the issue of the importance of weakly acidic reflux (as measured by 24 hour ambulatory pressure and pH impedance monitoring) in patients with chronic cough. The presence of asthma, postnasal drip, or use of angiotensin converting enzyme inhibitors was ruled out so that an association with gastro-oesophageal reflux was probable. They found that only 15% of cough bursts were preceded by reflux episodes, which in 4% of cases were weakly acidic and therefore not detectable by conventional automated analysis of oesophageal pH tracings. Although the temporal relationship between acid or weakly acidic reflux and cough was highly significant, it could not be demonstrated in most episodes. In this respect their findings are in agreement with a previous study by Laukka and colleagues,¹ who also used manometry for a more accurate timing of cough. Taken together, the results of the two studies suggest that the pathogenetic mechanisms usually proposed as a link between reflux and cough (micro/macro-aspiration of refluxate into the airways and vagally mediated cough reflex) may be involved, at best, in a minority of cough episodes.

A different explanation has therefore to be formulated, not requiring a strict temporal relationship between reflux and cough. We suggest that such an explanation is represented by a low cough threshold induced by repeated reflux.

We have previously demonstrated that patients with reflux oesophagitis present a tussive response to minute amounts of inhaled capsaicin.² In our series, the temporal relationship between irritant inhalation and cough bursts was so reproducible and immediate that a casual association with a single reflux was unlikely. Rather, our finding strongly suggests the presence of a reduction in cough threshold, related to the cumulated effect of repeated oesophageal acid exposures. These lead to nociceptor sensitisation, which has been reported to be reversible by proton pump inhibitor treatment.³ In fact, in our series of oesophagitis patients, only five days of omeprazole treatment produced a striking improvement in tussive reactivity, so that a dose of capsaicin 15-fold higher was required to elicit cough.⁴ Once this acid driven mechanism is activated, a variety of otherwise subliminal stimuli (smoke, pollution, etc) can cause cough.

For this reason, the temporal association of reflux with cough does not appear to be a reliable criterion to diagnose reflux associated cough, even using state of the art methodology. Future studies will clarify whether variations in cough threshold after proton pump inhibitor therapy has a role in identifying among patients with cough those in whom the symptom is due to reflux.⁵

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Author's reply

We are thankful to Dr Benini and colleagues for their comments on our article (*Gut* 2005;**54**:449-54). We appreciate their reading of our manuscript, which led them to question the relevance of the temporal relationship between reflux and cough. However, we disagree with them with regard to their statement that "the temporal association of reflux with cough does not appear to be a reliable criterion to diagnose reflux associated cough, even using state of the art methodology".

Our main finding was that there is a subgroup of patients with chronic cough that