Guidelines for the Management of Inflammatory Bowel Disease in Children in the United Kingdom

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1.0 INTRODUCTION (1)

Inflammatory bowel disease (IBD) encompasses 2 related but distinct disorders of as yet unknown aetiology. Crohn disease (CD) is a chronic, idiopathic, transmural inflammation that can affect 1 or several segments of the digestive tract. Ulcerative colitis (UC) is a chronic idiopathic inflammation of the rectum extending continuously over a variable length of the colon from the distal end to the proximal end. Indeterminate colitis (IC) is reserved for cases of colitis for which findings are not sufficient to allow differentiation between CD and UC (1).

1.1 Development of Guidelines (2–4)

These guidelines are the work of the IBD Working Group of the British Society of Paediatric Gastroenterology, Hepatology, and Nutrition (BSPGHAN) and are for use by clinicians and allied professionals caring for children with IBD in the United Kingdom. There is a paucity of paediatric trials of high methodological quality to provide a comprehensive evidence-based document. Thus, these clinical guidelines have had to be consensus based, informed by the best-available evidence from the paediatric literature and high-quality data from the adult IBD literature, together with the clinical expertise and multidisciplinary experience of IBD experts comprising paediatric gastroenterologists represented by BSPGHAN. They provide an evidence- and consensus-based document describing good clinical practice for the investigation and treatment of IBD in children, which will promote consistency of the management of such conditions. Individual cases must be managed on the basis of all of the clinical data available for that child. Parent and patient preferences must be sought and joint decisions made. These guidelines will be published on the BSPGHAN Web site (*www.bspghan.org.uk*), which will allow simple and regular updating in the future and easy access for society members and others.

The IBD Working Group of BSPGHAN performed a comprehensive literature search of treatment modalities in paediatric IBD intervention studies using electronic databases (MEDLINE, PubMed, Cochrane, and Ovid). Evidence was graded using the Scottish Intercollegiate Guidelines Network (2). Methodology and detailed evaluation of evidence are published in a separate article in this issue. The British Society of Gastroenterology (BSG) produced evidence-based guidelines for the management of IBD in adults (3) for which a comprehensive literature search was also performed using electronic databases (MEDLINE, PubMed, and Ovid; key words: ''inflammatory bowel disease,'' ''ulcerative colitis,'' and ''Crohn's disease''). The format of the paediatric guidelines is based on the BSG guidelines but uses, where available, paediatric data and practice. Where there are no or little paediatric data or there is controversy, the evidence-based evaluation by the authors of the BSG guidelines for adults with IBD has been used together with the European Crohn's and Colitis Organisation consensus document (4).

2.0 INFLAMMATORY BOWEL DISEASE

2.1 Definitions (1,4,5)

UC is characterised by diffuse mucosal inflammation limited to the colon. Disease extent can be divided into distal or more extensive disease. ''Distal'' disease refers to colitis confined to the rectum (proctitis) or rectum and sigmoid colon (proctosigmoiditis). More extensive disease includes ''left-sided colitis'' (up to the splenic flexure), ''extensive colitis'' (up to the hepatic flexure), and ''pancolitis'' (affecting the whole colon).

CD is characterised by patchy, transmural inflammation, which may affect any part of the gastrointestinal (GI) tract. It may be defined by location (terminal ileal, colonic, ileocolic, upper GI), or by pattern of disease (inflammatory, fistulating, or stricturing). These variables have been combined in the Montreal classification (5). About 10% of children with IBD affecting the colon are unclassifiable after considering clinical, radiological, endoscopic, and pathological criteria because they have some features of both conditions. This is termed indeterminate colitis (IC).

2.2 Epidemiology

The only prospective national survey of IBD in children younger than 16 years in the United Kingdom (6) showed the incidence to be 5.2/100,000 individuals per year (60% CD, 28% UC, and 12% IC). It is slightly more common in boys and there is a

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slightly higher rate of UC in Asian children than in other ethnic groups. The mean age at diagnosis was 11.9 years. For CD there were approximately equal proportions of ileitis, colitis, and ileocolitis, and for UC almost 90% of children had a pancolitis (7). A systematic review of the epidemiological studies in North American cohorts estimates the incidence at 3 to 4/100,000 individuals per year (8). UC and CD are diseases of young people with a peak incidence between the ages of 10 and 40 years. Data from Scotland and Wales suggest that the incidence has risen during the last 20 years (9,10), with 25% of all cases presenting in children and young people. The incidence of CD may now have plateaued and that of UC may be increasing (11), so there is a need to determine current incidence trends again across the United Kingdom. IBD can affect any age; of the children presenting with IBD, 5% are younger than 5 years (7) and only 15% of adults are older than 60 years at diagnosis. Projected estimates suggest that up to 240,000 people are affected by IBD in the United Kingdom (12).

2.3 Pathogenesis

The etiologies of both UC and CD remain unknown. The consensus is that both diseases are probably a response to environmental triggers (infection, drugs, or other agents) in genetically susceptible individuals. The genetic component is stronger in CD than in UC. Smoking increases the risk of CD but decreases the risk of UC through unknown mechanisms (13).

Theories and evidence for pathogenetic mechanisms are too complex to be considered in this document. The broad areas examined are epidemiology, the gut/environmental interface, the inflammatory process, and genetics of each disease. Epidemiological studies have considered diet, drug, and vaccination history; seasonal variation; water supply; and social circumstances. The gut/environmental interface includes work on luminal bacteria, biofilms, the epithelial glycocalyx and mucus, epithelial barrier function, epithelial remodeling, and immune/epithelial interactions. The inflammatory process has been examined through cell signalling pathways, cytokine profiles, eicosanoid and other inflammatory mediators, lymphocyte trafficking, cell surface molecules, interactions between stromal and immune cells, and neuroimmune communication. Researchers in genetic susceptibility to IBD have adopted a candidate gene approach, genome-wide screening through microsatellite markers, and, most recently, both genome-wide association scans and studies on functional gene expression. Mutations of 1 gene (*CARD15/ NOD2*), located on chromosome 16, have been associated with small intestinal CD in white (but not Asian) populations and link innate immunity and the bacterial population of the gut. Recent genome-wide association scans have implicated 2 new pathways: T cell regulation by the IL-23 pathway via the gene *IL23R* and the process of autophagy, which controls intracellular bacteria, by the genes *ATG16L1* and *IRGM*. Other genes have yet to be identified, although their existence is strongly suggested by replicated linkage to a number of chromosomes.

2.4 Clinical Features and Pattern of Disease (7,14–20)

In children with UC, blood loss (84%), diarrhea (74%), and abdominal pain (62%) are common (7). Weight loss is less common in UC (35%) than CD (58%). Other symptoms include lethargy and anorexia. The most common reported extraintestinal symptom is arthropathy (10%). Skin manifestations are rare. Children with IC have predominantly colitic symptoms. With modern medical and surgical management, the disease now has a slight excess of mortality in the first 2 years after diagnosis but little subsequent difference from the non-IBD population (14,15). A severe attack of UC is still a potentially life-threatening illness. The clinical course of UC is marked by exacerbation and remission. About 50% of patients with UC have a relapse in any year. An appreciable minority has frequently relapsing or chronic, continuous disease. In children with moderate to severe disease at diagnosis, the colectomy rate is around 25% at 5 years. Disease severity at diagnosis is predictive of long-term outcome. Symptoms of CD are more heterogeneous and the nonspecific symptoms in children with CD may delay diagnosis. Abdominal pain, diarrhoea, and weight loss were considered to be the ''classic triad'' of CD, but now only a minority present in this way. The clinical presentation of childhood CD during the last 2 decades has changed. Data from the Hospital for Sick Children, Toronto, during 1980 to 1989, showed that 80% of children with CD presented with the classical triad (16), but a more recent large population-based survey of childhood IBD in the United Kingdom during 1998 and 1999 found only 25% presented in this way (7). Of patients with CD, 44% have no diarrhoea, but the majority (72%) complain of abdominal pain. Many children with CD present with vague complaints such as lethargy, anorexia, and abdominal discomfort or with isolated growth failure. A significant minority have markedly impaired final adult height (17,18). Neglect to record growth parameters, particularly for those not presenting to a paediatrician, has been identified (7,17,20). Other symptoms may include fever, nausea, vomiting, delayed puberty, psychiatric disturbance, and erythema nodosum (7). The clinical course of CD is characterised by exacerbations and remission. CD tends to cause greater disability than UC (Table 1).

2.5 Diagnosis and Investigations (1,21–24)

The need to diagnose children with IBD in a systematic way to provide tissue diagnoses and disease distribution was recognized more than 25 years ago (22). To ensure all children receive optimal care, members of the IBD Working Group of the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition have developed a consensus protocol for investigation of these children (1). The diagnosis of IBD is confirmed by clinical evaluation and a combination of biochemical, endoscopic, radiological, histological, or nuclear medicine investigations (Fig. 1). The diagnosis of UC is made on clinical suspicion supported by appropriate macroscopic findings on colonoscopy, typical histological findings on biopsy, and negative stool examinations for infectious agents. For CD, the diagnosis depends on demonstrating focal lesions with transmural inflammation and granuloma in, at most, 40% to 60%.

2.5.1 History and Examination

A full history should include recent travel, medication, dietary and family history, and a detailed bowel history with stool frequency, consistency, urgency, and presence of blood, mucus, or pus per rectum. Abdominal pain, malaise, fever, weight loss, and symptoms of extraintestinal manifestations of IBD (joint, cutaneous, and eye) should be sought. General examination includes well-being, weight and height centiles, pubertal status using Tanner staging, pulse rate, blood pressure, temperature, abdominal examination for tenderness, distension, masses including inspection of perianal area for skin tags, fissures, ulcers, and/or oedema suggesting CD.

2.5.2 Initial Investigations (1)

Laboratory investigations should include full blood count (FBC), C-reactive protein (CRP), erythrocyte sedimentation rate,

TABLE 1. Presenting symptoms and signs of children in the UK with CD (7)

	Patients		
	CD (n = 379)	IC (n = 72)	UC (n = 172)
Common symptoms			
Abdominal pain	274 (72%)	54 (75%)	106 (62%)
Diarrhoea	214 (56%)	56 (78%)	127 (74%)
Bleeding	84 (22%)	49 (68%)	145 (84%)
Weight loss	220 (58%)	25 (35%)	53 (31%)
Lethargy	103 (27%)	10 (14%)	20 (12%)
Anorexia	94 (25%)	9 (13%)	11 (6%)
Other symptoms			
Arthropathy	28	3	11
Nausea/vomiting	22	1	1
Constipation/soiling	4		
Psychiatric symptoms	3		
Secondary amenorrhoea	1		1
Signs			
Anal fistula	17		
Growth failure/delayed puberty	14	1	
Anal abscess, ulcer	8		
Erythema nodosum/rash	6		1
Liver disease	3	2	5
Appendicectomy	2		
Toxic megacolon			1

CD, Crohn disease.

and liver function tests (especially albumin). Reduced levels of haemoglobin, raised inflammatory markers (CRP, erythrocyte sedimentation rate, and platelets), and reduced serum albumin are suggestive of IBD. In some patients with UC, however, the levels may be typical. Stool cultures should be carried out to exclude infectious diarrhoea and stool tested for *Clostridium difficile* toxins A and B. Additional tests may be needed for patients who have traveled abroad. Identification of the pathogen, however, does not necessarily exclude a diagnosis of IBD because a first episode of IBD may present after documented enteric infection. In children from populations at risk for tuberculosis (TB), this should be excluded.

Perinuclear anti-neutrophil cytoplasmic antibody is positively associated with UC and anti-*Saccharomyces cerevisiae* antibody with CD, but the diagnostic sensitivity of these serological markers only ranges between 60% and 80%, so they are of limited clinical use. The noninvasive stool tests of faecal calprotectin and lactoferrin may become increasingly important both for screening and monitoring disease activity to avoid more invasive investigations. Abdominal radiography is essential for assessment of patients with suspected severe colitis to exclude colonic dilatation and silent perforation.

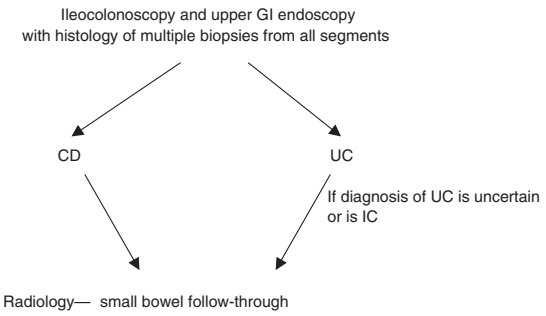

FIGURE 1. Porto criteria for diagnosis of inflammatory bowel disease in children (1).

2.5.3 Upper GI Endoscopy and Colonoscopy (1)

Ideally, all children suspected of having IBD should have upper and lower GI endoscopy preferably with intubation of terminal ileum and multiple biopsies from all of the segments in the upper (oesophagus, stomach, duodenum) and lower intestinal tract (ileum, caecum, ascending colon, transverse colon, descending colon, sigmoid, and rectum) for histological diagnosis. A barium meal and follow-through should be performed in all children who may have CD to evaluate the involvement of the small bowel. Disease distribution may be important to aid diagnosis when pathognomic histological features are not present. Histological evidence of CD in the upper GI tract can be present in up to 30% of cases even in the absence of upper GI symptoms. Unlike adults, more than 90% of children with UC have a pancolitis, making full colonoscopy advisable. Sigmoidoscopy does not have a role except in severe UC where the risk of bowel perforation is higher, making flexible sigmoidoscopy a safer option. It may be appropriate to defer investigations until the clinical condition improves. The majority of IC behaves like UC, but a few are later diagnosed as CD. Once tissue diagnosis and disease distribution are documented, appropriate treatment can be chosen. Histology of terminal ileal biopsies may help to exclude other diagnoses (eg, TB, Behcet syndrome, lymphoma, vasculitis) as well as assess the extent of IBD, and in children from a population at high risk for TB, tissue should be sent for TB culture.

2.5.4 Other Investigations

Technetium white cell scanning documents areas of inflammation and is undertaken in several centres. It is a safe, noninvasive investigation that may lack specificity but can be helpful to define disease extent. It may give a false-negative result if the child is taking steroids and also may not show oesophageal or pelvic inflammation. Ultrasound in skilled hands is a sensitive and noninvasive way of identifying thickened small bowel loops in CD and may identify abscesses or free fluid in the peritoneum. Computed tomography and, increasingly, magnetic resonance imaging (MRI) of the pelvis, for example, may help clinicians to evaluate activity and complications of disease (eg, fistula). Due to decreased radiation exposure, small-bowel MRI is replacing small bowel follow-through in some centres. Laparoscopy may be helpful in selected patients, for example, if intestinal TB is possible. Capsule endoscopy is not widely used in children at present but may become increasingly valuable in the diagnosis of disease of the small intestine. Capsule endoscopy cannot be used in the presence of strictures because it may be retained.

2.6 Histopathology

Histopathological examination of biopsy specimens should be carried out according to the principles outlined by the BSG (23). The type of IBD should be clearly defined along with other coexistent diagnoses or complications and the presence or absence of dysplasia recorded.

2.7 Imaging

It is desirable that clinicians discuss imaging with an appropriate radiologist to avoid unnecessary exposure to ionizing radiation (24). A multidisciplinary forum is best to review the results of imaging in the context of the clinical history so that appropriate management can be planned.

3.0 TREATMENT OF INFLAMMATORY BOWEL DISEASE

Treatment of IBD consists of bringing active disease into remission followed by prevention of relapse (Figs 2 and 3). Choice of treatment is influenced by disease type, distribution, and associated presenting features such as weight loss, short stature, and pubertal status. Recent data (7) suggest that, in CD, involvement of the GI tract is much more widespread, with only 9% of children having isolated small bowel disease and 7% having isolated colonic disease. The majority have both colonic and small bowel involvement, nearly 50% have gastroduodenal disease, and 20% have jejunal disease. Not only is paediatric-onset IBD characterised by extensive intestinal involvement at diagnosis but also the majority of children show rapid progression of disease (25). Evaluation of treatment efficacy includes assessment of symptomatic improvement, weight gain, and later, improved height velocity, biochemical remission (eg, resolution of abnormal blood inflammatory markers), and, in some cases, re-evaluation of disease activity by endoscopy to confirm mucosal healing. There are few randomised controlled drug trials in children. Many medications are unlicensed for use in children and are unavailable in child-friendly formats (eg, large tablets rather than liquid form). The choice of medication depends on the child's cooperation and the parents' willingness to administer treatment; for example, a child with distal colitis may not accept treatment with enemas. Therapy for IBD is a rapidly evolving field, with many new biological agents under investigation that are likely to change therapeutic strategies radically in the next decade.

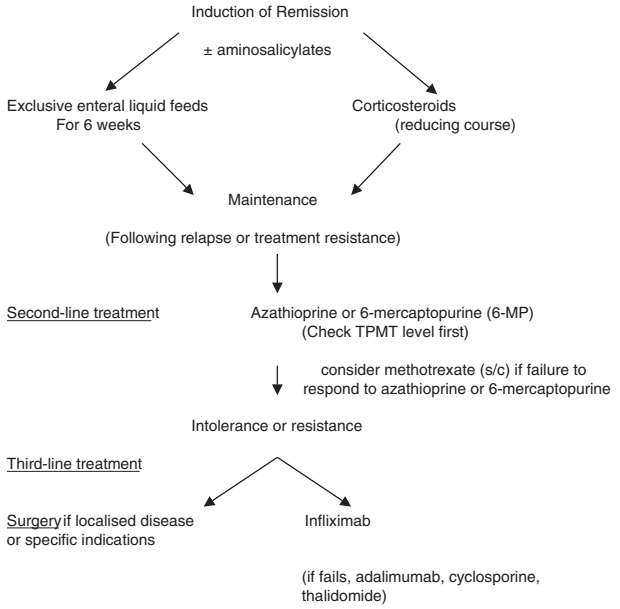

FIGURE 2. Crohn disease treatment.

3.1 Management of Crohn Disease

The benefits and risks of any treatment should be discussed openly with patients and their family, particularly in relation to steroids and immunomodulators. Factors such as the potential risk of immunosuppression, bone marrow suppression, and malignancy

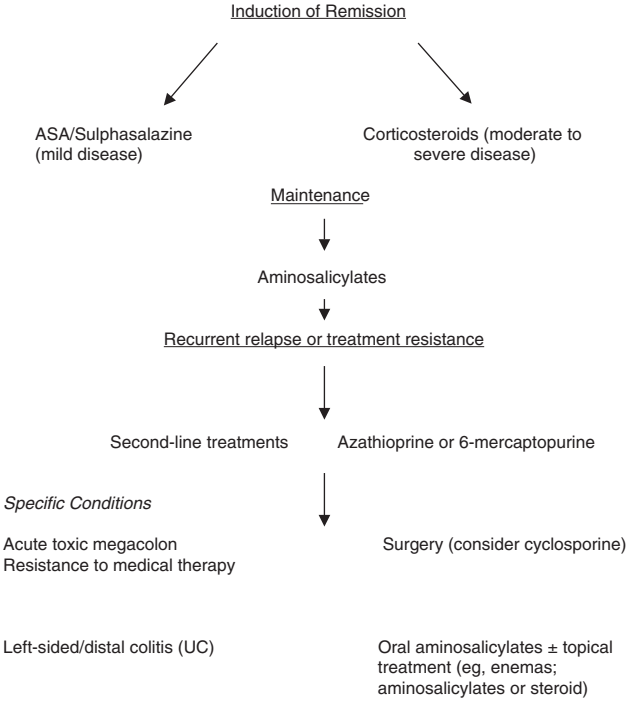

FIGURE 3. Ulcerative colitis treatment.

must be discussed and the discussion recorded in the case notes. Disease activity can be expressed using a disease activity index such as the Paediatric Crohn's Disease Activity Index (26).

3.1.0 Induction of Remission at Diagnosis or Disease Relapse (27–72)

The choice of treatment in most cases is between exclusive enteral nutrition and oral corticosteroids. This is concordant with the BSG guidelines, which also state that there is insufficient evidence to recommend the use of other agents outside trials/specialist centres. Recently, some centres have started using azathioprine at diagnosis for those with severe disease. Azathioprine prevents relapse, but it is not fully effective until at least 3 months after starting the drug.

3.1.1 Exclusive Enteral Nutrition (27–35) Evidence Levels (EL) 1+ to 1-, 2-, 3, and 4

- Exclusive enteral nutrition is an effective first-line therapy for small and large bowel disease, inducing remission in 60% to 80% of cases.
- Factors that influence the use of exclusive enteral nutrition include patient and parent choice, compliance, palatability, lack of corticosteroid toxicity, and potential benefits in terms of improved nutritional status and growth.
- The choice is between polymeric (eg, Modulen IBD, Alicalm) or elemental (eg, EO28) feeds. There appears to be no significant difference in efficacy between the 2. Both feeds are available in different flavours and it has been suggested that polymeric feeds may be more palatable. Administration via a nasogastric tube or gastrostomy is an option.
- Duration of exclusive enteral nutrition is usually 6 weeks. Most children need approximately 120% of reference nutrient intake; this, however, needs to be tapered according to individual needs, and dietetic support is essential. Food may be reintroduced cautiously during the course of 1 to 3 weeks, dependent on patient symptoms whilst weaning the enteral feed.

3.1.2 Corticosteroids (35–40) EL1-, 2-, 3, and 4

- Prednisolone 1 to 2 $mg \cdot kg^{-1} \cdot day^{-1}$ (maximum 40 mg/day) is an effective first-line therapy for small and large bowel disease.
- Treatment should be at full dose for 2 to 4 weeks until remission achieved (with review at least every 2 weeks in clinic or via telephone, until clinical remission) and thereafter gradual reduction of the dose for 4 to 8 weeks depending on the response.
- Ensure adequate dietary intake of calcium and vitamin D and if insufficient, consider supplement (eg, Calcichew D_3 tablet daily).
- Gastric acid suppression with proton pump inhibitors (eg, omeprazole) may be required in the presence of gastritis.

3.1.3 Other Management Strategies at Induction (41–50)

- Antibiotics (EL3): metronidazole (7.5 $mg \cdot kg^{-1} \cdot dose^{-1}$ tds) ± ciprofloxacin (5 $mg \cdot kg^{-1} \cdot dose^{-1}$ bd) for perianal disease
- Aminosalicylates (EL1-, 3) in high dose (mesalazine 50–100 $mg \cdot kg^{-1} \cdot day^{-1}$, maximum 3–4 g/day or sulphasalazine 40–60 $mg \cdot kg^{-1} \cdot day^{-1}$, maximum 3 g/d, can increase to 100 $mg \cdot kg^{-1} \cdot day^{-1}$ if tolerated): may be effective in mild disease. Topical mesalazine is effective in mild to moderate left-sided colitis. Regular blood monitoring of liver and renal functions every 6 months is essential.
- Budesonide 9 mg/day (EL1-, 3): less effective than prednisolone as first-line therapy for isolated ileocaecal disease, but it has fewer side effects
- Intravenous (iv) steroids (EL3): iv steroids (hydrocortisone 2 mg/kg qds, maximum 100 mg qds, or methylprednisolone 2 mg/kg od, 60 mg/day maximum) should be given to children with severe disease at presentation.
- Azathioprine (EL3): may be introduced immediately (after checking thiopurine methyltransferase [TPMT] levels are satisfactory) in those with severe disease, but takes at least 3 months to be fully effective.
- Surgery for complication (eg, abscess/fistula) after MRI pelvis to assess extent of perianal disease
- Parenteral nutrition (EL3) may be required as nutritional support for patients with severe complicated disease.

3.1.4 Refractory or Nonresponsive CD (51–78)

Patients in whom standard induction therapy, including high-dose intravenous steroids, has failed to induce remission either at diagnosis or during subsequent relapse are defined as having nonresponsive CD. Steroid refractory CD may be defined as active disease despite an adequate dose (1–2 $mg \cdot kg^{-1} \cdot day^{-1}$; minimum 20 mg/day) and duration (at least 2 weeks) of steroid therapy. Such patients should be considered for treatment with immunomodulators if surgery is not an immediate consideration.

- Azathioprine (2–2.5 $mg \cdot kg^{-1} \cdot day^{-1}$) or 6-mercaptopurine (1–1.25 $mg \cdot kg^{-1} \cdot day^{-1}$) (EL3), after checking that TPMT levels are satisfactory. Of the patients who are intolerant to azathioprine, up to 50% will tolerate 6-mercaptopurine.
- Methotrexate 15 mg/m^2 (EL3), once weekly given subcutaneously. Remission usually occurs within 4 weeks but further improvement may be seen after 16 weeks. Parenteral weekly administration is of benefit if nonadherence to oral medications is a major issue. If it is not an issue, then patients can switch to oral methotrexate, provided there is no significant small bowel disease, which may interfere with absorption.
- Infliximab 5 $mg \cdot kg^{-1} \cdot dose^{-1}$ at weeks 0, 2, and 6 (EL2-, 3) can be effective in patients who are refractory or intolerant to steroids in combination with immunomodulators and in whom surgery is inappropriate. There should be a plan at the outset for using infliximab, with the length of course clearly defined (eg, 3 doses and then reassessment). Before initiating infliximab, sepsis should be excluded including TB (chest x-ray/Mantoux skin test and molecular quantification tests). Patients already taking immunosuppressive drugs may have a false-negative Mantoux. Before starting treatment, the patient and his or her family should be counseled about infliximab, including a discussion about the risks of malignancy, and written consent should be obtained. Guidelines for infliximab use in adults have been produced by the National Institute for Clinical Excellence.

- Surgery should be considered, especially for isolated ileocaecal disease, strictures, or fistulae and for those in whom medical treatment has failed. Close collaboration between gastroenterologists and a surgeon experienced in paediatric IBD is essential.
- In CD, surgery is not curative and management is directed at minimising the impact of disease. At least 30% of patients require surgery in the first 10 years of the disease and approximately 70% to 80% will undergo surgery in their lifetime.

3.1.5 Other Disease Sites

- Oral: CD can be managed with exclusive enteral nutrition, exclusion diet (benzoate and cinnamon free), topical steroids, and/or intralesional steroid injections. Azathioprine, infliximab, and thalidomide may be considered for resistant disease (EL3).
- Gastroduodenal disease: proton pump inhibitors, used with standard therapy, may reduce symptoms.
- Fistulising and perianal disease:
  - Metronidazole ($7.5\,mg \cdot kg^{-1} \cdot dose^{-1}$ tds) (EL4) for at least 6 weeks and/or ciprofloxacin ($5\,mg \cdot kg^{-1} \cdot dose^{-1}$ bd) is appropriate treatment for simple perianal disease.
  - Azathioprine ($2–2.5\,mg \cdot kg^{-1} \cdot day^{-1}$) or 6-mercaptopurine ($1–1.25\,mg \cdot kg^{-1} \cdot dose^{-1}$) (EL3) may be an effective treatment for perianal and enterocutaneous fistulae (check TPMT before treatment), but there is a delay in onset of action.
  - Infliximab, intravenous: 3 infusions of 5 mg/kg each at 0, 2, and 6 weeks (EL2-, 3) may be an effective treatment for perianal and enterocutaneous fistulae but should be reserved for patients who are refractory to other treatments. A pelvic MRI scan should be carried out to exclude any abscess and to diagnose fistulae before starting infliximab.
  - Surgery: abscess drainage, fistulotomy, and seton insertion may be appropriate particularly before infliximab treatment. Image with pelvic MRI.

3.1.6 Maintenance of Remission in CD (77–97)

- There is no role for maintenance steroids for patients with CD in remission. For patients who are steroid dependent, every effort must be made to find other effective treatment.
- Azathioprine ($2–2.5\,mg \cdot kg^{-1} \cdot day^{-1}$) or 6-mercaptopurine ($1–1.25\,mg \cdot kg^{-1} \cdot day^{-1}$) (EL3): should be initiated as maintenance therapy in individuals who relapse in less than 6 months, relapse 2 or more times per year following initial successful therapy, and in all steroid-dependent patients; it also should be administered postoperatively for complex, fistulating, or extensive disease. TPMT should be checked before initiating treatment and is probably best done at diagnosis. In azathioprine nonresponders it may be useful to check serum thioguanine nucleotides levels to determine whether they are noncompliant or not absorbing. When to stop azathioprine is controversial. There is some evidence that more than half of all adults will relapse within 3 years of stopping azathioprine, and hence the usual practice of stopping at 4 years may not be valid. This should be discussed with the patient and parents and also adult gastroenterology colleagues as part of the transition plan. Certainly, it should not be discontinued at key times during pubertal growth and/or education, and most continue until the time of transfer to adult GI physicians.
- Methotrexate: $15\,mg/m^2$ once weekly subcutaneously (EL1-, 3), if azathioprine or 6-mercaptopurine is ineffective or poorly tolerated, with folic acid 5 mg 24 hours after each dose to ameliorate any GI side effects. FBC and liver function test results must be monitored every 2 weeks for the first 4 weeks, thereafter once per month.
- Enteral nutrition (EL2-): supplementary therapy may reduce the risk of relapse and may improve growth and nutritional status.
- 5-aminosalicylic acid, mesalazine (EL4): little role in maintaining remission, but may be of limited benefit in high doses ($50–100\,mg \cdot kg^{-1} \cdot day^{-1}$ as tolerated) for mild disease.
- Infliximab (EL3): if remission is induced with infliximab, maintenance with infliximab may be necessary (5 mg/kg intravenous, 8 weekly). It may be necessary to escalate to a higher dose (10 mg/kg) for loss of responsiveness and if successful, should revert to lower dose for subsequent infusions. Consider reinvestigating first to exclude ongoing sepsis, stricture, and bacterial overgrowth. Stopping coexisting immunosuppression after 6 months should be considered (there are emerging data of lymphoma risk with infliximab, which may or may not be related to concomitant administration of azathioprine or 6-mercaptopurine with infliximab). Assess at least annually to consider whether infliximab can be discontinued. If patient develops hypersensitivity to infliximab, then these symptoms may be abolished or ameliorated with a dose of intravenous hydrocortisone $\pm$ antihistamine before infliximab infusion.
- Other anti-TNF therapy (EL3): in patients initially responsive to infliximab who become resistant or intolerant, alternative anti-TNF agents can be considered (eg, adalimumab (subcutaneous) 80 mg stat followed by 40 mg every other week). Reassess endoscopically and, if necessary, radiologically, before starting second-line biological therapy.
- Other agents (EL4): there is little evidence for a beneficial effect of probiotics, fish oil, and *Trichuris* (worm) therapy to maintain remission in CD.

3.2 Management of Ulcerative Colitis

Treatment of UC depends on disease activity and distribution. Disease activity can be expressed using a clinical activity index (98–100). If on evaluation the disease is severe, the patient needs to be admitted to a paediatric gastroenterology unit for intensive intravenous therapy. If the disease is fulminant, the patient needs urgent resuscitation, an abdominal x-ray to exclude perforation, and joint medicosurgical assessment and management. The majority (90%) of children with UC have pancolitis, fewer than 10% have left-sided colitis, 4% have disease confined to the rectum alone, and 4% have rectal sparing (7). Half of those without pancolitis at presentation will rapidly progress to pancolitis (25). Infective aetiology should be sought because this may coexist with

active disease, but in severe disease, immediate treatment with corticosteroids should not be delayed (Fig. 3).

3.2.1 Induction of Remission at Diagnosis or Disease Relapse (101–123)

3.2.1.1 Mild or Left-sided UC (101–107)

- Topical mesalazine (EL1-,3), or to a slightly lesser extent, steroids in liquid form, foam, or suppositories are effective therapy for mild to moderate left-sided colitis or isolated rectal disease (1–2 g daily); however, single therapy with topical mesalazine or steroids for distal disease is less effective than a combination of oral and topical therapy.
- Oral mesalazine (50–100 $mg \cdot kg^{-1} \cdot day^{-1}$, maximum 3–4 g daily) or sulphasalazine 40–60 $mg \cdot kg^{-1} \cdot day^{-1}$ (maximum 3 g/day, can increase to 100 $mg \cdot kg^{-1} \cdot day^{-1}$ if tolerated) (EL1-,3). Sulphasalazine is better tolerated if introduced for 10 days to attain full dosage and is particularly effective for UC or IC and for arthropathy. Only sulphasalazine is available in liquid form. Olsalazine and balsalazide are alternatives if intolerant to those above and newer, once-daily preparations are becoming available. Monitor liver and renal function every 6 months.
- Oral steroids (EL1-, 3): prednisolone 1 to 2 $mg \cdot kg^{-1} \cdot day^{-1}$, maximum 40 mg/day) for patients in whom 5-aminosalicylic acid preparations (± topical agents) are ineffective.

3.2.1.2 Moderate to Severe UC (108–123)

- Corticosteroids (EL3): usually prednisolone 1 to 2 $mg \cdot kg^{-1} \cdot day^{-1}$ (maximum 40 mg/day).
- Treat at full dose for 2 to 4 weeks until remission (review at least once every 2 weeks in the clinic or via telephone, until clinical remission).
- Gradually taper for 4 to 8 weeks.
- If the child relapses during weaning, then consider moving back a step.

3.2.1.3 Acute Severe Colitis/Toxic Megacolon (108–123)

Children with severe colitis should be admitted to hospital for intravenous therapy and close monitoring of temperature, pulse rate, stool frequency, CRP, FBC, and a plain abdominal x-ray as a baseline to look for colonic dilatation. Regular reassessment is essential.

- Early surgical opinion is essential and patient should be managed jointly between physician and surgeon.
- Intravenous fluids/blood transfusion, if required.
- Intravenous steroids (EL4): hydrocortisone 2 mg/kg qds (maximum dose 100 mg qds) or methyl prednisolone 2 $mg \cdot kg^{-1} \cdot day^{-1}$ (maximum dose 60 mg/day). Failure to respond by 72 hours suggests the need for escalation of therapy or colectomy (98).
- At least daily plain abdominal x-ray if toxic/unwell.
- Intravenous antibiotics (EL4) only if infection is suspected or sometimes before surgery (eg, cefotaxime 50 $mg \cdot kg^{-1} \cdot dose^{-1}$ tds, metronidazole 7.5 $mg \cdot kg^{-1} \cdot dose^{-1}$ tds).
- Urgent surgical review is also indicated with a view to early colectomy if there is evidence of toxic megacolon (diagnosed if diameter >5.5 cm transverse colon and/or >9 cm in caecum, based on adult data) and in patients whose condition is deteriorating.
- Intravenous cyclosporine (EL3): 2–4 $mg \cdot kg^{-1} \cdot day^{-1}$, aiming for trough levels of 100–200 ng/mL, can be considered in patients not responding to steroids as a temporary measure to delay/avoid colectomy, allowing recovery and initiation of second-line immunosuppressant. Tacrolimus may be an alternative.
- Intravenous infliximab (EL3): there is some evidence that infliximab could be considered in nonresponding acute severe UC.

3.2.2 Maintenance of Remission (124–135)

- Aminosalicylates (EL4): maintenance therapy with aminosalicylates is recommended for all patients, but clinicians can consider stopping medication in distal and mild disease in remission for >2 years.
- Oral mesalazine, 50 to 100 $mg \cdot kg^{-1} \cdot day^{-1}$, maximum 3 g/day (EL4), should be continued as first-line maintenance therapy (monitor liver and renal function every 6 months). Once-daily mesalazine preparations are licensed in the United Kingdom for use in adults.
- Sulphasalazine 30 to 60 $mg \cdot kg^{-1} \cdot day^{-1}$ (EL4) is an alternative, but it may have greater side effects. It is the only formulation available in liquid form. It may be helpful in patients with associated arthropathy.
- Steroids (EL3, 4): there is no role for steroid therapy in the maintenance of remission.
- Azathioprine (2– $mg \cdot kg^{-1} \cdot day^{-1}$) or 6-mercaptopurine (1–1.25 $mg \cdot kg^{-1} \cdot day^{-1}$) (EL3): should be initiated as maintenance therapy in patients who fail to wean off steroids, or relapse in less than 6 months, or relapse 2 or more times per year despite adequate maintenance therapy with 5-aminosalicylic acid. Monitoring of FBC and liver function tests every 3 months is necessary because bone marrow suppression or autoimmune liver disease can develop. In azathioprine nonresponders, serum thioguanine nucleotide levels can be measured to determine whether they are noncompliant or not absorbing.
- Generally continue aminosalicylates with azathioprine for their cancer-protective effect.
- When to stop azathioprine is controversial. There is some evidence in adult patients that more than half will relapse within 3 years of stopping azathioprine, and hence the usual practice of stopping at 4 years may not be valid. This issue should be discussed with the patient and parents and also adult gastroenterology colleagues as part of the transition plan. Certainly, it should not be discontinued at key times during pubertal growth and/or education and most continue until the time of transfer to adult GI physicians.

3.3 Management of Indeterminate Colitis

Manage patients with IC the same as patients with UC. Re-evaluate periodically because the histological picture and/or disease distribution may change to CD or UC.

4.0 ASSOCIATED ASPECTS OF INFLAMMATORY BOWEL DISEASE

4.1 Nutrition (27–34,136–146)

- Nutrition is an integral part of the management of children with IBD, and nutritional status should be assessed at presentation and at follow-up.
- Exclusive enteral nutritional therapy modifies disease in children with CD.
- Nutritional support should be considered as an adjunctive therapy for any patient with CD or UC with malnutrition. Nasogastric/gastrostomy tube feeding can be considered.

4.2 Growth (17,18,21,143–151)

- Growth is an important marker of well-being in children with chronic disease.
- Routine assessment of growth (height and weight) and pubertal status (Tanner staging) are required at presentation and every 3 to 6 months throughout the course of the disease. Patients may prefer pubertal self-assessment.
- Growth suppression in IBD may be related more to poor disease control than to corticosteroid use.
- IBD may also be influenced by treatments used and thus is 1 of the parameters that may influence which therapy is chosen for children.
- Children with CD have improved short-term growth when enteral feeds were used to induce remission, compared to those given corticosteroids.
- Supplemental enteral feeding or cyclical enteral nutrition for children with CD in remission may improve growth and help maintain remission.
- In children with CD with localized disease and poor growth who are in early puberty, impressive catch-up growth has been documented postresection of the diseased segment.
- Close collaboration with an endocrinologist (preferably in a joint clinic) is important for managing children who have growth failure.

4.3 Bone Health (152–157)

- In children with CD, osteopenia may be present at diagnosis.
- Dual-energy x-ray absorptiometry scans can be used to document bone density, but there is no indication for routine use.
- Improved nutritional state may improve bone health.
- The role of routine calcium and vitamin D supplementation is unclear. Calcium and vitamin D supplementation should be considered in children with significant nutritional impairment during the pubertal growth spurt and during steroid treatment.
- In severe osteopenia, the opinion of an endocrinologist/rheumatologist should be sought.

4.4 Pain Management

- Few patients require long-term analgesia, and persistent severe pain may indicate poor disease control or complications that need to be identified (eg pending perforation).
- Adequate management of pain is important, however, and some children require regular analgesia. Care must be taken with opiate use in the acute phase.
- Consider engaging the pain management team if control is difficult.
- An element of functional pain may coexist with that due to disease.

4.5 Routine Monitoring

- On azathioprine, monitor 2 weekly blood draws for the first 4 weeks, once monthly the next 2 months, then once every 3 months monitor FBC, liver function tests, amylase (and CRP for disease activity). Aim to keep the lymphocyte count between 1000 and 1500 as an indicator of drug efficacy.
- TPMT level should be checked before starting azathioprine. Start at lower dose of azathioprine if TPMT is borderline low and monitor carefully. If extremely low (ie, homozygous for deficient gene), avoid azathioprine. In azathioprine non-responders, serum thioguanine nucleotide levels may indicate noncompliance or lack of absorption.
- Record vaccination history and any previous chickenpox infection. If negative, then check varicella status and if possible vaccinate before starting treatment. If a patient is not vaccinated, then consider immunoglobulin postexposure. Advise no live vaccines to be given while taking immunosuppressives.

4.6 Morbidity and Mortality (14,15,158–161)

- It is not known if there is an increased mortality in children in the first few years after diagnosis.
- In adults there is a morbidity rate but there is also a small increase in mortality for both UC (hazard ratio 1.44, 95% confidence interval 1.31–1.58) and CD (hazard ratio 1.73, confidence interval 1.54–1.96). This increase is largely dependent on age and distribution of disease.
- Adult data have shown that UC and, to a much lesser extent, Crohn colitis are associated with an increased risk of colonic carcinoma.

5.0 SERVICE DELIVERY

5.1 Impact of IBD on Patients and Society

- 25% of individuals with IBD present before the age of 18 years, and diagnosis is commonly made in the second and third decades.
- IBD in children can result in growth failure, delayed sexual development, and loss of education.
- Nutrition and growth are important issues in paediatric IBD, particularly CD, the aim of treatment being to induce and then maintain disease remission with minimal side effects on growth and puberty.
- The treatment priority is thus slightly different from adult practice, with not only symptom control and quality of life being priorities but also ensuring that disease control is

sufficient to facilitate normal growth and pubertal development.
- Patients find symptoms of UC or CD embarrassing and humiliating and can develop significant psychological problems.
- Medical treatments such as corticosteroids or immunosuppressive drugs can cause secondary health problems.
- Side effects such as weight gain and acne can be significant issues with adolescents.
- Procedures such as unprepared sigmoidoscopy in the clinic are poorly tolerated by children and teenagers and may damage their trust in IBD clinicians.
- Surgery may be complicated by future reduced fertility, impotence, or even intestinal failure and these should be discussed with the patient and parents.
- The impact of IBD on children is disproportionately high for the patient, his or her family or other caregivers and society, because presentation is at a young age with the potential to cause lifelong ill health.
- Initial investigation and treatment should ideally be managed by a specialist pediatric gastroenterologist and follow-up shared with the referring district hospital and paediatrician as part of a regional clinical network. For the physically mature adolescent who has completed growth, is emotionally mature, and without ongoing psychological or educational problems, investigations may be possible locally with an adult GI physician experienced in the management of adolescents with IBD, provided the care is shared with the local paediatrician with a GI interest and standards are within the National Strategic Framework for children. These patients should at least be discussed with the lead paediatric gastroenterology centre.

5.2 Approach to Caregiving

The complexity of cases means that facilities and expertise are necessary beyond those normally provided in district hospitals. Shared care pathways are essential between specialist pediatric gastroenterology units and district general hospitals, particularly if the child is prepubertal. Service-specific and clinical standards are vital (eg, National Association of Colitis and Crohn's Disease (NACC)/BSG/BSPGHAN standards, government of Wales' standards for gastroenterology, hepatology, and nutrition).

Any specialty service must be arranged around the needs of the child and family with the child receiving the highest quality care but as close to home as possible (eg outreach clinics) as part of a managed clinical network. It is clear that the following are important elements in any clinical network:

- Shared care pathways between specialist paediatric gastroenterology units and district general hospitals are crucial for optimizing care. It is important to have within district general hospitals a designated paediatrician with an interest in gastroenterology (especially IBD), an adult GI physician with an interest in young people with IBD, a paediatric dietician, and, ideally, a nurse specialist with whom the specialist team and others can liaise, as part of a shared care clinical network. Investigations should be made in a setting appropriate for and experienced in the treatment of children with IBD. Younger patients should be managed in tertiary gastroenterology centres.
- At the regional lead centre there must be a specialist multidisciplinary team including paediatric gastroenterologists, paediatric surgeons, an IBD nurse specialist, a dietician with knowledge of IBD, a histopathologist, an anaesthetist, a radiologist, and a psychologist.
- Access to upper and lower GI endoscopy including urgent access in a child-friendly environment for all children with symptoms of IBD
- Rapid access to advice and clinic or day case unit appointments in the event of a relapse or complications
- Adequate time and space in outpatients and wards to meet the unpredictable pattern of disease to allow discussion, explanation, and counseling, and to provide information and education material
- Easy access to private, clean toilet facilities for inpatients and outpatients and at school
- Administrative and clinical support including a specialist IBD nurse for supporting shared care pathways
- Participation in local and national specialist audit
- Transition care arrangements must be an integral part of any service, preferably with joint clinics held between adult and paediatric gastro teams, which young people can attend for as long as it is appropriate. Transition guidelines endorsed by BSPGHAN are now available from Crohn's in Childhood Research Association (CICRA) and the National Association of Crohn's and Colitis (NACC), with separate sections for patient, parent, and professional.

5.3 Sources of Patient/Parent Information

Explanations or advice given by clinical staff can be complemented by other sources of information. Patients usually welcome additional information, but it needs to be appropriate and relevant to their condition. The following and many other sources provide access to information:

Crohn's in Childhood Research Association (CICRA)
Parkgate House, 356 West Barnes Lane, Motspur Park, Surrey KT3 6NB, UK
Information: 020-8949-6209
E-mail: support@cicra.org
Web site: *www.cicra.org*

National Association for Colitis and Crohn's Disease (NACC)
4 Beaumont House, Sutton Rd, St Albans, Herts AL1 5HH, UK
Information: 01727-844296
e-mail: support@nacc.org.uk
Web site: *www.nacc.org.uk*

Crohn's and Colitis Foundation of America (CCFA)
386 Park Ave S, 17th floor, New York, NY 10016
Information: 800-932-2423
Web site: *www.ccfa.org*

Digestive Diseases Foundation
CORE, 3 St Andrews Pl, London NW1 4LB, UK
Web site: *www.digestivedisorders.org.uk*

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