

## Refractory Inflammatory Bowel Disease in Children

RIBD Working Group: \*M. Oliva-Hemker, †J.C. Escher, ‡D. Moore, §M. Dubinsky,  
¶H. Hildebrand, ||Y.K.L. Koda, \*\*S. Murch, ††B. Sandhu, ††J.K. Seo, §§M.N. Tanzi, and  
¶¶B. Warner

\*Johns Hopkins University School of Medicine, Baltimore, MD, †Erasmus Medical Center–Sophia Children’s Hospital, Rotterdam, The Netherlands, ‡Children, Youth, and Women’s Health Service, Adelaide, Australia, §Cedars-Sinai Medical Center, David Geffen School of Medicine at UCLA, Los Angeles, CA, ¶Astrid Lindgren Children’s Hospital, Stockholm, Sweden, ||Child Institute–Hospital das Clinicas, Faculty of Medicine of São Paulo University, São Paulo, Brazil, \*\*Warwick Medical School, Coventry, UK, ††Bristol Royal Hospital for Children, Bristol, UK, ††Seoul National University Children’s Hospital, Seoul, Korea, §§Centro Hospitalario Pereira Rossell, Montevideo, Uruguay, and ¶¶Washington University School of Medicine, St Louis, MO

Crohn disease (CD) and ulcerative colitis (UC) are 2 chronic, relapsing inflammatory bowel diseases (IBDs) of unknown etiology. Approximately 25% of patients are diagnosed by the age of 20 years. Originally, the highest incidence rates were reported in northern and Western Europe and in North America. However, the gap that previously existed between areas of high and low incidence rates is shrinking because IBD is now being reported with increasing frequency in Africa, South America, and Asia (1). In children, the incidence of CD appears to have risen above that of UC (1,2). CD and UC can follow an active and remitting course and their response to therapies can be highly variable. In severe disease, inducing and maintaining remission can be difficult. The purpose of this report is to highlight 3 refractory IBD phenotypes for which medical and surgical management can be particularly challenging. These include refractory UC and Crohn colitis, which have differences in prognosis and management depending on the underlying diagnosis, and refractory perianal CD, which can result in substantial morbidity. Recommendations by the authors are provided at the end of each section and in the consensus guidelines.

### CURRENT ISSUES

#### Refractory Ulcerative Colitis

In the literature, refractory UC often is defined as active colitis that does not respond to an adequate induction dose of corticosteroids (corticosteroid refractory) or colitis that initially responds to corticosteroids but relapses quickly

upon drug withdrawal or dose tapering (corticosteroid dependent). However, the widespread and early use of thiopurine immunomodulators (6-mercaptopurine [6-MP] and azathioprine [AZA]), usually in conjunction with aminosalicylates, has modified these definitions so that currently chronic UC may not be considered refractory unless the patient has not responded to additional immunosuppression with 6-MP or AZA. UC tends to declare itself as refractory early in disease presentation. Using thiopurine introduction as a marker of refractory UC, the prevalence in children ranges between 23% to 65% (3,4). Alternatively, the reported frequency of 25% of children requiring colectomy provides another surrogate marker of refractory UC incidence (5). In comparison, the reported prevalence of refractory disease appears less in adults, with 17% having refractory UC in a US study and 34% in Singapore (6,7). Studies also have highlighted an important difference in UC extent in children, with pancolitis noted at diagnosis in 69% to 90% of pediatric patients in contrast to adults in whom only one third have extensive colitis (3,5). Although the discovery of NOD2/CARD15 as the first susceptibility gene for CD enabled significant advances in understanding the genetic variation associated with CD, no similarly dramatic gene has been found for UC (8). However, genetic variants in the multidrug resistance gene *MDR1*, the *IBD2* gene, and HLA DRB1\*0103 (an infrequent allele of the human leukocyte antigen complex) have been associated with extensive or severe UC and the need for surgery (9–11). More data will be required before these genetic findings impact clinical practice in the management of UC.

#### Medical Management

Assessment of UC disease severity is based on the physician’s global assessment and supporting laboratory, endoscopic, histopathological, and radiographic evidence.

Address correspondence and reprint requests to Maria Oliva-Hemker, MD, Division of Pediatric Gastroenterology and Nutrition, Johns Hopkins University School of Medicine, 600N Wolfe St, Brady 320, Baltimore, MD 21287-2631 (e-mail: moliva@jhmi.edu).

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Enough evidence has been published to suggest that corticosteroids are beneficial in inducing partial or total remission for acute or severe UC (4,12). As discussed, aggressive early therapy with thiopurine immunomodulators is increasingly used to treat refractory or anticipated refractory UC, although when compared with CD there is less supporting medical evidence (13,14). Measurement of thiopurine methyltransferase (TPMT), a genetically controlled enzyme active in 6-MP/AZA metabolism, may identify some patients at risk for drug-induced neutropenia (15,16). Although the US Food and Drug Administration suggests that TPMT genotype or enzyme activity be assessed before commencing thiopurine therapy to avoid potential adverse events, prospective studies evaluating dose optimization based on measurements of TPMT are lacking (17,18). For patients with normal TPMT genotype or enzyme activity, doses of about 1.0 to 1.5 mg · kg<sup>-1</sup> · day<sup>-1</sup> of 6-MP and about 2.0 to 3.0 mg · kg<sup>-1</sup> · day<sup>-1</sup> of AZA have been recommended. Once therapy is initiated, thiopurine metabolite monitoring (eg, measuring thioguanine levels) may be useful when determining medical noncompliance, monitoring toxicity, or optimizing dose, but this approach continues to be a source of debate, and the feasibility of obtaining these types of tests can vary significantly among health providers, institutions, and countries (18,19).

Beyond thiopurines, therapy for refractory UC may typically include the calcineurin inhibitor cyclosporine or the anti-tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) agent infliximab. In severe or fulminant acute corticosteroid-refractory UC, intravenous or oral cyclosporine A can be rapidly effective in adults and children, but its role as maintenance therapy is limited because colectomy rates are high within the first year after its initiation (20–22). Thus, if a patient's UC does initially respond to cyclosporine, this drug should be considered more as bridging therapy, with attention given to other medications for maintenance, such as 6-MP/AZA (if not already being used) or infliximab.

Controlled studies in adults with UC have shown infliximab to be more effective than placebo in inducing clinical remission and reducing the need for colectomy in patients with disease resistant to aminosalicylates, corticosteroids, and thiopurines (23). Limited data is available regarding infliximab's efficacy in UC in the pediatric age group; however, open-label trials and case series suggest both short- and long-term efficacy (24,25). Data are still pending on other anti-TNF- $\alpha$  agents in the treatment of UC.

In addition to the medications already mentioned, one may find open trials and case reports of other therapeutic interventions for refractory UC, including tacrolimus, leukocyte apheresis, interferon, and helminths (26–31). They are referenced here given the perceived need to offer additional medical options to a given patient.

### *Surgical Management*

Although multiple series describe the surgical management of UC in children, relatively little has been published regarding operative intervention in the very young patient (<10 years old). Typical indications for surgery are poor response to medical treatment, dependence on corticosteroids with significant side effects, delay in growth and maturation, and severe extraintestinal manifestations. Emergency operations for toxic megacolon, unremitting bleeding, or fulminant colitis are not common today. The actual timing of surgery remains controversial, and with the therapies available it should not be considered to be the primary treatment. Colectomy should not be thought of as a measure of "last resort" because many patients may significantly improve their quality of life by having the diseased colon removed and discontinuing medications that were achieving only marginal success while increasing their exposure to adverse effects. Before embarking on surgery, it is essential that the diagnosis of UC is certain (32,33). Ideally, a thorough investigation of the gastrointestinal tract should be performed. Tests to consider include upper endoscopy and colonoscopy with multiple biopsies of the upper and lower gastrointestinal tract (including the distal ileum), together with visualization of the small intestine with barium, magnetic resonance imaging (MRI), ultrasound, or capsule endoscopy (33–36).

Previously, the surgical gold standard for refractory UC was proctocolectomy with permanent ileostomy. Since the 1970s, restorative proctocolectomy with ileoanal anastomosis has gained acceptance as the standard operation of choice for adults and children. The most frequently used techniques in pediatric patients are colectomy with straight ileal-anal pull-through or with ileal pouch-anal anastomosis (IPAA). Today, most surgeons construct a J-pouch ileal reservoir because is easier to construct, but the choice is still arguable. Meta-analyses comparing straight ileal-anal pull-through and IPAA suggest that pouch procedures are favorable in terms of reconstruction survival and functional outcomes such as bowel frequency, incontinence, and nocturnal defecation (37,38). In pediatric patients the reported complications (13%–51%) vary by surgical experience and the technique used but do not generally worsen functional outcomes (39,40).

Dysplasia as an indication for colectomy is typically not an issue that a pediatric patient needs to face, but the possibility of colorectal cancer should be considered in the adolescent with extensive and prolonged UC. The risk of colon cancer for any patient with UC is estimated to be 2% after 10 years, 8% after 20 years, and 18% after 30 years (41). Currently, there are no evidence-based practical surveillance guidelines for pediatric patients with UC. However, regular colonoscopies at 1- to 2-year intervals starting 7 to 10 years after diagnosis are used in adults and should probably be recommended in adolescents (42).

*Consensus Guidelines*

1. Thiopurine immunomodulators (6-MP and AZA) should be considered early in the treatment course of patients with anticipated corticosteroid-dependent UC
2. Cyclosporine and infliximab are therapeutic options for refractory UC patients that are unresponsive or intolerant to corticosteroids or thiopurine immunomodulators
3. Colectomy with ileoanal anastomosis is the surgical option of choice for refractory UC if the surgical expertise is available

**Refractory Crohn Colitis**

Refractory Crohn colitis remains a distinct phenotype of CD that can behave similarly to refractory UC, but in which the hope of a potential surgical “cure” is not as readily available. Isolated disease of the colon has been noted in up to 25% of CD patients, and recent data suggests that more colonic involvement is being seen in younger children (43–45). Variants of the *NOD2/CARD15* gene increase risk for ileal and ileocolonic CD, but not for colon-only CD (8).

Studies reporting the prevalence of serological markers in patients with IBD have noted that anti-*Saccharomyces cerevisiae* antibodies are more strongly associated with ileal CD while perinuclear anti-neutrophil cytoplasmic antibodies have been more strongly associated with UC (46,47). However, approximately 25% of all CD patients also express perinuclear anti-neutrophil cytoplasmic antibodies, and their disease appears to behave in a “UC-like” manner. It may be possible that study of antibodies such as those to CBir-1 flagellin will aid in further distinguishing colonic CD from UC (48). Although the findings reported to date of serological markers provide intriguing hypotheses, the practical use of serology in distinguishing between colonic CD and UC remains controversial.

*Medical Management*

As in UC, Crohn colitis may become corticosteroid-refractory or corticosteroid-dependent. Early use of 6-MP/AZA also has become the norm in treating refractory, or anticipated refractory, Crohn colitis (13,49). Dosing and monitoring for adverse effects are similar to that previously described for UC. For patients with Crohn colitis who are intolerant or nonresponsive to 6-MP/AZA, weekly methotrexate given intramuscularly or subcutaneously has been shown to induce and maintain remission (50). Since the late 1990s, adult and pediatric trials have shown that a 3-infusion regimen of 5 mg/kg infliximab given at 0, 2, and 6 weeks is effective in

inducing remission in severe CD (51–53). For patients who respond to an induction course, infliximab 5 mg/kg every 8 weeks is effective for maintenance of remission. Escalation of the infliximab dose to 10 mg/kg or increasing the dosing frequency to every 4 to 6 weeks may be necessary in certain patients. Other anti-TNF- $\alpha$  agents also are efficacious in the management of adults with CD; however, data on pediatric patients is scarce (54,55). Care should be taken in patients classified as having refractory disease that other diagnoses such as gastrointestinal infections, strictures, fistulas, or irritable bowel syndrome are considered rather than assuming that disease severity is solely due to the idiopathic inflammatory process.

Recent documentation of a small series of adolescents and young adults with IBD who developed a rare, fatal hepatosplenic T cell lymphoma on combination therapy with infliximab and 6-MP is leading to caution in the use of infliximab and other similar biological agents (56). It remains uncertain whether 6-MP/AZA and infliximab should be used concomitantly, whether 1 of these drug classes should be discontinued, or whether other therapy should be considered, such as methotrexate or surgery. Thus, when using these drugs, patients and their families should be brought into a discussion that weighs the disease severity and course with the risks and benefits of the current treatment strategy (57).

Nutritional therapy with exclusive elemental or polymeric formulas can be of significant benefit to a child with refractory Crohn colitis, especially if there is associated poor weight gain and suboptimal growth (58,59). There is a considerable geographical difference in the use of nutritional therapy with a recent survey reporting that only 4% of North American gastroenterologists use this modality versus 62% of Western European gastroenterologists (60).

*Surgical Management*

Between 70% to 90% of patients with CD require 1 surgical intervention within their lifetime, and as many as 50% of them may undergo further procedures. In general, when there is both small and large intestine involvement the judicious use of surgical intervention is paramount to avoid the consequence of short bowel syndrome. Unlike UC, no surgical option for cure exists for isolated CD of the colon, and thus elective surgery should not be performed without an adequate trial of medical management. As suggested for UC, it is important to ensure that the correct diagnosis is made to guide the surgical intervention and discuss prognosis.

Surgical options for refractory Crohn colitis include simple diversion, subtotal colectomy with ileostomy or ileorectal anastomosis, limited segmental resection, and proctocolectomy. Opinion remains varied as to whether limited resection or more extensive resection, such as

total proctocolectomy, is the best approach. An 18-year prospective study of 179 patients with Crohn colitis reported decreased surgical recurrence rates and postoperative corticosteroid and thiopurine use for adults undergoing total colectomy compared with those undergoing segmental colectomy (61). A recent meta-analysis of 6 studies comprising nearly 500 adult patients suggested that segmental colectomy and colectomy with ileorectal anastomosis were both effective treatment options, but that disease recurrence was noted significantly earlier in the segmental colectomy group (62). A trend in favor of better outcomes with ileorectal anastomosis was noted in patients with 2 or more colonic segments involved. There is a paucity of literature regarding functional outcomes and complications in children with Crohn colitis, but a study of 26 children suggested a better prognosis after subtotal or proctocolectomy with ileostomy compared with segmental resection (63). The presence or absence of perianal disease in association with colitis can impact outcomes following colonic resection, with there often being a frequent need for a permanent stoma in those with perianal disease (64). Although there may be a subgroup of patients without evidence of small intestine or perianal disease who may be good candidates for IPAA, the surgical literature generally supports avoidance of performing colectomy with IPAA in patients with Crohn disease because of high postoperative complication and pouch failure rates (65,66).

To avoid the potential need for colectomy for dysplasia, it should be kept in mind that as in UC, patients with colonic CD also have an increased risk of colon cancer (41,42). Patients diagnosed with colonic CD before age 30 years appear to have an even higher relative risk of colon cancer than those diagnosed later. Upon comparing UC and colonic CD of similar disease extents, the age of cancer development, disease duration, presence of dysplasia, and overall prognosis appear similar. Thus, the guidelines provided above also apply.

#### *Consensus Guidelines*

1. The drugs 6-MP and AZA should be considered early therapeutic agents in the treatment of corticosteroid-refractory or corticosteroid-dependent Crohn colitis.
2. Methotrexate is an alternative for patients who are intolerant or nonresponsive to thiopurines.
3. Infliximab should be considered in the treatment of patients with refractory Crohn colitis.
4. Segmental resection for limited colonic CD or subtotal colectomy with ileorectal anastomosis for more generalized colonic disease are reasonable options for medically refractory Crohn's colitis.

### **Refractory Perianal Crohn Disease**

Perianal CD refers to the involvement of the perianal area in the inflammatory process, and includes a wide spectrum of lesions such as skin tags, hemorrhoids, anal ulcers, fissures, abscesses, and fistulas. These can result in substantial morbidity, including scarring, continual seepage, and fecal incontinence. Perianal disease is present at diagnosis in approximately 15% to 20% of pediatric patients and is frequently associated with active inflammatory disease (67). In some cases, perianal disease may precede any abdominal symptom and be the only sign leading to the diagnosis of CD. Although the spontaneous resolution of anal lesions is observed in up to 50% of patients, the penetrating nature of perianal CD may lead to more complicated secondary lesions. In some patients, this can lead to the gradual destruction of the sphincter apparatus and anal incontinence.

#### *Medical Management*

The primary treatment of patients with perianal CD combines medical and surgical management with the aim of alleviating suffering, preventing possible complications, and improving quality of life. Before treatment is begun, the perianal anatomy should be fully delineated with consideration given to endoscopic evaluation, an examination under anesthesia (requiring surgical expertise), and MRI or endoscopic ultrasound of the pelvis. For patients with perianal fistulizing disease, this evaluation will allow for broad categorization of their fistulas as either "simple" or "complex." Simple fistulas include those that are superficial or low intersphincteric/transsphincteric, have only a single external opening, and are not associated with pain, fluctuation, or anorectal stricture. Complex fistulas include those that are high intersphincteric/transsphincteric, have multiple external openings with evidence of abscess, rectovaginal connections, strictures, or active rectal inflammation (68). Treatment is more difficult and less successful in complex perianal disease.

Current treatments include antibiotics, thiopurines, and anti-TNF- $\alpha$  agents. Unlike in luminal disease, corticosteroids are usually not beneficial in perianal CD and may even retard wound healing and exacerbate abscess formation. Aminosalicylates are ineffective for closing fistulas. However, treatment of active rectal inflammation with topical corticosteroids or mesalamine may improve anal symptoms.

Metronidazole and ciprofloxacin are established as a mainstay of therapy in perianal CD, although despite widespread use there are no controlled trials of efficacy. In general, antibiotics are typically continued for 3 to 4 months. Clinical response may be anticipated in approximately 50% of patients and generally occurs after 6 to 8 weeks of treatment, but fistulas usually recur after

cessation of antibiotics (69). Antibiotics may therefore be used as a bridge to thiopurine immunomodulator treatment.

A meta-analysis of 5 controlled trials using 6-MP/AZA to treat adults with CD (including perianal CD) demonstrated fistula closure in 54% of treated patients versus 21% of controls (70). Two uncontrolled studies in children also report thiopurines to be effective treatments for healing significant perianal CD (71,72). Controlled trials in adults have demonstrated efficacy of infliximab for treating symptomatic perianal fistulizing disease (68). In 1 of these studies, overall fistula closure after 3 infusions of infliximab was seen in 55% of treated patients versus 13% of the placebo group (73). Median time to fistula closure was 3 months. Adalimumab, a fully humanized monoclonal TNF- $\alpha$  antibody, is also beneficial in treating fistulizing CD (54).

The efficacy of tacrolimus in patients with fistulizing CD has been reported in 1 multicenter placebo-controlled trial, suggesting that it may be a potential therapeutic agent in patients not responding to 6-MP/AZA or infliximab (74). Topical tacrolimus has shown some efficacy in perianal ulcerating CD, but not fistulizing perianal CD (75).

#### *Surgical Treatments*

It is once again important to emphasize that interdisciplinary care by gastroenterologists and surgeons provides the best outcome for patients. Surgical treatment for perianal CD can include initial emergency treatment, mainly aimed to control perineal sepsis by adequate drainage, and elective treatment of sequelae such as perianal fistulas and anal strictures. Operative management of a fistula depends on whether it is simple or complex. Fistulotomy, combined with medical treatment, is often effective in symptomatic simple fistulas. In complex fistulas, placement of draining and noncutting setons, which can be left for prolonged time periods, combined with medical treatment is advised. If perianal disease is extensive or disease progresses despite abscess drainage, then an alternative procedure is formation of a defunctioning stoma (76). The perianal procedure should be effective enough to control sepsis or alleviate suffering, but not so aggressive as to cause sphincter function damage. Despite intensive medical and surgical therapy, a small percentage of patients will ultimately require proctectomy (77).

#### *Consensus Guidelines*

1. Before starting treatment of refractory perianal CD, endoscopic assessment of disease activity, examination under general anesthesia, and imaging studies

(MRI and/or endoscopic ultrasound) of the perianal area should be performed.

2. In symptomatic, simple perianal fistulas, first-line medical treatment can consist of antibiotics but to maintain remission a thiopurine immunomodulator may be necessary.
3. If a perianal abscess is present, immediate surgical drainage should be performed.
4. In thiopurine refractory perianal CD, or when complex fistulas are present, combined therapy with infliximab and seton placement should be considered.

### **CONCLUSIONS AND SUGGESTIONS FOR FUTURE RESEARCH**

1. As younger and younger children are diagnosed with IBD, and its worldwide prevalence increases, there is a need for comprehensive longitudinal, prospective databases to provide information about the natural medical and surgical history of IBD in the pediatric age groups and the long-term prognosis of adults diagnosed with IBD in childhood.
2. We are not able to systematically predict at diagnosis those individuals at highest risk for developing refractory IBD and who are thus more likely to require intensive medical or surgical interventions. Identification of pharmacogenomic, serological, or clinical markers that can more accurately predict response and disease outcomes to medical and surgical therapies is needed.
3. With the relatively rapid influx of new medications on the market, especially biological agents aimed at those with moderate to severe IBD, multicenter clinical trials designed to ask important pediatric-specific questions and that incorporate the experience of pediatric gastroenterologists should be developed.
4. If prolonged medical remission in refractory CD or UC is achieved with drugs such as 6-MP/AZA or infliximab, it is unclear as to when these drugs can be safely discontinued. Additionally, given the recent focus on hepatosplenic T cell lymphoma, there is insufficient evidence to provide recommendations for the continuation or discontinuation of concomitant thiopurine and infliximab therapy. Thus, in general, attention and resources need to be given to the development of evidence-based treatment algorithms in pediatric IBD.
5. Accurate malignancy risk measurements are needed for children diagnosed with IBD for the disease process alone, and with the addition of chronic immunosuppressive therapies including biological agents.

The different phenotypes of UC and CD discussed result from a number of genetic, immune, and environmental influences. We suspect that “individualized” or “personalized” medicine will become key buzzwords for management of complex, chronic disorders such as CD and UC, and that future systems will emerge in which disease behaviors, responses to medical and surgical interventions, and prognoses will be predicted at the individual rather than the group level. For this to occur, we will need to focus on the identification of multiple genetic, immune, and clinical markers that will help predict natural history and therapeutic responsiveness at diagnosis. Ideally, the knowledge gained in this process will allow us to learn more about the specific pathways involved in the inflammatory cascade and enable the development of therapeutic targets not just to ameliorate the inflammatory bowel diseases but to cure them.

## REFERENCES

- Lakatos PL. Recent trends in the epidemiology of inflammatory bowel diseases: up or down? *World J Gastroenterol* 2006;12:6102–8.
- Levine A, Kugathasan S, Annesse V, et al. Pediatric onset Crohn's colitis is characterized by genotype-dependent age-related susceptibility. *Inflamm Bowel Dis* 2007;13:1509–15.
- Kugathasan S, Judd RH, Hoffmann RG, et al. Epidemiologic and clinical characteristics of children with newly diagnosed inflammatory bowel disease in Wisconsin: a statewide population-based study. *J Pediatr* 2003;143:525–31.
- Hyams J, Markowitz J, Lerer T, et al. The natural history of corticosteroid therapy for ulcerative colitis in children. *Clin Gastroenterol Hepatol* 2006;4:1118–23.
- Howarth LJ, Wiskin AE, Griffiths DM, et al. Outcome of childhood ulcerative colitis at 2 years. *Acta Paediatr* 2007;96:1790–3.
- Faubion WA Jr, Loftus EV Jr, Harmsen WS, et al. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. *Gastroenterology* 2001;121:255–60.
- Ling KL, Ooi CJ, Luman W, et al. Clinical characteristics of ulcerative colitis in Singapore, a multiracial city-state. *J Clin Gastroenterol* 2002;35:144–8.
- Cho JH, Weaver CT. The genetics of inflammatory bowel disease. *Gastroenterology* 2007;133:1327–39.
- Daniel F, Lorient MA, Seksik P, et al. Multidrug resistance gene-1 polymorphisms and resistance to cyclosporine A in patients with steroid resistant ulcerative colitis. *Inflamm Bowel Dis* 2007;13:19–23.
- Yap LM, Ahmad T, Jewell DP. The contribution of HLA genes to IBD susceptibility and phenotype. *Best Pract Res Clin Gastroenterol* 2004;18:577–96.
- Achkar JP, Dassopoulos T, Silverberg MS, et al. Phenotype-stratified genetic linkage study demonstrates that IBD2 is an extensive ulcerative colitis locus. *Am J Gastroenterol* 2006;101:572–80.
- Turner D, Walsh CM, Steinhart AH, et al. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. *Clin Gastroenterol Hepatol* 2007;5:103–10.
- Timmer A, McDonald JW, Macdonald JK. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2007;1:CD000478.
- Verhave M, Winter HS, Grand RJ. Azathioprine in the treatment of children with inflammatory bowel disease. *J Pediatr* 1990;117:809–814.
- Dubinsky MC, Lamothe S, Yang HY, et al. Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. *Gastroenterology* 2000;118:705–13.
- Ooi CY, Bohane TD, Lee D, et al. Thiopurine metabolite monitoring in paediatric inflammatory bowel disease. *Aliment Pharmacol Ther* 2007;25:941–7.
- Maitland ML, Vasisht K, Ratain MJ, et al. TPMT, UGT1A1, and DPYD: genotyping to ensure safer cancer therapy? *Trends Pharmacol Sci* 2006;27:432–7.
- Lichtenstein GR, Abreu MT, Cohen R, et al. American Gastroenterological Association Institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology* 2006;130:940–87.
- Fargher EA, Tricker K, Newman W, et al. Current use of pharmacogenetic testing: a national survey of thiopurine methyltransferase testing prior to azathioprine prescription. *J Clin Pharm Ther* 2007;32:187–95.
- Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994;330:1841–5.
- Castro M, Papadatou B, Ceriati E, et al. Role of cyclosporin in preventing or delaying colectomy in children with severe ulcerative colitis. *Langenbecks Arch Surg* 2007;392:161–4.
- Shibole O, Regushevskaya E, Brezis M, et al. Cyclosporine A for induction of remission in severe ulcerative colitis. *Cochrane Database Syst Rev* 2005;1:CD004277.
- Lawson MM, Thomas AG, Akobeng AK. Tumour necrosis factor blocking agents for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2006;3:CD005112.
- Eidelwein AP, Cuffari C, Abadom V, et al. Infliximab efficacy in pediatric ulcerative colitis. *Inflamm Bowel Dis* 2005;11:213–8.
- Fanjiang G, Russell GH, Katz AJ. Short- and long-term response to and weaning from infliximab therapy in pediatric ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2007;44:312–7.
- Ogata H, Matsui T, Nakamura M, et al. A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis. *Gut* 2006;55:1255–62.
- Ziring DA, Wu SS, Mow WS, et al. Oral tacrolimus for steroid-dependent and steroid-resistant ulcerative colitis in children. *J Pediatr Gastroenterol Nutr* 2007;45:306–11.
- Abreu MT, Plevy S, Sands BE, et al. Selective leukocyte apheresis for the treatment of inflammatory bowel disease. *J Clin Gastroenterol* 2007;41:874–88.
- Ruuska T, Lahdeaho ML, Sutas Y, et al. Leucocyte apheresis in the treatment of paediatric ulcerative colitis. *Scand J Gastroenterol* 2007;42:1390–1.
- Tilg H, Vogelsang H, Ludwiczek O, et al. A randomised placebo controlled trial of pegylated interferon  $\alpha$  in active ulcerative colitis. *Gut* 2003;52:1728–33.
- Summers RW, Elliott DE, Urban JF Jr, et al. Trichuris suis therapy for active ulcerative colitis: a randomized controlled trial. *Gastroenterology* 2005;128:825–32.
- Satsangi J, Silverberg MS, Vermeire S, et al. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006;55:749–53.
- Bousvaros A, Antonioli DA, Colletti RB, et al. Differentiating ulcerative colitis from Crohn disease in children and young adults: report of a working group of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the Crohn's and Colitis Foundation of America. *J Pediatr Gastroenterol Nutr* 2007;44:653–74.
- IBD Working Group of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition. Inflammatory bowel disease in children and adolescents: recommendations for diagnosis—the Porto criteria. *J Pediatr Gastroenterol Nutr* 2005;41:1–7.
- Mow WS, Lo SK, Targan SR, et al. Initial experience with wireless capsule enteroscopy in the diagnosis and management of inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2004;2:31–40.

36. Mann EH. Inflammatory bowel disease: imaging of the pediatric patient. *Semin Roentgenol* 2008;43:29–38.
37. Tilney HS, Constantiniades V, Ioannides AS, et al. Pouch-anal anastomosis vs straight ileoanal anastomosis in pediatric patients: a meta-analysis. *J Pediatr Surg* 2006;41:1799–808.
38. Rintala RJ, Lindahl H. Restorative proctocolectomy for ulcerative colitis in children—is the J-pouch better than straight pull-through? *J Pediatr Surg* 1996;31:530–3.
39. Mattioli G, Castagnetti M, Gandullia P, et al. Stapled restorative proctocolectomy in children with refractory ulcerative colitis. *J Pediatr Surg* 2005;40:1773–9.
40. Wewer V, Hesselheldt P, Qvist N, et al. J-pouch ileoanal anastomosis in children and adolescents with ulcerative colitis: functional outcome, satisfaction, and impact on social life. *J Pediatr Gastroenterol Nutr* 2005;40:189–93.
41. Eaden J. Review article: colorectal carcinoma and inflammatory bowel disease. *Aliment Pharmacol Ther* 2004;20 (Suppl 4):24–30.
42. Xie J, Itzkowitz SH. Cancer in inflammatory bowel disease. *World J Gastroenterol* 2008;14:378–89.
43. Freeman HJ. Natural history and clinical behavior of Crohn's disease extending beyond two decades. *J Clin Gastroenterol* 2003;37:216–9.
44. Amre DK, Lu SE, Costea F, et al. Utility of serological markers in predicting the early occurrence of complications and surgery in pediatric Crohn's disease patients. *Am J Gastroenterol* 2006;101:645–652.
45. Heyman MB, Kirschner BS, Gold BD, et al. Children with early-onset inflammatory bowel disease (IBD): analysis of a pediatric IBD consortium registry. *J Pediatr* 2005;146:35–40.
46. Zholudev A, Zurakowski D, Young W, et al. Serologic testing with ANCA, ASCA, and anti-OmpC in children and young adults with Crohn's disease and ulcerative colitis: diagnostic value and correlation with disease phenotype. *Am J Gastroenterol* 2004;99:2235–41.
47. Vasiliaskas EA, Plevy SE, Landers CJ, et al. Perinuclear antineutrophil cytoplasmic antibodies in patients with Crohn's disease define a clinical subgroup. *Gastroenterology* 1996;110:1810–9.
48. Targan SR, Landers CJ, Yang H, et al. Antibodies to CBir1 flagellin define a unique response that is associated independently with complicated Crohn's disease. *Gastroenterology* 2005;128:2020–2028.
49. Markowitz J, Grancher K, Kohn N, et al. A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. *Gastroenterology* 2000;119:895–902.
50. Uhlen S, Belbouab R, Narebski K, et al. Efficacy of methotrexate in pediatric Crohn's disease: a French multicenter study. *Inflamm Bowel Dis* 2006;12:1053–7.
51. Clark M, Colombel JF, Feagan BC, et al. American gastroenterological association consensus development conference on the use of biologics in the treatment of inflammatory bowel disease, June 21–23, 2006. *Gastroenterology* 2007;133:312–39.
52. Cezard JP, Nouaili N, Talbot C, et al. A prospective study of the efficacy and tolerance of a chimeric antibody to tumor necrosis factors (remicade) in severe pediatric Crohn disease. *J Pediatr Gastroenterol Nutr* 2003;36:632–6.
53. Hyams J, Crandall W, Kugathasan S, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology* 2007;132:863–873.
54. 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;132:52–65.
55. Schreiber S, Khaliq-Kareemi M, Lawrance IC, et al., PRECISE 2 Study Investigators. Maintenance therapy with certolizumab pegol for Crohn's disease. *N Engl J Med* 2007;357:239–50.
56. Rosh JR, Gross T, Mamula P, et al. Hepatosplenic T-cell lymphoma in adolescents and young adults with Crohn's disease: a cautionary tale? *Inflamm Bowel Dis* 2007;13:1024–30.
57. Rosh JR, Oliva-Hemker M. Infliximab use and hepatosplenic T cell lymphoma: questions to be asked and lessons learned. *J Pediatr Gastroenterol Nutr* 2007;44:165–7.
58. Griffiths AM, Ohlsson A, Sherman PM, et al. Meta-analysis of enteral nutrition as a primary treatment of active Crohn's disease. *Gastroenterology* 1995;108:1056–67.
59. Knight C, El-Matary W, Spray C, et al. Long-term outcome of nutritional therapy in paediatric Crohn's disease. *Clin Nutr* 2005;24:775–9.
60. Levine A, Milo T, Buller H, et al. Consensus and controversy in the management of pediatric Crohn disease: an international survey. *J Pediatr Gastroenterol Nutr* 2003;36:464–9.
61. Fichera A, McCormack R, Rubin MA, et al. Long-term outcome of surgically treated Crohn's colitis: a prospective study. *Dis Colon Rectum* 2005;48:963–9.
62. Tekkis PP, Purkayastha S, Lanitis S, et al. A comparison of segmental vs subtotal/total colectomy for colonic Crohn's disease: a meta-analysis. *Colorectal Dis* 2006;8:82–90.
63. Ba'ath ME, Mahmalat MW, Kapur P, et al. Surgical management of inflammatory bowel disease. *Arch Dis Child* 2007;92:312–6.
64. Polle SW, Slors JF, Weverling GJ, et al. Recurrence after segmental resection for colonic Crohn's disease. *Br J Surg* 2005;92:1143–9.
65. Brown CJ, Maclean AR, Cohen Z, et al. Crohn's disease and indeterminate colitis and the ileal pouch–anal anastomosis: outcomes and patterns of failure. *Dis Colon Rectum* 2005;48:1542–9.
66. Panis Y, Poupard B, Nemeth J, et al. Ileal pouch/anal anastomosis for Crohn's disease. *Lancet* 1996;347:854–7.
67. Sawczenko A, Sandhu BK. Presenting features of inflammatory bowel disease in Great Britain and Ireland. *Arch Dis Child* 2003;88:995–1000.
68. Sandborn WJ, Fazio VW, Feagan BG, et al., American Gastroenterological Association Clinical Practice Committee. AGA technical review on perianal Crohn's disease. *Gastroenterology* 2003;125:1508–30.
69. DeJaco C, Harrer M, Waldhoer T, et al. Antibiotics and azathioprine for the treatment of perianal fistulas in Crohn's disease. *Aliment Pharmacol Ther* 2003;18:1113–20.
70. Pearson DC, May GR, Fick GH, et al. Azathioprine and 6-mercaptopurine in Crohn disease. A meta-analysis. *Ann Intern Med* 1995;123:132–42.
71. Jeshion WC, Larsen KL, Jawad AF, et al. Azathioprine and 6-mercaptopurine for the treatment of perianal Crohn's disease in children. *J Clin Gastroenterol* 2000;30:294–8.
72. Macdonald A, Wilson-Storey D, Munro F. Treatment of perianal abscess and fistula-in-ano in children. *Br J Surg* 2003;90:220–1.
73. 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;340:1398–405.
74. Sandborn WJ, Present DH, Isaacs KL, et al. Tacrolimus for the treatment of fistulas in patients with Crohn's disease: a randomized, placebo-controlled trial. *Gastroenterology* 2003;125:380–8.
75. Hart AL, Plamondon S, Kamm MA. Topical tacrolimus in the treatment of perianal Crohn's disease: exploratory randomized controlled trial. *Inflamm Bowel Dis* 2007;13:245–53.
76. Singh B, George BD, Mortensen NJ. Surgical therapy of perianal Crohn's disease. *Dig Liver Dis* 2007;39:988–92.
77. Rutgeerts P. Management of perianal Crohn's disease. *Can J Gastroenterol* 2000;14:7C–12C.