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THERAPY IN PRACTICE

Pediatric Ulcerative Colitis: A Practical Guide to Management

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Abstract Ulcerative colitis (UC) is a chronic inflammatory disorder of the gastrointestinal tract of unknown etiology that frequently presents in the pediatric population. The evaluation of pediatric UC involves excluding infection, and a colonoscopy that documents the clinical and histologic features of chronic colitis. Initial management of mild UC is typically with mesalamine therapy for induction and maintenance. Moderate UC is often initially treated with oral prednisone. Depending on disease severity and response to prednisone, maintenance options include mesalamine, mercaptopurine, azathioprine, infliximab, or adalimumab. Severe UC is typically treated with intravenous corticosteroids. Corticosteroid nonresponders should either undergo a colectomy or be treated with second-line medical rescue therapy (infliximab or calcineurin inhibitors). The severe UC patients who respond to medical rescue therapy can be maintained on infliximab or thiopurine, but 1-year remission rates for such patients are under 50 %. These medications are discussed in detail along with the initial work-up and a treatment algorithm.

1 Introduction

Ulcerative colitis (UC) is a chronic inflammatory disorder of the gastrointestinal tract of unknown etiology. It most commonly has its onset in teenagers and young adults but can present at any age. Pediatric UC has a more severe phenotype reflected by more extensive disease (i.e., disease more likely to involve the entire colon), and a higher rate of acute severe exacerbations [1]. The basic tenets in the management of inflammatory bowel disease (IBD) are achieving remission while minimizing medication toxicity and long-term disease complications. This review will involve an overview of the diagnosis of UC, metrics to monitor disease activity, principles of "step-up" vs. "top-down" therapy, and medications used to treat the disease. While surgical management (colectomy, ileostomy, and ileal pouch anal anastomosis) is essential in managing medically refractory cases or dysplasia, we do not discuss surgeries in detail. We summarize by providing a suggested algorithm for managing cases of pediatric colitis.

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2 Presentation and Diagnosis

The clinical course for patients with UC is one that follows a relapsing and remitting course, with flare symptoms of bloody diarrhea, abdominal cramping, and tenesmus [2]. The initial evaluation of a patient presenting with these symptoms begins with excluding an infectious etiology. Fecal samples may be sent for culture for enteric pathogens, parasites, and *Clostridium difficile*. In addition, initial laboratory assessment includes complete blood count with differential, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and serum albumin.

The intestinal inflammation in UC is limited to the colon in most patients, though the terminal ileum may also be mildly inflamed with "backwash ileitis". In children, approximately 60 % of patients will also have histologic gastritis at the time of diagnosis; this "upper tract

involvement" should not be confused for Crohn disease (CD) [3]. On colonoscopy of the untreated UC patient, the endoscopist generally identifies diffuse mucosal inflammation (e.g., friability, granularity, erythema, loss of vascular pattern, and superficial ulceration). The inflammation involves the rectum in 95 % of cases and extends proximally involving parts or all of the colon [4].

Patients with UC may develop inflammation in the distal ileum thought to be due to "backwash" ileitis of cecal contents. In adults, the prevalence is approximately 20 % in patients with pancolitis; backwash is rarely seen in patients with proctitis or left-sided disease. The inflammation is generally mild in nature (villous atrophy, increased inflammation, scattered crypt abscesses), and is not associated with an increased rate of ileo-anal pouch complications, dysplasia, or carcinoma. Strict histopathologic criteria for backwash ileitis have not been established [5].

In the biopsies of the colon in UC patients, the diagnosis established by the typical histologic features of chronic colitis (crypt branching, crypt distortion, lymphoplasmacytic cell infiltrate, Paneth cell metaplasia) are seen. However, chronic changes may not necessarily be identified on the initial presentation; in this case, the clinician must use other clinical features to determine if this is UC or acute self-limited colitis.

In a subset of patients with colonic IBD and atypical features, the clinician may have difficulty differentiating between CD and UC despite a thorough evaluation. Such atypical features include: rectal sparing, significant growth delay, transmural inflammation in the absence of severe colitis, duodenal or esophageal ulcers not explained by other causes, multiple aphthous ulcerations in the stomach, atypical serologies, and focal inflammation on biopsies. In these cases, the clinician may classify the patient as "IBD unclassified" or "indeterminate colitis". The initial treatment of IBD unclassified is similar to the treatment of UC [6, 7].

In addition to the colonic inflammation, patients may develop a wide array of extra intestinal manifestations of UC, including: peripheral arthritis, sacroiliitis, ankylosing spondylitis, osteoporosis, erythema nodosum, pyoderma gangrenosum, aphthous stomatitis, uveitis, scleritis, episcleritis, hepatobiliary disease, primary sclerosing cholangitis, and thromboembolic events [8]. Thus, after the diagnosis is made, the clinician must look "outside the gastrointestinal tract for other manifestations of the disease". Table 1 provides a suggested diagnostic evaluation and assessment for the child or young adult with new-onset IBD.

Table 1 Signs and symptoms that can be seen in ulcerative colitis

Bloody diarrhea
Growth failure
Anemia
Chronic watery diarrhea
Chronic abdominal pain
Oligoarticular arthritis
Laboratory abnormalities (ESR, CRP, albumin, fecal blood, calprotectin, or leukocytes)
Fever of unknown origin

ESR erythrocyte sedimentation rate, *CRP* C-reactive protein

Table 2 Work-up for suspected inflammatory bowel disease

Laboratory assessment	
Inflammatory markers	Erythrocyte sedimentation rate
	C-reactive protein
Complete blood count	Evaluate for anemia
Iron studies	
Fecal markers	Calprotectin
	Guaiac
	Lactoferrin or calprotectin
Stool testing for infectious processes	
Clostridium difficile evaluation	
Stool culture	*Salmonella*, *Campylobacter*, *Shigella*, *Yersinia enterocolitica*, *Escherichia coli* 0157:H7, *Aeromonas*, *Plesiomonas*
Endoscopy–colonoscopy with evaluation of the terminal ileum with ileal and colonic biopsies	
Upper endoscopy if concern regarding upper tract involvement of IBD (i.e., CD)	
Radiology–magnetic resonance imaging enterography or UGI with SBFT	
Consider video capsule enterography if suspect diagnosis but other tests normal	

CD Crohn disease, *IBD* inflammatory bowel disease, *UGI* upper gastrointestinal series, *SBFT* small bowel follow-through

3 Monitoring Disease Activity

Initial evaluation for patients presenting with bloody stool involves ruling out infection, with stool culture and *C. difficile* toxin or polymerase chain reaction assay (Table 2). Evaluation of the degree of inflammation is assessed by measurement of ESR, C-reactive protein (CRP), and platelet count as well as fecal lactoferrin or a fecal calprotectin. Ongoing loss of occult or gross blood in stool leads to anemia, with low hemoglobin hematocrit, MCV, wide red cell distribution width, and low iron studies.

The Pediatric Ulcerative Colitis Activity Index (PUCAI) is a noninvasive reliable index to assess disease activity in pediatric UC. Six items are assessed, abdominal pain, rectal bleeding, stool consistency, number of stools in 24 h,

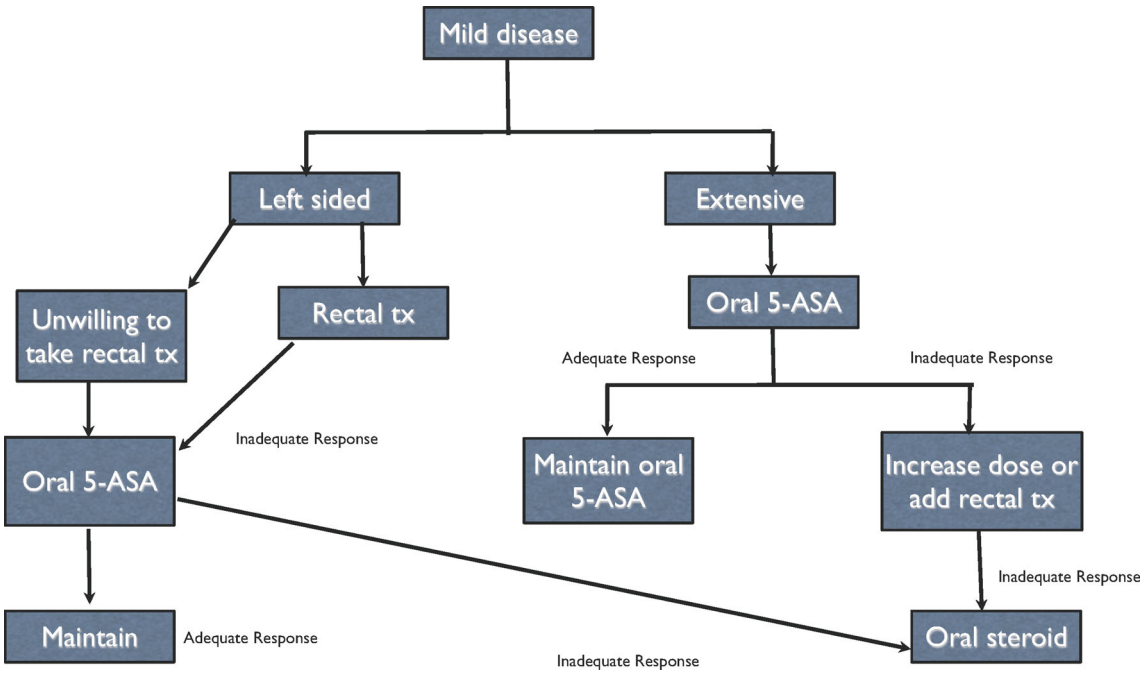

Fig. 1 Treatment of mild ulcerative colitis in patients with disease limited to the rectosigmoid; topical rectal therapy with either 5-aminosalicylate (5-ASA) enema or hydrocortisone enemas is effective for induction. If a patient responds, they can then be transitioned to oral 5-ASA. If there is lack of response to topical treatment or the patient is unwilling to take rectal therapy, oral agents can be attempted for induction. Salicylate-unresponsive patients or patients unresponsive to topical treatment should receive oral corticosteroids. In contrast, patients with sub-total or pan-colonic disease should be treated with oral 5-ASA and corticosteroid can be used in those that do not respond to oral 5-ASA after 3–5 weeks

nocturnal stools, and activity level, assigning values in each category with a total range of 0–85. Values <10 indicate no disease activity, 10–30 indicate mild disease activity, 35–60 indicate moderate disease activity, and values >65 indicate severe colitis. Disease activity and treatment options correlate with PUCAI score [9].

Serologic markers are measureable titers of various immune responses in patients in whom IBD is suspected. The suggested uses for these markers include ruling out IBD, and discerning CD from UC in cases where the presentation is not clear, i.e., cases of diffuse colitis with some involvement of the ileum, or patchy distribution in the colon without presence of granulomas, which are seen in cases of CD. Specific markers include ASCA (anti-*Saccharomyces cerevisiae* antibodies), pANCA (perinuclear antineutrophil cytoplasmic antibodies), and the more recently investigated OmpC (anti-outer membrane protein C), and anti-flagellin (CBir1) [10]. At the time of this publication the exact role of these markers, and others currently being evaluated, is unclear in pediatric IBD.

4 Overview of Therapy

The concept of "step up" vs. "top down", while commonly discussed in CD, is infrequently mentioned in UC [11]. However, the practicing gastroenterologist commonly stratifies patients with UC to stronger immunosuppression vs. milder agents using two factors: disease severity and corticosteroid responsiveness (Figs. 1 and 2). Severe disease (as characterized by PUCAI scores of ≥65, diarrhea, dehydration, or bleeding requiring transfusion) requires urgent attention, admission, hydration, and medical therapy [1]. In the case of massive hemorrhage or toxic megacolon (a rare complication of UC), emergency surgery may be indicated [12]. In most cases, however, intravenous (IV) corticosteroids are used as first-line therapy. Approximately 50 % of patients will respond to IV corticosteroid therapy. For those who do not respond within 5 days, treatment with either infliximab (IFX) or a calcineurin inhibitor constitutes second-line medical therapy [13]. In the responders with severe colitis, some form of long-term immunosuppressive maintenance therapy (IFX or thiopurine) will be required.

In contrast, the majority of children with UC have less severe disease and can be managed as outpatients with "step-up therapy". For a patient with mild disease, (e.g., PUCAI <35, or two or three bowel movements per day with small amounts of blood), aminosalicylate (ASA) can be used for both induction and maintenance. For moderate disease, oral corticosteroids (budesonide or prednisone) are used to induce remission, and ASA can be attempted for

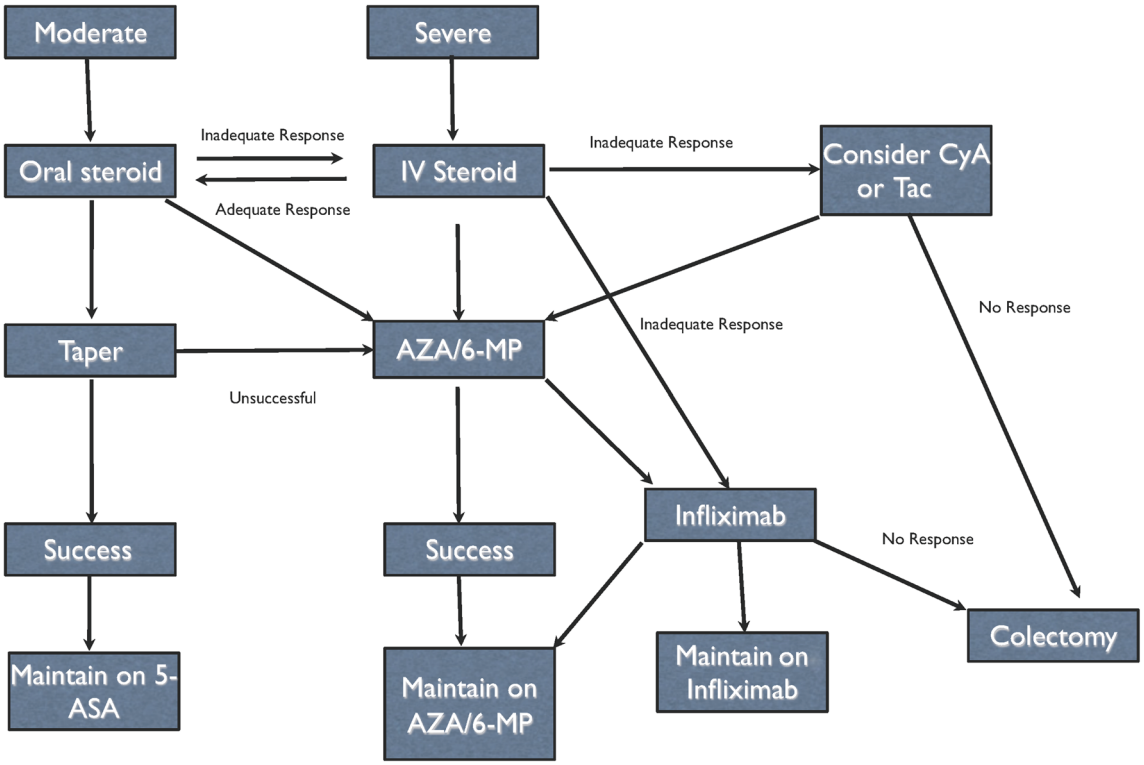

Fig. 2 Treatment of moderate to severe ulcerative colitis (UC). Moderate UC can be treated with oral corticosteroids, either prednisone or budesonide. If a patient responds, corticosteroids can be tapered while aminosalicylates are added as a maintenance therapy. In patients who cannot be maintained on 5-aminosalycylate (5-ASA), either immunomodulators or anti-tumor necrosis factor agents can be used for maintenance. In contrast, patients with severe UC should be hospitalized and treated with intravenous corticosteroids. If a patient does not respond to treatment in 5–7 days, rescue therapy such as infliximab or calcineurin inhibitors should be used. In patients who do respond to rescue therapy, maintenance agents include immunomodulators or infliximab. Colectomy should be offered as an option to any patient who does not respond to intravenous corticosteroid therapy, and in a patient who does not respond to rescue therapy with either calcineurin inhibitors or infliximab. *AZA* azathioprine, *CyA* cyclosporine, *6-MP* 6-mercaptopurine, *Tac* tacrolimus

maintenance. Approximately 50 % of children cannot be maintained on ASA [14]. In these patients, either thiopurines or IFX has been used as maintenance.

Recommendations are for tuberculosis screening prior to initiating "step-up therapy" beyond mesalamine and consideration for screening for hepatitis B and C and possibly varicella, prior to initiating therapy. This would also be appropriate time to measure thiopurine methyltransferase level or genotype, to help determine the starting dose of thiopurine if this is desired medical route (discussed more in depth in the thiopurine section).

If medical therapy for UC is inappropriate or ineffective, the best option is a colectomy to remove the diseased organ [15]. A colectomy is indicated for those patients who do not respond to medication, for patients who develop complications of medical therapy (e.g., allergic reaction, recurrent infection, or lymphoma), or for patients who develop dysplasia. In addition, some patients will choose surgery over medication because they are concerned about the potential complications of long-term immunosuppression. Surgical treatment of pediatric UC (involving proctocolectomy and ileoanal anastomosis) can be performed either as an open procedure or laparoscopically; complications include pouchitis, CD of the pouch, or infertility in women.

5 Medications for Pediatric Ulcerative Colitis

5.1 Mesalamine

Mesalamine is a 5-ASA compound used in induction and maintenance treatment of UC. It was discovered as the active anti-inflammatory moiety of sulfasalazine, which has been used to treat UC since the 1940s [16]. More than 88 % of all UC patients receive treatment with 5-ASA; however, fewer than 50 % of children with UC can maintain long-term corticosteroid-free remission on ASA monotherapy [14].

Sulfasalazine contains mesalamine bound to sulfapyridine via an azo bond, which is released by bacterial azoreductase in the small bowel and colon. Sulfapyridine is

inactive, but is absorbed in the colon and is mostly responsible for hypersensitivity reactions and adverse effects associated with sulfasalazine [17]. Overall, 30 % of the bound 5-ASA is then absorbed rapidly in the small intestine, metabolized locally and by the liver to N-Ac-5-ASA (an inactive metabolite) by *N*-acetyltransferase 1 (NAT1), which is present in intestinal epithelial cells and the liver. It is then excreted in the urine as free 5-ASA and N-Ac-5-ASA [17]. The mechanism of action of mesalamine in UC is unclear, but it appears to have a topical effect [17]. 5-ASA is believed to interact with the damaged epithelium, be converted to acetyl-5-ASA (inactive acetylated form), and then absorbed and excreted into the urine or excreted in stool. Another purported mechanism of action is 5-ASA is via inhibition of interleukin (IL)-2 production in peripheral mononuclear cells, and thereby inhibiting T-cell proliferation, altering cell adhesion expression pattern, inhibiting antibody production and mast cell release, and interfering with macrophage and neutrophil chemotaxis [18].

5-ASA may also decrease IL-1 and tumor necrosis factor (TNF), induce apoptosis of lymphocytes, and regulate nuclear factor-kappa B [19].

Peroxisome proliferator-activated receptor gamma (PPAR-γ) is a transcription factor that modulates the inflammatory response of monocyte and macrophages but inhibits the production of nitric oxide (iNOS) and macrophage-derived cytokines such as TNF-α, IL-1, and IL-6 [20]. Normally highly expressed in the colon, PPAR-γ is significantly reduced in inflamed mucosa from patients with UC, which is restored by topical rosiglitazone, a PPAR-γ ligand [21]. Recent data have suggested a role for mesalamine as an additional ligand of PPAR-γ, which may explain some of its pharmacologic effect [22].

The types and formulation of therapy recommended for patients with UC are dependent on both the location of the disease and the degree of severity. In some patients, the inflammation is limited to the rectum only (distal), but other affected individuals have colonic disease that extends along the length of much of the colon (extensive including pancolitis). Topical (rectal) therapy is the starting point for patients with disease limited to the rectum or left colon, with oral therapy added for patients with more extensive disease [2]. Fewer pediatric patients present with limited left-sided disease (proctitis or procto-sigmoiditis) than adult patients [23].

Using topical and oral mesalamine together may be more effective than either alone in patients with extensive colitis [24]. If effective, once clinical remission has been achieved, mesalamine suppositories or enemas are recommended for maintenance of remission in patient with limited proctitis [25].

Adult literature suggests that rectal 5-ASA is superior to rectal corticosteroids in the management of distal UC [26].

Long-acting formulations of mesalamine are available. However, there is no US Food and Drug Administration (FDA)-approved pediatric dose. They are available as a delayed-release multi-matrix formulation (Lialda) and a pH-controlled granule that releases active mesalamine at pH >6 (as in the colon) (Apriso). In adults, studies show comparable safety and have demonstrated "non-inferiority" in achieving endoscopic remission in comparison with twice-daily formulations of mesalamine [27].

5.2 Corticosteroids

Corticosteroids have long been proven effective in the short-term treatment of UC, and even at that early date, the need for long-term maintenance medications for management has been identified [28]. In a prospective study performed by Beattie et al., 20 children were treated with corticosteroids in combination with 5-ASA medications. Patients received both oral prednisolone (1–2 mg/kg/day), and in some cases rectal corticosteroids as well as 5-ASA. After 8 weeks, 85 % (17/20) of patients were in clinical remission, and 40 % were in endoscopic remission [29]. This study did show the efficacy of corticosteroids in children with UC, but also demonstrated that clinical response does not always correlate with histologic response.

There are no dose-ranging trials of corticosteroids in pediatric UC. Adult literature has shown 40 mg and 60 mg given orally are equally effective, and more effective than 20 mg per day [30]. Corticosteroid dependence has been defined as more than 3 months on corticosteroids to control symptoms and either continuous or repeated courses of corticosteroids in the first year, or weaned off corticosteroids by 3 months but restarted within the first year to control symptoms. Retrospective data of 97 pediatric patients with UC found 45 % of them to be corticosteroid dependent even with the use of immunomodulators [31].

Short-term corticosteroid use is associated with generally mild side effects, including cutaneous effects, electrolyte abnormalities, hypertension, hyperglycemia, pancreatitis, and hematologic, immunologic, and neuropsychological effects. Long-term use may be associated with osteoporosis, aseptic joint necrosis, adrenal insufficiency, gastrointestinal, hepatic, and ophthalmologic effects, hyperlipidemia, growth suppression, and possible congenital malformations [32].

The high frequency of side effects with traditional systemic corticosteroids such as prednisone has led to the development of corticosteroid preparations with high first-pass metabolism and fewer systemic effects. Beclomethasone dipropionate (BDP) shows potent topical anti-inflammatory activity in adults, but has limited systemic activity [33]. BDP enemas have been shown to be effective

in treating distal UC without the systemic side effects seen with oral prednisone [34].

A prospective, randomized, pediatric study comparing oral 5-ASA with BDP 5 mg/day in patients with mild to moderate UC found BDP responded faster and showed more effective clinical and endoscopic improvement. At 4 weeks, the BDP group demonstrated 80 % achieving clinical remission compared with 33 % treated with only 5-ASA ($P < 0.025$). In 73 % of BDP-treated patients, a colonoscopy showed remission compared with 27 % of 5-ASA treated patients. CRP showed a more significant decrease in the BDP group versus 5-ASA. Cortisol levels were unchanged at 1 month after the start of therapy in the BDP group [35].

A new formulation of budesonide approved for adults with UC uses a multi-matrix system (MMX) for delivery of budesonide [36]. The MMX formulation allows delivery to the colon, much like the mechanism of the pH-dependent release of BPD that has been effective delivering the drug to the distal ileum and proximal colon [37].

5.3 Immunomodulators

The term "immunomodulator" is used by gastroenterologists for drugs with broad effects on lymphocyte activity, including 6-mercaptopurine (6-MP), azathioprine (AZA), and methotrexate (MTX). AZA is the prodrug for 6-MP, and the two drugs have identical mechanisms of action, but are dosed differently. The mechanism of action of 6-MP and AZA is to interrupt RNA and DNA synthesis, thereby down-regulating cytokines, T-cell activity, and delayed hypersensitivity reactions and by inducing T-cell apoptosis by blocking the activation of the gene rac-1 [38]. The use of thiopurines in UC as corticosteroid-sparing maintenance agents is long established. A recent, prospective, multicenter registry study looking at the outcome of thiopurine use in children with UC found 50 % of children with UC starting thiopurine therapy were disease free 1 year later, without the need for rescue therapy [39].

The metabolism of AZA/6-MP is a well-studied complex pathway in which AZA is converted to 6-MP, and then to 6-thiouric acid, 6-methyl mercaptopurine (6-MMP), and 6-thioguanine nucleotide (6-TGN) [40, 41]. The 6-MMP fraction is felt to be responsible for the hepatotoxic effects of AZA/6-MP. The 6-TGN moiety is felt to be the active component, leading to DNA breakage, and inhibition of lymphocyte proliferation. There have been multiple studies that show increased 6-TGN levels correlate with an increased response in treating IBD [42, 43]. A meta-analysis by Osterman et al. also found strong support that higher 6-TGN levels were associated with clinical remission [44]. The dose of AZA found effective for IBD is 2.0–3.0 mg/kg/day, and as AZA is the prodrug of 6-MP, the dose of 6-MP is lower, at 1.5 mg/kg/day [45]. Prior to the availability of 6-MP metabolites, many clinicians would use half the target dose and generally titrate up while monitoring full blood count and liver biochemistry. With the availability of metabolites, the target 6-TGN level is found to be >235 pmol/8 $\times$ 10^8 red blood cells and <400 pmol/8 $\times$ 10^8 red blood cells [42, 43]. A threefold increased risk of hepatotoxicity is noted with 6-MMP levels $>5{,}700$ pmol/8 $\times$ 10^8 red blood cells [42]. In patients that metabolize thiopurines toward an increased 6-MMP fraction, the addition of allopurinol, a xanthine oxidase inhibitor, whose primary indication is gout, has been used to shift the metabolic pathway to increased 6-TGN fraction. This has allowed lowered overall dose of thiopurine, while resulting in an increase in 6-TGN fraction, and a lower 6-MMP fraction. Adult literature has established that combination therapy with only 50 mg allopurinol and 50 mg AZA daily is sufficient, efficacious, and safe in most IBD patients with inadequate thiopurine metabolite concentrations to optimize AZA-based IBD therapy [46]. There are limited published data for dosage in pediatric IBD patients [47]. Split-dose thiopurine administration has been found to be effective in decreasing the 6-MMP fraction while maintaining adequate 6-TGN concentration in a recent, retrospective, adult study. Maintaining the same daily dose, the thiopurine is divided into twice-daily dosing, and may allow continued use of these medications without untoward effects such as elevated transaminases and flu-like symptoms, which may be seen with elevated 6-MMP concentrations. This practice has been used in pediatric patients as well, but there are no current data in this patient population [48].

5.4 Methotrexate

MTX is a dihydrofolate reductase inhibitor effective in both remission induction and maintenance in patients with CD [49]. At low doses, the mechanism of action of MTX is not clearly defined. At high doses, it works through antiproliferative and cytotoxic effects by inhibiting dihydrofolate reductase, leading to defective DNA synthesis and cell death [50]. At low doses, it works primarily as an immunomodulator [51]. The mechanism of action as an immunomodulator is not clearly understood, but involves increased adenosine [52], inhibition of cellular proliferation and induction of apoptosis [53], and decreased production of inflammatory mediators such as interleukin and eicosanoids [54]. There is evidence from open-label trials in adults to suggest the use of MTX monotherapy as maintenance treatment in UC. A retrospective cohort in 91 adult patients with UC found that one-third of patients were weaned off corticosteroids and maintained on MTX with a follow-up of up to 15 months [55]. Another small

retrospective adult case series found 20 mg MTX per week orally was moderately effective in corticosteroid-dependent or -refractory UC patients, with 42 % in remission and 54 % with "good" response [56]. However, an adult multicenter, randomized, controlled trial of MTX use in chronic active UC found weekly oral MTX at 12.5 mg was no better than placebo in the induction or maintenance of remission in patients with chronic active UC [57].

A small retrospective pediatric paper reported immunomodulator use of MTX at a mean dose of 13.7 ± 3.6 mg/m^2/week did show response or remission in 72, 63, and 50 % of patients at 3, 6, and 12 months, respectively [58]. Larger, controlled, prospective trials would be needed to show clear benefit for MTX use in pediatric UC patients for monotherapy. Discrepancies between response in pediatric patients and adult patients may be expected owing to the different phenotypic expression of disease and the different course seen in pediatric patients with UC. Pediatric patients are found to have a more extensive disease and a higher frequency of corticosteroid dependency as well as a more severe disease course compared with adult UC patients [59].

The dose of MTX found to be effective in an adult study of 50 patients with UC was 20 mg/week orally [56]. A dose of 15 mg/m^2 is often used in pediatric patients. There remains debate regarding the bioavailability of MTX in IBD. The mean oral versus subcutaneous MTX area under the curve falls outside the 90 % confidence interval for the bioequivalence limits. Subcutaneous MTX is more bioavailable than oral MTX, but nearly met the FDA bioequivalence standard [60].

5.5 Calcineurin Inhibitors (Cyclosporine and Tacrolimus)

5.5.1 Cyclosporine

Cylosporine is an immunosuppressant widely used to prevent organ rejection following transplant. Cyclosporine works by inhibiting evolutionary conserved, signal transduction pathways by inhibiting calcineurin. Inhibition of the action of calcineurin results in a complete block in the translocation of the cytosolic component of the nuclear factor of activated T cells (NF-AT), resulting in a failure to activate the genes regulated by the NF-AT transcription factor. These genes include those required for B-cell help such as IL-4 and the CD40 ligand as well as those necessary for T-cell proliferation such as IL-2 [61].

A randomized controlled trial comparing cyclosporine (4 mg/kg) to placebo in 20 patients with severe UC not responding to 7 or more days of IV corticosteroids found 82 % responded within a mean of 7 days compared with none in the placebo arm. All five of those in the placebo arm who were subsequently treated with cyclosporine also had a response to therapy [62].

The main concern with cyclosporine is nephrotoxicity, including hypertension as well as concern for neurologic side effects including paresthesias and seizures, possibly associated with hypomagnesemia or hypocholesterolemia affecting the blood-brain barrier [63]. For these reasons, cyclosporine is most commonly used as short-term (4–8 months) induction therapy, and as a "bridge" to immunomodulators or surgery.

5.5.2 Tacrolimus

Tacrolimus is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*, first approved in 1994 for liver transplantation. Its mechanism of action is in T cells, preventing the dephosphorylation of NF-AT, thereby altering the activity of calcineurin–calmodulin and inhibiting IL-2 transcription [64].

Tacrolimus has been used to induce remission in adult and pediatric patients with UC, primarily as a bridge to long-term management with thiopurines, thereby avoiding side effects of corticosteroid induction [11, 65]. There are data demonstrating that tacrolimus is effective in corticosteroid-refractory colitis in pediatric literature, again typically as a bridge to thiopurines; however, the long-term colectomy rate remains at approximately 60 % over time [66].

A randomized dose-finding study of oral tacrolimus in adult patients with UC found an effective and tolerated dose target trough range of 10–15 ng/mL at 2 weeks, with a post induction target of 5–10 ng/mL. Dosage was reduced if adverse drug reactions were observed, which included tremor, sleepiness, hot flush, nausea, and abdominal discomfort [65].

Pediatric data have also used an induction trough range of 10–15 ng/mL, with a trough of 5–10 ng/mL once in remission [11].

5.6 Biologic Agents

5.6.1 Infliximab

TNF-α is a proinflammatory cytokine known to play an important role in the pathogenesis of CD [67].

IFX is a chimeric IgG monoclonal antibody to TNF-α. TNF-α was noted to be a cofactor in the production of inflammatory cytokines, interferon-γ, and IL-2 [68]. Infliximab is FDA approved for both adult and pediatric ulcerative colitis. IFX won its initial approval by the FDA for the treatment of CD in August 1998.

Corticosteroids are effective for short-term treatment but up to 45 % of pediatric patients develop corticosteroid dependence in subsequent years putting them at risk for corticosteroid-related side effects [31, 69].

IFX is considered safe and effective for the treatment of UC in adults based on two randomized, double-blind, placebo-controlled trials, ACT1 and ACT2. Pediatric subjects with moderate to severe CD were found to respond to IFX in the REACH trial [70, 71].

A prospective pediatric study found IFX safe and effective, inducing a response at week 8 in 73.3 % of pediatric patients with moderate to severely active UC who did not respond to 5-ASA, immunomodulators, and IV corticosteroids [71].

Adult data have shown a combination of IFX and AZA to be superior to monotherapy with IFX or AZA alone in patients who were mainly AZA naïve with UC and CD [72].

However, in evaluating primary studies showing efficacy of IFX in patients, most of whom had previously been treated with immunomodulators, no benefit to combination therapy can be found.

A recent study in adult patients with UC did demonstrate superior effect at achieving corticosteroid-free remission at 16 weeks in combination therapy of IFX plus AZA. This was a randomized double-blind study comparing IFX monotherapy, AZA monotherapy, and a combination of IFX plus AZA in TNF-α naïve adults with moderate to severe UC. The remission rate in combination therapy was almost twice that of either IFX or AZA monotherapy, with significantly improved mucosal healing in the combination group as well. However, the study was limited in numbers because of early termination of the trial as a result of the increased risk of psoriasis suspected in intermittent maintenance treatment with IFX, which would be part of the protocol. There are no similar studies in the pediatric patient population [73].

The potential risks of combination therapy including the possible development of lymphoma as previously discussed, as well as the above data, make the risk versus benefit evaluation of combination therapy critical.

5.6.2 Adalimumab

Adalimumab is a fully human monoclonal antibody that binds to TNF-α. It was approved in 2012 in adults for moderate to severe UC for induction and maintenance. It is currently not approved for use in pediatric UC patients. A recent, randomized, controlled trial comparing adalimumab with placebo in patients, some of whom were previously treated with other anti-TNF agents, shows a significantly higher rate of clinical remission at both week 8 (17 vs. 9 %, respectively) and week 52 (17 vs. 9 %). Mucosal healing was also higher in the treatment group (41 vs. 32 % at week 8 and 30 vs. 18 % at week 52). Prior exposure to IFX did influence response with double the response in naive patients versus those previously treated (21 vs. 9 % at week 8 and 22 vs. 10 % at week 52, respectively) [74].

An open-label follow-up study at 52 weeks demonstrated efficacy in maintaining clinical remission in anti-TNF naive patients with moderate to severely active UC who did not adequately respond to conventional therapy (29 % in clinical remission, 53.6 % with a clinical response, 53.6 % showing mucosal healing). Of those patients who were on corticosteroids at the onset of the study, 56 % were corticosteroid free at 1 year [75].

There are no pediatric studies of adalimumab for the treatment of UC at the time of this paper with the exception of small retrospective case series of both CD and UC pediatric patients.

5.6.3 Antibody Measurement and Drug Concentrations

The use of IFX antibody measurement (HACA, human chimerical antibody concentration) and IFX drug concentrations can be useful if there is loss of response to IFX. Detection of HACA would indicate the likelihood of increasing the dose would be infective, as the loss of response is likely a result of fast clearance of IFX owing to antibody precipitation with the medication. Low trough levels would indicate fast clearance, but increasing dose or frequency may overcome this low level. The clinical utility of adalimumab concentations is unclear at the time of this paper [76].

6 Conclusion

The management of UC in children is complex, and requires accurate diagnosis, knowledge of disease location, assessment of disease activity, and awareness of the pharmacologic armamentarium. The primary induction therapies for UC include 5-ASA for mild disease; corticosteroids for moderate to severe disease; and biologics or calcineurin inhibitors for corticosteroid-unresponsive disease. Surgery should always be considered if the risks of medical therapy are perceived to outweigh the benefits.

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