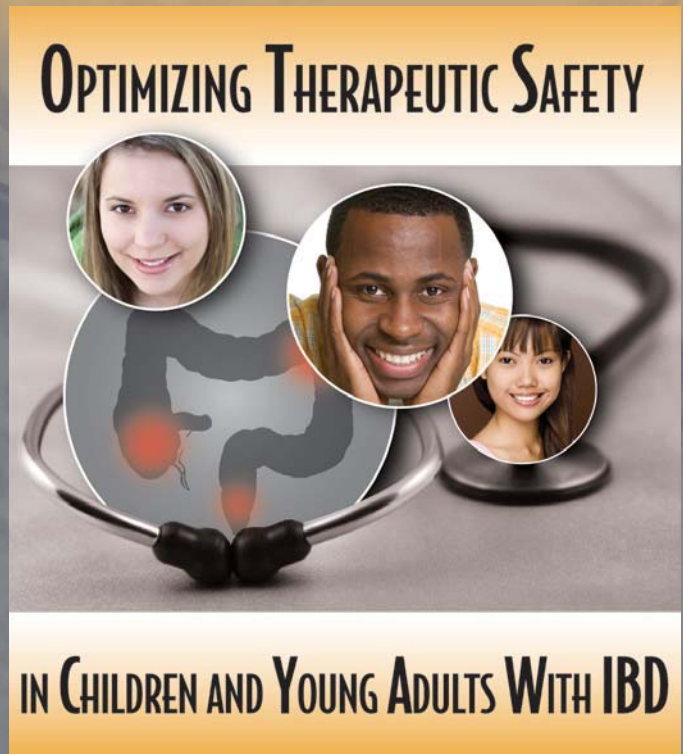


# A Case-Based Monograph Focusing on IBD



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## INTRODUCTION

The incidence of pediatric inflammatory bowel disease (IBD) appears to be increasing, and since pediatric IBD often presents during a critical period of growth and development, its successful management is crucial to achieve normal physical and psychosocial development. Pediatric IBD, especially Crohn's disease (CD), is often associated with impaired growth and skeletal development. These effects result from a number of factors, including the direct effect of pro-inflammatory mediators upon growing bone, as well as poor nutritional intake and impaired caloric utilization in the face of increased metabolic demand. The goals of therapy are to eliminate symptoms, ensure normal growth, and to gain steroid independence. Many clinicians consider mucosal healing to be an important step in achieving these goals. Pediatric IBD treatment strategies are often drawn from adult studies, especially when managing aggressive or resistant disease.

New details about the pathophysiology of IBD, including its association with an underlying state of immune dysregulation, have led to therapies that target the immune pathways, including the development of biologic agents like anti-TNF- $\alpha$  antibodies. It has become an active area of investigation to see whether such a treatment approach can lead to better long-term outcomes in children with inflammatory bowel disease. This monograph presents important safety considerations discussed by thought leaders in the area of pediatric gastroenterology as they review currently available treatment options for IBD within the context of 3 patient vignettes.

## TARGET AUDIENCE

This activity is designed for gastroenterologists, physician assistants, nurse practitioners, and other clinicians who treat children with IBD using immunomodulators and biologics.

## LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Increase the understanding of how to minimize adverse events of drug therapy for pediatric IBD
- Implement monitoring strategies for the management of potential adverse events in pediatric IBD patients receiving medical therapy
- Employ long-term treatment and maintenance strategies that minimize the potential associated risks toward growth and development in pediatric IBD patients

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## OVERVIEW

Implementing a therapeutic approach that is tailored to the individual needs of each child with inflammatory bowel disease (IBD) requires clinicians to weigh the risks and benefits of therapeutic agents. Increasingly, pediatric IBD treatment has focused on anti-inflammatory and steroid-sparing strategies because children's growth and development can be negatively affected by persistent inflammation or corticosteroid dependency. The concept of early introduction of immunomodulatory therapy was spearheaded by pediatric data and represents the earliest attempt at so-called "top-down" therapy.<sup>1</sup> Alternatively, biologic immune-targeted IBD therapy appears to significantly improve pediatric bone metabolism and, at least in part, reverse growth failure.<sup>2,3</sup> Identifying the patients who are most prone to develop a complicated disease course, or who might benefit from early, more aggressive therapy, is still a challenge. New developments in the use of clinical, genetic, immunologic, and microbial markers will serve to more precisely define clinical prognosis and facilitate risk adjustment in IBD therapy.<sup>4</sup> The available therapeutic agents (Table 1)<sup>5,6</sup> for treatment of IBD will be discussed below, focusing on safety risks and monitoring.



approximately 20% of pediatric patients.<sup>6</sup> There have also been rare reports of pericarditis and pneumonitis (Table 2).<sup>5,7-10</sup> Sulfasalazine is contraindicated in infants and children up to 2 years of age.<sup>9</sup> The potential for sulfa allergy should be kept in mind when using sulfasalazine. The sulfa moiety also decreases folate absorption, so patients treated with sulfasalazine should receive daily folate (1 mg) supplements.<sup>6</sup> Supplementation prevents the complications of folate deficiency, including neural tube defects and anemia.<sup>6</sup> Mesalamine agents are associated with adverse effects that include rash, occasional fever, and flulike syndrome, including diarrhea and/or worsening colitis, and are infrequently associated with pancreatitis, anemia, proteinuria, and interstitial nephritis.<sup>8,10,11</sup> Balsalazide and olsalazine have similar adverse effect profiles, but olsalazine appears to be more frequently associated with watery diarrhea.<sup>6</sup>

**Agent-Specific Issues** – 5-ASA therapy has been associated with interstitial nephritis, so kidney function should be checked prior to initiating mesalamine or sulfasalazine therapy and should continue to be monitored during their ongoing use.<sup>12</sup> It has been noted that sulfasalazine has a significantly stronger association ( $P < 0.001$ ) with blood dyscrasias like agranulocytosis and pancytopenia.<sup>11</sup> Although blood dyscrasias were the most common adverse event among mesalamine users in the aforementioned study, the frequency was significantly less than that of sulfasalazine users. Pancreatitis was also seen in patients using mesalamine and should be considered in the correct clinical setting.

**Table 1. Pharmacologic Agents Commonly Used in the Treatment of IBD<sup>5,6</sup>**

Medication	US Food and Drug Administration-Approval	
	Crohn's Disease	Ulcerative Colitis
<b>5-Aminosalicylates</b>		
Mesalamine	Off label	Adults
Olsalazine	Off label	Adults
Balsalazide	Off label	Adults/children
Sulfasalazine	Off label	Adults/children > 2 years of age
<b>Corticosteroids</b>		
Prednisone	Adults	Adults
Prednisolone	Adults	Adults
Budesonide	Adults	Adults
<b>Immunomodulators</b>		
6-Mercaptopurine	Off label	Off label
Azathioprine	Off label	Off label
Methotrexate	Off label	Off label
<b>Calcineurin Inhibitors</b>		
Cyclosporine	Off label	Off label
Tacrolimus	Off label	Off label
<b>Biologics</b>		
Adalimumab	Adults	Off label
Infliximab	Adults/children	Adults
Certolizumab	Adults	Off label
Natalizumab	Adults	Off label

## 5-AMINOSALICYLATES

The 5-aminosalicylate (ASA) agents hold an important position as an initial therapy for mild cases of ulcerative colitis (UC). They have traditionally been used in mild pediatric Crohn's disease (CD), especially when there is colonic involvement.<sup>6</sup> As a class, 5-ASA agents are generally well-tolerated; however, the sulfa moiety of sulfasalazine is a potential allergen in some patients. Newer formulations use alternative mechanisms to deliver mesalamine to the affected site (ie, colon), but appear to be somewhat less effective without sulfa.

**Dose-Limiting Adverse Effects** – Adverse effects of sulfasalazine, such as headache, nausea, photosensitivity, severe skin rashes, pancreatitis, leukopenia, and hepatitis, have been reported in

**Table 2. Adverse Events Associated With 5-ASAs and Sulfasalazine<sup>5,9,10</sup>**

5-ASAs and Sulfasalazine	
<b>Most Frequent Complications</b>	Headache Nausea Anorexia Diarrhea
<b>Rare but Important Complications</b>	Allergic reactions Deficiency of folic acid (sulfasalazine) Pancreatitis Proteinuria Blood dyscrasias (leukopenia) Interstitial nephritis
<b>Recommended Monitoring</b>	Complete blood count (CBC) with differential Liver chemistries BUN and creatinine Urinalysis

## CORTICOSTEROIDS

Corticosteroids should, as a rule, be used as induction agents only; weaning patients to a maintenance agent as soon as possible. For mild-to-moderate ileocolonic CD in patients who can swallow the capsules, budesonide should be used preferentially given the fact that it yields much less systemic steroid exposure.<sup>13</sup> Budesonide has shown a slightly better side-effect profile than either prednisolone or prednisone in children who have active CD, particularly with the incidence of cosmetic side effects, such as "moon face" and acne.<sup>14,15</sup> The appropriate

use of conventional corticosteroids is guided by the following considerations<sup>16</sup>:

- **Are the symptoms caused by inflammation?** Other causes should be excluded, such as infectious colitis, dietary triggers, bile salt malabsorption, small bowel bacterial overgrowth, diarrhea caused by drugs such as nonsteroidal anti-inflammatory drugs or antibiotics, or overflow diarrhea arising from constipation.<sup>17</sup>
- **Would the use of conventional corticosteroids put the patient at increased risk?**
  - Does the patient have fistulizing disease?
  - Does the patient have an abscess?
  - Extended use of high doses preoperatively?
- **What is your exit strategy (ie, plan for stopping steroids)?** A plan for stopping corticosteroids should already be in place when corticosteroids are initiated. The plan may include addition of steroid-sparing agents, such as immunomodulators or biologic agents.<sup>17</sup>

**Adverse Effects** – Adverse effects are common with corticosteroid use (Table 3).<sup>5,10,16,18,19</sup> In a study of children being treated for CD with either budesonide or prednisone, adverse events were noted in 32% of the budesonide group and 71% of the prednisone group.<sup>15</sup> At high doses, early effects of corticosteroids include cosmetic (acne, moon face, and edema), sleep and mood disturbance, dyspepsia, or glucose intolerance.<sup>10,14,16</sup> Potential complications may also include osteonecrosis of the femoral head and neurologic and occasional psychiatric disorders, including psychosis.<sup>6,17</sup>

**Growth Failure** – The risk of growth impairment is of special concern for children with CD.<sup>3</sup> Growth failure has been estimated to affect anywhere from 10% to 40% of all children with IBD, and is 3 times more likely to be permanent in patients with CD than in those with UC.<sup>20</sup> Molecular mechanisms underlying impaired growth in IBD patients, including inflammatory cytokines, altered hormone and sex-steroid levels, and insufficient nutrition, are currently under investigation.<sup>3</sup> The risk of growth impairment in children with IBD can be compounded by further growth impairment due to the corticosteroid therapy itself.<sup>21</sup> Corticosteroid therapy should certainly be minimized in children with profound growth impairment and a limited opportunity for further growth due to their age and Tanner stage.<sup>20</sup>

**Metabolic Bone Disease** – Corticosteroid therapy and the disease process of CD itself are both associated with osteopenia, osteoporosis, osteonecrosis, and osteomalacia in children.<sup>10,22,23</sup> Up to 70% of IBD patients may be affected by metabolic bone disease.<sup>2</sup>

**Infectious Complications** – There is a high likelihood that in CD patients, corticosteroids will increase the risk of infection and may worsen the complications of abscesses and fistulae, or increase the risk of postoperative infections if used preoperatively at high doses.<sup>16</sup> An analysis of adverse events in the Crohn's Therapy Resource, Evaluation and Assessment Tool registry population associated corticosteroid therapy with acquired and opportunistic infections.<sup>24</sup> CD patients were treated with infliximab (n = 3179) or other therapies

(n = 3111), including prednisone, immunomodulators, or narcotic analgesics. Multivariate logistic regression analysis suggested that infliximab was not an independent predictor of serious infections (odds ratio [OR] 0.99 [95% CI, 0.64-1.54]). Serious infections were instead associated with prednisone (OR 2.21 [95% CI, 1.46-3.34]; P < 0.001), narcotic analgesics (OR 2.38 [95% CI, 1.56-3.63]; P < 0.001), and moderate-to-severe disease activity (OR 2.11 [95% CI, 1.10-4.05]; P = 0.024). An apparent increase in the risk of serious infection with infliximab was likely due to disease severity or concomitant prednisone use. Similarly, Marehbian et al recently associated corticosteroids, immunosuppressives, or anti-tumor necrosis factor (TNF) agents with an increased risk of infection in CD patients, and further demonstrated that concurrent use of 2 or 3 of these medications increases the risk of infection above that of monotherapy with any one of these agents.<sup>25</sup>

**Table 3. Adverse Events Associated With Corticosteroids<sup>5,10,16,18,19</sup>**

Corticosteroids	
<b>Most Frequent Complications</b>	Growth disturbance Bone loss/disease Elevated blood pressure Elevated blood sugar Acne Hirsutism Facial swelling Weight gain
<b>Rare, but Important Complications</b>	Increased risk of infections
<b>Recommended Monitoring</b>	Monitor growth Eye examination including pressure measurement Purified protein derivative (PPD) Chest x-ray if symptomatic Draw Varicella titer; if possible, immunize before therapy

**Suggested Monitoring of Corticosteroid Therapy**

- **Dual energy x-ray absorption (DEXA) scanning:** Diagnosis of bone disease is made through radiologic studies.<sup>10</sup> A DEXA study is particularly useful for identifying patients at risk for fractures. However, the extent of bone disease may be overestimated unless results are interpreted using a Z-score corrected for bone age or height age rather than a T-score based on chronological age.

**IMMUNOMODULATORS**

**Thiopurines**

The known adverse effects of thiopurines include hepatotoxicity, pancreatitis, allergic reactions, fever, rash, infectious complications, and bone marrow suppression (Table 4).<sup>5,10,13,18,26-28</sup> Allergic reactions and pancreatitis tend to be idiosyncratic and independent of dose, and preclude the ongoing use of these agents.<sup>29</sup> Bone marrow toxicity and hepatotoxicity are dose-related and can be minimized through pharmacogenetic prescreening and dose adjustments.

**Table 4. Managing Adverse Events Associated With Thiopurine Therapies<sup>5,10,18,26-28</sup>**

Adverse Events	Characterization	Suggested Precautions	Treating Adverse Events
<b>Common Events</b> Gastrointestinal hypersensitivity	Nausea, vomiting, possible diarrhea	Instruct patients to report symptoms	Administer drug in divided doses and/or after meals
Drug intolerance	Rash, fever, malaise	Instruct patients to report symptoms	Dose reduction and possible need for drug withdrawal if persistent
Hematologic toxicities	Leukopenia, thrombocytopenia, pancytopenia, severe myelosuppression	Thiopurine methyltransferase (TPMT) testing prior to starting therapy (see Table 4)  <u>CBC w/ platelet count</u> Weeks: 0, 2, 4, and 8, then every 3 months	Prompt reduction in dosage or temporary withdrawal of the drug may be necessary if there is a rapid fall in, or persistently low, leukocyte count
Hepatotoxicity	Elevated serum alkaline phosphatase, serum transaminases, bilirubin (jaundice may appear within 1-2 months)	<u>Monitor liver enzymes</u> Weeks: 0, 2, 4, and 8, then every 3 months	Dose reduction or possible drug withdrawal if persistent  If hepatic veno-occlusive disease is clinically suspected, drug should be permanently withdrawn
Pancreatitis	Vomiting with pain	Instruct patients to report symptoms  Measure pancreatic enzymes if there is clinical suspicion of pancreatitis; routine testing not needed	Responds rapidly to withdrawal of drug  Pancreatitis is likely to recur if drug is resumed
<b>Rare but Important Events</b> Serious infections: viral, fungal, bacterial, protozoan	Can include herpes simplex virus (HSV) or human papillomavirus (HPV) (see text under "Opportunistic and Other Infections")	Instruct patient to report signs and symptoms of infection  Check viral titers before initiating thiopurines and immunize if possible  Recommend HPV vaccine where appropriate	May require drug interruption until infection resolved
Increased risk of neoplasia	Hodgkin's and non-Hodgkin's lymphomas  Nonmelanoma skin cancer (NMSC)	<u>CBC w/ platelet count</u> Weeks: 0, 2, 4, and 8, then every 3 months  Routine skin examinations	Instruct patients to use sun screen and otherwise avoid sun exposure while using thiopurines

**Genetic Screening** – Pharmacogenetic screening centers on thiopurine methyltransferase (TPMT), an enzyme that plays an important role in thiopurine metabolism. Available TPMT testing includes enzyme activity levels (phenotype) and genetic analysis (genotype). Mutations in the TPMT gene can result in varying degrees of TPMT enzyme activity across the patient population (Table 5).<sup>29</sup> TPMT testing is recommended for all patients before starting thiopurine therapy.<sup>13,20</sup> Patients with homozygous expression of nonfunctional TPMT alleles are not candidates for thiopurine therapy as they will have little or no TPMT enzyme

activity and are therefore at risk of accumulating high levels of the active metabolite 6-thioguanine nucleotide (6TGN), which can cause severe bone marrow suppression and early leukopenia. Conversely, patients with very high TPMT activity are less likely to respond well to thiopurine therapy due to low circulating levels of 6TGN and metabolic shunting toward the metabolite, 6-methylmercaptopurine (6-MMP). Heterozygotic expression of TPMT leads to an intermediate level of enzyme activity with a higher level of 6TGN production and greater likelihood of a satisfactory response to therapy. Accordingly,

**Table 5. TPMT Genotype Testing Prior to Initiating Thiopurine Treatment<sup>29</sup>**

TPMT Genotype	TPMT Activity (% of Patients)	Corresponding Risk	Suggested dosing	Suggested Monitoring
Homozygous nonfunctional (nonfunctional alleles <sup>†</sup> )	Low or absent (0.3%)	Rapid, life-threatening bone marrow suppression with usual dosing	Thiopurine therapy not recommended	Not Applicable
Heterozygous (1 nonfunctional, 1 functional)	Intermediate (≈11%)	Increased risk of myelosuppression with usual dosing	Reduce usual dosage by 50 to 70%	CBC w/platelet count Weeks: 0, 2, 4, and 8, then every 3 months
Hematologic toxicities	High (≈89%)	Possible myelosuppression with usual dosing	Usual dosage: 6MP: 1.0-1.5 mg/kg/day	

<sup>†</sup> Most common nonfunctional TPMT alleles: TPMT\*2, TPMT\*3A, TPMT\*3C

heterozygotic patients may be started on a smaller dose of thiopurine followed by monitoring of the clinical response and CBCs within the first 2 weeks of starting therapy. It is critical to recognize that not all bone marrow suppression is related to TPMT activity and, therefore, it is important to screen for this possibility with serial CBC, even in patients who have normal TPMT enzyme activity.

**Thiopurine Use and Cancer Risk** – Thiopurine therapy is associated with an increased risk of lymphoma in IBD patients.<sup>30</sup> A meta-analysis of 6 studies examining adult IBD patients treated with azathioprine or 6-MP derived a pooled relative risk of lymphoma of 4.18 (95% CI, 2.07-7.51; 11 observed cases, 2.63 expected). There is presently no screening available to identify the IBD patients who are most at risk for developing lymphoma. Clinical vigilance and careful explanation of this risk within the context of treatment options and expected disease course are the best current methods in dealing with these overall rare events.<sup>31</sup>

In adult IBD patients, thiopurine agents have also been associated with an approximately 60% increase in the risk of non-melanocytic skin cancer (NMSC).<sup>32</sup> The association was similar in both CD and UC patients. Thus, vigilant monitoring for skin cancer in IBD patients under thiopurine treatment is advisable.

**Opportunistic and Other Infections** – A study of 230 adult IBD patients who were being treated with either azathioprine (n = 169) or a nonimmunosuppressive therapy (n = 61) found that significantly more of the immunosuppressed patients experienced new-onset or worsening viral warts (17.2% vs 3.3%; P = 0.004).<sup>33</sup> In a separate study, immunosuppressive IBD therapy over a period of more than 6 months in adult women raised the risk of having an abnormal Pap smear result associated with HPV infection (OR 1.5 [95% CI, 1.2-7.1]; P = 0.021).<sup>34</sup> The former study also reported that the incidence of HSV flares was significantly greater among immunosuppressed patients (1.0 ± 2.6 vs 0.2 ± 0.8 per year; P = 0.04), thus new guidelines recommending HPV vaccine in girls and young adolescent women are especially important to pediatric IBD patients.<sup>35</sup>

Immunization guidelines suggest that protection against vaccine-preventable illness is beneficial in immunocompromised IBD patients, and that most killed/attenuated vaccines can be administered to immunocompromised patients.<sup>36</sup> Melmed et al recently demonstrated that CD patients who were treated with combination therapy using immunosuppressive agents together with TNF- $\alpha$  inhibitors mounted an impaired immune response to pneumococcal polysaccharide vaccines more often than patients using TNF- $\alpha$  inhibitors alone.<sup>37</sup> This and other studies suggest that newly diagnosed IBD patients should undergo vaccination before initiating immunosuppressive therapy whenever possible. Careful attention to this recommendation will increase the likelihood of vaccination early after IBD is diagnosed.

#### Additional Monitoring for Thiopurine Agents

- **Metabolite measurement (TGNs):** In the appropriate setting, measurement of TGNs can be considered to aid in adjusting dosage, confirming compliance, or choosing to use another agent when the clinical response is not adequate.<sup>13</sup>

- **Vaccinations:** Live vaccines are contraindicated while using immunomodulators; include this information in letters to primary care providers.<sup>4</sup> Some centers determine *Varicella* immune status early after diagnosis, providing opportunity to immunize prior to initiating immunomodulator therapy. HPV and influenza vaccinations should be encouraged whenever appropriate.

#### Methotrexate

The most frequent adverse effects associated with methotrexate include bone marrow suppression leading to leukopenia and gastrointestinal events like nausea, vomiting, stomatitis, anorexia, or diarrhea.<sup>6,10</sup> Hepatotoxicity is reported less often.<sup>38</sup> Other infrequent complications include upper respiratory infections, pneumonitis, and some dermatologic hypersensitivity reactions.<sup>39</sup> In contrast to thiopurine agents, an increase in the risk of NMSC in CD patients using methotrexate therapy has not been reported, but routine skin examination still seems prudent until there is more experience with methotrexate in this setting.<sup>32</sup>

#### Risks and Suggested Monitoring for IBD Patients Using Methotrexate Therapy<sup>39</sup>:

- **Pregnancy is absolutely contraindicated** due to fetal risks; this risk must be discussed before starting methotrexate and should be revisited during follow-up visits.
- It is important to note that methotrexate dosing is **once weekly**.
- **Nausea/vomiting (most common):** Antiemetics before each dose can improve and even abort symptoms.
- Routine supplementation with folic acid 1 mg/day is recommended to avoid folate deficiency.<sup>17</sup>
- Recommendations for monitoring bone marrow suppression and hepatotoxicity are the same as those listed above for thiopurine therapy (ie, CBC and liver enzyme monitoring).
- **Persistently elevated liver enzymes (“transaminitis”):** Consider dose reduction or methotrexate withdrawal.
- **Vaccinations:** Counsel IBD patients that live vaccines are contraindicated while on immunomodulators and include this information in letters to primary care providers. Some centers determine *Varicella* immune status early after diagnosis to increase opportunity to immunize prior to initiating immunomodulators. Encourage vaccination against HPV.<sup>34</sup>
- **Pulmonary toxicity:** Low index of suspicion with prompt and early referral to pulmonology. Consider baseline pulmonary function testing with serial repeat testing.

#### Tacrolimus and Cyclosporine

Adverse event profiles of the calcineurin inhibitors cyclosporine and tacrolimus include hypertension, nausea, increased liver function values, infections, nephrotoxicity, glucose intolerance, and seizures.<sup>6</sup> Hypomagnesemia and hypocholesterolemia are known risk factors for seizures; hypomagnesemia responds to oral supplementation.<sup>6,40</sup> Hyperglycemia, especially with tacrolimus, has been noted.<sup>41</sup> Cosmetic side effects, such as gingival hyperplasia, hirsutism, and coarsening facial features, are less common with tacrolimus than they are with

cyclosporine.<sup>6</sup> Fatal opportunistic infections (eg, *Pneumocystis carinii* pneumonia [PCP], *Aspergillus fumigatus* pneumoniae) have been reported in 3.5% of 86 adult patients with severe UC who were being treated with cyclosporine.<sup>42</sup>

### Suggested Monitoring

When cyclosporine or tacrolimus is initiated (typically as an inpatient):

- Start prophylaxis against PCP
- Check baseline electrolytes including Ca<sup>2+</sup>; Mg<sup>2+</sup>; Phos; BUN/Creatinine, CBC, and liver enzymes; lipids; and cholesterol.
  - Both hypomagnesemia and hypocholesterolemia are independent risk factors for seizure
  - Monitor frequently as therapy is initiated
- Nutrition: monitor serum albumin and serum cholesterol
- Fasting glucose should be assessed regularly
- Trough drug levels should be assessed regularly
- Routine monitoring of metabolic and hematologic systems should be performed as clinically warranted

When a stable, well-tolerated dose has been established (typically outpatient):

- Continue PCP prophylaxis
- Frequent monitoring of electrolytes, CBC, liver enzymes, serum cholesterol, fasting glucose, renal function, and trough drug levels
- Initiate a long-term maintenance agent (eg, these agents are commonly used as a bridge to thiopurine therapy)

## BIOLOGIC THERAPY

The currently available biologic agents, including infliximab, adalimumab, certolizumab, and natalizumab, are approved for the treatment of moderate-to-severe CD in adult patients, while infliximab has also been approved for use in pediatric CD patients and adult UC patients.<sup>43</sup> Adverse events most often experienced by IBD patients using these agents include infusion reactions, symptoms due to immune response directed against anti-TNF- $\alpha$  agents, opportunistic infections, and neoplasia (Table 6).<sup>5,10,18,43-45</sup>

- **Immediate infusion reactions:** These typically present as flushing, rash, dyspnea, and headache and can be substantially improved or resolved through adjustment of the infusion rate plus treatment with acetaminophen, antihistamines, steroids, and/or epinephrine.<sup>13</sup>
- **Delayed infusion reactions:** These are less common than immediate reactions and are often characterized by joint pain/stiffness, muscle pain, fever, general malaise, and/or a lupus-like syndrome.<sup>46</sup> Delayed reactions are typically managed with acetaminophen, antihistamines, and steroids.<sup>44</sup> Complete resolution may take 1-2 weeks.

**Immunogenicity of Biological Agents** – Most monoclonal antibodies are immunogenic.<sup>47</sup> Initiation of infliximab therapy with 3 doses administered at 0, 2, and 6 weeks, followed by regularly scheduled doses, can significantly reduce formation of infliximab-clearing antibodies and improves the safety and efficacy of infliximab therapy compared with episodic administration.<sup>48</sup> In the case of infliximab, anti-infliximab

antibody and drug levels are commercially available and can guide the clinician in patients who have a loss of infliximab response. Antibody formation against infliximab can also be addressed with concomitant immunosuppressive therapy.<sup>49</sup> This approach remains an area of active study and debate as the risks and benefits are weighed (see the discussion of the risk of hepatosplenic T-cell lymphoma below).

### Increased Infections

- **Common Infections:** IBD patients treated with biologic agents have an increased risk of infections. The infections are most often uncomplicated respiratory tract or urinary tract infections.<sup>43</sup>
- **Rare, but Serious Infections:** Serious infections associated with biologic agents are: tuberculosis (TB) reactivation, histoplasmosis, and hepatitis B reactivation.<sup>50</sup> Due to the risk of TB, a PPD skin test should be performed prior to beginning treatment and repeated annually after beginning anti-TNF- $\alpha$  therapy. Subjects with a high suspicion of TB, a positive PPD skin test, or those who present with a persistent cough should also have a chest x-ray. Latent TB infections should be treated prior to using a biologic therapeutic agent to treat IBD.

Combining infliximab with other immunosuppressant IBD therapies significantly increases the risk of infection in adult IBD patients.<sup>51</sup> Interestingly, however, a recent cohort study comparing 734 adult IBD patients using infliximab plus immunosuppressant and 666 control patients treated with immunosuppressant found that concomitant steroid treatment was the only independent risk factor for increased infections in patients using infliximab therapy (OR 2.69 [95% CI, 1.18-6.12];  $P = 0.018$ ).<sup>45</sup>

### Risk of Malignancy

- **Hepatosplenic T-cell lymphoma (HSTCL):** A growing number of cases of HSTCL have been reported in adolescent and young adult CD patients under treatment with a combination of thiopurines (azathioprine or 6-MP) and infliximab.<sup>52</sup> This report also examined 10 patients receiving thiopurine monotherapy. A separate, potentially important observation is that no cases of HSTCL have been reported in rheumatology or dermatology patients treated with infliximab alone or in combination with methotrexate.<sup>47</sup>
- **NMSC:** In the study already discussed (see thiopurines and NMSC) there was also a statistically significant doubling of skin cancer risk associated with biologic therapy in CD patients.<sup>32</sup> Monitoring for appearance of skin cancer is advisable during treatment with any anti-TNF- $\alpha$  agent.

### Lupus-Like Reactions, Demyelination, and Psoriasis

On rare occasions, treatment with an anti-TNF- $\alpha$  agent can lead to the formation of autoantibodies and subsequent development of a lupus-like syndrome.<sup>53</sup> Demyelinating neuropathy is a rare adverse event reported in some patients using infliximab, etanercept, or adalimumab.<sup>54</sup> Improvement usually occurs after drug interruption and/or in association with usual treatments for demyelinating neuropathies. Psoriasis, including new onset pustular and primarily palmar/plantar, has appeared in postmarketing reports of adverse events associated with infliximab.<sup>43</sup> Improvement is seen with drug withdrawal.

**Table 6. Adverse Events Associated With Biologic Agents**<sup>5,10,18,43</sup>

Biologics	
<b>Common Complications</b>	Infusion reactions Nausea Fever/chills Hives Fatigue
<b>Rare, but Important Complications</b>	HSTCL Other lymphomas (Epstein-Barr virus positive and negative) NMSC TB Cytopenia, increased liver chemistries Psoriatic rash Demyelination syndromes Lupus-like reactions
<b>Recommended Monitoring</b>	PPD Chest x-ray, if symptomatic Routine skin examinations Also: CBC, liver chemistries

**Suggested Monitoring With Biologic Therapy**<sup>18</sup>

- CBC
- Liver enzymes
- All patients must be screened for prior exposure to TB by PPD skin tests and possibly chest x-ray, when indicated
- Active disease should be treated before anti-TNF is initiated. Prior to starting anti-TNF therapy, adequate anti-TB therapy should be given.
- **Vaccinations:** Counsel patients and families that live vaccines are contraindicated while receiving immunomodulators or biologic agents and include this information in letters to primary care providers. Some centers determine *Varicella* immune status early after diagnosis to increase opportunity to immunize prior to initiating biologic therapy.<sup>50</sup>

**CASE STUDY 1: APRIL**



April is 14 years old and was recently diagnosed with ileocolonic CD. April reports having experienced IBD symptoms for about 5-6 months prior to diagnosis. It is noted that April's present height has fallen from the 60th percentile to the 25th. She will be treated, in the long term, with immunomodulator therapy using 6-MP.

**Case Question:**

- What key points should be discussed with April and her parents, and what testing will be required now and down the road as she takes 6-MP?

**Discussion of April's Case**

As with any new medication, it is important to explain all of the risks, benefits, and potential side effects associated with 6-MP. A discussion of the risks and benefits should include the rare but

increased risk of infections and malignancy, including lymphoma and skin cancers. Emphasis should focus on the importance of following your recommendations for having serial blood tests to monitor for myelosuppression and hepatotoxicity. You should ask if she has been immunized for HPV and, if not, recommend that she receive it. Confirmation of immunity to *Varicella* is recommended as well. April and her parents should be told that she should not receive live vaccines while taking 6-MP and therefore, if able, prompt administration of all such vaccines with ample time to respond would be ideal prior to starting thiopurine therapy.

**Appropriate Testing, Monitoring, and Follow-up With 6-MP Therapy**

Before initiating 6-MP therapy, April needs to undergo TPMT genotyping or phenotyping. Together, you plan for serial CBCs and liver chemistry panels and have a system in place with your office staff to ensure that you review the results when they are sent over from the outside laboratory (her home is a 3-hour drive from your office).

You see April every 3 months in your office. One year after starting 6-MP, April returns for a follow-up visit and reports that she is doing great. You note growth acceleration and she is excited that her parents are taking her on a cruise during a winter break in her school schedule. She has been using a tanning bed in anticipation of the trip. April should be strongly discouraged from using a tanning bed and you should recommend she avoid excessive sun exposure for as long as she continues using 6-MP therapy (protective sun screen and clothing).

**CASE STUDY 2: CECILY**



Cecily is 17 years old and was diagnosed with ileal CD at age 13. She was initially given prednisone for the induction of remission and has continued on 6-MP monotherapy for maintenance therapy. Over a 4-year period, she had 2 disease exacerbations that responded quickly to brief courses of prednisone. Three months ago, she developed her third exacerbation, which initially responded to prednisone, but she is now unable to taper off of it despite optimizing her 6-MP dose. You decide to start anti-TNF therapy.

**Case Question:**

- What do you need to discuss with Cecily and her parents, and what testing will be required now and down the road?

**Discussion of Cecily's Case**

A discussion of the risks and benefits should include the risk of serious infections and malignancy, outlined in the black box warnings for all anti-TNF agents. You counsel Cecily and her parents to contact your office or be seen by her primary care physician if she has unexplained fever or other symptoms of infection. You should also discuss the risk of infusion reactions (for infliximab) and immunogenicity, including the formation of anti-infliximab antibodies, auto-antibodies, and lupus-like reactions.

### Testing/Monitoring/Follow-up

Before starting therapy, Cecily has a PPD and chest radiograph since she is on steroids. You determine her *Varicella* immune status. You ensure that she returns to see you regularly. You check for adenopathy at each examination and are aware that this is a manifestation of only some lymphomas, so you also look for enlargement of the liver and spleen. Cecily has an excellent response to therapy and her disease is in remission within 6 weeks. After 6 months of therapy, she presents to the emergency department with headache, fever, chills, and fatigue. Because she is on anti-TNF therapy, the treating physician contacts you for advice. She has mild tachycardia, her temperature is 104.1°F, and there is no obvious focus of infection.

#### Case Question:

- What do you recommend?

Serious infections, including viral, bacterial, and fungal etiologies, have been reported in patients on anti-TNF therapies. You recommend sending blood cultures (including fungal blood cultures), viral cultures, CBC, electrolytes, and chemistries (liver-associated enzymes, etc). She is admitted to the hospital and given broad spectrum antibiotics. Because she is having headaches, a lumbar puncture is performed. She is ultimately found to have *Listeria monocytogenes* meningitis.

### CASE STUDY 3: JAY



Jay is 17 years old. Eight months ago, he was diagnosed with ileocolonic CD. He was initially given 6-MP, but developed pancreatitis 3 weeks after starting it. Since then, he has been successfully maintained on methotrexate. Jay comes for a follow-up visit and his disease appears to be in remission; however, he now complains of a cough that is dry and says it began 2 weeks ago. He is also having exertional dyspnea and reports feeling “feverish.” He has a history of exercise-induced asthma and recently started football practice. He is using an albuterol inhaler, but it provides only partial relief. When you examine him you hear occasional crackles at the bases of both lungs.

#### Case Question:

- Are Jay’s symptoms important, and what steps do you need to take?

### Discussion of Jay’s Case

Although Jay may be having an asthma exacerbation and/or community-acquired pulmonary infection, you must consider whether he is experiencing methotrexate pulmonary toxicity. You obtain a chest x-ray and consult with a pulmonologist who agrees to see him and does pulmonary function testing. You also tell Jay to discontinue the methotrexate until a cause is identified for his symptoms.

Jay’s chest x-ray shows a pattern of interstitial infiltrates bilaterally and the pulmonary function tests demonstrate a restrictive pattern, which can be seen with methotrexate toxicity. A workup is required to identify or exclude infections. Jay has a bronchoscopy and bronchoalveolar lavage (BAL). There are a number of findings that are common in patients with methotrexate pulmonary toxicity, including the presentation

above and the radiographic and pulmonary function test results. Other common findings include peripheral eosinophilia, a ground-glass patchy appearance of the pulmonary parenchyma using high-resolution computed tomography scanning, and the absence of infectious organisms. BAL can demonstrate increased CD-4 cells and an increased CD-4:CD-8 ratio. Lung biopsy is not always required and can be nonspecific.

### Conclusion of Jay’s Case

Polymerase chain reaction testing from his BAL demonstrates *Mycoplasma* infection. Jay is treated, his symptoms resolve, and he is able to continue therapy with methotrexate.

### CONCLUSION

The primary goal of IBD therapy is to induce remission in patients with active disease, and to provide maintenance therapy to sustain remission. During treatment, drug toxicity should be minimized and objective parameters of active disease should return to normal (eg, C-reactive protein, normalized growth velocity, and, perhaps, mucosal healing). Short of curing IBD, the overall goal of treatment is focused on maintaining the highest achievable quality of life. For this reason, IBD therapy should take an individualized approach with a well-balanced appreciation of the ratio of risk to benefit.

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