Primary Care Considerations in the Management of Inflammatory Bowel Disease Patients

Multiple pharmacologic interactions are noted between current Inflammatory Bowel Disease (IBD) medications and drugs used to treat more common diseases. In an effort to evaluate these important, clinically significant side-effects, the Lexi-Comp and Epocrates databases were used to analyze interactions between IBD medications and those of several common conditions (hypertension, diabetes, asthma, dyslipidemia, and chronic pain). Additionally, Pub Med Searches were performed to evaluate recent literature discussing the relationship between IBD and these co-morbidities.

INTRODUCTION

Managing Inflammatory Bowel Disease (IBD) in the primary care setting can often be difficult because of the potential for interactions between IBD medications and medications commonly utilized to manage more prevalent disease processes. The incidence of IBD in the North American continent ranges from 2.2 to 14.3 cases per 100,000 person-years for UC and 3.1 to 14.6 cases per 100,000 person-year for CD (1). In contrast, hypertension (HTN) affects approximately 30% of the population (2); currently it is estimated that there is a 33-39% lifetime risk for developing diabetes in the United States (3). One or more of these common medical disease processes may occur in patients with concomitant IBD. Current IBD treatment regimens may include corticosteroids, 5-ASA drugs, immunomodulators, methotrexate and biologic agents, all of which may interact with medications commonly encountered in the primary care setting. The Lexi-Comp and Epocrates databases were used to analyze possible interactions between various medication classes. Additionally, Pub Med Searches were performed to evaluate recent literature pertaining to IBD management with these medical conditions.

IBD Medications

IBD typically is managed with medications in several drug classes including corticosteroids, 5-ASA agents, biologic agents, methotrexate and immunomodulators. Each of these agents works by a different mechanism in altering disease processes. Corticosteroids act by decreasing inflammatory cytokines; side effects may occur secondary to altered immune status and adrenal suppression. 5-ASA medications work through an unclear anti-inflammatory mechanism which directly acts upon the colonic mucosa. This medication class is commonly utilized in maintenance therapy...
for patients with ulcerative colitis. Immunologic agents such as mercaptopurine inhibit DNA synthesis and biologics such as infliximab alter inflammatory cytokines (TNF-alpha).

5ASA (mesalamine) preparations are considered Pregnancy Class B drugs, with the exception of the Asacol® brand, which is considered a Class C drug do its Eudragit® resin covering. Overall, medications in this drug class are generally well tolerated. Their most common reactions include headache, nausea, and mildly increased Bun/Cr levels. Major side effects, albeit uncommon, include renal failure, hepatotoxicity, pericarditis, and aplastic anemia. Due to the potential alterations in Bun/Cr, periodic monitoring of renal status is appropriate. Patients with underlying renal disorders require more frequent surveillance.

Mercaptopurine is considered a Class D for use during pregnancy. Mild GI distress including nausea and diarrhea are the most common reaction but anemia can occur. Major reactions to medications in this drug class include immunosuppression myelosuppression, pancreatitis, and hepatotoxicity. Baseline laboratory values for anemia and liver function tests should be evaluated prior to starting these medications and then followed at appropriate intervals.

Azathioprine is considered a Class D drug during pregnancy. Common reactions include nausea, diarrhea, and rash. Major reactions include leukopenia, myelosuppression, pancreatitis, hepatotoxicity, and lymphoma. Once again do to the possibility of significant alterations in myelopoesis as well as hepatotoxicity, monitoring with CBCs and liver chemistries is recommended.

Infliximab is considered a Class B medication during pregnancy. Medications in this anti-TNF subclass each have fairly significant side effects, some of which may be specific to a medication. Prior to starting medications in this subclass, tuberculosis and viral hepatitis B should be screened for and properly treated. Infliximab itself has multiple major reactions include increased risk of lymphoma, increased risk for opportunistic infections, photosensitivity, Hepatitis B virus re-activation, and seizures. More common adverse effects include fever, chills, myalgias, rash, elevated LFTs, facial and extremity edema.

Lastly methotrexate is considered a Class X during pregnancy. Therefore, it should be avoided in all women of child bearing age. Serious reactions in this medication class may include leukopenia, hepatotoxicity, nephrotoxicity, pulmonary fibrosis, and skin reactions including Stevens-Johnson Syndrome.

**Hypertension**

Within the last decade, the prevalence in the United States has been estimated to be approximately between 29-31 percent (2). Hypertension is the major contributing factor to premature coronary artery disease, heart failure, ischemic strokes, and chronic kidney disease. There is a wide range of medications used to treat this medical condition which include medication classes such as beta
blockers, diuretics, calcium channel blockers, ACE-Inhibitors, angiotensin receptor blockers, and nitrates. In evaluating these medications for interactions, Lexi-Comp and Epocrates databases were employed and interactions between typical Hypertension and IBD medications were analyzed. Medications evaluated for HTN include metoprolol, lisinopril, nifedipine, diuretics (HCTZ, spironolactone). IBD medications included prednisone, 5-ASA, biologics, and immunomodulator agents. Corticosteroids themselves, may lead to an elevation of blood pressure. Noted interactions between these classes include those between the diuretic classes and prednisone. Combinations of these medications have the potential to decrease diuretic efficacy and increase the risk of hypokalemia. The most significant interaction noted between these medications was that of lisinopril and azathioprine, which can lead to an increased risk of leukopenia and significant hematologic toxicity.

MESH terms Hypertension, IBD, Inflammatory Bowel Disease, Crohn’s Disease, Ulcerative Colitis were searched together using the PubMed Database under the clinical queries filter. One paper noted that patients with refractory IBD treated with cyclosporine were at increased risk for hypertension and renal insufficiency (10); seizures are an additional risk of this agent. Another paper discussed the increased risk of side effects, including hypertension, in patients with the use of Tacrolimus to treat IBD (11).

**Diabetes**

Over the last thirty years, the incidence of diabetes in the United States has increased by 176% (4) and the age adjusted increased is 151% (4). Overtime, having diabetes leads to an increased risk for the development of cardiovascular disease, progressive renal disease, and compromised immune status. The major goal in management of this disease is to maintain a consistent glycemic level.

Corticosteroids are often used in treatment of IBD flares and may lead to significant disturbances in glycemic levels. Additionally, any patients with diabetes using biologic and immunologic agents are at further increased risk of opportunistic infections. Medications used to treat diabetes include biguanides, sulfonylureas (metformin), thiazolidinediones, and long/short acting insulins. In evaluating these medications for interactions the Lexi-Comp database was used to evaluate interactions between typical Diabetes and IBD medications. Medications evaluated for IBD include prednisone, 5-ASA, mercaptopurine, azathioprine, infliximab, and methotrexate.

Treatment of IBD flares sometimes involve the use of IV steroids followed by an oral prednisone taper. One of the major side effects of corticosteroids is significant hyperglycemia. Prednisone use and steroids in general may lead to decreased efficacy in all drugs used to treat diabetes due to hyperglycemia. Other significant side effects include those between mesalamine and prednisone.

**Table 2. Diabetes and IBD Medication Interactions**

<table>
<thead>
<tr>
<th>Biguanide (Metformin)</th>
<th>Prednisone</th>
<th>Mesalamine</th>
<th>Mercaptopurine</th>
<th>Azathioprine</th>
<th>Infliximab</th>
<th>Methotrexate</th>
</tr>
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<tbody>
<tr>
<td>Interaction</td>
<td>Interaction</td>
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<td>None</td>
<td>None</td>
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<tr>
<td>Sulfonureas (glyburide)</td>
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<td>None</td>
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<tr>
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</tr>
<tr>
<td>Glargine (Lantus)</td>
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<tr>
<td>Intermediate Acting Insulin (NPH)</td>
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</tr>
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</table>

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metformin and methotrexate and metformin; both combinations may lead to an increase in metformin levels. Elevated levels of metformin may theoretically lead to significant lactic acidosis, especially in patients with underlying renal disease. In all patients using this combination of medications baseline renal function should be noted and monitoring may be indicated. Lastly the combination of infliximab and glyburide may lead to lowering of sulfonylurea levels do the TNF inhibitor down regulating CYP450 enzymes.

Dyslipidemia
Elevated LDL cholesterol in patients with or without known cardiovascular disease has been shown to lead to increased risk for coronary heart disease (7). Meta Analysis studies have demonstrated that decreasing LDL levels lowers one’s risk of coronary heart disease (6). ATP III guidelines may be used to stratify patients’ risks for disease and determine target LDL and HDL levels. In patients in whom diet and exercise do not demonstrate improved lipid levels, a variety of cholesterol medications may be used. Dyslipidemia medications include HMG-COA reductase inhibitors, bile acid sequestrants, fibrates and niacin. Using the Lexi-Comp and Epocrates databases interactions between typical Dyslipidemia and IBD medications were evaluated. Medications evaluated for IBD include prednisone, 5-ASA, mercaptopurine, azathioprine, infliximab, and methotrexate.

After analysis, combinations of medications in these drug classes yielded few interactions. The mainstay therapy of dyslipidemia at this time is HMG-CoA reductase inhibitors or statins, which work by inhibiting 3-hydroxy-3 methylglutaryl coenzyme. One side effect that was noted between simvastatin and infliximab was the downregulation of CYP450 enzymes which lead to a decrease in statin levels. The most significant interaction noted between these classes was between prednisone and cholestyramine due to the bile acid sequestrant; the lack of bile acids may reduce corticosteroid absorption. It is recommended that for patients using this combination of medications that the steroids are given at least one hour before or four-six hours after bile acid sequestrant to avoid interaction.

Pain Medications
Chronic pain is among the most common reasons for which patients present to primary care physicians (9). Pain may be managed in a variety of ways including the administration of PO, IV, and topical pain medications, rehabilitation with focused exercises, cognitive based

### Table 3. Dyslipidemia and IBD Medication Interactions

<table>
<thead>
<tr>
<th></th>
<th>Prednisone</th>
<th>Mesalamine</th>
<th>Mercaptopurine</th>
<th>Azathioprine</th>
<th>Infliximab</th>
<th>Methotrexate</th>
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<td>Simvastatin</td>
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<tr>
<td>Fenofibrate</td>
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<td>None</td>
<td>None</td>
<td>None</td>
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<tr>
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<td>None</td>
<td>None</td>
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<tr>
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</tr>
</tbody>
</table>

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therapy and even surgical intervention(8). Typical
pain medications include NSAIDS, PO and IV opioid
receptor agonists, acetaminophen, and Tramadol. 
Tramadol is a medication that works via a somewhat
unclear mechanism that involves the binding of
mu opioid receptors for pain relief. Using the Lexi-
Comp and Epocrates databases interactions between
typical pain medications and IBD medications were
evaluated. Medications evaluated for IBD include
Prednisone, 5-ASA, mercaptopurine, azathioprine,
infliximab, and methotrexate.

Non-steroidal anti-inflammatory drugs (NSAIDS)
appear to have the greatest interaction with IBD
medications. As in patients without IBD, the chronic
use of NSAID medications may lead to increased risk
of GI bleeding including peptic ulcer disease, salicylate
toxicity, and renal injury. Baseline laboratories
including Hemoglobin, Hematocrit, and Bun/Cr should
be performed prior to initiating chronic NSAIDS.
Specific interactions are noted between NSAIDS and
IBD medication groups. The combination of aspirin and
5-ASA may potentiate the risk for salicylate toxicity.
NSAIDS and high dose methotrexate in combination
may lead to increased serum methotrexate levels.
Renal status in these patients, especially the elderly,
must be closely monitored. Tramadol levels may be
increased when used with infliximab. Accordingly, liver
chemistries should be monitored. Lastly infliximab may
decrease fentanyl levels when used together.

MESH terms Chronic Pain, Chronic Pain Treatment,
Inflammatory bowel disease, IBD, Crohn’s Disease,
Ulcerative Colitis were searched together using the
PubMed Database. An article of note discussed the use
of chronic narcotics in IBD patients (17).

Asthma
The lifetime asthma prevalence in the United States per
2010 CDC survey is approximately 13.5% (18). Asthma
therapy is typically based on the frequency, severity,
and time of day of asthma symptoms. Mainstays in the
therapy of asthma include both short and long acting
inhaled beta 2 adrenergic receptor agonists (albuterol,
salmeterol), anticholinergics (ipratropium), inhaled
glucocorticoids (budesonide, fluticasone), leukotriene
receptor antagonists (montelukast), theophylline,
and anti IgE therapy (omalizumab). Using the Lexi-
Comp and Epocrates databases interactions between
Asthma and IBD medications were evaluated.
Medications evaluated for IBD include prednisone,
5-ASA, mercaptopurine, azathioprine, infliximab, and
methotrexate.

Interactions between these drug classes include
an increased risk of hypokalemia with prednisone and
either long or short acting beta 2 receptor agonists.
The combination of infliximab and theophylline may
lead to decreased levels of theophylline levels due to
altered hepatic metabolism. Methotrexate should be
avoided in these patients do to the increased risk of
pulmonary fibrosis. Finally a significant side effect was
noted between the combination of methotrexate and
theophylline. Used in conjunction these medications
may increase theophylline levels and decreases
methotrexate levels.

MESH terms Asthma, Inflammatory bowel disease,
IBD, Crohn’s Disease, Ulcerative Colitis were searched together using the PubMed Database. A pediatric study from the Mayo Clinic looked for the association of T-Helper Cells 2 and IBD (20).

**CONCLUSION**

There are multiple significant interactions between IBD medications and those of more prevalent diseases. In evaluation of concurrent Hypertension, Diabetes, Dyslipidemia, Asthma and Pain it is important to know that most of these medications can be taken together with little side effects. Overall caution should be used with NSAIDS in patients with IBD, and the potency of diabetes medications can be affected by IBD medications. Most medications treating Hypertension, asthma and dyslipidemia have little interactions with IBD medications.

**References**

4. http://www.cdc.gov/diabetes/statistics/incidence/fig2.htm Data Source: Centers for Disease Control and Prevention (CDC), National Center for Health Statistics, Division of Health Interview Statistics, data from the National Health Interview Survey. Data computed by personnel in CDC’s Division of Diabetes Translation, National Center for Chronic Disease Prevention and Health Promotion.
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