Dr. Lashner: Hello. My name is Bret Lashner from the Cleveland Clinic, and I'm joined by Gary Lichtenstein from the University of Pennsylvania. We'll be talking to you about optimizing the medical management of IBD by primary care clinicians. I'd like to start by telling you about 2 types of patients you might see in your practice. The first is a 23-year-old woman who presents with a 3-month history of watery, non-bloody diarrhea as well as right lower quadrant pain and weight loss. She’s a cigarette smoker and her physical examination shows a definite 5-cm mass. In this young woman we are thinking about Crohn’s disease, which would be very high in the differential diagnosis for her. A different patient, a 19-year-old man, complains of 2 months of diarrhea, bleeding, and diffuse abdominal pain following his return from a vacation in Mexico. An enteric infection was successfully treated, but symptoms of diarrhea and bleeding remain. He is a non-smoker. This would be a prototypical case for ulcerative colitis triggered by an enteric infection. Once you’ve treated the infection, if the symptoms remain, you need to think about ulcerative colitis.

These 2 diseases, ulcerative colitis and Crohn’s disease, have very different clinical features and for the most part we can distinguish between the 2 of them. For example, ulcerative colitis involves only the colon, always involves the rectum, has continuous inflammation from the
rectum to a point proximally, has mucosal disease only, diffuse ulceration, granularity, friability, bleeding, and exudate. There are no fistulae or granulomas. These people tend to be non-smokers and curiously they’ve not had appendectomies. Appendectomy seems to protect you from ulcerative colitis. Patients with Crohn’s disease may have inflammation in any segment of the GI tract. There’s often rectal sparing, skip lesions, transmural disease through the wall of the bowel, aphthous ulcers, serpiginous ulcers, cobblestoning, fistulas, and granulomas; and these patients tend to be smokers.

On sigmoidoscopy a patient with ulcerative colitis has hemorrhagic mucosa diffusely involved with granularity and friability. Typically when patients with ulcerative colitis present for the first time they’ll have left-sided disease or proctitis and proctosigmoiditis. Over time, though, the disease progresses and more extensive disease develops. An endoscopic view of someone with Crohn’s disease might show punched-out lesions, a cobblestone appearance, or skip areas with relatively normal mucosa in between these ulcerated lesions. Crohn’s disease can affect any part of the gastrointestinal tract. Typically the most common place is the terminal ileum and the proximal colon, seen in about 45% of patients. But Crohn’s colitis can be seen in about a third of patients, pure small bowel Crohn’s disease in 22%, and upper GI Crohn’s disease is rare, seen in about 6%.
Three different behaviors we see in patients with Crohn’s disease are inflammatory, obstructive, and fistulizing disease. With inflammatory disease patients often present with signs of inflammation of the bowel, like abdominal pain, tenderness, diarrhea, and weight loss. These people also will usually have an inflammatory mass, often in the right lower quadrant. Patients with obstructive disease tend to have cramping, distension, vomiting, and signs of obstruction. These patients typically do not respond to anti-inflammatory therapy. And patients with fistulizing disease have abnormal communication between loops of bowel or bowel and other organs like the skin or the bladder with some features such as pneumaturia or fecaluria, as well as pain and diarrhea. Interestingly, pretty much everybody with Crohn’s disease will start off by having inflammatory type disease but over time, as the disease progresses, more fibrosis sets in, more fistulizing disease sets in, and fewer and fewer people have pure inflammatory disease. These people are therefore less likely to respond to anti-inflammatory medications and will need other forms of treatment to treat their penetrating and structuring disease.

The incidence rates are about 13 to 15 per 100,000 for ulcerative colitis, a little bit lower in Crohn’s disease. Since Crohn’s disease patients have many more complications requiring medical care, you’ll see probably more Crohn’s disease than ulcerative colitis in your practice. It is a disease of young people. The peak age of incidence is between 10 and 19
years. There is a second peak between 50 and 60 years of age, but people are suspicious that possibly that second peak could be related to other more common diseases that affect older people such as diverticulitis or ischemic colitis. An ulcerative colitis diagnosis requires a typical history of chronic diarrhea and bleeding, negative stool cultures, an endoscopy that shows the disease of inflammation in the rectum with superficial ulcerations, granularity, and friability. The hallmark on histology is crypt abscess with mucosal inflammation. Typically when patients are admitted to the hospital for severely active ulcerative colitis, a KUB X-ray is done to rule out megacolon or toxic colitis.

We can grade the severity of patients with ulcerative colitis based on the ACG guidelines from 2010 into mild, moderate, severe, and fulminant disease. This will generally help us determine the best course of therapy for these patients. For example, most patients with fulminant disease will need surgery, and delaying surgery with medical therapy is probably not in the patient’s best interests. Likewise, people with mild or moderate disease often will not need admission to the hospital but will be able to be treated with some of the therapies Dr. Lichtenstein is going to talk about in a few minutes. The place you need to concentrate on when you see a KUB is the transverse colon. You’ll also see thumb printing or edematous folds throughout the transverse colon as well as a very thin lumen in the left colon with a very edematous mucosa. A patient with these characteristics is quite ill and almost certainly will need colectomy
for his disease.

Diagnosis of Crohn’s disease can be made with a clinical history that includes diarrhea, right lower quadrant pain, fatigue, fever, and in younger people, growth retardation. We sometimes see people who look like they’re 12 years old when they’re really 23 years old, a very sad problem. Of note, growth retardation is often treated by excessive nutrition in these people. Giving tube feedings or total parenteral nutrition (TPN) will help reverse some of the growth retardation. Once again, negative stool cultures are necessary and on endoscopy you might see skip lesions, aphthous ulcers, cobblestoning, serpiginous ulcers, rectal sparing, and perianal disease—hallmarks of Crohn’s disease. Granulomas are rarely seen but very useful to make the diagnosis of Crohn’s disease, and transmural inflammations are also important. Radiology is done to rule out strictures and fistulas, which will help determine the best route or the best type of therapy for these patients. A small bowel X-ray of a patient with Crohn’s disease may show a very narrow lumen of the terminal ileum. This is called a string sign. There can also have a mass effect. A patient with these characteristics will have an inflammatory mass and will almost certainly need surgery. It’s doubtful that this person will respond to medical therapy only.

And now we’ll ask Gary to talk about the safety of medical therapy in patients with inflammatory bowel disease. Gary?
Dr. Lichtenstein: Thank you, Bret. What I’m going to try to focus on is what you might see patients on in the office, different medications, or in the hospital and some of the primary issues relating to safety of medical therapy. The first thing we have to do when we look at safety of anything is ask: What is the evidence for causality? And additionally, are these common or uncommon scenarios? Are they high relative and high absolute risks? And additionally, what potential cofactors or risk factors are present for adverse events? And these should be kept in mind when evaluating any safety of any medical therapy.

So to determine the relationship of an adverse effect to a medication, the things one needs to know are the expected occurrence in the general population, any disease-specific expected occurrence, and also the potential risk factors. Is someone’s age a risk factor? Is concurrent medication a risk factor? Additionally, one needs to know the characteristics of the adverse events, such as when did they occur? Did they occur early on in treatment, later in treatment, or at any time of treatment? What’s the relative risk of recurrence? The risk/benefit determination should be made with any medical therapy when treating patients. And what are the alternate treatment options that we have available?

So with this in mind I’d like to go through the different medical therapies
that are available to treat patients with inflammatory bowel disease. The mesalamine derivatives are aspirin analogs, and these have been in use for many years in treating patients with ulcerative colitis. And, they are used frequently to treat people with Crohn’s, as the evidence is less supportive of their benefit in Crohn’s. We’ll talk about the other agents as well, corticosteroids, immune modulators, cyclosporine, anti-TNF therapy, and methotrexate as well, in an effort to focus on the agents that we have available—and most recently vedolizumab, which has just gained regulatory approval.

If we look at the mesalamine derivatives in general, there’s a relatively low incidence of adverse events. Some of the more common non-severe events we might see are diarrhea, abdominal pain, headache, dyspepsia, rash, and nausea and vomiting. The diarrhea may be such that an individual is started on a mesalamine derivative and suddenly gets worse. High-volume watery diarrhea might be the clue to suggest this is a medication-related side effect. Some of the more serious side effects are nephrotoxicity and pancreatitis. We’ll talk about the nephrotoxicity, but pancreatitis can occur in patients as well, which is a hypersensitivity type of reaction that an individual may get directly related to the treatment. It’s relatively uncommon. The rate of renal toxicity per hundred patient-years of follow-up on mesalamine versus no mesalamine is highlighted by a study done in the Great Britain Practitioners’ Database. The main side effect we look at when talking about renal
disease is interstitial nephritis. The overall occurrence is approximately 1 in 500 patients, with half of these cases occurring in the first year and others occurring many years later. Initial baseline creatinine and urinalysis looking for protein is suggested in patients who initiate therapy with mesalamine. Subsequently, a period of time later—perhaps 2 or 3 months—the patient is checked to see if there’s any change from the baseline, and then it has been my practice to check on an annual basis thereafter because 50% of individuals may develop interstitial nephritis years out. So it’s an ongoing surveillance to look to see if these are coming about. If someone does develop interstitial nephritis, then avoidance of mesalamine in the future is advocated. There are some who say that monitoring for renal toxicity is not a cost-effective maneuver, but it’s more a medicolegal maneuver given that it’s recommended on the package insert. So this is something that’s done historically and is relatively infrequent, and many will say they’ve never seen a patient develop this. But it’s recommended for the safety of the patients, just as “surveillance.”

Corticosteroids are widely used. They were introduced back in the 1950s as one of the therapies to use to treat patients with inflammatory bowel disease. It’s a double-edged sword, though. Corticosteroids are quite effective and act very rapidly, but the side effect profile is significant. Hypertension, infectious complications, and osteonecrosis occur in some series in up to 5% of patients, but in general it’s relatively low—0.25% to
0.75% overall for general population cohort studies. Osteoporosis—we do bone density assessment on patients exposed to corticosteroids. Myopathy, cataracts, and glaucoma are possible, so ophthalmologic evaluation is advocated annually or frequently for those individuals that are exposed. And, of course there are the psychiatric complications: psychosis, depression. Diabetes is another adverse event. So the complications are significant, so this is not advocated as a maintenance drug. It’s used only acutely to obtain a state of clinical benefit, clinical remission, or clinical response in patients, and serves as a bridge, if you would, for other medical therapies, whether it’s mesalamine, an immune modulator, or an anti-TNF. The side effects of conventional steroids are such that other agents have come into development.

There is a study that looked at MMX budesonide, a colonic-release budesonide, to assess if patients were able to tolerate medication more effectively and have fewer adverse events. And this study really highlights that the MMX formulation of budesonide has fewer adverse events than for individuals who have received other agents, but more so it’s comparative to placebo. And if we look at the numbers for moon face, striae, flushing, fluid retention, mood changes, sleep changes, insomnia, acne, and hirsutism, they’re all rather low. And this is comforting. So the standard is to use these agents for approximately 8 weeks and then stop therapy.
Bone loss can occur. Many factors are involved in bone loss in individuals that have inflammatory bowel disease. Malnutrition, malabsorption, lack of physical activity, delayed puberty, and corticosteroid use, which is the main area we’ll focus on, as well as the inflammation from various cytokines, all have a role in bone loss itself. Hence, individuals exposed to corticosteroids for any prolonged period of time need a bone density assessment with a DEXA scan at some point to ensure that they don’t have bone loss. We can lessen that bone loss with budesonide, but again, any steroid exposure at some point should be followed up.

Immune modulators have been introduced as steroid-sparing agents and these agents, in particular azathioprine, 6-mercaptopurine (6-MP) and methotrexate, are used more in Crohn’s than in ulcerative colitis, but they’re used as well in ulcerative colitis. Individually we can check pharmacogenetics to see if individuals who are starting azathioprine or 6-MP have thiopurine methyltransferase activity. Approximately 0.3% of individuals are deficient in this enzyme and should not receive treatment with azathioprine or 6-MP, because this can cause aplasia, which has been associated with sepsis and death. So we check this in patients prior to initiation as is recommended by the FDA; 11% are partially deficient or heterozygous or have indeterminate or intermediate, if you would, activity, and these individuals perhaps need lower doses of azathioprine or 6-MP. Standard dosing of azathioprine is 2.5 mg per kilogram at
highest and 6-MP is approximately 1.5 mg per kilogram. It takes approximately 2 to 6 months, depending on the study, for these medications to start benefiting patients with regard to the immune suppressant effect.

One key PMT genotype is associated with early but not late severe myelosuppression. The study by Jean-Frédéric Colombel and his group showed that those individuals that have low methylators—in other words, they have low enzyme activity—can develop leukopenia early on myelosuppression and it’s in the first 6 weeks that these tend to benefit patients with regard to lowering the immune system, the low white cell count. So it’s an early event. Frequent monitoring, every week or two, with CBCs is advocated for this general population. Another study looked at severe leukopenia, and this study demonstrated that early leukopenia was preceded by mild leukopenia in the majority of patients. Frequent monitoring of patients in the first 8 weeks is important and subsequent monitoring can occur less frequently. Individual monitoring would be with a CBC initially every week or 2, and subsequently after a period of time, perhaps every 3 months at a minimum, is advocated. So again, monitor with CBCs and also liver-associated chemistries periodically.

Adverse events do occur with azathioprine and 6-MP, but the majority of patients tolerate medical therapy. Based upon various different studies, 10 to 20% don’t tolerate therapy, but early on (in the first 3 to 4 weeks)
pancreatitis can occur. So if mid-epigastric left-sided abdominal pain occurs in someone newly starting azathioprine or 6-MP, one should think of pancreatitis. Bone marrow depression we talked about. Allergic reactions, a rash, hives, wheezing, or anaphylaxis can occur with these medications as well. A drug-induced chemical hepatitis can occur, so monitor the ALT and the AST. Infections can occur with these medications as well. Given that these suppress the immune system, this is something that is clearly a defined side effect profile of medical therapy, though less so than steroids but clearly a suppression of the immune system. Neoplasms can occur as well; there’s clearly a problem with individuals being exposed to azathioprine and 6-MP with a risk of lymphoma and lymphoproliferative disorders.

In a study that has recently been done by our group we did a meta-analysis of the literature of all the studies looking at azathioprine and 6-MP, and we grouped these into either referral studies or population studies. And the overall standard incidence or new cases of lymphoma compared to that of the general population in this SEER database was 4.49. The population studies are lower, 2.4-fold. Of course as you would expect the referral studies were higher, suggesting the referral bias is present in this population. If you’re currently using azathioprine or 6-MP, your risk is higher than if you have previously used and stopped medical therapy. In fact, for those who’ve stopped therapy with azathioprine or 6-MP, the risk for lymphoma goes back to that of the
general population risk. But active users have the highest risks overall. It’s interesting to find that men had twice the risk of women for developing lymphoma when we looked at the studies available that could evaluate such. But more importantly, a young age and an elder age is the highest risk. The highest standard incidence ratio is 6.99 or about 7-fold for individuals younger than 30. Younger men had the highest risk, but the absolute risk was the highest in patients over 50. So, be cautious when using these medications and always assess the risk-to-benefit ratio in individuals younger than 30 and over the age of 50. So if someone develops fever, abdominal pain and a CAT scan with multiple lymph nodes who’s on an antimetabolite, one has to think that this is potentially related to a lymphoma.

Age-specific risk was looked at in another abstract. The impact of age-related risk of non-Hodgkin’s lymphoma and hepatosplenic T-cell lymphoma was really not addressed prior to this, and it was just generally said to try to avoid this. This study is a Markov model that looked at expected risks and incremental effectiveness calculated for people initiating therapy across the 25- to 75-age range with the base model being a 35-year-old male with severe Crohn’s. Combination therapy was a preferred strategy in the baseline case and resulted in fewer surgeries, deaths, and patients with active disease. The benefit persisted across all ages in the base model, but the margin of benefit decreased as the age decreased. And one would expect that with common
sense. When you account for life years lost due to mortality, monotherapy was preferred if the hazards ratio of non-Hodgkin’s lymphoma was over 11.5 in those age 65 or greater than 6.9 in those age 75. For 25-year-old males, accounting for the risk of hepatosplenic T-cell lymphoma, monotherapy resulted in fewer deaths and was the preferred strategy. And the incidence of hepatosplenic T-cell lymphoma was greater than 24 per 100,000. I think there are several take-home messages from this. It’s a complicated way to say if you’re age 35 to 65, then combination therapy is a preferred strategy, so that’s something that’s commonly used in many patients you’ll see with azathioprine and infliximab or another anti-TNF. And for those over 65, particularly those over 75, stick with monotherapy because the risk of lymphoma and related mortality to non-Hodgkin’s lymphoma is higher. Due to hepatosplenic T-cell lymphoma risk, combination therapy in young males may result in more deaths without providing substantially greater quality-adjusted life years. This study established a clear model to mathematically demonstrate findings that support common strategies.

Skin cancers are elevated in patients taking thiopurines. Laurent Peyrin-Biroulet has demonstrated that non-melanoma skin cancer is higher in those individuals as they get older. It’s an age-related phenomenon. If they discontinue medical therapy, the risk still remains elevated. So contrary to the lymphoma risk, the skin cancer risk remains high, although not too high in individuals who stop medical therapy. So skin
exams on individuals that had used thiopurines are important. The skin exam might be something to be done as routine on an annual or on a several-year basis just to be certain these people are not developing the non-melanoma skin cancers—basal cell and the squamous cell cancers in particular.

Now cyclosporine has its own set of toxicities. It’s not used very frequently in patients that have ulcerative colitis, and in Crohn’s it’s not been shown to be very effective. Its use has dropped off with the advent of anti-TNF therapy. In the event you see someone using IV cyclosporine, side effects that might be encountered include headache; hirsutism, excess growth of facial hair or body hair; fevers, chills, sweating; liver-associated chemistries may be elevated; hypertension; and paresthesias. A major but less frequent side effect is nephrotoxicity. So initially when treating patients we’ll monitor a minimum of every 3 days or so for nephrotoxicity but also recall that these individuals are very immune-suppressed. They’re often in the hospital on steroids, cyclosporine, and then may get placed on immune modulators. So remember to prophylax for *Pneumocystis* and also be careful. Infections can come about. When you’re triple-immune suppressed, your body may not be demonstrating the standard signs and symptoms that an individual has. And it’s important to consider CT scanning or cross-sectional imaging if abdominal pain develops, given the severe immune suppression. Seizures may come about and have been classically noted in individuals with low
serum cholesterol. So these are things to be concerned with and be carefully paying attention to.

Since the introduction of infliximab in 1998, anti-TNF therapy has grown and there are now 4 FDA-approved agents for the treatment of inflammatory bowel disease: infliximab, adalimumab, golimumab, and certolizumab pegol. The thing to recall is these are safe in general, but they do have potential significant side effects. There is a black box warning for serious infections and malignancy for all anti-TNF therapies, and there is a black box warning for hepatosplenic T-cell lymphoma, particularly with adalimumab and infliximab. We had published some data on this: these individuals who develop hepatosplenic T-cell have all been on a minimum of 2 years of azathioprine. So it’s the concurrent use of azathioprine that perhaps is the driver for lymphoma. Hepatitis B reactivation can occur, so we check for hepatitis B surface antibody and a core antibody in all individuals before initiation of the anti-TNF therapy. And hep B vaccination should be contemplated as well. Melanoma skin cancer is escalated in people that have Crohn’s disease based on a recent meta-analysis that’s been done, but also anti-TNF therapy is thought to escalate the risk for melanoma-related skin cancer. Pustular psoriasis can come about in individuals using anti-TNF therapy. And it can come about with any of the agents in general. It’s thought that higher levels of the anti-TNF agents drive this. There’s been no trial looking at lowering the dose to see if this is effective. But again this is a
specific form of psoriasis, pustular psoriasis. If it’s less than a 5% Psoriasis Area and Severity Index (PASI) score, the percent area of surface involvement, then topical therapy might be contemplated in these patients. But if it’s higher, then cessation of anti-TNF therapy needs to be discussed versus the risk of continuing medical therapy. And probably it’s time to get a dermatologist involved when this is the scenario. A lupus-like reaction with different serologies being positive is lower, less than 1% of individuals in general. And the issue is you don’t get lung involvement and there’s no kidney involvement in these individuals directly or CNS involvement. Antibodies may develop against any of the anti-TNFs, whether they’re fully human or partially human. Demyelinating disorders are higher as well. Individuals that have inflammatory bowel disease have a higher risk for optic neuritis and multiple sclerosis. We try to avoid anti-TNF therapy in individuals who have these disorders. It’s also been linked to congestive heart failure. In fact, in infliximab there is a study by Chung, et al in the journal Circulation that showed that people with class III/class IV CHF have a higher mortality. It was double the mortality of individuals that had been treated without anti-TNF therapy. And, as a consequence of such, it should be avoided in this general population. Liver toxicity has been defined as well. If you look at the studies that look at hepatotoxicity, most individuals recognize that they were on other agents that could be incited. But we certainly can’t exclude the potential that anti-TNF therapy itself has been the cause of such, so be careful.
Patients with multiple sclerosis had higher increased CSF TNF-alpha levels, and I would argue that anti-TNF therapy is contraindicated in patients with multiple sclerosis. Exacerbation or onset of multiple sclerosis, demyelination, and optic neuritis in people that have treatment with anti-TNF therapy has been described. In fact, one of the trials with one of the anti-TNFs not used in treating IBD—lenerecept—showed that there was more severe attacks of multiple sclerosis. So the concept is there and it makes logical sense.

Infections can occur with steroids. You’re seeing a patient in the hospital, the patient is postoperative and they have abdominal pain and fever, what are your thoughts? Of course infection, particularly if they’ve been on steroids. And our group published these data years back showing that individuals that have been treated with steroids have a postoperative infectious complication rate that is substantially higher than those individuals not on steroids. The treatment of patients with steroids has a 2-fold risk of serious infections based on data from the TREAT registry. And opportunistic infections have to be thought of as well in individuals on corticosteroids—a 3-fold risk based upon one large series. So again, when steroids are used and there are problems, think of infections.

Azathioprine and 6-MP on the other hand do not really have a substantially higher risk of infectious complications compared to that of
the general population. But it is something that in general we think of—viral infections. And the viral infection could be herpes zoster, for example, which should be thought of in people on immune modulators—azathioprine and 6-MP directly. So, in an effort to combat this, we vaccinate patients. If someone is treated with medical therapy and we know they’re going to be on an immune modulator in the future, or they’re on azathioprine less than 2.5 mg per kilogram or 6-MP less than 1.5 mg per kilogram and prednisone less than 20 mg a day, then you can initiate vaccination for zoster based on the American Society of the Infectious Diseases. We try not to use other live viruses in an effort to not have the diseases occur. So, for example, rotavirus is a live virus—not that many adults get rotavirus vaccine, but it’s something to consider. Other vaccinations, such as pneumococcal pneumonia, are important for anyone on an immune suppressant. For influenza, the nasal spray should be avoided given that’s a live virus, but the influenza vaccine is appropriate. Hep A and hep B, meningococcal, etc are the things we need to think about in an effort to potentially lessen future infectious complications in individuals.

Methotrexate is not widely used in people that have inflammatory bowel disease, but it is used and there are clear-cut side effects that need to be looked for. The common side effects are nausea, vomiting, rash, and alopecia. Folate helps lessen the nausea, the mucositis, and the diarrhea; and ondansetron before methotrexate injections is also helpful.
Sometimes taking these at nighttime can help, so if the patients then go to sleep they can get nauseous as they’re sleeping and not recognize this as much. Suppression of the bone marrow can occur, so monitor the CBC, the liver-associated chemistries as well. Hypersensitivity pneumonitis is a rare side effect. Patients get a baseline chest X-ray to look for this and then if they get short of breath, particularly when doing stairs or other exercise, they should call immediately, be placed on steroids, and stop using methotrexate. These are things that can come about, and the chest X-ray will show interstitial prominence directly.

Hepatic fibrosis and cirrhosis are described as well, and the general recommendations are check the ALT and the AST every 2 to 4 weeks. If the ALT or the AST are elevated greater than 50% of the time, after about a gram and a quarter, a gram and a half, then a liver biopsy is indicated to look to see if there’s any evidence for hepatotoxicity.

Hepatotoxicity risk factors are obesity, alcohol, and diabetes; and one might consider baseline biopsies in these particular groups of individuals. Monitor the dose accordingly, so if someone is on 25 mg subcutaneously once a week and they develop ALT/AST abnormality, one might need to drop down to 15 mg once a week directly. Screen for other abnormalities like hep B and hep C. Look on biopsy for the different gradations, and if it’s grade 1 toxicity where it’s steatosis, then individuals might be continued. It’s the fibrosis that’s clearly the concern. And not all people on long-term methotrexate need to have liver
biopsies. It’s an area of controversy and evolving, but in general we try to avoid it.

Now the pulmonary toxicity is such that about 2% to 7% of treated patients can get this, and there can be a multitude of different findings. Hypersensitivity pneumonitis is the most feared, but bronchiolitis obliterans organizing pneumonia (BOOP) can come about, interstitial pneumonia, pleuritis, and effusions. And the risk factors are patients that have diabetes, age over 60, have rheumatoid arthritis with pulmonary involvement, and a low albumin. It can present as a culture-negative pneumonia, a dry cough with dyspnea, abnormal pulmonary function tests, and subacute presentation, and you can get restrictive pattern decreased diffusing capacity and sometimes lung biopsy or bronchoalveolar lavage (BAL) is needed. Hold the methotrexate and consider steroids if it’s contemplated to be related to the drug.

So I think there are several take-home messages that we have when we look at medical therapy. Adverse events occur with every medication. And the old saying is “hurry up and use it” before we learn the side effects. I think this is something that we now recognize very well what the side effects are. The most serious adverse events are rare: lymphoma, multiple sclerosis, renal failure. But again look out for these. Generally the benefit of standard IBD therapy outweighs the risk, particularly if the patient responded to the therapy for active disease.
Now there are certain things we can do to minimize the risk. The risk can be minimized with monitoring and dosing. When someone is contemplating use of an anti-TNF, check a PPD, QuantiFERON® gold, and maybe a chest X-ray as well. I do all 3 in general because it’s better to be sensitive and detect someone has exposure to tuberculosis, but this is not necessarily recommended. And then if they’ve had prior TB, treat it with isoniazid, B₆. Additionally, check for thiopurine methyltransferase. I didn’t touch on 6-thioguanine (6-TG) nucleotides, but those are the metabolites we measure in people that have used azathioprine. And should we check these if the ALT and the AST are elevated? If the 6-TG is on the low side and the 6-methylmercaptopurine (6-MMP) is elevated, it suggests it’s an azathioprine-mediated hepatotoxicity. So treatment algorithms for mesalamine are to check your BUN, creatinine, and urinalysis. I do this initially at about 3 months and then once annually. And this of course varies. There are no standard recommendations as to how frequently to do it. For patients on azathioprine or 6-MP, get a CBC and a comprehensive metabolic every 3 months at a minimum. For methotrexate, get a CBC and CMP every 2 to 4 weeks. With anti-TNF therapy, check a TB status initially and check a QuantiFERON® gold or similar assay annually, and also check hepatitis B serologies. Now we don’t really understand the safety of medications until they’re marketed for many years, and this is part of the difficulty, we learn as we go.

Our case is a patient with a high potential for non-adherence: a 28-year-
old man with a 10-year history of ulcerative colitis with a flare of his disease who’s complaining of diarrhea, hematochezia, and abdominal pain. He’s been given mesalamine 2.4 grams a day, but he admits it’s hard for him to remember to take the midday dose. And this is a very common scenario. Twice daily or once daily dosing is easier to remember. Another case, a 45-year-old woman with ileocolonic Crohn’s for 5 years has abdominal pain and diarrhea, and despite being given azathioprine 2.5 mg per kilogram, check the TPMT initially prior to use of medication, and also check a thiopurine metabolite level. And, if there are low or undetectable levels of each metabolite, this could mean that the patient is malabsorbing the medication or more likely not taking medical therapy.

There is 40% to 60% adherence to mesalamine. Non-adherence is associated with disease flares. Susie Kane has shown this very nicely in mesalamine use. The risk factors are a psychiatric diagnosis of someone with depression, who has mail order medications, is female, younger age, and heavy pill burden. If the patient is single, he or she is less likely to be adherent; and the high cost of medical therapy also influences adherence. Once daily dosing has been shown to improve this. And the medications we have currently that are once daily are the mesalamine derivatives Apriso, Lialda, and Asacol-HD. And again, any medication once a day is easier to take than taken 3 or 4 times a day.
In a study looking at adherence and recurrence, 99 ulcerative colitis patients were in remission for over 6 months on mesalamine. Non-adherence is defined as less than 80% of the prescribed refills. There was 30% non-adherence to mesalamine. At 6 months 12% recurred, all of those were non-adherent. At 12 months it was 22%; 68% were non-adherent. So the risk of recurrence among non-adherent individuals was a relative risk of 5.5. If you stop medications, you’re likely to flare more so than if you’re adherent. And it makes common sense that this is the case.

Thiopurines have weight-based dosing according to the enzyme activity and can take 3 months or longer to become effective. So if you’re on an adequate dose and you’ve gone at least 3 months, then you’re not responding. One might consider dose escalation or check a 6-TG and a 6-MMP. High 6-TG levels result in a low white cell count and myelosuppression, and high 6-MMP could indicate hepatotoxicity. But if you have non-adherence, look for low levels of both. And these are things to consider when looking at adherence. Greater than 235 is generally considered to be a good response with the 6-TG. If it’s lower then this, something to consider is a dose escalation. But safety beyond 2.5 to 3 mg per kilogram is not well recognized. A 6-MMP less than 5700 is considered in the safer range, though just having a high 6-MMP in itself is not a danger. It’s the liver-associated chemistries we need to look at directly.
So the algorithm one might use to address non-adherence, inadequate dose, and a shunter as we described—so someone makes more of the 6-MMP versus the 6-TG—and we might consider either different medication or off-label use of allopurinol in this population to shunt them to make more of the 6-TG and benefit them. But with the advent of anti-TNF therapy, we’re less inclined to do so unless all other options are off the table. If the dose is too high for 6-TG and 6-MMP and they’ve gained a remission, then consider a dose reduction. And the goals are really 6-TG greater than 235 and 6-MMP less than 5700 directly.

So at this point in time I’d like to turn things back to Dr. Lashner and, Bret, if you could elucidate some of the health issues associated with inflammatory bowel disease that are not necessarily involving the GI tract.

Dr. Lashner: Thank you, Gary. Yes. An important point to understand is that inflammatory bowel disease is a systemic disease. There are many organs that can be involved and some with very serious consequences. I’d like to start off with a case. A 26-year-old man with Crohn’s disease describes multiple tender erythematous nodules on both shins that are associated with active disease. In other words, when he treats the bowel disease these nodules resolve. He also has chronic lower back pain and has been found to be HLA-B27 positive. So we’ll go over some of the
extraintestinal manifestations of inflammatory bowel disease and, in particular, how they might relate to this patient. Many different organ systems are involved in extraintestinal manifestations. Both peripheral arthritis and ankylosing spondylitis and sacroiliitis of the joints can be peripheral as well as axial. Pyoderma gangrenosum and erythema nodosum are the principal lesions of the skin, although there are others. Episcleritis, uveitis, and cataracts can all affect the eyes. In the hepatobiliary system, gallstones are mainly in Crohn’s disease patients with malabsorption, and sclerosing cholangitis can be in both Crohn’s and ulcerative colitis but principally is in ulcerative colitis. Patients with IBD are hypercoagulable, can have both venous and arterial thrombosis, and in renal disease interstitial nephritis as well as renal stones. But in general about a quarter to a half of patients will have extraintestinal manifestations of their IBD.

So let’s start off with the skin manifestations. Erythema nodosum is the most common skin manifestation. It can occur in Crohn’s disease more often than ulcerative colitis in up to 5% of patients, parallel disease activity, and occurs on the extensive surfaces of the extremities, usually the lower extremities. And you can see as many as 30 or 40 of these lesions at any one time. The very troublesome dermatologic manifestation is pyoderma gangrenosum, ulcerating lesions anywhere on the body, but again found mostly in the extremities. The examples are peristomal ulcerations of pyoderma gangrenosum and pyoderma...
gangrenosum of the face, a very disfiguring, troubling finding. These are destructive cutaneous lesions independent of disease activity. About 50% of patients need to be treated aggressively and, in fact, the anti-TNF agents have been shown to treat these lesions very well. Other skin lesions associated with inflammatory bowel disease are psoriasis, Sweet’s syndrome (otherwise known as neutrophilic dermatosis), and metastatic Crohn’s disease, granulomatous inflammation of the skin not in contiguity with the bowel.

The most common extraintestinal manifestation of IBD is musculoskeletal, namely peripheral arthritis, and can be seen in up to 15% of patients. The male-female ratio is one. It’s very different from rheumatoid arthritis because large joints are affected, it’s asymmetric, migratory, non-deforming, and non-erosive. The spondylitis seen in 1% to 26% of patients usually affects males more often than females and sacroiliitis can be diagnosed with both X-ray as well as a nuclear scan. A patient with axial arthritis characteristically has the bamboo spine and is seen in HLA-B27 positive patients. Kidney stones are another extraintestinal manifestation of inflammatory bowel disease.

There are many ocular manifestations that can occur either from the disease or from the treatment; for example, steroids can cause cataracts. But the one you need to worry about most is uveitis because if that is left untreated it can lead to blindness. These people will have photophobia, a
red eye, and decreased vision. They need to be treated immediately and ophthalmologists know this and will clear room on their schedule to see these people.

Thrombosis in IBD occurs anywhere from 1% to 6% of patients and mostly follows disease activity related to the inflammatory process. But it is multifactorial. Factor V Leiden deficiency has been associated with it, thrombocytosis from all the inflammation, and hyperhomocysteinemia from low folic acid levels are common problems in patients with inflammatory bowel disease. Increased anticoagulant antibodies as well as catheters all can lead to thrombosis and its sequelae.

Another fearsome complication of inflammatory bowel disease is primary sclerosing cholangitis (PSC). Once again, about 75% of patients with PSC will have ulcerative colitis and 25% of patients with PSC will have Crohn’s disease. There’s a 2 to 1 male prevalence. It can lead to cholangiocarcinoma and frequently leads to liver transplantation. Unfortunately, by transplanting the liver you have not cured the disease. The PSC comes back. Fatty liver, another extraintestinal manifestation involving the liver, as well as gallstones all can be part of the disease.

The risk of colorectal cancer in patients with colitis, either ulcerative colitis or Crohn’s colitis, is considered about 3 times what it is of the general population. And that risk arises relatively exponentially after 8 to
10 years of disease. The cumulative incidence by colitis duration is 2.5% after 20 years and 7.6% after 30 years. Risk factors include a family history for colorectal cancer, PSC, which triples the risk again on top of what you get for having inflammatory bowel disease, and patients with Crohn’s disease of the small bowel have an increased risk for small bowel cancer. There are also possible chemopreventive agents you should consider giving to your patients to minimize—not eliminate, minimize—their cancer risk, namely the mesalamine products, folic acid, ursodeoxycholic acid low-dose in patients who have PSC, and calcium. Surveillance colonoscopy is done every 1 to 3 years depending on their risk to detect dysplasia, a benign but premalignant lesion. And if dysplasia is detected, colectomy is recommended because the cancer risk is so high. The patients with the very highest risk of cancer, those with PSC, should have colonoscopies every year, while those with average risk inflammatory bowel disease can delay their surveillance colonoscopies to every 3 years.

And, Gary, you want to tell us about educating patients about their inflammatory bowel disease?

Dr. Lichtenstein: Sure. I think it’s very important to educate patients about inflammatory bowel disease so they can be very responsible and better caregivers for themselves. And if you look at some of the studies done most patients do not believe that they have the appropriate amount
of information at diagnosis. A study that looked at this showed 10% to 36%, at most a third, believed they had the appropriate amount of information. And we certainly have places where we can help people go to read. The Crohn’s Colitis Foundation, for example, is one of the national organizations that focuses on such. And there’s great educational material. Self-management is also a very important aspect of education. If we educate patients on how to self-manage, they help themselves improve. It entails giving them very clear goals, understanding the disease, giving them a plan of action to reduce the symptoms or to prevent disease activity; and it really entails a good patient-clinician relationship. So helping people understand things and when they should call you or when they should do things on their own is very important. We have patients that have active ulcerative colitis, they’re on oral mesalamine, they might add topical mesalamine therapy and then give a call just to say, “Hey, I’m having a flare.” And this is part of self-management. Shared decision making is all part of the aspects of care, and individual patients’ characteristics have to be taken into consideration. So someone that has more difficult-to-treat disease, it might be less appropriate to do so. But when we discuss things with patients it’s also important to take into account adverse events and educating them. If we don’t communicate well about the risk, then the individual patients will feel that they’re not going to take a medication. For example, if we talk about a risk of lymphoma, it’s important to put this into context. And when we discuss small numbers we have to
consider absolute versus relative risk. So the relative risk may be 10-fold but the absolute risk may be very small. And visual presentations are helpful. For example, saying 5 out of 100 patients experience a serious infection, it’s nice to show, as is illustrated by some work Corey Siegel did, that these are the numbers of patients that had the problem. So 95 out of 100 do well. And one can say it’s akin to the chances almost of winning the lottery. So if you say it’s 1 in a million and say that’s your chance of getting a side effect then people are more likely to consider its use. Additionally, it’s important not to use vague descriptions such as rare or common. Use various formats, graphs, and numbers. Show pictures. Use a common denominator for comparisons, not 1 in 10,000 and 4 in 100 and things of that nature because it confuses people. Absolute numbers are better than relative numbers because the absolute risk in the general population is often not known for individual patients. And don’t use 0.01%. It’s better to say 1 in 10,000 and individualize the estimates. I think these are all factors that really help people better understand when putting these in the correct context.

So I think we have several take-home messages from our discussion that Bret and I have tried to really stress. Diagnostic strategies can include clinical history, which is obviously one of the most important factors we do; but we have to back that up with blood tests, serologies, endoscopies, X-rays, and histology. Adverse events from different therapies that we’ve discussed should be reviewed and also monitored appropriately based
upon the frequency and the timing of occurrence. IBD is a systemic disorder. Ulcerative colitis and Crohn’s involve different organ systems, not just the gastrointestinal tract: the joints, the eyes, the skin, the kidneys, the hepatobiliary system, as well as the blood, a hypercoagulable state. And this is critical to keep in mind. We treat the individual, not the disease. As with any disorder and any patient care, a good patient-clinician relationship is paramount. It’s important for self-management. And we’d like our patients to help in their management because together we can achieve better goals. So I’d like to turn it back to you, Bret, to focus on some areas that might be of importance.

Dr. Lashner: Thank you, Gary. As you know, we practice in different regions of the country and I’d like to see your take on how some problems I’ve had difficulty treating you’d treat. I’d like to learn from you. For example, some of the most difficult problems patients with Crohn’s disease get are perianal fistulas and rectovaginal fistulas. What’s the approach you take to treat these patients?

Dr. Lichtenstein: I think the first thing is just to review—a fistula is obviously a communication from an organ to another organ, and it’s a tract. And perianal is from the bowel to the skin in the perianal region, and I think it requires first of all a multidisciplinary approach to treatment—radiologists, gastroenterologists, surgeons, IBD specialists, and nursing staff working together. And our true goals of treatment are
resolution of fistulas, the discharge, preservation of continence, avoidance of prostatectomy and a stoma if we can, and to drain an abscess if it’s present. So if someone has a fistula and it’s draining and it’s causing pain, then that signals that there’s potentially an abscess and we need to do a cross-sectional imaging study. We recognize that a CAT scan is good for the abdomen but an MRI scan is needed for the perianal region. So refer to and work closely with a GI surgeon, a colorectal surgeon, or the appropriate surgeon in your practice that can help to ensure this is drained. And non-cutting setons can be placed, antibiotics administered, and therapy initiated to seal these over. A low superficial or a low intrasphincteric fistula, in other words low down, not involving higher up, is a more complex scenario; this can be treated surgically and medical therapy might not be needed. However, if it’s more complex, then a combination of surgical and medical therapy is needed for the perianal approach. When we look at things such as enterocutaneous fistulas or rectovaginal fistulas or others, once again the multidisciplinary approach is needed. And something that I say that’s important is an acronym we tend to use, SNAP, s-n-a-p. This entails management of sepsis and skin care for the S, nutritional support, definition of anatomy of the intestinal tract, and development of a surgical procedure if it’s needed. We try to delay surgery until both local and systemic conditions have been optimized. It should not be the primary treatment directly, and if you have a fistula that is from a loop of bowel that’s inflamed and it goes into another organ, if it can’t be treated
aggressively with medical therapy then surgery has to be contemplated. 
And, recognizing that recurrence rates are high after surgery, appropriate 
medical therapy is important as well.

Dr. Lashner: That’s terrific. Let’s just assume that you have all the sepsis 
drained, the setons in, and you’re deciding on medical therapy. I guess 
you can change it now to SPAM, right, s-p-a-m or something? And what’s 
your favorite medical therapy for people with aggressive or severe 
perianal Crohn’s disease?

Dr. Lichtenstein: Usually we like to use anti-TNF therapy alone or in 
combination with immune modulators. Mesalamine derivatives don’t 
truly work and antibiotics such as a cipro- or a levofoxacin-like 
antibiotic and metronidazole are effective to lessen the acute 
inflammation, but not a long-term strategy. We try to avoid giving 
corticosteroids because these can potentiate inflammation and 
abscesses. And immune modulators alone are effective in some but not 
quite as effective as the anti-TNF therapy. And these are the agents that 
we try to use, recognizing about a third at a year will have some benefit 
based on some retrospective and prospective studies that have been 
looked at in this population.

Dr. Lashner: And people actually get worse if the sepsis is not drained 
properly. Small infections in the perianal area will turn into big ones and
make it very much more difficult to treat. Let’s move on, Gary, to drugs that are safe to use in pregnancy and breastfeeding. Anything we need to avoid here or use preferentially?

Dr. Lichtenstein: So I think the main thing, Bret, that we try to avoid is category X, and methotrexate is the big one in pregnancy. It’s category X, it is an abortifacient, so it’s something we try to avoid. Mesalamine in general is safe, and most of them are class B, in other words safe in pregnancy. Steroids are class C. They’re known to be associated with cleft lip or cleft palate and premature rupture of the membranes, but if we need to use them then we use them. It’s based upon the severity of illness. The old saying is the punishment needs to fit the crime. If the patient has active disease it’s more impressive to get that disease into a state of remission, and steroids work rapidly so we use that and we try to avoid them in the first trimester during which time organogenesis is occurring. Antibiotics in general are safe, such as amoxicillin; again, metronidazole is safe. Certain others we try to avoid, the fluoroquinones, given they can affect cartilage development, so we try to avoid those early on. The anti-TNFs are an interesting class B in treating patients directly. There are also data through a meta-analysis that suggests azathioprine or 6-MP, though they’re labeled as class D, are not teratogenic necessarily in human fetuses; but they are associated with a lower birth weight and earlier delivery of the babies when treatment is initiated. And the latest medication that has gained regulatory approval is vedolizumab,
which is a small adhesion molecule inhibitor. And this is something that is class B in pregnancy as well. So we have several different agents available, and we try not to use medications that are new in general if we don’t have to. However, it’s better to be in a state of remission because about 80% of women that have disease that is in remission at the time of conception will remain at that state in remission. If you have active disease, we generally say try not to conceive because it can be problematic. So a state of remission is the best thing to have when trying to conceive.

**Dr. Lashner:** Let’s keep at this for a little bit. There have been some recent studies of the anti-TNF agents that show just by the design of these molecules infliximab, adalimumab, cross the placenta and babies that are born to mothers on these medications are born with these anti-TNF agents in them. Certolizumab does not. Is this a reason to use, let’s say, certolizumab in a pregnant woman? Or should you change the timing of infliximab use so that they don’t get it in the third trimester when these antibodies cross the placenta? What do you do in women on anti-TNF who are pregnant?

**Dr. Lichtenstein:** So initially that was a concern, given that these do cross and get into the baby’s circulation. And there were some initial highlights of this being an issue. But when looked at more recently it’s not been as much of an issue. The PIANO study by the Crohn’s Colitis
Foundation compared the outcome of individuals exposed to thiopurines and anti-TNFs, and it reinforced the claim that therapy in pregnancy didn’t lead to any adverse event, whether it be fetal or maternal outcomes. And exposure to anti-TNF alone didn’t yield any higher rates of low birth weights, rate of cesarean sections, or neonatal ICU care stay directly. So this is something that was initially of concern because of a case report of a baby that had infectious complications, but there have been other side effects looked at in rheumatologic literature as well that reinforces the general safety.

**Dr. Lashner:** I’m still wary of anti-TNF agents circulating in a newborn’s blood when you know they don’t have their own antibodies to control infections. I think if there are alternatives like certolizumab or delaying infliximab to not be given in the third trimester, you should think about doing that maybe more than you are.

**Dr. Lichtenstein:** Interesting. Uma Mahadevan has just recently presented data. She’s at UCSF and has an interest in this. And she looked at immune responses of infants of IBD mothers exposed to infliximab in utero including those exposed during the third trimester, and all infants got the standard 6-month vaccine course and they mounted appropriate IgG and IgA responses. The mean age was 13 months, and the range was anywhere from 6 to 28. A suppressed IgM response was noted in 4 infants. So all patients mounted appropriate
responses to tetanus and 7 of 8 to H flu vaccine. So the question is: is this something of concern in these 4 that did not? But there was no abnormal response to pneumococcus and H flu, so one could argue that there is some response that’s being knocked down, if you would, because of this. These are small numbers so far, and I think appropriate caution should be taken in individuals and not be cavalier, and to discuss this with women directly. And one would prefer not to have immunogenicity develop when stopping medical therapy, nor a flare of disease.

**Dr. Lashner:** I agree. We need to be cautious especially in this population.

**Dr. Lichtenstein:** Yes.

**Dr. Lashner:** How about breastfeeding? Is there anything we should know or avoid about breastfeeding?

**Dr. Lichtenstein:** Well we recognize that infliximab and adalimumab have very low concentrations in breast milk of exposed women based upon some recent studies. Shomron Ben-Horin in Tel Aviv had shown us that information, but the fact that large molecules are broken down by enzymes in the gut before being absorbed is something we recognize and this further reduces the chance of affecting the neonate on ingesting breast milk. So the anti-TNFs, in my opinion, are not of concern.
Dr. Lashner: I agree. I'm more worried about the thiopurines.

Dr. Lichtenstein: To date these have not been shown to be transferred in breast milk at any large level. The issue is: are low levels of concern? And I think the answer is not out yet. But again use cautiously. There are reports of babies getting mesalamine from mothers through the breast milk. There are reports of diarrhea in the babies, so if the baby gets diarrhea one could then stop breastfeeding. But these are rare and few reports in the medical literature.

Dr. Lashner: Okay. Very good. Medical therapy doesn’t always work in patients with inflammatory bowel disease. Another issue to address is surgery in patients with ulcerative colitis. I talked about the patient who presents with fulminant disease, more than 10 bowel movements per day, anemia, high sedimentation rate, distended abdomen, abdominal pain. These people are not going to do well with medical therapy. In fact, at surgery about 10% of these people are already perforated. Their colon is like wet tissue paper and they’re just not going to regain any function from their colon. So they need immediate surgery. Other indications are disease refractory to medical therapy. You give them all the agents Gary talked about and it just doesn’t work. Exsanguination, of course, if you’re bleeding too much and the transfusions can’t keep up with it; prednisone dependence, the side effects of long-term prednisone use are
much worse than the adverse effects of colectomy. And then the last one I touched on, cancer or dysplasia. People who have cancer or are at very high risk of developing cancer in the near future should be considered for colectomy. Am I missing something there, Gary?

Dr. Lichtenstein: I think those are the major ones. Occasionally there will be patients that we see that say they don’t want to take the potential risk of medical therapy and their quality of life is adequately impaired by disease, so I guess impaired quality of life is another one that we can consider. And I think that’s paramount to all of these, except for the dysplasia/cancer. Many times people are asymptomatic.

Dr. Lashner: I agree with that. We have between a half a dozen and a dozen patients a year who are just fed up with the disease, not considered relatively refractory to therapy, but they just don’t want to do the struggle anymore and are asking for colectomy. And that’s a fine indication I think.

Dr. Lichtenstein: I would agree.

Dr. Lashner: You really don’t want to operate on a patient with Crohn’s disease because you’re not curing the disease. The disease pretty much always comes back. So what’s your approach to sending someone to the surgeon with Crohn’s disease, Gary?
Dr. Lichtenstein: So it all depends on the scenario. If you have someone that has obstructive symptoms you, always want to investigate and see if it is due to a stricture that’s fibrotic or if it is due to active inflammation. If it’s due to active inflammation, I would argue it’s perhaps best to consider continued medical therapy. Because as you point out, Bret, the disease often will recur. So the stricture with obstructive symptoms is truly an appropriate indication. Another scenario might be the individual who comes to see you, has had treatment with various different medications, perhaps 2 anti-TNFs, an immune modulator or a combination, and they have persistent disease activity. And you could even throw in that they’ve tried something recently such as vedolizumab and they don’t respond. So I think refractory disease with quality of life impairment that is such that the appropriate course is surgery—now it is important to say with Crohn’s disease it can affect the small bowel in a significant number of patients. So if someone has 3 feet of small bowel disease, one is less inclined to consider operation and would mostly try to exhaust medical therapy before trying to go to surgery. But again treatment might include strictureplasty. So specific things to preserve the bowel, if there are just strictures present in the bowel. But if it’s a 2-cm area in the ileum and it’s a young male that’s had 15 years of disease with minimal inflammation and he has not responded to a couple of agents, one might try surgery at that point. So it has to be looked at with the individual scenario. Hemorrhage, perforation, and abscesses are all
indications as well. And once again dysplasia/cancer is a factor because people that have colonic Crohn’s have a higher risk of colon cancer and they need to undergo surveillance. So if you’re an internist in the office and you see someone that has 8 years of Crohn’s disease involving more than a third of the colon, disease could be active or inactive; that person needs to follow up with their gastroenterologist or their colorectal surgeon or whomever is doing their colonoscopies and get a surveillance colonoscopy to be sure that they’re not getting dysplasia, because dysplasia can be something that predates the development of carcinoma.

**Dr. Lashner:** You’re ready to give an anti-TNF agent to a patient, they’re PPD positive, and you mentioned that they should be on INH. For how long? They’ll be treated for about 9 months, but when can you safely give the anti-TNF agent?

**Dr. Lichtenstein:** So this is an area of concern. And the main issue is making sure that they’re not getting INH-related hepatitis and they tolerate medication. There are some groups of individuals, the Thoracic Society and other pulmonary societies, that suggest 2 to 3 months at a minimum. And that’s been my standard practice, to wait to see and to monitor liver-associated chemistries directly. Because you don’t want to have that person on an anti-TNF and suddenly the tolerance for the INH is not good, and they then can’t take the INH. This is a population to worry about TB reactivation.
Dr. Lashner: Patients with hepatitis B surface antigen positivity are at risk for reactivating hepatitis B and getting fulminant hepatic failure. I believe there have been 4 cases that have been described. What do you do with those people?

Dr. Lichtenstein: I think what you really want to do is to see are they acutely infectious? There are various combinations of hepatitis B surface antigen positivity. You want to look at the core, you want to look at the surface antibody, and then if so you can prevent reactivation by different agents. Lamivudine, for example, has been used to look at this. And you want to refer them to someone who’s experienced with hepatology. In other words, the hep B nucleosides are examples of agents that should be used directly in an effort to lessen that this will reactivate. Fulminant failure is something that is a major concern.

Dr. Lashner: I agree. And we’re pretty much exclusively using the nucleoside/nucleotide agents for hep B in those that are positive. Should people on anti-TNF, or actually people on any of these agents you’ve talked about, be prophylaxed for *Pneumocystis*?

Dr. Lichtenstein: I think this is something that’s a relatively uncommon infection, but you think of it mostly when you have triple immune suppression, including steroids. So examples might be an anti-TNF, an
immune modulator, and steroids because occasionally an individual will have this occur. Sulfamethoxazole, a sulfa combination, or dapsone if they’re sulfa allergic can be used to prophylax against *Pneumocystis jiroveci* infection. It’s again uncommon but it can be rather debilitating. And I’m sure you have seen it as I have.

**Dr. Lashner:** Oh it can be debilitating is right. The prophylaxis is not difficult. It’s just a few cheap antibiotic pills a week. There’s no reason not to. And I’ve been doing that lately.

**Dr. Lichtenstein:** Agreed.

**Dr. Lashner:** So, Gary, I learned an awful lot from you. Thank you very much for participating. I certainly enjoyed participating myself. Any final words?

**Dr. Lichtenstein:** I think it was very educational for me as well, and I’m hoping this is of value to practicing practitioners who see patients with inflammatory bowel disease. These are not rare diseases. These are diseases that are rather common, and the medications used and the clinical scenarios we described are seen nearly daily in clinical practice.

**Dr. Lashner:** Well thank you.