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Virtual IBD Clinic: Diagnosis and Medical Treatment



Narrator:

Welcome to CME on ReachMD. This activity, entitled "Virtual IBD Clinic: Diagnosis and Medical Treatment" is jointly provided by Postgraduate Institute for Medicine, the Crohn's & Colitis Foundation, and RMEI Medical Education, LLC. This activity is supported by educational grants from AbbVie Inc., Celgene Corporation, a Bristol Myers Squibb company, and Takeda Pharmaceuticals U.S.A., Inc. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the Learning Objectives.

Dr. Afzali:

Slide 1: Virtual IBD Clinic: Diagnosis and Medical Treatment

Hello, I am Dr. Anita Afzali and I am a gastroenterologist at the Ohio State University Wexner Medical Center and also the medical director of the Ohio State University Inflammatory Bowel Disease Center.

In this CME activity, I will be discussing the clinical case of a newly diagnosed IBD patient, as well as principles and guidelines for the diagnosis and medical management of inflammatory bowel disease.

Slide 2: Jack – History of Present Illness

So, here is a clinical case. Jack is a 23-year-old male college student with no past medical history, who presents for evaluation of weight loss, abdominal cramps, and non-bloody diarrhea for 3 months. He also complains of mouth sores, joint pain, and anal pain with defecation.

His symptoms started about 3 months prior to this visit. Originally, he was told by his primary care physician that he probably had irritable bowel syndrome. However, over the past month, his symptoms progressed, including a 30-lb weight loss.

Slide 3: Jack – Family and Social History

Jack's family history is significant for his mother with rheumatoid arthritis and his uncle with celiac disease. He denies a family history of inflammatory bowel disease. He is a college junior who denies smoking, alcohol, or other illicit drug use. He denies any recent travel, camping, or drinking well water.

Slide 4: Jack – Physical Examination

His physical exam is significant for the following: he is a thin male in no significant distress; vital signs are stable with a blood pressure of 120/80; a pulse of 90; a respiratory rate of 18. His head and neck exam is unremarkable for the exception of several aphthous ulcers in the buccal mucosa and gum line; his sclera are anicteric. His abdomen exam is tender to palpation in the midepigastic, left upper quadrant, and both lower quadrants. On perianal exam, there is severe rectal tenderness, large skin tags, large visible ulcer in the anal canal, and no masses or hepatosplenomegaly.

Slide 5: Challenge Question

Given Jack's presentation, which of the following would not be part of an initial routine diagnostic testing? So, this is a Challenge Question. (A) Labs, including CBC, ESR, CRP, fecal calprotectin; (B) Ileocolonoscopy with biopsy; (C) Small bowel imaging with CT enterography; or (D) Deep enteroscopy.

The correct answer is (D) Deep enteroscopy. Jack's clinical presentation is consistent with Crohn's disease. In order to confirm the diagnosis, the initial work-up should include a CBC, ESR, CRP level, as well as a fecal calprotectin. An ileocolonoscopy with biopsy, small bowel imaging with either a CT enterography or MR enterography is indicated. A deep enteroscopy is not part of routine diagnostic testing in suspected cases of Crohn's disease.

Slide 6: Jack – Labs and Radiography

So, let us go back to Jack's clinical presentation and let's look at his blood work. His blood work reveals an elevated CRP of 4, an ESR at 97, and an elevated fecal calprotectin at 350. His stool tests are negative for *C. difficile*. His colonoscopy revealed perianal skin tags, multiple ulcers in the anus, rectum, and sigmoid, as well as descending colon. Biopsies revealed patchy, severe, chronic active colitis with non-necrotizing granuloma and stain negative for CMV. The CT enterography revealed thickened segments of the distal and terminal ileum and the entire colon.

Slide 7: Commentary on Jack's Case

Based on the results of Jack's endoscopies, the biopsies, which showed deep ulcers in the colon with anal involvement and presence of granulomas, an elevated CRP level, calprotectin elevated as well, and ESR also elevated, in the absence of infectious etiologies, his diagnosis is Crohn's ileocolitis.

His severe Crohn's disease is likely to develop complications or require surgery unless early appropriate medical therapy is initiated for his aggressive disease phenotype.

The treatment options for Jack include, induction with steroids, an immune modulator, such as thiopurine or methotrexate, biological therapies, or even a combination of biologics with an immune modulator. If Jack does not respond to the initial treatment, the options may include surgical intervention if he continues to have, for example, fibrostenotic disease.

Slide 8: Diagnosis of Inflammatory Bowel Diseases

Now, I will discuss some very important considerations in the diagnosis of IBD.

Slide 9: First Goal of Management in IBD: Obtain a Clear and Accurate Diagnosis

When considering a diagnosis of IBD in Jack or any patient with gastrointestinal symptoms, it is most important to obtain a clear diagnosis, one that explains the patient's current symptoms, provides prognostic information, and makes a distinction in management decisions such that therapy chosen now affects both the short-, as well as the long-term outcome. There is a need to differentiate disease activity, which takes into account how sick the patient is today or how is a patient doing at their initial presentation in the short-term, compared to disease severity, which includes prognostic factors, long-term assessment, and risk for disease progression.

### Slide 10: Clinical Diagnosis of IBD

It is important to ask all patients when they initially present, to help you make the clinical diagnosis of IBD, a few questions. First of all, how did the symptoms start? What does the patient mean by diarrhea, abdominal pain, or bleeding? Could they quantify it? Always consider red flags, such as nocturnal symptoms, weight loss, and anemia. It is important to ask about a family history of IBD or other gastrointestinal disorders, as well as extraintestinal manifestations, which should include the skin and the eyes. Always do a full and complete examination, looking for abdominal masses or perianal disease.

### Slide 11: Clinical Features

There are some clinical features that differ between ulcerative colitis and Crohn's disease. In ulcerative colitis, there's continuous inflammation involving the colon only. In Crohn's disease, there is patchy inflammation and this inflammation could be anywhere from the mouth to the anus. The pathology in ulcerative colitis is superficial inflammation, whereas in Crohn's disease the inflammation is full thickness. Fistulas and strictures are characteristic of Crohn's disease and the risk of cancer is in both colon and small bowel. In ulcerative colitis, the risk of cancer is the colon alone. Extraintestinal manifestations can be seen in both ulcerative colitis and Crohn's disease.

### Slide 12: Considerations in the Differential Diagnosis of IBD

The differential diagnosis of IBD includes, irritable bowel syndrome or IBS, microscopic colitis, infectious colitis, such as *C. difficile* or CMV, drug-induced enterocolitis in the appropriate patient, a solitary rectal ulcer syndrome, diversion colitis, or radiation colitis, again in the appropriate patient. Women of childbearing age, you should consider endometriosis. Malignancy and diverticular disease should all be in your differential diagnosis.

### Slide 13: Refining the Diagnosis in IBD

In refining the diagnosis in IBD, there are several studies that should be used to establish this. This includes an ileocolonoscopy, fecal calprotectin, which is often useful to make a distinction between IBS and IBD, an expert pathologist or a reliable pathologist to review your biopsies, evaluation of the small bowel with either a CT enterography or an MR enterography, or as needed, a wireless capsule endoscopy. For patients with perianal symptoms, a perianal disease on initial examination, as well as examination under anesthesia, is often necessary. And, in the patient with recurrent small bowel obstructions, for example, sometimes even an exploratory laparotomy may be necessary, although this is rare. And other clues, such as family history or even serologies, may be useful in the appropriate patient.

### Slide 14: Importance of Accurate Colonoscopy and Upper Endoscopy in IBD

A colonoscopy and upper endoscopy are of the utmost importance in IBD. Indeed, the first colonoscopy is the most important and should include assessment of the ileum and colon. Evaluation of the ileocecal valve and biopsies of both normal and abnormal areas. An upper endoscopy is useful for identifying upper tract disease that could be suggestive of Crohn's disease.

### Slide 15: IBD Diagnostic Algorithm for First Presentation

Here is an IBD diagnostic algorithm for the first presentation, for Jack's presentation. The labs should include a CBC, CRP, LFTs, albumin, and stool studies should be ordered first. We could also include an iron panel here for the appropriate patient. Upper and lower endoscopy with duodenal and ileal and colonic biopsies should be performed. If these are suggestive of Crohn's disease, staging should be done with small bowel imaging, either a CT scan or an MR enterography, or even a small bowel follow-through. If the endoscopy is normal, small bowel imaging with the CT, MRI or small bowel follow-through should be done. If that is normal, a capsule endoscopy should be performed. All should be done for the high-risk patient or the patient where there is a high predictive value or probability for Crohn's disease.

### Slide 16: Mayo Score for Assessment of Ulcerative Colitis

This slide depicts the Mayo Scoring System for the assessment of ulcerative colitis. Recall that here the inflammation is of the colon alone, the mucosal appearance at endoscopy is graded in the score of 0 to 3, with 0 being normal or an inactive disease, and 3 being severe disease. So here, the Mayo Score is used and could be used at the time of your colonoscopy.

### Slide 17: Simple Endoscopic Score (SES) for Crohn's Disease

For Crohn's disease, this slide depicts the Simple Endoscopic Score or SES. The values range from 0 to 3, based on size of ulcers, ulcerated surface, affected surface, and presence of stenosis. This score is based on 5 segments: the ileum, the right colon, the transverse colon, the left colon, and the rectum.

### Slide 18: Making the Diagnosis

The diagnosis of IBD is dependent upon a careful history and physical examination in combination with the clinical, radiographic, endoscopic, and histologic findings described.

### Slide 19: Challenge Question

Turning again back to our patient Jack. So, given that Jack has moderate-to-severe Crohn's disease, which of the following is the most appropriate initial therapy? (A) Oral mesalamine; (B) Azathioprine; (C) Vedolizumab; or (D) Cyclosporine.

The correct answer is (C) Vedolizumab. For patients with moderate-to-severe Crohn's disease and active inflammation, anti-integrin therapy with vedolizumab can be considered for induction of remission. Oral mesalamine, azathioprine, and cyclosporine should not be used for induction of remission in Crohn's disease.

### Slide 20: Medical Management of Inflammatory Bowel Diseases

Now, I will discuss some very important considerations in the medical management of IBD.

### Slide 21: Goals of Therapy for IBD

There are several key goals of managing IBD and this includes both for induction and maintenance of remission. We need to restore and maintain nutrition, achieve mucosal healing, minimize complications, enhance the quality of life for our patients, and avoid colectomy. We need to be able to select the optimal therapy in order to avoid the surgery but, recognizing that sometimes we may not be able to avoid surgery in some patients.

### Slide 22: Sequential Therapies for Ulcerative Colitis

There are several considerations for sequential therapies, induction, and maintenance for ulcerative colitis. Therapy for ulcerative colitis is step up, so to speak, according to the severity at presentation or non-response at a prior step. For mild disease, aminosalicylates can be used for both induction and maintenance. For moderate ulcerative colitis, corticosteroids can be used for induction and aminosalicylates or thiopurines can be used for maintenance. For moderate-to-severe disease, there are a variety of options for induction, including anti-TNF agents, cyclosporine in the appropriate patient, or tofacitinib, which can be used for patients with moderate-to-severe ulcerative colitis, who have had an inadequate response to, or are intolerant of TNF blockers. However, it should not be combined with azathioprine or cyclosporine or used in combination with other biologics for ulcerative colitis.

Vedolizumab, which can be used for patients with moderate-to-severe ulcerative colitis who have had an inadequate response with, loss of response to, or are intolerant of TNF blockers or immune modulators, or they did not respond to, or have become dependent on corticosteroids.

Ustekinumab can also be used for induction and maintenance of therapy.

For moderate-to-severe disease, the options for maintenance include, anti-TNF agents, thiopurines, tofacitinib, vedolizumab, or ustekinumab.

And of course, colectomy should be considered in circumstances where medical therapy is not working or in cases where there is a clear need for surgery.

### Slide 23: Therapeutic Approach for Crohn's Disease

When considering the therapeutic approach for Crohn's disease patients, therapeutic selection should be based on disease phenotype, disease severity, and prognostic factors. If the patient is at a high risk for disease progression, early appropriate therapy with biologics is warranted in order to achieve mucosal healing and perhaps change the natural progression of their disease.

### Slide 24: Aminosalicylate (5-ASA) Drugs

Now I would like to discuss the individual drug classes used to treat IBD patients, beginning with aminosalicylates or 5-ASA drugs.

These are oral therapies and aminosalicylate is first-line therapy for induction and maintenance of remission in mild-to-moderate ulcerative colitis.

It is important to treat the release of medication to the site of active disease. For the colon, sulfasalazine or balsalazide or olsalazine. For the terminal ileum, delayed release mesalamine. For the duodenum, ileum, and colon, controlled release mesalamine formulations can be considered.

The aminosalicylates are associated with a low incidence of serious side effects. The major ones are agranulocytosis, pancreatitis, and interstitial nephritis.

### Slide 25: Corticosteroids

The next drug class for IBD are corticosteroids. For patients with moderate-to-severe active ulcerative colitis or Crohn's disease, oral steroids are usually effective and may be used alone or with an aminosalicylate for ulcerative colitis. For patients who do not respond to oral steroids, it may be necessary to administer steroids rectally or for severe and extensive disease, intravenously. Controlled-release budesonide is used for mild-to-moderate Crohn's disease that is confined to the ileum or the right colon. Budesonide is gut-selective, so it has a better safety profile than traditional corticosteroids do, but it can cause headaches, respiratory infections, and nausea, along with other steroid-associated side effects.

Steroids should not be given long term for maintenance therapy because they are associated with a relatively high risk of serious adverse effects, as listed below. These can involve nearly every major body system, including adrenal suppression, cataracts, glaucoma, cognitive impairment, psychosis, hypertension, serious infections, myopathy, osteoporosis, and pseudotumor cerebri.

Some of these toxicities are insidious and/or potentially irreversible, so steroid therapy requires careful monitoring. When prescribing steroids, you should always consider your next treatment step, in other words, steroids should be a bridge to what, what next.

### Slide 26: Immunomodulators

Now, turning on to immune modulators. Azathioprine and 6-mercaptopurine are collectively known as thiopurines. These oral drugs can be used to maintain remission in ulcerative colitis and Crohn's disease of any severity. They have a slow onset of action, so they are often given with a steroid. Serious side effects include, pancreatitis, allergy, bone marrow suppression, liver toxicity, serious infections, lymphoma, and non-melanoma skin cancer.

Methotrexate, given intramuscularly or subcutaneously or orally, is used to induce and maintain remission in Crohn's disease. Its' serious side effects include bone marrow suppression, acute and chronic liver toxicity, serious infection, nephrotoxicity, and severe dermatologic reactions. It is teratogenic and it is absolutely contraindicated during pregnancy.

Cyclosporine can be used intravenously in high doses as rescue treatment for acute, severe, steroid-refractory UC.

None of these immune modulators are FDA approved for treatment of ulcerative colitis or Crohn's disease.

Slide 27: Anti-TNF Therapies for Moderate-to-Severe IBD

Turning now to anti-TNF therapies for moderate-to-severe IBD. For treatment of ulcerative colitis and Crohn's disease, the FDA has approved 4 anti-TNF drugs, which have similar efficacy and safety profiles. Adalimumab and infliximab are approved for the treatment of Crohn's disease and ulcerative colitis. Certolizumab pegol is approved for the treatment of Crohn's disease, and golimumab is approved for the treatment of ulcerative colitis.

The delivery routes of these drugs differ. Infliximab must be injected intravenously, whereas adalimumab, golimumab, and certolizumab pegol are given subcutaneously.

Slide 28: Safety Issues with Anti-TNF Therapy: Rare but Serious Side Effects

There are some rare but serious side effects of anti-TNF therapies. All anti-TNF therapies approved for ulcerative colitis or Crohn's disease carries a black box warning for serious infection and malignancy. And this is, to also remember, melanomatous skin cancers as a risk.

Use of anti-TNF agents may increase the risk of reactivation of hepatitis-B virus in patients who carry the virus. The risk of skin cancer and psoriasis is also increased in patients who receive TNF antagonists. Patients receiving regular therapy with an anti-TNF agent may develop an immune response that can lead to allergic reactions and even a loss of response. Very rarely a lupus-like syndrome may occur. Demyelinating disease has been seen in patients receiving TNF antagonists. Patients treated with an anti-TNF therapy have an increased risk of worsening congestive heart failure, as well as new onset heart failure. Patients are also at increased risk of liver toxicity.

Slide 29: Natalizumab and Vedolizumab

Turning now to the integrin receptor antagonists, natalizumab and vedolizumab.

Natalizumab and vedolizumab are humanized monoclonal antibodies that target alpha-4 integrins and the alpha-4-beta-7 integrin, respectively. Vedolizumab appears to be gut-selective and does not seem to induce systemic immune suppression. Natalizumab is indicated for inducing and maintaining clinical response and remission in adult patients with moderate-to-severe active Crohn's disease and with evidence of inflammation who have had an inadequate response to or are unable to tolerate conventional Crohn's disease therapies and inhibitors of TNF antagonists. But, I will say natalizumab is no longer commonly used. And, this is because vedolizumab is now available. Vedolizumab is indicated for adult patients with moderate-to-severe active ulcerative colitis or Crohn's disease, who have had an inadequate response with, loss of response to, or were intolerant to a TNF blocker or immune modulator. Or, had an inadequate response or intolerant or dependent on corticosteroids.

Natalizumab carries a black box warning of PML or progressive multifocal leukoencephalopathy, which is a life-threatening condition that is caused by the JC virus. No cases of PML have been observed in clinical trials of vedolizumab, but an increased risk of PML cannot be ruled out. It is now possible to assess a patient's likelihood of PML by testing for the JC virus. But even so, patients on natalizumab or vedolizumab should be monitored closely.

These drugs should not be combined with each other or with an anti-TNF agent, and natalizumab should not be combined with an immune modulator.

Slide 30: Ustekinumab

Now turning to ustekinumab. Ustekinumab is an anti-p40 monoclonal antibody that inhibits binding of interleukin-12 and 23 to their respective receptor complexes. It is indicated for moderately-to-severe active Crohn's disease or ulcerative colitis. Some possible serious events include, infection, tuberculosis, malignancies, non-infectious pneumonia, and one rare report of reverse posterior leukoencephalopathy or also known as RPLS. This is not PML. RPLS is a rare and potentially fatal syndrome characterized by headache, confusion, and seizures.

Slide 31: Janus Kinase Inhibitors

Now turning to the Janus kinase inhibitors. Tofacitinib is an oral, small molecule inhibitor of JAK1, 2, and 3. It is approved for adults with moderate-to-severe ulcerative colitis, who are intolerant or failed anti-TNF therapy. Other JAK kinase inhibitors are listed below, including filgotinib, upadacitinib, and others as listed.

Slide 32: Biosimilars

The final drug class that I would like to discuss are biosimilars. Biosimilars are a similar copy of an originator biologic therapy. There are no comparative studies in IBD, so the data have been extrapolated mostly from rheumatology studies, including bioequivalence to the originator biologic for approved biosimilars in the United States. And, clinical response and efficacy have been confirmed in clinical trials in rheumatology.

Preliminary data supports the interchangeability of biosimilars and originator anti-TNF therapies. However, more data is needed for switching and interchangeability is not currently FDA approved.

Safety profiles are consistent with the originator biologic.

Slide 33: Biosimilars for IBD

There are several biosimilars for IBD as listed here and each of these I have described and listed are indicated for adult and pediatric Crohn's disease and ulcerative colitis patients, as listed, and many other biosimilars are now available.

Slide 34: IBD Treatments Summary

So, to summarize, inflammatory bowel disease therapies include the 5-ASA agents, which are effective and safe for induction and maintenance of remission in patients with mild-to-moderate ulcerative colitis. Systemic and conventional corticosteroids are effective inductive agents in ulcerative colitis and Crohn's disease. They are not used for maintenance therapy because they can be associated with a range of serious side effects as discussed. The immune modulators most often used to treat ulcerative colitis and Crohn's disease are azathioprine, 6-mercaptopurine, methotrexate, and cyclosporine in the appropriate patient. Anti-TNF agents, vedolizumab and ustekinumab, are effective for induction and maintenance of remission in patients with moderate-to-severe IBD. The role of biosimilars needs further exploration. Earlier use of biologics in Crohn's disease, and possibly severe ulcerative colitis, may improve outcomes for our patients. Surgery is not a failure of treatment. It is sometimes a necessary component of the treatment of both ulcerative colitis and Crohn's disease.

Slide 35: Thank you!

I thank you for participating in this CME activity. Please do not forget to take the post-test and complete the evaluation to receive CME credit. Thank you.

Narrator:

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