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# Virtual IBD Clinic: Updates in Diagnostic, Therapeutic, and Prognostic Strategies

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**Dr. Sushila Dalal:**
**Slide 1: Virtual IBD Clinic: Updates in Diagnostic, Therapeutic, and Prognostic Strategies**
Hello, I'm Dr. Sushila Dalal and I'm a gastroenterologist at the University of Chicago. In this CME activity I'll be discussing the clinical case of a newly diagnosed IBD patient, as well as principles and guidelines for the diagnosis and medical management of IBD.

**Slide 2: History of Present Illness**
We'll first start with the 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: 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 IBD.

He's a college junior who denies smoking, alcohol, or illicit drug use. He denies any recent travel, camping, or drinking well water.

You can see here his height is 5'11" and his weight is 145 lbs.

**Slide 4: Physical Examination**
His physical exam is significant for the following. He's a thin male in no distress, he has a blood pressure of 120/80, a pulse of 90, and a respiratory rate of 18. He's sclera anicteric, he has several aphthous ulcers in the buccal mucosa and at the gum line. His abdomen is tender to palpation in the midepigastric, left upper quadrant, and both lower quadrants.

On perianal exam he has severe rectal tenderness. He has very large skin tags and he has a large, visible ulcer in the anal canal. No masses or hepatosplenomegaly.

**Slide 5: Challenge Question**
So we'll have a challenge question. Given Jack's presentation, which of the following would not be part of his initial routine diagnostic testing? **A,** labs, including a CBC, ESR, CRP, and fecal calprotectin; **B,** ileocolonoscopy with biopsy; **C,** small bowel imaging with CT enterography; or **D,** deep enteroscopy.

So 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 the labs listed, a CBC, ESR, CRP, and fecal calprotectin, an ileocolonoscopy with biopsy, and small bowel imaging, with either a CT enterography or MR enterography. Deep enteroscopy is not a part of routine diagnostic testing.

**Slide 6: Labs and Radiography**
Moving on with Jack's case, Jack's blood work revealed an elevated CRP at 4, an ESR rate that was elevated at 97, and a fecal calprotectin that was elevated at 350. His stool was negative for a *C. diff* infection. His colonoscopy revealed perianal skin tags, multiple ulcers in the anus, rectum, sigmoid, and descending colon. Biopsies revealed patchy, severe, chronic active colitis, with non-necrotizing granuloma, and stain negative for cytomegalovirus. CT enterography revealed thickened segments of the distal and terminal ileum and the entire colon.

**Slide 7: Commentary on Jack's Case**
So, based on endoscopies, biopsies, and laboratory values, Jack's diagnosis is Crohn's ileocolitis. His treatment options include induction of remission with steroids, use of an immunomodulator such as a thiopurine or methotrexate, a biologic therapy, or a combination of biologics and immunomodulator. If he has no response to initial treatment, he may have more medical therapy, if he has continued ongoing active inflammation, or surgical intervention if he has fibrostenotic disease that would not respond to our current therapies.

**Slide 8: Diagnosis of Inflammatory Bowel Diseases**
Moving on, we'll talk a little bit more about the diagnostics of inflammatory bowel disease.

**Slide 9: First Goal of Management in IBD: Obtain a Clear and Accurate Diagnosis**
The first goal of management in IBD is to obtain a clear and accurate diagnosis. A clear diagnosis should provide information that explains the patient's current symptoms and problems, provides prognostic information, and makes a distinction in the management decision, such that therapy chosen now affects both the short and the long-term outcomes.

We need to think both about disease activity, which is the short-term, how the patient is doing right now, and the disease severity, which includes prognostic factors and risks for disease progression.

**Slide 10: Clinical Diagnosis of IBD**
For the clinical diagnosis of IBD we want to think about things such as how symptoms start. What does the patient mean by diarrhea, abdominal pain, or bleeding. Think about red flags such as nocturnal symptoms, weight loss, anemia, family history can be helpful, extraintestinal manifestations such as joint pains or mouth sores, eye inflammation, a fullness or a mass on abdominal exam, and a perianal exam to investigate for perianal disease.

**Slide 11: Clinical Features**
The clinical features of ulcerative colitis and Crohn's disease. In ulcerative colitis there's continuous inflammation involving the colon only. The pathology is more consistent with superficial inflammation. It can have a variable extent, it can be limited to the rectum, can go up to the left side of the colon, or it can involve the whole colon. We know that there's colon cancer risk with time with ulcerative colitis, and extraintestinal manifestations can occur.

In Crohn's disease there's patchy inflammation, anywhere from the mouth to the anus. The pathology can reveal full thickness inflammation, complications such as fistulas and strictures can develop, and there is a risk of cancer, both in the small bowel if inflammation is located there, or the colon, if inflammation is located in the colon. Extraintestinal manifestations can occur in Crohn's disease as well.

**Slide 12: Considerations in the Differential Diagnosis of IBD**
Some considerations in the differential diagnosis of IBD are functional symptoms, microscopic colitis, infectious colitis including *C. diff*, ischemic colitis, drug-induced enterocolitis, which include a drug such as NSAIDs, solitary rectal ulcer syndrome, diversion colitis, radiation enterocolitis, endometriosis, malignancy, or diverticular-associated colitis.

**Slide 13: Refining the Diagnosis of IBD**
In refining the diagnosis of IBD, there're several tools at our disposal. One is ileocolonoscopy with biopsy. Fecal calprotectin is a test that is approved to distinguish between irritable bowel syndrome and inflammatory bowel disease. Reliable expert pathology interpretation of biopsies. Evaluation of the small bowel which could be done with CT enterography, MR enterography, or video capsule endoscopy. For perianal disease, sometimes examination under anesthesia with a colorectal surgeon is necessary. Rarely necessary is an explorative laparotomy. There're some other clues we can use in our diagnosis such as family history or serologies.

**Slide 14: Importance of Accurate Colonoscopy and Upper Endoscopy in IBD**
The importance of an accurate colonoscopy and upper endoscopy in IBD is really quite high. So the first colonoscopy is very important in really describing where the disease is located and the severity. And it's really important in our reports we're really specific about that.

A staging exam should include assessment of both the ileum and the colon, assessment of the ileocecal valve for strictures. If you can't intubate the ileum it's important to discuss why that might have been, if it was because of a strictured valve, or not. Biopsies of areas that are normal as well as those that are abnormal. Accurate endoscopy report to really help the pathologist interpret what he or she sees as well as to help other medical providers understand the extent and severity of the disease.

And, upper endoscopy is useful for identifying upper GI tract involvement that may be suggestive of Crohn's disease as well.

**Slide 15: IBD Diagnostic Algorithm for First Presentation**
The IBD Diagnostic Algorithm for the first presentation. To start with we do labs, the CBC, CRP, LFTs and albumin, and stool studies, which is the calprotectin. Then we move on to upper and lower endoscopy with duodenal, ileal, and colonic biopsies. If that's suggestive of Crohn's disease, we complete the staging work-up with small bowel imaging with a CT enterography, MR enterography, or small bowel follow-through. If those studies are normal, but there's still a high suspicion, small bowel imaging should be pursued with CT or MRI. If that's normal, a video capsule endoscopy could then be pursued.

If endoscopy and biopsies are consistent with ulcerative colitis, then at that point a treatment can be initiated.

**Slide 16: Mayo Score for Assessment of UC**
The Mayo Score can be used to assess UC severity of endoscopy. A Mayo Score of zero indicates normal, there's no active disease; 1 is mild disease with erythema, a decreased vascular pattern, mild friability; Mayo 2 is moderate inflammation that has marked erythema, absent vascular pattern, friability, and erosions; Mayo 3 is characterized by spontaneous bleeding and ulcers.

**Slide 17: Simple Endoscopic Score (SES) for Crohn's Disease**
In Crohn's disease we use the Simple Endoscopic Score for Crohn's disease assessment during endoscopy. This assigns a value from 0 to 3 for each segment that's examined, including the ileum and each segment of the colon. The score is comprised of the size of the ulcers noted, the ulcerated surface area, the total affected surface area, and the presence or absence of a stenosis.

**Slide 18: Making the Diagnosis**
In making a diagnosis a careful history and physical exam is used in combination with clinical, radiographic, endoscopic, and histologic findings to make the diagnosis.

**Slide 19: Challenge Question**
We'll have a challenge question. 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; **D,** cyclosporine.

The correct answer is **C,** vedolizumab. For patients with moderate-to-severe Crohn's 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**
We'll now turn to medical management of IBD.

**Slide 21: Goals of Therapy for IBD**
The goals of therapy for IBD are to induce and maintain remission, restore and maintain nutrition, minimize complications, avoid surgery or select the optimal timing for surgery, enhance the quality of life, and achieve mucosal healing. Based on recent patient focus group findings conducted by the Foundation, it's important to have a direct conversation with patients about what remission looks like, how likely they are to achieve it, and how long the remission might last. Patients aren't quite sure whether to expect some level of ongoing symptoms due to their diagnosis or whether they can expect a complete return to normalcy and their quality of life that they had before their diagnosis. And it's important to talk about how you're going to assess that and what they can expect.

**Slide 22: Therapies for Ulcerative Colitis**
There are many medication classes that are FDA approved therapies for ulcerative colitis. We'll talk about these in detail in the slides to come, but in general the classes include the 5-aminosalicylate acids, steroids, immunomodulators, JAK inhibitors, S1P receptor modulators, and biologics, which include the anti-TNF medications, anti-integrin, and anti-IL-12/23.

**Slide 23: Therapeutic Approach for Crohn's Disease**
The therapeutic approach for Crohn's disease. The therapeutic selection should be based on the disease phenotype, the disease

severity, and the prognostic factors. If the patient's at high risk for disease progression, early therapy of biologics is warranted in order to achieve mucosal healing.

**Slide 24: Aminosalicylate (5-ASA) Drugs**
Now we'll take the drug classes one at a time.

Aminosalicylate drugs or 5-ASAs are used for mild-to-moderate ulcerative colitis. They vary in their sites of delivery. So some of the medications, such as sulfasalazine, olsalazine, or balsalazide are targeted for colonic release. Other formulations such as delayed release mesalamine, MMX mesalamine, or granulated mesalamine are targeted to release in the terminal ileum and colon. Controlled release mesalamine can release into the duodenum, ileum, and colon. So it's important to choose the formulation that will be delivered to the site of your patient's inflammation.

There's a very low incidence of serious side effects. Agranulocytosis occurs just in 6 of 10,000 patients, pancreatitis occurs in 7.5 of 1 million prescriptions, and interstitial nephritis occurs in 6 of 10,000 patients, which is same as in the general population. So these really are very low-risk therapies.

**Slide 25: Corticosteroids**
Corticosteroids are fast-acting, you can use an oral steroid plus a 5-ASA for moderate-to-severe active IBD. We can use oral, rectal, or IV delivery if necessary. We also have controlled release budesonide for mild-to-moderate Crohn's, so it's confined to the ileum or right colon, as well as controlled release budesonide for ulcerative colitis delivery to the colon.

Steroids should only be used to achieve remission. They're not appropriate for maintenance due to the risk of serious side effects. Steroids cause adrenal suppression and metabolic disturbances, including diabetes, cataracts, and glaucoma, cognitive impairment, psychosis, emotional disturbance, high blood pressure, infections including bacterial sepsis, myopathy, osteoporosis, osteonecrosis, pseudotumor cerebri. We really know that these are high risk therapies that should only be used for the shortest time necessary.

**Slide 26: Immunomodulators**
Immunomodulators include thiopurines, such as azathioprine or 6-mercaptopurine. Those are oral therapies that are used to maintain remission in ulcerative colitis and Crohn's disease. They have a slow onset of action and take about 6 to 12 weeks to work, and so they're therefore not appropriate for induction of remission. Because of that they're often given with corticosteroids or in combination with anti-TNF medications, both of which can induce remission.

There are some serious side effects that are associated with thiopurines, such as pancreatitis, which occurs in about 4% of people, allergy, bone marrow suppression, liver toxicity, serious infections, lymphoma, the risk of lymphoma is about 4 to 5 times higher than the general population, and non-melanoma skin cancers, such as squamous cell or basal cell skin cancer. The risk of those skin cancers is 5 to 7 times higher than the general population.

Methotrexate can be used intramuscular, subcutaneously, or oral. It is not proven to be effective in ulcerative colitis, however, it can be used to induce and maintain remission in Crohn's disease.

Serious side effects of methotrexate include bone marrow suppression, acute and chronic liver toxicity, serious infection, nephrotoxicity, and severe dermatologic reactions. It's absolutely contraindicated in pregnancy. It's also contraindicated in breastfeeding.

Cyclosporine can be used IV for acute severe steroid-refractory ulcerative colitis.

**Slide 27: Anti-TNF Therapies for Moderate-to-Severe IBD**
Anti-TNF therapies can be used for moderate-to-severe inflammatory bowel disease. There are 4 FDA approved anti-TNF therapies. Adalimumab and infliximab are approved for both ulcerative colitis and Crohn's disease. Certolizumab pegol is approved for Crohn's only and golimumab is approved for ulcerative colitis only. Infliximab is given as an IV infusion. And there are others, adalimumab, certolizumab, and golimumab are given as subcutaneous injections.

The efficacy appears similar between these therapies. The toxicity profiles are also similar, though they do differ in their delivery routes.

**Slide 28: Safety Issues with Anti-TNF Therapy: Rare but Serious Side Effects**
The safety issues to think about with anti-TNF therapy are rare, but there are some serious side effects that can occur. So skin cancers can occur, demyelinating disorders, new onset psoriasis, liver toxicity, reactivation of hepatitis B and this is one of the reasons we check for hepatitis B before starting anti-TNF therapy, chronic heart failure, anti-TNF medications are contraindicated in people with Class 3 or 4 heart failure, immunogenicity, you can form anti-drug antibodies to anti-TNF therapy, and there are some autoimmune reactions you can have what's called a lupus-like reaction to anti-TNF therapy.

**Slide 29: Natalizumab and Vedolizumab**
Moving on then to natalizumab and vedolizumab, the anti-integrins. These medications are both integrin receptor antagonists. Vedolizumab appears to be gut-selective. They differ in their indications. Natalizumab is approved for Crohn's disease only. It is not commonly used now that we have vedolizumab. Vedolizumab can be used for both ulcerative colitis or Crohn's disease.

There is a risk of progressive multifocal leukoencephalopathy or PML. It is rare with natalizumab and there've been no cases to date with vedolizumab.

You can test for antibodies to the JC or John Cunningham virus to assess possible risk for this condition. Though this is not commonly done with vedolizumab. Close monitoring is important. Do not combine these drugs with each other or an anti-TNF agent, or combine natalizumab with an immunomodulator.

**Slide 30: Ustekinumab**
Ustekinumab is an anti-p40 monoclonal antibody that blocks IL-12 and IL-23 binding to their receptors. It is indicated for moderate-to-severe Crohn's disease or ulcerative colitis, and it's given as a one-time IV loading dose, followed by a subcutaneous injection every 8 weeks.

Serious events with this medication can occur, which include infections, TB, malignancies, non-infection pneumonia. Rare, but very serious, would be reverse posterior leukoencephalopathy syndrome or RPLS. That's a rare and potentially fatal syndrome that is separate and distinct from PML. It's characterized by headache, confusion, seizures, and visual loss.

**Slide 31: Janus Kinase Inhibitors**
Janus kinase inhibitors or JAK inhibitors include tofacitinib, which is an oral small molecule inhibitor of JAKs 1 through 3, so it's a non-selective JAK inhibitor. It's currently approved for adults with moderate-to-severe ulcerative colitis who are intolerant to or have failed anti-TNF therapy.

Filgotinib is a more selective JAK 1 inhibitor. It's being investigated for ulcerative colitis and Crohn's disease, but does not yet have an IBD indication.

Upadacitinib is a selective JAK 1 inhibitor that's approved for adults with moderate-to-severe ulcerative colitis, who are intolerant to or have failed anti-TNF therapy.

There are several other JAK inhibitors that are also under investigation for IBD.

**Slide 32: Ozanimod**
Ozanimod is a Sphingosine-1 phosphate receptor modulator. It is approved for moderate-to-severely active ulcerative colitis in adults and it's an oral small molecule inhibitor as well.

The serious adverse effects associated with ozanimod include infections, cardiovascular risk, it can cause bradyarrhythmia, AV conduction delays, and that's why a pretreatment ECG is necessary to look for heart block. Liver injury, fetal risk, it's contraindicated in pregnancy at this time. Decline in pulmonary function and macular edema.

**Slide 33: Risankizumab**
Risankizumab is a selective IgG1 antibody that binds to the p19 subunit and blocks IL-23 specifically. It is given as 3 IV infusions, followed by an on-body injector every 8 weeks. It's currently approved for moderate-to-severe Crohn's disease, plaque psoriasis, and psoriatic arthritis.

Adverse events include infections, including tuberculosis, eczema, and rash.

**Slide 34: Biosimilars**
Biosimilars are a similar copy of an originator biologic therapy. They're not an identical copy because they can differ in the glycosylation. There are many comparative and bioequivalent studies in IBD for the anti-TNFs, infliximab and adalimumab with their biosimilar. The safety profile is consistent with the originator biologic.

Providers should be having a discussion with and educating patients on biosimilars due to the changing regulatory environment and the implications it has for patients. I often tell my patients that biosimilars have been studied, that they have comparative efficacy and single switch between originators and biosimilars, has been studied and found to be safe. If patients develop an anti-drug antibody to an originator drug, they cannot switch to the biosimilar of the same drug. Those antibodies would cross-react.

**Slide 35: Biosimilars for IBD**
There are several biosimilars that are available for IBD. For infliximab there are 3 biosimilars that are both FDA approved as well as

available. For adalimumab there are 3 biosimilars that are FDA approved, but not yet available. For infliximab, there is also unbranded infliximab, which is different than a biosimilar in that it's identical to the originator drug, which is also now approved and available.

**Slide 36: IBD Treatments Summary**
In summary of these IBD treatments, 5-ASA agents are effective and safe for induction and maintenance of remission in patients with mild-to-moderate ulcerative colitis. Systemic and conventional steroids are effective for induction, but they are never to be used for maintenance because they have so many adverse effects and side effects. Immunomodulators that are most often used to treat IBD are azathioprine, 6-MP, methotrexate. Those are slow-acting medications that are not good for induction, but can be used for maintenance of remission. And cyclosporine, which can be used as a salvage therapy for induction of remission in ulcerative colitis. Biologics, such as 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 and their place in the treatment paradigm needs further exploration. Earlier use of biologics in Crohn's disease and possibly severe ulcerative colitis can improve outcomes. Surgery is not a failure of treatment, it's sometimes a necessary component of the treatment of both ulcerative colitis and Crohn's disease

**Slide 37: Future Directions for IBD Prognostics and Evaluation of Treatment Targets**
We'll now turn to Future Directions for IBD Prognostics and Evaluation of Treatment Targets.

**Slide 38: Risk Stratification Tools Available or in Development in the US**
So there are a few risk stratification tools that are available or in development in the United States. The first one is a Crohn's disease prognostic laboratory panel, and this tool uses clinical information and lab data to provide an individualized risk profile for Crohn's disease 3-year risk of serious complications. It takes into account the disease location, some serologic data, such as the anti-Saccharomyces cerevisiae antibody, anti-flagellin or CBir1 antibody p-ANCA, as well as genetic data for a NOD2 frameship mutation or SNP13.

There's also a Crohn's disease prognostic profile that uses a blood sample to assess for the presence of 4 antibodies to determine complication risk and it's associated with complicated disease behavior or surgery, increase with the number and concentration of those antibodies.

There's another Crohn's prognostic panel that uses blood samples to analyze for serologic and genetic markers to provide probability of Crohn's disease progression.

And then, there's a real time PCR test for IBD that again is looking at some gene expression to assess individualized risk.

So these tools are in development and may assist in looking at the overall prognosis of patients.

**Slide 39: Evaluation of Appropriate Therapy**
And, thinking about evaluating what is the most appropriate therapy for patients, we need to think about a few different factors.

Anti-TNF immunogenecity is common amongst those with IBD and that can lead to loss of response or infusion reactions. There is now some testing available to help us predict this. There's the anti-TNF immunogenecity risk testing, the blood-based genetic test. So, this is a genetic test to identify variant characters of HLADQA1 05, which is an allele that's associated with increased immunogenecity and development of anti-drug antibodies against anti-TNF therapy. If you do have that allele, there's a 7-fold increased risk of developing anti-infliximab antibodies in patients that are carriers of this. And so, it can inform decisions regarding anti-TNF therapy level monitoring. And, it can help you assess for risk prior to starting therapy.

In terms of thiopurines, there's TPMT or thiopurine methyltransferase testing. You can test for that enzyme's activity and you can also test for NUDT15 genotyping. And this will help you predict potential for toxicity to the thiopurine drugs, such as 6-MP, 6-thioguanine, or azathioprine.

**Slide 40: Evaluation of Treatment Targets**
There are some treatment target testing that is under development. There's a test for monitoring of Crohn's disease, it's a serum test to evaluate biomarkers and mucosal damage. And it can provide an Endoscopic Healing Index score. And it's useful for periodic assessment of endoscopic disease activity in Crohn's disease.

There's also an Ulcerative Colitis Response Index, which is a blood test to evaluate biomarkers for the detection of mucosal healing after anti-TNF treatment.

**Slide 41: Thank you!**
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