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Virtual IBD Clinic: Surgical and Pharmacological Therapeutics

Announcer Opening:
Welcome to CME on ReachMD. This activity, entitled "*Virtual IBD Clinic: Surgical and Pharmacological Therapeutics*." is provided by RMEI Medical Education, LLC and the Crohn's & Colitis Foundation and this activity is supported by educational grants from AbbVie Inc., Coherus BioSciences, and Takeda Pharmaceuticals U.S.A., Inc

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Jenny Sauk:
Slide 1: Virtual IBD Clinic: Surgical and Pharmacological Therapeutics
Hello, my name is Jenny Sauk, I'm an Associate Professor of Medicine and the Director of Clinical Care at the Inflammatory Bowel Disease Center at UCLA in Los Angeles. In this CME activity I will be discussing the clinical case of a patient with inflammatory bowel disease as well as principles and guidelines for disease management and indications for surgery.

Slide 2: Initial History and Physical Examination
So this is our patient case. This is Jack, he's a 23-year-old college student with Crohn's disease. He initially presented with persistent non-bloody diarrhea, abdominal cramps, weight loss, and pain with defecation. At presentation, his physical exam was remarkable for oral aphthous ulcers, diffuse abdominal tenderness, perianal skin tags, and rectal tenderness with a visible anal ulcer.

His initial colonoscopy revealed perianal skin tags and multiple ulcers in the anus, rectum, and sigmoid and descending colon. The biopsy of the left colon revealed patchy severe chronic active colitis with rare poorly formed non-necrotizing granuloma.

Slide 3: Initial Diagnosis and Treatment
Based on the results of Jack's colonoscopy and the clinical presentation, he was diagnosed with moderate-to-severe Crohn's disease and he was initially treated with prednisone 40 milligrams a day and azathioprine 150 milligrams a day.

Slide 4: Emergency Department Visit
A few months after his initial diagnosis Jack was seen in the emergency department for severe perianal pain and purulent drainage from his rectum. An MRI demonstrated a perianal abscess and he was discharged from the emergency department on oral antibiotics and with instructions to meet with a surgeon in 1 week. Unfortunately, his pain persisted and increased. He presented for further evaluation and treatment.

Slide 5: Follow-up Visit
During his follow-up visit Jack had developed symptoms consistent with perianal complications of Crohn's disease. He is advised that he will need an exam under anesthesia in order to further evaluate his symptoms. An anorectal exam under anesthesia revealed a large perianal abscess and fistula, and this abscess was surgically drained and a seton was placed in the fistula tract.

Slide 6: Challenge Question
So this is our challenge question for our patient Jack. Which of the treatment options is appropriate for Jack at this time? **A,** would you

continue treatment with prednisone at 40 milligrams a day and azathioprine at 150 milligrams a day; **B,** increase the prednisone to 60 milligrams a day; **C,** continue the azathioprine and add infliximab; or **D,** remove the seton after 1 week.

So the correct answer is **C,** which is to continue the azathioprine and add infliximab. So continuing with azathioprine and prednisone is not an option since Jack's disease is progressing on that therapy, and increasing the dose of prednisone may worsen Jack's existing infection, his rectal abscess. So continuing azathioprine and adding infliximab is an option for Jack. Combining immunomodulator therapy with anti-TNF therapy has demonstrated efficacy in fistulizing Crohn's disease. Seton placement significantly improves the rate and duration of fistula response in Crohn's disease patients, subsequently treated with infliximab, so the seton should not be removed within a week.

Slide 7: Case Summary
So to summarize our case, Jack has severe Crohn's disease that is complicated with a perianal abscess and fistula, requiring surgical drainage and seton placement. This impacts current treatment decisions. Jack is made aware of the detrimental effects of corticosteroids, especially with an abscess, and the need for the avoidance of this medication in the long-term. The long-term complications of corticosteroids can include bone loss, elevated blood sugar, elevated blood pressure. The prednisone will be tapered as quickly as possible. The azathioprine is continued at 150 milligrams a day and infliximab is started at a standard dose of 5 mgs per kg at zero, 2, and 6 weeks. By the second infliximab dose Jack is feeling better and his abdominal pain is improved and his bowel movements are more formed. He's only having 2 bowel movements a day. His appetite is improving and he's gaining weight.

So another important point to remember with perianal Crohn's disease is that it's important to evaluate this patient carefully prior to the initiation of treatment, and this includes a good MRI pelvis, which he did have, to evaluate the fistula tract. And an exam under anesthesia, with any intervention required, such as drainage of abscess with or without seton placement, perianal fistula management, it's a multidisciplinary effort, so usually involves a colorectal surgical colleague.

Slide 8: Long-term Management of Moderate-severe Crohn's Disease and Ulcerative Colitis
So we're going to move on and I'd like to discuss some important considerations in the management of both severe Crohn's disease and ulcerative colitis.

Slide 9: Bowel Damage: Crohn's Disease
So let's start by talking about the natural history of Crohn's disease.

For the majority of people Crohn's disease will present as an inflammatory phenotype that usually presents with symptoms of diarrhea, abdominal pain, and possibly some weight loss. However, with ongoing inflammatory activity that is uncontrolled, there can be a series of flares and inflammatory episodes that contribute to overall bowel damage and over time strictures and fistulas can develop.

Within 1 year of diagnosis, roughly 10 to 15% of Crohn's disease patients may require surgery and this percentage is higher if we look 20 to 25 years out after initial diagnosis. Ideally soon after diagnosis there is a sweet spot for intervention that can change the natural history of the disease and prevent the inflammatory episodes that contribute to the formation of strictures and fistulas and abscesses, and potentially decrease that need for surgery in the future. We're hoping to heal the bowel and not just treat the symptoms.

Slide 10: Symptoms Do Not Correlate Well with Endoscopic Findings in Crohn's Disease
So we know that patients' symptoms can fluctuate, so our goal is not only to improve the symptoms and quality of life of our patients in the short-term, but also to achieve mucosal healing and prevent bowel damage. Crohn's disease is tricky since the symptoms don't always correlate well with endoscopic activity. It's not uncommon for someone to present with no symptoms, but have significant activity on imaging or colonoscopy, and likewise we can see the opposite where symptoms can be very active, but there's very little activity endoscopically with good mucosal healing. So the treatment strategy would be different in both scenarios, so it is important to obtain objective evidence of disease activity in Crohn's disease.

Slide 11: Risk Factors in Crohn's Disease
Regardless of the symptoms, though we want to think about risk stratification, as some of our patients may be at higher risk for more aggressive Crohn's disease than others. Ultimately this risk profile will help contribute to how I counsel a patient and make recommendations for treatment. So if patient has more moderate-to-high risk features, including younger age of disease with extensive anatomic involvement, perianal and/or severe rectal disease with presence of deep ulcers and strictures, or penetrating behavior, I will likely consider biologic therapy sooner than in those who present with more low risk features.

Slide 12: Improved Outcomes with Early Treatment
And, we know from the landmark SONIC trial that for patients with moderate-to-severe Crohn's disease, so this is our higher risk patient, who are biologic-naive, that the combination therapy with azathioprine and infliximab is more effective in achieving a corticosteroid-free clinical remission than infliximab monotherapy alone and azathioprine alone. That is why in our patient case scenario

we recommend Jack to start on infliximab and azathioprine for his perianal fistulizing Crohn's disease rather than azathioprine monotherapy or infliximab monotherapy.

Slide 13: Proposed Update to STRIDE (STRIDE 2): Treatment Targets in IBD
So, as we think about as a whole our strategy for Crohn's disease, it's moved away, as I mentioned, from focusing on just the short-term symptom response, while symptom response is important, it is also important to consider intermediate targets like symptom remission, normalization of CRP, and decreases in calprotectin, as well as normal growth in children, but also more long-term targets like endoscopic healing, normalized quality of life, and absence of disability. This is called a treat-to-target approach.

In this treat-to-target algorithm the primary target for treatment should be absence of endoscopic ulceration. After starting a new therapy, patients should be assessed every 6 months and treatment should be optimized, switched, or added, until disappearance of ulceration. Once mucosal healing has occurred, the treatment should be continued and mucosal healing should be re-evaluated every 1 to 2 years.

Slide 14: Monitoring Disease – CALM Trial: Efficacy Results
There's an important prospective study called the CALM Trial, evaluating this concept, this treat-to-target strategy. So this is an open-label, multicenter, Phase III study in Europe and Canada, where patients first received a steroid taper for active Crohn's disease and then were randomized to 2 different management arms. In the conventional treatment arm, treatment intensification was based only on symptoms or steroid usage. And in the treat-to-target arm, the tight control arm, treatment intensification was not only based on symptoms or steroid use, but also on CRP or fecal calprotectin levels. The primary endpoint was endoscopic remission at week 48.

The study visits occurred every 12 weeks with labs that were done 1 week prior, and for each study arm, the need for treatment intensification was assessed at every visit, according to pre-specified criteria. And that intensification sequence was no treatment, and if there were more objective criteria they would move on to adalimumab every other week, and if they needed to have further treatment, adalimumab weekly, and lastly, if there was criteria for needing further treatment, it would be adalimumab plus azathioprine.

So, what you can see here is that significantly more patients in the tight control group, so 45.9% achieved that primary endpoint of mucosal healing, compared with the clinical management group, so that's our conventional management treatment group at 30.3% at 48 weeks. And, we can also see that significantly more patients also achieved a biologic remission, which is a combination of reduced CRP and calprotectin with mucosal healing, and deep remission, which is a combination of steroid-free remission and mucosal healing with no deep ulcers in that tight control group.

Slide 15: CALM Trial: Outcomes
And then there're some follow-up studies to this that also showed the benefits of treat-to-target management was this data presenting 2-year follow-up, looking at Crohn's disease-related hospitalizations, Crohn's disease-related surgeries, and Crohn's disease-related hospitalizations or serious complications? And what you can see here is that the rate of Crohn's disease-related hospitalizations were significantly lower in the treat-to-target group, compared with the events in the conventional management group. The rate of surgical procedures or Crohn's disease-related surgical procedures and Crohn's disease-related hospitalizations or serious complications were not significantly different between the 2 groups. This could be related to the relatively short duration of follow-up, so we'll be seeing future follow-up data to this, but seeing that decrease in Crohn's disease-related hospitalizations itself speaks to the potential long-term benefit of a treat-to-target approach.

Slide 16: Progression of Ulcerative Colitis
So, we have mainly focused on the Crohn's disease progressive nature, but ulcerative colitis is also a progressive disease. Patients with ulcerative colitis have a 30% risk of needing a colectomy, and patients with histologic inflammation for over 8 years, so more than just proctitis, have an increased risk of colon dysplasia as well.

Chronic inflammation in the left colon can also lead to scarring/lead pipe colon, which is associated with looser stools and increased frequency. So a treat-to-target approach is likely also relevant for ulcerative colitis as well.

Slide 17: Treatment Options in Moderate-to-Severe Ulcerative Colitis and Crohn's Disease
Let's shift gears and talk about treatment options in moderate-to-severe Crohn's disease and ulcerative colitis.

Slide 18: Treatment Options for Severe Crohn's Disease
So, there're several induction and long-term treatment options that can be considered for patients like Jack with severe Crohn's disease. The ACG 2018 guidelines for Crohn's disease recommends treatment with a biologic with or without an immunomodulator. The choices for approved anti-TNF biologics for Crohn's disease include infliximab, adalimumab, certolizumab pegol, and biosimilars. Vedolizumab is the recommended anti-integrin biologic and ustekinumab, an IL-12 and IL-23 inhibiting biologic, is also an option.

More recently risankizumab, an IL-23 inhibitor biologic, was also approved for Crohn's disease.

The recommended immunomodulators are azathioprine, 6-mercaptopurine, or methotrexate, which are typically used in combination therapy.

Combination therapy of anti-TNF with an immunomodulator is more effective than monotherapy with either agent as has been shown earlier with the SONIC trial.

Slide 19: Treatment Options for Moderate-to-Severe Ulcerative Colitis
Similar to Crohn's disease there are several treatment options for patients with severe ulcerative colitis at high risk of requiring a colectomy. The 2020 AGA guidelines for moderate-to-severe ulcerative colitis recommend early use of biologic agents, such as anti-TNF agents like infliximab, adalimumab, or golimumab, or anti-integrin therapy like vedolizumab, or anti-IL-12 and IL-23 agents like ustekinumab.

Small molecule therapy like Janus kinase inhibitors, tofacitinib, are also approved. More recently a selective JAK 1 inhibitor, upadacitinib, is also available for treatment for ulcerative colitis. With recent FDA changes JAK inhibitors can only be used after anti-TNF failure.

Also another small molecule therapy, a Sphingosine-1 phosphate modulator, ozanimod, was recently approved for ulcerative colitis.

Monotherapy as maintenance with thiopurines, such as azathioprine and 6-mercaptopurine can be used, but methotrexate is not recommended as monotherapy.

Slide 20: Therapeutic Drug Monitoring
We are going to briefly touch upon therapeutic drug monitoring. We have the ability to measure drug metabolites with our thiopurines and drug levels with several of our biologic agents.

There are 2 types of therapeutic drug monitoring, reactive monitoring, when patients do not respond to therapy or have lost response, it is shown to improve clinical care and be cost-effective. Proactive monitoring is assessing drug levels during induction or maintenance therapy, or before withdrawing therapy in patients with an appropriate clinical response and who are feeling well.

Retrospective data do show some benefit of practicing therapeutic drug monitoring on clinical outcomes in patients, however, prospective data are more controversial.

Slide 21: AGA Guideline on Therapeutic Drug Monitoring
So the AGA has made several recommendations regarding therapeutic drug monitoring for thiopurines, including azathioprine and 6-mercaptopurine. Prior to starting the thiopurine we should be doing a routine thiopurine methyltransferase, so TPMT test, to see how the patients will metabolize the drug and to see if it will be safe to consider the medication. Some patients have low or high TPMT activity, and we sometimes need to consider adjusting the medication or not starting it all, depending on that activity.

So for adults already on a thiopurine, if the IBD appears to be active or if the patient is having an adverse effect, the AGA has recommended reactive testing and checking thiopurine metabolites. But the AGA does not recommend routine thiopurine monitoring in patients that have quiescent IBD or doing well with their IBD.

So, with anti-TNF agents, drug monitoring, as I mentioned earlier, somewhat controversial. The AGA recommends that patients with active IBD, treated with an anti-TNF agent, can utilize reactive therapeutic drug monitoring to assist in management. However, benefits of that collective monitoring are less established, so with more data the guidelines may be updated in the future. It's also unclear what barriers are encountered with respect to proactive drug monitoring, with respect to insurance and costs, so we'll have more information about that hopefully in the future.

Slide 22: Follow-up Visit
So let's go back to our case. So Jack had Crohn's colitis with perianal disease and was treated with infliximab 5 milligrams per kilogram every 8 weeks and azathioprine 150 milligrams a day, and has been doing well for the last 3 years. The Seton fell out 1 year ago and he's had no further problems with the fistula. And during this visit, though, he's complaining of abdominal bloating and right lower quadrant pain a few hours after eating, especially after ingesting popcorn or nuts. Jack states that this is very different from the way that his Crohn's felt a few years ago when he was sick.

Slide 23: Diagnostics and Surgery
So, a CT enterography is performed and there is a 6 centimeter stricture at the ileum. There's also dilation of the small bowel above the stricture. A colonoscopy confirms that there is a stricture and the scope cannot be passed into the ileum. So based on these findings, Jack undergoes an ileocolonic resection with an ileocolonic anastomosis.

Slide 24: Challenge Question

This is our challenge question. Which of the following is an approach to managing the patient who is at high risk for postoperative recurrence of Crohn's disease? **A,** is it to prescribe no medication and repeat colonoscopy 24 months postoperatively;**B,** to prescribe anti-TNF therapy and repeat the colonoscopy 6 to 12 months postoperatively; **C,** to prescribe mesalamine and repeat colonoscopy 12 months postoperatively; or **D,** to prescribe 6-mercaptopurine and repeat the colonoscopy 18 months postoperatively.

The correct answer here is **B**. So it's to prescribe anti-TNF therapy and repeat the colonoscopy 6 to 12 months postoperatively. So some patients are at higher risk for Crohn's recurrence than others and we'll go over this later in a few slides coming in the future. So in those patients we would start postoperative therapy relatively soon after surgery, so it's very important to perform the colonoscopy 6 to 12 months out after surgery, regardless of when we're starting treatment to evaluate for postoperative recurrence.

Slide 25: Surgery for IBD
So, before we go into postoperative recurrence, let's talk a little bit about the surgical options for Crohn's disease and ulcerative colitis.

Slide 26: Indications for Operative Management of Inflammatory Bowel Disease
So, there are overall indications for operative management for inflammatory bowel disease. An acute complication in ulcerative colitis would be toxic megacolon. This is a clinical diagnosis. You have to have a very high clinical suspicion for toxic megacolon. When its colon is already very dilated, this might be late, so you have patients where you have to be aware of this ahead of time and try to catch it soon. Other acute complications include hemorrhage, acute obstruction that is not resolving, and perforation. And, a lot of patients will also be going to the OR for more chronic complications as well and medically refractory disease that is not responding to multiple biologics or immunosuppressants would be one of those. Recurrent abdominal abscesses, chronic small bowel or large bowel stricturing disease, clinically symptomatic enteroenteric fistulas, an entero-vesicular fistula, neoplasia, or growth retardation in children to the severity of disease are all examples of chronic complications of disease.

Slide 27: Crohn's Disease Surgery
So, some of the more common surgeries for Crohn's disease include strictureplasty and this is a surgical procedure to repair a stricture by widening the narrowed areas without removing a portion of the intestine. For someone with multiple small bowel strictures throughout the small bowel this could be an appropriate surgery to prevent a lengthy resection. And we briefly touched upon Seton placement with our patient Jack. Jack had a Seton placed for perianal disease. A Seton is a surgical material that's left in a fistula to promote drainage of fluid and help the fistula tract to heal.

Slide 28: Crohn's Disease Surgery
So our patient Jack also had ileal disease that was not clearly present on his initial presentation. He eventually developed a stricture and required an ileocolonic resection. This is where the cecum and distal portion of the ileum is resected and a connection is created between the colon and ileum.

Another common surgery for Crohn's disease, if the colon is involved, is an ileorectal anastomosis, where the small bowel is connected to the rectum, if there is rectal sparing, which is commonly seen in Crohn's disease of the colon.

Slide 29: Natural History of Crohn's Recurrence
So let's go back to our challenge question about postoperative recurrence. Once the patient with Crohn's disease has a surgical resection, it is not a cure and we do need to monitor for recurrence. Histologic recurrence can occur as early as 1 week after intestinal resection and endoscopic recurrence can occur in about 70 to 90% of patients within 1 year of surgery. Clinical recurrence occurs in 30% of patients within 3 years of surgery and 60% of patients within 10 years of surgery.

Slide 30: Predictors of Clinical Recurrence
So, since endoscopic and histologic recurrence appear to occur before symptoms, waiting for symptoms to occur may be too late to intervene. So in a prospective cohort follow-up study of patients with Crohn's disease, 73% of patients had endoscopic recurrence at 1 year but only 20% had symptoms within 1 year of surgery. The Rutgeerts Score assessed at 6 to 12 months, predicts recurrence following surgery. So patients with a Rutgeerts Score of i0 or i1 have less than 10% clinical recurrence rate at 10 years, while patients with a Rutgeerts Score of i2 or greater, have a clinical recurrence rate of 20% or higher at 5 years. And patients with Rutgeerts Score of i3 or i4 have a 50 to 100% clinical recurrence rate with high rates of reoperation.

Slide 31: AGA Risk Stratification for Crohn's After Surgery
The next question is: when do we need to start people on therapy and are there certain patients that are at higher risk for recurrence than others? So this is where risk stratification comes in. So we can classify patients as being at low or high risk for clinical recurrence and adopt the postoperative medical therapy accordingly. We currently define the risk of clinical recurrence as low if a patient has longstanding Crohn's disease and if this is their first surgery for a very short stricture. If the patient is considered higher risk, if they have penetrating disease that's present or if the patient is young at presentation, or if there is recurrent surgery for Crohn's disease, or if the

patient is a smoker. So, they are considered a higher risk for a postoperative recurrence.

Slide 32: PREVENT Study
So 1 multicenter trial that evaluated the benefit of using anti-TNF therapy, specifically infliximab in the postoperative setting, is the PREVENT Study. This was a multicenter prospective study of 297 patients with Crohn's disease who had undergone ileocolonic resection within 45 days before randomization to infliximab or placebo. Although they did not hit their primary endpoint of clinical recurrence, there were significantly lower endoscopic recurrences, only 30% versus 60% endoscopic recurrence in the infliximab arm versus the placebo arm. And the reason they did not hit that clinical recurrence rate goes back to what we were talking about earlier, that clinical recurrence rates are low early on and symptoms usually occur after endoscopic recurrence sets in.

Slide 33: Surgery for Ulcerative Colitis
Okay, so we're going to talk a little bit now about surgery for ulcerative colitis. So in the setting of therapy for refractory ulcerative colitis or ulcerative colitis with neoplasia, a total abdominal colectomy with an ileoanal pouch anastomosis should be performed. And this is usually performed as a total abdominal colectomy with ileoanal pouch over 3 steps. So in the first step they remove the entire colon. They usually leave a small segment of rectum behind and this is usually because the rectum has a lot of inflammation at the time of surgery and the thought is that creating the connection later would be safer, after the inflammation cools down, and the patient is off of steroids for a while.

In the second stage, the rectum is removed and the J-pouch is created from the small bowel and there is a connection created between the very small segment of the rectum and then a J-pouch. So the surgeon keeps a diverting ileostomy to allow the anastomosis to heal and mature.

And the third surgery is where the ileostomy is taken down. So patients usually do quite well with the surgery and it can be lifesaving in some cases.

Slide 34: Ileal Pouch Anal Anastomosis
So, when we look at complication rates for ileal pouch anastomoses, there can be some early and long-term complications. Small bowel obstruction, anastomotic stricture, and pouch leakage can be early complications that can be managed perioperatively. And we look at late complications, there can be decreased fecundity. This is different than fertility. Fecundity means that there is a decreased chance that women can get pregnant per cycle, but this can be due to the scarring around the fallopian tubes during the surgery. But patients with pouches have done very well with IVF, so their fertility is not affected.

Pouchitis can occur in up to 50%, however, the vast majority of patients can be treated with short courses of antibiotics. And pouch failure rate is generally low.

Slide 35: Ileal Pouch Anal Anastomosis
So in this long-term study looking at clinical outcomes in patients with ileoanal, pouch anastomoses, this was an image review of 1,885 operations over 20 years. This is from a prospective database, looking at complications and functional outcome and quality of life measures following surgery. The overall rate of pouch success was pretty high, so 96.3% at 5 years, 93.3% at 10 years, and 92.1% at 20 years. So this is important to let our patients know about, that this is a viable option that should be considered if a patient is really having a difficult time achieving remission with our current therapies available.

Slide 36: Ileal Pouch Anal Anastomosis
So, when you're talking to a patient about what they should expect after the ileal pouch and anal anastomosis, there is a difference in frequency of bowel movements after, so they can have a new normal of daytime stool frequency, about 5 to 6 bowel movements a day. There can be an increase in nocturnal bowel movements and possibly small increases in incontinent episodes. However, quality of life is generally unchanged and work is not affected by surgery in 83% in this 1 study.

So overall, quality of life is significantly still improved compared to preoperatively.

Slide 37: Summary
So in summary, the treatment of Crohn's disease and ulcerative colitis has evolved to earlier, more aggressive therapy, and reliance on mucosal healing, and this is that treat-to-target approach.

Patients with extensive bowel involvement, fistulizing disease, or deep ulcers in the bowel should receive a combination of biologic therapy with immunomodulator from the start, so biologic therapy usually being anti-TNF therapy.

Despite better Crohn's disease treatments, more than 50% of patients still require an intestinal resection, but treating patients earlier may decrease that percentage.

Surgery is not a cure for Crohn's disease and the majority of patients will have recurrence after surgery, so it's important to continue to monitor patients after surgery.

And, postoperative treatment should be initiated in patients that have a high risk for recurrence.

Slide 38: Thank you!
So thank you for participating in this CME activity. And please do not forget to take the post-test and complete the evaluation to receive CME credit. Thank you.

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