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Virtual IBD Clinic: Disease Management and Surgery



Narrator:

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Dr. Hudesman:

Slide 1: Virtual IBD Clinic: Disease Management and Surgery

Hello, I am Dr. David Hudesman. I am Associate Professor of Medicine and the Co-Director of the Inflammatory Bowel Disease Center at NYU Langone Health in New York City.

In this CME activity I will be discussing the clinical case of a patient with inflammatory bowel disease, as well as the principles and guidelines for disease management and indications for surgery.

Slide 2: Jack – Initial History and Physical Examination

So, our patient's name is Jack and Jack is a 23-year-old college student with Crohn's disease. He had initially presented with persistent non-bloody diarrhea, some abdominal cramps, weight loss, and pain with defecation. At presentation, his physical exam was remarkable for some oral aphthous ulcers, diffuse abdominal tenderness. On perianal exam, they noticed some skin tags and there was rectal tenderness with a visible anal ulcer.

Initial colonoscopy revealed the perianal skin tags noticed on exam, as well as multiple ulcers in the anus, rectum, sigmoid, and descending colon. Biopsies from the left colon showed patchy severe chronic active colitis and there were rare poorly formed non-necrotizing granulomas.

Slide 3: Jack – Initial Diagnosis and Treatment

Based on the results of Jack's initial colonoscopy and his 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: Jack – Emergency Department Visit

About a couple of months after his initial diagnosis, Jack was seen in the Emergency Department for severe perianal pain and purulence draining from his rectum. An MRI demonstrated a perianal abscess. He was discharged from the emergency department on

oral antibiotics and with instructions to meet with a surgeon in about a week. Unfortunately, his pain persisted and increased, so he presented back for further evaluation and treatment.

Slide 5: Jack – Follow-up Visit

Jack has developed symptoms consistent with perianal complications of Crohn's disease. He is advised that he will need an exam under anesthesia by the surgeon in order to further evaluate his symptoms. An anorectal exam under anesthesia revealed a large perianal abscess and fistula, the 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 following treatment options is appropriate for Jack at this time? (A) Continue treatment with prednisone 40 milligrams a day and azathioprine 150 milligrams a day; (B) Increase prednisone to 60 milligrams a day; (C) Continue azathioprine and add infliximab; or (D) Remove the seton after 1 week.

The correct answer here is answer C, which is continue azathioprine and add infliximab. The reason that is the correct answer is when we are managing our patients with complicated Crohn's disease and perianal fistulizing Crohn's disease, our best evidence is with infliximab or anti-TNF. That will improve fistula drainage, as well as fistula healing. And, that should be added to the treatment with azathioprine, as we will discuss in a little bit, that combination therapy is recommended for these more complicated Crohn's patients.

Slide 7: Case Summary

So, to summarize our case, Jack has severe Crohn's disease, complicated with a perianal abscess and fistula, requiring surgical drainage and seton placement. Jack is made aware of the detrimental effects of long-term steroids, especially with an abscess, the need for avoidance of this medication again, as I mentioned, long-term, due to other side effects including bone loss, elevated blood sugar, and blood pressure. The prednisone is going to be appropriately tapered as quickly as possible over time. Azathioprine continues at 150 milligrams a day and infliximab was started at a standard dosing of 5 milligram per kilogram at 0, 2, and 6 weeks.

In follow-up with this case, by the second infliximab dose, Jack is feeling a lot better. He has less abdominal pain, his bowel movements are more formed and now only twice a day and his appetite is improving, he is eating more, and he is starting to gain weight.

And, I think one more part, just to summarize that is key with this case, is evaluating a patient with perianal Crohn's disease prior to initiation of treatment, ideally you would like to do a good MRI, which was done here, to evaluate the fistula, the abscess, and the different possible fistula tracts, and then an exam under anesthesia with any intervention, such as drainage or seton placement. And, that is key for every patient with perianal Crohn's prior to starting therapy.

Slide 8: Long-Term Management of Severe Crohn's Disease and Ulcerative Colitis

So, for the first part of this talk I am going to speak about long-term management of severe Crohn's disease and ulcerative colitis. And, I would like to start with first talking a little bit about the natural history of Crohn's and ulcerative colitis and understanding that for most patients with both of these diseases and especially most patients with Crohn's disease, that this is a progressive disease. Meaning, if you look at older natural history studies of patients with Crohn's, the vast majority of people, about 80%, will initially present with an inflammatory phenotype. What that means is you will have your typical symptoms of diarrhea, usually non-bloody, abdominal pain, possibly some weight loss. However, these patients are followed out over 20, 25 years and they are not started on appropriate therapy, now over 80% of them will develop either fistulas or strictures. Furthermore, if you look at the natural history of surgery in Crohn's disease within a year of diagnosis, about 10 to 15% of patients with Crohn's disease will require surgery. And, if you follow these patients out for 20, 25 years, over two-thirds of these patients will now require surgery.

And, what we think is happening is although symptoms could fluctuate, as many of your patients that you see in the office, some will at some points in time, they will have more active symptoms, and other points of time they might have more mild symptoms. But, if we are not healing inside, over time this amount of bowel damage or irreversible bowel damage is slowly increased, which will lead to strictures, fistulae, and again eventually surgery.

And, there was one other comment, is that when I speak to patients with Crohn's disease, I think it is key to explain to them that

symptoms do not correlate with how they are feeling inside. So, it is not uncommon for somebody to come into the office feeling relatively well and then you do a colonoscopy and some type of imaging study and they have moderate-to-severe Crohn's disease. And, the flip side could be true as well, where we know they have Crohn's disease and their symptoms are severe and we look inside and everything actually looks pretty good and it is healed inside and maybe their symptoms are driven by something else, such as stress or infection.

Slide 9: Progression of Ulcerative Colitis

Now, I think it is also important here to talk about ulcerative colitis and I think people do not always realize that ulcerative colitis is also a progressive disease. About 30% of patients with ulcerative colitis will require colectomy. There is an increased risk of dysplasia and this is in patients with histologic inflammation, meaning that even if endoscopically it looks normal, but on biopsy there is inflammation. If they have this histologic inflammation, they have had symptom onset for over 8 years, that is when that dysplasia risk starts going up. And, we usually focus on patients with histologic evidence of disease more than just the rectum, so more than just proctitis.

And also, patients that have had disease for many, many years, this chronic inflammation, especially in their left colon, could lead to scarring, otherwise known as lead-pipe colon. And, these patients could have urgency, looser stools, increased frequency. And, that is just from chronic damage as well. So, not only Crohn's disease is a progressive disease.

So, as I mentioned, over time with our diseases, with both Crohn's and ulcerative colitis, that the disease may progress. So, when we are treating our patients with Crohn's and ulcerative colitis, our goals are not only to treat the symptoms, now the symptoms are extremely important, we want to improve their symptoms, we want to improve the quality of their life, however, symptoms are not enough, and our goal should be to heal them inside or to improve what is happening on the inside.

Slide 10: CALM Trial: Efficacy Results

Now, a lot of our older studies are retrospective, meaning looking back, showed benefit, but more recently we have a prospective study, randomized study, looking at this concept of treat-to-target strategy. And, this was called the CALM trial. And, what they did here was they took 244 patients with moderate-to-severe Crohn's disease, and they randomized them to 2 treatment arms. And essentially, 1 treatment arm was based on symptoms, meaning that at timepoint 0, if the symptoms were active, they were started on adalimumab, induction, and then every other week. And then, they would reassess symptoms every 3 months and based on clinical judgment, if their symptoms were not well controlled, now increase the adalimumab from every other week to once a week. And then, 3 months later if they were still not well controlled, they would add on an immune modulator like azathioprine.

In the treat-to-target strategy, every 3 months of that timepoint they not only looked at clinical symptoms, but they looked at objective markers of inflammation. So, CRP, fecal calprotectin, and so forth. So, for example, if a patient in the study was started on adalimumab induction, and then every other week maintenance, at around 3 months, even if they were feeling well, if their CRP was still elevated, if their calprotectin was high, they were going to move to that once weekly, so was the standard practice in treat-to-target arm.

And, you can see here in this slide that the primary endpoint of mucosal healing at 1 year was significantly higher in the tight control group, at close to 46%, versus the clinical management group, which was at 30%. And, when you look at some key secondary endpoints, really looking at deep remission, meaning mucosal healing and feeling better, improvement in their biomarkers, complete endoscopic healing, overall, the tight control group did better.

Slide 11: CALM Trial: Outcomes

There were some follow-up studies. This is a 2-year follow-up, looking at Crohn's disease-related hospitalizations, Crohn's disease-related surgeries, and then the composite outcome. And, you can see here at 2 years, we start seeing patients that were in the treat-to-target group have less hospitalizations. The surgical arm was not statistically significant and that is more likely due to the short-term follow-up. We even have some longer-term follow-up in abstract form, not fully published yet from this study, suggesting that patients that use this tight control, this treat-to-target, that achieved healing 2 years later they were less likely to develop fistulas, less likely to develop strictures, less likely to be hospitalized, or come to the ER. So, this is our first study, prospective study, randomized study, looking at the treat-to-target approach and really supports that.

Slide 12: Proposed Treat-to-Target Algorithm

So really, this is our new algorithm here. When we are treating somebody with moderate-to-severe Crohn's disease or ulcerative colitis or really in any case, we want to align our goals from the beginning. So, we have our target. And, the target might vary, based on the patient, based on the severity of their disease, and so forth, but you are going to have your initial target and if our target, as we were just discussing in certain patients are to heal the mucosa, we start treatment and then over those first 6 months we are constantly evaluating, meaning we are seeing them in the office, we are talking to them about their symptoms, we are looking at biomarkers, whether it is CRP, whether it is fecal calprotectin. We are repeating a colonoscopy 4 months later, 6 months later, depending on the patient, and if we are satisfied the patients are feeling better and we hit our target, then we continue with our strategy. If we are not satisfied and we are not hitting our target, then we reevaluate and make some necessary changes.

Slide 13: Non-Response to Anti-TNF Therapy

And, that sort of brings us nicely to the next part of the talk, is sort of non-response to our anti-TNF therapy.

Slide 14: Treatment Options for Severe Crohn's Disease

So, first just to touch on some of our recent guidelines and recommendations from our national organization. So, if you look at treatment options for severe Crohn's disease, the American College of Gastroenterology or ACG, put out their recommendation, and they recommended starting biologic therapy, whether it is an anti-TNF agent, whether it is an anti-integrin agent, or whether it is an IL-12/23, with or without combination with an immune modulator. We know trials from the SONIC data, showing the benefit of combination therapy, but they, depending on the situation, they recommended this with or without combination therapy, and the immune modulators we are speaking about are thiopurines, such as azathioprine or 6-mercaptopurine, as well as methotrexate.

Slide 15: Treatment Options for Moderate-to-Severe Ulcerative Colitis

Looking at the treatment options for moderate-to-severe ulcerative colitis, the AGA recommended anti-TNF agents, specifically infliximab, adalimumab, or golimumab, our anti-integrin therapy of vedolizumab, IL-12/23 inhibitor, ustekinumab, and Janus kinase inhibitor or JAK inhibitor tofacitinib, however, with the recent FDA changes only after failure of an anti-TNF agent. And, as monotherapy we could use thiopurines, such as azathioprine or 6-mercaptopurine, and methotrexate is not recommended as monotherapy for ulcerative colitis.

Slide 16: AGA Guideline on Therapeutic Drug Monitoring

So, if we have a patient that is failing therapy, this is where therapeutic drug monitoring comes into place. And, this is the AGA guideline on therapeutic drug monitoring. First, to talk about thiopurines, so that is azathioprine or 6-MP. In adult patients with IBD, that start on the thiopurine, prior to starting really we should be doing routine TPMT testing to see how they are metabolizing and whether it is safe to start azathioprine or 6-MP, and whether we need to adjust the dosage and how often we should be monitoring our patients. And then, for adult patients that are already on the thiopurine, again either azathioprine or 6-MP, if their IBD is active or if they are having adverse effects, then the AGA has recommended reactive testing. So, checking thiopurine metabolites, looking at the 6-TG, seeing if the 6-MMP is high and they are having hepatotoxicity, is the 6-TG high and they are having bone marrow suppression or it is a little bit low and we need to push that dose. The AGA, however, does not recommend routine thiopurine monitoring in patients that are quiescent or that are doing well with their IBD.

Now, an anti-TNF agent and drug monitoring, this is a pretty controversial topic, and what the AGA recommends, that patients with active IBD, treated with an anti-TNF agent, that they recommended reactive therapeutic drug monitoring. However, they do not recommend proactive drug monitoring.

Slide 17: Therapeutic Drug Monitoring

And, when we are talking about biologic TDM or therapeutic drug monitoring, specifically anti-TNF, there is reactive TDM and proactive TDM. Just to define these 2 conditions, reactive therapeutic drug monitoring occurs when symptoms worsen and the goal is to improve

clinical care, and it is shown to improve clinical care and to be cost-effective. Proactive TDM is when you are checking a drug level when patients are feeling well. So, this could be during induction or shortly after induction. This could be during maintenance when they are feeling well. And again, retrospective data has shown the benefits of proactive TDM on clinical outcomes in patients. However, our prospective data has not shown those outcomes and that is why it is not recommended by our societies across the board.

However, certain scenarios where I think if you are somebody that does not do proactive drug monitoring, where it could be helpful, is if you are thinking about withdrawing therapy or backing off on an immune modulator, such as 6-MP, azathioprine, or methotrexate. Checking a drug level at that time I think is very important. And patients, if you have had a drug holiday, whether it is insurance reason, whether it is another reason, and you want to restart therapy, I think that is where we want to definitely proactively monitor. But, across the board, it is not recommended by our societies.

Slide 18: Therapeutic Drug Monitoring

So, this just summarizes what I just said. Reactive TDM has been accepted as important. Benefits of proactive monitoring were less established. Again, there is a lot of variation. And, as we get more data, we will be published, and the guidelines will be updated.

Slide 19: Jack – Follow-up Visit

So, coming back to the case. Jack had perianal Crohn's and Crohn's colitis and he was on infliximab 5 milligrams per kilogram every 8 weeks and azathioprine 50 milligrams a day and he was doing well. About a year prior to presentation now, the seton fell out, and he had no further problems with his fistula. However, during his current visit he complains of abdominal bloating, right lower quadrant pain that occurs a few hours after eating, and especially after he eats certain foods like popcorn or nuts. Jack says that this feels different than any of his Crohn's symptoms, his Crohn's abdominal pain that he had a few years back when he was sick with his fistula and active colitis.

Slide 20: Jack – Diagnostics and Surgery

He had a CT enterography and there was a 6-centimeter stricture at the ileum and there was also dilation of the small bowel proximal or above the stricture. Colonoscopy was then done, confirmed the stricture in the ileum, and the scope could not be passed fully into the ileum due to the stricture. Based on these findings, Jack undergoes an ileocolonic resection with a primary ileocolonic anastomosis.

Slide 21: Challenge Question

So, this is our second Challenge Question for Jack. Which of the following is an approach to managing a patient who is at high risk for postoperative recurrence of Crohn's disease? Is it (A) Prescribe no medication and repeat a colonoscopy 24 months postoperatively; (B) Prescribe anti-TNF therapy and repeat a colonoscopy 6 to 12 months postoperatively; (C) Prescribe mesalamine and repeat a colonoscopy 12 months postoperatively; or (D) Prescribe 6-mercaptopurine and repeat a colonoscopy 18 months postoperatively.

The answer is B, prescribe anti-TNF therapy and repeat a colonoscopy 6 to 12 months postoperatively. And, we are going to go into a little more detail in the next few slides of why that is. But in general, certain patients with Crohn's are at increased risk for recurrence, so in those patients we want to start therapy postoperatively, relatively soon after surgery, but the key point, whether somebody gets started on therapy or not, it is extremely important to do that colonoscopy 6 to 12 months after surgery.

Slide 22: Surgery for IBD

So, let us talk a little bit about surgery for inflammatory bowel disease.

Slide 23: Indications for Operative Management of Inflammatory Bowel Disease

So, these are overall indications for operative management of inflammatory bowel disease. So, acute complications or a patient urgently needs to go to surgery is toxic megacolon. A key point with toxic megacolon, this is a clinical diagnosis. If you are seeing a colon dilate on imaging you might already be too late, so you need to have a high suspicion for toxic megacolon. For an acute hemorrhage and

acute bowel obstruction that is not resolving and for a perforation. And then, a lot of the patients that are going to the operating room are more for chronic disease complications, so not these extremely urgent surgeries. So, this is medically refractory disease, failed multiple biologics or immune suppressants, recurrent intra-abdominal abscesses, chronic small or large bowel stricturing or penetrating disease with recurrent symptoms, neoplasia, and then also in certain situations, growth retardation in children due to the severity of disease.

Slide 24: Natural History of Crohn's Recurrence

So, let us talk about the natural history of Crohn's recurrence. So, if you take all patients that had surgery for Crohn's, once they are reconnected, so the key is once the fecal stream is reintroduced, there has been some studies, small studies, that showed as early as 1 week after resection and reconnection, that there could be histologic recurrence. If you look at all-comers of patients, follow them out a year, without putting them on appropriate therapy, 70 to 90% of patients will have endoscopic recurrence of disease after surgery. However, looking at clinical recurrence, the clinical recurrence in the short-term is pretty low. Only about 30% of patients with Crohn's will have symptoms 3 years after surgery, and 60% may have symptoms 10 years after surgery.

So, this goes back to that challenge question of Jack, where waiting for symptoms is too late. We are already seeing early histologic, early endoscopic recurrence, and if we wait a couple of years for symptoms, we are already going to be behind the 8-ball.

Slide 25: Predictors of Clinical Recurrence

So, how do we, predictors of clinical recurrence. The other thing I mentioned earlier was that doing a colonoscopy 6 to 12 months after surgery is extremely important. And the reason that is important is, it could help frame and predict what is going to happen with this patient down the road. And, this is called, when you do the colonoscopy we like to assess, using something called the Rutgeerts score. And, what you are looking at is that the anastomosis and the neoterminal ileum or the small bowel, just proximal to the anastomosis. And, we grade this from a score of i0 to i4. i0 is perfect, i1 is less than 5 aphthous ulcers, i2 is more than 5 aphthous ulcers, i3 is diffuse inflammation, and i4 is more significant inflammation, deep ulcerations, stricturing, and narrowing.

And, if you have an i0 or i1, that shows less than a 10% clinical recurrence rate at 10 years, or that is predictive of that. So, when we do the colonoscopy, if somebody has a normal looking neo-TI or less than 5 aphthous ulcers, that is somebody that we are happy with whatever therapy that they are on. i2, if you start seeing more than 5 aphthous ulcers, that has about a prediction, about a 20% clinical recurrence rate at 5 years. And, if you already see i3 or i4, so significant inflammation in that neo-TI, you have 50 to 100% clinical recurrence rates in the short-term. And, i4 patients have high rates of reoperation.

The other part that we talk about with Jack's case is, so we know we need to do a colonoscopy after surgery, to evaluate for recurrence. And then, we have our Rutgeerts score to help predict recurrence rates. But the question is, do we need to start people on therapy immediately after surgery or within 4 weeks after surgery. And, that is when we risk stratify our patients.

Slide 26: Risk Stratification for Crohn's After Surgery

So, somebody with low risk is somebody that has a short stricture that has had Crohn's for a long period of time. Somebody that is at higher risk of recurrence is somebody that has penetrating disease, fistulizing disease, somebody that is a smoker, or this is their second surgery. And then, moderate is something that is in between, so ongoing inflammatory disease, longer strictures, and so forth. So, somebody that is at high recurrence, moderate recurrence, these are patients that you are going to consider and most likely should put on some type of therapy, whether it is an anti-TNF, which I use in my practice, or a thiopurine within 4 weeks after surgery, and after reconnection if they were diverted.

Slide 27: PREVENT Study

So, one study to discuss the benefit of using anti-TNFs, specifically infliximab in this postoperative setting, is the PREVENT study. This is a multicenter trial of 297 patients with Crohn's disease. They had undergone ileocolonic resection within 45 days, and they were randomized to infliximab or placebo. And, you can see here that although they did not hit their primary endpoint of clinical recurrence, that there was significantly lower endoscopic recurrence, only 30% versus 60% in 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 pretty low early on postoperatively.

Slide 28: Surgery for Ulcerative Colitis

To touch on surgery for ulcerative colitis, for most patients we are offering a total abdominal colectomy with a J-pouch or ileoanal pouch anastomosis, and this most commonly is done over 3 steps. What they do in the first step, they do remove your entire colon, however, you leave the rectum behind. And, the reason we leave the rectum behind initially is most of these patients that are having surgery done have a lot of inflammation, have been recently on steroids or other types of immunosuppressive therapy, so we want to minimize complication from going into the pelvis. The second stage, the rectum is removed, they make the J-pouch out of the small bowel, and then they connect everything. However, they still keep a proximal diverting ostomy to allow all those anastomoses to heal and mature. And then, the third surgery is a quicker surgery, where you just reconnect.

Patients do very well with this surgery and with surgery in general for IBD, it should not be looked at as the last possible option. Patients that are very sick, they have their colon out, they have a J-pouch, they are going to do very well.

Slide 29: Ileal Pouch Anal Anastomosis

If you look at complication rates, there are some early complication rates, however, these are easily, for the most part, sort of taken care of in the short-term. When we are talking about long-term complications, there is decreased fecundity, meaning the chance of getting fecundity is different from fertility, with fecundity being the chance of somebody getting pregnant per cycle. However, what we learned is a lot of the reason we think this is happening is that during the surgery there could be some scarring around the fallopian tubes, so if there is scarring around those tubes, patients with pouches have shown to do very well with IVF.

Pouchitis or inflammation of the pouch can occur and could occur in up to 50% of patients. However, the vast majority are easily treated with antibiotics.

And then, looking at, you know, in expert hands, pouch failure is extremely low, and these pouch failure rates in certain studies, when you are following these patients out for 20, 25 years, range around from 5 to 7%.

Slide 30: Ileal Pouch Anal Anastomosis

This is just one study I always like to show and discuss with my patients, looking at clinical outcomes, what they could expect. Pouch success, as you see here, 20 years later, 92%.

Slide 31: Ileal Pouch Anal Anastomosis

And when you are talking to patients about what they could expect after a J-pouch, their new normal is going to be about, you know, I tell them about 6 bowel movements a day, could be 6 to 8, could be 4 to 6. About 10 to 20% of patients might have 1 or 2 of those bowel movements at night. However, their quality of life and their work is significantly improved from preoperatively.

Slide 32: Summary

So, just to summarize. Treatment of Crohn's disease and ulcerative colitis has evolved. We want to select the right patients that we are worried about progression, and if these patients we are worried about progression of their disease earlier, more aggressive therapy is key. And, I do not even love to use the term aggressive, I think earlier, more appropriate therapy is key. So, starting on our biologics earlier on in the right patient. And, our goal, although treating the symptoms, improving the quality of life is extremely important, that alone is not enough, where we have to target, we have to target the gut, target the mucosa, and we have to heal the mucosa. When we are starting therapy in our more complicated patients, somebody with extensive small bowel involvement, penetrating disease, deep ulcers in the colon or the small bowel, we want to start with a biologic therapy. A lot of times we are combining that with an immunomodulator. Practically speaking, more than half of our patients with Crohn's will still require an intestinal resection and that is usually because by the time they present or by the time we start therapy, the disease has already progressed and had irreversible damage to the bowel. So, surgery should not always be looked at, especially in Crohn's disease, as the last line of therapy. Sometimes should be used earlier on. But, realize that surgery is not a cure, the disease can recur after surgery, and keep close monitoring with colonoscopy and using anti-TNFs early on, postoperatively in certain patients, is critically important.

Slide 33: Thank You!

So, I want to thank you for your time and 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.

Narrator:

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