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Diagnosis, Management, and Monitoring of IBD: Early Diagnosis and Individualizing Therapy

Announcer:
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Dr. Sands:
Hello, and thank you for participating in this educational program entitled IBD Resource Center for Primary Care and Gastroenterology Professionals; Your One-Stop Shop for Managing IBD. This module is part of a core IBD curriculum provided by the American Gastroenterological Association, and Partners for Advancing Clinical Education in partnership with Practicing Clinicians Exchange, and Clinical Care Options. This activity is supported by educational grants from Amgen, Ferring Pharmaceuticals, and Takeda Pharmaceuticals USA.

I'm Bruce Sands, Chief of the Dr. Henry D. Janowitz Division of Gastroenterology at Mount Sinai Hospital, and Chief of the Division of Gastroenterology at Mount Sinai Health System, and Director of the Digestive Disease Institute at the Icahn School of Medicine at Mount Sinai in New York.

Today, in the first six Medical Minute presentations, I'll be discussing diagnosis, management, and monitoring of IBD, early diagnosis and individualizing therapy. The objectives for this Medical Minute are for you to be better able to describe early signs and symptoms of IBD to prevent delays in diagnosis and treatment initiation and to implement strategies for individualizing initial therapy in patients with IBD based on available agents and guidelines.

We'll start with early diagnosis. We'll begin with a case study of Kate who's 24 years old, and who presents with complaints of chronic diarrhea, intestinal cramping, that's been going on for 2 months, preceded by mildly aching joints. She has an exam that's notable for right-sided abdominal tenderness without a mass, and no hepatosplenomegaly. On perianal examination, she has prominent skin tags, but no joint effusions or other skin lesions. She does, however, have an oral ulcer.

So what are the signs and symptoms of inflammatory bowel disease? Well, the cardinal signs are chronic diarrhea and abdominal pain, and a particular feature that suggests an organic etiology would be nocturnal diarrhea, or the presence of bleeding. Many patients if they have perianal disease as part of a diagnosis of Crohn's disease might also have perianal fistula or abscess, and might therefore have anal pain. Patients may have systemic manifestations such as unexplained weight loss or fever, or may have anemia that's chronic or recurrent. And on laboratory examination, they may have a high fecal calprotectin. Also notable is that inflammatory bowel disease are chronic conditions that also involve extraintestinal manifestations that can involve joints, eyes, skin, and other organs.

As you can see here, there are many potential extraintestinal manifestations. Some of these may be related to the underlying IBD activity, and others seem to be independent of existing IBD inflammation in the bowel. So for example, uveitis and iritis tend to run a course separate from the bowel inflammation and are not directly related, and the same would be true of spondyloarthritis. But

peripheral arthralgias tend to correlate with the presence of active inflammation. In all, something between 25 and 40% of patients will develop extraintestinal manifestations associated with their IBD over time.

IBD has a very broad differential diagnosis, most prominently including irritable bowel syndrome, which might occur in up to 20% of women in the general population of the United States. Patients may also have infectious colitis that may be chronic or ischemic colitis or microscopic colitis. Various infections that would be common would include C. difficile infection, and occasionally you'll find a patient with celiac disease or lactose intolerance, who may have diarrhea as a consequence of an adverse event from medications or rarely colorectal cancer. All of these things are in the broad differential of inflammatory bowel disease.

The American Gastroenterological Association recommends a laboratory workup for chronic diarrhea that includes the use of stool markers of inflammation, such as fecal calprotectin or fecal lactoferrin to screen for IBD, but does not recommend the use of blood markers such as erythrocyte sedimentation rate or C-reactive protein. They do recommend testing for Giardia, which would be a common infectious cause of chronic diarrhea, but do not suggest more broadly testing for ova and parasites, unless the patient has recently traveled to or immigrated from a high-risk area. It would be prudent to check the patient for the presence of celiac disease by using a tissue transglutaminase IgA and a second test for celiac disease if there's IgA deficiency that makes the first test invalid. And you may also test for bile acid diarrhea; however, the recommendation is conditional on the quality of evidence for this as low.

Returning now to our patient, the initial workup included a fecal calprotectin, which was elevated at 326 micrograms per gram. Tests for Giardia, celiac disease, and bile acid diarrhea were found to be negative. So what are the next steps in the diagnostic process as you continue to suspect IBD? Well, every patient who has a diagnosis of inflammatory bowel disease should undergo ileal colonoscopy. On the left-hand side, you can see a smooth glistening mucosal appearance within mucosal folds and very clear vascular pattern. On the right, you can see a variety of different appearances of various ulcers, which may include cobblestoning, serpiginous, or aphthoid ulcerations, segmental involvement, and healthy mucosa in between very diseased-appearing mucosa. You might also see the occurrence of stenosis or fistulas, which are complications of chronic inflammation in many patients with Crohn's disease. And typically, you'll see rectal sparing in Crohn's disease.

In ulcerative colitis, the appearance is typically inflammation that starts at the anal verge and proceeds proximately to involve more and more the colon, perhaps the entire colon, or perhaps just lesser segments, including left-sided colitis, or proctosigmoiditis, or even just proctitis. The inflammation is diffuse, it's symmetric, and it has this rectal origin proceeding proximately but also shows edematous and ulcerated mucosa in many cases. There doesn't have to be inflammation, as evident by ulceration; the inflammation could also be more like a granular appearance, such as you see in Panel B, with very little ulceration. But you might see in more severe disease, even spontaneous bleeding that occurs. And with healing, over time, there can be the presence of pseudopolyps.

We would like to try, before we choose a path to embark upon for therapy for a patient, a risk stratification approach so we can select the right therapeutic approach. And we would like to divide patients into those who are at low risk for progression and those who are at high risk for progression. Patients who are at high risk are generally younger patients less than 30 years of age, have more extensive anatomic involvement, may have the inclusion of perianal or severe rectal disease, they will have the appearance of deep ulceration, and if the patient has already had prior surgical resection or has had complicated disease behaviors, such as stricture or fistula, those patients are considered to be at high risk for their Crohn's disease.

In ulcerative colitis, the risk factors for a progression of disease are slightly different. Here, we see younger patients also at risk, but at a dividing line of 40 years of age. And a greater anatomic extent also is – confers more risk, more severe inflammation is seen endoscopically or deeper ulcers once again all weigh toward a higher risk for progression. Patients with more severe disease may also have a decrease in albumin, as well as elevation is C-reactive protein in the most severe disease. And if the patient has prior history of hospitalization, they're also at high risk for progression.

So how do we choose an individualized treatment for a given patient? Well, returning to our patient, a specialist workup reveals on MR enterography, that there's 20 centimeters of terminal ileal inflammation. And there's also complicated behavior of a fistula from the ileum to the cecum with chronic inflammation, highly suggestive of Crohn's disease. The colonoscopy and biopsy show both acute and chronic inflammation, and non-caseating granulomas, such as may be seen in up to 25 to 40% of patients with Crohn's disease, but it's not specific for a diagnosis of Crohn's. Nevertheless, the gastroenterologist determines that Kate has Crohn's disease. So what is the best therapeutic approach for her?

Well, early treatment is really quite an important thing in patients, particularly with Crohn's disease, but probably also ulcerative colitis. As symptoms continue to go up and down over time with waxing and waning flares, underneath it all, there's an accumulation of damage to the bowel with occurrences of strictures, fistulas, and fibrosis. Whereas we think that with early institution of effective therapy, you can decrease bowel damage and prevent the need for multiple surgeries, especially in a patient with Crohn's disease. Effective treatment is needed in both ulcerative colitis and Crohn's disease to provide adequate control of symptoms and of mucosal

inflammation, done in the treat-to-target approach.

There are some principles by which we can select early therapy for a patient so that we can choose an ideal and appropriate therapy. And here, we can differentiate between disease activity, which are the symptoms at the moment that you're seeing the patient, which may be categorized as mild, moderate, or severe, and is really a snapshot of those symptoms, not what we're seeing over time, which is really disease severity. That is the movie reflecting the entire course of the disease, and includes a range of variables that include not only symptoms, but also objective findings, past treatment experience, the prior need for surgery, elevation of inflammatory biomarkers, and other functional aspects. So if we consider disease severity, rather than just disease activity, we can likely personalize therapy and help the patient choose according to their risk-benefit preferences and their desire for convenience, also considering comorbidities, demographic factors, and their prior treatments.

So there are many pieces in the therapeutic puzzle for IBD. There are factors related to the drug, particularly efficacy and safety factors, that will help you choose the correct positioning and sequencing of therapies. And there are also characteristics of the patient, their individual characteristics such as their age, stages of life, presence of comorbidities, and their own preferences, and the disease characteristics for that patient, such as we said before, the extent of disease, early versus late disease, and most importantly, prior treatment success or failure.

In our armamentarium, we have both small molecules and biologic therapies. There are advantages and disadvantages to each of these kinds of agents. For small molecules, we have a simple well-defined structure, which may be stable at a range of temperatures. And these are produced by chemical synthesis, which in theory will be cheaper to produce though not necessarily cheaper to purchase. And these are nonimmunogenic in contrast to biologic agents, which have the potential to be immunogenic in nature. Because small molecules are mostly well absorbed, they can be given orally, whereas biologics, so far, need to be given parenterally, either subcutaneously or intravenously. With small molecules, drug-drug interactions are potentially problematic. Whereas with biologics, such drug-drug interactions are very unlikely. And with regard to adverse events, you can see both off-target and on-target adverse events with small molecules, whereas with biologics, the adverse events are very likely to be on-target effects.

So what are the agents that we can use for the treatment of IBD? Starting with the small molecules, we have classes of agents that include corticosteroids and anti-inflammatories, comprising the class of amino salicylates such as mesalamine and sulfasalazine. And we have immune modulators, such as the thiopurines, azathioprine and 6-mercaptopurine and methotrexate. And as you can see, corticosteroids would be useful for induction but not for maintenance. Amino salicylates are useful in ulcerative colitis for induction and maintenance but not really effective in Crohn's disease, whereas the thiopurines are really utilized for maintenance therapy primarily and as combination therapy with anti-TNF antibodies. And methotrexate has some limited benefit as monotherapy in Crohn's disease and no benefit in ulcerative colitis.

So, turning now to the biologic agents, we have the TNF inhibitors, adalimumab, certolizumab, pegol, golimumab, and infliximab, which are all useful for induction and maintenance. We have an alpha 4 beta 7 integrin inhibitor called vedolizumab used in induction and maintenance for both conditions. We have an anti-IL23 and 12 inhibitor called ustekinumab, again useful in both conditions for induction and maintenance. And now recently approved we have an anti-IL23 antibody called risankizumab, useful for induction and maintenance in Crohn's disease. But we also have advanced therapies that are small molecules used and approved in ulcerative colitis, including an S1P modulator, ozanimod, and two Janus kinase inhibitors tofacitinib and upadacitinib.

There are a number of guidelines available to direct therapy for the treatment of IBD. In this one from the AGA, we see the initial treatment of Crohn's disease, and we have treatments targeted to the low-risk patient, or to the moderate- and high-risk patient. For the low-risk patient, we look at the location of disease, and if the patient has ileal and/or right colonic disease and little to no symptoms, we might choose budesonide as the initial treatment with or without azathioprine, and a tapering course of the steroid, again, with or without azathioprine, to maintain. If the patient has diffuse or left colonic disease, again, with just mild symptoms, we might again choose a course of prednisone, with or without maintenance with azathioprine.

But if these courses of action fail, then the patient moves into the moderate- to high-risk category, and we would be reaching for biologic therapies like anti-TNF antibodies with or without a thiopurine, or methotrexate if they don't tolerate a thiopurine, but also reasonable would be ustekinumab or ibalizumab. And while the guideline says immunosuppressing medication can be used in combination with use ustekinumab and vedolizumab, data to date do not show the benefit of adding that in combination in monotherapy, but these two biologics seems to be fine.

There is also an algorithm for severe disease and Crohn's disease, and here we would probably reach for an anti-TNF agent such as infliximab or adalimumab, in combination with the thiopurine or methotrexate. And these are patients with higher inflammatory burden, higher disease severity, perianal disease, or severe extraintestinal manifestations, or who are also obese and need more drug. So a patient would do better probably within infliximab than with adalimumab, and combination therapy is preferred over monotherapy. But if

the patient has significant comorbidities, or contraindications to a TNF inhibitor, then the agent of choice is likely to be ustekinumab monotherapy. If the patient, on the other hand, is risk averse, or has prior serious infections, or prior malignancy, is an older patient with multiple comorbidities, for the patient with moderate disease severity, vedolizumab monotherapy might be a good choice. And if the patient has higher disease severity, ustekinumab is probably going to be the better choice.

Returning to our patient, colonoscopy with biopsy reveals instead, continuous symmetric inflammation from rectum to splenic flexure, and acute and chronic inflammation with normal mucosa proximal to the splenic flexure. So in this case, the patient now really has ulcerative colitis, and the GI specialist determines that diagnosis. So how does having ulcerative colitis have an effect on the therapeutic approach? Well, the AGA guidelines look at mild to moderate ulcerative colitis as being prime targets for the use of 5-amino salicylates of various sorts as being preferred to budesonide therapy. If there's a suboptimal response to low-dose mesalamine, you can increase the dose. And if they're refractory to optimized therapy, then you will use a steroid in addition, such as prednisone or budesonide MMX. Also you can give different routes of administration in ulcerative colitis because if the patient has proctitis, you can give mesalamine suppositories, if they have proctosigmoiditis or left-sided colitis, a rectal enema would be just fine. For patients with disease extensive beyond the splenic flexure, then oral and rectal therapy will probably do better. And always we prefer to start with mesalamine over topical steroid therapy.

If the patient is in remission on sulfasalazine or has prominent arthritis, you may choose to continue therapy with that agent. Also, it's a cheaper agent to use. And if you're using once daily dosing with oral mesalamine, there's no difference in induction outcomes as compared to split-day dosing but better compliance. So patients could place a higher value on convenience over efficacy may choose oral therapy alone in consideration of the rectally administered therapies.

For patients with moderate to severe ulcerative colitis, here the AGA recommends turning to biologic therapies with infliximab preferred over adalimumab based upon relative efficacy. Vedolizumab preferred over adalimumab, and ustekinumab is affected but not ranked in these particular guidelines, except in patients who have previously failed infliximab or had primary non-response. And ustekinumab here would be preferred over adalimumab to vedolizumab. Also, tofacitinib can be used after failure of a TNF antagonist, and it's preferred over adalimumab or vedolizumab in that situation.

Other considerations for positioning of therapies and moderate to severe IBD include the age of the population, whether they're an inpatient, their history of cancer perhaps, or lymphoma, whether they might be pregnant, whether they have steroid responsive or mild to moderate disease, or the presence of extraintestinal manifestations, such as arthritis, or whether they've had previous TNF inhibitor failure. And you can see that depending on these spectrum of different factors, you may choose one agent or approach over another.

The different treatments that we use have different adverse events. Corticosteroids have well-known many different negative consequences, including a rare occurrence of a vascular necrosis of the hip. Amino salicylates are generally quite safe agents that may have rare effects of interstitial nephritis or pancreatitis. And immune modulators, in addition to being immune suppressing to some degree and making patients susceptible to various infections, also increase the risk of lymphoma and non-melanoma skin cancer in the case of purines, and also with methotrexate, fibrosing alveolitis is a very rare occurrence. Here with the biologics, you can see a variety of different risk factors, the safety of vedolizumab and ustekinumab and risankizumab seems to be much better than with the TNF inhibitors, where there clearly is an increased risk of infections, as well as lymphoma, melanoma, lupus-like syndrome, and other things that we see the TNF inhibitors, but not these newer biologic agents.

With the small molecules, you can see a variety of different adverse events, including effects on pulmonary function, hypertension, macular edema in the susceptible patients, bradyarrhythmias, and other cardiac effects, and I would say drug-drug interactions.

For the JAK inhibitors tofacitinib and upadacitinib, you can see an elevation in total cholesterol and creatinine phospho kinase. But we see serious infections only in the occurrence of increased risk of herpes zoster, which you can vaccinate for, but also potentially the risk of major adverse cardiovascular events, malignancy, and even increased risk of mortality and thrombosis.

So in summary, there are many choices in IBD therapy, but very limited head-to-head data. So a variety of individual patient characteristics do come into play, considering whether a patient is considering starting a family or is pregnant, whether they've had previous history of failing anti-TNFs, whether they're newly diagnosed, whether there are important lifestyle considerations such as convenience and the ability to travel, and in special situations where pharmacokinetics of certain drugs may be unfavorable, or the presence of perianal disease.

So you can find other educational offerings with Section 1 of this program at the links on this slide. Additional program components will be released over the next couple of months. Find more CCO and PCE educational coverage on IBD and more online.

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