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Managing Postoperative Crohn's Disease: Key Therapeutic Approaches

Dr. Buch:
Managing postoperative Crohn's disease can be challenging. What are the therapeutic approaches we should be considering?

You're listening to *GI Insights* on ReachMD. I'm your host, Dr. Peter Buch. Here to help us better understand this topic is Dr. Robert Battat. Dr. Battat is the Director of the Center for Clinical and Translational Research for Inflammatory Bowel Disease at the University of Montreal. He's also the lead author of "Advances in the Comprehensive Management of Postoperative Crohn's Disease," which appeared in Clinical Gastroenterology and Hepatology, which was published in July 2022.

Welcome to the program, Dr. Battat.

Dr. Battat:
Thanks for having me.

Dr. Buch:
Dr. Battat, to start us off, what are the confounders in diagnosing and treating postoperative Crohn's disease?

Dr. Battat:
It's important to start by saying that it's a period in Crohn's disease where symptoms really don't line up well with the actual inflammation that is happening to the colon or small intestine. What I mean by that or to illustrate, you know, there have been a lot of studies that have come out. Particularly, there was a randomized controlled trial of infliximab in postoperative Crohn's disease, and what they showed was that, you know, they had a whole bunch of patients that had both kind of symptomatic assessments, and then they had colonoscopies, and they were able to show that in fact, if you're sitting in a clinic with a patient and you're trying to use symptoms to diagnose the inflammation that's going on in the organ, the sensitivity and specificity is approximately, you know, in the 50 percent range. So, it's quite poor. And what that means is that if you have symptoms, there's about a 50 percent chance that you actually have inflammation, but there's also a 50 percent chance that you don't have inflammation. And vice versa, if you don't have symptoms, there's a 50 percent chance that you have inflammation still even if you don't have any symptoms, so there are issues with, you know, basing any management on symptoms.

In terms of confounder, for the people who actually do have symptoms, so you've had a surgery, you're sitting in clinic with your doctor, the two main confounders that are thought to be, causes of, say, diarrhea or abdominal pain; obviously there's the Crohn's disease in and of itself, which obviously has to be thought of, but if it's not Crohn's, there's bile acid diarrhea. And then we've also looked at small intestinal bacterial overgrowth. There's data essentially showing that bile acid diarrhea seems to be the main confounder of diarrhea in postoperative Crohn's disease, which is not particularly surprising. And there was a large study recently presented at DDW, and they showed that there's approximately 300 patients with SIBO testing but positive or negative, and they haven't shown that SIBO test, a positive SIBO test actually confounds symptoms. So really, the main confounder is bile acid diarrhea.

Dr. Buch:
Thank you for those insights. That's great. Are there any limitations that come with using faecal calprotectin in predicting Crohn's disease recurrence?

Dr. Battat:
I found it interesting how faecal calprotectin is thought of as a predictive tool. And the reason I say that is because faecal calprotectin is a marker of active intestinal inflammation. And so, when a calprotectin is elevated, one would think, "Well, doesn't that mean that the intestines are currently inflamed, like now, not in the future?"

And so, you know, and maybe I'm being a little bit picky in terms of the wording, but I find that really calprotectin's use is not in predicting a future occurrence but actually diagnosing a current recurrence. And if it is elevated, that probably means that you do have active inflammation at the time, and something should be done about it.

One of the issues with calprotectin is that in ileal Crohn's but also in postoperative Crohn's there are sensitivity and specificity issues. So, what that means is that depending on the cutoff that you use for calprotectin you could have different problems with its test characteristic. So, for example, if a faecal calprotectin is 50, it's very sensitive to rule things out. So, what that means is that, like, if a faecal calprotectin is less than 50, you can be fairly certain the sensitivity is like in the 90, 80 to 95% range. You could be certain that if it's less than that, that there's very low chance that you currently have active inflammation.

The problem is that very few patients are less than 50, so, when you look at higher cutoffs like 200 or 250, then the sensitivity of that is not great. So, if it's less than 250, um, it's not great for ruling out active inflammation at that point. Same thing, you know, on the other end of the spectrum. You know, is it good to confirm, like to rule in? The specificities depending on the cutoff have issues too. And the problem is a lot of patients lie in—You know, you might get a calprotectin of 130, and, you know, what does that mean? It probably is not great to say you don't have. And so, in those contexts, you typically need to do a colonoscopy. And so, I think that's why there was a study called the POCER trial, and they really did show that, you know, doing a colonoscopy six months postoperatively, was associated with improved patient outcomes, and I think that's, you know, because we don't really have great noninvasive diagnostic tests.

Dr. Buch:
That's great insight. Thank you. So, this is an issue that we all are faced with, and I'd love to see how you answer this. Dr. Battat, how do you treat a patient who has postoperative inflammatory Crohn's disease with no symptoms yet mild recurrence seen on endoscopy?

Dr. Battat:
Yeah. No, that's a great question. There was this study, the PREVENT trial, which was where, you know, infliximab was compared to placebo to prevent postoperative recurrence in Crohn's, and, you know, I'm bringing this up because, you know, at the follow-up visit, there were, you know, between groups approximately 20 odd percent of patients recurred with symptoms, like had symptomatic recurrence, but about 60 odd percent had endoscopic recurrence, so, you know, actual inflammation. So, what that tells us is that a lot of patients who have recurrence of their actual disease visualized in their colon don't feel it yet.

Then there's other studies that have really shown that either if you're looking at the anastomosis, so, like, looking at whether there's, you know, what we call a Rutgeerts i2, which essentially just means that there's more than five ulcers or large ulcers or distant ulcers, but also now as things evolve, we're learning that ulcers in the ileum, so above the anastomosis, is really associated with worse outcomes in terms of hospitalization, a second surgery, and then future symptomatic recurrence as well. And so, in patients who I see ileal ulcers, I'm very quick to augment therapy, in patients who really have what we label the i2 recurrence, even in the absence of symptoms, I will, you know, sit down with our patients and say, 'Listen,' you know, 'there are good data to say that if we augment your therapy,' whether that be that they're not on therapy and then we add or they're on therapy and we augment it, that it's actually associated with better outcomes. And so, we do that, and then six months after that we'll take another look.

Dr. Buch:
For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Robert Battat about postoperative Crohn's disease.

Now, as we know, some patients may fail anti-TNFs pre-op because they're given too late. Dr. Battat, can you tell us when they're worthy of a retry post-op?

Dr. Battat:
I think that obviously, there are certain scenarios, where a preoperative TNF antagonist was given, and probably shouldn't be given postoperatively. You know, most importantly is the ones where you've had immunogenicity to, say, both of them and then to retry that, you know, so antibodies to the drug.

And so, there was actually an analysis that was presented at the last DDW that actually looked at that question specifically, there was a comparative analysis of TNF antagonists versus ustekinumab in post-op, and what they showed was that in all patients, actually, the TNF antagonists were the best, but, you know, within the group that had seen TNF antagonists preoperatively, the best medicine postoperatively was still TNF antagonists. So, it tells us that these are very good medicines that have randomized controlled trial data, and it's possible that the mechanism of failure in the context of a huge inflammatory burden, it's not that, you know, the mechanism didn't work for you. It's just that the mountain was too high to overcome. So, yes, they can be given, you know, a TNF antagonist postoperatively, and it's probably in a high-risk patient the best thing to try.

Dr. Buch:

Perfect. And continuing with a similar theme, which of our patients may benefit from both an anti-TNF plus an antimetabolite post-op?

Dr. Battat:
I think that if you have prior immunogenicity, so prior antibodies to one type of anti-TNF, then the postoperative, let's say you're trying a second anti-TNF. It clearly makes a lot of sense to add an immunomodulator to your TNF antagonist.

In terms of other contexts, well, we know that the SONIC trial showed that combination therapy is better than monotherapy with either azathioprine or infliximab. So, in the highest-risk patients who've kind of run out of options and they have now lost also intestine, I think those patients do warrant, the best therapy that we have, which currently is combination therapy. I think it's also when we're talking about combination therapy it's important to note, that there have been meta-analyses that have shown if you give less than 12 months of azathioprine, it is not associated with increased risk of malignancy, and so it seems as that risk, although very small, the risk of malignancy with azathioprine is only really once you start taking it chronically. So clearly, in a very high-risk patient, I start, you know, on the combination therapy, and then you reevaluate, at some time, you know, six months postoperatively and even, you know, again a second time before one year and if really there's no evidence of disease, at that point you can consider pulling off. And there were recent data also presented where there was a randomized controlled trial from France where they had people on combination therapy and then they withdrew the azathioprine, and they actually showed that if you did well on the combination therapy and then you withdraw after, you could actually the outcomes are the same, so you could translate that to the postoperative context. So, typically, I'll try, you know, if they're doing well for a year with the combination therapy then you could attempt a withdrawal.

Dr. Buch:
Before we close, are there any other thoughts you would like to share with our audience today?

Dr. Battat:
I think the main thought is that a majority of patients with Crohn's disease at some point in their life have required a surgery, and often the patients had had medications that did not work for them. They have lost intestine. And I think it's a phase in which, you know, makes a lot of patients very nervous. Is the disease going to come back? What happens if it comes back? Will the medicines work? Will I lose more intestine? Will I end up on TPN? It's an area that I believe requires a lot more focus, a lot more research and very, very clinically close surveillance of these patients.

Dr. Buch:
This was an excellent discussion on postoperative Crohn's disease. I want to thank my guest, Dr. Robert Battat, for sharing his insights on managing postoperative Crohn's disease. Dr. Battat, thanks so very much for joining us today.

Dr. Battat:
Thank you so much.

Dr. Buch:
For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit ReachMD.com/GIInsights where you can be Part of the Knowledge. Thanks for listening, and see you next time.