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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

The Pediatric Perspective of Crohn's Disease & Ulcerative Colitis

Dr. Buch:
The drug selection for Crohn's disease and ulcerative colitis is largely empirical. But is this about to change? This is Dr. Peter Buch, your host for *GI Insights* on ReachMD. Today we have the opportunity to discuss Crohn's disease and ulcerative colitis in the pediatric population with Dr. Jeffrey Hyams. Dr. Hyams is Division Head of Gastroenterology and the Director of the Inflammatory Bowel Disease Center at the Connecticut Children's Medical Center. He is also one of the world's leading experts in pediatric inflammatory bowel disease. Welcome to the program, Dr. Hyams.

Dr. Hyams:
Thank you so much, Peter. It's a pleasure to be here.

Dr. Buch:
Thank you so much for joining us. To start out, how is ulcerative colitis and Crohn's disease different in children than adults?

Dr. Hyams:
Well that is the million-dollar question that is often posed by regulatory agencies when we are looking at drug trials, interestingly enough, and we try to extrapolate from adults to children. But I have to say that we have no evidence that there are biological differences between the two, but there certainly are phenotypic differences between pediatric onset and adult onset IBD.

Let's talk about ulcerative colitis first. In contradistinction to adult U.C. where most patients have distal disease, proctitis, proctosigmoiditis or left-sided disease, in the pediatric population, about 70 to 80% of children at the time of presentation will actually have pan-colitis. The majority of children who present have moderate-to-severe disease. The majority of children who present actually require corticosteroids. And those are differences, again, than in the adult population where it's really more of a mild-to-moderate and certainly for many patient mesalamine is the initial drug of choice. It's really not an option for us with our children who may even present with acute severe colitis, necessitating hospitalization.

With Crohn's, we actually see the following distribution of disease: about 50% of children with Crohn's present with L3 or ileocolonic, about 20% with L1 or distal ileocecal disease, and about 20% will present with primarily colonic disease. 10% are more mid-small bowel or upper tract. In adults, certainly terminal ileal disease as the primary location is much more common. The other very big thing that we have to worry about for us in pediatrics is the effect of disease on growth. Particularly important for Crohn's where we know that continued bowel inflammation and the elaboration of inflammatory cytokines actually antagonizes the growth hormone to IGF1 access in the liver and can cause growth failure even in the absence of severe systemic symptoms.

Dr. Buch:
That's very useful information for all of us. Why do you suspect that anti-TNFs have no effect on stricture formation in the pediatric population?

Dr. Hyams:
So I have to tell you the risk study of which I was an author, and this was published in *Lancet* a few years ago and we did indeed show in that particular inception cohort that early institution of anti-TNF therapy seemed to statistically, significantly decrease perforating complications, but not decrease stricturing complications.

I have to also say that that's not necessarily consistent with my clinical experience. So we have this dichotomy between a really good rigorous study and clinical experience. And I think it has to do with when in the disease evolution someone starts therapy. For example, if at the time of institution of anti-TNF, there are already significant structural changes with significant fibrosis, which may be irreversible,

then starting an anti-TNF in that patient, in fact, may not change trajectory.

On the other hand, there may be people who have both inflammation and fibrosis, and it may depend upon the relative balance of the two. There may also be people whose gene expression may be more of a collagen matrix deposition, which is not affected by anti-TNFs verus the inflammatory storm that one might see in perforating disease. So I think our observation from the RISK study was really important, but I wanna see how it plays out for us over time because obviously that has huge clinical implications for us down the road, both for pediatrics and adults.

Dr. Buch:
That was a perfect segue into the next question, which is the gene predictors for Crohn's disease and ulcerative colitis. Can you tell us a little bit about them?

Dr. Hyams:
Sure. That's the holy grail, isn't it? I mean, that's the whole concept of precision medicine that when we as gastroenterologists make a diagnosis of inflammatory bowel disease, there is a panel that we can have in front of us that could combine clinical expression, laboratory expression, genetics, and also gene expression. What is happening at the cellular level? How are the genes in the colonocytes, in the immune cells, all of the cells that populate the bowel and there, indeed, are many, what are those cells doing and how are they going to react to different interventions? I suspect as we move forward with these studies, and I have to put a plug in for pediatric gastroenterologist, at this moment, and the reason for that is pediatric IBD in some ways is a more pure laboratory experiment. Kids do not have a lot of the confounders that adults do. They don't have smoking. They don't have age. They don't have a variety of other medications, birth control pills, for the most part. They don't have alcohol. They don't have things that adults do, which may have epigenetic influences on disease expression. So the whole basis of my career really has been spent on how best to understand expression of disease in children and how can that serve as a model? So the big studies that we're doing with a very large group called the PRO-KIDS consortium, twenty-five centers in North America and these really are a group of investigators who are extraordinarily selfless, who are not looking for aggrandizement, but who at the time of diagnosis of children with IBD are obtaining biospecimens before any intervention because that's really when you need to obtain this information to develop these models.

Dr. Buch:
For those of you just joining us, this is *GI Insights* on ReachMD. I'm your host Dr. Peter Buch. Joining me today is Dr. Jeffrey Hyams, who's discussing the pediatric perspective of Crohn's disease and ulcerative colitis.

So Dr. Hyams, how has the addition of vedolizumab, ustekinumab, and tofacitinib changed your practice?

Dr. Hyams:
Well I wish it changed it more, but we're using all of them. So an important point to make here for the audience is the following: although in pediatric GI, we use vedolizumab, ustekinumab, and tofacitinib, it's always off-label for us, because none of those drugs yet have received regulatory approval for pediatric use. And unfortunately, that's the history of drug approval for IBD in children. It was eight years between infliximab being approved in adults and in children. Many years for adalimumab as well. But as you can imagine, when there are new and effective medications on the market, pediatric IBD docs do not want to be left out of the arena because if these medications offer an advantage for our patients, we obviously want to go in that direction.

So we've been using vedolizumab since 2014. It is a very effective medication. I think it tends, in my experience, to work better for those with colonic IBD, whether U.C. or mostly colonic Crohn's. It clearly has a role.

Our use of ustekinumab is a little bit more recent. As you know, it's only been a couple of years since it's been approved for adults with either Crohn's or U.C. I think it's finding a place with us, probably more so with Crohn's than it is with U.C.

Tofacitinib is something that we continue to explore, but I have to say it's mostly in our mid-adolescent and late adolescents and adults, where I think we can easily extrapolate dosing data from the adult trials. There now are, finally, tofacitinib trials beginning in pediatrics where really, I don't think we're looking for efficacy, I think we know the drug is gonna work. There's no drug that has been approved in adults that has not worked in children. But what you cannot extrapolate is you can't extrapolate dose and you can't extrapolate safety. So I think all of these drugs have a place for us. We'll have to see exactly what that is over the next few years.

Dr. Buch:
Let's move ten years in the future. How will we match a patient to a therapy?

Dr. Hyams:
Peter, I hope I'm still practicing in ten years, it may not be. But it's such an exciting time for us because we are finally starting to unravel some of the mysteries. Do I think we will have a cure in the next ten years? I don't. I really don't. But I think probably the most important

and exciting area is the role of diet in the management, particularly of Crohn's disease, maybe less so ulcerative colitis. And secondly, we'll be able to identify individuals at high risk for developing disease by virtue of genetics, by virtue of family history, by virtue of other markers? And intervene early in life and maybe even prevent the inflammatory bowel diseases from occurring. We know that early life events with diet, particularly with antibiotic exposure, there are compelling data now that suggest early life antibiotic exposure, meaning in the first two years is a significant risk factor for lifetime risk for IBD, hazard ratios of 4:8. We also know that Western diets, high fat, high sugar, emulsifiers, which are in many of our foods are not good. They alter the microbiome. They change intestinal permeability, and those things may be bad. So what I hope is prevention. I think we're gonna have a much better idea, some very great studies that are being done all around the world. And what I hope also is that our therapies become more and more targeted.

And as you know, there are a number of agents which are still in clinical trials, which are not as broad-based as the anti-TNFs, which are used for many things, but they're also great medications. It's gonna be hard to supplant them because of their efficacy but people still worry about potential side effects, allergy, other immune mediated disorders, malignancy, the dermatologic manifestations that we sometimes see with anti-TNFs, so I see more targeted therapy. And my hope is that they'll filter down to pediatrics much more quickly because in fact, we will be doing clinical trials in children at the same time we're doing them in adults.

Dr. Buch:
Before we conclude Dr. Hyams, is there anything else you would like to share with our audience?

Dr. Hyams:
Early, early detection. High index of suspicion. I'm a big advocate of fecal markers of inflammation, maybe not so much to follow, but really when you're screening patients and you think bowel inflammation may have a role, you're not ready to do a colonoscopy, bloodwork is helpful, for sure, if it's abnormal. But I have to tell you, I'm a big advocate of fecal markers of inflammation.

Dr. Buch:
That's great. I want to thank my guest, Dr. Jeffrey Hyams for joining me to share his insights. Dr. Hyams, it was great speaking with you, today.

Dr. Hyams:
Thank you, Peter. It was my pleasure.

Dr. Buch:
For ReachMD, this is Dr. Peter Buch. To access this episode, as well as others from this series, visit ReachMD.com/GIInsights, where you can Be Part of the Knowledge. Thanks for listening and see you next time.