THE LACNETS PODCAST

With David Metz, MD
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Transcription:

Lisa Yen 0:15
Welcome, Dr. Metz! Would you like to share a little bit about yourself and what you're up to now?

Dr. David Metz 0:21
Yeah, sure. I'm a gastroenterologist. I've been in practice for 20 plus years, actually 30 plus years. I've primarily been doing neuroendocrinology for about 20 something of those years and was previously at the University of Pennsylvania, where we had a very big multidisciplinary team. I've just retired. I've actually moved to the Southern California area. And at the moment settling in and enjoying California lifestyle. So I'm very happy to be joining you guys at LACNETS today.

Lisa Yen 0:59
Congrats on your retirement and we're so glad that you're now one of us! And you get to enjoy the sun and the beaches along with us. And hopefully, we can see you in person soon. So as you know, we've gathered the top 10 frequently asked questions, and we thought that perhaps you could help shed some light on some of these things with our community if that's okay with you. So the first question is, what is the difference between carcinoid syndrome and carcinoid tumor?

Dr. David Metz 1:32
Well, very important question because everybody really needs to be on the same baseline from which we discuss whatever situation you had. And the term carcinoid is actually a very confusing term. Because different people mean different things by using the same word carcinoid. Carcinoid really means like a carcinoma, meaning like a cancer. And neuroendocrine tumors were called carcinoids, because they sort of look relatively like cancers that grew and metastasize. But they weren't really cancers because they were slow growing morphologically and interesting, boring sort of cells. And so the pathologists carrying the term carcinoid, meaning like a carcinoma, and that's got absolutely nothing to do with the carcinoid syndrome. Carcinoid tumors would be better referred to as neuroendocrine tumors, tumors that have

neuroendocrine elements, some from nerves, some from endocrine cells. And they really look very similar whether they come from the thyroid, the abdomen, the pancreas, the small bowel, the lungs. And although they do have some distinct, distinguishing features, generally speaking, neuroendocrine tumors look like neuroendocrine tumors. Some neuroendocrine tumors are productive, other neurendocrine tumors are silent. We talk about the production, the hormonal syndrome is a consequence of what these tumors make in different elements. So some neuroendocrine tumors will make substances that cause the carcinoid syndrome. Some will make substances that cause other syndromes, and some will make substances that don't cause any syndrome, where they won't make substances at all. So a carcinoid syndrome implies a collection of signs and symptoms that develop as a consequence of a neuroendocrine tumor. You may have the carcinoid syndrome and the neuroendocrine tumor, or you may have the neuroendocrine tumor without the carcinoid syndrome. Most people feel you should not be able to get the syndrome without a tumor. And whenever that occurs, we generally think the tumor is so small that it can't be found. So we really need the patients and the physicians that treat them to distinguish between the syndrome and the presence of a tumor. Hope that helps.

Lisa Yen 4:02
That's really helpful. Thank you for your really clear explanation of these terms, so that we can start off making sure we're all on the same page with what these terms and concepts are. So the second question would be, what are the most common causes of diarrhea? And I guess a follow up question to that is how do I know that if my diarrhea is from NET, a neuroendocrine tumor, as you mentioned, for medications, diet, or another reason?

Dr. David Metz 4:29
Correct! Another important distinction to be made. And so you can look at this from two ways. You can look at it from the gastroenterologist perspective. In other words, the doctor that the patient would come to complain of the symptom of diarrhea and then they've got an enormous differential diagnosis to think of a very small proportion of those would be from neuroendocrine patients, and even smaller from carcinoid syndrome neuroendocrine patient. On the other hand, you can look at it from the oncologic perspective where you already have a diagnosis of a metastatic neuroendocrine tumor. And you've now developing diarrhea and then the oncologist is saying, well, what is the cause of this particular diarrhea? Is it diarrhea from syndrome which this guy may or may not have had before? Or is it some other kind of diarrhea as a result of the treatment they've received, the surgery they've gone through, with the fact they just like anybody else, and they've got irritable bowel syndrome? Or they picked up a parasite? So the way to look at this thing depends on which side you're looking at this from, and as a diarrhea doc, as a gastroenterologist, when somebody walks into my office and they say, I've got diarrhea, my thought isn't, oh, I've got to go check a 5HIAA. My first thought is, well, this is probably going to be infectious, or it's going to be an inflammation of some kind, or it's going to be irritable bowel syndrome, or it could be celiac disease. And so you don't really think about the neuroendocrinology as the major issue. Now on the other hand, if you don't think of it, you'll never find it. And by the time it occurs, it's metastatic. So there are some clues to suggest a syndromic diarrhea. In other words, diarrhea, that is a consequence of the release of products

like 5HIAA, serotonin and whatever else these products are, none have been very well defined. So if you measure a hormone or a hormone product, and you show that that's elevated in diarrhea, it goes together. And you'd also want to see that the diarrhea occurs with other symptomatic components of the syndrome. So if you get diarrhea, but you never ever, ever, ever, ever flush, [it] may not be carcinoid syndrome. On the other hand, if you're flushing all the time, and you don't get diarrhea, maybe you're flushes from something else. But you need to realize that if you get both together, that's a very common predictor. Treating patients with carcinoid syndrome, unfortunately, has a multitude of diarrheal side effects. And then is the problem from the oncologic perspective. So from the gastrological perspective, how do you make this diagnosis of a syndromic diarrhea in the first place? You need to think about it and do the right tests. On the oncologic perspective, on the other hand, when you get somebody who has a known neuroendocrine tumor, whether they do or do not have syndrome and they are getting diarrhea, the question is, is it from the tumor? Is it from the syndrome? Or is it from something else? And unfortunately, with all the things we do to our neuroendocrine patients, we cause diarrhea, so let's go through some of those. First of all, most important are the somatostatin analogs. If you're on somatostatin analog for any reason, whether it's for tumor control, symptom control, or whatever, you are going to be switching off multiple endocrine systems throughout your body. Number one, as everybody knows, you'll get gallbladder sludge and the gallbladder doesn't contract very well and has a predisposition to gallstones but as a consequence, you're not going to make very good bile. So if you have very fatty meals, you're not going to emulsify them well and you're not going to necessarily absorb them as well. In addition, SSAs cause the pancreas to dry up. The pancreas does two jobs. Job one is to just release hormones for diabetes and insulin control and glucose control. And the other job is exocrine pancreas. The exocrine pancreas squirts out enzymes to help you digest your food. Well if you eat the food and you don't have enough enzymes, because your octreotide or lanreotide has dried up your pancreas, you'll get malabsorption of those contents and especially fatty diarrhea, which is called steatorrhea. Very smelly, floats oily, difficult to flush. And somatistatin, in addition, has an impact on the contractions of the bowel and low dose somatostatin analogs may improve fertility and high dose somatostatin analogs, which is what we really use for symptom control and tumor control, can retard motility, so the bowel doesn't contract very well, the stool ferments and the bacteria in there multiply and you get overgrowth and bacterial overgrowth is yet another cause of diarrhea. Now carcinoid syndrome patients predominantly get the diarrhea from tumors that develop in the small bowel down towards the junction of the small and the large bowel. That terminal ileal area is often resected and if you resect that particular area you don't absorb vitamin B12 well, or the fat soluble vitamins A, D, E and K. And most importantly as you don't get good circulation of bile because bile only comes out of the liver into the bowel, joins through the food, helps it getting absorbed and then gets absorbed in a terminal ileum to be recirculated and if it ain't there, it doesn't get recirculated and that bile acid can irritate the colon and give you a bile acid colitis. So there's another cause for diarrhea. So there's the causes by surgery, the causes by treatments. Think of all the pancreatic neuroendocrine patients who've had half their pancreas removed, well there goes half your diabetic management stuff and half of your enzyme production. Many people have had surgery to the stomach which impacts in terms of grinding up the food and allowing it to be

properly absorbed. So there's a lot of cramping and abdominal discomfort associated. So there's the diarrhea from the syndrome. Is the diarrhea from the tumor? There is the diarrhea from the treatment, whether it's surgical or medical. And then we have to realize there's all the other causes of diarrhea that any other human gets. And we talk about chronic diarrhea only if it's been there for at least two but probably up to six weeks. So we are not talking about acute sudden diarrhea, went to a bad restaurant last night. And boy, I had a tough time in the toilet the whole night. That's an acute diarrhea or I went to my kid's birthday party and they were a whole lot a little sniffling babies there and oh my god, I got norovirus and I had bad diarrhea in it lasted two weeks. Or I went traveling to Mexico and I came back with the parasites and I've got turista. That we're not talking about. We're talking only about chronic diarrheas that are persistent. And the last point I'd make that I think is very important for patients to understand and to discuss with their doctors who may not be completely on board about this. There is a specific distinguishing point between the diarrhea of neuroendocrine tumors, whether it's carcinoid, whether it's medullary thyroid carcinoma, whether it's Zollinger Ellison syndrome, these are all called secretory diarrheas. And in a secretory diarrhea, the bowel is stimulated to secrete fluid into the lumen, into the center of the of the GI tract, and that fluid is overwhelming the ability to reabsorb. And therefore you get diarrhea as opposed to an osmotic diarrhea. And osmotic diarrhea does occur when you ingest a substance that is very tonic, hypertonic and sucks fluid in, for example, because you can't digest lactose. So lactose intolerance patients would get osmotic diarrhea, which occurs after eating during the day, and goes away if you starve. The neuroendocrine secretory diarrheas occur all the time. They don't go away if you starve. And also they will wake you up at night to poop. And it's the liquid secretory component in the rectum that overwhelms your ability to retain it that gives you that urge of urgency to rush and enter the rectum. So an important clue for neuroendocrine causes for diarrhea, secretory diarrhea, are they wake people up at night, they have a lot of urgency and a very watery. Everybody will lose control if you have enough volume that you can't hold in. And so it's not that the rectum and the anus doesn't work properly, it's that it's getting flooded with a high volume of secretions.

Lisa Yen 13:25
Thank you for that that's really helpful. And now there are so many different causes. I can imagine if I was living with this diarrhea, or I think any of us, there's probably components of it that are like, well, that could be me, that could be me. So how would I know what my diarrhea is caused from? What might I expect my doctor to order? Or what could I ask my doctor to order to figure out which one it is?

Dr. David Metz 13:51
Well, that's a very good question. Because you couldn't do a sort of bomb blast, I'm going to test for everything under the sun. And get your patient having all sorts of studies and lab tests and in and out of hospital and getting equivocal results and nothing's definitive, and you can just go on forever, or on the other hand, have good history, and a good understanding of what the anatomy is like and what medicines you're on and how you live your lifestyle. And the fact that you insist on having ice cream before you go to bed or whatever it is, that may or may not

be involved. That's the clue. So it's a good history and a good discussion and medicine really is a personable experience, all be it that everything's now gone virtual. But really a good history and a good physical exam is very, very important. But there are certain tests. So you will see that many, many people will rush to getting chromogranin As or nonspecific markers, because they've now got significant diarrhea. And I would tell you that is a not a very useful way to work out causes of diarrhea because you would have them elevated anyway from the tumor whether you have diarrhea or not. And since you may or may not be on a somatostatin analog, those levels could be suppressed on the treatment, yes or no, regardless still with diarrhea. In terms of measuring the functional markers, so in carcinoid syndrome, you'd be measuring serotonin or 5HIAA, that's reasonable, even in the presence of treatment, because if it's still elevated, then you may well be having syndrome. Obviously, if you're having your diarrhea with flushing that would fit or if you've got a history of ulcer disease, and now you're getting abdominal pain and diarrhea despite taking your proton pump inhibitors, for Zollinger Ellison, that would be another case where you could be undertreated. So, syndrome markers do help. Nonspecific markers don't really help. And then we've got a lot of new sort of tests that we can do. Traditionally, anybody who presents with diarrhea gets a stool for ova and parasites and culture and sensitivity and white cells. And that really is not very useful for us. But it is useful to do stool elastase and sometimes stool alpha-1 ntitrypsin. And what I like, when I can get it, is stool for electrolytes. And I will talk about those stool studies very briefly. Now people don't like getting stool. And we used this in the olden days, forced people to do 72 hour collections, and it was horrendous. But now you can just get a spot fresh stool, and it's important that it's spot, meaning just one episode fresh to the lab before it desiccates and dries out. You can measure elastase. Elastase is an enzyme that is produced by the pancreas and is not absorbed or digested. So if your body is making normal amounts of pancreatic enzymes, the pancreatic elastase will be measurable in the stool. And if it's there at an appropriate level, then your pancreas is not suppressed. So it's not the somatostatin analog drying up your pancreas. I also get stool for Alpha-1 Antitrypsin, it's a very unusually positive finding. Alpha-1 antitrypsin is a protein in the stool that is normally too large to get absorbed and is going to be seen in people who have secretory diarrheas and it's basically, as a consequence of what's called protein losing enteropathy. So if you've got enough inflammation that you leak out of your bowel, and that would be from conditions like ischemic bowel or inflammatory bowel disease, or occasionally in some neuroendocrine patients who would have, let's say, an ischemic segment or something like that he could have an alpha-1 antitrypsin, but it's a very unusual thing. I wouldn't put it at the top of anybody's list. What I do do is if you truly are having watery diarrhea, you send a specimen to the lab and you could get a lot of answers back. One answer back is stool too solid to test. Well, that is either a patient who thinks they've got real diarrhea, but it's really more like frequency. And so it's not true diarrhea, or it sat on the bench in the lab long enough that it dried out. Be wary of that it needs to be a fresh specimen. But if it is a watery stool, you can measure electrolytes in the stool. So just like you have electrolytes measured in your blood, when you measure sodium and potassium to make sure that you're properly hydrated and all the balancing and mechanisms are working, if you measure the electrolytes in the stool, you can get an idea of if it's a secretory diarrhea or an osmotic diarrhea. So most stool that comes out of your body is going to be at the same tonicity as your blood in your body. Because if it was too

tonic, it would suck fluid in and if it was hypertonic it would send fluid out. So as the stool gets delivered, it should have an osmotic measurement that is the same as your blood and you will get blood osmolarity stool osmolarity and electrolytes at the same time. And as long as that's the case, taking your sodium and potassium concentrations in the stool you can tell if it's a secretory diarrhea or an asthmatic diarrhea. So secretory diarrhea is where there are blocks of sodium and potassium. And osmotic diarrhea will have less sodium and potassium because most of the osmoles are made up poorly digested lactose. For example, or some other badly digested stuff. So if you can send us fresh stool for osmolarity and lytes and compare that with a blood osmolarity, you can really get a good handle on secretory or non secretory diarrhea. And I personally in my practice did that quite a lot. Scoping for biopsies aren't really that useful for most patients with neuroendocrine tumors, but if you've got negative tests and you don't think it's somatostatin analog related, what are you left with? The one thing you have to realize is that short gut is a big problem in patients who've had wide resections. Especially if you've lost the terminal alien, as we've already discussed, the vitamin A, D, E, K, and fat soluble vitamins and B-12 get absorbed there. But if you just don't have enough small bowel at all, then you can just overwhelm it and get short gut syndrome. And unfortunately, that can occur even in patients who have had relatively small resections because the lymphatic drainage is a consequence of the surgeries may actually render them relatively ischemic and fixed from the fibrosis and those sorts of activities. And they could end up with some diarrhea and ultimately, some of those diarrheas require really, opiate therapies if it's just impossible to manage and I have used that on occasion in some patients. So bacterial overgrowth occasionally you treat with antibiotics, if you think it's worth it. I don't test for bacterial overgrowth, because after surgery, there's not much value of doing those standard tests. You just assume it's a positive. We've spoken about gallbladder resection, we spoke about pancreas resection, we spoken about overwhelming tumor. I think that's sort of the major problems but there are many, many, many causes. And I think good discussion with your doctor is going to be the way to answer that question.

Lisa Yen 21:32
I think that's really helpful. We often rely on the tests and like you said, rush to order tumor markers or hormone markers. But like you said, a really good discussion. That conversation kind of goes back to that relationship and measuring or tracking your symptoms and sharing that with your doctor. You kind of touched on this a little bit, but the next question is, when should someone have an upper endoscopy, colonoscopy, or capsule endoscopy, and how might it affect symptom management?

Dr. David Metz 22:02
That's another important perspective and you have got to look for both sides again. So if you're talking about a gastroenterologist working a patient for a syndrome with diarrhea who might have calcitonin elevation or might have irritable bowel syndrome or might just be anxious and having frequency, they are going to primarily start looking for the acute causes of diarrhea, and then the common causes of diarrhea. Inflammatory bowel disease, most important of all is irritable bowel disease, which is not a true organic problem, but it's a big problem for many, many patients. Hyperthyroidism, mastocytosis, a whole lot of causes of those kinds of diarrhea.

And in those cases, especially if you're getting to the age of about 50 or so, you really should exclude a condition called microscopic colitis. And microscopic colitis is an inflammatory condition of the colon. It doesn't look abnormal endoscopically, but biopsies will show it. And it's a sort of variant of inflammatory bowel disease. We don't understand much about it, but it's usually treated with steroids. And if you don't do biopsies, you don't find it. Those common causes of some of these, for example, can be medicines. And so some people will have severe chronic disabling diarrhea, not necessarily the overwhelming syndromic diarrhea that your patients know better, but they can really be limited by it and you need to get a colonoscopy and a biopsy. Other causes that you can really find from colonoscopy would be looking for things like inflammatory bowel disease, or infections, and anybody over the age of 50, whether you've got diarrhea or not needs a colonoscopy. Anyone over the age of 45, if you've got change in bowel habits, my sense is you need a colonoscopy regardless, but you may not find it. Many colonoscopists get into the terminal ileum when they do their screen, and if they're lucky, they can pick up carcinoids that way. I have had a number of patients over the years, and somebody said to me, oh my god I did a colonoscopy, look what I found. How do I handle it? Because those gastroenterologist aren't afraid for the treatment but they graded the diagnosis on it. Many do not get into the terminal ileum at screening and sometimes you can't get in at screening and so an appropriate colonoscopy from a legal perspective doesn't require an intubation, but it's really good to try and do that. Well, let's switch over to the upper tract. So the upper tract, you're going to be doing biopsies of the duodenum, which could also look potentially normal and it's the biopsy that you're looking for and there you're looking specifically for celiac disease. Celiac disease occurs in 1 in 100 Americans and as a consequence of gluten intolerance, so you can't digest gluten. That results in an osmotic effect and severe diarrhea and the gluten sensitive patients are best diagnosed either with serologies or with biopsies of the duodenum. I also do a lot of endoscopy in patients with pernicious anemia and atrial fib gastritis. That's a cause of vitamin B-12 deficiency that is not from the small bowel being malabsorption, it's that the stomach cannot make a product that's required for the small bowel to absorb. And pernicious anemia is actually not a rare condition, and it's associated with atrophic gastritis, absence of acid secretion in the stomach, and therefore, believe it or not, carcinoids of the stomach and gastric carcinoids type one carcinoids not related to the typical syndromic type things we're talking about, those patients need surveillance and screening because they can get cancer and I think they get a diarrhea as well from bacterial overgrowth because they don't actually make acid. Also, obviously the Zollinger-Ellison syndrome patients who are hyper secretory of acid, their diarrhea is from an overflow and secretory. And in those patients, you'd either identify the tumor in the duodenum, or potentially biopsy the stomach to show atrophy. If it's the pernicious anemia, or if you think it might be a pancreatic neuroendocrine tumor based on ultrasound and cross sectional imaging or even gallium dotate scanning, an endoscopic ultrasound allows you to put a needle in and do some biopsies. And finally, to talk about the small bowel enteroscopy, the capsule endoscopy, the capsule is less of an issue, because it goes in and out, you don't need sedation and stuff. The problem is that it can impact and in carcinoid syndrome, that is a concern because if you get any fibrosis in the abdomen, which is not an uncommon thing with carcinoids, you can get a kinking in the bowel and these capsules can get stuck. So sometimes we do what's called a patency capsule. You swallow the

capsule, you take a picture, if it's gone, it means it went through. If it didn't go through, I don't want to use a real one, I'm going to wait for this to dissolve and come through but you don't get tissue. So with enteroscopes and modern enteroscopes that are various designs, you can now really look at the entire bowel. So you can go in there and have a look at the small bowel and maybe even biopsy a carcinoid and once in a blue moon maybe even think about trying to remove one. The danger is risk of perforation is real in that setting. And so from a diagnostic perspective, the gastroenterologist will be happy to run those tests to run the bowel, so to speak. From the oncologic perspective, if you now got a patient who has neuroendocrine tumor and diarrhea, sometimes there's an unknown primary you can sort of look for with enteroscopies, although gallium dotate is really good and a good surgeon will tell you they don't think they get a benefit because they see the lymph nodes and once they see the lymph nodes, they can follow them back. But the the value of sending a patient already established for enteroscopy I think is limited. Although endoscopies and colonoscopies are sort of needed at times. The diagnostic utility of these tests is important. The management long term I think other than for specific surveillance requirements, probably not that useful in the era of our modern cross sectional imaging and functional scanning with dotatate scanning. Endoscopic ultrasound specifically and biopsy may be quite useful in many patients. And also, which I haven't mentioned is ERCPs. So that's an endoscopic retrograde cholangiopancreatography. A bit of a mouthful that basically says putting a catheter into the pancreatic and bile ducts and squirting in dye. We tend to avoid those if possible, because they can cause pancreatitis. But if you have a patient with biliary obstruction from tumor or lymph nodes, or pancreatic stricture or pancreatic leak after surgery, we often would need to do those kinds of tests but they do have more of a side effect. So we try and limit ERCP and actually do what's called an MRCP with an MRI scan, often to just get the lay of the land and if we have to go ahead we do the ERCP where you can actually intervene.

Lisa Yen 29:33
Wow, thank you for that. You went above and beyond, not just talking about the basics well not basics, but upper endoscopy, colonoscopy and not just capsule endoscopy, but adding in the small bowel enteroscopies, the ERCPs, and many other potential procedures that someone might have to to do as part of the diagnosis and workup. We're already talking a lot about diarrhea, but let's kind of shift gears a little bit to other symptoms. So cramping, bloating, abdominal pain also come up, as you know, for patients or not. So are cramping, bloating, and abdominal pain part of the carcinoid syndrome? And how do I know if it is or isn't?

Dr. David Metz 30:18
So that's a really good question. The famous paper we all refer to as Beaumont, that has a few 1000 patients and they compared neuroendocrine tumors to neuroendocrine tumors with carcinoid syndrome, to controls. And they showed that the carcinoid syndrome quality of life was even worse than that of the neuroendocrine tumor alone, so that the syndrome does impact. So that's great. What is syndrome? Well, a syndrome by definition is a collection of signs and symptoms. Doesn't tell you much, right? It's not caused by a specific disease and it's not treated in a specific way and it basically means we really don't know what it is. So we're calling

it a syndrome, irritable bowel syndrome. Which means belly pain and either diarrhea or constipation and interferes with your life but no organic abnormality that we can identify, right? Zollinger-Ellison syndrome consists of diarrhea, peptic ulcer disease, and a neuroendocrine tumor in the pancreas. But that syndrome is the result of the tumor making a product. So in carcinoid syndrome, we believe that the most prominent symptoms are diarrhea and flushing, and I don't think anybody would agree with that. And we disagree with that, and I think we feel that serotonin and its products are potentially causative of that, which is why we use that as its marker. But in those old studies, they would have called cardiac disease as a sort of general term and said that that related to carcinoid syndrome. Well, cardiac disease, calcium, coronary artery disease, congestive heart failure, muscle problems, congenital problems, and the cardiac disease associated with seratonin overproduction is usually a right sided heart failure from fibrosis along the veils, especially the pulmonic or tricuspid valves. And that takes years and years and years and years and years and years to develop, and may be impacted by somatostatin, analogs and or other therapies. But the point I'm making is it's a very late finding. And in the modern world, we really don't see this much. Although once in a blue moon, a patient will walk in the door with congestive heart failure as their presentation for the carcinoid syndrome, but it's very rare. They also talk about pellagra as being associated because you don't get enough niacin because you got such an active tumor that it's sucking up all this and you end up with a deficiency and you get pellagra which is classified as a rash around the neck and with diarrhea and other cause, and dementia. And I don't think we really see pellagra in the modern world anymore, we just don't see it because people get enough regardless. And I think it's an overrated causes, go find this for the syndrome. And then abdominal pain and rectal bleeding and discomfort is a very difficult one, because as you know, neuroendocrine tumors are associated with fibrotic changes in the abdomen, in the stroller of the mesentery, that cause kinking of the bowel, and can definitely cause obstruction and can cause ischemia and can cause bleeding and pain. And again, these are usually very late findings. And to sort of get triggered by pain and diarrhea to think carcinoid syndrome, I think is a little bit of a stretch, but pain is a component. But even if you have a neuroendocrine tumor in the small bowel, and you don't have fibrosis, and you don't make serotonin, and you still get adhesions from your surgery, it's however difficult to make the true distinction. So pain is real, but I don't know how well it is as a defining difference. Now, what I'm telling you is that this is a syndrome, a collection sciences. And this doesn't have to be absolutely specific and say, well, you can label somebody who's having syndrome. But what happens if somebody has diarrhea and is a little bit close to menopause and is maybe having a little bit of flashing? And now they think they've got syndrome, when in actual fact you measure their serotonin and it's normal? And they could just have short bowel or they should have neuroendocrine tumors, it causes an overgrowth, and in SSAs and they don't really have true syndrome. It sort of looks like syndrome. So although the syndrome does not require identification of a positive tumor marker, if you're going to study carcinoid syndrome, you better make sure you put patients with typical symptoms and a marker because otherwise you're never going to know exactly who's the real deal patient. But for in the big wide world. When we are seeing patients with diarrhea and whether symptoms and pain and whatever you could very well call them syndrome without knowing definitively that their markers are elevated. And even if their markers aren't elevated, it's possible that they are

suppressed from therapy or whatever it is. So it's very difficult to really prove syndrome. You don't get many true naive patients that walk in the door and say, I've been feeling perfectly well. But over the last three months, I've gone from three BMs a day to seven BMs a day. And I used to flush when I ran the marathon and now I'm finding every day after I get out of the bathroom, I'm bright red, pink. And that's an easy diagnosis to make. Very, very few people walk in that way.

Lisa Yen 35:37
Thank you for that. That's really helpful to provide some reassurance about that. You touched on taking out the gallbladder. The next question is, why do NET experts or people take out the gallbladder? And what effect does this have on GI symptoms?

Dr. David Metz 35:59
So if we go to normal individuals who get cholecystitis, inflammation of the gallbladder, and they have their gallbladder removed because it's infected and at risk of killing them, you'll find that after surgery, most of them actually recover without any problems whatsoever and life goes on. But there is definitively a group of patients who now, because they don't have the ability to store bile in the gallbladder before meals, they lose the coordinated secretion of bile and pancreatic juice relative to meals. So normally when you eat and your food hits your stomach, that switches on all sorts of pathways. One of the pathways as soon as acid gets out of the stomach into the duodenum, it tells the pancreas the pH is low here guys, squirt. So the pancreas starts making enzymes and bicarbonate. Similarly, there's hormonal measurements of signals that go from the duodenum to the gallbladder that say, "Hey guys food arriving! Deliver some bile to emulsify it!" So the gallbladder will contract and the pancreatic juice, the bile, and the food all arrive at the same time with the gastric secretions. And it's all nicely done. And that's how you get great absorption. But if you've lost your gallbladder, you can't store bile, and your bile is continually being released and dribbling through and gets down. And if you've lost your terminal ileum, irritating your colon and giving you potentially a diarrhea. So in our neuroendocrine patients who have had both those parts removed, diarrhea from bile salt is a real issue. And the treatment usually is called cholestyramine or some medicine like that, that binds up bile must be given away from meals and not with meals. Most people are given cholestyramine to control the cholesterol, and there you want it to bind the cholesterol with the bile. So you take it at meals. In our patients, we want bile with meals because they don't have a store. So you want better absorption. But you don't want bile when there's no meals because that's going to go straight through and irritate your colon. So when I prescribe cholestyramine for bile salt diarrhea, I always prescribe it at about 11 o'clock in the morning, and at about three o'clock in the afternoon, away from all meals and all other medications. So when a neuroendocrine patient has had a gallbladder loss, those same things are at risk and so the downside is real. However, the upside of removing the gallbladder when you get in there is very real too. And I can tell you over the years I've had a couple of patients who we know the gallbladder that has been in we've watched it, we've seen it get bigger in one. Occasionally these things can perforate and then you need to have a tube put in because you get infected and so taking the surgery becomes a big deal and you end up with tubes that can last for a very

long time and developing chronic cystitis and or rupturing the gallbladder is a life threatening issue. And so if you're going to be doing a surgery on any neuroendocrine patient upfront, and they have metastatic disease, and they're going to potentially be on an SSA, and that is going to potentially giving life threatening cursor status, while you're there you whip it out. Because you can do without it. Although the bile salt diarrhea does become an issue to address. Now also we have to realize not all of our neuroendocrine patients have normal anatomy. So just losing the terminal ileum at least you're still in some sort of continuity. But if you've had a Whipple operation for a neuroendocrine tumor, then your stomach enters the GI tract, the small bowel, at a completely different place from where the bile comes in and from where the pancreatic juice comes in. In fact, they are all in separate places and don't get as coordinated a delivery of food stuff. So you can get cramping, abdominal pain and dumping syndrome, just because you've had the Whipple. And of course, in that kind of setup again, you've got to add that into all the other potentials that somebody could have. So gastroenterology management of GI complaints in neuroendocrine patients, both diagnostic or in long term follow up, really does require more than just saying, oh, it's a somatostatin and I'll just give you some antibiotics.

Lisa Yen 40:28
It's very complicated for sure. So, we talked a lot about removing the gallbladder if you're going to already be in there, but what if someone already had surgery, the gallbladder wasn't removed? So basically, if they didn't have their gallbladder removed, should they have it removed?

Dr. David Metz 40:50
So once you've already done your surgery, which as most of you out there who have had one know, it takes a long time to get better. And it's a major deal. People will say, Is this a big operation? Yeah, any neuroendocrine operation is a big operation, even if they don't take out much because they've got to move a whole lot of parts around. And they've got to go looking in there. And they are going to have to remove some essential things. And let me tell you, any one of these operations is a big deal. So the usual recovery after a big laparotomy, that is six weeks or so maybe more. And then you want to go back later when it's a higher risk deal, because now you've got adhesions to deal with. And you don't know where all the pieces are, and you got to be careful about it. And it could be inflamed by that stage, and it could have perforated by that stage. So the problem is you try and avoid the second operation, so we don't do elective cholecystectomy. But whenever you're in there, I support taking it out. And if you develop cholecystitis rapidly, because if you don't get there rapidly and you perforate then you got a real big problem. So, I've had a couple of patients now that I regret, and I say over many years, potentially saying, well, I think your gallblader is okay, I don't do that no more, because they will get you into trouble. And so if you have a palpable gallbladder, for example, they should come in, or at least be decompressed.

Lisa Yen 42:17
Thank you for that. Speaking of gallbladder, since many people have heard about creon, this question comes up a lot. So I'm a NET patient, I've heard of creon. Should I be taking it? And if I do take it, how do I know if I'm taking enough?

Dr. David Metz 42:33
Okay, so pancreatic enzymes, you would use in somebody who's classically got pancreatic insufficiency. How are you going to know they got pancreatic insufficiency? They're going to have a positive stool elastase, or they're going to have a positive stool fat. To test for the elastase and fat you need to do that on a regular diet. So if you don't have any fat in your diet whatsoever, you're not going to have any fat in your stool and your pancreas may be malabsorbing and you're not going to know it. So it's got to be on a regular diet. And it's going to be one of those stool fats for osmolarity and a spot specimen for fat. I've actually forgot to mention that earlier. That's a very important test. You just do what's called a Sudan stain. And if you have a regular human normal, American diet, you should not get more fat in your diet, then would cause a Sudan stain to go positive. So it's not definitive, but it's helpful. And it's better than doing 24 hour collections. That's the sort of test you want to really get a handle on before you start throwing enzyme without it. Because enzymes make most people's stools firm up a little bit. And if you want to really be sure you're going to be on a long time, it's better to try and make a diagnosis upfront and then I think it's essential and you can start using enzymes empirically. But as you point out, you really don't know what's the right dose and if you go up very, very high on pancreatic enzymes, they always used to be this concern about pancreatic diaphram, small bowel diaphragm disease and fibrotic problems from long term chronic enzymes that may not be happening as much with a modern formulations, but I'm not sure of that. But using creon or Zenpep or any of the other pancreatic replacement enzymes, they should work and you should take with meals and you should take the dose as prescribed and advised with a good nutritionalist looking after you. And it's important to know that if you eat anything your pancreas squirts. So even if you have a small little something as a snack for dinner, you should have enzymes with snacks and you should have enzymes with diet and you should modify the dose according to the amount of fat in your diet. And you need clearance support from a nutritionist in that story. During meals, you take before you swallow the first bite, while you're in the middle of the meal, and then at the end of the meal. So if you're taking three capsules, you take them one in the beginning, one of the and, then one in the middle, depends on what your dosage is, but it's got a mix in quite well and many people have had bowel surgery so they don't mix as well or gastric surgery so they don't grind as well. If you've had a Whipple, for example, you're not going to grind up your food, which is why dumping occurs and which malabsorption might partly be for because you don't render the food consistency enough for the evening enzymes to work. So those are important considerations. But we have many, many, many, many, many patients on pancreatic enzymes. And a point I would make that I don't think I have a personally good handle on but just as a thought, when you take your injection once a month of a depot drug, maybe there's a difference between the beginning of the month and the end of the month in the middle of the month as to how suppressive your doses are. So you might get it the beginning of the month, be a little bit more

on the steatorrhea, and at the end of the month, a little bit more of a sort of syndromic diarrhea. We don't know that we haven't done studies on patients but you need to realize that your diet changes, the drug levels change, the tumor secretion changes. So you will have little episodes here and there and nobody's going to be regular like my grandmother used to want to every day one good poop in the morning. It's not going to happen.

Lisa Yen 46:22
Yeah, we're humans. We're not robots, so things are in flux. So other than creon this question obviously comes up a lot. What else can I do other than creon to control my diarrhea?

Dr. David Metz 46:37
Okay, so diarrhea as we've already gone through, is caused by a multitude of diseases and the right treatment depends on the right disease. So if you've got microscopic colitis because you were on a PPI, you stopped your PPI. If you've got celiac disease, you stop taking in gluten. So you need some kind of diagnostic direction for what the causes of the diarrhea or any chance of the syndromic neuroendocrine tumor diarrheas, you can switch off syndrome with an SSA. You can switch off syndrome with mechanical intervention. So taste would reduce your tumor burden and potentially reduce the products. So in the example insulinoma, widespread insulinoma patients who we just cannot control, TACE is an important therapy. Because their sugars can go so low, they can get really, really sick and knock their heads and fall down and get really hurt. So there are different sort of approaches. So number one, control the syndrome appropriately. And if you can do that with mechanical medical methods or medications, the next step of course, post carcinoid syndrome specifically, would be to telotristat. Telotristat being a drug that blocks the production of serotonin and 5HIAA, and has been shown to make a significant impact on patients with carcinoid syndrome on an SSI who still have diarrhea even though they have stable disease. With all of those things in place, it's a good drug. It works well. Bacterial overgrowth is something I often treat with 10 days of antibiotics. I like to use Rifaximin for that because it's a non-absorbed antibiotic. The problem is the insurance does not tend to improve it for approval for short courses. They will approve it for irritable bowel syndrome as a maintenance drug but they won't improve it for 10 days in overgrowth and there's no value to doing a breath test because they previously had surgery so we often have to fight about it. Sometimes we win, sometimes I use augmentin instead. Then whatever I run out of, and ultimately if you get really bad diarrhea just to use anti-diarrheal. So imotil, immodium, and lomotil and even tincture of opium in some patients that are really overwhelmed and not commonly anymore now that we've got new drugs and new therapy. So you have to sort of work it out it might be that you're having too much fat and if you just cut fat out of your diet, your diarrhea gets better. So it's trial and error. A good nutritionist which I recommend trace element measurements. We don't really know much about all of these but we do know that people who have a diarrhea are going to have issues with malabsorbing things,. And every now and then you get a fibroid that creeps in if you don't check your thyroids. And I always want to get a B-12 in people who have terminal ileum just because that can be a horrible deficiency that can have bad side effects.

Lisa Yen 49:55
Yeah, that's really helpful. Like you said, it's really important to nail down the cause before we determine treatment, right? That's going to determine the treatment, and treating the tumor is important to treat the symptoms, as well. And a multi-pronged approach. It's good to know there's a lot of tools in the toolbox for treating diarrhea. And the last question is, what is the best diet for diarrhea?

Dr. David Metz 50:21
Yeah, so what's the best diet? I always say to everybody, do what I say not what I do, because food is one of the most favorite things we have in life. And if there's anything I've learned over the years, restricting or limiting, one of the pleasures of life is really not a good thing. So I always say, eat a normal diet, eat a healthy diet. And don't deny yourself something just because you love it. But realize there may be side effects. So, for example, if you're lactose intolerant, and you want to have some ice cream, you know what's going to happen, there's nothing you can do to stop it. So you can take lactaid, which is lactose in a pill form, just like pancreatic enzymes in a pill form for pancreas. Then, if you don't, you're going to get diarrhea. So I think the issue is to live a healthy life and have a balanced diet. I do think if you're on an SSA, and you're getting diarrhea, think about limiting your fat intake, and/or considering enzymes. I think it's important to have a good intake of solid, good protein. Because you really want to be building up. You're feeding two things, you're feeding yourself and you're feeding a tumor. If you don't eat enough, your tumor beats you to the food. And weight loss for me becomes an important sign in neuroendocrine tumor management. If you're losing weight despite eating, that's something we get concerned about. People always ask about using resveratrol and vitamin E or this enzyme that's for long health or the stuff that's advertised on TV that makes you live longer and think clearer. And I always say show me the data. If theris a study that shows is a benefit, I don't want to deny you anything. But let's be frank, a lot of this is hocus pocus sort of stuff. But from a dietary perspective is, you really need to maintain that input at the volume enough to keep your weight going. Limit the food that are poorly tolerated, and that's usually fat. Make sure it's a balanced diet. And if necessary, take supplements. I don't think resveratrol, red wine, garlic, vitamin E, milk, thistle, and that sort of stuff makes much difference.

Lisa Yen 52:48
Thank you, Dr. Metz. Thank you for all your time! We went through 10 questions. You gave us such a wealth of knowledge and information here. We really appreciate your time and energy and we hope to see you in person soon.

Dr. David Metz 53:03
I look forward to it and all the best in California!

Lisa Yen 53:07
Thank you.