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# Test Your Skills and Learn From Experts on Best Practice in Diagnosis and Management of Systemic Mastocytosis

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**Dr. Bitar:**
So we’re going to go ahead and start with the session. So, what is mastocytosis? So this is, this is an important definition. So mastocytosis is a neoplastic disorder. It’s not just like a dysfunction of the mast cells. So there is increase in number and accumulation of those clonal mast cells in different part of the body. So it can be divided into cutaneous mastocytosis where you have skin-only involvement, and you can have systemic mastocytosis where you have other cutaneous, extracutaneous involvement, like liver, spleen, bone, and other internal manifestation as well. And then you can have mast cell sarcoma, which is a super rare disease, and it could be like really aggressive. Systemic mastocytosis is really not the same as mast cell activation syndrome where mast cell activation syndrome you can have symptoms of mast cell activation, and then systemic mastocytosis could have symptoms as well, but not all MCAS would have clonal distribution, and you have like an actual clone in MCAS. Not all of them will have that, so this is an important distinction.

Symptoms in the spectrum of mast cell disorders, and as you can see, they can be multiple symptoms, and that’s why the patients are most of the time delayed to be diagnosed because you do have, like, symptoms all over the place. So you can have, in the skin, pruritus, flushing and hives; and then the patient would mention nausea, vomiting—in the GI tract—diarrhea, abdominal pain. Also, neurologic is very, very important. They have, like, memory fog. They feel, like, down or like sleep disturbances or headaches. And then the cardiovascular is a big one as well, so they can have syncopes, dizziness and palpitations. And then if they do get like on the more severe side, they start having anaphylaxis where hypotension is much more prominent than angioedema, and that’s a very important distinction. They can have this like bee sting. Does that ring a bell for you all? So that bee sting is a sign of drugs and food allergy or anaphylaxis to those. And then you can have bone involvement as well where you have osteopenia, osteoporosis, back pain and bone pain. And then they have these, like, constitutional symptoms, very nonspecific: fatigue, weakness, malaise. And then when you do actually have like a more progression and, like, organ involvement for these mast cells, you can have actual pathologic fracture because of the involvement of the bone, lymphadenopathy, splenomegaly and hypersplenism and hepatomegaly, as we talked before, cytopenias, and then also you can have protein-losing enteropathy when you have a GI involvement. So it goes on the spectrum from that disease burden from prediagnostic systemic mastocytosis so indolent, which are like most of our patients are in that family, smoldering systemic mastocytosis, and you can have the aggressive type where you do have associated pathologic neoplasm And then you can go all the way to mast cell leukemia, which is really aggressive where you have involvement of, like, multiple organs as well.

So systemic mastocytosis, again, is considered an orphan disease, so prevalence about 32,000 people in the US, and then you have prevalence of one in 10,000. And the diagnosis within the systemic mastocytosis, as I mentioned before, is usually indolent, more than

90 % of systemic mastocytosis patients, and then you have with heme disorders about 6%, which is very rare, and then the mast cell leukemia, which is super rare, is 0. 5%. Again, it takes a long time before we get a good diagnosis, about a mean of 6. 5 years before the—from the onset of symptom to the actual diagnosis, and this is, again, because of all these different, like, nonspecific symptoms that can happen in this setting of this disease.

And also it's divided. Like, so mastocytosis is divided into adult and pediatric onset, and some people think these are two different diseases because they do manifest differently. They actually have a little different prognosis. So in adult, as we just mentioned, if you do have a cutaneous manifestation, most of the time you can find an indolent systemic mastocytosis. It's a chronic disease. There is a high risk of having anaphylaxis, about like 50, up to 50%. Tryptase level is usually high in adults compared to kids, more than 20. In kids, most of the time it's still—it remains in the skin and actually resolves as they get older, and then the anaphylaxis is much less likely. The KIT mutation is most of the time in adults the D816V, like the famous mutation. However, in pediatrics you either don't find a mutation or you have, like, other exons, 8, 9, 11, 17. And then the morphology of the lesion also is different, and then we're going to talk more about that in adults. You do get these like orangey-brown monomorphic papules and macules all around like the trunk area, and in kids you have more like polymorphic lesion, much larger. They can look actually more scary in kids, but it's actually behaved really fine. Size of the lesion much smaller in adults, larger in kids. And then the distribution is also very important. So you start on the thigh and could move up to the trunk in adults, and in kids you can have that head involvement. That's very, very characteristic in kids, especially in that forehead distribution and the scalp distribution, so this is also important. This distribution you don't really see in adults with mastocytosis.

So this is the typical lesion that we just mentioned, so polymorphic small lesions like reddish-brownish. They look all kind of cookie cutter on that trunk in adults, and in kids you see those like bigger patches and plaques. You can have Darier's sign that we're going to talk about in a minute. And then in kids actually it can blister, so you can have bullous mastocytosis as well.

So again, like all adults with cutaneous mastocytosis, you really need to rule out an internal involvement, especially with a bone marrow to rule out an indolent systemic mastocytosis. It's very, really a cutaneous disease. It presents more than 80% of patients where they have cutaneous lesion. Darier's sign could be present where you rub a lesion and you form, like, more wheel, wheeling of the lesion. And then, again, they start on the thigh and go up to the trunk and distal extremities, and usually no head involvement, no acral involvement for those.

So the diagnostic criteria, so that like was another focus for us today. So, how do you diagnose those patients with systemic mastocytosis? So, if you are using the WHO classification, you need one major and one minor criteria or more than three minor, and the International Consensus you can use one major criteria or more than three minor criteria. So the main major criteria is those, like, multifocal dense aggregates of mast cells, more than 15 cells in the aggregates in the bone marrow and/or other extracutaneous organs. That's number one, major criteria. And then the minor criterias are multiple, so more than 25% of the mast cells with atypical morphology, so they become a little spindly; they look a little different than your regular egg-shaped mast cell that you're used to see. They do have aberrant expression of CD2, 25 and 30 on the mast cells, and this is more important on the bone marrow than on the skin. I don't really test those markers on the skin. The KIT mutation D816V is another minor criteria, and this is tested on the bone marrow. It could be tested on the skin as well. It's more accurate on the bone marrow. And then the baseline serum tryptase of more than 20 is another minor criteria, definitely in the absence of other associated myeloid neoplasm because these could not count, like because these could contribute to the tryptase level and at that point does not count as a minor criteria. So you need one major and one minor to diagnose a systemic mastocytosis.

Differential diagnosis, you—it's all over the place again, like the symptoms, so you can have other mast cell disorders. So you have like mast cell activation. You could have anaphylaxis, or you can have other conditions that give you symptoms that look like mast cell disease, and that's why we get to see a lot of these patients. So like chronic spontaneous urticaria, atopic dermatitis, rosacea, all of these could present with flushing and redness and rashes that comes and goes. You could have thyroid disease, so thyroid is a big one here; adrenal insufficiencies; you could have carcinoid syndrome that also could present with flushing; GI. They do have a lot of GI complaints, so definitely you want to make sure you don't have like IBDs or IBS. And neurologic is another big one, so I do have a lot of patients that come in and they were like, "Oh, they think I'm crazy. I'm having, like, seizures," or like "psychoses" or "anxiety" or "panic attacks," so this is very, very important to kind of rule out other things before we put or label these patients into these categories and these families.

So adult-onset mastocytosis, they usually present with cutaneous lesion. Again, this is the new terminology of maculopapular cutaneous mastocytosis, so this is like the bigger term now that kind of encompass every single lesion of mastocytosis except for kids. You could still have mastocytosis and diffuse mast—mastocytosis, which we're not really going to ask us today. But those monomorphic lesions that we talked about, if you see them in a patient, you have a biopsy on the skin that favor mast—cutaneous

mastocytosis, you really are to look for indolent disease. So this is the workup that I usually do for my patients. I get a serum tryptase. I get a KIT, make sure to get the KIT mutation. You can do it, again, on the skin and the bone marrow, a skin biopsy and definitely a bone marrow with other appropriate studies, and then definitely like a DEXA scan as well to look for bone involvement.

So this is, these are the subtypes. You have multiple—what we see mainly in that is that indolent systemic mastocytosis where you don't have—you have nonadvanced disease. You have the typical skin lesions, so these are like the most common that present with cutaneous lesion, less likely to have B signs like cytopenia, hepatomegaly, splenomegaly or lymphadenopathy. You can have high tryptase in those patients as well. The bone marrow mastocytosis is kind of like a tricky one because really, you don't have skin lesions, and you don't have any B or C findings, but you have some cells in the bone marrow, but they're not fitting all the criteria, so that one is kind of like in the middle. And then you do have the smoldering systemic mastocytosis where you start having more B findings but no C findings. And then as you get more advanced in this disease, you get actually like more infiltration of other organ and damage, and then this is where you can get all the way to MC leukemia where you have like bone marrow involvement; you might have peripheral blood involvement. So I think about it like that. If you are really in that indolent family, you can have cutaneous lesion, and as you go more deep, those, those mast cells can leave the skin, and they go internal, and this is where you less likely have actually skin lesion when you have more advanced disease, and then you end up with more internal involvement and then other involvement like liver, spleen, bone marrow and all of those.

So back to our question. So this is the 36-year-old man who presents with these—what looks like red skin lesion. They look acne form. He was treated for acne for two years, not getting better. He's having these hyper pigmentation on the trunk. So, which of the following most strongly indicates that he should be actually assessed for systemic mastocytosis and not acne? Absence of Darier's sign, occasional once-weekly double vision, severe hornet sting allergy, or telangiectasias? Okay, I like it. So we have definitely some improvement there. Seventy-four percent did agree on that hornet sting allergy, which is, which is the right answer there. Darier's sign is a plus if we have it, but if we don't have it, that doesn't really rule out mastocytosis. And then double vision, it's not really a sign or symptom. Telangiectasias is a tricky one because you can see it on the skin a lot of time, but really, it's not a diagnostic criteria for mastocytosis. So, as we just mentioned, this is one of the signs of mast cell activation.

Question number 2 is the—we're going to look at the WHO criteria to qualify this patient for systemic mastocytosis. So A is dense multifocal bone marrow mast cell aggregates; B, dense multifocal bone marrow mast cell aggregates and the serum tryptase of more than 20; C is identification of the KIT D816V mutation; and then D is identification of the KIT D816V mutation and a serum tryptase of more than 20. Okay, so we do have some improvement there. I know you'll really like that mutation that one, gets everyone every time. So the mutation is actually minor criteria not a major criteria, so together with the tryptase makes it two minor criteria, and you need three to make a diagnosis, so you need really to have that bone marrow infiltrate multifocal and one minor criteria, which in this question was serum tryptase 20. So just remember that the mutation is very important but really it's not a major criteria because we're still kind of discovering more and more mutations for those as well. So with this, this is like the rational that we just talked about. So you need either more than three minor, so that's why D is wrong because it's only two minor, and then B is the right answer, one major and one minor.

And then I'm going to hand over for clinical data on new emerging therapies.

**Dr. Giannetti:**
Yeah, excellent. Thank you, Dr. Bitar. So as we discussed before, my name is Matt Giannetti. I'm from Brigham. I'm an immunologist by training. My section of the talk will be here to discuss on clinical data regarding the new therapies for mastocytosis as well as a couple slides on kind of the basic therapy for all patients with mastocytosis.

Okay, so before we start, let's do a couple of pretest questions. So first one: Which approved targeted therapy specifically targets the D816V mutation? All right, good answers. Pay attention to approved, so FDA approved here. We'll circle back to these in a little bit at the end of my talk.

So question 4: Your patient has indolent systemic mastocytosis with the KIT D816V mutation. For six months, a combination of anti-mediator therapies improved itching and diarrhea, but now symptoms are worsening. Based on the PIONEER trial, what statement would be correct when discussing therapy with the selective KIT inhibitor avapritinib for indolent SM? So I'll let all of you read the questions and answer A, B, C, or D. Great. B. So we'll again circle back to this once we have completed my section of the talk.

All right, so let's talk about some of the actual data. So first off, before we get to the new novel therapies, I think it's important to start with the basics. So, when I think of treatment for mastocytosis, I think of kind of two pathways. You know, pathway one is going to be treatment of the mast cell mediator-related symptoms, so blocking the bad things mast cells release, and then path two is going to be cytoreduction of mast cells. And we'll talk about that in terms of the novel therapies.

So for the first path here, treatment for mast cell mediator-related symptoms, I like to think of a specific organ and therapy for that organ. So, for example, for the skin, most commonly people will have pruritus, itching, flushing, hives. They often term flaring of their cutaneous lesions or flaring of their spots. Typically for this, H1 and H2 are very helpful, so I like second-generation antihistamines. My go-to regimen is cetirizine, 10 mg twice daily, and then you can kind of go up or go down depending on how the patient is doing. Leukotriene receptor antagonists also can be quite helpful. Aspirin, ketotifen, these are probably more in the domain of allergy, I would say. Second, for GI symptoms, probably the second most common organ system involved in my experience in mastocytosis. Many patients have received kind of long lists of diagnoses, from ulcers to irritable bowel syndrome, et cetera. And so we do see a lot of acid hypersecretion in mastocytosis, so histamine actually directly activates parietal cells, so the acid-producing cells of the gut or of the stomach, so H2 blockers can be really helpful in this regard, so typically, famotidine. Many patients will need to be escalated to proton pump inhibitors as well. And then finally, I'm not going to cover kind of all of the rest of these. It's basically H1 and H2 is what I would say, really for everybody. If they have a lot of symptoms, a good starting regimen is twice daily H1 and twice daily H2, and then depending on how they're doing, kind of adjusting from there, both above more meds as needed or less meds. And then one kind of final callout here for omalizumab, this is really helpful for anaphylaxis, so for patients who've had hypotensive syncope, or truthfully, really poorly controlled skin lesions and flaring of their spots, often with some hives despite antihistamines, omalizumab is an excellent option.

So moving more towards the cytoreductive therapies, a couple of older medications. So imatinib was really first reported in the 1990s for mastocytosis. As it turns out, most people with systemic mastocytosis have the KIT D816V mutation. You can see here the indications, adult patients with aggressive—or there are nonaggressive forms as well that I will use imatinib—but very importantly without the KIT D816V mutation, so you need to check for it. You need to check for it using a PCR-based method. D816V is resistant to imatinib, so it's really important that it's—you know, we have the molecular diagnostics correct before using imatinib.

Midostaurin is a recently approved medication for advanced aggressive mastocytosis. It's approved for all the aggressive forms of mastocytosis or the advanced SM forms. It's only other approval is FLT3-positive AML, so it has a considerable amount of toxicity associated with it, but in the more aggressive forms, it is quite useful.

So let's spend the bulk of our time talking about the KIT mutations and then specifically how we can target KIT mutations with our novel therapy. So, as I mentioned before, most everybody who has systemic mastocytosis has an activating mutation in the KIT protein. Classically, we think of KIT D816V. Depending on the data you look at, really between 85 to 95% of patients have KIT D816V. If you focus here on this little graph to the right, you see KIT protein. It's a dimer. And when stem cell factor binds, it kind of comes together and then sends an activation signal down here. What KIT D816V does is it's just constitutively active, so it's always on; it's always sending a signal; it's always telling the mast cell to grow and divide and proliferate. And so, you know, there are very few diseases that have 85–95% of the disease caused by a single mutation, so this observation kind of led to the genesis of these targeted tyrosine kinase inhibitors.

So moving forward on that note, the first targeted therapy we had against the KIT D816V was avapritinib. It received FDA approval about two and a half or so years ago for indolent systemic mastocytosis. So you can see here in this kind of pictorial graph of a mast cell, KIT D816V, KIT protein is here. It's an intracellular protein that spans the membrane, but the intracellular part is a D816V part, and avapritinib basically fits into that pocket and kind of blocks activation or blocks signaling through the mutated KIT protein. I won't talk too much about kind of all these chemicals that mast cells release, but it is important to note a couple of things. One, histamine, right? why we give antihistamines to these people. Two, leukotrienes. So probably most of us have heard about montelukast, or Singulair, also another medication that can block mast cell mediators, such as leukotrienes. And finally, prostaglandins. These patients release a lot of prostaglandins. We used to use aspirin therapy much more in the past. We use it a lot less now, but aspirin blocks cyclooxygenase and inhibits synthesis of prostaglandins, so important to have a general understanding of the things mast cells release, mostly so we can contextualize why we're giving these medications.

All right, moving on to the medications that have recent clinical trial data. So avapritinib was studied in the PIONEER trial. This was published in 2023 in *the New England Journal of Medicine Evidence*. It's a pretty large study, large at least in terms of mastocytosis, so 212 patients with moderate to severe symptoms. They all had to fill out a symptom survey and screen in based on the severity of their symptoms. And maybe more importantly, they had to be on at least two medications and have uncontrolled symptoms despite these two medications.

So, what do we look for in this trial? The primary endpoint is the leftmost column here, Total Symptom Score. This was that TSS score. So it's a series of about 11 questions across skin, GI, anaphylaxis, cognitive, lots of different physical symptoms. You can see here a significant reduction in this primary endpoint. The secondary endpoints, there were three primary secondary endpoints, all related to the quantity of mast cells that each person had. So serum tryptase, KIT D816V, and bone marrow mast cell burden all decreased, indicating that avapritinib was effectively cytoreducing or killing off—to use a more colloquial term—mast cells.

Moving forward, there's also been shown that these responses are both durable and in fact improve over time. So avapritinib at the approved dose of 25 mg works quite well, but in many patients with a chronic disease, some of the other questions are How long does it last? Do patients lose response? And as it turns out, with 96-week follow-up, they consistently have an improvement in their TSS score over baseline. And somewhat surprisingly, over the longer term, it continues to improve. There's a couple of theories behind this, probably related to dose, et cetera, but you can see, though, that patients do not lose response. At least most patients do not lose response to the medication over the course of a couple of years. If you start breaking those down into individual symptom domains, you can see that in the GI, skin, and neurocognitive domain, symptom scores maintain significant improvement and in fact deepen in all three domains over time. And then same thing in quality of life. This is a more general score about like How is your quality of life? Are you impacted in daily living activities, et cetera?

Moving a little bit more forward towards the oncologic data, so avapritinib was also tried in the more advanced cases of mastocytosis. So you can look here at the phase 1 EXPLORER and phase 2 PATHFINDER study. So this is a very different population of people. These people were pretty sick. So SMAHN is mastocytosis plus another blood cancer. Aggressive systemic mastocytosis, 16%, these people have organ failure, typically fulminant cytopenias, hepatic failure with portal hypertension, and mast cell leukemia is really invariably fatal at this time. And so in this very sick patient population, avapritinib pretty significantly extended the survival rate of these patients. Again, when we think of the trials with indolent systemic, we're looking at symptom improvement because these patients have a normal lifespan. In this kind of data, the outcome is very different. We're looking at survival because life expectancy of patients with advanced mastocytosis is quite a bit shorter. I think for most of the audience here, this is a little bit outside the scope of what they'll be prescribing, so we'll move on to the next slide here.

So cautions and warnings with avapritinib, a couple of adverse reactions that we see. So intracranial hemorrhage was first reported. This has been reported really only at higher doses of the medication in patients with more advanced disease. From a practical standpoint, for people with ISM, normal functioning bone marrow and normal platelets, I've never seen any of this, nor has anything ever been reported in the data, so I think this is more a dose and disease-dependent phenomenon. Maybe some of the more practical things that we will see, so cognitive effects. Some people do describe a little bit of forgetfulness, you know, difficulty remembering things, particularly early on. Photosensitivity, I mean, I don't really counsel patients on this. I'm not sure that I've seen much photosensitivity. I think, you know, at all times people should be careful, particularly with mastocytosis given they have an active skin disease, but maybe the dermatologist can comment more on this. I don't tell people to avoid the sun on avapritinib. And then the last one here, this is an important one. So this is absolutely a teratogenic medication, so you cannot, you cannot have children while on this. There's been reported harm in animal studies, and it's an absolute contraindication probably for—during pregnancy.

So in addition to avapritinib, we have a couple of other clinical agents that are in clinical trials or recently completed clinical trials. So, as I mentioned before, avapritinib is currently FDA approved for indolent systemic mastocytosis. These two newer medications, bezuclastinib and elenestinib, are not FDA approved. Bezuclastinib's large study has completed in the end of 2025, so we're waiting on more information. Elenestinib is currently enrolling patients for a phase 2/3 clinical trial on the HARBOR trial.

So in the early data for both of these medications, you can see here, looking at the endpoints we talked about before, symptom improvement, primary endpoint for all of these trials; reduced tryptase; reduced KIT D816V; and reduced mast cell burden; all secondary endpoints in markers of mast cell burden. You can see X's across the board, so these medications do all of it. The main benefit of these two new medications is that they do not cross the blood-brain barrier, so we see much less cognitive effects. And theoretically, the risk of intracranial hemorrhage should be zero. So probably more coming in the next couple of years on these medications.

All right, so other emerging therapies. Masitinib had a phase 3 study a while ago. This doesn't hit D816V. It hits a little bit of chemicals downstream, so they're called the Src kinases. You know, maybe some mixed-use. We haven't had final data yet from the trial, so I think the jury is still out there. This is a different drug, TL895. It's a BTK inhibitor. There is a good bit of precedence for the BTK inhibitors in the oncology literature, particularly in B-cell cancers. This has some positive early data, but it's still very early in clinical trials, so much more to come on this. I think it's still a little bit early to comment too much on it.

So with all that said, let's circle back to some of the questions here. So post-test question number 3. Again, please pay attention to the verbiage and the wording here. Which approved FDA-approved targeted therapy specifically targets the KIT D816V mutation? Great. Excellent. We have learned stuff. So avapritinib, yes, is the correct answer. It is FDA-approved, and it does specifically target the D816V. Imatinib is important because it does not actually target the D816V mutation. So, yeah, rationale, avapritinib is the only FDA-approved one here for—that targets D816V.

Okay, the second pretest question, let's repeat that here, I think. Yes. So for this patient with indolent systemic mastocytosis, starting on or talking about avapritinib, which would be correct when discussing therapy with the selective KIT inhibitor avapritinib? Yeah, great.

So basically, everybody chose mast cell burden decrease. Clinical trial data here shows that the mast cell burden decreased by greater than 50% in 53 patients. The reason why we reported, this is kind of like oncologic convention. We report things as greater than 50% improvement, and so in more than half of the patients, we reduce their bone marrow mast cell load by more than 50%.

All right, so with that, thank you so much for your attention. I will hand the microphone and speaker presentation over here to Dr. Ungar.

**Dr. Ungar:**
All right. Fantastic. Thank you. So I—Can I just get confirmation that I'm audible? Okay, excellent. So we're going to be discussing patient-centered management strategies in systemic mastocytosis. And before jumping in, we will do a couple of pretest questions. So a 46-year-old patient presents to your dermatology clinic with persistent red-brown macules in a trunk with a positive Darier's sign, flushing, unexplained GI comfort. Which of the following referral pathways is most appropriate to ensure timely and accurate diagnosis of systemic mastocytosis? Refer to gastroenterology to evaluate abdominal symptoms while managing cutaneous findings in dermatology, continue dermatologic management and repeat biopsy in six months, refer to endocrinology to evaluate for flushing-related hormonal disorders, or refer to allergy immunology for mast cell disorder evaluation while managing cutaneous findings in dermatology. I'll give everyone a moment to answer. Okay, and the majority of people have selected the last option, allergy immunology.

And then we will go on to the next question. How confident are you in applying shared decision-making strategies to reduce disease burden experienced by patients with systemic mastocytosis? Not at all confident, not very confident, somewhat confident, confident, or very confident. And again, we'll give everyone a moment to answer. Okay, a mix of confidence.

All right, so with that said, we'll, we'll proceed. And there, there are a few, I think, themes that I want to touch on here, three in particular, the first being the multidisciplinary kind of aspect of care that this condition requires. The second thing we're going to talk about is shared decision-making with patients, which really ties into a lot of that, and then ultimately what we can do as dermatologists in terms of ensuring these patients really get the care that is needed. And so some of the considerations for the management of systemic mastocytosis—and again, as derms, we may not be necessarily the lead or focal point for all of these individual kind of aspects, but it's important to know about them and ensure that patients are getting connected, either doing it ourselves or connected with someone who can ensure that they're getting that management and care. So whenever possible, referral to specialized centers is strongly recommended, so that's certainly something to keep in mind if that's at all an option. Because of the osteoporosis, baseline DEXA scan is warranted. Patients need to be educated, counseled on signs and symptoms of the disease. Given how complex this is, how many organ systems can be involved, often the relatively unclear nature of some of the symptoms, it's important that they're aware what aspects might be affecting them even if they haven't fully connected the dots yet or haven't yet experienced those symptoms. It's certainly important to counsel them to avoid known triggers of mast cell activation, and we'll go into some more of the triggers, but many, many times patients will be aware of triggers that are associated with worsening of their disease or symptomatology, but it's not always so clear-cut. And there are certain things like bee stings and so on that they may not have experienced yet, and they need to be aware of in advance of having that experience. Every patient needs to have injectable epinephrine, so they need EpiPens to manage anaphylaxis, very high risk. And then in general, this is a disease with a very high symptom burden, quality of life impact, and so quantifying that, measuring that and ensuring that we're actually tracking and improving using quality of life instruments can be very helpful.

So some of the triggers—you know, we mentioned in the last slide, but true here as well—temperature changes, stress, fatigue, certain foods and beverages, certain medications, infections. You know, obviously, a lot of these triggers are going to be ubiquitous, and, and patients are often going to already know the, the kinds of specifics that affect them. Hymenoptera venom, bee stings, wasps, very, very important, high risk of anaphylaxis. And then surgical surgery procedures, anesthetics and so on may be triggers, and patients, and then ultimately when they speak with their surgeons and so on, need to be aware of the potential risk with their systemic mastocytosis.

So one of the maybe most important things that we can do as dermatologists from the get-go is educate about anaphylaxis. Patients with systemic mastocytosis are extremely high risks. Up, up to 50% of people will experience anaphylaxis, and they're using epinephrine frequently, so they need to know what anaphylaxis looks like. We need to ensure that they have access to an EpiPen. And because anaphylaxis is an emergency, symptoms come on rapidly. It can be extremely stressful. It's important that patients know in advance when they are not in that stressful environment what to do, how to deal with it, how to use the EpiPen. You can imagine if you're not trained and experiencing anaphylaxis, you're not going to use the EpiPen correctly, so, so having that in advance is crucial. And, you know, here is one tool that can help in a more formal way, this Anaphylaxis Emergency Action Plan, to go with the patient, to understand here is what happens if the symptoms of anaphylaxis develop or there's an exposure like a bee sting, wasp sting, that may be very high risk.

We've talked, I think, pretty extensively, and it's worth highlighting that the aspects of patients' health that are affected by this are quite

varied, and the reality is very often it's not going to be one specialist that is managing everything, and so one of the crucial things is that patients have that multidisciplinary care to ensure they're getting the holistic approach needed for their condition. And that's the benefit of a specialized center where that's actually streamlined and we have people who are specifically focused on treating that, you know, whenever possible. And this is just kind of an example of some of the specialists that may be involved in care. You know, we talked about osteoporosis. Vertebral fractures can be quite common, and that's often very debilitating, so having an endocrinologist ensure that they're on top of care for osteoporosis. You know, allergists, immunologists, they're going to play a crucial central role in the majority of cases in treating this, and that's, you know, whether it's specific allergies, Hymenoptera, management of the mast cell mediator-related symptoms, anaphylaxis and so on. Certainly as dermatologists we're treating the cutaneous lesions, psychiatrists, GI doctors, pathologists who know what they're doing in, in specifically with systemic mastocytosis. So it's very complicated, and the more kind of connected and streamlined we can get, the better off patients will be in, again, in terms of their holistic care.

With such a complicated condition, it is, I think, easy to imagine that patients are going to be getting a lot of medications, particularly if they haven't really been formally diagnosed or they've been bouncing around in a really disconnected set of specialists, going to GI doctor for the GI symptoms, and that's not necessarily being connected to, you know, the endocrinologist and so on. And so, even when things are streamlined, patients are going to be getting a lot of medications, and this is just one example of the various types of intervention: bisphosphonates, epinephrine, antihistamines, topical therapies and all that. So polypharmacy is very, very common. You can see here 50+ percent are using at least three prescription medications and over-the-counter medications. There's a high risk of polypharmacy. And when there's not this kind of maybe centralized or streamlined process of care, that's going to be a high risk of things falling through the cracks and not to mention, you know, drug interactions and so on. And this is probably in most cases too complicated for a primary physician and so on to care for, and that's why—or, or really to, I would say, to oversee, and that's why specialized care is needed.

Now, part of the, the process of achieving, I think, hopefully optimal care is shared decision-making. Now, shared decision-making as a concept is not unique to systemic mastocytosis. This is, hopefully, something that's being integrated really into care across different diseases. But I think it's fair to say that there are certain conditions where it may be even more important to integrate just because this is very complicated and there are a lot of moving parts. Shared decision-making really means, as the first box here says, "seeking the patient's participation," having the patient be actively involved in their care, whether that is involved in decisions of treatment, understanding which specialists they're connected to, who's taking the lead on their care, which aspects of their specific experience are affecting them the most. You know, part of it is educating on risks and so on but also what they're experiencing, patient values, preferences, challenges, hurdles. You know, it's easy to say, "Oh, go see," you know, "XYZ," and if they have logistical hurdles to doing that, you know, ultimately that's not going to be an effective treatment, and the only way really to understand that is to engage in that dialogue with patients, eliciting their perspective, priorities and, and personal experience.

And then, ultimately, when there are various treatment options, various parts to this, when patients participate in the decision to pursue a certain treatment and so on, the likelihood is that they're going to be more adherent to treatment. They have buy-in to the process to say to themselves, you know, "I'm part of this, and it's not just someone telling me what to do with my life and my, my condition, but I'm involved in that." And so, ultimately, that's going to just lead to better outcomes. And integrating that with a multidisciplinary care really, I think, works together to achieve the goal of addressing the huge, you know, symptom burden, quality of life burden that these patients experience. And so the shared decision-making, we kind of talked about this, but really, I think that individualizing treatment is really at the core of this. So, yes, education is important—having patients understand what is happening to their disease, what treatments are available with the evidence supports, monitoring, follow-up, support resources—but, but ultimately, that's all going to center around individualizing treatment for that patient and what really works best with their life.

Patient support resources can be extremely helpful. You know, this is complicated and, you know, often we're not going to have time to sit for two hours to go through various aspects, and so part of the education process can be done with the patient at their own time. And, you know, here's a list of some, some resources that can be available.

Okay, so with, with that said, we'll return to the question. So 46-year-old patient presents to your dermatology clinic, reddish-brown macules on the trunk with a positive Darier's sign, flushing, unexplained GI comfort. Which of the following referral pathways is most appropriate to ensure timely and accurate diagnosis of cystic mastocytosis? Refer to GI for the abdominal symptoms while managing cutaneous findings by derm, continue dermatologic management and repeat biopsy in six months, refer to endocrinology to evaluate for flushing-related hormonal disorders, or refer to allergy immunology for mast cell disorder evaluation while managing cutaneous findings in dermatology. So we'll give everyone a moment to revisit this. Okay, so the vast majority of people identified allergy immunology, and I certainly would agree with that. So, so this is just, I think—I want to emphasize one of the points. You know, it's multidisciplinary, but someone in a sense needs to take the lead, and typically speaking, allergists and immunologists are going to be positioned to do that.

All right, question 6: How confident are you in applying shared decision-making strategies to reduce disease burden experienced by patients with systemic mastocytosis? Not at all confident, not very, somewhat confident, or very confident. Again, give everyone a moment to answer this again. Okay, so we have a shift in confidence from less confident to more confident. Excellent. All right.

So some key takeaways just to round this out. Refer patients for further assessment if you suspect systemic mastocytosis. And, you know, again, dermatologists can play a role in the potential diagnosis with skin biopsy and evaluation of skin lesions, and that referral, preferably whenever possible, to a center that specializes in systemic mastocytosis care. Treatment options for people with systemic mastocytosis include anti-mediator and cytoreductive therapies. KIT mutations, particularly KIT D816V, are the drivers of systemic mastocytosis pathophysiology and that mutation in the vast majority of cases, and because of that, selective KIT inhibitors are important emerging treatment options, or emerged treatment options in some cases. And patients with systemic mastocytosis commonly receive many treatments and need treatment adjustments, communication, and reassessment with, with patients and the care team, and so having that care team well set up is crucial for optimal care.

And so with that we'll go to the Q&A session, and Drs. Bitar and Giannetti will, will join here.

**Dr. Giannetti:**
Great. So I can handle the first. I see a couple of questions here. So the first two questions are mostly the same with little bit of permutation, so maybe I'll go ahead and handle these, and then I will pass over to Drs. Ungar and Bitar.

So the first question is, What is the cause of osteoporosis? And the second is, How often should patients have a bone density scan done? So bone density scan is first most important because, well, that's how you get the diagnosis of osteoporosis, so in general, for everybody with systemic mastocytosis, I will order it at diagnosis. If it's normal, I check it every five years. If there's any evidence of osteopenia, I do vitamin D, calcium, and then check it every three years or so. Anybody with osteoporosis really mandates therapy, so I send these patients to, to endocrine. And, and I do have a couple of youngish males, 30, 40-year-olds with vertebral fractures, so even in atypical populations, you can absolutely have fractures. What is the cause of osteoporosis and vertebral fractures? Active area of research, so the, the real answer is it's unknown. It's related to mast cell burden. Probably, mast cells release a variety of chemicals, cytokines, chemokines, that put a little bit more pressure on osteoclasts to break down bone rather than osteoblasts to build up bone, but I think the pathogenesis is not completely understood, is what I would say, at present.

So for next question, maybe, Dr. Bitar, I'm going to pick on you. Why don't you handle one of the remaining questions?

**Dr. Bitar:**
Sure. And I do agree with all what you said regarding the bone. This is, this is what I do too. For the—I think the second one is referral to allergy and immunology, always the gold standard when suspecting patient who has systemic mastocytosis or symptom specific. So what I typically do, I, I think for my patient with systemic mastocytosis, I do have allergy and immunology involved all the time, so that will make Dr. Giannetti really happy, which is, which is what I usually do. We do have—In our institution we do have some GI that do have specific interest in mast cell disease, so I do tend to refer to, to GI that do have that specific interest, and they know about the disease more than any regular GI. Endocrinology, I don't think they're involved all the time, depending on the symptoms that we're seeing. I do have HemOnc involved as well, obviously for the bone marrow and all of that.

**Dr. Ungar:**
Maybe, Dr. Giannetti, do you want to take the, the next one?

**Dr. Giannetti**:
Yeah. So, good question. Do you ever see patients with hereditary alpha tryptasemia who don't have SM at the time of diagnosis go on to develop SM? No. So they're totally separate. I mean, they're, they're related because you have an elevated baseline serum tryptase, but hereditary alpha tryptasemia is not a clonal mast cell disorder. It's a genetic trait. It's not currently considered a disease. Approximately, 5–7% of the United States has hereditary alpha tryptasemia. You could maybe make the argument that people who have very severe anaphylaxis have a low burden of SM that we can pick up with some of our fancy tests in the future, but I, I really, when I do in clinic, I try to kind of bucket patient in one or the other. They, they can both overlap, and you can have patients with both, but in, in general, if somebody has a mild elevation in tryptase and they have the appropriate tryptase genotype, that's enough for me to satisfy, satisfy myself. But this is more—Probably, allergy can answer this question. So this is more in our domain with tryptase and anaphylaxis, et cetera.

**Dr. Ungar:**
Okay, I think we—So I see a question here. Would everyone who has had anaphylaxis or angioedema more than once be recommended to check for systemic mastocytosis? So I'll briefly answer, and Dr. Giannetti as an allergy immunologist probably should weigh in as well. There are obviously many causes of anaphylaxis and angioedema that are not systemic mastocytosis related, so I

don't think the assumption is necessarily that if the presenting symptom is anaphylaxis, that patients have systemic mastocytosis. You know, we talked about the, the prevalence of skin lesions, you know, so I think it's reasonable to think about that as a potential etiology for anaphylaxis, but a lot of that will also depend on history. You know, if someone has an exposure to a food or, or in a kind of a repetitive scenario, you know, there, there may be more likely explanations for the anaphylaxis, but having it in mind, particularly in the context of other symptoms that may, may point to it, the GI, flushing, and so on, I think it's something to keep in mind. Dr. Giannetti or Bitar, I don't know if they have a different perspective.

**Dr. Giannetti:**
Yeah, I agree. I mean, there's lots of reasons they have anaphylaxis. If you can find a clear trigger, you know, if somebody ate a peanut, they have a known peanut allergy and they have anaphylaxis, probably we don't need to be looking for systemic mastocytosis in that person. It's more like the idiopathic anaphylaxis where we really have no specific reason for this. And maybe even more particular, the type of anaphylaxis in mastocytosis involves cardiovascular symptoms, so it's often hypotensive syncope without hives. In our domain in allergy, it's pretty unusual to have people passing out without hives, so that particular type of anaphylaxis really should trigger a little bit more of an evaluation.

**Dr. Bitar:**
Yeah, I agree. I do—Every time they come in with anaphylaxis, I do try to tease out if it's really like more with cardiovascular symptoms or like really actually with skin symptoms, because whenever it's with skin symptoms, it's kind of like a little easier for us to figure out that it could be like urticaria angioedema or like other exposure-related rather than like really mast cell activation. But if you do have a lot of cardiac involvement and cardiac signs, I would be on—err on the side of like definitely kind of look out for like more for those patients.

**Dr. Giannetti:**
Absolutely, yeah.

**Dr. Ungar:**
So with that said, it looks like we have some questions here to wrap up for the discussion, so maybe we'll ask our final polling questions. And then it was a pleasure speaking to everybody today.

**Dr. Bitar:**
I guess you all want to try to do these last two questions about—We have two more about experience of patients who got undiagnosed for a long time. So I do think I would say like most of the patients are in that bucket, unfortunately, because a lot of physicians are really not aware of this condition, and that's the goal of these seminars and webinars, to try to get people to know more about this condition and try to suspect it as early as possible without just dismissing the patient.

**Dr. Ungar:**
Maybe one final question here. Are there recommendations for patients in the perioperative phase in reducing mast cell reactions? Yeah, typically, it's like the contrast protocol that we use in allergy, so it involves oral antihistamines, often cetirizine 10 mg, or Benadryl 25 mg, and prednisone 40 mg, typically given at 13 hours and one hour before. Some people will add seven hours before as well. But the, the general thought is that by giving them steroids and some antihistamines, you're anticipating adverse reactions. I don't do it for everybody. People who have a history of anaphylaxis or clear-cut reactions, I will often premedicate, but I would say it's not mandatory, and it is best utilized in higher-risk patients or patients with a clear history of having adverse reactions during surgery or some other kind of procedures.

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