PANEL DISCUSSION

Venolymphatic Ulcers: What You Always Wanted to Know (But Didn't Want to Ask)

Experts weigh in on the challenges of VLU care, including red herrings, patient expectations, and lack of a common language, and propose a classification system to improve patient outcomes and clinical data.

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First and foremost, what is a venous leg ulcer (VLU)? What are some of the telltale indicators of a VLU?

Dr. Kolluri: Telltale factors for the surrounding tissue include congestion of the leg, edema or lipodermatosclerosis, hemosiderin deposition (ie, darkness of the skin and iron deposition), and sometimes scratch marks due to venous eczema. The congestion eventually leads to partial- and full-thickness ulcers. For the ulcers themselves, a majority are pretty oozy and wet. Most are not

painful, although atrophie blanche ulcers are associated with a significant amount of pain.

Dr. Fukaya: Dr. Kolluri and I are pretty much on the same page of what we think of as a VLU. The pathology of VLU is venous hypertension and inflammation. What's really interesting is that we are using the term "venous leg ulcer," but I come from Japan where we use the term "congestive leg ulcer." The reason is, when you say "venous leg ulcer," you may assume there is a structural venous disease. This is just a reminder that VLU can occur without structural venous disease as long as there is venous hypertension.

Venous hypertension can be due to "anatomic" or "structural" (venous reflux and obstruction) issues and/or "functional" causes with elevated central pressures such as dependent edema, weak calf muscle, obesity, obstructive sleep apnea, and right heart failure.

Dr. Madassery: I tend to agree with my colleagues' comments. Venous insufficiency and its sequelae can cause a predilection for VLU, which is a wound (typically in the lower extremities) related to tissue-fluid imbalance and resulting in congestion of the tissues and fragility of the epithelium. Once this epithelium is disrupted with trauma, which can be as simple as scratching the skin, the congestion prohibits skin regeneration in that area. Many patients have venous insufficiency due to prior venous insults (deep vein thrombosis [DVT], pregnancy, obesity, standing for work) that cause chronic, gravity-dependent edema. Compared to isolated ischemic/diabetic wounds, these wounds in isolation have a different geographic location in the extremities and an appearance as described. Often, we will see partial- or full-thickness wounds, which are usually wet and actively draining, in the background of edema and chronic stasis changes of the skin. At the basic level, if patients have wounds with edema, varicose veins, and stasis changes, this can usually be considered a VLU. However, there can be nonvenous reasons for the edema, making categorization difficult.

What are some red herrings or confounding factors? How does the spectrum of presentation affect the ability to accurately identify a VLU?

Dr. Fukaya: One of the difficulties is a lack of consensus on what we're considering a VLU. Let's say at a wound center, a patient has bumped their leg and gotten a skin tear. That's not really a VLU, but it can be labeled as one. There's a whole slew of things that we could call VLUs that are really not, such as cellulitis with blistering and traumatic skin tears. It's so important for us to be on the same page about what we call VLUs. Once we have that, then you can go into the nuances, such as treatment strategies and how to determine atypical presentations and mimickers.

Dr. Madassery: Some of the most confounding issues with VLUs in my practice are superimposed lymphedema and mixed arteriovenous disease that may be contributing to lack of wound healing. It's important to address the underlying arterial issues so that proper venous compression therapy can be applied. Failure to detect and treat significant peripheral artery disease (PAD) can make wounds worse if compressed aggressively. Additionally, VLU patients with concomitant lymphedema can benefit with lymphatic therapies such as specialty clinic or pumps. Addressing these often difficult to manage factors can often speed up or start the healing process and prevent recurrence.

Dr. Kolluri: We know that > 60% of leg ulcers presenting to the wound center are VLUs. But as Dr. Fukaya said, these may be inflated as several leg ulcers are miscoded as VLUs, perhaps due to billing purposes (eg, to use as an indication to apply skin substitutes) or perhaps lack of awareness. There are many wounds that could be misdiagnosed as VLUs: squamous cell carcinoma, sickle cell ulcers, inflammatory disease–related wounds, warfarin skin necrosis, and even a bite from a brown recluse spider. It's a Sherlock Holmes–type thing to go after. You must be a medical detective and look at every possible option for the etiology of the wound.

What are your options when you truly aren't sure if the patient has a VLU, but you suspect it might be?

Dr. Kolluri: To summarize: (1) Make sure that the congestion pathology is worked up; (2) if the wound doesn't appear to be in the regular location for a VLU or is not healing as it should, question it; and (3) always look at the entirety of the patient's past medical history.

I love the terminology from Japan of "congestive ulcer." The reason is ultimately at the venule level where there is hypertension. Ask yourself where the pressure is coming from. Valve damage? Muscle pumps that are not working? Is the person sedentary or obese? Do they have chronic DVT or obstruction? Is there exogenous obesity that impedes venous return? Are pulmonary vascular and other issues like sleep apnea creating central venous hypertension? Or, maybe there are other causes of systemic edema, such

as drugs, congestive heart failure, and renal dysfunction resulting in increased excretion of protein in the urine. I keep all these etiologies in mind as I order a venous reflux study with or without axial imaging to determine whether there are functional or mechanical issues with the veins. Sometimes, you may realize that this isn't just due to a structural venous issue, and sometimes, it is not a VLU at all.

I saw a patient in the clinic for a second opinion as she was told that she would need "four stents," two in each of the iliac veins. She's in her early 80s and had some swelling after ankle surgery on the left side. The MRI still showed that there was ankle and midfoot arthritis. The site's duplex report stated that there was pulsatile flow noted in the veins. Is stenting going to make her feel better? No, for obvious reasons—not to mention the exposure to short- and long-term complications from the stent placement.

The most important aspect I want to stress here is to go down the path of testing—not just vein workup but think of it as leg congestion workup. If those results don't clarify the situation, then ask, "What am I looking at?" and get a tissue biopsy. Don't forget to look at the rest of the medical history as well, because issues can coexist. For example, my partner ran a case by me the other day. The wound was in the medial ankle, and he had ablated a refluxing great saphenous vein a few months ago. He had since been compressing it with a boot, but the wound was not healing. He discovered squamous cell carcinoma with a biopsy. Malignant conversion is not infrequent in chronic wounds. VLUs can also turn into pyoderma gangrenosum, in our experience, and require steroid injections and potentially systemic steroids and disease-modifying agents. Atrophie blanche ulcers can be associated with livedoid vasculopathy and may require additional disease-modifying agents and/or anticoagulation.

Dr. Fukaya: When you see a patient with a leg wound, you should first try to characterize the type of wound, including determining if this is a chronic VLU. One of the first things you might ask is the duration of the wound being open. If it occurred 1 or 2 weeks ago, you may first need to rule out a traumatic etiology or other transient etiologies. If you identify that there is chronicity to the wound, you need to then figure out if this is due to prolonged venous hypertension. If it is, the elements contributing to this should be considered. For example, in an obese person, venous reflux may play 10% while obesity-related concerns play 90% as cause of venous hypertension. In this case, treating the 90% is more effective than targeting the 10%. It is not black and white regarding what is the best approach. If there are multiple factors contributing to the venous hypertension and you think that the venous component is big enough, you would want to treat that. But if you think it's contributing 10%, control the other 90% first rather than jumping at the venous aspect. You cannot make this purely algorithmic, and that's why it's hard to develop a standard workflow. This is not like dealing with a numeric value that you treat as in the case of something like blood pressure or cholesterol, where you see a high number and then treat it. With VLUs, there are many nuances that you need to understand and put together.

Dr. Madassery: As my colleagues have mentioned, it's critically important to not just use VLU as a blanket term for all nonischemic/diabetic wounds. For most patients presenting with wounds that we suspect are VLU related, we start with the same steps regardless of other potential causes, including a full history and vascular exam. We then treat the wound while beginning a systematic strategy to determine any underlying causes. This involves the following steps: (1) Look for infection (culture and empiric antibiotics if appropriate); (2) debride if safe to do so and tolerable; and (3) apply wound-based dressings and multilayer compression therapy. If there are signs of venous (and arterial) insufficiency, we will order noninvasive imaging for reevaluation the next week during wound care follow-up. At the same time, we discuss the need for any diabetic, cardiac, renal, and nutritional follow-up that the patient may be not optimized with. These are some of the most difficult chronic issues to optimize, but we must be aggressive with coordinating these concerns with the patient's other care providers or send new referrals with direct communication.

As others have mentioned, it is important to consider uncommon presentations of malignancy, such as Marjolin ulcer, pyoderma, or calciphylaxis. Although the immediate treatment strategy remains the same as previously mentioned, if healing does not improve in the first few weeks, continual investigations and altering treatment strategies should ensue. Sending tissues and biopsies can often make a significant difference in the trajectories of these wounds.

What challenges do you encounter in classifying VLUs?

Dr. Madassery: Having an agreed-upon classification system for a disease state allows for effective and optimized communication, treatment planning, and transfer of care for the patient and practitioners. For

patients with cancer, the National Comprehensive Cancer Network has several dedicated classification systems with guideline-based staging that help the different specialties involved know the patient's clinical status in an instant. Similarly, in PAD and chronic limb-threatening ischemia (CLTI), use of classifications allows us to immediately know how urgent, aggressive, or conservative we need to be for a patient. Without a dedicated system for VLU, we often struggle to clearly and effectively evaluate, communicate, and manage these complex patients. Because there are numerous stakeholders involved in wound care, we need to make these processes better to optimize patient care and outcomes.

Dr. Fukaya: One of the difficulties is that we aren't all on the same page. Is what I'm referring to as a VLU the same thing another physician is referring to? VLUs encompass such a wide spectrum, and I think it would be helpful if we had a common language to describe it. In chronic venous disease, we have the CEAP (clinical, etiology, anatomy, pathophysiology) classification to allow us to describe the disease.

When it comes to VLUs, we need to ask—What is the cause? Is it actually an anatomic/structural issues such as a reflux or maybe a thrombotic issue? Do neither exist but the patient still has a congestion issue leading to venous hypertension and an ulcer?

This is why the question of what makes a VLU is important. How do we define it? How can we better classify it so we are all talking about the same thing? We can talk about management and treatment of VLUs, but we need to hone in to make sure we're on the same page about what a VLU actually is.

Dr. Kolluri: Ultimately, a wound is the result of multiple different processes leading to skin breakdown, the main reason being the elevation of pressure in the veins. In medical school, we are taught that VLUs are painless ulcers in the ankle/gaiter areas. However, we have all seen pretty painful atrophie blanche ulcerations that not very many people recognize. We have also seen wounds that are associated with stasis eczema all around the leg, and instead of treating the underlying eczema itself, people have received bilateral iliac vein stents, which are unnecessary. For all these reasons, it's important to understand the different manifestations of VLUs and potentially have a classification system for the VLU that includes etiology and anatomy, for example.

I would also add—if one does not have the appropriate training in identifying wounds, find an appropriate colleague to bounce ideas off on. As I tell my patients, this is *chronic* venous insufficiency. There's nothing acute about it, so we have time to figure it out. We don't need to be abrupt in our care for these patients.

EXAMPLE OF ELEMENTS FOR VLU CEAP

CLINICAL

- Periwound skin appearance and condition (lipodermatosclerosis, hemosiderin, blister, weeping, scar tissue, inflammation, etc)
- Wound bed condition (granulation condition)
- Infection
- Swelling
- VLU location, depth, size
- Wound duration

ETIOLOGY

- Trauma
- Infection
- Swelling
- Spontaneous skin breakdown
- Other

ANATOMY (affected vein, location, size, multiple vs single)

- Above groin (inferior vena cava, iliac veins)
- Above knee (femoral vein, great saphenous vein, popliteal vein, etc)
- Below knee (perforator, small saphenous vein, periulcer venous network, etc)
- No anatomic disease
- Lymphatic dysfunction

PATHOLOGY

- Anatomic: Valvular insufficiency, obstruction
- Functional: Increased central pressure, obesity, right heart failure, obstructive sleep apnea, calf dysfunction/dependent edema
- Mixed

What might a VLU classification system look like?

Dr. Fukaya: I really do think that there should be an effort to come up with a VLU classification, and I have been thinking about what a potential VLU classification tool with a clinical, etiology, anatomy, pathophysiology component might look like (see *Example of Elements for VLU CEAP* Sidebar). This is really just a

start—maybe it looks like this, maybe this is a building block to creating something entirely new. But the goal is to start having these conversations about wound VLU classification.

Dr. Madassery: A "VLU CEAP" system is much needed, and this example looks appropriate. If a classification system becomes the standard, and I hope it does, we would benefit from an app to help people better understand and stage this disease, as well as to develop electronic medical record (EMR) smart phrases or lists so it can be part of standard communication. This system would also help with outcomes tracking for regional, national, and global studies of this patient population. We could then learn more about the varying factors in these patients, which may change their practice patterns and increase wound healing and prevention.

Dr. Kolluri: This proposed "VLU CEAP" and the descriptors make sense, and we could easily have overlap of all the categories listed there.

How would you summarize this need for a common language and its utility, for the person identifying it but also for communicating with other care practitioners who see your patients?

Dr. Kolluri: It is important to get out of our venous specialist box and look at the bigger picture. We need to identify the VLU manifestations in patients presenting with leg ulcers. Take the LIFE-BTK trial of critical limb ischemia (CLI). Approximately 30% of the enrolled wounds were mixed etiology, such as ischemia and VLUs. Is this because the enrolling physicians were unaware of what an ischemic ulcer looks like and what a VLU looks like? Or, was it because the Rutherford classification simply mentions "tissue loss"? These are the questions I started thinking about as we were more objectively assessing these wounds.

I did not receive much training about these ulcers until my vascular medicine fellowship training at the Cleveland Clinic. There are many mimickers that can present as ulcers. The education aspect of what a VLU looks like and its multiple manifestations are basics that vascular physicians need to understand.

Dr. Madassery: As mentioned, patient care is improved when all health care providers can communicate treatment needs and plans effectively. By developing and standardizing a true dedicated classification system, we would have the ability to create management algorithms that would make the plan easier for all, including patients and their caregivers. If the system is in place, then our colleagues in infectious disease, endocrinology, and primary care all can better assist the patient in their care and continue to set unified expectations for all involved. Additionally, as in cancer and PAD scenarios, primary care and other physicians will know over time to go ahead and order certain tests and start conservative treatments ahead of time, before the patient is able to get to a wound care specialist. This puts the patient on the optimized track earlier in the process. The reality is that it is not easy for patients to find or get into wound care centers; however, the management of many wounds can be started early on by anyone, while in the process of getting to a specialist. I strongly believe a classification system would aid this process significantly.

Dr. Fukaya: A classification system will of course help physicians. The act of classifying a leg ulcer makes you stop to think about what is causing it and what you need to address. This also helps the patient and patient education specifically. When you've identified the causes and have a treatment algorithm, you can explain to the patient your plan for each specific presentation in the classification, as well as what doesn't need to be addressed. A classification system would allow us to make more tailored recommendations. For example, right now, we are putting compression on everyone. But does each patient need that, or would they benefit more from something else?

The goal is to help overall healing and reduce the revolving door of patients with recurrence because the main underlying issue was not addressed. Recurrence will likely still happen, but in addressing the right things, recurrence might go from 50% to 20%. That is a huge win for everyone.

What are the next steps?

Dr. Madassery: The hardest step in this process, as seen in many other disease states, is getting all stakeholders to agree on and solidify a system. To get everyone on board, this system should be as easy and straightforward as possible. With American Venous Forum (AVF) championing the project, the involved vascular societies as mentioned above should be able to get this enacted in short order. Once it is agreed upon, it is imperative that we communication this information to all wound care entities and societies involved in the care of these patients. This should be also incorporated into health care education, particularly anywhere wounds and venous disease are involved. Without it, we will be no better off than we are now.

Dr. Fukaya: This a big question because there are a lot of stakeholders in venous leg ulcerative care: wound care specialists, surgeons, podiatrists, vascular medicine, interventional radiology, etc. We need a consensus that everyone agrees on rather than one person creating an algorithm. There are plans for an upcoming VLU guideline from AVF, and the guideline committee will be very knowledgeable in this area. That would be a good opportunity to discuss these issues.

Dr. Kolluri: As Dr. Fukaya noted, a common language may be necessary here for various reasons. It is needed for communication between practitioners and also to set appropriate patient expectations. For instance, if it is a simple venous leg ulceration? In that case, I may say I'll see you in the wound center for appropriate wound care and compression wraps, take care of the underlying venous problem, and that wound will eventually heal. On the other hand, a more complex workup may involve the addition of an echocardiogram and referral to a sleep apnea specialist or workup for other conditions that mimic VLU. Once you have a common language, the outcomes for these patients may be better.

Moving from the real-world scenario to the clinical trial world, what does that common language mean in a clinical trial setting?

Dr. Kolluri: We need a tool that allows for the proper identification of VLUs in a systematic manner. In the clinical trial setting, let's say we're hypothetically assessing technology in the veins and enrolling patients with VLUs. If the device is placed in a patient with a VLU that is infected, it would be easy to blame the device for a poor outcome for that patient because we did not properly identify or classify the wound from the start. Did we try to treat the infection? A classification tool would allow much cleaner data to appropriately test the device's clinical success.

Dr. Madassery: As anyone who has been involved with trials knows, a very difficult aspect is determining how effective a device/drug is on wound treatment because wound status is very vague and operator dependent. We have seen this in PAD trials, in which we need to continually come up with better tools to stratify wounds and monitor them. However, without specific, detailed, and reproducible terminology/factors, it becomes very difficult to compare outcomes. Similarly, having a standardized system for VLUs would enhance the ability to better test advances in technology and disease management. Use of imaging can also help in this process, such as was done in CLTI trials.

What are your thoughts on the potential role of artificial intelligence (AI) in classifying VLUs?

Dr. Madassery: I think it might be difficult to confidently use AI for VLUs because the intricacies of the presentations and nuances may be cumbersome for logarithmic processing. However, we don't know exactly where AI will take us in the future, so I won't say it isn't feasible. Before AI can help, we need better human intelligence and agreement on these wounds. AI could help us filter through and stratify patients' underlying comorbidities, histories, incidents, and treatment summaries to reduce the redundancy in many people painstakingly going through EMRs. I have seen many times that through a deep dive into records, in one institution's EMR or even looking at other records, we can often find things that could be instrumental for patient treatment. Examples include noting through exhaustive detective work that a patient had an inferior vena cava filter placed years ago during a traumatic incident/stroke or a prolonged stay in the intensive care unit with numerous access lines, all of which may relate to possible underlying central venous disease that was never acutely found. For some of these patients, we've managed to reconstruct their venous pathways and ultimately help heal a wound that has been lingering for years (yes, years!). It would be a game changer if AI could reduce that burden and quickly give us the layout of a patient's entire history and put the patient into certain risk/disease categories. This is just one thought—I'm sure we'll see more with AI as we go, both the good and the bad.

Dr. Kolluri: In my opinion, it would be hard to train an AI model because of the heterogeneity of the VLU presentation. Vascular medicine cannot be replaced by AI, at least in the near future.

What do your conversations with VLU patients look like?

Dr. Kolluri: It's important to set appropriate expectations. It's not uncommon to say to a patient that the ulcer may be slow to heal even with appropriate care of the venous issues due to the other concomitant issues that increase the venous congestion. In the absence of concomitant conditions, the chances of the VLU healing in the next several weeks are quite reasonable. I tell the patient we need to work together to get these ulcers treated, and they might see me for a lot longer than they thought they would. It is helpful to lay down those expectations and have a comprehensive thought process about not just taking care of the ulcer but taking care of the patient as a whole.

Dr. Madassery: Talking to patients with VLUs requires a lot of expectation management discussions. I tell them, and their families if possible, that this a lifelong process. We often cannot reverse the process that caused them to develop a VLU (such as post-thrombotic syndrome). However, with aggressive and lifelong conservative and physical therapies, we can attempt to speed up wound healing and reduce recurrence. I tell patients that optimizing their underlying issues, such as increasing mobility, reducing weight, and having their cardiac and renal parameters evaluated, can help in the long run. Unlike my PAD patients, I often have frank discussions, like seeing if they can change their job requirements if they are sedentary or on their feet all day. This seems hard to fix with work from home changes over the years, but I tell them that standing desks and walking devices at their workstations can make significant changes in their current wounds and wound prevention. I also advise that their skin is more fragile once diseased, such as with recurrent VLUs, and that subtle fluid balance/edema changes can trigger new wounds. Many patients have a hard time understanding why the VLU won't heal as fast as other wounds, such as traumatic/surgical or ischemic wounds.

Dr. Fukaya: It is also important to remember that this is a chronic disease, so approximately half will recur. You must set an expectation with the patient that unless they take care of themselves, VLUs will recur. I like to use this analogy with my venous and lymphedema patients: Think of yourself like a boat with a hole in it. The water is coming in. You can't plug it up, so you need to keep pumping out the water or you'll sink. If you keep pumping out the water, you will stay afloat.

For chronic venous disease, lymphedema, anything that's chronic, you must do your maintenance of "pumping out the water" and keeping things decongested. Otherwise, you'll start sinking, and that's when you have recurrence. ■

D*isclosures*
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