Emerging Evidence On Advanced Wound Care For Diabetic Foot Ulcerations

Applying evidence-based medicine and the standard of care to improve patient outcomes

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Introduction

Chronic diabetic foot ulcers (DFUs) represent a major concern for patients with diabetes with an annual incidence rate of 2 percent and a lifetime risk of 15 to 25 percent.1-3 Approximately 85 percent of lower extremity diabetic amputations are preceded by a DFU and 15 percent of DFUs lead to amputation.1,4 Delayed healing can impair patient mobility and quality of life, and can significantly increase the risk of serious complications including drug-resistant infection, hospitalization and amputation.5-7

In November 2009, a panel of experts from various disciplines related to wound care convened to evaluate current standards for the management of DFUs in light of newly emerging techniques and treatment modalities. The panel balanced scientific evidence with the practicality of applying various methods, and concluded that objective assessment of wound severity and healing progress followed by responsive treatment decisions was essential to achieve timely healing. In April 2010, the panel published the “Consensus Recommendations on Advancing the Standard of Care for Treating Neuropathic Foot Ulcers in Patients with Diabetes.”8

Practitioners are encouraged to utilize the consensus recommendations in conjunction with their own deductive reasoning and good clinical judgment to improve healing outcomes for patients with DFUs.

In the following articles, based on lectures given at the Superbones West conference in October 2010, we discuss the implementation of the 2010 consensus recommendations for the treatment of DFUs in a practical clinical setting and share our strategies for facilitating improved healing and optimal outcomes in this patient population.

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By Lee C. Rogers, DPM

It has been estimated that the number of people with diabetes will nearly double worldwide in the next 18 to 20 years.9 Currently, in the United States, there are nearly 24 million people with diabetes, approximately 8 percent of the population.10 Foot complications are the most common reason for people with diabetes to be admitted to the hospital in both the U.S. and the United Kingdom.11 The lifetime risk of a diabetic foot ulcer ranges between 15 to 25 percent among patients with diabetes and approximately 15 percent of diabetic foot ulcers will result in some type of amputation.1-4

Given the challenges of treating this high-risk population, it is critical to have a strong understanding of the current standard of care in managing diabetic foot ulcerations. A consensus panel of thought leaders in this arena recently published “Consensus Recommendations on Advancing the Standard Of Care For Treating Neuropathic Foot Ulcers In Patients With Diabetes.”9 I would like to discuss these recommendations that were published in 2010 as a supplement to Ostomy Wound Management and WOUNDS. The supplement offers a concise, informative document of the standard of care for diabetic foot ulcerations.

Not only is it important to look at this from a morbidity standpoint and a quality of life standpoint, one should also consider mortality rates among those who have had a diabetic foot ulcer and amputation. One study cites a 68 percent mortality rate in five years after an amputation.12 In a 10-year prospective study, Iversen and colleagues found a history of diabetic foot ulcers to be a significant predictor of mortality in patients 65 years of age and older.13 If you look at these studies they reviewed in this consensus supplement, just having a neuropathic ulcer has a 45 percent mortality rate in five years.14 This is not to say that having an ulcer is going to tip the scale and the patient is going to die in five years. However, when somebody has a diabetic foot ulcer, it really is the tip of the iceberg of what is going on systemically inside of that patient. These are very sick people and they do have a high risk of death and, in many cases, a higher risk than some cancers.14

There is also a significant economic burden. A couple of years ago, Armstrong, Lavery and I looked at 2007 data and estimated that $30 billion was spent in the U.S. that year on diabetic foot ulcers and amputations.15 More recently published estimates suggest that somewhere between $70 and $80 billion is spent yearly on diabetic foot ulcers, amputations and peripheral arterial disease in the U.S.16

Citing a systematic literature review on the quality of care in the U.S., the panelists for this consensus supplement noted that somewhere between 30 and 50 percent of patients are not being treated according to current evidence, and I think that is probably an underestimation.17 Whether you work in a wound center or an office, you see people come in who are referred from a general doctor. What are the things they are doing with these wounds? They are putting on betadine or a wet to dry dressing or Silvadene. I see this a lot. These therapies are not evidence-based at all so you get an idea of the type of treatments that are out there for diabetic foot ulcers and the quality of the evidence behind those treatments.

The consensus panel also note estimates that somewhere between 20 and 30 percent of the care is either inappropriate or dangerous, and I think that some of these examples can be lumped into the same category.17 Putting undiluted betadine on an uninfected wound kills not only the bacteria but kills the good cells as well.

In the consensus supplement, the panelists discuss several aspects of treating a diabetic foot ulcer but they also review the various assessments that need to be done to come up with the appropriate diagnosis. They discuss the appropriate history and physical, laboratory screening tests, and nutritional assessment as well as lifestyle and psychosocial assessments, which are really important but often are not considered in these patients. The consensus panel also discuss the neurologic and vascular evaluations, how to evaluate the...
foot ulceration, various wound classification systems, how to look for infection, different imaging modalities and when hyperbaric oxygen therapy (HBOT) comes into play.

One of the key concepts that came out of this consensus supplement is that any wound that stalls after two to four weeks needs to be re-evaluated. What is the definition of stalling? Well, in some of the work that I do, I review these cases in which the physician notes are pretty subjective and lack anything objective. For example, there may be a note saying the wound is getting better or it is staying the same. Noting objective measurements can help ensure sound documentation. The best way to do something like this is to make sure that you have accurate measurements. Most people use a ruler to measure wounds or you can use something more advanced like a three-dimensional Silhouette camera (ARANZ Medical). It gives you an exact measurement of the wound as opposed to length times width, which is only accurate for a box. Whatever approach you use to measure wounds, just make sure you are using the same approach every time so you are consistent.

**Insights On Diagnostic Screening**

When it comes to laboratory screening, you definitely need to be paying attention to the patient’s glucose control. You cannot just rely upon the patient’s general doctor, the internist or his or her endocrinologist for this. Every person on the multidisciplinary team plays a role in helping educate these patients about their glucose control.

The American Diabetes Association (ADA) recommends a hemoglobin A1c (HbA1c) level of below 7%. I am also the chair for the Foot Care Council for the ADA and I will be a little critical of our own association because in Europe the HbA1c recommendation is below 6.5% and I think the ADA is looking at this now. One good thing that has come out recently is that the ADA now recognizes the use of the HbA1c for the diagnosis of diabetes and not just for the tracking of the patient’s overall glucose control. That is important because previous to this, you were either having to use fasting blood sugars or a glucose tolerance test, and often patients would have to come back on a separate visit or have a scheduled lab test done. Now the ADA says you can just use the HbA1c for diagnosis.

We all know how to do neurologic screenings for those at risk for diabetic foot ulcers. Often when somebody comes into your office and he or she has a diabetic foot ulcer already, the patient is going to have neuropathy. The late Paul Brand, MD, was an orthopedic surgeon who studied neuropathic injuries in feet in India. He once observed that any patient who walks into your office with a wound and is not limping on that foot has neuropathy, and I think that is true.

Armstrong and colleagues noted that patients who have a neuropathic ulcer have a 45 percent mortality rate in five years. They also found that patients with diabetic foot ulcers, in many cases, have a higher mortality risk than some cancers.

In regard to the vascular examination, the panelists for the consensus supplement recommend doing a tiered approach via primary, secondary and tertiary tiers. Your primary tier is your clinical exam. The clinical exam always involves the palpation of pedal pulses. While the absence of pedal pulses is a good indicator of poor blood flow, the presence of pedal pulses is not a good indi-
cator of good blood flow. One cannot assume the blood flow is good if the patient has pedal pulses. You need to do something else to look at the patient’s blood flow. If the patient has an ulcer, he or she is going to have to get some type of noninvasive test and there are a number of noninvasive tests that can be done. If the patient has an ulcer and has gangrene or necrosis, you need to get a vascular consult as well.

Keys To Assessing The Wound

When it comes to the foot and ulcer examination, there are different wound classifications you can use. While people are most familiar with the Wagner classification, the problem with this classification is that it lumps the depth of the wound and whether there is gangrene present into the same linear relationship. When you are assessing the prognosis of these patients and whether an amputation is necessary, this does not end up being a linear relationship.

When Lavery and Armstrong were at the University of Texas, they developed a different system, which is similar to how you grade and stage cancers. They were grading and staging wounds. They looked at the combination of wound depth and the presence of infection/ischemia. When you are assessing the wound and the potential risk for amputation, this diabetic wound classification system is a pretty powerful indicator of who is going to have an amputation. It just makes sense that as the wound becomes deeper or as the wound becomes more complicated, the risk of amputation increases.

When you are assessing for infection, it is important to realize that infection is a clinical diagnosis. There is not one single lab test you can do to diagnose an infection. Your culture and sensitivity should only be taken if there is an infection, and that is only used to ensure your patient is on the right antibiotic. It is not used to diagnose an infection so that is an important concept.

The probe to bone test was popularized right after Grayson and colleagues published their article in 1995. It was coined as the “5 cent bone scan” because it had an 89 percent positive predictive value for osteomyelitis. However, the problem with the probe to bone test in that study is that it was done in a population of people who had moderate and severe diabetic foot infections. They already had a high risk of having osteomyelitis when they entered into the study. Accordingly, this inflates the positive predictive value of the probe to bone test.

Fleischer and colleagues did a study and looked at the probe to bone test in a clinic population, similar to what we see in our offices or our wound centers. They found that the probe to bone test was no better than flipping a coin in determining the presence of osteomyelitis so it is important to consider that as well. Therefore, the probe to bone test is a useful modality but should be limited to the same type of environment and scenario (moderate to severe infections) that Grayson and colleagues studied.

Pertinent Treatment Principles

In regard to treatment, the consensus panel discussed the management of arterial disease; addressing the wound environment; infection control; offloading; hyperbaric oxygen therapy; advanced therapies; and amputation.

When you look at the factors that lead to limb loss, the three most common factors are gangrene, infection and a chronic or non-healing wound. So those are paramount when you are evaluating these patients.

When it comes to debridement of foot wounds, it is important to remove all the undermining tissue. Shear forces will prevent this tissue from ever re-adhering to the underlying wound bed. You can also consider something like hydrosurgical debridement or maggots. We only use maggots in cases in which patients are too sick to go to the operating room (OR). I would much rather take patients to the OR to perform a thorough surgical debridement over using maggots but they do have their place.
One of the important concepts with debridement is how it plays into the whole paradigm of wound healing. In a randomized, multicenter study, Steed and colleagues looked at the use of a recombinant human platelet-derived growth factor (Regranex, Systagenix) and debridement for diabetic foot ulcers. They noted lower rates of healing in centers where less debridement was performed and this was independent of the treatment group.26

For example, for the placebo group at center #1, wound debridement occurred on 19 percent of patient visits and only 10 percent of the patients healed over 16 weeks. In the Regranex group at center #1, wound debridement occurred on 15 percent of patient visits and only 20 percent of patients healed at 16 weeks. At center #6, wound debridement occurred on 87 percent of the visits for the placebo group and 25 percent healed in 16 weeks. However, the combination of Regranex and debridement at center #6 occurred on 81 percent of visits and 83 percent of patients healed over 16 weeks.26

No matter what you are using, whether it is bioengineered tissue, negative pressure wound therapy or Regranex, it is important to combine debridement with that and perform debridement on a weekly basis.

I will not go into a lot of detail on how to treat infections. It is important to take an appropriate culture. Do not swab the top of the wound as doing so will lead to recurrence of contaminating bacteria.

**Offloading: When The ‘Gold Standard’ Isn’t Practical**

Offloading is where the podiatrist plays a key role on the wound healing team because nobody else on the multidisciplinary team understands anything about offloading and we can really help bring that understanding to the team and educate the other members.

It is often said that the total contact cast is the gold standard in offloading and there is literature to support this.27-30 However, practical use of this modality is another issue. There are a lot of impediments to doing a total contact cast. It is time consuming and the materials are sometimes difficult to get. The TCC-EZ (MedEfficiency) is a relatively newer device. I just started using this but it seems to be a lot easier to put on than the other total contact cast.

You can also consider taking a removable cast walker and rendering it irremovable. One of the problems with removable cast walkers is in the name. They are removable so patients will get home, take it off, walk and fail to adhere to recommendations.

**Knowing When To Consider Advanced Therapies**

There are five tenants to good wound care. These tenants include:

- management of vascular disease;
- management or ruling out of infection;
- offloading;
- debridement; and
- providing a moist wound healing environment.

However, even when conservative wound care is provided, there is still a pretty pitiful healing rate. In a study involving 622 patients with neuropathic ulcers, Margolis and colleagues found that after employing these five tenants of wound care, only 24 percent of these patients healed at 12 weeks and only 31 percent of them healed at 20 weeks.31 This is a big problem and you need to know when to move to something more advanced.

One of the problems with considering advanced therapies is that we as clinicians used to think of advanced therapies as last resorts and I think this consensus panel supplement is helping to change the way we think about advanced therapy modalities. While these modalities are not first-line options, they should be put into the paradigm a little bit earlier than where they are used now.

Sheehan and colleagues looked at the rate of wound closure for diabetic foot ulcers and found that if the wound had not closed by at least 50 percent over four weeks, there was a 91 percent chance it was not going to heal in 12 weeks.32 This is a very powerful indicator to move to a more advanced modality. This four-week indicator for moving to advanced therapy is one of the main tenants of the consensus panel supplement. Snyder and co-workers noted similar findings.33 They actually saw a dichotomy between healers and non-healers after two weeks of conventional wound care, but they still recommended four weeks as the strongest indicator. (See “Assessing The Percent Area Reduction (PAR) In DFUs At Four Weeks” on page 6.)

When you are talking about advanced therapies, there are only a handful of products that have gone through the rigors of an FDA trial. The modalities that are FDA-approved for diabetic foot ulcers are Regranex, Apligraf (Organogenesis) and Dermagraft (Advanced BioHealing).26,34-36 There are a lot of other devices and modalities that you hear about for diabetic foot ulcers, but they don’t have the same level of evidence behind them as the FDA-approved treatments do. Vacuum Assisted Closure (VAC) therapy (KCI) may be an exception since it was originally FDA approved via 510K equivalency. However, there are now large randomized, controlled trials proving its efficacy.37

The consensus panel shows that since prolonged healing times increase the risks of morbidity, infections and hospitalizations, expeditious wound closure is a primary goal of diabetic foot ulcer treatment. The consensus panel recognizes that the aforementioned 50 percent area reduction at four weeks should be used as a clinical decision point to consider advanced therapies, and they view this as the new standard of care in treating diabetic foot ulcers.3
First of all, we have to define what is a chronic wound. Lazarus defined a chronic wound as one that fails to proceed through the normal temporal sequence of wound repair. This is in contrast to an acute wound which does follow the normal temporal course of repair in a timely fashion. We know that chronic wounds have great social, psychological, physical and economic cost in our country. Chronic wounds consume a great deal of our healthcare dollars not just in the United States but worldwide. Diabetic foot ulcers are a major problem. There are reportedly over one million patients developing diabetic foot ulcers in the U.S. each year, and approximately 15 percent of diabetic foot ulcers will progress to amputation.

It is important for us to understand the important complex interrelationships between the underlying pathophysiology of the diabetic lower extremity and how they can merge to create a foot ulcer. We discussed pathways to ulceration and amputation in the diabetic foot guidelines we published in the Journal of Foot and Ankle Surgery in 2006.

We know that the primary risk factor for almost any lower extremity problem in diabetes is usually neuropathy. Whether the patient has an infection, amputation, foot ulceration or a deformity like a Charcot deformity, neuropathy is always a primary risk factor. When it comes to neuropathy, we shouldn’t just consider sensory neuropathy. We also need to consider the important roles of motor neuropathy and autonomic neuropathy. Autonomic neuropathy leads to many of the microvascular changes that we see. The microneurovascular changes found in these patients are primarily due to increased arteriovenous shunting due to the sympathetic failure. There is an inability to mount a maximally hyperemic response to injury. These microneurovascular changes, as a result of autonomic neuropathy, play an important role in the vascular dysfunction found in diabetes. When we think of vascular disease, we cannot always just consider macrovascular occlusive disease. We must also remember the important role of these microneurovascular changes as well.

When there is a high-risk foot in a patient with diabetes, there may be neuropathy as well as vascular disease, both microvascular and macrovascular. When trauma is applied to that high-risk foot, this is the precipitating event that leads to foot ulcer. In the presence of a sensory deficit, these people keep walking on the injured foot without the “gift of pain,” as the late Paul Brand, MD, had said. This creates more problems as these wounds can become infected. Once they become infected, gangrene can set in and then amputation ensues.

Now the same risk factors for ulcers are always important risk factors for amputation as well because ulcers are so closely associated with this complication in the diabetic foot population. So we need to have at least a basic understanding of these various underlying pathophysiologic deficits or aberrations that may occur in patients with diabetes. Not all patients will have every one of these deficits but they are very common. When a patient is seen with a diabetic foot ulcer, that patient has a lot of underlying comorbidities and many underlying physiologic changes that one needs to be aware of because these problems can impair the patient’s ability to heal.

A Closer Look At The Molecular Differences Between Acute Wounds and Chronic Wounds

When speaking of chronic wounds, we must also be aware of the difference in the biologic milieu that is present in the chronic wound versus the healing or the acute wound. In his 2005 paper in Diabetes Care, Lobmann discussed the molecular environment of wounds. It is a good summary for what is going on in these chronic diabetic foot wounds and what we have to do to change this in order to facilitate healing.
With the chronic ulcers, the cells, especially the fibroblasts, have low mitogenic activity and there is an increased level of inflammatory cytokines. Chronic ulcers also have an increased level of proteases, which are very hostile to growth factors, growth factor receptors, fibroblasts and deposition of matrix. There are also senescent cells that are not physiologically active. These are incompetent cells. The molecular picture of these chronic wounds is in contrast to healing wounds that are characterized by cells with high mitogenic activity, low levels of inflammatory cytokines, low levels of harmful proteases and mitotically competent cells.

Our goal in the management of these chronic wounds is to tip the balance to the characteristics of a good acute wound and subsequent healing. (See “An Overview Of The Molecular Environment Of Wounds” on the right.)

Emphasizing Aggressive Management To Prevent Diabetic Foot Complications

It is important to put diabetic foot complications into proper perspective. In 2003, Belch and colleagues noted that the five-year mortality rate for peripheral arterial disease (PAD) (32 percent) is worse than the five-year mortality rates for prostate cancer (8 percent), Hodgkin’s disease (19 percent) and breast cancer (22 percent).44,45 In 2010, Van Baal and co-workers reported a 41 percent five-year mortality rate for Charcot foot and they found that it was not significantly different than the five-year mortality rate (44 percent) for diabetic foot ulcers.46 As I noted earlier, we need to recognize that people who have diabetic foot ulcers have very significant underlying comorbidities that put them at risk for earlier mortality. The five-year mortality rate for amputation is 68 percent and the five-year mortality rates for lung cancer and pancreatic cancer are 86 percent and 95 percent, respectively.12,45

These sobering numbers in regard to diabetic foot complications underscore the importance of aggressive management when indicated. While we cannot always stop the development of ulceration, we can certainly prevent ulceration from progressing to an amputation if we are aggressive with our wound healing modalities. However, we need to pay attention to the basic tenets of wound care. After all, it does not matter what kind of advanced products you put on a wound if you have not paid attention to the basic tenets of wound care.

Keys To The Diagnostic Workup

Accordingly, our treatment approach emphasizes medical management in partnership with our medical team. Recognizing the important role that PAD plays in the etiology of these wounds, we always assess the vascular status of these patients. We are seeing an increasing number of neuroischemic wounds in comparison to primarily neuropathic wounds. My colleagues in America and Europe are seeing the same trend in which people are living longer and those with ulcerations have more neuroischemic ulcers than neuropathic ulcers. We need to be very aware of the role of vascular disease even if it is not the main predisposing risk factor for failure to heal.

Accordingly, we need to do a very vigorous vascular assessment. We always try to palpate pulses. We are also very liberal in terms of getting our ankle-brachial indices and toe pressures, and assessing transcutaneous oxygen (TcPO2) and skin perfusion pressure (SPP). We correct those problems as we see them, working very closely with our vascular colleagues.

When it comes to infection, we always need to drain abscesses, perform appropriate debridement, determine whether osteomyelitis is present and consider appropriate antibiotics for infected wounds. Unfortunately, there are many times when indolent, smoldering infection is present under these apparently non-infected ulcers. That is why we are so aggressive with our probe to bone test, which has been under attack in recent years.47 We call the probe to bone test our “five cent bone scan” because if I can see bone, feel bone, touch bone or probe to bone, I treat that patient as though he or she has clinical osteomyelitis as this will prevent these chronic wounds from healing.

Initial Treatment Considerations

After we have done our assessment, we can then focus on proper
wound care and again the basics are always debridement, wound bed preparation by a variety of means, proper offloading or compression if one is treating a venous leg ulcer. Without the offloading, debridement and proper assessment, you are not going to be successful in your wound healing protocols.

I do not worry about advanced wound care products when I am initially seeing a patient with a relatively uncomplicated wound. We focus entirely on the basics and those basics are offloading and adequate debridement. Then we think about therapeutic agents. What do we want to put on that wound after we have considered and evaluated all of these other things? We know there are many possible agents. Unfortunately, very few of the things that you put on a wound have sufficient evidence to support their efficacy when it comes to treating diabetic foot ulcers. We recognize this and just have to admit that we do have preferences, and sometimes some things seem to work better for us in certain circumstances than others.

There are many topical agents. Diluted antiseptics include povidone-iodine, super-oxidized solution (Dermacyn Wound Care, Oculus Innovative Sciences) and peroxide. I admit some of these are cytotoxic. However, if I have a very nasty wound that is draining a lot, I like to get it dry and cleaned up. Then there are hydrogels, saline hydrogels, topical antimicrobial creams and ointments. The latter are not wound healing agents. They just help to correct the bioburden that we know is present on these wounds. In regard to enzymatic debridement agents, the only one on the market now is the collagenase product (Collagenase Santyl, Healthpoint). We do use collagenase to help with what we call maintenance debridement. Patients may apply this themselves on a daily basis between visits.

There are many types of wound dressings ranging from gauze pads, foams and silver dressings to hydrocolloids, alginites and collagen-based dressings. Manuka honey is a new type of dressing on the market that we use on occasion as well. Most of these wound dressings are secondary dressings that we put over a freshly debrided wound. Sometimes these are primary dressings as well.

### When Do You Turn To Advanced Modalities?

### What The Literature Reveals

At what point do we need to consider advanced products? In 2003, Sheehan and colleagues examined the data from the failed Promogran study and found that the majority of their patients with diabetic foot ulcers who healed at 12 weeks had achieved 53 percent healing by four weeks, regardless of what treatment they were on. As a result of the Sheehan findings and an extension of the 1999 consensus panel convened by the American Diabetes Association, the recommendation came that if you do not achieve 50 percent reduction in wound size at four weeks, you need to step back, reassess and consider the use of advanced therapeutic agents. Boulton and colleagues corroborated this in 2004 as did Snyder and co-workers in 2010.

### Examining The Role Of Regranex

When it comes to advanced wound care technologies, becaplermin (Regranex, Systagenix) was the first agent for diabetic foot ulcers to receive biologics license application (BLA) approval from the FDA.

In a randomized, double-blind multicenter trial, Steed and colleagues found that 48 percent of patients treated with Regranex healed at 20 weeks in comparison to 25 percent of patients in the placebo group. In 1998, Wieman and co-workers published findings from a phase III multicenter trial showing significantly improved efficacy in the Regranex group dosed at 100 µg/g (50 percent) versus another Regranex group dosed at 30 µg/g (36 percent) and the placebo group (35 percent) at 20
weeks.\textsuperscript{50} Not many of us use too much Regranex anymore although it does have its role in our wound care armamentarium.

**An Overview Of Extracellular Matrix Products**
These are multiple extracellular matrix products. These include: Oasis Wound Matrix (Healthpoint); Integra Bilayer Matrix Wound Dressing (Integra LifeSciences); GammaGraft (Promethean Life Sciences); Graftjacket Regenerative Tissue Matrix (KCI); Pegasus/Unite (Synovis Orthopedic and Wound-care); and Bacterin Pericardial Matrix (Bacterin International). These acellular matrix scaffolds deliver a matrix, usually of collagen, across which fibroblasts can travel, develop angiogenesis and granulation tissue, and keratinocyte migration.

A randomized clinical trial found that Oasis Wound Matrix was as effective as Regranex in healing full thickness diabetic foot ulcers at 12 weeks.\textsuperscript{51} In a multicenter, randomized controlled trial (RCT), Reyzelman and colleagues found the use of Graftjacket demonstrated a shorter time to healing (5.7 weeks) than standard wound management (6.8 weeks) for diabetic foot ulcers.\textsuperscript{52}

**Assessing The Evidence On Negative Pressure Wound Therapy**
There is also vacuum-assisted closure (VAC therapy, KCI). In 2008, Blume and colleagues published a randomized controlled trial on diabetic foot ulcers in which they found documented evidence of the efficacy of VAC therapy in terms of accelerated closure at 16 weeks.\textsuperscript{37} They found that the use of VAC therapy improved ulcer closure, the Kaplan-Meier median time to healing was faster and there were fewer secondary amputations.

There are other negative pressure wound therapy (NPWT) devices on the market. They include the NPD 1000 (Kalypto Medical), the SNaP Wound Care System (Spiracur), the Svedeman Wound Treatment system (Innovative Therapies) and Reناسys (Smith & Nephew). However, most of the data on NPWT is with the KCI device.

**A Closer Look At Cell-Based Tissue Technologies**
We also have cell-based tissue technologies that I use quite frequently. The only two on the market in the U.S. are Apligraf (Organogenesis) and Dermagraft (Advanced BioHealing). Apligraf is a bilayered product with keratinocytes and neonatal fibroblasts. Dermagraft is a dermal replacement therapy with neonatal fibroblasts on an absorbable mesh.

These FDA-approved, premarket approval (PMA) products have very good data behind them. In 2001, Veves and colleagues published their findings on Apligraf in a prospective randomized controlled trial.\textsuperscript{35} They found that 56 percent healed in the active group versus 38 percent in the control group at 12 weeks.
with a 47 percent increased rate of healing in the Apligraf group.

In a multicenter, randomized controlled trial of Dermagraft for chronic diabetic foot ulcers, Marston and colleagues found that 30 percent of the Dermagraft group had complete healing at 12 weeks in comparison to 18.3 percent in the placebo group.34 This represented a 64 percent greater rate of closure in the Dermagraft group versus the control group.

What You Should Know About Other Wound Care Therapies

Other wound care therapies include platelet-rich plasma (Autologel, Cytomedix), hyperbaric oxygen therapy (HBOT), ultrasonic spray (MIST Ultrasound Healing Therapy, Celleration), super-oxidized water (Dermacyn Wound Care), manuka honey (Medi-Honey, Derma Sciences), pulsed radio frequency energy (Provant, Regenesis Biomedical), electrical stimulation and low intensity pulsed ultrasound (Exogen, Smith & Nephew).

In regard to HBOT, there have been multiple trials, including the recently published study by Londahl and colleagues, who showed increased rates of healing with the use of HBOT in patients with diabetic foot ulcers.53

Ennis and co-workers evaluated the use of MIST therapy, an ultrasonic spray, in chronic diabetic foot ulcers in a multicenter, randomized controlled trial.54 They found a higher proportion of healed wounds in the active treatment group (40.7 percent) at 12 weeks in comparison to the control group (14.3 percent).

Piaggesi and colleagues assessed the use of super-oxidized water in managing wide post-surgical lesions in the diabetic foot.55 They found that the use of Dermacyn Wound Care facilitated a shorter duration of antibiotic therapy and less re-interventions in comparison to patients treated with povidone iodine.

Summing Up The Current RCT Evidence On The Advanced Modalities

It is important to put things in proper perspective so you can make your own decisions. Ask yourself the following questions: Why am I using this product? What is the scientific basis for this?

Consider the percentage of improvement over control groups in published RCTs of modalities that demonstrated significant differences in healing with diabetic foot ulcers in comparison to the gold standard of total contact casting (81 percent). There was a 43 percent improvement over control with Regranex; 47 percent with Apligraf; 51 percent with Graftjacket; and 64 percent with Dermagraft.26,34,35,52,56 (See “Assessing The Percentage Of Improvement Over Control Groups In RCTs” on page 11.) In regard to the one FDA-approved BLA product and the two FDA-approved PMA modalities for diabetic foot ulcers, Dermagraft has the greatest efficacy in the intent to treat analyses with these three products.

I would caution that direct comparisons between modalities are difficult to make due to variability in study designs and analyses.

Final Notes

By using a combination of these advanced therapeutic products based on their underlying clinical science and evidence, we can make a good dent in these very difficult problems. However, we need to remember that nothing supplants the role of good basic wound care. That means proper offloading, proper debridement, management of any existing infection and, of course, managing ischemia as necessary.

The use of multimodal therapies is probably most consistent with current clinical practice but you also need to remember that wounds change over the course of treatment. You need to be prepared to change your therapy as the wound characteristics change.

If a wound looks soupy and there is too much bioburden, one needs to hold off on an advanced tissue product for a week or so. Clean up that wound, ensure adequate wound bed preparation and then reinstitute an appropriate advanced therapy. Always pay attention to the basics of wound care and always reassess the wound as necessary, especially if the wound is not healing.

Granted, not everything we have available is based on RCTs. Otherwise, we would not have too much to use. However, you should always ask yourself the question: Is there evidence to support what I am doing?
References


50. Wieman TJ, Smiell JM, Su Y. Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic...


**Additional References**


