Introducing Bromelain-Based Enzymatic Debridement

There is a potential paradigm shift towards non-surgical wound bed preparation.

BY ROBERT J. SNYDER, DPM, CYAANDI DOVE, DPM, AND VICKIE DRIVER, DPM, MS

Overview: The Problem Defined

Foot ulceration in patients with diabetes (DFU) will likely affect up to 34% of diabetics (DFUs) at some stage in their lives. These figures are indeed disturbing as these ulcerations can lead to catastrophic results including infection, osteomyelitis, sepsis, limb loss, and death, the stairway to septicemia. "The prevalence of diabetes is estimated to include 7% (4.8 million) in the United Kingdom, 9.4% (30.3 million) in the United States, and 7% (366 million) of the world's population."[1] Current statistics reveal that every 1.2 seconds someone in the world will develop a DFU and non-traumatic amputations are performed every 20 seconds in this group[2]—a truly sobering statistic. Armstrong opined that foot ulcers in patients with diabetes are as serious as some cancers, with higher 5-year mortality rates with direct costs of approximately $237 billion as of 2017.[3] In reality, just having a DFU is a marker for death!

Foot ulceration in patients with diabetes (DFU) will likely affect up to 34% of diabetics (DFUs) at some stage in their lives.

Debridement remains the centerpiece in accelerating ulcer healing, thus decreasing the risk of serious complications.[4] The underlying pathogenic abnormalities in chronic wounds cause a continual build-up of non-viable tissue.[5] Optimum debridement should achieve a balance between the removal of necrotic tissue while preserving healthy tissue and subsequent healing.[6] Therefore, debridement re-establishes the balance between the production and degradation of molecules, a process often lost to chronicity.

This methodology transitions the wound from a chronic state of inflammation to a normal wound healing cascade. Procedurally, this is included in multiple guidelines and algorithms. Various techniques of removing devitalized (non-viable) tissue serves to shift the environment of the chronic wound to one consistent with acute wound biochemistry.[2,7] Chronic, non-debrided tissue becomes a 'petri dish' for higher bacterial loads leading to infective processes and poor healing. It therefore remains a pivotal step in the wound bed preparation model—a simplistic yet powerful holistic algorithm to approaching wound management and promoting the well-known acronym 'DIME' (Debridement, control of Infection and Inflammation, Moisture balance, and Wound Edge preparation).[8]

The reasons for this are multifactorial. Devitalized tissue acts as a barrier to healing by fostering senescent cells (and replicative senescence), a hyperproliferative wound edge, high levels of bacteria (planktonic and biofilm) and proteases coupled with a paucity of growth factors/receptor sites. It further fosters the ability to evaluate abscess and tunnels and may aid in controlling and managing pathology.[9]

Current Debridement Techniques and the Unmet Medical Need

Removal of non-viable tissue consists of "both non-mechanical (autolytic, enzymatic) and mechanical methods (sharp/surgical, wet to dry debridement, aqueous high-pressure lavage, ultrasound, and biosurgery/maggot debridement therapy)".[10]

In a survey of 75 patients performed by Nube, et al., weekly conservative sharp wound debridement was the predominant methodology performed.[11] In a retrospective cohort study of 312, 744 wounds, Wilcox, et al. concluded

Continued on page 110

New Concepts and Studies

"Clinical Innovations" is PM's ongoing series of articles dedicated to introducing new concepts, technologies and studies to the podiatric community. Readers should be aware that Podiatry Management does not specifically endorse any of the technologies, concepts, or products being discussed.

that more frequent (weekly) sharp debridement led to better outcomes.[12]

However, sharp debridement must be performed by a trained medical professional in a clinic, wound care center, or hospital. Sadly, many patients are homebound, have fears relating to COVID-19, or are too sick to be treated in this environment. Large cohorts, particularly in patients with diabetes, suffer from peripheral vascular disease, uncontrolled disease, and other underlying co-morbidities that preclude sharp debridement.

Sharp debridement must be performed by a trained medical professional in a clinic, wound care center, or hospital.

Therefore, these patients are relegated to treatment with enzymes or autolytic techniques in the home, often by untrained/uninformed healthcare professionals, family members, or patients who may marginalize this serious malady.

The currently available enzymatic agent (Clostridial collagenase) has been studied in two randomized controlled trials relating to DFUs. In one study, 48 neuropathic diabetic patients with foot ulcers were randomized in a 12-week open-label trial comparing collagenase to saline-moistened gauze and selective sharp debridement over four weeks, followed by an eight week follow-up.[13] Although no significant differences were noted in the two groups after four weeks, there was a statistical difference in percentage change -44.9% (collagenase) vs + 8.1% for saline gauze at the end of follow-up (P = 0.012).

A second 12-week, open-label randomized clinical trial (RCT) studied 55 neuropathic patients with diabetes comparing collagenase with 'investigator-selected' therapies consisting of five different dressings {silver dressing (n = 12), silver sulfadiazine cream (n = 5), wet-to-dry gauze (n = 5), alginate dressing (n = 4), hydrogel (n = 1)}.[14] The treatment phase consisted of six weeks with serial sharp debridement in both groups followed by a follow-up phase of another six weeks.

The researchers reported a significant change in wound size reduction from baseline with collagenase and serial sharp debridement at 6 and 12 weeks and concluded that collagenase in conjunction with serial sharp debridement could provide a benefit over standard care alone. "Researchers reported a significant change in wound size reduction from baseline with collagenase and serial sharp debridement at 6 and 12 weeks (comparing to baseline)".[12]

Based on these trials, researchers found that collagenase may be beneficial to wound healing through acceleration of percent area reduction, and its ability to remove devitalized tissue in multiple ulcer groups, albeit as an adjunct to sharp debridement. If debridement of wound bed slough/eschar is minimal after two weeks of topical treatment, then multiple applications are often required for extended periods of time. Of interest, a recent and comprehensive systemic review and meta-analysis conducted by Patry and Blanchette regarding enzymatic debridement with collagenase proffered that RCTs studying this therapy lacked adequate methodological

Continued on page 111

Debridement in Out-patient Management

FIGURE 1

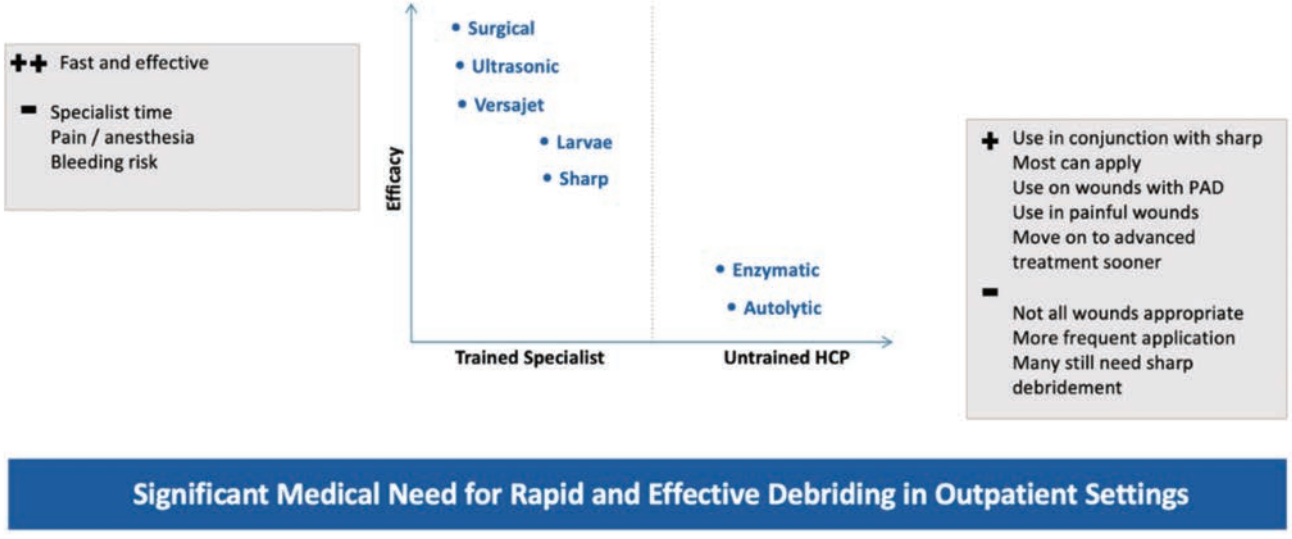


Figure 1: The conundrum of performing debridement without the need of a blade.

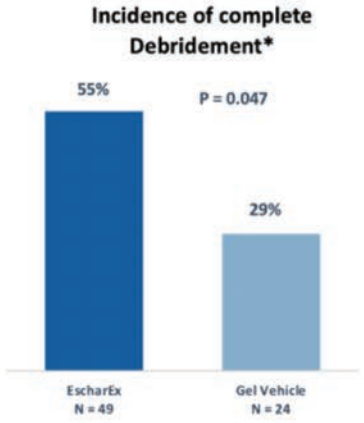
quality and included studies with a high risk of bias.[15]

None the less, although potentially beneficial in these scenarios as an adjunct to sharp debridement, therapies in this class that can efficiently and quickly remove devitalized tissue in days (not weeks) without the need of a surgical blade remain elusive, thus representing an unmet medical need (Figure 1).

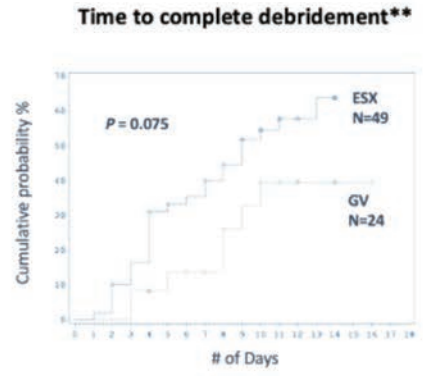
Continued on page 112

Study Met Its Primary Endpoint

FIGURE 2



Significantly higher incidence of complete debridement

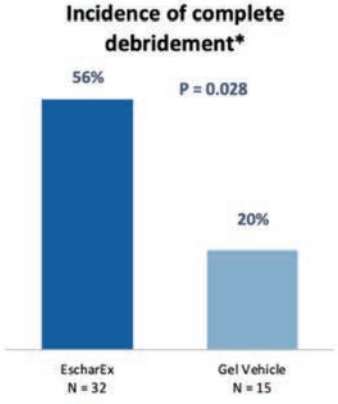


Shorter time to achieve complete debridement

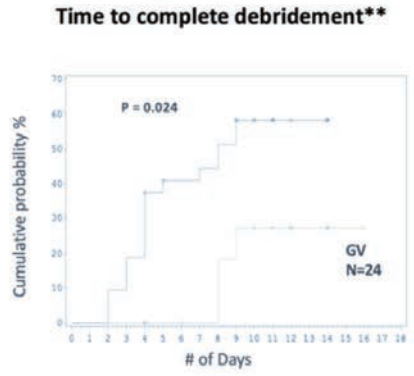
>90% of the patients who completed debridement with EscharEx were debrided within 7 days (after 4-5 daily applications)

VLUs and DFUs Post-Hoc Analysis

FIGURE 3



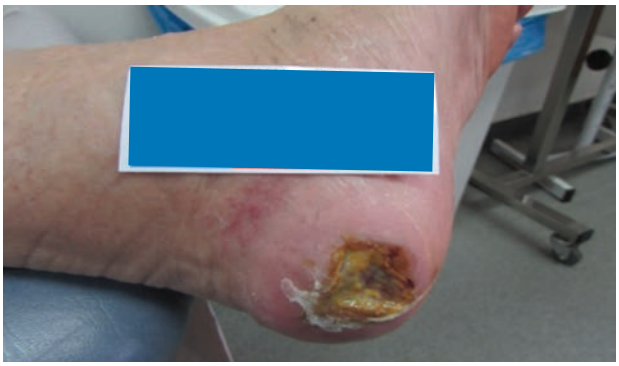
Significantly higher incidence of complete debridement



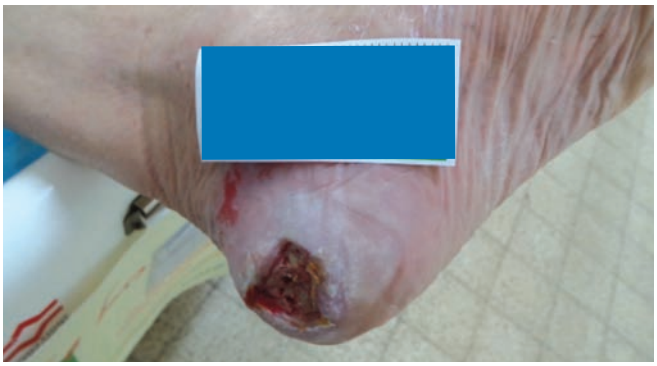
Shorter time to achieve complete debridement

EscharEx was safe and well tolerated in all tested doses and dosing regimens

Figures 2 & 3: show that EX-01 is significantly more effective than the GV in debridement of hard to heal wounds (p=0.047)



Subject 1—Photo 1 (A): This photograph shows pre-application of the IP. It shows a full thickness left heel ulceration with yellow, necrotic fatty tissue comprising the entirety of the wound bed.



Subject 1—Photo 2 (B): This photograph is status post 3 applications of IP. Photograph shows a wound bed comprised of vibrant, red granulation tissue with smooth beveled borders.

EscharEX™ (EX-01): A Paradigm Shift in Non-Surgical Debridement

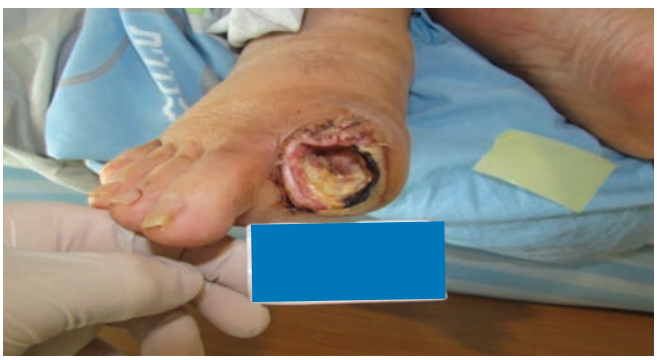
EscharEx™ (EX-01) is a new biological product currently under investigation that has been developed for debridement of non-viable tissue in patients with hard-to-heal wounds (DFUs and VLUs). Its active pharmaceutical ingredient is a complex and concentrate mixture of proteolytic enzymes enriched in bromelain, derived from the stem of the pineapple plant. The mechanism of action of the product is mediated by the proteolytic activity of the enzymes' mixture which allows debridement of non-viable necrotic tissue in hard-to-heal wounds.

Shoham, et al.[16] reported on a Phase 2 prospective, randomized, assessor blinded, multicenter controlled trial comparing EX-01 to a gel vehicle (2:1). The primary endpoint was to determine the incidence of complete debridement of non-viable tissue vs. Gel Vehicle (GV) and to ascertain the safety of EX-01 over an extended period of application. Secondary endpoints included time to complete debridement, quality of granulation tissue, incidence, and time to wound closure and Quality of Life (QoL).

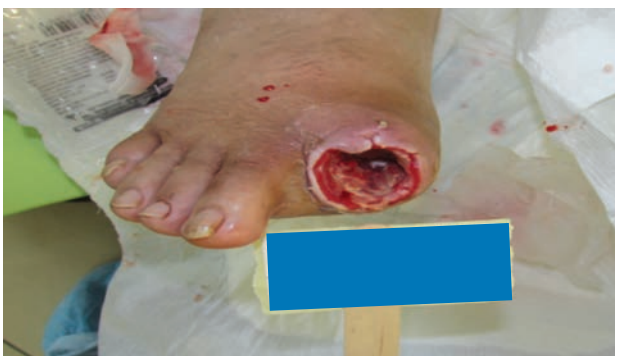
In Stage I, 73 patients with venous leg ulcers, diabetic lower extremity ulcers, and traumatic/post-operative wounds were treated with 5% EX-01 up to 10 applications of 4 hours each, with up to six months of follow-up. In Stage II, 38 patients experiencing venous leg ulcers, diabetic lower extremity ulcers were treated with 2.5% EX-01 up to 8 applications of 24 hours/3 times weekly. The results represented in Figures 2 and 3 show that EX-01 is significantly more effective than the GV in debridement of hard-to-heal wounds ($p = 0.047$). The secondary endpoint of time to complete debridement shows a positive trend towards faster debridement with EX-01 compared to GV.

EscharEx™ (EX-01) is a new biological product currently under investigation that has been developed for debridement of non-viable tissue in patients with hard-to-heal wounds (DFUs and VLUs).

Continued on page 113



Subject 2—Photo 1 (A): This photograph was taken prior to application of IP. It displays a distal hallux amputation site. The wound bed is primarily compromised of non-viable fatty slough with a medial crescent of black eschar at the medial border.



Subject 2—Photo 2 (B) This photograph was taken after 4 applications of the IP. It demonstrates a complete debridement with robust, red granulation tissue.

Post-hoc analysis shows that EX-01 was significantly more effective and faster than the GV in a subgroup population of DFU and VLU. However, the key 'take-away' remains that greater than 90% of the patients who completed debridement with EX-01 were debrided within 7 days (average of 4-5 daily applications) without sharp debridement yet consistent with the wound bed preparation model, thus paving the way for the use of advanced cell and tissue-based products to facilitate healing.

Discussion

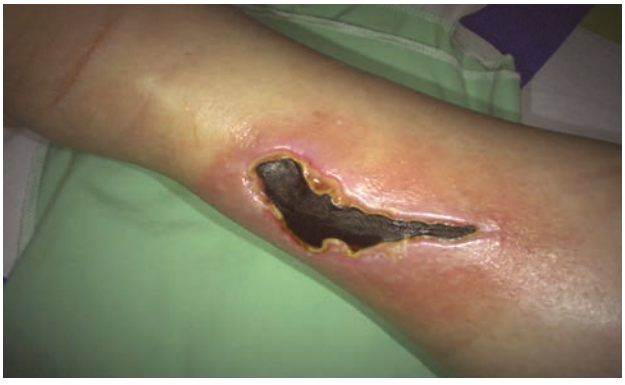
The following cases demonstrate a seismic shift in the treatment algorithm for recalcitrant diabetic foot ulcerations, without concurrent use of sharp debridement. The aforementioned literature clearly elucidates the required expediency in treating diabetic foot ulcers, lest the patient succumb to potential life-altering sequelae. A rapidly debrided wound bed is crucial, as a fully debrided wound bed physiology mimics an acute state. A key article teaches that failure of the percent of the wound area to decrease by half, while utilizing standard of care, at the 4-week mark, demonstrates that a wound is unlikely to progress to healing.[17]

The cases vividly illustrate recalcitrant diabetic foot ulcerations that were successfully debrided without adjunct sharp debridement. The debridement occurred over a span of 3-10 treatment days, without the use of surgical debridement. Upon examination, the debridement was not overly aggressive and did not result in increased depth or area of the wounds.

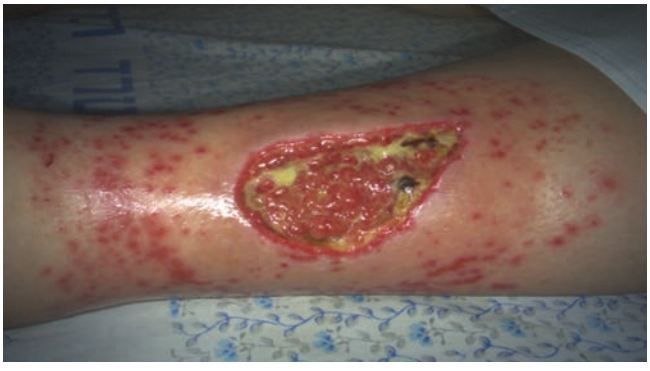
Post-hoc analysis shows that EX-01 was significantly more effective and faster than the GV in a subgroup population of DFU and VLU.

The third case in particular shows the potential of EX-02. Wound bed debridement was achieved after eight treatments of the investigational product. The wound then proceeded to complete epithelialization, ten weeks after application of a split thickness skin graft. Thus, the

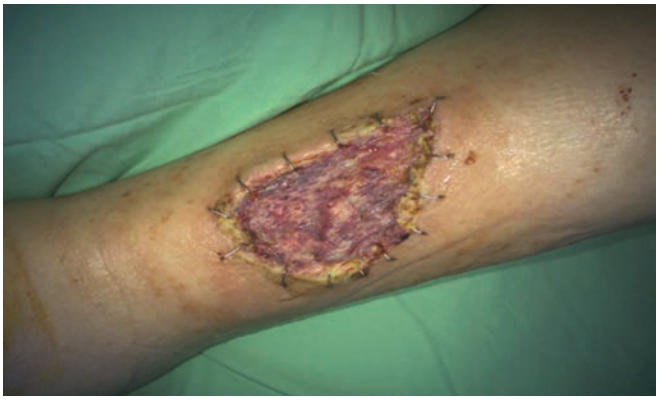
Continued on page 114



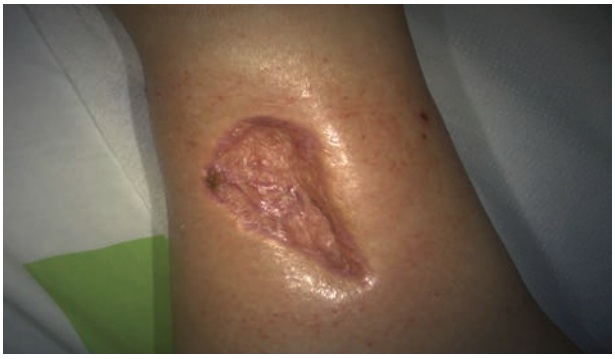
Subject 3—Photo 1 (A): This photograph is taken prior to application of the IP. This is a diabetic patient with a geographic ulcer, comprised of an adherent eschar.



Subject 3—Photo 2 (B): This photograph was taken after 8 applications of the investigational product. The wound is 90% free of nonviable tissue, and has primarily robust granulation tissue. There are small islets of black necrotic tissue and loosely adherent slough.



Subject 3—Photo 3 (C): After a fully debrided wound bed was achieved via treatment with the investigational product, a split thickness skin graft was harvested and secured with staples.



Subject 3—Photo 4 (D): This photograph was taken 10 weeks following the placement of the split thickness skin graft. The wound is 100% epithelialized. The peri-ulcer dermatitis from the previous photograph is resolved.

time span from a completely necrotic wound to a fully healed wound is less than two weeks, without adjunctive sharp debridement.

Conclusion

Diabetic patients with ulcers plagued with peripheral vascular disease, poorly controlled co-morbidities, or exquisitely painful diabetic neuropathy are often not candidates for surgical debridement. Wound bed preparation represents a cornerstone in facilitating recalcitrant/poorly responding wounds to progress efficiently through the wound healing cascade. The current tools for non-surgical debridement offer gradual removal of slough or eschar and may be ineffective when used independent of cold steel.

Wound bed preparation represents a cornerstone in facilitating recalcitrant/poorly responding wounds to progress efficiently through the wound healing cascade.

New and innovative enzymatic therapies that remove non-viable tissue in days, not weeks, could facilitate a paradigm shift fostering complete re-epithelization by secondary intention, the use of flaps and grafts or other cell and tissue-based therapies in an effective and efficacious manner. **PM**

References

[1] Diabetes.org.uk. (2019). Diabetes reports and statistics. Diabetes.org.uk.

[2] Armstrong DG, Boulton AJM, Bus, SA (2017). Diabetic foot ulcers and their recurrence. New England Journal Medicine, 376:2367-2375.

[3] Armstrong DG, Swerdlow MA, Armstrong AA et al (2020). Five-year mortality and direct costs of care for people with diabetic foot complications are comparable t cancer. Journal Foot Ankle Research, 13(1):16.

[4] Steed DL, Donohoe D, Webster M, et al. (1996) Extensive debridement of human diabetic foot ulcers is a vital adjunct to healing. 5th Annual Meeting of the European Tissue Repair Society. August 30-September 2, 1996; Padova, Italy., 371.

[5] O'Brien M: Methods of debridement and patient focused care.(2003). J Comm Nurs 17(11): 17-25.

[6] Schutz, GS et al. (2003). Wound bed preparation: a systemic approach to wound management, Wound Rep Reg Supplemental, 11:1-28.

[7] Lebrun E, Tomic-Canic M, Kirsner RS. (2010). The role of surgical debridement in healing of diabetic foot ulcers. Wound repair Regeneration. 18(5): 433-8.

[8] Sibbald R, Williamson D, Orsted H, et al. (2000). Preparing the wound bed-debridement, bacterial balance, and moisture balance. Ost/Wound Manag 46(11):14-22, 24-8, 30-5.

[9] Mulder GD, Vande Berg JS. (2002). Cellular senescence and matrix metalloproteinase activity in chronic wounds. JAPMA, 92.(1):3407.

[10] Dayya D, O'Neill OJ, Huedo-Medina TB, et al.(2021). Debridement of diabetic foot ulcers. Advances in Wound Care.

[11] Nube, V.L., Alison, J.A. & Twigg, S.M (2021). Frequency of sharp wound debridement in the management of diabetes-related foot ulcers: exploring current practice. J Foot Ankle Res 14, 52 https://doi.org/10.1186/s13047-021-00489-1149(9): 1050-158.

[12] Wilcox JR, Carter MJ, Covington S. (2013). Frequency of debridements and time to heal: a retrospective cohort of 312, 744 wounds. JAMA Dermatology.

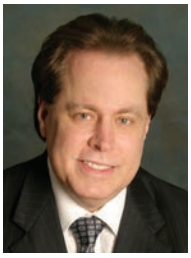
[13] Tallis A, Motley TA, Wunderlich RP, Dickerson JE Jr, Waycaster C, Slade HB (2013). Collagenase Diabetic Foot Ulcer Study Group. Clinical and economic assessment of diabetic foot ulcer debridement with collagenase: results of a randomized controlled study. Clin Ther, 35:1805–20.

[14] Motley TA, Lange DL, Dickerson JE Jr, et al. (2014). Clinical outcomes associated with serial sharp debridement of diabetic foot ulcers with and without clostridial collagenase ointment. Wounds, 26:57–64.

[15] Patry J, Blanchette V. (2017). Enzymatic debridement with collagenase in wounds and ulcers:a systematic review and meta-analysis. International Wound Journal, 14; 1055-1065.

[16] Shoham, et al. (2021). Bromelain-based enzymatic debridement of chronic wounds: Results of a multicentre randomized controlled trial, Wound Rep Reg, 29:899–907.

[17] Snyder RJ, et al. (2010). A post-hoc analysis of reduction in diabetic foot ulcer size at 4 weeks as a predictor of healing by 12 weeks. OstomyWoundManage.2010Mar 1:56(3):44-50.



Dr. Snyder is Dean, Professor, and Director of Clinical Research at Barry University School of Podiatric Medicine. He has served as Principal Investigator on more than 60 randomized clinical trials. In 2018, Dr. Snyder was inducted as Faculty Fellow of Podiatric Medicine, Royal College of Physicians and Surgeons (Glasgow).

Dr. Driver is System Wide Medical Director and Chief of the Wound Care and Hyperbaric Centers at INOVA Healthcare and is Professor, University of Virginia, School of Medicine. She is also Fellow, Royal College of Physicians and Surgeons-Glasgow, PM and Inaugural Fellow, Assoc for the Advancement of Wound Care, FAAWC. Dr. Driver is Chair, Board of Directors for the Wound Care Collaborative Community, an important collaboration with the FDA, CMS, and the NIH. She is Board Certified with the American Board of Podiatric Surgeons and is a Fellow at the American College of Foot and Ankle Surgeons.

Dr. Dove currently runs a private practice in Las Vegas, Nevada. She has served as a Principal Investigator in nearly 50 clinical trials, over the past twenty years. Before opening her practice, Dr. Dove was the director of podiatry at the Diabetic Foot and Ankle Center—Hospital for Joint Disease—NYU. Concurrently, she served as the sub-investigator for multiple Phase I-IV clinical trials. Dr. Dove has multiple publications in the Lancet and other peer-reviewed journals.