

Decreased Amputation through Evidence-Based Wound Healing

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Introduction

Numerous clinical references highlight the economic impact of treating diabetic foot ulcers (DFUs).¹⁻⁴ As the rate of American patients diagnosed with diabetes mellitus increases each year so does the group of patients most susceptible to developing DFUs, namely those over the age of 65.⁵⁻⁶ Recent figures revealed that from 1980 through 2008 the number of diabetic Medicare beneficiaries aged 65 or older increased from 2.3 million to 7.4 million, representing a greater than 300% increase.⁷ This is truly alarming to those who care for veterans in the Veterans Affairs system as the number of patients being cared for and treated in the Federal segment continues to escalate. Many veteran patients with diabetes present with numerous metabolic and clinical abnormalities that predispose to ulceration including peripheral neuropathy, peripheral arterial disease (PAD), poor glucose control, foot deformities, and even callus.^{8,9,10} Long standing, non-healing diabetic foot ulcers complicated by infection, renal failure, and/or PAD are important components in the causal pathways leading to amputation.^{11,12} Both foot ulcers and lower extremity amputations have been shown to be associated with higher mortality than found in those diabetic patients without such complications.¹³ As this trend continues and more patients present to the healthcare provider in the outpatient clinic with potentially, limb threatening disorders, a strict

care path must be implemented.

Specific treatment strategies must be established based on available clinical research and evidence-based outcomes to insure that patients are being treated with the most cost effective and proven therapies available. Since it has been estimated that 77% of all costs incurred in treating DFUs are due to inpatient costs, the importance of employing clinically effective treatments becomes clearly evident.¹⁴ In one study, the risk of hospitalization was 55.7 times greater for patients who developed a lower extremity infection and their risk for amputation is 154.5 times compared to a non-infected DFU.¹⁵ Accordingly, infection and amputation are major causes of hospital costs incurred in the patient with diabetic foot ulcer that fails to heal in an optimum time frame. Unhealed DFUs greater than 30 days is independently associated with a 4.7 times increased risk for infection.¹⁵ When an infection becomes established in a person with diabetes, a blunted immune response, and reduced peripheral blood flow, the bacteria can invade beyond local soft tissue and ultimately infect contiguous bone (i.e., osteomyelitis). Once bone infection has occurred, inpatient admission for parenteral antibiotics over extended periods and potential removal of infected bone by various resections or amputation strategies is required.

Since many diabetes related admissions are due to infected DFUs, their attendant costs are high. One study investigating 1995-96 Medicare claims data revealed average costs of \$25,713 (2011 USD) per episode of inpatient care in patients with an ulcer.¹⁶ Such events result in escalating costs through extended hospital stays, operations, excessive morbidity and even mortality.¹⁷

The goal of wound care is to establish an aggressive and effective strategy to heal the wound as expeditiously as possible to prevent those complications (such as infection or gangrene) that require inpatient admission. In this paper, we will discuss how we utilized available clinical evidence as a basis for implementing aggressive algorithm based medical practices to heal DFUs. Using such protocols to guide the care of increasingly more complex wounds and complicated patients can result in improved patient outcomes, fewer inpatient admissions, fewer amputations, and accordingly, lower costs.

Depending on source claims and insurance provider analyzed, costs of healing DFUs and amputation procedures are variable and are based upon medication costs, clinic visit charges, hospitalization charges, and various finite costs. Regardless, the consistent finding in the majority of medical reviews is that caring for patients with a DFU is an expensive but necessary process since the alternative of having an unhealed ulcer may be more devastating. On average, diabetic patients with foot ulcers have been estimated to have over 13.5 outpatient visits per year and are hospitalized 0.25 times per year for their DFU and hospitalized 1.5 times per year for any reason.¹⁸ The costs of caring for patients impacted by this life-altering illness increases with each episode. Harrington et al. conservatively estimated that it costs over \$28,000 (2011 USD) per year in Medicare reimbursement per patient with a lower extremity ulcer.¹⁶ The economic burden of diabetes continues to escalate and thus the collateral damage of other medical issues is multiplied. It has been noted that as many as 20% of diabetic patients who undergo lower extrem-

ity amputation return to the hospital for another amputation within 12 months.¹⁹ This highlights the importance of a prevention strategy versus allowing the typical amputation cascade to continue unabated.

In the last decade, there have been four evidence-based treatment protocols published recommending the utilization of FDA-approved agents to heal DFUs at a faster rate than conventional wet-to-dry wound care. Much confusion is apparent when discussion of "PMA" or "BLA" versus "510K" or "HCT/P" products is brought up in medical dialogue. The critical differentiator is that PMA (Pre-Market Approval) products or BLA (Biologics License Application) product have been shown in comparative randomized clinical trials (approved by the FDA) to heal DFUs more completely and faster than conventional therapy alone.. There are only three products that have this designation: PMA products Dermagraft® (Advanced BioHealing) and Apligraf® (Organogenesis), and the BLA product Regranex® (Healthpoint Biotherapeutics). Other wound products available to healthcare providers have been cleared vs. approved as "510K" or "HCT/P" (human cellular and tissue based product) designation.

HCT/P products are regulated by the FDA to allow for human cells or tissue intended for implantation, transplantation, infusion, or transfer into a human recipient. The FDA generally permits products regulated solely as human tissue to be commercially distributed without premarket clearance or approval or randomized clinical trials to demonstrate efficacy. 510K products use a pre-existing similar device in the market called a "predicate device" for comparison. It does not have the FDA "approval" but rather a 510K product is generally referred to as "510K cleared device" that can be marketed and sold since it is similar to an already existing device identified by the FDA as available device prior to May 28, 1976. No randomized clinical trials to prove efficacy are required for this process.

As a result, these agents have been “cleared” for wound management but are not FDA-indicated to heal wounds. As with this critical difference, various consensus panels and published guidelines provide support as to when use of PMA products should be implemented. Sheehan and colleagues found that the percent change in wound area of DFUs over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial.²⁰ While the trial study agent failed to show efficacy, they were able to determine with high sensitivity and specificity that any DFU that fails to reduce in size by at least 50% in the first 4 weeks of therapy is unlikely to heal in a reasonable period of time. The American Diabetes Association Consensus Development Conference (1999) stated that “Any wound that remains unhealed after 4 weeks is cause for concern, as it is associated with worse outcomes, including amputation”.²¹ In 2004 Boulton and colleagues stated “The failure to reduce the size of an ulcer after four weeks of treatment that includes appropriate debridement and pressure reduction should prompt consideration of adjuvant therapy.”²² Therefore, therapy that has been shown in randomized controlled clinical trials to demonstrate efficacy in healing DFUs compared to conventional therapy (PMA and BLA products) should be considered after 4 weeks if the DFU achieved less than a 50% PAR (Percent Area Reduction) in wound size. In certain higher-risk patient subgroups with increased risk of poor outcomes, such as those with a history of renal insufficiency, prior amputation, or poor metabolic state, this timeline may be considered longer than clinically necessary. While the recommendations for early intervention with advanced therapies are cited extensively in the literature, there are limited outcome data available to support what implementing this into clinical practice can provide in regards to patient outcomes, amputation prevention, and overall economic impact.

The providers at the authors’ High Risk Foot Clinic implemented such a strategy based on the hypothesis that an evidence-based therapy would increase consistency of treatment approach, provide rapid wound progression, and ultimately provide an aggressive treatment of wounds not

responding to conventional therapy. All of these factors would be evaluated to determine if enhanced patient outcomes and lower cost could be documented. We believe that our treatment protocol effectively promotes our goal of limb preservation. Although costs are certainly of importance, reduction or prevention of amputation is our primary outcome of interest. As previously mentioned, avoidance of hospitalization necessitated by infection or gangrene has been demonstrated to decrease not only costs but also morbidity and mortality.¹⁷

Our center is one of the largest High Risk Foot Ulcer Clinics within the Veterans Affairs Health Care System. The volume of patients with DFUs alone has grown by 20% in the last two years with almost 4,000 DFU patient encounters in 2010. Patients are referred to this clinic if the following are observed: 1) the patient has not responded to conventional care as defined by less than 50% PAR at four weeks; or 2) the patient has a non-healing postoperative wound. The amputation rates for the eight years prior to 2009 had never been below 3.0% in any calendar year. In July of 2009, the Phoenix VA High Risk Clinic began utilizing a human fibroblast-derived dermal substitute (HFDS) in concert with a continued focus on the basic tenets of wound care: debridement, infection control, validation of vascular status, and aggressive off-loading. In those patients who did not achieve the 50% PAR level at four weeks, HFDS was also implemented. Dermal replacement therapy was occasionally used with concurrent Negative Pressure Wound Therapy (NPWT) to promote granulation and rapid closure. A primary goal of treatment has been to rapidly heal foot ulcers in order to minimize the need for hospitalization and amputation. In the presence of necrosis, gangrene, and PAD, revascularization and partial foot amputation are performed to allow for limb preservation. Accordingly, a healed minor amputation is considered to be a limb salvaging procedure. Indeed, major amputations have frequently been avoided by using this strategy in patients otherwise destined for limb loss.

Results

Since initiating our amputation prevention protocol with the incorporation of HFDS, our center experienced a 23% absolute reduction and a 33% relative reduction in amputations despite experiencing a 20% increase in the volume of patient encounters with DFUs. (Figure 1)

2 year Amputation Reduction achieved after Implementing Evidence-Based Protocol

Year	Amputations	Ulcer Encounters	Amputation %
2008	101	3300	3.00%
2009	87	3600	2.40%
2010	78	3950	1.97%

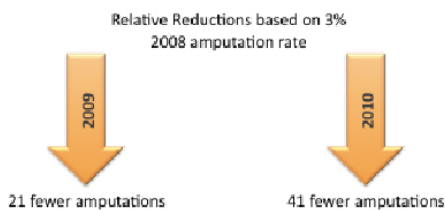


Figure 1: Crude and Relative amputation reductions relative to 2008 amputation rate

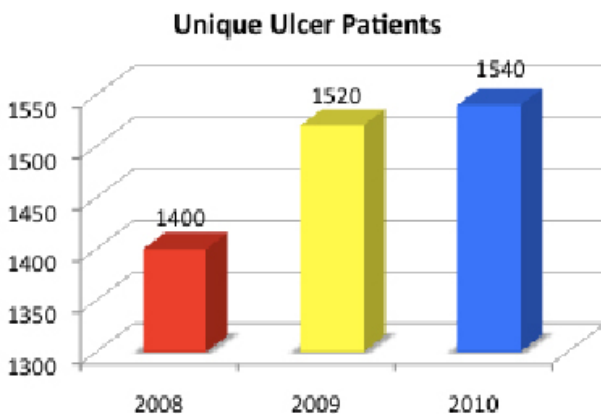


Figure 2: Modest increase in crude number of unique DFU patients is illustrated from 2008 through 2010.

We had 21 fewer relative amputations in 2009 and 41 fewer in 2010 as compared to 2008. As can be seen in Figure 2 the crude number of ulcerations in our diabetic population showed a modest 10 percent increase from 2008 through 2010. This is also reflected in an increase in the number of ulcer encounters seen in the previous figure. With 62 fewer relative amputations than previously performed in 2008, using the average two year follow up costs associated with an

amputation published by Carls and colleagues in 2011,²³ the total accrued savings for surgery costs and follow-up alone is calculated at \$4.34 million. This savings occurred despite the rising number of diabetic patients with significant co-morbidities in our clinic.

Discussion

The amputation rate at the Phoenix VA achieved an all time low in 2009 despite caring for greater volume of patients with diabetic foot ulcers and then again in 2010. No other wound care strategy was added or altered other than the implementation of a standardized approach to utilization of HFDS. These results are a direct reflection of a focused practice of basic wound care fundamentals (defined by debridement, validation of vascular status, infection control, and off-loading). These basic tenets of standard wound care are routinely followed and remain our primary approach to chronic wounds including DFUs. Patients are educated about the need for a total contact cast, walker boot, or other off-loading device. In patients non-compliant with maintaining appropriate utilization of removable off-loading devices, other non-removable devices (such as total contact casts) are used to achieve this essential aspect of DFU care.

The economics of health care are a much needed debate in American society. While many continue to use a narrow perspective and focus on each department, device, or wound care product as an individual piece and compare the cost of various segments, it is critical to instead review the economics per positive patient outcome. If patient outcomes are enhanced and utilization of expensive inpatient therapies, procedures, and costs are avoided, it is obvious that overall medical costs to the entire system can be reduced. It is necessary to evaluate the entire spectrum of treatment and costs incurred during common DFU care and evaluate the economic

outcomes as seen by the overall expenditures rather than piecemeal costs. Even if a strategy implemented costs slightly more up-front but is able to reduce overall costs throughout the entire treatment regimen, it is best for the patient, provider, and the healthcare system. In this regard, a recent study by Zhang et al. has shown that the higher initial costs incurred from using advanced products, such as HFDS, actually represent medium to long-term accrued cost savings by avoidance of hospitalization and amputation.²⁴ The mean cost of an amputation has been estimated at \$40,081 per amputation and two year follow up costs associated with each amputation at \$79,658 by Carls et al.²³

Conclusion

This review demonstrates that a more focused and aggressive approach to wound care by utilizing HFDS resulted in reduced costs to the healthcare system while also showing decreased morbidity and risk of mortality due to decreased major limb amputations. Limitations to our review are as follows: 1) Retrospective cohort of patients and experience over the last 2 years. 2) Amputation costs are based on estimates attained through the Depart-

ment of Health and Human Services and may be an over- or underestimation depending on procedure because an average was utilized. Nonetheless, we believe that our treatment protocols expedite wound closure in the majority of patients and thereby avert the costly and life-altering complications that can ensue when chronic DFUs remain unhealed in the high-risk diabetic population.

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