

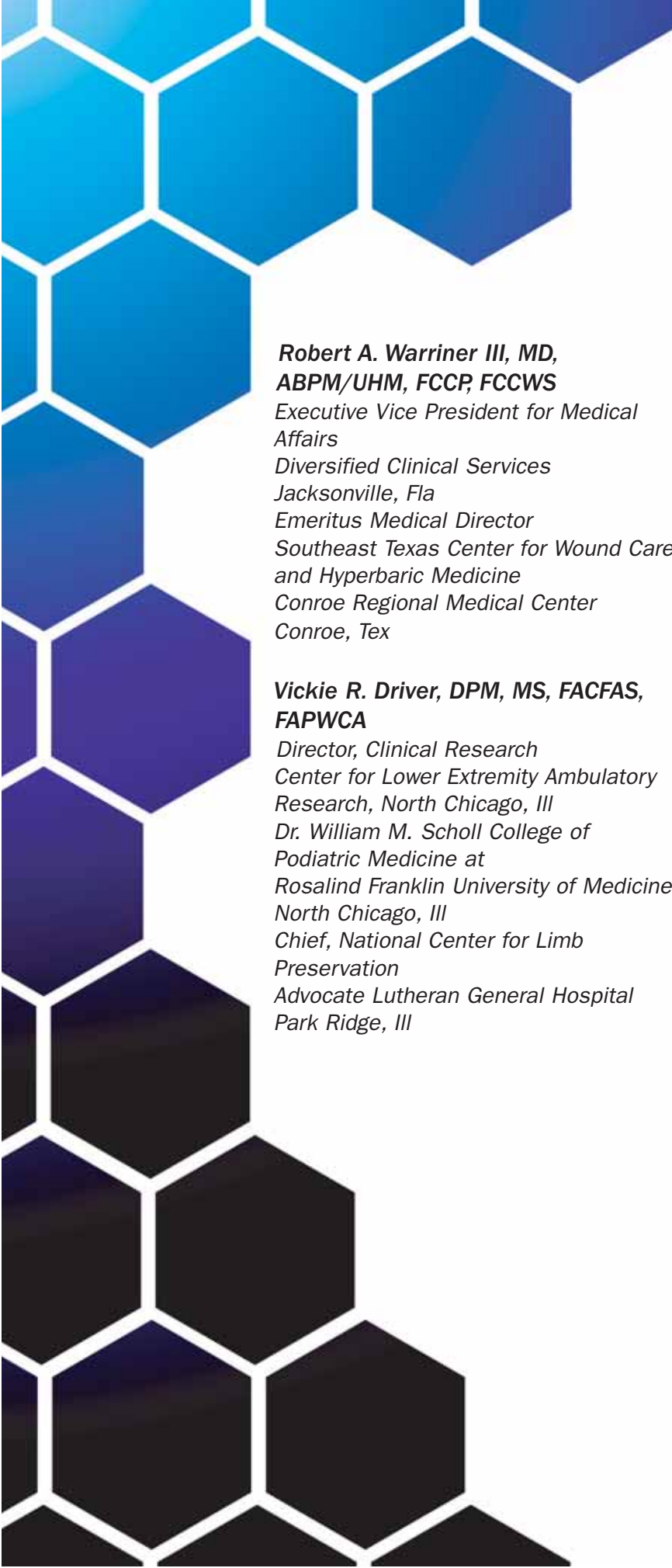


Supplement to

WOUNDS

The True Cost of Growth Factor Therapy in Diabetic Foot Ulcer Care





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Continuing Education

Completion Time: The estimated time to complete this activity is 1.5 hours.

Target Audience: Physicians, nurses, and podiatrists

Objectives: Upon completion of this educational activity, participants should be able to:

- Describe the value of topical growth factor therapy in diabetic foot ulcer care based upon published, randomized, controlled clinical trials
- Discuss the application and rationale of a cost-effectiveness-based patient care algorithm utilizing topical growth factor therapy in diabetic foot ulcer care
- Discuss the epidemiology of diabetic foot ulceration and pathophysiology of diabetic foot ulcer care based upon published, randomized, controlled clinical trials
- Describe the value of topical growth factor therapy in diabetic foot ulcer care based on published, randomized, controlled clinical trials.
- Describe and apply a cost-effectiveness-based patient care algorithm utilizing topical growth factor therapy in diabetic foot ulcer care.

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The True Cost of Growth Factor Therapy in Diabetic Foot Ulcer Care

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This review will address several important questions concerning the management of patients with neuropathic diabetic foot ulcers (DFUs). Specifically, the epidemiology of diabetic ulceration and its association with lower-extremity amputation, as well as the economic costs of diabetic ulcer healing failure, will be examined. What is currently known about the pathophysiology of diabetic ulceration and ulcer healing failure will also be addressed, and that information will be linked to the current understanding of what constitutes good standard care for the patient with a DFU. Once that background is established, evidence for the clinical effectiveness of becaplermin in treating neuropathic DFUs will be reviewed, as will clinical effectiveness in light of the cost effectiveness of this therapy, which will require an introduction of some of the concepts involved in cost-effectiveness analysis. Finally, a reasonable recommendation for clinical practice will be given based upon the best information currently available today.

DIABETES AND FOOT ULCERS

Diabetes constitutes a major and escalating health problem in the United States. The Centers for Disease Control and Prevention (CDC) reports that 20.8 million people (7.0% of the population) have diabetes.¹ Of these, 6.2 million are

currently undiagnosed.¹ The fact that 10.3 million of the total diabetes population are age 60 years or older accounts for a prevalence in this group of 20.9%.¹ There is a higher incidence of diabetes among non-Hispanic blacks, Hispanic/Latino Americans, and Native Americans as compared to non-Hispanic whites.¹

Diabetes complications are significant contributors to overall morbidity and mortality and include increased risk for heart disease and stroke, hypertension, blindness, renal disease, periodontal disease, peripheral neuropathy, and lower-extremity ulceration and amputation.¹ Diabetes is costly. Based on 2002 data, the total direct and indirect costs of diabetes and diabetes-related complications was \$132 billion.¹ Direct medical costs constituted \$92 billion of that figure.

More than 60% of all non-traumatic lower-extremity amputations in the United States occur in people with diabetes.¹ In 2002, patients with diabetes accounted for approximately 82,000 lower-extremity amputations.

In a Behavioral Risk Factor Surveillance System survey completed by the CDC in 2003, the overall age-adjusted prevalence of foot ulcer history in persons with diabetes was 12.7%.² The percentage of individuals with foot ulceration decreased with increasing age and increased with longer duration

of disease.

Foot ulcers were more prevalent in persons who were obese and among those who were using insulin. The prevalence of foot ulceration was also increased by smoking (10.3% among nonsmokers, 11.9% among former smokers, and 15.8% among current smokers). Data suggest that 85% of lower-extremity amputations in persons with diabetes are preceded by a foot ulcer.³ Effective measures for identification of persons at risk, instituting appropriate preventative strategies and surveillance monitoring, and more effective treatment of foot ulcerations when they occur could significantly impact lower-extremity amputation rates in this patient population.⁴

In a retrospective cohort study, Ramsey et al⁵ followed 8,905 individuals with type 1 and type 2 diabetes from 1993 to 1995. Of these individuals, 514 developed an ulceration (cumulative incidence of 5.8%), 77 (15%) had osteomyelitis at the ulcer site diagnosed at the time of ulcer presentation or some time during the course of care, and 80 (15.6%) required amputation. Survival at 3 years for the patients with foot ulcers was 72% compared to 87% for a group of age- and sex-matched patients with diabetes without ulceration. The attributable cost for a

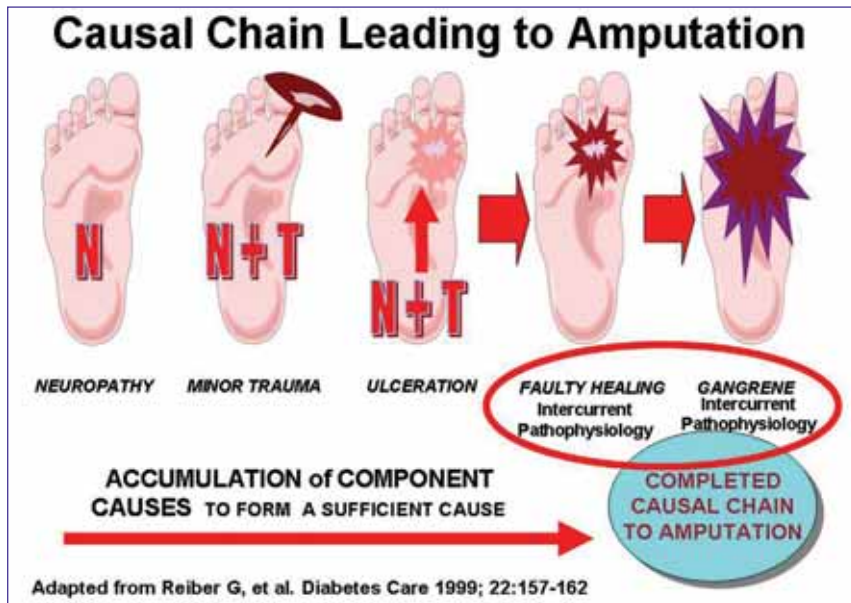


Figure 1: An illustration of the causal chain for developing a diabetic foot ulcer, as well as the related events that lead to lower-extremity amputation. Adapted from Reiber et al.⁸

Also, the proportion of major amputations (transtibial or higher) was substantial (47.4%) and did not parallel other recent findings of amputation rates of neuropathic foot ulcers treated in wound care clinics where major amputations have declined to less than 30%.⁷

Diabetes represents a major and increasingly important health risk in the United States. Diabetic foot ulceration is a major contributor to lower-extremity amputation in this population. See the sidebar “Good Standard Care for the Diabetic Foot Ulcer” on page 5 for an outline of management considerations.

DFU HEALING FAILURE

The causal chain for developing a DFU and the subsequent events that lead to lower-extremity amputation have been well described by Reiber et al⁷ and are outlined in Figure 1. Peripheral sensory neuropathy increases the likelihood of unrecognized local trauma producing injury leading to ulceration.⁸ Peripheral motor neuropathy may produce foot deformity, increasing the likelihood of ulceration developing from areas of high contact pressure or shearing stress that also go unrecognized until significant injury is present. Reiber identified the triad of neuropathy, foot deformity, and minor trauma as being present in greater than 63% of patients’ causal pathways to foot ulceration.⁸ Callous formation associated with higher subcallous plantar pressures was associated with ulcer development in 30% of the pathways. Edema and ischemia were also significant contributors to ulceration occurring in 37% and 35% of ulcer pathways, respectively.

This study did not identify further the pathophysiology of faulty healing, which frequently occurs in patients with diabetes and foot ulceration. While other causes of

40- to 65-year-old man with a new foot ulcer in this study was \$27,987 for the 2 years after the diagnosis of the ulcer. Additionally, the risk of contralateral amputation is estimated to be as high as 56% within 3 to 5 years after the first amputation.

Markowitz et al reported an analysis of amputation rates calculated in patients diagnosed with DFUs in the MEDSTAT Marketscan database between January 2000 and December 2002 with a prediagnosis coverage of 90 days.⁶ The 5,911 eligible patients yielded an incidence density rate of 2.30 amputations per 100 person years. Of the 116 cases proceeding to amputation matched to 1,153 matched controls, 5 risk factors were associated with increased risk of amputation:

1. Male gender
2. Charlson co-morbidity scores of 4 to 5 and 6+
3. Renal disease
4. Peripheral vascular disease
5. By 5+ outpatient DFU services.

There appeared to be an overall association with increased numbers

of comorbid conditions influencing the likelihood of amputation, suggesting the greater overall disease burden further impairs DFU healing and should be factored into risk assessment and treatment planning. Peripheral vascular disease had the strongest effect on the progression to lower-extremity amputation, more than tripling the risk even in the setting of treatment by a multidisciplinary wound care team.

Supplemental treatment with becaplermin in this study was linked to a 22% reduction in the risk of amputation, although this difference was not statistically significant in the adjusted multivariate analysis. The 20-week follow-up in most randomized clinical trials of treatment modalities for DFUs was felt by these authors not to be of sufficient duration to capture amputation outcomes in settings offering usual care.

In the sample considered for this study, only 25% of the patients underwent amputation within the first 4 months, while 75% underwent amputation within 10 months.



neuropathy, such as Hansen's disease and heavy metal-induced neuropathy, may be associated with ulceration, they are not typically associated with the kind of chronic healing failure seen in patients with diabetes with otherwise similar ulcerations. There are a number of potential explanations for this difference that characterize the unique challenges in successfully managing DFUs, including the earlier development of lower-extremity peripheral arterial occlusive disease, altered fibroblast function, and impaired local and systemic host immune response. Mustoe has described a model for chronic wound healing failure that can be readily applied to the DFU patient.⁹ The essential elements of this model include:

- Most chronic wounds occur in older individuals. Increased age is associated with progressively impaired wound healing, decreased fibroblast proliferative capacity with prolonged doubling times and eventual replicative senescence, and altered stress-related gene expression in response to oxidative or ischemic stress.
- Bacterial colonization is usually present, producing an excessive and persistent inflammatory response. The bacteria in chronic wounds, the leukocytes they attract, and the high protease and oxidant environment results in sustained or progressive wound bed necrosis, degraded extracellular matrix, and local cytokines, further inhibiting cell migration, replication, protein synthesis, and eventual wound healing.¹⁰
- Most chronic wounds occur in the setting of some degree of local tissue ischemia and hypoxia. In lower-extremity wounds, this may occur as the result of macrovascular occlusion, microvascular dysfunction impairing diffusion, or

intermittent ischemia-reperfusion injury (the intermittent absence of arterial perfusion caused by high local pressure followed by partial restoration of flow when pressure is relieved, which produces activation and margination of circulating leukocytes that adhere to the vascular endothelial lining and release vasoactive substances that impair flow through the microcirculation).¹¹

Aged cells are not as well equipped to deal with ischemic or inflammatory stress, increasing the local tissue injury in response to these abnormal stimuli. Additionally, there is evidence that a stress-induced premature senescence phenotype of fibroblasts in the wound bed may be induced by the continuing inflammatory state seen in many chronic wounds.¹² Exogenously administered growth factors via bioengineered dermal substitutes or pharmacological preparation may reverse this premature senescence in some wound bed fibroblasts.

There is increasing evidence that diabetes itself confers additional pathophysiology leading to chronic ulcer healing failure.¹³ Marston performed a secondary analysis of data from a prospective, randomized trial involving 245 patients with DFUs treated with a bioengineered human dermal substitute.¹⁴ In this patient population, those whose hemoglobin A1c (HgbA1C) increased during the study, 20.7% of all wounds and 21% of dermal substitute-treated ulcers healed while in those whose HgbA1C remained stable or decreased, 26.3% of all ulcers and 47% of the dermal substitute ulcers healed ($P < 0.05$).

Ahmed has reviewed the role of increased glycation end products in a variety of diabetic complications.¹⁵ In diabetic ulcer healing, advanced glycation end products (AGE) interact with receptors for AGE (RAGE),

Good Standard Care for the Diabetic Foot Ulcer

Offloading

- Footwear modification
- Total contact cast
- Bed rest

Debridement

- Sharp
- Early
- Aggressive

Dressings

- Prevent trauma
- Minimize infection risk
- Optimize wound environment
- Manage moisture in wound: not too much, not too little

Prevention and treatment of infection

- Infection increases risk of amputation
- Debridement
- Aggressive management

Surgical intervention when appropriate

- Limb preservation
- Distal procedures
- Conserve articulations
- Preserve function

resulting in the release of pro-inflammatory cytokines, such as TNF- α , and increased production of matrix metalloproteinases (MMPs). AGE interaction with RAGE reduces collagen deposition by ulcer bed fibroblasts. Glycated fibroblast growth factor 2 (FGF-2) *in vitro* has significantly reduced mitogenic activity and reduced proliferation of endothelial cells, capillary tube formation, and angiogenesis, although this has not yet been demonstrated *in vivo* in patients with diabetes.

The protease imbalance seen in DFU healing failure and mentioned previously in relation to the effects of increased glycation end products has been confirmed in diabetic wounds compared with trauma wounds in



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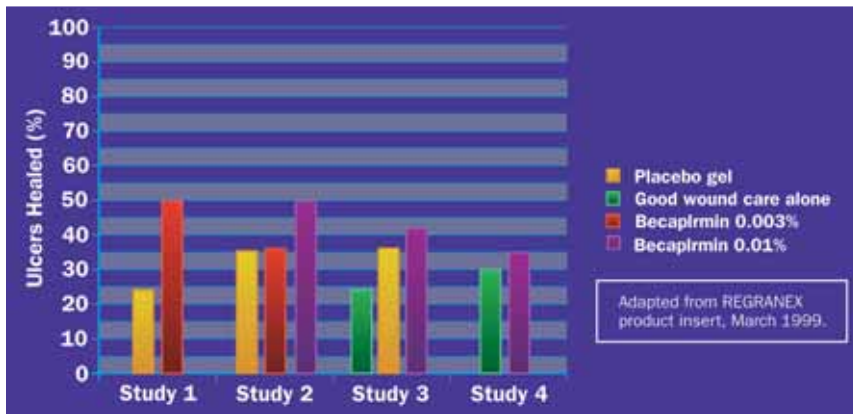


Figure 2: Summary of becaplermin gel 0.01% clinical trials.

the control wounds of patients with normal glucose metabolism.¹⁰ Correcting this proteolytic imbalance has become a major focus of efforts to address wound bed preparation and enhance the effects of exogenously applied recombinant platelet-derived growth factor (PDGF).

Pecoraro et al identified the importance of adequate local perfusion in diabetic ulcer healing.¹⁶ They demonstrated that periwound transcutaneous PO₂ values less than 20 mmHg were associated with a 39-fold increased risk of early healing failure and proposed the importance of adequate local perfusion and oxygenation as influential determinants of successful tissue repair. They also speculated that cutaneous oxygenation was a function not only of large vessel arterial supply but also of local physiological conditions that independently affect the regulation and effectiveness of the capillary circulation.

BECAPLERMIN THERAPY IN DFU CARE

Becaplermin (REGRANEX Gel 0.01%, Johnson & Johnson Wound Management, Somerville, NJ) is a human recombinant form of PDGF known as rhPDGF-BB. In December 1997, the FDA approved becaplermin for the treatment of DFUs that extend into the subcuta-

neous tissue or beyond and have adequate blood supply. Becaplermin stimulates fibroblast migration and collagen synthesis and is an important co-factor, along with vascular endothelial growth factor, in stimulating vascular proliferation by recruiting the smooth muscle cells and pericytes necessary to stabilize newly formed vessels.¹⁷ In 4 clinical trials, becaplermin was compared to placebo and to standardized good wound care to assess the incidence of wound closure and the time required to achieve complete healing.¹⁸ All patients had deep diabetic neuropathic ulcers that extended into the subcutaneous tissue or beyond. All wounds had an adequate blood supply. Ninety-three percent of patients had foot ulcers, and 7% had ankle or leg ulcers. All ulcers were of at least 8 weeks' duration with a median duration of 32 weeks. Ninety-five percent of ulcers were ≤ 10 cm² and median ulcer size ranged from 1.4 cm² to 1.5 cm². In all, 922 patients were studied, of which 478 received becaplermin.

The 4 trials were summarized by Wieman¹⁸ and are graphically summarized in Figure 2. All patients in all trials received a standardized regimen of good ulcer care. Patients were randomized to receive placebo gel, 30 or 100 μ g of becaplermin, or

good ulcer care alone.

In studies 1 and 2, the incidence of complete healing was significantly higher in patients receiving becaplermin (30 μ g in study 1 and 100 μ g in study 2) compared with that in patients receiving placebo gel. In study 3, which was not powered for statistical analysis, the incidence of complete healing in patients treated with 100 μ g becaplermin gel was approximately twice that of patients treated with good ulcer care alone. In study 4, there was no significant difference in the incidence of complete healing in patients treated with becaplermin gel versus good ulcer care alone.

Becaplermin can benefit patients both by increasing the fraction of ulcers that heal primarily and, in those that do heal, by shortening the average healing time.¹⁸

THE COST EFFECTIVENESS OF BECAPLERMIN THERAPY IN DFU CARE

Five studies evaluated the cost effectiveness of becaplermin in DFU healing. These studies will be summarized in the following sections, but before reviewing the findings of those studies, the basic concepts behind cost-effectiveness analysis will be discussed. The sidebar "Factors Affecting the Cost and Effectiveness of Ulcer Care" on page 7 offers some aspects to consider.

Because of the differences in environment and control, cost efficacy does not necessarily equal cost effectiveness. (Cost effectiveness is the net resource use per unit of outcome achieved in a real world setting. Cost efficacy is the net resource use per unit of outcome in controlled clinical studies.) Costs include cost of materials or technology, labor, and other resources per unit of time. Cost effectiveness assessments are important in circumstances where therapeutic need



outweighs available resources or in clinical decision making when no single modality or intervention has an overwhelmingly superior efficacy over standard or other therapy.

Cost-effectiveness studies take several forms. Direct measurement of actual costs in a series of patients is possible but is not frequently done. Closed claims data can be used for major health expenditures in some circumstances, but indirect costs frequently are not included in these analyses. Alternatively, various modeling systems can be applied using defined actual or theoretical patient populations with projected outcomes based on published data from controlled clinical trials or large patient cohorts. Markov modeling was used in several of the cost-effectiveness studies.¹⁹ This model is useful when risk is continuous over time, when the timing of events is important, and when important events may occur more than once. The model assumes that a patient is always in one of a finite number of discrete health states referred to as “Markov states.” (In a DFU model, for example, states could include uninfected ulcer, infected ulcer, gangrene, healed ulcer, healed ulcer-history of amputation, etc.) Probabilities are then developed that define the likelihood of transition from one state to another.

The model also allows for representation of repetitive events and for simulating the experiences of patient cohorts when sufficiently detailed long-term clinical data is not available. In all circumstances, attention should be given to direct medical and non-medical costs, indirect costs, and intangible costs.

With regard to chronic wound care, the costs of care are assumed to increase as wound severity increases as well as with the presence of infection (cellulitis or osteomyelitis).²⁰ For example, the monthly cost of wound

Factors Affecting the Cost and Effectiveness of Ulcer Care

- Specialized setting of care
 - Experience/knowledge/training of provider(s)
- Type of wound and its chronicity
- Health status of patient/comorbidities
- Concomitant medications that may interfere
- Cost drivers in diabetic lower-extremity ulcer care
- Advanced care modalities that are cost effective
- Timely selection of interventions that address defects in wound microenvironment
- Monitoring/practicing evidence-based medicine
- Cost effectiveness and efficacy of therapies
- Multidiscipline wound care/limb preservation team⁴

care for an ulcer not complicated by infection is \$775.55, compared to the monthly cost of \$2,048.52 for an ulcer complicated by cellulitis and \$3,798.27 for an ulcer complicated by osteomyelitis. In general, hospitalizations represent the most significant contribution (70–80%) to the cost of care. Drug costs generally do not drive total costs.

Using Swedish cost data in 2000, **Persson et al**²¹ developed a Markov simulation model including 6 health states:

1. Uninfected ulcer
2. Infected ulcer
3. Gangrene
4. Healed ulcer
5. Healed ulcer, history of amputation
6. Deceased.

The prediction of clinical outcomes was based on a prospective, 9-month follow-up study of 183 consecutive neuropathic patients from a US cohort treated with good wound care. Cost of treatment data was derived from a cohort of 314 Swedish patients.

The efficacy of becaplermin was assumed to be equal to that reported in the pooled analysis of the 4

randomized, clinical trials of becaplermin submitted for FDA approval (20-week healing rate for good wound care alone = 35%, for good wound care with becaplermin = 47%). Annual treatment costs per patient were estimated using the treatment practice and unit prices from Sweden.

The model for becaplermin administration followed European guidelines, which assumed application to an initially uninfected ulcer with treatment continuing until healing occurred, the ulcer progressed, the patient expired, or a 5-month time limit was reached. Only 1 episode of treatment is approved for use in Europe so that ulcer recurrences are treated with good wound care only. In the model cohort simulated with only good wound care, 30.4% of patients healed from the initial ulcer within the first 5 months. In the becaplermin-treated cohort, 42.1% healed from the initial ulcer during the 5-month treatment phase. The increase in the healing rate translated into a 24% increase in the number of ulcer-free months and a decline in the amputation rate by



Table 1: Estimated Cost Effectiveness of Treatment Models

	GWC	GWC in WCC	Becaplermin	Platelet Releasate
Effectiveness at 12, 20 wks	30.9% (26.6, 35.1)	35.6% (34.8, 36.4)	43.0% (37.3, 48.7)	36.8% (35.4, 38.2)
Incremental cost of increasing odds of healing by 1% over GWC			\$36.59	\$414.40

Results of a comparison of good wound care (GWC), good wound care in a wound care center (GWC in WCC), treatment with becaplermin, and treatment with platelet releasate. Effectiveness was estimated at 12 and 20 weeks.²³

9%. These health gains translated into cost savings over 12 months. The expected costs of US \$12,078 for an individual treated with good wound care alone decreased to \$11,708 with becaplermin including the cost of \$1,262 for becaplermin. The conclusion of the authors was that treatment of DFUs with good wound care and becaplermin was less expensive than treating with good wound care alone in Sweden, even when various model parameters were altered.

Ghatnekar et al repeated the model described above in 2001, assessing the cost effectiveness of becaplermin in 4 European countries with somewhat different cost models.²² In this model analysis, over the course of 1 year, becaplermin plus good wound care increased the ulcer-free interval by 24% and reduced amputation risk by 9% compared to good wound care alone and produced a net cost savings in Sweden (\$370–\$384), Switzerland (\$279), and the United Kingdom (\$468). In France, the addition of becaplermin added US \$19 to the cost of each ulcer-free month obtained. The model also demonstrated substantial intercountry differences in treatment practices contributing to the costs of treating DFUs.

In 2001, **Kantor and Margolis** estimated the cost effectiveness of com-

mon treatment models for DFUs using data from published clinical trials and meta-analyses and the Curative Health Services database of more than 26,000 patients with diabetic neuropathic foot ulcers seen in wound care centers.²³ Cost data were expressed in 1999 US dollars. Four options were determined to be available for treatment:

1. Standard care
2. Standard care in a specialized wound care center
3. Treatment with becaplermin
4. Treatment with platelet releasate.

The results of the analysis are shown in Table 1.

Baseline effectiveness (with 95% confidence intervals) for good wound care, becaplermin, platelet releasate, and good wound care in a wound care center were 30.9% (26.6, 35.1), 43.0% (37.3, 48.7), 36.8% (35.4, 38.2), and 35.6% (34.8, 36.4), respectively. Cost-effectiveness ratios for platelet releasate versus good wound care and becaplermin versus good wound care were 414.40 and 36.59, respectively. The resulting incremental cost of increasing the odds of healing by 1% over standard therapy was \$414.40 for platelet releasate and \$36.59 for becaplermin. Platelet releasate, becaplermin, and good wound care in a wound care center all provided improved

healing rates over standard care. Becaplermin was less expensive and more effective than platelet releasate after 20 weeks of care.

In 2002, **Albert** reported an informal analysis of 10 patients (all men with a mean age of 61.7 years, a mean ulcer duration of 6.34 months, and a mean ulcer volume of 0.45cm³).²⁴ Patients were treated in a VA Medical Center, and costs were determined for each intervention or therapy. Eight of 10 patients healed completely with becaplermin treatment for an 80% rate of effectiveness. One patient who had been projected to heal was lost to follow-up. Average healing time with becaplermin therapy was 8.875 weeks (range 2–21 weeks), compared to an average of 30.375 weeks on previously unsuccessful therapies. Becaplermin treatment costs, on average, were \$1,113 less than traditional therapies (Figure 3).

Sibbald et al evaluated the cost effectiveness of adding up to 20 weeks of becaplermin to standard wound care²⁵ using a 1-year decision analytic model based on data from a previously controlled clinical trial completed in Canada.²⁶

To evaluate the cost effectiveness of adding up to 20 weeks of becaplermin to a regimen of best clinical care, a 1-year decision-analytic model was developed and



tested using data from a previously published controlled clinical study involving 251 people with diabetes (124 becaplermin/127 control) and adequate vasculature presenting with an infection-free ulcer that had failed to heal despite appropriate therapy.

A 20-week healing rate was estimated based on the clinical trial data assuming becaplermin treatment was terminated at 10 weeks in nonresponding ulcers, and follow-up data were extended to 1 year. Resource utilization was estimated by an expert panel using a modified Delphi approach. Using the model, it was found that incorporating becaplermin with best clinical care resulted in 26 fewer ulcer-days per patient per year compared to best clinical care alone with an incremental cost-effectiveness ratio of \$6 per ulcer-day averted. The net result was \$156 saved per year for becaplermin-treated patients. Results were sensitive to becaplermin cost, efficacy, and effect on infection and recurrence rates.

The key is to understand how to place this knowledge into daily practice and make it clinically meaningful. This can be done by practicing evidence-based medicine and understanding the many factors that affect the cost of care. It is now known that many factors influence the outcome of wound care, especially the setting of care, including the practice patterns, experience, and knowledge of the provider and the timely selection of proper interventions.

CONCLUSIONS

While diabetes and subsequent DFUs are common and costly, the use of becaplermin results may be an overall cost savings in the treatment of DFUs. Growth factor therapy is an effective strategy for wound management in a high-risk patient population. It should be considered

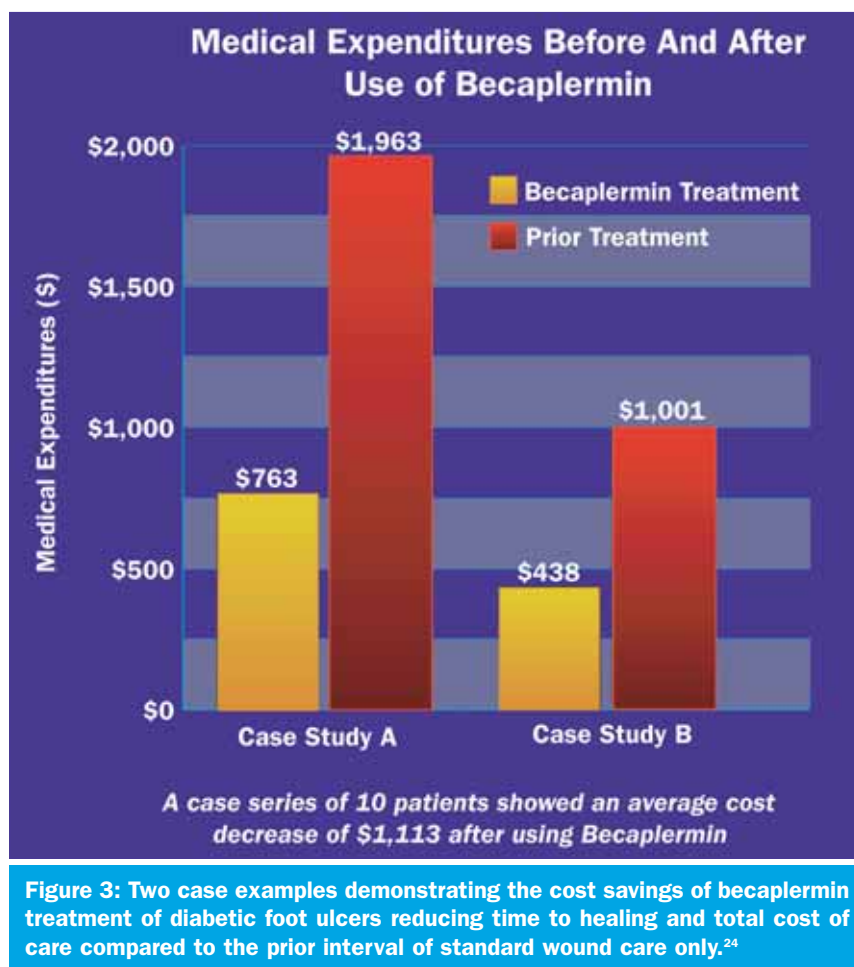


Figure 3: Two case examples demonstrating the cost savings of becaplermin treatment of diabetic foot ulcers reducing time to healing and total cost of care compared to the prior interval of standard wound care only.²⁴

early in the treatment pathway of DFUs to help prevent a chronic wound, infection, or amputation. It is clinically and economically beneficial to prevent and aggressively treat ulcerations and infections. If therapy is aggressive and effective, we may be able to prevent patients from needing costly hospitalizations and unnecessary amputations.

Hospitalization and infections are key cost drivers in wound care. Drug costs do not impact cost-effective ratios the way adverse outcomes do. Advanced therapies in wound care have short-term expense yet long-term gain. It is important to consider advanced therapies and modalities in chronic wound care because physicians know that a prevented ulcer does not become infected, a prevented

infection does not require hospitalization, and a successfully treated infection will not require amputation. Also, shorter ulcer duration yields less exposure to infection.

The primary goal of fewer infections will yield large savings from fewer hospital days and fewer admissions. Therapies that promote rapid and complete healing and reduce the need for expensive surgical procedures would impact these costs substantially. This review suggests that becaplermin, when added to standard care, may be more cost effective for the treatment of chronic DFUs than standard care alone, despite its higher initial dollar cost. This finding may be attributed to a combination of factors.

First, expenses incurred in more prolonged treatment, such as office



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visits and the need for additional dressings, can be avoided when healing is completed in a shorter period. Second, rapid and complete ulcer healing may reduce the incidence of significant morbidities (such as amputation or infection) and premature mortality. Consequently, the financial burden associated with these complications would be reduced. Finally, the value of improved quality of life in patients with healed ulcers and the reduction in financial burden for patients who return to work cannot be ignored. ■

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Test Questions

1. Diabetic foot ulcer healing is uniquely impacted by:

- a. Altered host immune response to increased bacterial bioburden
- b. Altered angiogenic response to injury
- c. Altered protein expression in response to injury
- d. Altered patterns of cellular proliferative capacity in response to injury
- e. All of the above

2. Essential components in the minimum standard care for patients with diabetic foot ulcers include all of the following except:

- a. Plantar offloading or absolute non-weightbearing
- b. Correction of large vessel lower-extremity arterial occlusive disease
- c. Immediate application of advanced wound care technologies (eg, growth factor therapy, bioengineered tissue grafts, negative pressure wound therapy, hyperbaric oxygen, etc)
- d. Initial surgical debridement with repetitive debridements as indicated
- e. Treatment of active local infection

3. Wound bed preparation and debridement is essential in optimizing the beneficial effects of exogenous topically applied growth factor therapy.

- a. True
- b. False

4. Randomized, controlled clinical trials of the topical application of becaplermin to diabetic foot ulcers have demonstrated all of the following except:

- a. Statistically significant increased incidence of complete ulcer healing compared to placebo gel



- b. Greater incidence of ulcer recurrence compared to placebo gel
- c. Improved effectiveness of topically applied becaplermin when ulcers were frequently as opposed to rarely debrided
- d. No significant local adverse reactions in the becaplermin groups
- e. Correlation of wound response to treatment at 10 weeks with final closure

5. Several cost-effectiveness studies have demonstrated that topically applied becaplermin added to a regimen of standard diabetic foot ulcer care is cost effective when compared to standard care alone.

- a. True
- b. False

6. All of the following are associated with an increase in the risk of diabetic foot ulceration except:

- a. Obesity

- b. Current smoking
- c. Marital status
- d. Insulin dependence
- e. Presence of neuropathy

7. Osteomyelitis as a complication of delayed healing of diabetic foot ulcers is a significant contributor to lower-extremity amputation.

- a. True
- b. False

8. All of the following are true of cost effectiveness except:

- a. Cost effectiveness is the net resource use per unit of outcome achieved in a real world setting
- b. Cost effectiveness can be assessed by direct measurement of actual costs or by modeling studies
- c. Costs included in cost-effectiveness studies generally include direct and indirect costs
- d. Cost effectiveness is always equiva-

lent to cost efficacy

- e. Markov modeling is used in cost-effectiveness studies when the risk is continuous over time

9. In chronic wound care, costs are assumed to increase as wound severity increases and with the presence of infection.

- a. True
- b. False

10. Becaplermin may contribute to cost-effective diabetic foot ulcer care by:

- a. Healing more ulcers
- b. Providing more ulcer-free days
- c. Earlier closure reducing the risk of developing deep infection or osteomyelitis
- d. Reducing the frequency of subsequent amputations
- e. All of the above

Evaluation

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Please fill in your responses below to the questions on pages 10 and 11:

- 1. a. b. c. d.
- 2. a. b. c. d. e.
- 3. a. b.
- 4. a. b. c. d. e.
- 5. a. b.
- 6. a. b. c. d. e.
- 7. a. b.
- 8. a. b. c. d. e.
- 9. a. b.
- 10. a. b. c. d. e.

Course Evaluation: rate on a 1-5 scale

5 = Strongly Agree 4 = Agree 3 = Neutral 2 = Disagree 1 = Strongly Disagree

- 1. The stated learning objectives were met _____
- 2. Faculty was knowledgeable on the subject matter _____
- 3. Content was objective _____
- 4. Content was balanced _____
- 5. Content avoided commercial bias or influence _____
- 6. Content was timely and related to my practice _____
- 7. Content will assist me in enhancing patient care _____
- 8. Information presented will improve my practice/patient outcomes _____
- 9. What other topics would be of interest to you? _____

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