Lower Extremity Major and Minor Amputations in the High Risk Patient

These procedures come with high morbidity and mortality rates.

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Partial lower limb amputation is a common outcome in the high risk patient with lower extremity chronic ulcerations, ischemia, and infection. The significant decline in the quality of life and economic burden caused by lower extremity infections leading to amputations in the high risk population warrants further study in order to better understand the elements that improve limb viability and the causal factors related to major limb loss (below or above the knee).[1]

The unfortunate pathway to amputation in the high risk patient with a lower limb ulceration or infection can be caused by major and minor etiologies, mainly diabetes and peripheral arterial disease (PAD). The literature recognizes that approximately 80%-85% of non-traumatic amputations are preceded by lower extremity ulcers.[2,3]

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Complications of non-healing wounds increase the longer the wound is present. Factors leading to the chronicity of a wound are variable and must be constantly evaluated and treated to promote wound healing. For example, patients with ischemic wounds may require revascularization to restore proper blood flow to heal.

Diabetic neuropathic ulcers resulting from increased pressure due to osseous deformities may require a variety of podiatric surgical interventions, conservative methods to offload the area, such as total contact

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casting, or advanced wound healing therapies. Of note, only three products are approved by the Food and Drug Administration (FDA) to treat diabetic foot ulcers (Figure 1).

Topical Wound Healing Agents

Apligraf and Dermagraft are both bio-engineered skin substitutes (by Organogenesis) and Becaplermin (Regranex) is a recombinant platelet-derived growth factor (PDGF) applied topically as a gel.[4,5] The forecast for other diabetic foot ulcer treatments is promising, with multiple products currently in clinical trial (Figure 1).

Topical wound healing agents likely to be available within the next five years include: Aclerastide by Derma Sciences (angiotensin analog NorLeu3-A[1-7] with the active pharmaceutical ingredient DSC127), Trafermin by Olympus Biotech (recombinant human basic fibroblast growth factor engineered using Escherichia coli), and CureXcell® by Macrocure (activated leukocyte suspension).[4,5] The two first topical antibacterials are also likely to be on the market within the next five years: Locilex™ by Dipexium Pharmaceuticals (Pexiganan acetate cream 1%) and Cogenzia by Innocoll (gentamicin collagen sponge).[5]

In the more distant future, gene encoding growth factors via viral vectors, cytokine inhibition, topical neuropeptides, and stem cell-based therapies may be available.[4] Unfortunately, the cost of the aforementioned wound care products (old and new) is high and, without consistent off-loading and debridement, failure of the products is likely, and the risk for partial limb amputation remains.[4]

Common Complications

Common complications affecting diabetic and ischemic patients are chronic and poor healing lower extremity ulcers, soft tissue and bone infections requiring a plethora of clinical outpatient visits, multiple hospital admissions for intravenous (IV) antibiotics, use of expensive adjunctive treatments (i.e., hyperbaric oxygen therapy and negative pressure wound therapy), and surgical procedures that often lead to non-traumatic lower extremity amputations. Approximately 185,000 lower limb amputations occur in the United States of America annually, with the majority (54%) performed to treat peripheral arterial disease (PAD) with or without diabetes.[6,7] Diabetes has recently reached pandemic status with approximately 387 million people worldwide suffering from the disease and 4.9 million deaths in 2014 caused directly by diabetes.[8,9] It is estimated that in the United States, 29.1 million people (or 9.3% of population) have diabetes, with 21 million being diagnosed and 8.1 million being undiagnosed.[10]

It has been estimated by the United States government that approximately two out of every five Americans will develop type 2 diabetes at some point during their adult lives.[10] These statistics correspond with high expense, with costs in the United States reported in 2014 to be around $612 billion (see Figure 2).[9] Chronic diabetes causes peripheral arterial disease (PAD) and sensory neuropathy, a combination that leads to ulcers, diabetic foot infections, and often the need for lower extremity amputation.[11]

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FIGURE 1:

Diabetic Foot Ulcer Wound Care Products[4,5]

FDA approved:

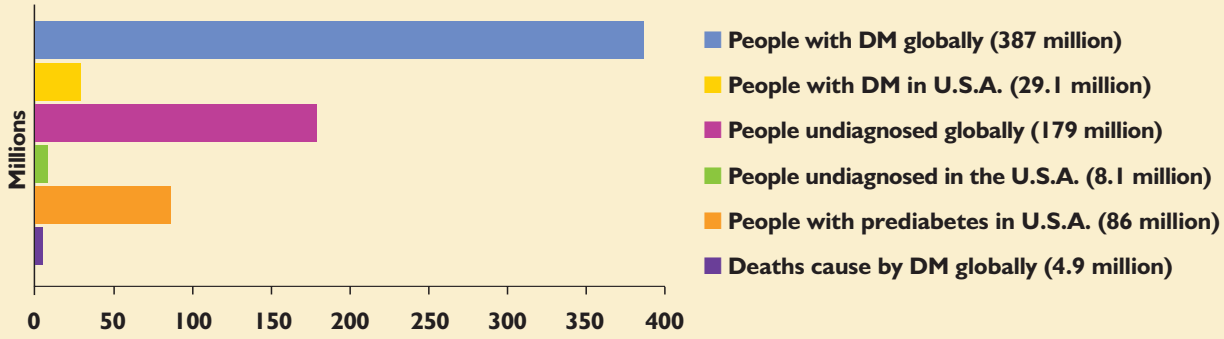
Regranex/Becaplermin (by Smith & Nephew) Pharmacologic wound healing agent	Recombinant platelet-derived growth factor (PDGF)
Apligraf® (by Organogenesis) Bioengineered bi-layered skin substitute	Cultured cells from neonatal foreskin and bovine type I collagen
Dermagraft® (by Organogenesis) Bioengineered skin substitute	Human neonatal dermal fibroblasts

Clinical trials in progress:

Aclerastide (by Derma Sciences) Wound healing agent	Angiotensin analog NorLeu^3-A(1-7), active pharmaceutical ingredient DSC127
Trafermin (by Olympus Biotech) Wound healing agent	Recombinant human basic fibroblast growth factor engineered using Escherichia coli
CureXcell® (by Macrocure) Wound healing agent	Activated leukocyte suspension
Locilex™ (by Dipexium Pharmaceuticals)	Pexiganan acetate cream 1%
Cogenzia (by Innocoll)	Gentamicin collagen sponge

FIGURE 2:

Diabetes Statistics[9,10]



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About 50% of patients who have foot amputations die within five years, which is a worse mortality rate than most cancers.[12] It has been reported that 55% of diabetics with a lower extremity amputation will require amputation of the contralateral leg within two to three years.[13] Foot ulcers are expensive to treat, with uncomplicated diabetic foot ulcers costing up to $8,000 and infected foot ulcers up to $17,000.[14] If amputation is required to resolve the ulcer, the cost skyrockets to $45,000.[14]

In 1998, a large study obtained the hospital discharge records for all veterans hospitals to examine the epidemiology of lower extremity disease in veterans with diabetes.[15] It was found that only 16% of the population was comprised of diabetics; however, half of all patients hospitalized due to lower extremity ulcerations had diabetes.[15] A more recent study from 2012 stated that 20% of veterans using the Veterans Health Affairs Hospitals are affected by diabetes (or more than one million veterans at any given time).[16] The 1998 study showed that 10,532 hospital discharges consisted of diabetics with ulcerations.[15] 34% of peripheral vascular disease procedures and 64% of amputations were performed on patients with diabetes.[15]

Vascular Disease as an Etiology

82% of vascular-related lower extremity amputations in the United States are associated with diabetes; however PAD, with or without diabetes, is another leading cause of lower extremity amputation.[17-19] PAD is a progressive disease and leads to Critical Limb Ischemia (CLI) in its most advanced form.[19] The global prevalence of PAD is overall 3%-10% with an increase to 15%-30% in age groups greater than 70 years old, and is even greater in the diabetic population.[19] Of patients with CLI, 50% will require revascularization and 25% will require amputation.[19]

Initial work-up for PAD is prompted by risk factors (i.e., smoking history, claudication, diabetes, lower extremity ulceration, etc.).[20] Non-invasive vascular studies, using ankle brachial index (ABIs) and pulse volume recordings (PVRs), may or may not indicate an occlusive lesion.[20] If a lesion is suspected, it must be localized, usually through conventional angiogram.[20]

Revascularization is then completed if adequate vessels or collateral vessels are seen proximal and distal to the occlusion via open surgery versus endovascular surgery.[20,21] The gold standard is open revascularization,

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which surpasses endovascular procedures in terms of durability and reduced re-occurrence. For this reason, if a patient is expected to live beyond two years, open revascularization is generally recommended.[21] However, endovascular surgery does hold an important place in modern practice due to reduced surgical complications and faster recovery rates, and is often chosen over open revascularization for this reason.[22]

Vascular surgical procedures, although often initially successful, frequently fail over time. According to one study, limb loss with a patent bypass is reported to be only be 4%-9% effective.[23] However, within the amputation group, the incidence of amputations performed with a patent bypass is higher (up to 50%) in certain patient subgroups, including those with diabetes mellitus, end stage renal disease, and limited runoff.[23] This goes to show that despite vigorous efforts by the medical and surgical teams, these high-risk patients may go on to limb loss, as this is the natural progression of the disease.

The vast economic burden of the aforementioned is projected to worsen as time goes on and the rate of diabetes increases. However, modern-day limb preservation team services have been shown to reduce costs associated with foot ulcers.[3,14,24]

A Multidisciplinary Team Approach

A multidisciplinary team approach to treatment of the diabetic foot could lead to avoidance of 47% of amputations.[3] Higher cost in treatment of wound care is associated with ulceration, infection, hospitalization, and amputation. Therefore, prevention is cost-effective.[14] However, early referral is needed for prevention to be successful.[14]

Unfortunately, within the United States, limb preservation teams are habitually consulted late in the disease process, after foot infections have caused significant pathology, which commonly results in necessity of partial foot or limb amputation.[3] Distal lower-limb amputations (i.e., partial or complete toe amputation, partial ray amputation, total ray amputation, Lisfranc joint amputation, trans-metatarsal amputation (TMA), Chopart joint amputation, sub-total calcanectomy, etc.), when unavoidable, are performed to treat severe wound pathology and are considered to be advanced limb salvaging procedures, as they can prevent the need for partial leg amputation, if successful.[25]

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Partial Leg Amputations

Partial leg amputations are major surgeries and include below-knee amputation (BKA) and above-knee amputation (AKA) and come with higher mortality and morbidity rates as compared to the limb salvaging amputations. Before choosing a type of amputation procedure, the surgeon must evaluate the entire clinical status of the patient including but not limited to nutrition, kidney function, blood glucose control, cardiac reserve, neuropathy, and anemia. A complete evaluation of the patient's ulcer must be done, which includes imaging studies (i.e., x-rays, magnetic resonance imaging (MRI), computed tomography scan (CT scan)), possible bone biopsy if osteomyelitis is suspected, debridement, post-debridement wound culture and sensitivity (with gram stain), and infectious disease specialists should be consulted, if necessary.[24]

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Non-invasive vascular studies should be completed when evaluating all patients with chronic non-healing ulcerations and vascular surgery should be consulted in the setting of PAD.[24] Arterial blood flow must be restored prior to debridement or amputation for a successful outcome. If arterial flow cannot be reconstituted via open bypass or an endovascular approach, a BKA or AKA may be the necessary amputation of choice. If the patient does have adequate blood flow, the surgeon will evaluate the extent of the infectious process and amputate at the appropriate level.

For example, in the setting with minimal involvement of a toe, a partial toe amputation may be warranted. Although less may seem more appropriate, there are times when amputating further proximally and removing unaffected toes is warranted (such as TMA) due to biomechanical benefit. For example, if a patient has gangrene of digits 1, 2, and 4, the patient may benefit from a TMA over amputation of the affected digits alone.

Overall, the long-term outcomes of major amputations have been suggested to include a five-year survival rate of 30%-40%.[26] The long-term outcomes of minor amputation is debatable due to the lack of literature, but one study suggests a survival rate of 89.3% at one year and 43.5% at five years.[27] Although good outcomes

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are common, distal minor amputations in the high-risk patient population often lead to the need for more proximal amputation, with one study reporting the need of almost 42.4% of partial 1st ray amputees going on to a more proximal amputation within an average time of 25 months.[28] Surgical amputation gives the benefit of treating the patient's infection or chronic foot ulcer immediately and, if the surgery is successful, many patients do very well with custom shoes and/or prostheses.

Lower limb amputation to treat foot ulcers with infections and/or ischemia remains a real problem.

Delaying treatment within high-risk patient populations often leads to amputation, which may cause potential decreased patient quality of life and definitive loss of millions of dollars in healthcare costs. Despite this, surgery does not come without risk. In general, any amputation holds the risk of infection, bleeding, severe pain, phantom pain, significant edema, nerve damage, wound dehiscence, and death. Minor amputation (i.e. partial foot amputation) holds a significantly lesser risk than major amputation (i.e. partial leg amputation) and this must be considered. Patient selection is very important.

Frail patients with end-stage renal disease may not live through a major amputation (or even a minor amputation for that matter) and thus all benefits versus risks should be identified in order for the patient to have the best outcome and quality of life.

VHA Directive

The structure of the medical data storage and the large relevant veteran patient population with moderate- and high-risk disease for limb loss presents a unique opportunity to collect real world data and accurately examine the outcomes. This will eventually allow for developing an improved standard of care model that can decrease major amputations and improve the durability of distal limb-preserving procedures.

Amputation prevention has received increased attention in the Veterans Health Administration (VHA) over the years. In 1993, a special VHA directive established the Preservation Amputation Care and Treatment Program, mandating a multidisciplinary team at each facility to track every patient with amputations and those at risk for limb loss.[15] As part of this directive, discharge records contained in the Patient Treatment File from all VHA hospitals between 1989 to 1998 were analyzed to determine the overall effect of the program. The total number of discharges with amputations over a 10-year period declined by 80 discharges per year.[15]

This directive is ongoing and currently is due to expire in August of 2017. Despite this, lower limb amputation to treat foot ulcers with infections and/or ischemia remains a real problem. Although the amputation rate has decreased, it is important to study the outcomes of patients who have already undergone both distal minor limb preserving amputations and proximal major amputations. There is a lack of research in this area, and these data may direct an improved standard of care and help us understand what impacts the durability of distal limb procedures.

A principal investigator-initiated retrospective chart review of amputations has been developed at the VA and focuses on major and minor surgical amputation types of the lower extremity to treat infections (i.e., osteomyelitis, soft tissue emphysema, necrotizing fasciitis, gangrene, chronic non-healing ulcer) mainly secondary to diabetic mellitus and/or peripheral arterial disease (PAD)/critical limb ischemia at the PVAMC. **PM**

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