DIABETES & DIABETIC FOOT ULCERS

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INTRODUCTION

Diabetes Mellitus (DM) represents a group of metabolic disorders resulting in both glucose over production, peripheral underutilization or both ultimately leading to hyperglycemia, glycosuria, and severe cases intermittent ketoacidosis. According to the Centers for Disease Control (CDC), DM was the 7th leading cause of death in 2016.[1] The incidence of DM is predicted to increase by 165% between the years 2000-2050.[2] According to the World Health Organization (WHO), the global diabetic population has risen from 108 million in 1980 to 422 million in 2014.[3]

Diabetic foot ulcer (DFU) prevalence is as high as 25% and it is estimated that approximately 40-80% of DFUs become infected.[4] The economic burden of DFU costs Medicare $9-13 billion/year.[5] A 10-year prospective study on DFU and mortality, found that a history of diabetic ulcerations could be a significant predictor of mortality.[6] Patients who had a record of DFU's revealed a 49% increased risk of mortality when compared to patients with diabetes with no DFU's in their past medical history.[6]

DIABETES & DIABETIC FOOT ULCERATIONS

DM is a complex, chronic disorder of carbohydrate, fat, and protein metabolism. Acute manifestations are primarily caused by decreased glucose uptake, increased protein catabolism and lipolysis. Environmental and genetic risk factors can trigger a cascade of autoimmune reactions, immunosuppression, and induce metabolic stress.

The American Diabetes Association (ADA) classifies DM into the following general categories: type 1 & 2, gestational diabetes and other specific types of DM caused by other factors **(Figure 1).**[7] DM is generally diagnosed based on the following plasma glucose tests; fasting plasma glucose (FPG), 2-h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT), or A1C criteria **(Figure 2)**.[7]

Figure 1. American Diabetes Association diabetes mellitus classification. Adapted from the American Diabetes Association 2017.[7] DM= diabetes mellitus

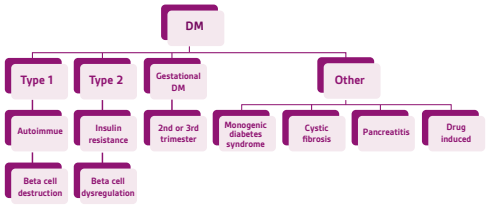
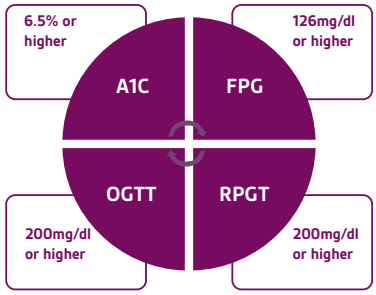


Figure 2. American Diabetes Association criteria for the diagnosis of diabetes mellitus. Adapted from American Diabetes Association 2017.[7] FPG= Fasting plasma glucose; OGTT= Oral glucose tolerance test; RPGT= Random plasma glucose test



Normal glucose homeostasis is regulatedby three biochemical processes: gluconeogenesis, uptake and utilization of glucose by peripheral tissues of the body, and insulin secretion via the pancreas. The main function of insulin is to increase the rate of transport of glucose from the bloodstream into various cells of the body such as striated muscles. In type 2 DM, metabolic stress can dysregulate Beta-cell function and violate the intrinsic homeostatic and hormonal mechanisms that control serum glucose levels causing a permanent state of hyperglycemia.[7] The liver behaves in a gluconeogenic unregulated manner producing excess glucose. The pancreas responds to the chronic hyperglycemic state with a perpetual influx of insulin. Ultimately, causing Beta cell dysregulation and insulin resistance.[7]

The pathogenesis is more established and definitive in type 1 diabetes than in type 2 diabetes.[7] It is now evident that immediate family members of patients with type 1 DM presenting with two or more autoantibodies is an almost certain predictor of DM.[7] It should be noted that the rate of progression of type 1 DM is dependent on multiple factors; detection of antibodies, number of antibodies, antibody specificity and antibody titer. It should be noted that A1C and glucose levels rise prior to the clinical onset of DM.[7] Current treatment modalities have been insufficient to stop the progressive trajectory of this metabolic syndrome and prevent the development of

chronic diabetic complications. One potential explanation is that the diagnosis of diabetes is primarily based on measurement of only one metabolite (glucose).[7-9]

"Pre-diabetics" also pose a major concern. The Centers for Disease Control and Prevention (CDC) estimates approximately 86 million Americans are considered to be pre-diabetic.[10] It should be noted that pre-diabetic patients may not present with clear symptoms. This manifestation is also known as impaired fasting glycaemia, is typically diagnosed when with an A1C of 5.7% – 6.4%, fasting blood glucose of 100 – 125 mg/dl, or an OGTT 2-hour blood glucose of 140 mg/dl – 199 mg/dl.[7] Studies have revealed that there is a 50% risk over 10 years of progressing to type 2 DM.[8] However, many newly identified pre-diabetic patients can progress to DM in less than 3 years.[7;8] Pre-diabetic patients can lower their risk for type 2 DM by 58% by losing 7% of their total body weight and exercising moderately 30 minutes a day, five days a week.[11]

FOOT ULCERS IN PATIENTS WITH DIABETES (DFU): A POTENTIALLY DEVASTATING COMPLICATION OF THE DISEASE

Patients with DM and neuropathy are at risk of developing ulcerations.[12] Distal symmetrical polyneuropathy (DSPN) is the more common form of DM neuropathy that generally affects the toes and distal foot but has the tendency to progress proximally in a stocking distribution.[12] A chronic hyperglycemic state causes sensory nerve hypoxia (within the endoneurium) thus altering their electrical stability leading to nerve damage.[12] There is increasing evidence that oxidative stress is triggered by increased free radical formation due to impaired glucose metabolism itself and/or deficits in antioxidant defense.[13] Patients that suffer with diabetic neuropathic pain (DNP) characterize their symptoms as burning, tingling, sharp and shooting sensations.[12] The pain could be a major culprit to the withdrawal of social and reactional activities and has been associated with depression.[12;13]

In addition to neuropathy, DFU's are a form of chronic wounds that fail to heal due to several key factors: ischemia, decreased angiogenic response systems, endothelial dysfunction and increased susceptibility to wound infection.[14] Hence, these wounds are classified into three distinct subtypes: neuropathic, ischemic, or neuro-ischemic **(Figure 3)**. Approximately, 50% of DFU's are neuropathic, 35% are neuro-ischemic and about 15% are ischemic.[15] Having a solid understanding of these variants will help dictate treatment pathways and optimize patient outcomes. Increased blood glucose levels activate a series of events that trigger an accumulation of lipid deposits within the arterial network of large and small vessels.[16] This can lead to stroke, myocardial infarction, and inadequate perfusion to the lower extremity.[16] Peripheral arterial disease (PAD) can predispose these patient populations to sores, skin ulcerations, or gangrene **(Figure 4)**.[6;17]

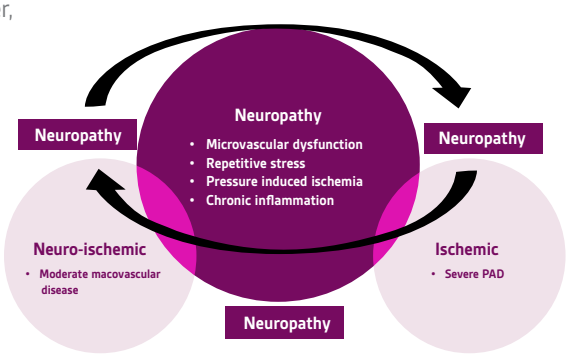


Figure 3. DFU Neuropathy VENN Diagram.
DFU = Diabetic Foot Ucler
PAD = Peripheral arterial disease

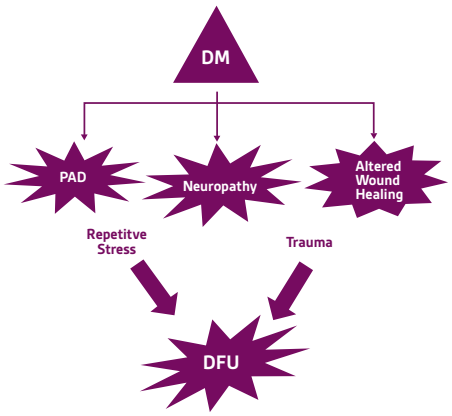


Figure 4. Pathophysiology of diabetic foot ulcers. Adapted from Snyder et al 2010 and Snyder et al 2009[6,17] DM= diabetes mellitus; PAD=Peripheral arterial disease; DFU= diabetic foot ulcer.

ASSESSMENT AND EVALUATION OF DFUs:

Management of DFU's is multifaceted and entails a systematic approach for optimal patient outcomes. For both outpatients and inpatients with a DFU or infection, medical establishments should attempt to provide a well-coordinated approach by utilizing a multidisciplinary diabetic foot care team. A comprehensive evaluation for patients with diabetes encompasses several criteria: the vital components include: a thorough history and physical examination, laboratory screening, and a lower extremity focused neurologic, musculoskeletal and vascular assessment.[17] Determining the ratio of systolic blood pressure in the ankle to the systolic blood pressure in the brachial artery (ABI) operating a sphygmomanometer and a hand-held Doppler machine is a simple, reliable, noninvasive, bedside procedure to assess for peripheral arterial disease.[17] However, there are patient populations with diabetes that may display falsely elevated ABI's secondary to medial arterial sclerosis.[17] In this scenario, a toe brachial index (TBI) should be administered since the pedal arterial network is not at risk of medial arterial sclerosis.[17]

If infection is present, the Infectious Disease Society of America recommends obtaining cultures prior to starting empiric antibiotic therapy.[18] Cultures should be taken from deep tissue via curettage, utilization of the Levine Technique or biopsy after the wound has been irrigated and debrided.[18] However, samples should only be obtained if the ulcer appears clinically infected or the patient is not responding to empiric therapy.[18] Infection should always be suspected in any foot wound in a patient with diabetes. However, it should be noted that diabetics and immunocompromised patients may exhibit only subtle or no signs of infection.[18] Evidence of infection generally includes classic signs of inflammation (redness, warmth, swelling, tenderness, or pain) or purulent secretions, but may also include additional or secondary signs (eg pain in an otherwise painless foot, wound deterioration, non-purulent secretions, friable or discolored granulation tissue, undermining of wound edges, and/or foul odor).[18] A positive probe-to-bone (PTB) test may be a clinical marker for osteomyelitis (OM) and should raise suspicion that this entity exists.[19] Although,

bone histopathology and culture studies are the gold standard for the diagnosis of OM, the resources or expertise to perform these invasive procedures are typically unavailable in general medical settings.[18] Therefore, many clinicians opt to utilize other diagnostic markers such as the PTB test. Magnetic resonance imaging (MRI) is considered the most effective imaging technique for detecting infections in bone and soft tissue.[17] Other tests may include Ceretec or Indium white blood cell scans.[17] While a triple phase bone scan lacks specificity, it may be used in conjunction with these test for dual peak imaging.[17]

BIOFILM COMPONENT:

Diabetic foot ulcerations are colonized by numerous bacterial communities. The concomitant factors of patients with diabetes with neuropathy increases the risk of the skin damage promoting bacterial colonization. The frequent bacterial genera that have been associated with the DFU ecosystem remain polymicrobial and commonly include staphylococcus, streptococcus, pseudomonas, Corynebacterium, enterococcus, Acinetobacter, porphyromonas, and other subgroups of the enterobacteriaceae family.[20] These deleterious networks have the potential to rapidly progress into deeper tissues causing increased complications.

Primary empiric therapy needs to be implemented based on the severity of the infection and all microbiological data, such as recent culture results and the local prevalence of pathogens, especially antibiotic-resistant strains.[20] In recalcitrant lesion's rapid PCR genetic testing has been the favored over traditional culture techniques.[20] Molecular analytic testing has not yet been able to differentiate biofilm from planktonic bacterial species.[20] However, molecular studies give the clinician a better understanding of the poly-microbial ecosystem versus standard culture techniques.[20]

The exact pathogenesis of the DFU microbiome is not well understood. However, bacterial biofilm formation seems to play an integral factor in the recalcitrant nature of these wounds. Biofilm consists of a self-generating extracellular matrix (ECM) of robust extra polymeric substances (EPS) that have the ability to irreversibility attach to various parts of the wound bed.[20] As these microbial cells begin to multiply and differentiate, their gene expression rapidly evolves in order to promote their survival. This process is known as quorum sensing.[20] This phenomenon makes these biofilm communities resistant to host immune responses and increased resistance to antimicrobial therapies. Malone et al determined that the prevalence of biofilm in chronic wounds was 78.2%.[21] There is a growing consensus that biofilms play a pivotal role in delaying keratinocyte migration and tissue granulation.[20] This has placed a greater emphasis on correctly diagnosing and managing biofilm associated chronic wounds. There is currently no diagnostic modality that helps us understand which biofilms are protective and which are virulent in nature. A biofilm should be clinically suspected when the following symptoms include: thick, tenacious fibrin slough that is non-responsive to sharp debridement or a friable- hyper-granular wound base.[22]

CLASSIFICATION SYSTEMS

The increased value of incorporating a classification guideline in the clinical setting cannot be overstated. Over that past several years, numerous foot-ulcer classification methods have been proposed, however, none of the proposals have been universally accepted. Currently, the two most implemented classification systems include: the Wagner and University of Texas (UT).[17] The Wagner system stratifies ulcers primarily on depth and the presence of osteomyelitis or gangrene by using a numeric grading method.[17] Vascular disease and the extent infection are not well defined in the Wagner system.[17] For instance, superficial wounds that are ischemic or infected cannot be adequately stratified in this classification system.[17]

The UT system improved on the limitations of the Wagner system by grading ulcers by depth and then staging them based on the absence or presence of ischemia and infection.[17] They incorporated a grading matrix scored 0 to 3 and scales (scored A to D) to assess ulcer depth along with the presence of lower extremity ischemia and wound infection.[17] This system allows clinicians to identify infection and vascular disease as independent factors (despite ulcer depth). However, the UT system fails to stratify the degree of vascular insufficiency.[23] A critical question for the specialist is to assess the potential benefit from a successful revascularization procedure which is an essential factor for successful limb preservation.[23]

Validated classification protocols such as the IDSA or wound, ischemia and foot infection (WIfI) classification systems should be used as a reference point in order to help stratify infections and to help define the severity of concerning cases.[23] In 2014, The Society for Vascular Surgery devised a stratification system for threatened lower limbs, grading and categorizing 3 vital risk factors that could potentially lead to amputation.[23] The benefit of utilizing the WIfI classification system is that it systematically classifies heterogenous populations with limb-threatening conditions by incorporating many of the preceding guidelines.[23] It should be emphasized that when classifications systems are used appropriately, it is a stride forward for quality reporting and patient data aggregation provided the ulcer metrics are consistent.

TREATMENT OF DFUs

Routine management strategies rely heavily on proper wound bed preparation (WBP). By establishing a proper wound environment, advanced products are able to optimize the wound-healing cascade. The DIME model starts by addressing all patient concerns and the underlying comorbidities **(Figure 5)**.[24] This methodical process calls for extensive WBP in order to accelerate endogenous healing and eliminate any factors that prevent the wound-healing cascade to take its natural course.[24] Snyder et al found if a DFU has not reduced by half its percent area reduction the first 4 weeks of care, it is wise to re-evaluate the causes of tissue damage and to consider advanced treatment modalities to avert further complications.[17;24]

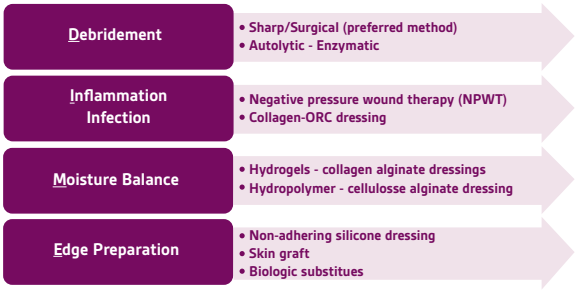


Figure 5. DIME Treatment options. Adapted from Snyder et al 2016.[24]

Single strategies used for the treatment of DFU's may not be effective if biofilm is

present. DFU's could present with delayed epithelialization as a result of decreased cellular proliferative and migratory capacity due to the formation of epiboly's (rolled in wound edges).[20] This can cause defective formation of the supporting stroma. Sharp debridement targets the physical factors such as insidious pressure formation by removing any excess callus or non-viable tissue that may plague wound environment.[20] In a retrospective study by Wilcox et al, in more than 300,000 wounds, they found that weekly debridement's were associated with faster healing times.[19;23] Frequent, disruptive, and sharp debridement of the wound bed provides a therapeutic window that may lower the biofilm burden. Topical antiseptics include silver, iodine and polyhexamethylene biguanide (PHMB).[20;25] These topical agents are more effective after debridement by actively penetrating the exopolymeric matrix of biofilm and eradicating the free planktonic bacteria.[20] It should be noted that recent studies have revealed that there is less than a 24-hour window in which these therapies are successful.[22] A mature biofilm may be present within 72 hours.[22] This emphasizes the importance of adhering to a robust and timely biofilm based "step-down" treatment algorithm (**Figure 6**).[20]

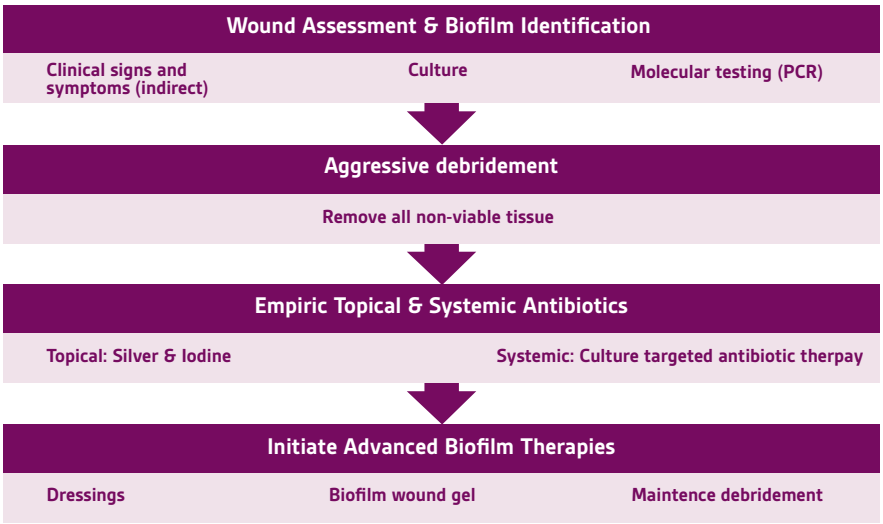


Figure 6. Step down biofilm treatment algorithm. Adapted from Snyder et al 2017.[20]

Moisture balance is a critical component to improve wound healing.[17;24] Excessive exudate formation may lead to maceration which can cause the wound to stagnate.[24] Therefore, it is paramount to minimize the negative biochemical factors by applying the appropriate dressings based on the wound bed characteristics (size, depth, and moisture levels). It is not recommended to use topical antimicrobials for clinically uninfected wounds. It should be noted that altered biomechanics may predispose to diabetic foot ulcers and impaired wound healing. Depending on the location of the DFU, redistribution of pressure off the wound (off-loading) should be implemented to help reduce the physical factors impeding the wound healing trajectory.[17;24] Micropore particle technology (MPPT) is a new treatment modality that does not incorporate antimicrobial activity.[26] This new technology exploits the skins microbiome with a dressing that consists of highly porous particles triggering a combination of capillary flow and evaporation to remove exudate.[24] Bilyayeva et al found MPPT, reduced the time to reaching a wound free of necrosis, pus, and infection by 60%.[27] They also found that MPPT promoted a 50% increase rate of granulation and epithelialization; the effects were independent of wound type.[26] Subsequent to debridement, silver and Cadexomer iodine based dressings have also shown promising results in the treatment of biofilm infested wounds.[27] Over the past couple decades, negative pressure wound therapy (NPWT) has revolutionized the management of complex wounds by its ability to promote granulation tissue formation and help remove infectious materials. With the rise of antimicrobial drug resistance there has been an increased effort investigating alternative treatment modalities. Probiotics, bacteriophages and antimicrobial peptides (AMP) have recently been hypothesized as potential alternatives in the treatment of biofilm infested wounds.[28]

ASSESSMENT AND EVALUATION OF DFUs:

A robust multi-modal and multidisciplinary framework should be adhered for all patients suffering with DFU's. A timely and accurate diagnosis of a DFU is the first essential step in determining the appropriate treatment pathways. Utilizing evidence-based classification systems can help medical teams stratify the extent of the condition and help dictate treatment protocols Patient centered factors such as diabetes management, nutrition, obesity management, uncontrolled infection, medications, and pain among others can obstruct the wound healing process. Proper wound bed preparation is essential in treating infected DFU's which involves debridement, managing infection and persistent inflammation, moisture balance, and wound edge optimization. Once the wound has been sufficiently prepared, a precise treatment plan can be determined based on the wounds specific criteria such as: biofilm/bioburden factors, vascularity, extent of infection and other systemic factors. Clinicians should be aware that if there is less than a 50% change in wound size in 4 weeks or not improved in a 2-week time period, advanced therapies should be considered.

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