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Diabetic foot ulcer, antimicrobial remedies and emerging strategies for the treatment: An overview

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***Abstract*---**According to the International Diabetes Federation's 2015 study, diabetes affects over 415 million people globally (5 million of whom die each year), and the incidence of diabetes is expected to climb to over 640 million (1 in 10) by 2040. (IDF 2015). Diabetes foot ulcers (DFU) are one of the most significant diabetic health consequences. Antimicrobial treatments, such as dressings, topical therapies, medicines, drugs, debridement procedures, molecular,

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cellular, and gene therapies, plant extracts, antimicrobial peptides, growth factors, devices, ozone, and energy-based therapies, would be the focus of this study. Scopus, Web of Science, Bentham Science, Science Direct, and Google Scholar were among the sources used to compile the English-language publications on DFU. DFU treatment requires a multidisciplinary approach that includes the use of proper diagnostic tools, competence, and experience. To prevent amputations, this starts with patient education and the use of new categories to steer treatment. New diagnostic methods, such as the 16S ribosomal DNA sequence in bacteria, should become available to acquire a better knowledge of the microbiota in DFUs. DFU is said to be polymicrobial in nature and to have some distinct characteristics depending on its geographical location, such as wound characteristics, antibiograms based on local epidemiology, individualised antimicrobial-driven treatment, routine debridement, regular wound examination, and dressing changes. The following qualities are often helped by new biological and molecular treatments that have been demonstrated to improve infection prevention, control of the local inflammatory profile, and the efficacy of the cicatrizing mechanism.

***Keywords*---**DFUs, diabetes mellitus, antimicrobial peptides, diabetic neuropathy, biofilms.

Introduction

According to the International Diabetes Federation's 2015 study, diabetes affects over 415 million people globally (5 million of whom die each year), and the incidence of diabetes is expected to climb to over 640 million (1 in 10) by 2040. (IDF 2015). Furthermore, diabetes treatment accounts for 12% of worldwide health spending (USD 673 billion)[1,2]. In diabetics, skin sores, especially chronic ulcers, are common, and are primarily caused by neuropathy (nerve damage) and arterial (blood vessel) illness or trauma. Peripheral neuropathy (nerve dysfunction in the feet) and peripheral artery disease (both) are common in persons with diabetes. The immune systems of many diabetics may be compromised in ways that have yet to be discovered, making it difficult for them to avoid or treat illness. As a result of their diabetes, diabetic people have an increased risk of getting foot ulcers[3]. As of 2008, an uninfected ulcer costing EUR 10,000 in Europe and an untreated ischemic ulcer costing EUR 17,000 in Europe were stated to represent a diabetic's lifetime risk of developing a foot ulcer[4]. When these wounds become clinically infected, they cause a large amount of morbidity.

Every 20 seconds, someone with diabetes loses a lower limb to the disease, according to estimates. Infection is defined as the presence of at least two of the standard symptoms of inflammation (pain or tenderness, warmth, redness, swelling) or purulent discharges in a diabetic foot wound (pus)[5]. Patients with diabetes now spend more time in the hospital due to foot issues than any other kind of diabetic complication. Lower extremity amputations are most often caused

by diabetic foot infections, particularly those that extend to the bone under the skin. This results in high medical costs, worse quality of life, and a higher mortality rate[6]. To reverse these negative consequences, eradicate foot infections or, if that is not possible, thoroughly manage untreated wounds. The most common way to treat infection is using antimicrobials, either systemically (through oral or parenteral (i.e. intravenous or intramuscular)) or topically (i.e. locally) applied as solutions, creams, gels, or ointments. To determine whether a diabetic foot wound is contaminated, the patient must have peripheral neuropathy or vascular disease. Furthermore, even in non-infected wounds, the presence of microorganisms, especially pathogenic ones, may slow wound healing[7]. To lower the bacterial "bioburden" and perhaps expedite healing or prevent infection, some clinicians consider antimicrobial treatment (particularly topically) for high-risk clinically uninfected wounds[8,9].

Diabetes foot ulcers (DFU) are a significant diabetic health condition. Diverse skills, competence, and experience are required for DFU treatment. To prevent amputations, patient education and improved care categorization are essential[10,11]. New diagnostic methods, such as the 16S ribosomal DNA sequence in bacteria, should be used to better understand DFU microbiota. Individualized antimicrobial driven therapy, debridement, wound assessment and dressing changes are stated to be polymicrobial properties of DFU[12]. New biological and molecular medicines that improve infection prevention, local inflammation control, and cicatrizing mechanism efficiency typically aid with the following qualities. Molecular, cellular, and gene treatments, plant extracts, antimicrobial peptides, growth factors, devices, ozone, and energy-based therapies are some of the newest advances in antimicrobial therapy.

Diabetic foot ulcers (DFU)

DFUs are frequently skin ulcers that spread down the legs, accompanied by peripheral vasculopathy and neuropathy. Several studies found DFUs to have greater morbidity, illness, mortality, and psychosocial costs than other devices. DFU may cause osteomyelitis and gangrene. Amputation of a substantial limb is commonly performed to treat severe DFU[13,14]. As a result, numerous categorization techniques have been developed to assess therapy response. It has yet to be proven in the marketplace. Convenience trumps clinical or theoretical benefit for most diabetics when selecting clinical data gathering equipment[15]. Classification according to the Wagner ulcer classification scheme examines the degree of the ulcer, the status of the osteomyelitis, and presence of gangrene and amputation as follows: Wagner Grade-0: intact Skin; Wagner Grade-I: superficial ulcer of skin or subcutaneous tissue; Wagner Grade-II: ulcers extend into tendon, bone, or capsule; Wagner Grade-III: deep ulcer with osteomyelitis, or abscess; Wagner Grade-IV: partial foot gangrene; Wagner Grade-V: whole foot gangrene[16].

Currently, 90% of diabetes patients with Wagner III or above will need an amputation. This study found that 45 percent of diabetic foot patients had Wagner III or higher, with an amputation rate of 18 to 28%. DFU patients die at a rate of up to 11%. A research in Tianjin found a 32.7 percent 5-year death rate for

DFU. The cost of treating DFU in 2017 was $727 billion USD in the US and $110 billion USD in China[16,17]. Despite the fact that endovascular and vascular bypass surgery are suggested therapies for ischemic foot ulcers, 40% of DFU patients may not meet the requirements. As a consequence, many DFU patients are advised to have their legs amputated. However, the 5-year death rate was 25–50%. After one year, 60 percent after three years, and 65 percent after five years, patients treated with traditional therapies experience recurrence. Novel therapies are thus urgently needed to improve DFU healing and limb salvage rates[18].

If osteomyelitis is present, all DFUs must be discarded. There are also blood tests (CBCL and CRP) and imaging (X-ray and/or MRI) that may be required in some cases (e.g., bone biopsy). Because primary care facilities rarely perform foot examinations during routine visits, routine health assessments are hampered. Besides diabetes, other risk factors include sensory, motor, and autonomous neuropathy, peripheral arterial disease (PAD), immune system factors, and repeated external or mild damage (which lead to skin breakdown and ultimately to the development of infection). Bony foot deformities (like bunions and hammertoes) can also cause pressing points (potential locations for ulceration). Extreme neuropathy patients report more mechanical pain than non-neuropathic diabetics. Inflammation, additional lost tissue, and systemic organ failure are the most common causes of amputation. Anemia (Hb less than 11 g/dL), age, and PAD prevalence all contribute to infection spread and, ultimately, severe amputation[19,20].

Pathophysiology of DFUs

DFUs have a complex etiology including diabetic neuropathy, PAD, and trauma. Both of these factors contribute to the development of ulcers, both before and after they appear as a stop in wound healing.

Diabetic neuropathy

Hyperglycemia produces oxidative stress on nerve cells, resulting in neuropathy. The polyol metabolic pathway absorbs nicotinamide adenine dinucleotide phosphate (NADPH), which enhances the growth of enzymes including aldose reductase and sorbitol dehydrogenase. These enzymes convert glucose to sorbitol and fructose[21]. Increased generation of reactive oxygen species (ROS) and impaired neuronal transmission occurs when these sugar compounds pile up in nerve cells[22]. The polyol pathway, higher hexosamine pathway flow, and altered formation of substance P, nerve growth factor, and calcitonin gene-related peptide all lead to additional nerve damage and ischemia[23]. Motor neuron damage in the foot musculature may induce anatomic abnormalities, skin ulcers, and flexor/extensor imbalance. Damage to the autonomic nervous system inhibits sweat gland action, resulting in epidermal fissures and skin disintegration[24]. Finally, diminished peripheral feeling might induce patients to avoid foot wounds by depleting intra-epidermal A-delta and C-fibers, which are nociceptors and only excited by noxious stimuli. Vitamin B12 deficiency, alcohol toxicity, and end-stage renal failure are all neuropathic illnesses that may exacerbate this condition. Epidemiological evidence links lipid lipoproteins, hypertension, and smoking to

PAD. Charcot's foot is the most well-known sign of motor neuropathy. The foot's architecture poses the greatest risk of infection since skin sheaths, tendons, and soft tissues (plantar aponeurosis and fascia) are exposed[25–27].

Immunological contribution to DFUs pathogenesis

DFU recovery is slower in diabetic individuals because of their particular immunological features. T-lymphocyte apoptosis, increased pro-inflammatory cytokines and degradation of polymorphonuclear cell functions like chemotaxis, adherence, phagocytosis and intracellular killing are only a few of these responses. Suppression of fibroblast proliferation, impairment of the basal layer of keratinocytes, and diminished epidermal cell migration are only a few of these reactions(26,27). Bacteria thrive in high blood glucose, especially aerobic Gram-positive cocci including Staphylococcus aureus (S. aureus) and -hemolytic streptococci. Insulin resistance, fibroblast and collagen deficit, and other structural issues are all exacerbated by diabetes' metabolic shortfall. Serum glucose levels more than or equal to 150 mL/dL were also considered to be an indicator of impaired immune function. These traits often lead to a chronic inflammatory disease[21,22].

PAD

As many as 78% of individuals with DFU have been found to already have PAD[28]. The foot's peripheral arteries are shifted by hyperglycemia, which begins at the cellular level. Endothelial cell dysfunction, which reduces the production of vasodilators, particularly nitric oxide, is the most critical feature of microcirculation dysfunction. Chronic vasoconstriction and plasma hypercoagulation increase plasma thromboxane A2 levels, increasing the risk of ischemia and ulceration[29]. There are changes in endothelial cell proliferation, basement membrane thickening, increased blood viscosity, modifications in microvascular sound, smooth muscle cell proliferation, reduced antioxidant capacity, and decreased local angiogenesis in the endothelium[30].

infection of DFUS

The International Working Group on the Diabetic Foot defines infection as the invasion and multiplication of harmful microorganisms inside the bodily tissues. An increased risk of amputation and morbidity are two possible outcomes of diabetic foot infections (DFIs)[31]. It is common for ulcers to result in DFU infections, which may be quite hazardous. It is estimated that DFU infection is the cause of 80% of non-traumatic lower-limb amputations, with 50% of DFUs being compromised at the time of diagnosis. Antibiotic treatment for DFI patients typically necessitates hospitalization. Skin infections may delay recovery and lead to systemic health issues if cared for incorrectly. Many aspects of wound microbiology have a role in the development of a fungal infection in the foot[32–34]. These parameters include the microbial load, microbe diversity, the existence of infective organisms, and the microbial species' synergistic interactions. Infection occurs when the microbial burden exceeds 105 species per gramme of tissue[35]. Skin commensal bacteria may colonies the wound after DFUs have

exposed the tissue, and this colonization does not elicit an immune response from the host, hence it cannot be considered an infection[35]. Triggers might be physical, chemical, or mechanical in nature. Cuts and ulcers on the diabetic foot are difficult to cure because of the weakened immune system, ischemia, neuropathy, edoema, and inflammation[36]. It is possible to determine whether an ulcer has been infected by using recommendations issued by the Infectious Diseases Society of America (IDSA). If at least two of the following symptoms are present: inflammation, induration, erythema perilesional, hyperesthesia, pain, local fire, and purulent exudate, an infection is identified by clinical examination[37]. 78 percent of DFU patients already have PAD, according to research. Endothelial cell dysfunction, which reduces the production of vasodilators, particularly nitric oxide, is the most critical feature of microcirculation dysfunction. Plasma thromboxane A2 levels are also linked to increased risk of ischemia and ulceration due to persistent vasoconstriction and hypercoagulation[38–40].

DFUs' microbiome has been studied extensively. The organism's immune system and physio-pathological features heavily influence the composition of this microbiota. Using molecular methods, researchers have found the polymicrobial nature of chronic wounds like DFUs, which comprises Gram-negative and Gram-positive bacteria, as well as anaerobic bacteria and certain fungus[36]. DFUs' microbiome has been studied extensively. The organism's immune system and physio-pathological features heavily influence the composition of this microbiota. Using molecular methods, researchers have found the polymicrobial nature of chronic wounds like DFUs, which comprises Gram-negative and Gram-positive bacteria, as well as anaerobic bacteria and certain fungus[36]. In the DFUs, bacteria have "preferred sites," which are distinguished by their oxygen consumption. Aerobic bacteria, for example, are located near the surface, where oxygen levels are comparably high, whereas anaerobes are found deeper within the niches created by aerobic oxygen intake[41].

A 16S amplicon sequencing analysis of fresh and chronic DFUs identified Staphylococcus aureus as the most commonly isolated Gram-positive bacterium, followed by Escherichia coli, Proteus spp. Enterobacter spp., and Citrobacter spp. Peptoniphilus and Anaerococcus were the most common Gram-negative bacterial species, respectively, in a microbiome analysis of fresh and chronic DFUs. Geography has an important role in the genesis of DFUs[42]. Gram-positive aerobic cocci are the most common microorganisms in Western countries; however, Gram-negative bacilli are more common in warmer climates (particularly Asia and Africa). S. aureus was the most widespread bacterium obtained in Mexico using normal methods. Pseudomonas spp. (22/29 percent), Enterobacter spp. (22/7 percent), and Staphylococcus spp. (13/13 percent) were found to be the most prevalent bacteria in DFUs samples in Bangladesh[43]. An Indian study also revealed that Gram-negative pathogens were the most common (58.5 percent), showing that Gram-negative bacteria are more common in Eastern nations[42]. Up to 95% of all instances of anaerobes found in severe diabetic wounds were caused by Peptostreptococcus spp., Bacteroides spp., and Prevotella spp. [44]. DFIs with bigger, more frequent, and more severe ulcers are the ones most likely to get them, as are those with a bad odour or necrosis[44].

An extra polysaccharide matrix with altered phenotype and development patterns has been described as a highly organized assembly of bacterial populations. The formation of biofilms is another factor that contributes to the chronicity of diabetic foot lesions[45]. Wound healing is slowed and infection is difficult to treat because biofilm impedes local access to antimicrobial medications and the host's immune system. Most biofilms were produced by Staphylococcus aureus, and many of the bacteria that cause chronic DFUs were multidrug resistant, according to a prospective study[46].

Preventative factors such as Patch, peripheral neuropathy (a loss of defensive sensation), changed foot structure and trauma do not produce ulcers[47]. Both conditions result in the loss of the skin's outermost layer of protection. DFU patients may have more frequent and severe infections as a consequence of pathogenic biofilm formation, resulting in slower healing of the ulcer[47]. Biofilms have been shown to inhibit wound healing in both animal and in vitro experiments. Biofilms may have a role in the development of diabetic foot ulcers and the persistence of infections because of a lack of data from human clinical investigations[48].

Researchers have employed DNA sequencing technology to investigate whether or not biofilms occur on the diabetic foot, which provides a more complete view of the diabetic foot microbiome[49]. However, the most common bacteria detected in DFUs with biofilm forms have already been reported in the diabetic foot literature. The vast majority of DFUs are covered with thick biofilms made up of several types of microorganisms. The staphylococci and streptococci, which are aerobic gram-positive cocci, are the most common[50,51]. Aerobic bacteria and fastidious anaerobes (particularly those of the Clostridiales Genus XI), Corynebacterium spp., and gram-negative rods are some of the bacteria often found in foot ulcers (namely, Klebsiella spp., Acinetobacter spp., Enterobacter spp., P. aeruginosa, and Escherichia coli).[52,53].

Multidrug-resistant bacteria's in DFUs

In diabetic foot ulcers investigations, drug-resistant species are overrepresented. Multidisciplinary Melbourne secondary treatment centre study in Australia is typical of other groups with a high prevalence of MRSA among patients attending. 653 specimens from 379 individuals had MRSA eliminated 23% of the time[54]. In a French study in 2008, 188 individuals brought to the hospital with an untreated foot ulcer had their recovery rates monitored by the MDR[55]. In the sample, two-thirds of the ulcers were evaluated as moderate to severe, indicating that they are complicated. Seventy percent of the ulcers are found to be neuroischaemic ulcers, with a fifth of the lesions showing resistance to antibiotics[56]. There was a greater risk of lower-limb amputation (35.6 percent compared to 11.2 percent for non-MDR infection) when MDR microorganisms were present, however most of these amputations were moderate (87.5 percent). The presence of MDR bacteria was shown to have no influence on the healing time when other factors were taken into account[57–59].

methods of treatment for DFU infection

In severe circumstances, DFIs may lead to the amputation of all or part of a patient's foot or leg, and even death. The combination of an infected diabetic foot with ischemia remains one of the most challenging challenges in the management of DFUs. It is important to prevent infection in DFUs because bacteria in the wound aggregate and emit local and systemic cytokines, which may lead to systemic inflammatory response (SIR) and shock. Topical and oral antibiotics for light to moderate infections, as well as intravenous antibiotics for more severe infections, are all frequently utilised, depending on the severity of the illness. An antibiotic course must be finished before all clinical symptoms have been eliminated and test results have returned to normal, if one has been started already. During infection management, the wound should be examined frequently (either at the time of dressing change or on a bi-weekly basis) to ensure that the treatment is working[60–62].

The removal of the bacterial biofilm (debridement)

Foot ulcer infection treatment includes debridement, which removes the bacterial biofilm and necrotic tissues from the lesion. It enables for a complete evaluation of the site, as well as providing tissue for microbiological culture and wound healing[63]. It is at this stage when necrotic tissues begin to accumulate around the site of the incision. While excess necrotic tissue inhibits the growth of new tissue by blocking its removal, debridement accelerates wound healing. Pre-antibiotic procedures include debridement and wound cleaning, which are often accomplished with isotonic saline solutions (0.9 percent NaCl)[64]. Plantar neurotrophic ulcers are known for their hyperkeratotic borders, which may be reduced with the use of sharp debridement. Typically, this procedure should take place once every seven to 14 days[65]. Active and autolytic debridement techniques are employed in the medical setting to remove the diseased tissue. When necrotic material has to be manually removed, such as surgical debridement in which a knife and tweezers are used to remove dead tissue, the wound bed may leak[66]. In hydro-surgical debridement, a solid stream of water is utilised to remove dead tissue. Debridement in the outpatient setting might benefit from ultrasonic assistance. To carry out this procedure, irrigation fluids and low-frequency waves (25 kHz) are both employed in combination. Autolytic debridement uses hydrocolloids and hydrogels to increase moisture in the wound area to aid in natural tissue loss during healing[67]. At six and twelve weeks, a review compared clostridial collagenase ointment (CCO) for enzymatic debridement to conventional therapy with hydrogel and found no change in wound duration[68,69].

Dressings

It is possible to promote new tissue growth and wound drying using autolytic debridement while yet protecting the wound from infection and exposure[70]. Endogenous proteolytic enzymes are activated during the autolytic breakdown of dead or damaged tissue. Hydrated starch, hydrolyzed starch, alginates and hydrospheres are all examples of dressing techniques. Absorbent dressings are

used to treat wet wounds, while absorbent dressings are intended to absorb wounds[71]. Dressings of both types are equally effective in aiding healing[72]. Figure 1 depicts some of the most often seen dressings in medical practice.

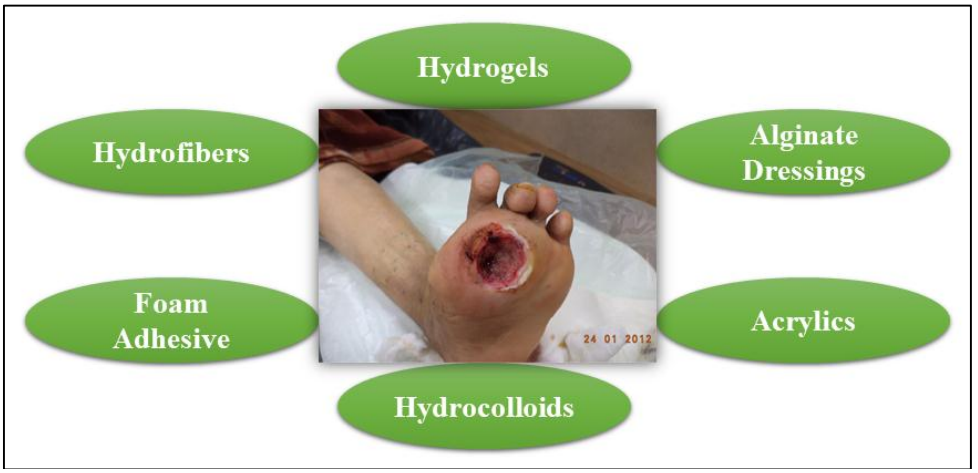

Fig 1. The types of dressings most often seen in medical practice

Antibacterial agents that are used to treat DFUs

Owing to their lack of commitment to moisture balance maintenance and autolytic debridement, as well as the danger of contact dermatitis, topical antimicrobials are not indicated for chronic wounds. Topical antimicrobials are recommended for their minimal toxicity to the host tissue while they are utilised. Any topical antiseptics/antimicrobials for DFIs are described in the following sections[19,72,73].

10 percent solution for Povidone Iodine

Wound healing is encouraged by the use of povidone iodine, a broad-spectrum antibacterial agent. When it comes to short-term treatments like this one (2-4 weeks), you'll often see it employed as such. Thyroid illness and granulated tissue are also possible side effects of long-term usage.

Chlorhexidine

This drug has a wide range of antibacterial properties and promotes wound healing. Aside from that, cartilage tissue might be injured.

Acetic Acid (5 percent)

Pseudomonas and other Gram-negative bacteria may benefit from this treatment. There is a possibility that it may cause tissue toxicity and limit fibroblast growth.

Treatment with compounds containing Silver

Silver nitrate sticks and sulfadiazine cream are effective against methicillin-resistant Staphylococcus aureus and E. coli, Klebsiella, and S. aureus, as do foams and calcium alginates (MRSA). The re-epithelialization process may be harmed by these substances, resulting in healing to be interrupted.

Hydrogen peroxide (H2O2)

Gram-positive bacteria are particularly vulnerable to peroxides that include this chemical. The risk of developing bullae is the most serious adverse effect. Some alternative topical antimicrobials have been investigated, but no obvious effects have been found. These include cadexomeriodine, carboxymethylcellulose hydrofiber, superoxidized formulations and tobramycin beads.

Systemic therapy with antibiotics

Systemic antibiotics are recommended when signs of localised, progressive, or systemic infections are present. Course of administration and antimicrobial agent to be employed are determined by the results of a microbiological culture, clinical symptoms, body composition and patient's immune-competence[62]. As a first line of defense, wheel-speed antibiotics are often employed during normal therapy, before being shifted to more targeted agents when results of bacterial culture are apparent." Hospitalizations and intravenous antibiotic (IV) treatment may be necessary in cases of severe, non-responsive, or spreading infections, or in cases of suspected osteomyelitis[43]. Gram-positive staphylococci and streptococci infections may be treated with oral antibiotics. If a particular antibiotic fails to treat the infection, a second one is injected. Experimentation with methicillin-resistant therapy Patients who have previously been infected with MRSA or who have developed an illness resistant to antibiotics are considered to have Staphylococcus aureus (MRSA) (74). While treating a minor illness, IDSA prescribes antibiotics for one to two weeks; when treating a moderate to severe infection, IDSA recommends two to three weeks of antibiotic treatment. Most often used broad-spectrum drugs are beta-lactam or beta-lactamase inhibitor combos, such as piperacillin/tazobactam, ampicillin/sulbactam, and ticarcillin/clavulanic acid[75–77].

some emerging therapies in brief for the treatment of DFUS

There are a number of new therapies for ulcers that are designed to speed up the healing process. As an example, they include adjuvant growth factors and inflammatory modulators as well as herb extracts and blood products as well as biological therapies and hazardous pressure injuries. These therapies, however, are not a replacement for regular diabetic foot care and should not be used in place of it[78–83]. Figure 2 depicts a collection of innovative treatments for treating DFUs that have been published in the literature.

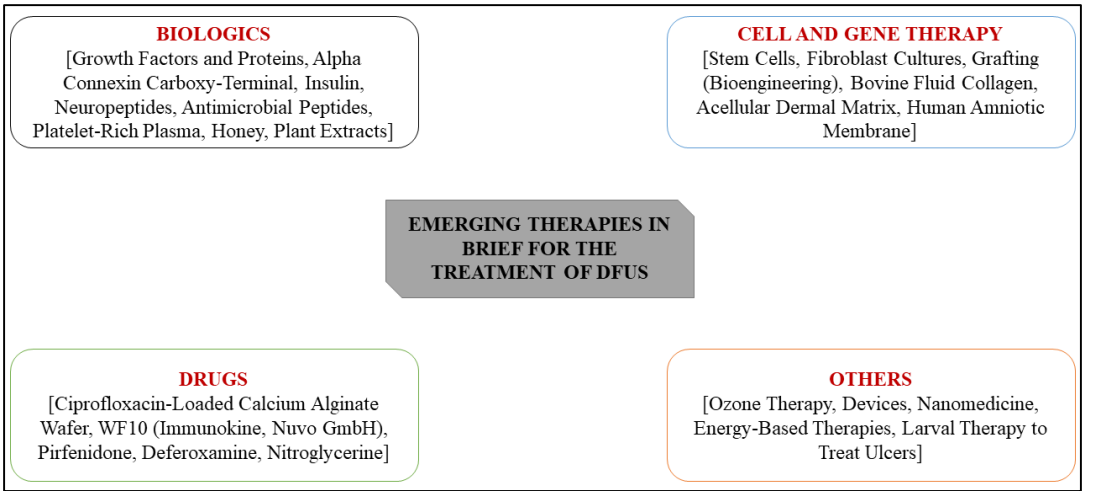

Fig 2. New therapy for DFUs that have been reported in the literature are included in this list

Conclusions

When diabetics develop foot ulcers and infections, they are putting their health at risk and putting their lives in danger. One of the most common causes of diabetic foot disease is reduced glucose tolerance, which may be brought on by diabetic neuropathy, vasculopathy, immunopathy, or inadequate glycemic control. When it comes to the appropriate diagnosis of diabetic foot concerns, a thorough clinical examination of the patient is necessary, as is early intervention with an emphasis on prevention. The most effective preventive measures include patient education, constant monitoring, and tight cooperation amongst a multidisciplinary team of doctors, hospitalists, endocrinologists, infectious disease specialists, and wound treatment experts. Further multicenter randomized controlled trials are needed to continue to inform treatment recommendations and intervention approaches. It is becoming more difficult to treat chronic wounds caused by diabetes, such as DFUs, which are both dangerous to the general public's health and detrimental to the well-being of those who suffer from them. There is no need to stop using traditional DFU therapy as long as they are properly controlled. A complete wound closure must be achieved before any of these medicines are approved by the FDA; consequently, more rigorous clinical studies are required to show their effectiveness. Using cells, genes, sensors, nanomaterials, and plant extracts in combination as therapy for different phases of DFUs need further investigation. Patients and their families may expect a better quality of life as a result of these discoveries, which will help standardize DFU treatment in the best possible manner.

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