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The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

INDEXING/ABSTRACTING

The *WJD* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJD* as 4.560; IF without journal self cites: 4.450; 5-year IF: 5.370; Journal Citation Indicator: 0.62; Ranking: 62 among 146 journals in endocrinology and metabolism; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yu-Xi Chen*; Production Department Director: *Xu Guo*; Editorial Office Director: *Jia-Ru Fan*.

NAME OF JOURNAL

World Journal of Diabetes

ISSN

ISSN 1948-9358 (online)

LAUNCH DATE

June 15, 2010

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Lu Cai, Md. Shahidul Islam, Michael Horowitz

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-9358/editorialboard.htm>

PUBLICATION DATE

June 15, 2023

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

What's old is new again: Insights into diabetic foot microbiome

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Specialty type: Endocrinology and metabolism

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Mostafavinia A, Iran;
Portillo R, Czech Republic

Received: December 26, 2022

Peer-review started: December 26, 2022

First decision: February 20, 2023

Revised: February 20, 2023

Accepted: April 10, 2023

Article in press: April 10, 2023

Published online: June 15, 2023



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Abstract

Diabetes is a chronic disease that is considered one of the most stubborn global health problems that continues to defy the efforts of scientists and physicians. The prevalence of diabetes in the global population continues to grow to alarming levels year after year, causing an increase in the incidence of diabetes complications and health care costs all over the world. One major complication of diabetes is the high susceptibility to infections especially in the lower limbs due to the immunocompromised state of diabetic patients, which is considered a definitive factor in all cases. Diabetic foot infections continue to be one of the most common infections in diabetic patients that are associated with a high risk of serious complications such as bone infection, limb amputations, and life-threatening systemic infections. In this review, we discussed the circumstances associated with the high risk of infection in diabetic patients as well as some of the most commonly isolated pathogens from diabetic foot infections and the related virulence behavior. In addition, we shed light on the different treatment strategies that aim at eradicating the infection.

Key Words: Diabetic foot infection; Chronic ulcer; Bacterial biofilm; Multidrug resistance; Methicillin resistant *Staphylococcus aureus*; Vancomycin resistance

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Core Tip: Diabetic foot infection is a common complication of diabetes that can lead to serious consequences, such as amputations and even death. The microbiome of the wound plays a crucial role in the development and progression of diabetic foot ulcer. The current review shed light on the most prevalent bacterial infections and their related virulence factors that are associated with diabetic foot complications. Additionally, various approaches for treatment were explored.

Citation: Rajab AAH, Hegazy WAH. What's old is new again: Insights into diabetic foot microbiome. *World J Diabetes* 2023; 14(6): 680-704

URL: <https://www.wjgnet.com/1948-9358/full/v14/i6/680.htm>

DOI: <https://dx.doi.org/10.4239/wjd.v14.i6.680>

INTRODUCTION

Diabetes is a chronic metabolic disorder that is characterized by the failure of the body to regulate blood glucose levels. The worldwide prevalence of diabetes has increased to epidemic levels in the last decade; the latest report from the International Diabetes Federation Diabetes Atlas stated a global diabetes prevalence of 10.5% in 2021 with the expected incidence to reach 12.2% in 2045. By comparing to the 2019 report, which stated a 9.3% global incidence of diabetes with a 2045 rate projection of 10.9%, the data suggest an exaggerated increase in diabetes prevalence worldwide[1,2]. Diabetes is associated with many complications that are commonly encountered in health care facilities, especially cardiovascular disease, retinopathy, neuropathy, nephropathy, and lower limb infections in addition to the high risk of amputations and systemic infections that are linked to high mortality rate[3,4]. Diabetic foot ulcer is a serious condition characterized by chronic lower limb wound that is often complicated by disseminating polymicrobial infections that can affect the underlying bone tissues. Diabetic foot infection (DFIs) require careful attention from health care providers regarding the proper diagnosis of the wound level and prompt management including debridement procedures, antimicrobial treatments, and follow-up of the wound healing process[5-7].

During the examination of the diabetic foot wound, the accurate evaluation of the wound plays a pivotal role in the proper management selection. Usually, the wound examination should include specimen collection from the deepest parts of the wound in order to identify the associated etiologic pathogens, accompanied by inspection of the underlying vascular and bone tissues. The Meggitt-Wagner guide is a commonly used system for classification of the DFI based on three parameters: the depth of the ulcer; the infection level; and the degree of necrosis. The guide classifies the DFI into five main categories, which are outlined in [Figure 1](#). A progressive DFI needs immediate management in order to minimize the risk of bone infection and osteomyelitis, which are common complications in 50%-60% of severe infections and associated with a high risk of limb amputations[8,9]. In this review, we discussed the most common pathogens related to DFIs along with the associated virulence factors and possible treatment options for eradication of the infection and subsequent minimization of comorbidities and mortality rates.

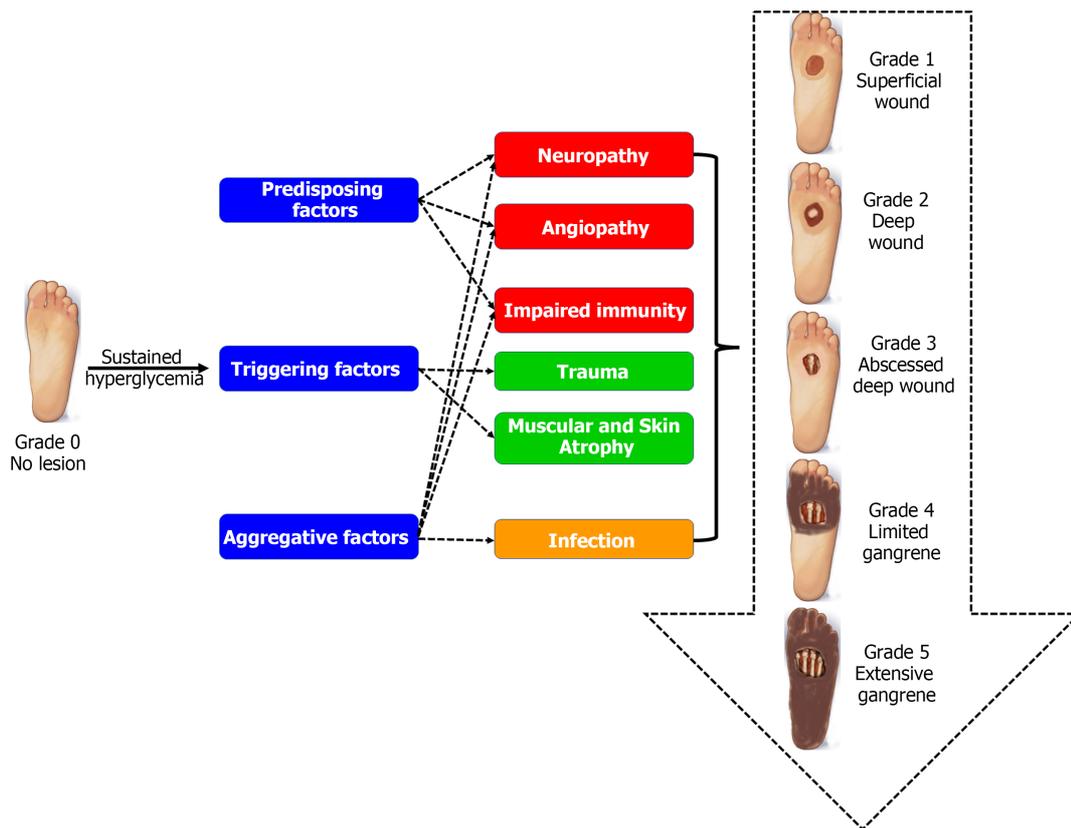
FACTORS THAT INCREASE THE RISK OF INFECTION IN DIABETIC PATIENTS

Impaired immunity

Impaired immune functions represent a defining element in diabetes that impacts both innate and adaptive immunity. The innate immunity is the first line defense against pathogens and foreign particles. The response is mediated through phagocytes, natural killer cells, and inflammation[10]. Diabetes is associated with elevated levels of tumor necrosis factor α , macrophages, and inflammatory cytokine release that predisposes patients to chronic inflammation and increased pathogenicity of infections[11]. Additionally, diabetes is associated with an impaired number and functioning of natural killer cells with high connectivity to autoimmune diseases and increased risk of cardiovascular disease, malignancy, and susceptibility to infection[12]. On the other hand, the decreased number and function of dendritic cells results in impaired antigen presenting function and subsequently deterioration of the function of adaptive immunity[12]. Likewise, diabetes is associated with marked suppression in release of interleukin 6, decreased antibody production, decreased effector T cell development, and impaired leukocyte recruitment, all of which are considered important mediators of the adaptive immune response against pathogens[10,13].

Hyperglycemia

Elevated blood glucose level is the main symptom of diabetes; failing to control blood glucose levels in diabetic patients will cause serious complications as a result of alterations in multiple metabolic pathways[14]. The high blood glucose level results in activation of the polyol pathway, increased glycation of end products, and eventually boosted release of reactive oxygen species and nitric oxide that contribute to oxidative stress and inflammation[15]. Hyperglycemia also contributes to immunosuppression through inhibition of cytokine release in response to pathogenic infection in addition to attenuation of macrophages, neutrophil dysfunction, and complement activation[10,13]. In addition, hyperglycemia is associated with stiffer blood vessels, which cause slower circulation and capillary dysfunction, predisposing to reduced tissue oxygenation[16]. Moreover, hyperglycemia contributes to



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Figure 1 Risk factors for the development of diabetic foot infections. Angiopathy and neuropathy are the main predisposing factors of diabetic foot infections (DFIs), together with muscular atrophy and extrinsic triggers, such as trauma, in the presence of abnormal immunity and ischemia as aggravating factors. These factors collectively result in the loss of skin integrity favoring the development of DFIs. The Meggitt-Wagner classification is commonly used to grade the DFIs (from 1 to 5) on three characteristics: the depth of ulcer; the degree of infection; and the necrosis.

increased virulence of some pathogens as observed in some coronavirus disease 2019 patients with type 2 diabetes mellitus where an uncontrolled blood glucose level was directly linked to increased severe acute respiratory syndrome coronavirus 2 replication and increased severity of complications[17]. This is in accordance with multiple studies that confirmed the association of hyperglycemia with increased bacterial load and virulence expression in *Staphylococcus aureus* (*S. aureus*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) infections accompanied by increased severity of the infection in diabetic patients[18,19].

Vasculopathy and ischemia

As mentioned earlier, persistent hyperglycemia results in overproduction of reactive oxygen species and superoxides especially peroxynitrite leading to increased nitrosylation and eventually causing endothelial dysfunction, vasoconstriction, and platelet aggregation. In addition, the diabetic proinflammatory environment results in vascular inflammation and proliferation of vascular smooth muscles predisposing to atherosclerosis and atherothrombosis[20]. Some of the common vasculopathy presentations in diabetic patients involve peripheral artery diseases giving way to peripheral cramps, numbness, discoloration of limbs, weak pulse in the affected limb, and critical limb ischemia[21]. Peripheral ischemia results in delayed wound healing and tissue necrosis as a result of a decreased supply of oxygen, nutrients, and immune cells; in addition, the reduced tissue perfusion would limit the delivery of antibodies and antibiotics. A combination of all the preceding factors would result in an environment that favors microbial proliferation at the injured tissues, which supports the development of chronic diabetic foot ulcers[22].

Neuropathy

Diabetic neuropathy is a neurodegenerative disorder that affects the peripheral sensory nervous system in 50% of cases. The condition is characterized by pain, numbness, and loss of sensory function that begins in the lower extremities[23]. Again, hyperglycemia along with the associated inflammation and oxidative stress play the lead role in the mechanisms predisposing to diabetic neuropathy, where Schwann cells and the myelin sheath are the first affected resulting in delayed signal transmission and eventually neuron dysfunction especially in distal terminals of motor nerve axons[23,24]. Diabetic neuropathy contributes to increased risk of infection in diabetic patients through inhibition of local

vasodilation of the microcirculation at the affected tissues, which is a normal response to injury or inflammation; the reduced vasodilation results in reduced local blood flow and further promotes local ischemia[25]. On top of that, the loss of sensory nervous function will impair pain sensation, thus diminishing the ability of the patient to sense or detect wounds and injuries in peripheral tissues especially toes and foot soles, which in turn leads to delayed response and management of the condition and increasing the risk of amputation[26]. Peripheral neuropathy is a common manifestation in 90% of hospital admissions of diabetic foot ulcers; in addition, 14%–24% of people with a diabetic foot ulcer will ultimately undergo an amputation procedure with subsequent high mortality rate[24].

BACTERIAL VIRULENCE FACTORS AND THEIR CONTRIBUTION TO PATHOGENICITY IN DFIS

Adhesins

Adhesins are fine protein extensions expressed on the bacterial cell surface usually represented by a small protein subunit at the tip of the fimbriae. Their primary function is to facilitate the attachment or adherence of bacteria to host cells, which is the first step in initiation of an infection[27,28]. Adhesins also play a pivotal role in establishment of biofilms. This fact was proven by many studies that reported that biofilm formation can be completely blocked by downregulation of pili expression or by using adhesins antibodies that can drastically inhibit bacterial attachment to the target tissues, hence inhibiting subsequent initiation of infection and biofilm formation[29,30]. Some adhesins are called hemagglutinins due to their ability to induce the agglutination and hemolysis of red blood cells. Hemagglutinins contribute to localized destruction of red blood cell (RBCs) and release of iron, which is an essential nutrient requirement for most pathogenic bacteria[31]. Additionally, bacterial adhesins play an important role in intracellular bone invasion as observed in the ability of *S. aureus* to invade osteoblasts and fibroblasts, which contribute to serious complications of diabetic foot ulcer as well as increased risk of amputation[32].

Biofilm formation

Biofilm formation represents an important virulence factor that plays a leading role in the persistence and recurrence of diabetic foot ulcers. Biofilms are closed microbial communities embedded in a mucoid extracellular polymer matrix consisting of a wide range of molecules including polysaccharides, proteins, glycoproteins, glycolipids, cell debris, wastes, and surfactants[33,34]. These molecules provide high viscosity to the biofilm matrix acting as a physical protective barrier that prevents penetration of host immune defenses as well as antimicrobial treatments[35]. In addition, diabetic patients suffer from reduced peripheral blood supply, which makes it even harder for the immune system and antibiotic treatments to eradicate biofilms in DFIs[36].

Within the biofilm, bacteria can coordinate their behavior using a communication system called quorum sensing (QS). This system is activated once the bacterial population reaches a certain threshold level beyond which the members of the biofilm initiate a coordinated group response that favors the public interests of the biofilm community; this coordinated activity aims at conserving energy and nutrients by reducing the metabolic activity of biofilm inhabitants[37-39]. Additionally, bacterial gene expression is directed towards increased expression of virulence factors especially extracellular toxins, which initiate extensive tissue destruction at the biofilm site; this ensures generous release of nutrients from the damaged tissues as well as facilitating the spread of infection to adjacent tissues, which further cements the biofilm and increases its persistence[40,41].

Another important feature of biofilms is the shift in bacterial phenotypes within the biofilm community towards the formation of persister cells that are inherently resistant to eradication by antimicrobial agents. Persister cells are dormant slow-growing cells with altered metabolic pathways that result in loss of the target site of most antibiotic treatments hence contributing to persistence and recurrence of biofilm ulcers[42]. At the same time, the high bacterial population within the biofilm results in an increased rate of horizontal gene transfer (HGT) between biofilm inhabitants, creating a rich pool of characteristics that eventually lead to natural selection of virulence genes and antimicrobial resistance genes[43]. Indeed, it was reported by many studies that biofilm formation is highly linked to an increased rate of antimicrobial resistance in DFIs, which contributes to a high incidence of chronic recurrent ulcers and higher risk of amputations[36,44].

Tissue damaging exoenzymes

Enzymes like proteases, collagenase, hyaluronidase, lipases, fibrinolysin, gelatinase, and elastase are all upregulated in diabetic foot biofilms under control of QS[45-48]. Such enzymes play an important role in inducing tissue damage, which helps in the release of nutrients that are required by the pathogens for growth[49-51]. Additionally, the vascular tissue damage would diminish tissue perfusion and contribute to the reduced ability of the immune system and antibiotic treatments to reach the site of the infection[52]. At the same time, the destroyed physical integrity of the tissues facilitate invasion of

adjacent tissues and spread of the infection. Moreover, proteases result in delayed healing of the affected tissues, which further contributes to the chronic nature of diabetic foot ulcers[16,49]. Immunoglobulin proteases represent a different category of proteases that target humoral components of immune defense (mainly immunoglobulin A, immunoglobulin M, and immunoglobulin G) rather than inducing generalized tissue damage[53,54]. Immunoglobulin proteases represent an important virulence factor in many pathogens that allows them to evade the host immune response[55,56]. Local therapy with protease inhibitors is an essential element in control of diabetic foot ulcer in order to improve wound healing and minimize the complications accompanying chronic wounds[49,57].

Hemolysins and leukocidins

Hemolysins and leukocidins belong to a group of pore-forming toxins that destroy blood cells by inducing perforation in the cell membrane and subsequent cell lysis[58-60]. Hemolysins are important virulence factors in pathogenic infections since they induce RBC lysis and release of iron, which is an essential nutrient requirement for pathogens. Iron is an important element for life since it is required for making important enzymes in all living cells[36,59,61,62]. However, iron is never found in a free form in biological tissues or in the extracellular fluids; the ability of most pathogens to survive in an iron-free environment highly depends on its iron acquisition talents including hemolysin and siderophore production[63].

S. aureus is one of the most common causative agents of DFIs. *S. aureus* is equipped with an arsenal of toxins including four hemolysins targeting a wide range of host cells: α -hemolysin (mainly targeting lymphocytes and monocytes); β -hemolysin (targeting human monocytes and sheep erythrocytes with no effect on human erythrocytes); γ -hemolysin (highly toxic to neutrophils); and δ -hemolysin (toxic to erythrocytes). The combined actions of these toxins result in RBC hemolysis as well as inhibition of leukocyte function and subsequent evasion of host immune defenses[64,65].

Antimicrobial resistance

Antimicrobial resistance is an escalating worldwide problem with increased prevalence among diabetic patients. As discussed previously, diabetic patients are at high risk of contracting microbial infections especially due to their immunocompromised status, which leads to higher rates of persistent difficult to treat infections, and such circumstances usually predispose to higher probability of development of antimicrobial resistance[66-68]. This relationship can be explained based on many factors: (1) The development of bacterial biofilms in chronic infections, like in cases of diabetic foot ulcers, is associated with activation of QS communication systems, which in turn induces upregulation of virulence gene expression including antimicrobial resistance genes[69-71]; (2) Bacterial biofilms are also associated with an increased rate of HGT between members of the biofilm community, which means increased rate of transfer of antibiotic resistance genes between different species within polymicrobial biofilm communities[72]; and (3) Chronic infections are usually associated with prolonged antimicrobial treatment courses, especially with broad spectrum antibiotics that exert stress pressure on pathogenic bacteria leading to natural selection of resistant strains[73,74].

Similarly, antibiotic self-administration and empirical prescription of broad-spectrum antibiotics by general practitioners are considered predisposing factors for higher rates of development of antibiotic resistance in diabetic patients[75-77]. One interesting observation was discussed in a previous study that reported a three-fold higher incidence of antibiotic resistance in diabetic foot patients in 2020 as compared with individuals admitted with the same diagnosis in 2019. The authors linked this observation to the circumstances that surrounded the coronavirus disease 2019 pandemic with increased administration of antibiotics for control of the infection complications, bearing in mind the fact that diabetic patients were among the high-risk categories at that point[78,79].

Additionally, some diabetic foot ulcers can result from impaired healing of wound tissues rather than the presence of wound infection. Therefore, it is highly recommended to avoid empirical antibiotic treatments before confirming the presence of an infection in diabetic foot ulcers. In addition, antibiotic therapy should not be given for uninfected foot wounds as prophylaxis against infection or as a method to improve wound healing[50,80]. Instead, it is advised to collect wound samples or swabs for microbiological examination in order to confirm the presence or absence of infection. This also allows for identification of the causative pathogen in cases of confirmed infection as well as performing antimicrobial susceptibility testing in order to identify the optimum antimicrobial treatment for every individual case [81,82].

On a similar basis, the administration of broad-spectrum antibiotics for recurrent episodes of diabetic foot ulcers is not required, as recommended by a recent study that concluded that a patient history of previous DFIs does not necessarily reflect a higher risk of antibiotic resistance in subsequent episodes [83]. Boschetti *et al*[84] documented the resistance patterns of the most prevalent bacterial species isolated from DFIs to different classes of antibiotics when administered as a monotherapy or as a combination treatment. The results presented in Figure 2 provide an alarming outlook at the dangerous growing levels of antimicrobial resistance in many antimicrobial groups[84].

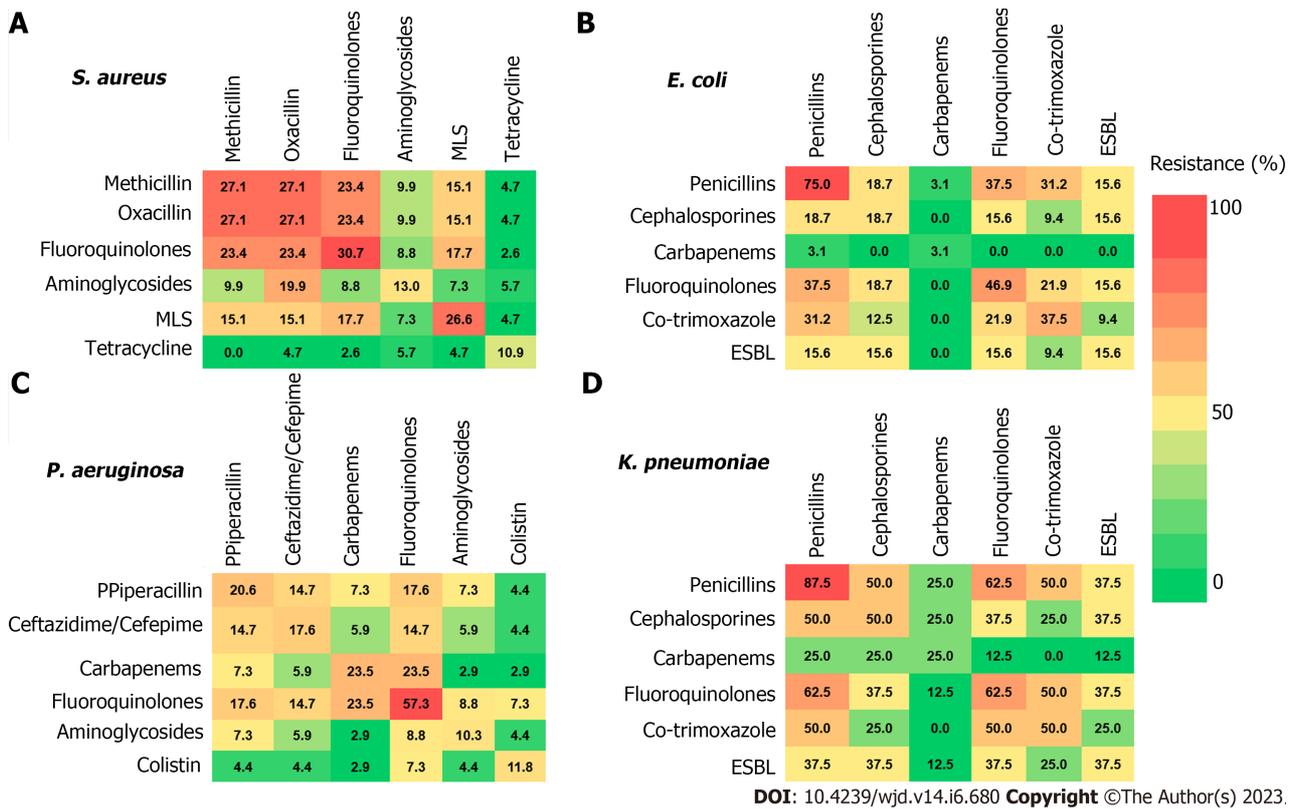


Figure 2 Resistance of bacteria isolated from diabetic foot infections to different classes of antibiotics as monotherapy or in combinations. A: *Staphylococcus aureus* (*S. aureus*); B: *Escherichia coli* (*E. coli*); C: *Pseudomonas aeruginosa* (*P. aeruginosa*); D: *Klebsiella pneumoniae* (*K. pneumoniae*). The data presented as percentages of resistance, adopted from Boschetti et al[84]. Resistance to oxacillin expects resistance to cephalosporines, carbapenems, and β-lactams. MLS: Macrolides, lincosamides, and streptogramines; ESBL: Extended spectrum beta-lactamases.

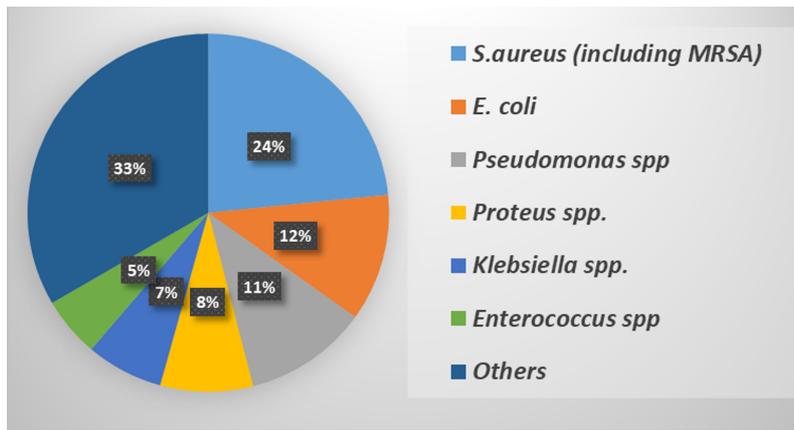
THE MOST PREVALENT BACTERIAL DFIS

The dwindled immunity of the diabetic patients paves the way for easy contraction of opportunistic pathogens from the patient’s environment, leading to high risk of the progression of minor foot injuries into life-threatening infections[85,86]. The Meggit-Wagner system is the most commonly used classification guide of DFIs that assesses the ulcer depth, the presence of osteomyelitis, and/or gangrene using an ascending level from 0 to 5[87,88]. The more aggressive pathogenic bacterial infections are usually denoted by a higher level number[85,89,90]. There are multiple variables contributing to the establishment and progression of the infection, mainly: (1) Host response; (2) Ulcer location; (3) Tissue perfusion; and (4) Ulcer depth[87,91,92]. Upon trying to identify the etiologic agents behind DFIs, it is hard to name one exclusive pathogenic agent since DFIs are always caused by polymicrobial infections [90,93,94].

It is noteworthy that the polybacterial nature of DFIs makes the identification of different bacterial species a difficult task and mandates the application of both phenotypic and genotypic detection methods[91,95]. Several studies documented that the most prevalent bacterial species isolated from DFIs are *S. aureus*, *Escherichia coli* (*E. coli*), *P. aeruginosa*, *Proteus* spp., *Klebsiella* spp., and *Enterococcus* spp. with variable prevalence rates that are presented in Figure 3[32,96]. The following section shed light on the most prevalent Gram-negative and Gram-positive bacterial DFIs especially those isolated from deep wounds with higher Wagner grades.

Staphylococcus spp.

Staphylococcus spp. are Gram-positive cocci that are ubiquitous in the environment. They are divided into pathogenic *S. aureus* and opportunistic coagulase negative *Staphylococcus* spp.[97-99]. However, the coagulase negative *Staphylococcus* spp. (*S. epidermidis*, *S. saprophyticus*, and others) are prevalent in the normal skin flora and could cause aggressive opportunistic infections in diabetic foot wounds[97,100]. *S. aureus* is considered by far the most commonly isolated species from macerated DFI especially in wounds of higher Wagner grade. It accounts for 20%-25% of all isolated bacteria[86,88-90,92]. The predominance of *S. aureus* in diabetic foot wounds can be attributed to: (1) Their ubiquitous presence in the environment; (2) The high ability of *S. aureus* to survive and resist bactericidal agents especially in healthcare settings giving rise to nosocomial infections; (3) A robust arsenal of virulence factors that facilitates anchoring of *S. aureus* infection; (4) The significantly high biofilm forming ability of *S. aureus*;



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Figure 3 Frequency of isolated bacterial species from diabetic foot infections. The presented data were collected from 57 studies that represented 6736 clinical samples, yielding 8418 microbial isolates[96]. *S. aureus*: *Staphylococcus aureus*; *E. coli*: *Escherichia coli*; MRSA: Methicillin-resistant *Staphylococcus aureus*.

and (5) The especially high rate of HGT between *S. aureus* and other members of a polymicrobial population leading to an increased ability of *S. aureus* to gain antibiotic resistant genes[85,86,88,90,91,94,95,101-103]. *S. aureus* has a collection of different virulence factors including the production of diverse extracellular enzymes such as coagulase, gelatinase, hemolysins, and proteases in addition to a cocktail of toxins, such as pore-forming toxins, α -toxin, exfoliative toxin, enterotoxin, toxic shock syndrome toxin, and the virulent pigment staphylolysin[32,95,97,98].

The recent increase in the rates of antibiotic resistance patterns requires careful attention during the choice of a proper antimicrobial treatment. Methicillin-resistant *S. aureus* (MRSA) is a problematic pathogen that continues to grow as a public health concern[95,101,102]. Unfortunately, several studies have reported an increased rate of MRSA in polymicrobial DFIs as demonstrated in Figure 4[85,88,94,95,102-135]. Although the complete identification of the full bacterial spectrum in a DFI is sometimes difficult, the detection of MRSA can be easily confirmed using the Kirby-Bauer antibiotic disk method in addition to genotypic detection methods[91,95]. Generally, vancomycin has been and still is the pillar therapy for MRSA. However, there is a growing mass of evidence that the minimum inhibitory concentrations of vancomycin to MRSA are increasing globally[106].

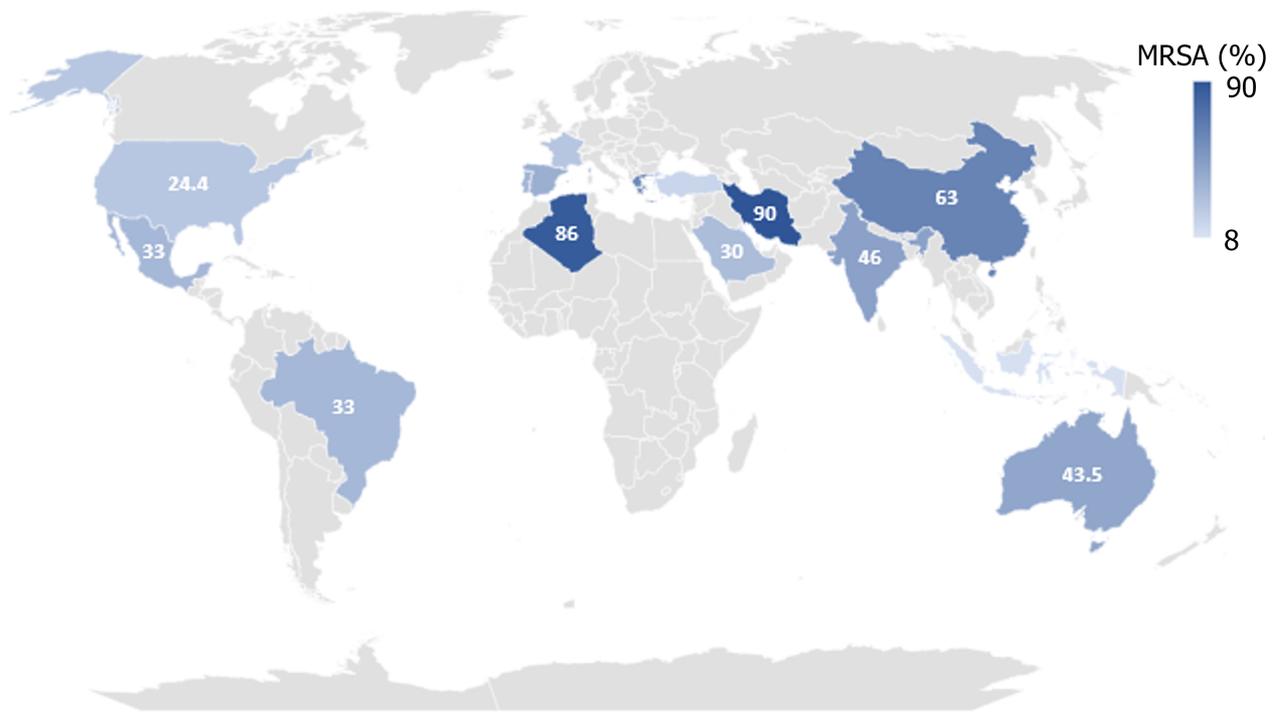
E. coli

E. coli is one of the most common causative pathogens of DFIs with a high incidence of biofilm formation[96] *E. coli* is also considered one of the most common causes of Gram-negative bacteremia in hospitalized patients[34,136]. *E. coli* is an opportunistic pathogen that is a common member of the human skin and colon flora[137]. The initiation of a pathogenic lifestyle in *E. coli* infection benefits from multiple virulence factors that allow for colonization and tissue destruction at different body organs especially in immunocompromised individuals. *E. coli* adhesins, mainly type 1 fimbriae and P fimbriae, are important virulence factors that are essential for adhesion and initiation of the infection[138,139]. Additionally, adhesins play an important role in diabetic foot pathogenesis due to their role in cytokine induction, tissue inflammation, and biofilm initiation[138]. *E. coli* also secretes hemolysin and siderophores that induce RBC damage and subsequent iron acquisition from the damaged tissues[140]. Importantly, many studies have confirmed a positive correlation between the hemolytic activity, biofilm formation, and high levels of antimicrobial resistance in *E. coli* infections[141,142].

P. aeruginosa

P. aeruginosa is a Gram-negative bacillus that is characterized with an armory of virulence factors including multiple bacterial surface structures such as pili and flagella in addition to a diverse array of extracellular toxins[143-145]. The observed prevalence of *P. aeruginosa* in DFIs is fluctuating from high to moderate levels, yet it is still among the most prevalent bacterial infections in DFIs[83,86,90,93,96,107,125,131,146-149]. *P. aeruginosa* employs five secretion systems (T1SS, T2SS, T3SS, T5SS, and T6SS) that are used to regulate bacterial survival and utilized in establishment of infection[143,145]. Additionally, *P. aeruginosa* has at least three types of QS communication systems that orchestrate the expression of several virulence factors such as biofilm formation, motility, resistance to host immunity, and production of extracellular toxins such as protease, lipase, hemolysin, elastase, and pyocyanin pigments [150].

Furthermore, *P. aeruginosa* has a remarkable ability to acquire antibiotic resistance against most of the commonly used antibiotics, making its eradication a difficult task[143,146,149]. *P. aeruginosa* can easily



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Figure 4 Prevalence of methicillin resistant *Staphylococcus aureus* isolated from diabetic foot infections around the world. The presented data are percentage of methicillin resistant *Staphylococcus aureus* (*S. aureus*) from the isolated *S. aureus* from diabetic foot infections.

establish an infection on intact healthy skin[147,148] and even more so on already vulnerable tissues in immunocompromised patients such as in diabetic foot wounds[146,148,149]. The guidelines provided by the American Infectious Diseases Society for DFIs state that empiric therapy directed against *P. aeruginosa* is usually not recommended[147,149]. However, once the infection is identified, it is recommended to perform antibiotic susceptibility tests of the bacterial isolates[151-153]. There are several classes of antibiotics that are proposed as a monotherapy or as a combination therapy for eradication of *P. aeruginosa* in DFIs, including fluoroquinolones, aminoglycosides, and colistin[83,84,143,147,151,152].

Proteus mirabilis

Proteus mirabilis (*P. mirabilis*) is a Gram-negative bacterium that is famous for its swarming motility and its remarkable survival in challenging environmental conditions[154,155]. The ability of *P. mirabilis* to initiate a pathogenic infection depends on multiple virulence factors such as multiple types of fimbriae and adhesins that allow attachment to different surfaces, giving rise to the remarkable stickiness and biofilm-forming ability of the bacterium onto many surfaces and at different conditions[156]. Additionally, *P. mirabilis* secretes a lethal cocktail of extracellular toxins including proteases, hemolysin, and urease, which all contribute to the extensive tissue damage and inflammation at the infection site [157]. Another significant feature of *P. mirabilis* is the formation of robust biofilms that are highly adhesive and persistent. Moreover, the biofilm formation in *P. mirabilis* is highly associated with increased rates of antimicrobial resistance and increased expression of toxins[155]. The combination of the aforementioned factors makes *P. mirabilis* a problematic pathogen in DFIs especially chronic ulcers.

Klebsiella pneumoniae

Klebsiella pneumoniae (*K. pneumoniae*) is a Gram-negative bacterium that is commonly isolated from chronic wound infections especially in immunocompromised individuals[158,159]. *K. pneumoniae* is known for its high adhesiveness as a result of its thick polysaccharide capsule that is enriched with type 1 and type 3 pili. The polysaccharide capsule in *K. pneumoniae* consists of two fibrous layers: An inner thick densely packed fibrous layer and an outer layer in which the fibers are loosely packed and become finer outwards, forming a fluffy network on the capsule surface[160,161]. This structure plays a leading role in the remarkable adhesiveness of the bacterium onto mucus membranes and inanimate surfaces followed by fast accumulation of bacteria as a result of entangled fibrous polysaccharide capsules of adjacent bacterial cells and subsequently rapid biofilm formation[161,162]. The thickness of the fibrous capsule of *K. pneumoniae* is known to be one of the thickest protective bacterial coats, which imparts extra protection against host immune responses such as phagocytosis and serum complement deposition. In

addition, its thick compact nature reduces the penetration of antibiotics and bacteriophages[163,164]. The overall result of the aforementioned factors is the formation of a highly adhesive biofilm that is resistant to immune defenses and antibiotic treatments and makes *K. pneumonia* challenging to eradicate in healthcare facilities, contributing to the high incidence of nosocomial infection associated with this pathogen especially in immunocompromised individuals and diabetic patients[165,166]. It is noteworthy that both *K. pneumonia* and *P. mirabilis* are linked to an increased risk of ascending urinary tract infections in diabetic foot patients as a result of self-infection[167,168].

Enterococcus spp.

Enterococci are facultative anaerobic Gram-positive cocci; there are two species considered the most common commensal organisms in the intestines of humans: *Enterococcus faecalis* and *Enterococcus faecium* [169,170]. *Enterococci* are opportunistic pathogens, commonly responsible for surgical wound infections, urinary tract infections, endocarditis, and intra-abdominal and pelvic infections among many others [171,172]. *Enterococci* are well adapted for withstanding harsh environmental conditions. This enables them to survive routine disinfection methods resulting in high persistence of these bacteria on inanimate surfaces in healthcare settings making them common causative agents of nosocomial infections[172]. It is widely documented that *Enterococci* are among the most prevalent bacterial infections in DFIs[96,117,121,122,124,125,173,174]. Interestingly, *Enterococci* are not considered true pathogens; their abundance in the gut flora provides them the opportunity to interact with other bacteria increasing the possibility of acquiring virulence genes and antimicrobial resistance genes[171, 172]. Lately, there has been an alarming increase in antimicrobial resistance patterns of *Enterococci*, especially associated with hospital-acquired infections affecting immunocompromised patients including DFIs[174]. Unfortunately, many studies reported an increase in the mortality rates related to the emergence of vancomycin-resistant *Enterococci* that are usually linked to hospital-acquired infections [170,171,173]. The current antibiotic choice regimen for control of stubborn multidrug resistant enterococcal DFIs includes antibiotic combinations of β -lactams, aminoglycosides, and fluoroquinolones[171, 174].

MANAGEMENT OF DFIS

Conventional antibiotic therapy guidelines for DFIs

As explained previously, antibiotic treatment should only commence after the confirmation of the presence of an infected wound. However, broad-spectrum antibiotics are typically used during routine care of progressive diabetic foot wounds as an empiric treatment until microbiology culture results are available. Then the treatment should be switched to targeted antimicrobial therapy[175]. Ideally, narrow spectrum antibiotic treatment is preferred in order to avoid antibacterial resistance. Additionally, the treatment should be used for the shortest duration possible in cases of mild and medium diabetic wound infections: For 2-4 wk for progressive wounds and up to 6 wk in cases of osteomyelitis. If the treatment is not effective then the case should be re-evaluated regarding the antibiotic choice[176,177].

The Infectious Diseases Society of America provides a detailed description of antibiotic choices regarding DFIs. However, the report highlights the absence of a single recommended antimicrobial regimen. Instead an appropriate regimen should be designed based on the results of antibiotic susceptibility testing, severity of the infection, possible side effects, price, interactions with other drugs, and other patient related factors. The report recommends including suitable coverage of Gram-positive cocci (mainly *S. aureus* and *Streptococcus* spp.) in empiric treatment protocols. For mild DFIs, the choices include: clindamycin, levofloxacin, and β -lactamase inhibitor combinations. For moderate to severe infections the antibiotic options are extended to include ertapenem, tigecycline, piperacillin-tazobactam combination, and imipenem-cilastatinb combination with the latter showing especially broad spectrum activity. An anti-MRSA agent should be included in the regimen choice in cases of severe infections or previously confirmed MRSA infection. The suggested anti-MRSA choices include: Vancomycin, linezolid, and daptomycin. However, these options are considered narrow spectrum activity, and they should be combined with other agents such as a fluoroquinolone, carapenem, aztreonam, or piperacillin-tazobactam to increase the activity spectrum especially in severe progressive infections[50,176].

Novel antibiotic options against multidrug resistant DFIs

The fierce increase in antibiotic resistance rates continues to be a growing worldwide crisis, which results in gradual erosion of the list of treatment options available for eradication of multidrug resistant infections, especially DFIs. For example, vancomycin, which is one of the last resort antibiotics that should be conserved for treatment of MRSA, has shown an alarming increase in resistance rates in the last decade[178,179]. Linezolid is considered an effective vancomycin alternative acting against both vancomycin-resistant *S. aureus* and MRSA. Linezolid showed good tissue and bone penetration and sufficient *in vivo* anti-MRSA activity in DFIs, even in cases of blood flow impairment[180,181]. However, linezolid suffers from serious side effects and high toxicity in cases of prolonged treatments. In addition it is not acknowledged by the United States Food and Drug Administration (FDA) for treatment of

osteomyelitis[50,182]. Daptomycin, on the other hand, is approved for intravenous treatment for MRSA in DFIs[106,183]. Additionally, it has a lower side effect profile and promising activity against both MRSA and vancomycin-resistant *S. aureus* that is accompanied by low rates of bacterial resistance development[184,185].

Streptogramins combination of quinopristin and dalfopristin represent another promising alternative treatment of MRSA, which inhibits both the early and the late protein synthesis stages showing significant activity against nosocomial MRSA isolates[186,187]. Tigecycline is a tetracycline derivative that has potent *in vitro* activity against MRSA[186]. However, a Phase III randomized, double-blinded clinical trial showed that tigecycline is significantly less effective and associated with more adverse effects than ertapenem in achieving clinical resolution of DFIs even in presence of osteomyelitis[188]. Ceftobiprole is a fifth generation cephalosporin that is approved for intravenous administration. Ceftobiprole was compared to vancomycin in a multicenter, multinational, double-blind, randomized trial concerning DFIs caused by Gram-positive bacteria. The rates for complete eradication of MRSA in infected patients using ceftobiprole and vancomycin as antimicrobial treatment were 92% and 90%, respectively. In DFI patients, the clinical recovery rate with ceftobiprole monotherapy was 86%, which is as effective as the combination of vancomycin plus ceftazidime[189].

Ceftaroline is another novel cephalosporine that showed significant activity against MRSA. In two randomized, observer-blinded studies to evaluate the efficacy of ceftaroline *vs* standard therapy with vancomycin in combination with aztreonam in adults, the clinical cure rates were comparable (about 86% in both treatments). Importantly, the adverse effects were similar in different treatment groups with a safety similar to that of the cephalosporins[190]. That being said, it is important to bear in mind that any novel antimicrobial treatment, no matter how effective it is against multidrug resistant pathogens, will eventually join the list of ineffective treatments as a result of the continuous evolution of bacterial resistance patterns, which is faster than our ability to develop and approve new alternative treatments.

Topical treatments

Topical antimicrobial treatments of medium to severe DFI wounds are generally considered ineffective [191,192]. Antiseptics are generally applied during surgical debridement procedures and wound dressing changes. This is important to diminish further wound contamination that usually thrives on polymicrobial infections[193]. However, it should be noted that most antiseptics that affect the wound tissues subsequently leave a negative impact on the wound healing process. Furthermore, improper and excessive application of antiseptics can encourage antimicrobial resistance within the wound microenvironment, especially those containing polymicrobial biofilms, thus giving rise to delayed resolution of the infection and increased risk of complications[194]. Based on these considerations, international guidelines do not suggest antiseptics as in the management of DFI wounds[193]. However, several studies documented the *in vitro* effectiveness of iodine-based preparations and dressings containing polyhexamethylene biguanide or silver in controlling DFI wounds[195].

It is reported that biofilm formation within DFIs is likely to increase the incidence of antimicrobial resistance 100 to 1000 times[196], which mandates employment of efficient drug delivery systems to ensure better penetration of the biofilm matrix and higher recovery rates. Some drug delivery suggestions include calcium sulfate beads and antimicrobials immobilized on collagen sponges[196]. Some studies reported a new generation of anti-biofilm hydro-fiber dressings containing carboxymethylcellulose silver, which showed efficient disruption and removal the bacterial biofilms[197].

Another promising dressing was suggested by Yang *et al*[198]. It is a surfactant-based gel dressing that showed promising recovery rates when applied *in vivo* on wounds infected with *P. aeruginosa*. The results showed significant reduction in bacterial growth and disruption in the formed biofilms[198]. Another surfactant-based dressing containing Pluronic F127 in combination with melatonin and chitosan was used to diminish the bacterial growth and biofilm formation in *S. aureus* wound infection [199]. On a similar basis, other studies reported promising *in vitro* antibacterial, anti-biofilm, and healing results upon using wound dressings coated with Chitlac-silver nanoparticles combined with alginate and hyaluronic acid[200].

Other studies went as far as using dressings loaded with mesenchymal stem cells that also showed improved wound healing rates especially in chronic ulcers[201]. The combination of wound dressings with natural products have also been reported in some studies that showed the use of honey[202,203], cranberry extracts[204], tannic acid[205], tea-tree oil[206], and cinnamon oils[207] were linked to improved resolution and healing of DFIs.

Interventional approaches

Surgical debridement is classically used to remove necrotized and infected tissues from DFI wounds. This surgical intervention is routinely used in combination with antibiotics, to control the spread of infection allowing early closure of the wound[208]. The proper removal of infected tissues and bacterial biofilms optimizes the healing and regeneration of the wound tissues, which in turn improves blood flow and improves the effectiveness of the treatment[206]. In association with surgical debridement, negative pressure therapy is commonly employed to promote wound healing in DFIs[209]. Negative pressure is generated using a vacuum source connected to the wound, resulting in suction of cellular

debris, diffuse toxins, and infected extracellular fluids that eventually reflects a positive impact on the resolution of the infection as well as wound healing progress[210].

Photodynamic therapy is a novel technology that is mainly used in oncology. The therapy depends on the use of a photosensitive agent that is activated by illumination to produce lethal oxygen species at the infection site. In a clinical trial, this method was employed for patients suffering from DFIs. The results showed that all the non-treated cases suffered from deterioration of the wound and eventually underwent amputation procedures in comparison to the treated group that showed only 1 case of amputation out of 18 patients who received the photodynamic therapy[211].

Hyperbaric oxygen therapy is another oxygenation-based approach in which pure oxygen is inhaled in a special compression chamber and increases oxygen supply all over the body, including the wound tissues. However, this therapy did not show beneficial results regarding short-term healing of DFI wounds[212].

Novel approaches for treatment of DFIs

The risk of amputation remains significantly high in progressive severe DFIs; such procedures are considered extreme treatment options that usually result in a drastic negative impact on the patient's psychology and productivity in real life. There are numerous new approaches that address this problem by minimizing the need for amputations in severe DFIs. Some of these approaches are discussed in the following points.

Stem cell therapy: One method describes the use of stem cell technology to regenerate the vascular tissues in an ischemic limb, hence increasing blood supply and healing rates in severe DFIs and minimizing the risk of amputations. Additionally, stem cells can be directed towards the release of cytokines, which enhance immunity, cell recruitment, and regeneration of neurons. Similarly, progenitor stem cells can be employed since they have the potential to differentiate into various cell types such as endothelial cells, keratinocytes, pericytes, and myofibroblasts all of which play an effective role in DFI wound healing[213,214]. Stem cell-based therapy has been approved by the FDA as an effective interventional treatment strategy to treat DFI macerated wounds[213]. Secretome stem cells are derived from undifferentiated human mesenchymal endothelial stem cells; they have been successfully deployed for the treatment of the DFIs. It was shown that secretomes enhanced *in vivo* wound healing and increased the proliferation of endothelial cells *via* promotion of the production of a cocktail of vascular endothelial and fibroblast growth factors in addition to angiopoietins[215].

Growth factors: Other approaches are based on the fact that chronic wounds are associated with decreased levels of epidermal growth factor. Hence the application of hormonal growth factors will promote the proliferation and differentiation of fibroblasts, gliocytes, and neo-epidermal cells leading to improved healing rates[213,214]. Other growth factors that modulate signal transduction and replication of epidermal cells were also reported to improve wound healing in DFIs[213,216]. Similar results were obtained upon using granulocyte colony-stimulating factors and human platelet-derived growth factors, which are frequently used for the treatment of DFI wounds and neuropathic ulcers[213].

Skin substitute matrices: One example involves the use of keratinocytes and fibroblasts that are immobilized onto an extracellular matrix that functions as scaffold supports for the wound healing process[217]. Another example is shown by the use of neonatal foreskin equivalent to allogeneic cultured skin apligraf/graftskin. It was shown that this supportive tissue significantly improved the healing of chronic wound ulcers[218]. Dermagraft is an isolated neonatal human dermal fibroblast. Its application significantly improved the healing rates up to 30% in DFI wounds[219]. Furthermore, the allogeneic membranes obtained from human placenta have been employed successfully in the treatment of DFI wounds; such membranes provide growth factors, cytokines, and structural collagen support, which improved the repair of deteriorated tissues[220]. Furthermore, allografts from human skin such as GraftJacket were also reported as successful scaffolds for support of vascular and cellular growth in severe wounds[213].

Phage therapy: Phage therapy is an old method that is starting to gain renewed worldwide attention. The method is based on the use of bacteriophages, which are viruses that infect bacteria. Bacteriophages are considered the natural predator of bacteria that are abundant in nature[221,222]. Phage therapy usually uses a cocktail of bacteriophages to increase the host spectrum range[223]. In one *in vitro* study, a phage cocktail was designed to target *S. aureus*, *P. aeruginosa*, and *Acinetobacter baumannii* isolated from DFIs. The results showed significant antimicrobial and anti-biofilm activity of the tested bacteriophages [224]. These results were supported by case reports that encourage phage therapy for DFIs[225,226]. Examples of *in vitro* tested bacteriophages against the most prevalent bacterial species in DFIs are listed in Table 1.

The use of bacteriophages for treatment of pathogenic bacterial infections offers many advantages: (1) High specificity of action because bacteriophages are highly specific in selection of their host, which is usually limited to one species or even one specific strain within a species; (2) Can be used against multidrug resistant bacteria because bacteriophages use a pathway that is different from all antimicrobial treatments. Therefore, most resistance mechanisms will not affect the phage pathway; (3) Phages

Table 1 Examples of anti-biofilm and anti-virulence agents against the most prevalent diabetic foot infections bacterial pathogens

Agent	Target microbe	Ref.
Bacteriophages		
vB_SauM_ME18 vB_SauM_ME126	<i>S. aureus</i>	[246]
Bacteriophage K	<i>S. aureus</i>	[247]
pSp-J and pSp-S	<i>Staphylococcus</i> spp.	[248]
Staphylococcus bacteriophage K	<i>S. epidermidis</i>	[249]
Bacteriophage cocktail	<i>P. aeruginosa</i>	[250]
<i>Pseudomonas</i> Phage	<i>P. aeruginosa</i>	[251]
vB_EcoS-Golestan	<i>E. coli</i>	[252]
Lytic bacteriophage cocktail	<i>P. mirabilis</i> , <i>E. coli</i>	[253]
Bacteriophage cocktail	<i>P. mirabilis</i>	[254]
vB_PmiS-TH	<i>P. mirabilis</i>	[255]
PhiS1	<i>P. aeruginosa</i>	[256]
PhiE2005-A	<i>P. aeruginosa</i>	[257]
Lytic bacteriophage	<i>K. pneumonia</i>	[258]
Anti-biofilm and Anti-virulence agents		
Sitagliptin (anti-diabetic)	<i>P. aeruginosa</i>	[46,235,259]
	<i>S. aureus</i>	[46]
Linagliptin	<i>P. aeruginosa</i>	[238]
Metformin (anti-diabetic)	<i>P. aeruginosa</i>	[45,236]
Diclofenac (analgesic)	<i>P. mirabilis</i>	[239]
Metronidazole (antibacterial)	<i>P. mirabilis</i>	[260]
Fluoxetine (antipsychotics)	<i>P. mirabilis</i>	[261,262]
Thioridazine (antipsychotics)		
Penfluridol (antipsychotics)	<i>E. faecalis</i>	[263]
Terazosin (adrenoreceptor blockers)	<i>P. aeruginosa</i>	[231,264]
Prazosin (adrenoreceptor blockers)	<i>P. aeruginosa</i> , <i>P. mirabilis</i>	[48,265,266]
Metoprolol (adrenoreceptor blockers)	<i>P. aeruginosa</i> , <i>S. enterica</i>	[233,267]
Atenolol (adrenoreceptor blockers)	<i>P. aeruginosa</i> , <i>P. mirabilis</i>	
Allopurinol (anti-gout)	<i>P. aeruginosa</i>	[47]
Azithromycin (antibiotic)	<i>P. aeruginosa</i>	[268]
Ciprofloxacin (antibiotic)	<i>S. enterica</i>	[269]
Resveratrol (anticancer)	<i>S. aureus</i>	[270]
	<i>E. coli</i>	[271]
Ribavirin (antiviral)	<i>C. albicans</i>	[272]
Theophylline (bronchodilator)	<i>C. albicans</i>	[273]
Stolon (fenugreek)	<i>P. aeruginosa</i>	[232]
Garlic extract	<i>P. aeruginosa</i>	[274]
Allicin (garlic)	<i>P. mirabilis</i>	[275]
Carvacrol (oregano)	<i>P. aeruginosa</i>	[276]
Emodin (<i>Polygonum cuspidatum</i>)	<i>S. aureus</i>	[277]
	<i>C. albicans</i>	[278]

Curcumin (curcuma)	<i>Acinetobacter baumannii</i> <i>C. albicans</i> , <i>P. mirabilis</i>	[279]
Tannic acid	<i>E. coli</i>	[280]
Sodium citrate	<i>P. aeruginosa</i>	[281]
Isolimonic acid (citrus fruits)	<i>E. coli</i>	[282]
Zingerone (ginger)	<i>P. aeruginosa</i>	[283]

S. aureus: *Staphylococcus aureus*; *S. epidermidis*; *Staphylococcus epidermidis*; *P. aeruginosa*; *Pseudomonas aeruginosa*; *E. coli*: *Escherichia coli*; *P. mirabilis*: *Proteus mirabilis*; *K. pneumoniae*: *Klebsiella pneumoniae*; *E. faecalis*: *Enterococcus faecalis*; *S. enterica*: *Salmonella enterica*; *C. albicans*: *Candida albicans*.

will only attack the target bacterial host leaving no effect on eukaryotic cells, which means localized activity at the infected tissues with minimal side effects; (4) Self-amplification of phages means that minimal doses will replicate exponentially at the infection site in relation to the wound infection burden; (5) High ability to penetrate deep tissues and bacterial biofilms, which further results in complete eradication of the infection; and (6) Minimal effect on the normal host flora[227]. On the other hand, there are limitations, mainly the lack of approval from the FDA and the need to formulate a phage cocktail that is based on accurate identification of polymicrobial infection members[227]. Moreover, it was observed that biofilm formation was induced by exposure to some phages[228,229].

Anti-biofilm and anti-virulence agents: Bacterial biofilms and bacterial virulence play major roles in the establishment and spread of DFIs. Anti-biofilm and anti-virulence agents are promising adjuvants to be used in combination with conventional antibiotic treatment of DFI wounds[206]. Bacteria employ several interplaying systems to control the expression of their virulence factors, most importantly the QS system. QS is used in both Gram-positive and Gram-negative bacteria to communicate between each other in an inducer-receptor manner[37,40,46]. Several approaches have been suggested to diminish the bacterial biofilm formation and virulence factor production based on targeting the QS systems[47,69,71]. QS inhibitors are known to reflect a significant reduction in bacterial virulence as well as reduced resistance development[230-234].

There are several chemical structures that have been screened for their anti-QS, anti-biofilm, and anti-virulence activities, with maximum attention given to the screening of already used and approved medications with the aim of using them for other applications than their originally intended use (Table 1). Some of the screened drug groups included several anti-diabetic agents. Fortunately, some anti-diabetics showed promising anti-QS, anti-virulence, and anti-biofilm activities. One promising example is the group of gliptins, which are dipeptidase inhibitors that are widely used as hypoglycemic agents. A detailed virtual study was performed to assess the anti-QS activity of some gliptins, mainly sitagliptin and linagliptin[46,235-238]. The results showed a significant ability to diminish biofilm formation in *S. aureus* and *P. aeruginosa* in addition to significant reduction in the expression of virulence factors such as protease, hemolysins, and other toxins[45,46,238]. There is a growing list of drug groups that are screened for their antibacterial and anti-QS activities, including analgesics and anti-inflammatory agents that are commonly used for symptomatic treatment of DFIs. Diclofenac is a commonly used anti-inflammatory agent that showed promising *in vitro* results regarding biofilm inhibition and downregulation of virulence factors in *P. mirabilis* isolates collected from deep DFIs[239]. There are many other drug groups and natural products that were screened for their anti-QS, anti-biofilm, and anti-virulence activities. Some of these agents are presented in Table 1.

There are other approaches that aim at inhibition of bacterial biofilm formation, for example chelation of essential metals, ethylene diamine tetra-acetic, and citrate[240]. Another approach is the use of enzymes for dispersion of bacterial biofilm, *e.g.*, α -amylase[241], proteinase K, trypsin[206], deoxyribonuclease I, hydrolases, and DNase[241-243]. In addition, some synthetic chemical agents such as 2-aminoimidazole showed powerful anti-biofilm activity against *S. aureus*[244].

In another study published by Barki *et al*[245], wireless electroceutical dressings were used successfully for the eradication of *P. aeruginosa* and *Acinetobacter baumannii* biofilms *in vivo*. It was shown that the dressing disrupted the formed biofilms and accelerated wound healing. Furthermore, this treatment was found to downregulate the QS-encoding genes and restore the skin barrier function by silencing the proteins required for skin barrier function (E-cadherin)[245].

CONCLUSION

Diabetes and its complications represent a growing public concern worldwide. DFIs are considered one of the most commonly encountered problems at healthcare facilities. The management of DFIs are usually problematic due to many factors, including the reduced immunity in diabetic patients, the

delayed wound healing, and the high incidence of a multidrug resistant polymicrobial infection. The delay or failure of treatment of DFIs will increase the risk of serious life-threatening complications such as amputations and systemic infections. There has been a global increase in the levels of bacterial resistance to antibiotics that reached a catastrophic level, especially with more and more antibiotics being added to the list of ineffective treatments. This has caused increased rates of mortalities caused by multidrug resistant infections. The proper selection of the antibiotic treatment course for DFI is crucial to avoid microbial resistance. Additionally, it is important to combine antimicrobial treatment with supportive therapy such as anti-biofilm agents, drug delivery systems, and rejuvenating dressings to ensure maximum outcomes of the treatment. In addition, the use of QS inhibitors will decrease the severity of the infection by downregulation of bacterial virulence factors, biofilm formation, and reduction of the incidence of antimicrobial resistance.

FOOTNOTES

Author contributions: Hegazy WAH contributed to conceptualization, writing the original draft, and the final revision; Rajab AAH wrote the original draft.

Conflict-of-interest statement: All authors report having no relevant conflicts of interest for this article.

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