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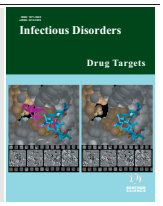
REVIEW ARTICLE

A Review on the Current Principles of Antibiotic Therapy for Diabetic Foot Infection



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Abstract: Foot infections, being one of the major complications, account for nearly 15% of people with diabetes, and increase their risk for amputation in lower extremities. Though various factors contribute to the development of diabetic foot infection, poor glycemic control poses a greater risk paving the way for a number of micro-organisms to colonize the wound.

In order to restore the lost granulation tissue at the ulcer site, the prime aim should not only be attaining glycemic control but also must focus on performing culture by clinically differentiating the stage of infection as well as to manage or control the infection by selecting a rational empiric antibiotic regimen, amidst the uncertainty that exists in choosing best antimicrobial therapy in emerging multi-drug resistance worldwide.

This review mainly analyzes that although among the existence of various undefined microbiome being prevalent in causing diabetic foot infections, how the current trend of antibiotics in use aids in treating foot infections in diabetes.

Keywords: Diabetic foot infections, matrix metallo-proteinases, wagner classification, methicillin resistant *Staphylococcusaureus*, antimicrobial therapy, microbiome..

1. INTRODUCTION

One of the most frequent and severe complications of diabetes mellitus are foot infections [1]. Among half of the diabetic foot, an ulcer developed cases, one-third of the population set off an infection, resulting in amputation, especially in the lower extremities, and has a deprived quality of life in their lifetime [1, 2]. Nearly 15% of people with diabetes develop diabetic foot infection (DFI). This serious consequence prolongs the days of hospitalization until an appropriate antibiotic therapy was implemented. Some of the usual causes of DFIs are peripheral neuropathy and trauma that would subsequently become unnoticed, hence after a skin abrasion or wound, the spread of infection at the ulcer site is not sensed by the diabetic patient unless pain or fever is present.

The colonization of various micro-organisms may produce damage to the tissue accompanied by host inflammatory response inevitably in the wound of some patients, which is determined to be a clinical infection. The extent of infectious spread even reaches deeper tissues and bone [3]. To enumerate an exact treatment regimen, a proper diagnosis is must, by not merely undergoing physical signs and symptoms or analyzing elevation of CRP or other laboratory information but to clinically differentiate the stage or grade of foot infection/ulcer and perform a culture of organisms from the wound site, to practice a relevant empiric antibiotic therapy.

2. INFLUENCE OF RISK FACTORS IN DFI DEVELOPMENT

The most predominant risk factors in DFIs are peripheral neuropathy (sensory, motor, autonomic), vascular insufficiency (peripheral artery/vascular disease – PAD/PVD), high foot plantar pressure and trauma. Contributive factors in diabetes include poor glycaemic control and previous foot ulcerations. The other secondary risk factor includes peripheral vascular disease like atherosclerosis, especially in femoropopliteal and few small blood vessels below the knee. In a non-diabetic patient, the primary causative factor was thought to be peripheral neuropathy, followed by PVD. Diabetic patients are possessed with a two-folded risk of ulcer rather than non-diabetic patients [3-7].

Among other types of neuropathy such as a motor (that affects muscles in the legs) and autonomic (characterized by dry skin, no sweating), many experiences sensory neuropathy, which heightens the risk of foot ulcer where one loses the capability of protective sensation due to some trauma as well as the kinaesthesia of foot position [7-9]. Restriction to joint movements (ankle, subtalar and first metatarsophalangeal joints) and foot deformities explains the high foot plantar pressure as a cause of foot ulcer. This clearly states

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that 28% with high plantar pressure will develop a foot ulcer than others, with peripheral neuropathy [10-17].

3. PROGRESSION OF DFI

In case of diabetes, the aldose sugars undergo an uncontrolled covalent bonding to macronutrients like protein or lipid, with no any enzymatic reaction, forming a solid product named Advanced GlycationEndproducts (AGEs), where these AGEs crosslink and accumulate in extracellular matrix (ECM) proteins, disturbing its pattern that would result in the uncontrolled hyperglycaemic condition. The cross-linking of AGE does bring increased stiffness on type I collagen and elastin. Though AGEs raise the production of type III collagen and laminin, its poor binding with type IV collagen and heparan sulfate proteoglycan and ability to elongate polymer decrease the potential binding of the basement membrane, which contributes to abnormal granulation tissue formation [18-20].

Apart from these, the deprivation of nitric oxide produced by L-arginine in diabetic patients is represented as a part of disease progression, owing to high glucose-related kidney dysfunction and pH-dependent enzyme nitric oxide synthase, resulting in a pile-up of nitric oxide synthase inhibitor exhibiting ketoacidosis in diabetic patients according to the proposed reasons in the literature. Along with the low generation of ECM proteins, retarded and vitiated wound constriction and restoration are probably exhibited by fibroblasts in diabetic foot ulcer (DFU) [18, 21].

Therefore to mend the wound, the lost extracellular matrix should be restored by undergoing degradation and re--modeling to form a mature tissue, provided by matrix metalloproteinases (MMPs) as well as transforming growth factor-β (TGF β) with appropriate tensile strength. To mention precisely, the sustained overexpression of MMP2 and MMP9 activity along with an imbalance in the ratio of MMP: TIMP (tissue inhibitor of metalloproteinases) and also the reduced levels of TGF β contribute to an abnormal and delay in the diabetic wound healing process [21]. Generally, DFU is classified, as per risk factors, into 3 types, namely: neuropathic (presence of peripheral neuropathy but no ischaemia due to peripheral artery disease), neuroischaemic (presence of both peripheral neuropathy and ischaemia because of PAD) and ischaemic (only due to PAD and not of neuropathy) [17, 22].

4. CLINICAL EVALUATION OF DFI

The common occurrence of the ulcer areas is a heel, metatarsal head on the palm, and the prominent fingertips (on the first and second fingers). Even in the malleolus area, it often becomes lacerated. Few uncommon regions are hypertrophic callus, brittle or broken nail, hammertoes and fissure [23, 24]. Getting the measure of neurological, vascular status, and the wound itself helps to evaluate foot ulcers. Semmes-Weinstein monofilament sensates a patient with 10-g monofilament to determine the “protective sensation” and assess neurological status. Similarly, 128 C tuning fork assess and sensate vibratory response at the ankle and first metatarsal-phalangeal joints. To evaluate eventual ulcer healing, vascular assessment is important and essential [25, 26].

To assess patient’s vascular status, pedal and tibial pulses are checked, and also the capillary filling time (CFT) at the digits is measured. When pedal pulses are non-palpable, for further assessment, the patient is referred to a non-invasive vascular technique like lower extremity arterial pressures and recording pulse volume waveform. Due to high foot plantar pressure, the ankle-brachial index (ABI) becomes a non-essential tool. But, measuring pressure at the toe would determine the healing potential of an ulcer. Transcutaneous oxygen measurements, in addition often, act as a useful tool to determine wound healing [17, 26, 27].

To estimate an ulcer’s state of infection, its location, size, shape, depth, base, and border need to be documented. For further evaluation, a wound must be scrutinized to detect sinus tracts, depth of reach to a tendon, joint, or bone using a sterile stainless-steel probe. Though X-rays have been ordered for infected wounds, MRI acts as an important tool, particularly in diagnosing osteomyelitis and deep abscesses due to its high sensitivity. In the case of purulent exudates, which clearly describes infectious state like cellulitis, both aerobic and anaerobic cultures should be obtained [25-27].

There exists diverse categorization of diabetic foot ulcer, namely: Wagner, University of Texas wound classification system (UT), International Working Group on the Diabetic Foot (IWGDF) (abbreviated with the acronym PEDIS), SINBAD and IDSA. Amidst, Wagner's is most accepted, elucidating both the range and load of the ulcer, but does not define the shortage of blood and treatment initiatives (Table **1**) whereas UT classification enumerates not only the depth and extent of infection but also the ischemic state of the lower extremity [28]. The PEDIS system is categorized as: perfusion, extent / size, depth / tissue loss, infection and sensation [29-32]. It is more favourably appropriate to the basic mechanism or pathogenesis of DFU [32].

To interpret the standard or basis of the diabetic foot ulcers, 2 or more of the ensuing manifestations are defined: Swelling, induration, erythema around the lesion, local pain, palpable local warmth and presence of pus [30, 31]. Ascertaining the infectious level is very vital, hence as per IDSA guidelines, it is grouped as (1) Mild infection: if erythema is obtained < 2 cm, (2) Moderate infection: if erythema is > 2 cm and (3) Severe infection: systemic infection [33].

Table 1. Wagner - Meggitt classification of diabetic foot [29].

Ulcer Grading	Description
0	Foot symptoms like pain, only
1	Superficial ulcers
2	Deep ulcers
3	Ulcer with bone involvement
4	Forefoot gangrene
5	Full foot gangrene

5. SPECTRUM OF MICROBES CAUSING DFI

In those who had a previous acute infection, does not tend any treatment, monomicrobial infection with aerobic

gram-positive cocci, especially *Staphylococcus aureus* (highly isolated whether alone or a combination) and *Streptococcus* species, are the predominant cause of pathogens in DFIs [34-36]. Those with deep or chronic wounds polymicrobial infection, such as *S.aureus, Streptococcus, Enterococcus, Enterobacteriaceae* and *Pseudomonas,* commonly appear [37, 38]. On the contrary, economically advanced countries, areas with warm conditions, for example, Asia and Africa, evidenced more habitats of *Pseudomonas aeruginosa* species rather than *S. aureus* [34, 39, 40]. As well as in countries like India and Pakistan [41, 42], aerobic gram-negative multi-drug-resistant pathogen *P. aeruginosa* [43] gave rise to more than one infection, which was principally established in a study conducted at a tertiary care centre. Conditions like gangrene or foul odour, necrosis and ischaemia are primarily related to anaerobes, which occurred as a result of ulcers that are extending far down and last long but are not yet clinically distinct [44].

The presence of polymicrobial biofilms in DFUs, explored by most studies, reported an extended view of the diabetic foot microbiome by employing molecular (DNA) sequencing technologies. However, the DFUs with biofilm formations are those commonly reported within the pre-existing diabetic foot literature. In addition to aerobic species, other bacteria commonly identified in the same foot ulcers include anaerobes (namely, those belonging to Clostridium*spp*), Corynebacterium*spp.,* and gram-negative rods (namely, Klebsiella*spp.,* Acinetobacter*spp.,* Enterobacter *spp., P. aeruginosa* and *Escherichia coli*) [45].

In summary, DFI is caused primarily by gram-positive bacteria such as *S. aureus* in North America and Europe. Although *S.aureus* remains a frequent pathogen in developing countries [46], gram-negative pathogens may be predominant strains in India, Pakistan, the Middle East, Africa, China, and Brazil [46-55]. To implement a rational antimicrobial selection in DFU, which is more often present with a large microbiome, collection of specimens to detect the exact microbial contamination and its vulnerability to antibiotics is vital. As mentioned earlier, the spread of these spectra of microbes varies from region to region, and as in cases like hospital-acquired infections, previous use of antibiotics and prolonged illness [34]. The appropriate choice of antibiotics becomes a gruesome job when there is irrelevant use of antibiotics, which drives a way for developing multidrug resistance in recent times [41].

5.1. Susceptibility of Micro-Organisms

Many recent studies in India have shown antimicrobial susceptibility, according to Mehta J *et al.*; gram-negative isolates showed 100% susceptibility to carbapenem followed by polypeptides, ureidopenicillin/beta-lactamase inhibitor and systemic aminoglycosides, whereas gram-positive isolates showed 100% susceptibility to vancomycin and linezolid followed by tetracycline (90%), neomycin (70%), co-amoxyclav and cotrimoxazole (40%) respectively [56]. According to Manikandan *et al.*; gram-negative isolates showed susceptibility to carbapenem, systemic aminoglycosides, 3rd generation parenteral cephalosporin, ciprofloxacin (48%), coamoxyclav (23.7%) and ampicillin (17.5%), whereas gram-positive isolates showed susceptibility to amikacin (100%), gentamicin (100%), gylcopeptides, 1st generation fluoroqinolones, macrolides, aminopenicillin/ beta-lactamase inhibitor, lincosamide antibiotics andoxacillin [57]. This certainly shows that still extended-spectrum beta-lactams and few narrow spectra anti-microbial are effective.

6. CULTURE AND EMERGENCE OF RESISTANCE

To obtain culture specimens from the diabetic wound as per the guidance of IDSA, clinically uninfected diabetic foot wound should not be cultured because it does not require antimicrobial therapy and advised clinicians to order culture before initiating empiric antibiotic as a feasible step on the case of infected wounds [31]. Cultures are not recommended for mild infections for those who have just not received an antibiotic. All appropriately diagnosed DFIs should be cultured to identify the micro-organisms and their susceptibility. It is mentioned that tissue (aseptic – deeper) specimens offer a defined specificity and sensitivity information compared to the swab specimens, which is quite inaccurate [58, 59]. Specimens obtained from both tissue (deeper) and swab provides adequate information about microbial spectra in living tissues with great susceptibility [60, 61]. The repeat culture has its significance only in conditions like when highly contaminated specimens were observed initially, that is, before therapy or in cases such as therapeutic failure [37]. Blood cultures are only needed for patients with evidence of sepsis syndrome.

More recent studies using molecular microbiological (genotypic) techniques have demonstrated that, compared to standard (phenotypic) microbiology, there are considerably more micro-organisms of many more species (especially obligate anaerobes) [62]. What remains unclear, however, is whether it is clinically beneficial to direct antimicrobial therapy against all of these identified organisms, many of which are not classic pathogens. Due to poor laboratory services, decreased irrational ESBL antibiotic use and a rise in quality of managing DFIs would build to implement a guideline for culture specimen, cost-effective [63].

Wounds that have lasted long (≥4 weeks), antecedent hospitalization of people, recent exposure to antibiotics and one possess bone infection, the largely secluded pathogen was methicillin-*resistant S. aureus* (MRSA) [64, 65]. Many studies in DFIs disclosed that 15-20% existence and universality of MRSA conducted in the 1990s and 2000s [64]. Since the late 1990s, there was a peak of MRSA load in many countries, but according to latest reports, a universal fall off is noticed particularly in economically strengthened countries by regulating strict measures for infection control at hospitals [66-69]. The antibiotic coverage targeted against MRSA due to its burden in DFIs has been declined yet remains unnecessarily; therefore, programs like antimicrobial stewardship is needed to decide empiric MRSA coverage [70]. In developing countries, the existence of Multi-drug re-

sistant (MDR) gram-negative micro-organisms, including *extended-spectrum beta-lactamase (ESBL) or* carbapenemase-producing *Enterobacteriaceae* and multi-drug resistant non-fermenters, has gained an earnest discussion at tertiary hospitals [41, 42, 71-73].

7. ANTIMICROBIAL THERAPY ON PRACTICE

Diabetic foot ulcers are grouped into: (1) Non-limb threatening where the presence of cellulitis is < 2cm and absence of bone or joint infection and (2) Limb threatening in which cellulitis of> 2 cm is seen and shows bone and joints, and systemic infection [23]. Just upon clinical experience, only an antibiotic is still instilled in diabetic ulcers because of less research studies. Entirely depending on the basis of a culture and susceptibility report, antibiotic therapy is advocated.

Generally, an empiric antibiotic regimen is initiated at first until culture results arrive. This regimen mainly aims to act against the most prevalent causative pathogens in parallel to its modified clinical severity to infection [74]. Mild infections are required to be treated in an outpatient set up with an oral narrow-spectrum antibiotic that shows activity against aerobic gram-positive microbes for a period of 2 weeks so that when the modification is needed, it can be done, which exhibits low risk. Managing frequently with broad-spectrum is found to be an irrelevant therapy.

Parenteral and broad-spectrum are preferred choice of antibiotic regimen since it brings only a small amount of changes in circumstances for severe infections. Patient's individual aspect, such as drug allergy, known resistance to the antibiotic, impaired kidney or hepatic function, and discomfort in consumption or compliance, should be taken into account in deciding an empiric regimen. Any regimen should shield the most common causative pathogens, especially Staphylococci and Streptococci. In gram-negative bacilli and Enterococci, particularly in those treated preliminarily or showing severe infection, extended envelopment is employed. While antibiotic activity against anaerobes is intended only for wounds that have got devitalized tissues like necrotic, gangrenous or foul-smelling wounds. Though anaerobes are less frequent, they play a major role in mixed infection with aerobic spectrum.

As per IDSA, on the basis of clinical severity of DFI, empirical anti-microbial therapy comprises both broad and narrow spectrum agents (*e.g.*, glycopeptide, lincosamide, lipopeptide antibiotics are combined with fluoroquinolones especially in moderate or severe polymicrobial suspected) and anaerobic coverage. In mild infections (*S.aureus,* Streptococci), oral agents such as cephalexin, amoxicillin-clavulanate, levofloxacin, dicloxacillin (narrow spectrum), clindamycin (community-associated MRSA), doxycycline and co-trimoxazole (active against many MRSA and some gram-negative) are preferred therapies [31].

In severity scale of moderate infections (earlier parenteral or oral agents are required) and severe (commonly initiated with a parenteral agent) infections, as per the microbiological spectrum, agents such as ampicillin-sulbactum, ertapenem, cefoxitin, ceftriaxone, moxifloxacin, ciprofloxacin or levofloxacin with clindamycin (MSSA, *Streptococcus* spp, *Enterobacteriaceae,* obligate anaerobes), Imipenem-cilastatin (ESBL) and vancomycin, linezolid, daptomycin (assess CPK), (MRSA) tigecycline (warning of higher mortality risk) can be used.

Finally,piperacillin-tazobactam is the preferred choice of agent for *P.aeruginosa,* as in Table **2**. According to WHO, MRSA was enlisted in 2017 as a 'high' priority pathogen due to a high prevalence of resistance, mortality rate, the burden on community and healthcare settings. In addition, in 2018, the ICMR and AMRSN group, based on their study, had alerted on the high prevalence of 38.6% of MRSA in India. Recently, DCGI has approved the novel antibiotic EMROK (both oral and parenteral) discovered by an Indian firm to treat acute bacterial SSSIs, exhibiting potent bactericidal activity [75].

Topical antibiotics act as adjuvant therapy in treating foot ulcers having mild to moderate levels of infection. Though the efficacy of topical antibiotics such as neomycin, polymyxin B, gentamicin and mupirocin as an adjuvant in diabetic foot infection is less than in SSTIs, its theoretical advantages such as obtaining high local drug levels, low systemic adverse effects and the possibility of using novel agents should be taken into consideration for its use in foot infections when the primary treatment fails.

Duration of antibiotic therapy, in case of mild to moderate foot infections, is usually adequate for 14 days (1 – 2 weeks), needs to be extended only in severe infection [76]. Discontinuation of antibiotics is suggested in the absence of infection, though the wound is not resolved entirely and initiates podiatric management. To evaluate the therapeutic effectiveness of antibiotic therapy-induced, elements such as body temperature, leucocyte, ESR, inflammatory marker (CRP) levels and glycemic index need to be monitored, apart from being aware of wound site inflammation.

7.1. Using Scores to Evaluate Antimicrobial Therapy Effect

Large trials never compared the habitual purpose of DFU classifications that were so far being educated in the literature. Feasibility to use and understand the PEDIS, IDSA, UT, and SINBAD classification systems aids to anticipate the disease prognosis. Although both DFI and DUSS wound scores are hard to understand, many huge trials have authenticated its use [77, 78]. Depending on certain defined wound attributes, the Diabetic Ulcer Severity (DUSS) Scoring system is related to repairing the wound at various phases. Despite the chance of being infected is high in co-morbidities, there is no appropriate link between soft tissue infection and wound healing, as stated in a few studies [79, 80].

Lipsky et al. developed a 10-item scoring system that measures the outcome of antimicrobial treatments for DFIs in studies, meant as DFI Wound Score [77]. This semi-quantitatively measures the size and depth of the wound along

Table 2. Empiric choice of therapy for DFI as per the severity.

Severity	Pathogens	Choice of Antibiotic	Comments
Mild Infection	*Staphylococcus aureus* (MSSA)*; Streptococcus* spp	Levofloxacin	Daily once; substandard use in *S.aureus*.
		Amoxicillin-clavulanate	Both broad spectrum and anti-anaerobic agent.
		Cephalexin	Requires QID dosing; inexpensive [31].
		Dicloxacillin	Administer four times a day; narrow-spectrum; Affordable.
		Clindamycin	Shows extensive activity in the community-associated MRSA, assess macrolide sensitivity index [31].
	Methicillin-resistant S. aureus (MRSA)	Doxycycline	MRSA and few gram-negative; undefined against *streptococcus species*.
		Trimethoprim/ sulfamethoxazole	MRSA and some gram-negative.
Moderate / Severe Infection	MSSA*; Streptococcus species; Enterobacteriaceae;* obligate anaerobes	Ertapenem	Daily once. Broad-spectrum anti-anaerobic activity, poor against gram-negative *P. aeruginosa*.
		Ampicillin-sulbactam	Sufficient at low detection of *P. aeruginosa*.
		Imipenem-cilastatin	Broad-spectrum; not active in MRSA; recommended only when ESBL producing pathogens identified.
		Levofloxacin/ ciprofloxacin with clindamycin	Both oral and parenteral dosage forms are suitable. Only a few studies clindamycin spectrum against severe *S. aureus* infections.
		Moxifloxacin	Daily once oral agent. Broad-spectrum also comprise activity against obligate anaerobes.
		Ceftriaxone	Daily once, a parenteral third-generation cephalosporin.
		Cefoxitin	IV Second-generation cephalosporin with anti-anaerobic activity.
		Tigecycline	Broad-spectrum highly active against MRSA. Reported with GI disturbances. Warning carries mortality risk. A similar spectrum was not proven by combining glycopeptide and carbapenem.
	MRSA	Linezolid	Not Affordable; Chance of toxicity in use of >2 wk
		Vancomycin	Shows a prominent rise in MIC for MRSA.
		Daptomycin	Daily once. Monitor CPK levels.
	Pseudomonas aeruginosa	Piperacillin-tazobactam	Most antibiotics are not useful. Four times or thrice daily. Broad-spectrum antibiotic.
	MRSA, *Enterobacteriaceae, Pseudomonas,* obligate anaerobes	Vancomycin plus one of the following: ceftazidime, cefepime,piperacillin-tazobactam, aztreonam or a carbapenem	Highly broad-spectrum; particularly used in severe infection. 3rd or 4th generation cephalosporin, monobactam is considered to cover obligate anaerobes [31].

with signs of inflammation. Scoring can be done by easily envisaged definitions of wound parameters. Once wound discharge (purulent and nonpurulent) is excluded, it turns out an 8-item score that provides better measurement statistics [77]. An outcome of the treatment trial employed in foot ulcers can be easily estimated using DFI Wound Score.

8. PODIATRIC MANAGEMENT IN DFI

The Closure of the wound is vital in the management of diabetic ulcers [81]. Based on ischaemic condition and severity of the ulcer, wound management is planned in diabetes patients. The main components of wound care include necrotomy/ debridement, minimize the pressure at the injured site (offloading), selection of clean and moist wound dressings and reduce infection using enough antibiotics [82-84].

8.1. Debridement

Debridement is the removal of debris, eschar, surrounding callus, or unhealthy tissue that may impede wound healing and foster infection [85]. Debridement must be executed in chronic wounds, thereby disposes of most of the necrotic tissue and debris [86, 87]. Mostly accomplished by pulling out the wound edge tissue such as callus, necrotic portion, debris and base of unusual injuries. Generation of the lost granulation tissue is essential for wound recovery, provided only by debridement, which is crucially known through many clinical studies [82, 83, 88].

According to Frank et al.'s hypothesis, new wound bleeding occurring at the time of debridement action, owes to increased vascular endothelial growth factor (VEGF) levels [89]. Although upon failure of antibiotic therapy, debridement is the only option available for any non-healing ulcer.

To enhance the speedy recovery of the wound, one requires recurrent debridement in DFU, but insufficient evidence exists [90]. Debridement is of 5 kinds: surgery, enzymatic, auto-lytic (hydrogels), mechanics and biologics. Among all, surgical debridement proved efficacy in trials [83]. To remove all dead tissue and bone, there is a type of sharp debridement called surgical debridement. To alter the state of wound healing from chronic to an acute domain, debridement is the available ground.

8.2. Offloading

Offloading is the redistribution of pressure off the wound or ulcer to the entire weight-bearing surface of the foot where it grows to be a part of podiatric management of DFU. High foot pressure areas are the main targets for ulceration. One best way to minimize pressure is bed rest; since it is not possible, an effective method called total contact casting (TCC) is approached. This TCC, which is formed of some specially designed casts, dissipates the burden at the ulcer site. It alleviates fluid build-up that is involved during wound recovery and permits a patient to be mobile. Though wearisome in use, TCC proved its healing capacity of 73-100% merely by decreasing pressure at the wound. The main drawback is plaster irritation that may be prone to fresh lacerations and hard to inspect wound daily whereas the use of Cam Walker, removable cast walker would up--bring the everyday wound examination, early infection and dressings easier. Apart from bed rest and TCC, wheelchairs and specially modified walkers to shoes are other few useful methods [91, 92].

8.3. Hyperbaric Oxygen

This technique lessens the probability of amputation, while healing has been proved at 6 weeks in DFUs concluded a Cochrane review in 2015. Stable culminations were not drawn because of insufficient quality trials, also no ease in one year of use [93].

8.4. Negative Pressure Wound Therapy (NPWT)

During the process of wound healing, the inflammatory period is prolonged by surplus fluid and cellular waste, which are removed using a vacuum, but studies proved it inconsistent despite its straightforward mechanism. Parameters such as actual time to begin NPWT, the time period between each treatment and pressure potential in the duration of chronic wound healing need to be optimized to carry out research [94].

9. SURGICAL INTERVENTION IN DFI

All surgical methods influence a biomechanical change in the affected foot [95]. The liability of late foot complications like major amputations can be delayed further by a few surgical approaches such as pus drainage, sharp debridement, removal of infected bone in diabetic foot infection. Few retrospective studies reported a combined therapy of antibiotics with podiatric care (surgery) is successful in treating non-limb-threatening foot infections, whereas for limb-threatening infections like diabetic foot osteomyelitis (DFO), management has highly relied upon conservative surgery followed by post-antibiotic treatment [95]. But the reliability of surgery in foot infection has increased recurrence, re-ulceration, re-vasularization, another surgical procedure, and amputation though long term limb salvage is achieved [95, 96]. Though the outcome of antibiotic use in deep infections was not followed up, it cannot predict a therapeutic failure when used alone in certain individuals; it lessens the surgical complications and duration of regimen compared to surgery. Since the studies comparing the efficacy of antibiotics versus surgery are sparse, and those were assessed on diverse endpoints [96]. Hence many evidence-based studies are encouraged to identify a definitive role, which would provide adequate cure and healing for foot infection in the near future.

CONCLUSION

Upon reviewing a considerable number of clinical studies, it is clear that there still exists variability in the use of drug regimens for DFI in relation to present microbial resistance. Also, the current scenario of management for DFI mainly concentrates only on the prevalent known microbial contamination rather than the unknown spectrum and other prevalent MDR strains. Hence, this study concludes that a prominent probe of undefined causative microbes and its susceptibility towards methodologically sound trials in a large population and its interventions would contribute to building better rational management of DFI in the crisis of growing antimicrobial resistance worldwide.

LIST OF ABBREVIATIONS

DFI	=	Diabetic Foot Infections
DFU	=	Diabetic Foot Ulcer
PVD	=	Peripheral Vascular Disease
MMP	=	Matrix Metallo-Proteinases
TGF-β	=	Transforming Growth Factor
UT	=	University of Texas wound classification system
MRSA	=	Methicillin-Resistant *Staphylococcus aureus*
MDR	=	Multi-Drug Resistance
IDSA	=	Infectious Diseases Society of America
ICMR	=	Indian Council of Medical Research
TCC	=	Total Cast Casting

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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