Issue Rehabil. Orthop. Neurophysiol. Sport Promot. 2025; 50: 15–25. ISSN 2300-0767
DOI: 10.19271/IRONS-000222-2025-50

REVIEW ARTICLE

TREATMENT OF DIABETIC FOOT SYNDROME: A COMPREHENSIVE REVIEW OF THERAPEUTIC APPROACHES

LECZENIE ZESPOŁU STOPY CUKRZYCOWEJ: KOMPLEKSOWY PRZEGLĄD METOD LECZENIA

Maria Potrykus[1,A,B,D,F], Agata Krupa[2,A,B,D,F], Anna Krawczyk[3,A,C,E,F], Michał Pałuchowski[4,A,C,D,F], Julia Kiełbratowska[5,A,B,D,F], Maciej Mozer[6,A,B,D,F], Wiktor Możarowski[7,B,C,D,F], Jan Mateńko[8,A,B,C,F], Wiktoria Pietruszka[7,B,D,E,F], Przemysław Klasicki[4,B,C,E,F]

[1]Oddział Kardiologiczny z Pododdziałem Chorób Wewnętrznych, Szpital w Puszczykowie im. Prof. S. T. Dąbrowskiego S.A., Puszczykowo, Poland
[2]Oddział Chorób Wewnętrznych, Diabetologii i Gastroenterologii, Mazowieckie Centrum Rehabilitacji "Stocer" Szpital Chirurgii Urazowej św. Anny w Warszawie, Warszawa, Poland
[3]Zakład Innowacji w Ochronie Zdrowia, Szkoła Główna Handlowa w Warszawie, Warszawa, Poland
[4]Klinika Chirurgii Ogólnej i Naczyniowej, Państwowy Instytut Medyczny MSWiA w Warszawie, Warszawa, Poland
[5]Oddział Chorób Wewnętrznych, Szpital Morski im.PCK w Gdyni, Gdynia, Poland
[6]Oddział Chirurgii Plastycznej, Rekonstrukcyjnej i Chirurgii Ręki, Państwowy Instytut Medyczny MSWiA w Warszawie, Warszawa, Poland
[7]Klinika Chorób Wewnętrznych, Endokrynologii i Diabetologii, Państwowy Instytut Medyczny MSWiA w Warszawie, Warszawa, Poland
[8]Oddział Chirurgiczny, Powiatowe Centrum Zdrowia Sp. z o.o. Otwock, Otwock, Poland
A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

ABSTRACT

Introduction

Diabetic foot syndrome (DFS) is a severe complication of diabetes that increases the risk of limb amputation and significantly affects quality of life. Effective management requires a comprehensive approach, integrating advanced imaging, accurate microbiological diagnostics, targeted antibiotics, and innovative treatments. This review highlights the latest advancements and emphasizes the importance of an interdisciplinary approach in improving outcomes.

Aim

This review aims to analyze current strategies for diagnosing, evaluating infection severity, and treating DFS, including antibiotic therapy, surgery, and treatments like negative pressure and hyperbaric oxygen. It provides guidance for clinicians and researchers and identifies areas requiring further research.

Author responsible for correspondence:
Maria Potrykus
Oddział Kardiologiczny z Pododdziałem Chorób Wewnętrznych,
Szpital w Puszczykowie im. Prof. S. T. Dąbrowskiego S.A.,
ul. Józefa Ignacego Kraszewskiego 11, 62-040 Puszczykowo, Poland
Email: maria.potrykus@op.pl
https://orcid.org/0009-0006-1815-7040

Authors reported no source of funding
Authors declared no conflict of interest

Date received: 9th March 2025
Date accepted: 11th May 2025

Material and methods
A literature review was conducted using the PubMed, ResearchGate, Web of Science, and Google Scholar databases, covering the years 1990–2023. Keywords related to the treatment of diabetic foot syndrome were used, including surgical methods, antibiotic therapy, and supportive treatments. Original and review articles published in Polish, English, German, and French were included. Non-peer-reviewed publications and those not addressing therapeutic aspects were excluded.

Results
Effective management of DFS depends on an integrated approach, combining advanced diagnostics, targeted antibiotic therapy, and innovative wound healing techniques. Surgical precision and a multidisciplinary team are essential to minimize complications and amputations.

Conclusions
An integrated approach involving early diagnosis, targeted therapy, advanced wound care, and surgical intervention significantly improves outcomes, reducing amputation rates and enhancing the quality of life for DFS patients.

Keywords: diabetic foot infection, surgical management of diabetic foot, supportive therapies in diabetic foot treatment

STRESZCZENIE
Wprowadzenie
Zespół stopy cukrzycowej (DFS) to poważne powikłanie cukrzycy, które zwiększa ryzyko amputacji kończyn i znacząco wpływa na jakość życia pacjentów. Skuteczne leczenie wymaga kompleksowego podejścia, obejmującego zaawansowaną diagnostykę obrazową, dokładne badania mikrobiologiczne, ukierunkowaną terapię antybiotykową oraz innowacyjne metody leczenia ran. Niniejszy przegląd przedstawia najnowsze osiągnięcia w tej dziedzinie i podkreśla znaczenie interdyscyplinarnego podejścia w poprawie wyników leczenia.

Cel
Celem tego przeglądu jest przedstawienie kompleksowej analizy obecnych strategii diagnozowania, oceny nasilenia infekcji i leczenia zespołu stopy cukrzycowej, w tym terapii antybiotykowej, interwencji chirurgicznych oraz zastosowania terapii podciśnieniowej i tlenoterapii hiperbarycznej. Przegląd dostarcza cennych wskazówek dla klinicystów i badaczy, a także wskazuje obszary wymagające dalszych badań.

Materiał i metody
Przegląd literatury przeprowadzono w bazach: PubMed, ResearchGate, Web of Science oraz Google Scholar, obejmując lata 1990–2023. Zastosowano słowa kluczowe związane z leczeniem zespołu stopy cukrzycowej, w tym metodami chirurgicznymi, antybiotykoterapią oraz terapiami wspomagającymi. Włączono prace oryginalne i przeglądowe w językach: polskim, angielskim, niemieckim i francuskim. Wykluczono publikacje nierecenzowane oraz niezwiązane z tematyką terapeutyczną.

Wyniki
Skuteczne leczenie zespołu stopy cukrzycowej opiera się na zintegrowanym podejściu, łączącym zaawansowaną diagnostykę, ukierunkowaną terapię antybiotykową oraz innowacyjne

techniki leczenia ran. Precyzyjne techniki chirurgiczne i zespół multidyscyplinarny są niezbędne do minimalizacji powikłań i amputacji.

Wnioski
Zintegrowane podejście, obejmujące wczesną diagnozę, ukierunkowaną terapię antybiotykową, zaawansowaną pielęgnację ran i interwencje chirurgiczne, może znacząco poprawić rokowania pacjentów z zespołem stopy cukrzycowej, zmniejszając wskaźnik amputacji i poprawiając jakość życia.

Słowa kluczowe: infekcja stopy cukrzycowej, chirurgiczne leczenie stopy cukrzycowej, terapie wspomagające w leczeniu stopy cukrzycowej

Introduction
Infections of the foot, especially in diabetic individuals, are frequently associated with ulcerations that can progress to serious infections such as osteomyelitis. In advanced cases, such conditions can necessitate limb amputation. Impaired perception in diabetics increases the risk of unnoticed skin trauma, including abrasions, blisters, and foreign bodies. The primary objective in managing an infected diabetic foot is to inhibit the progression of osteomyelitis and systemic infections while minimizing the risk of limb amputation. The treatment of diabetic foot ulcers (DFU) is a multidimensional approach encompassing antibiotic therapy, surgical debridement, optimization of glycemic control, and interventions aimed at enhancing peripheral blood circulation (Graninger, 2006).

Aim
This review discusses current diagnostic and treatment strategies for infected diabetic foot syndrome, including antibiotic therapy, surgery, negative pressure wound therapy, and hyperbaric oxygen therapy. It emphasizes early diagnosis and interdisciplinary care to prevent complications.

Metarial and methods
This review examines the literature published between 1990 and 2023 from PubMed, Google Scholar, Web of Science, and ResearchGate. Keywords included diabetic foot infection, antibiotic therapy, surgical treatment, and wound therapies. The review emphasizes peer-reviewed studies, evidence-based clinical guidelines, and recent developments in treating infected diabetic foot syndrome, highlighting the clinical value of multidisciplinary approaches in improving treatment outcomes.

Results
Diagnosis and assessment of infection severity in diabetic foot
Early and accurate diagnosis of infection is crucial for assessing the severity of the condition, selecting an appropriate antibiotic therapy regimen, and planning necessary interventions, including hospitalization or amputation (Lavery *et al.,* 2007). The diagnosis of infection relies on classic symptoms (pain, erythema, swelling, purulent discharge), as well as secondary features, which may be crucial when symptoms are masked by peripheral neuropathy or ischemia (Lipsky, 2007; Miyan *et al.,* 2017). Alterations in wound odor, such as putrid, acidic, or saccharine characteristics, may serve as clinical indicators of infection (Gardner *et al.,* 2009). In cases of deep contagions, systemic symptoms, such as fever, may indicate a more advanced or severe infection (Pittet *et al.,* 1999). Specimens collected through scraping the ulcer base with a scalpel, or through wound or bone biopsy, are more reliable than wound swabs, which may be contaminated by commensal flora (Dinh *et al.,* 2008). Bacterial culture confirms the

diagnosis, but the obtained results are associated with a 50% risk of errors (Graninger, 2006). Among imaging studies, conventional radiography has limited sensitivity (54%) in detecting osteomyelitis (Dinh *et al.,* 2008). MRI is characterized by high sensitivity (90–100%) but lower specificity (<80%) for this purpose. SPECT/MRI scanning and hybrid techniques (e.g., combined with computed tomography) enhance diagnostic efficacy (Zavadovskaya *et al.,* 2015). Aseptic aspiration of pus or tissue fluid using a needle is an alternative diagnostic method that allows for pathogen identification and precise selection of targeted treatment. Furthermore, in cases where imaging cannot be performed due to patient contraindications or lack of appropriate equipment, it may be the only diagnostic option (Chakraborti *et al.,* 2010; Senneville *et al.,* 2006). Specimens should be collected before the initiation of antibiotic therapy or at least 10 days after its discontinuation (Lipsky *et al.,* 2012).

Antibiotic therapy

In mild foot infections, the most common pathogens are aerobic Gram-positive bacteria, primarily Staphylococcus aureus and β-hemolytic streptococci (group B). Moderate and severe infections are more often polymicrobial, including Gram-positive cocci (*S. aureus*), Gram-negative rods (*E. coli*, *Proteus mirabilis*, *Klebsiella* spp.), and non-fermenting Gram-negative rods (*Pseudomonas aeruginosa*). Osteomyelitis is most commonly caused by *S. aureus*, both in monomicrobial and polymicrobial infections (Zanella *et al.,* 2016). Local wound treatment and prior use of antibiotics select for resistant strains, such as MRSA, cephalosporin-resistant enterococci, and anaerobes (e.g., *Bacteroides*, *Clostridium*, *Peptococcus*, *Peptostreptococcus*) in wounds with necrosis and deep tissue damage (Day and Armstrong, 1997; Lipsky *et al.,* 1990; Lipsky, 1999). Factors that increase the risk of antibiotic resistance include the overuse of antibiotics, their prophylactic use in non-infected wounds, and suboptimal treatment choices. Therapy should be directed based on culture results and microorganism susceptibility testing.

Treatment of infections in diabetic foot should be targeted towards a narrow spectrum of pathogens based on microbiological test results (Lipsky *et al.,* 2016). The use of antibiotic therapy in non-infected wounds is not supported by evidence, as it does not enhance healing or reduce infection risk. Excessive use of antibiotics increases the risk of microbial resistance (Abbas *et al.,* 2015).

Empirical antibiotic therapy is typically required before culture results are available, especially in severe or rapidly progressing infections. It should cover *S. aureus*, and in cases of moderate or severe infections, also include Gram-negative bacteria (Lipsky *et al.,* 2012; Lipsky *et al.,* 2016). In warm regions of the world, as well as in cases of sepsis or severe infections, coverage of Gram-negative bacteria and potentially anaerobes is essential. In patients at risk of MRSA infection, empirical antibiotic regimens targeting these strains should be considered (Chargui *et al.,* 2014). For mild infections, oral antibiotics can be used, while severe infections or systemic conditions initially require parenteral treatment, which can be continued orally once the patient's condition stabilizes. The transition from parenteral to oral therapy depends on the severity of the infection and the patient's condition, typically lasting from several days to a few weeks (Bader, 2008).

If clinical improvement is observed, empirical antibiotic therapy may be continued, although culture results indicating resistance should prompt careful reassessment. A lack of response to treatment requires modification of the therapy to include broader-spectrum agents, targeting all isolated organisms. Recurrent ulcers may require microbiome screening from nasal, perineal, or oropharyngeal sites (Lavery *et al.,* 2014). In cases of treatment failure, it is crucial to evaluate the adequacy of serum drug levels, absorption, or metabolism of the prescribed medications, as well as to

determine whether surgical intervention may be required (Lipsky *et al.,* 2016).

Osteomyelitis may affect up to 80% of diabetic foot infections (DFI), particularly in the case of extensive and deep ulcers. The most reliable diagnostic method is bone biopsy, since surface samples demonstrate only around 50% concordance with bone biopsy findings (Ha Van, 2019). Laboratory tests, such as the erythrocyte sedimentation rate (ESR) (>70 mm/h), may support the suspicion of infection but have limited sensitivity (Newman *et al.,* 1991). Conventional radiography has low sensitivity (54%) and is primarily used for monitoring changes over time (Dinh *et al.,* 2008). Histological analysis of bone is crucial in distinguishing Charcot neuroarthropathy from infection. A predominance of osteoclasts over osteoblasts suggests neuroarthropathy (Ertugrul *et al.,* 2013). The treatment should include *S. aureus* and be tailored to the chronic nature of the infection (Lipsky, 1999). The recommended duration of therapy is approximately 6 weeks, according to the IDSA (2012) and IWGDF (2016) guidelines (Abbas *et al.,* 2015). Limited antibiotic penetration into bone tissue may reduce their effectiveness. Antibiotics are classified by their bone-to-blood concentration ratios as having good (>0.3; e.g., clindamycin, fluoroquinolones), moderate (0.1–0.3; e.g., β-lactams, macrolides), or poor (<0.1; e.g., aminoglycosides, vancomycin) bone penetration (Ha Van, 2019). The definitive method for treating chronic osteomyelitis is the removal of infected bone through debridement, resection, or amputation (Lipsky, 1999).

The duration of antibiotic therapy depends on the severity of the infection, ranging from 1 week for mild infections to several weeks for severe infections and bone or bone marrow infections (Grayson *et al.,* 1994; Lipsky, 1997). Aiming to shorten the duration of therapy reduces the risk of resistance development, minimizes side effects, and lowers costs. Antibiotics can be discontinued once the symptoms of infection resolve, rather than continuing until complete wound healing (Aragón-Sánchez, 2011).

Surgery

Surgical intervention plays a critical role in the management of diabetic foot, especially in advanced cases involving tissue necrosis or deep infections. It involves various strategies aimed at effectively controlling the infection, preserving the limb, and restoring its function.

Effective treatment of diabetic foot syndrome (DFS) requires a multidisciplinary team, including surgeons, infectious disease specialists, and nursing professionals, working together to optimize care and treatment outcomes (Fisher *et al.,* 2010; Zgonis *et al.,* 2008). The fragile health of patients with diabetes and comorbid conditions (e.g., heart disease, chronic kidney failure) increases the risk of surgical complications.

Surgical treatment is tailored to the form of DFS (neuropathic or neuroischemic), with an emphasis on preserving as much of the foot and its function as possible. In neuropathic DFS, changes are primarily due to peripheral nerve damage, leading to loss of sensation, foot deformities, and the formation of ulcers, while maintaining good tissue perfusion that facilitates healing. In neuroischemic DFS, ischemia is caused by macro- and microangiopathy, often in combination with neuropathy. These differences define the surgical approach in each case. In neuropathic DFS, treatment is focused on structural protection of the foot and involves procedures aimed at reducing deformity and selective amputations limited to necrotic tissue. Treatment of neuroischemic DFS, however, is focused on restoring perfusion through endovascular methods, endarterectomy, or extensive amputations to prevent the spread of gangrene (Liapis *et al.,* 2001). The stepwise approach includes initial aggressive debridement to control the infection, assessment of vascular status and potential revascularization to improve tissue perfusion, followed by soft tissue and skeletal reconstruction

to close the wound and salvage the limb (Lyakhovsky *et al.,* 2023; Zgonis *et al.,* 2008).

Initial surgical management typically involves extensive and thorough debridement, which is considered a critical step in infection control. This involves the removal of all necrotic tissue and drainage of abscesses to reduce the bacterial load and support the healing process (Ivanusa *et al.,* 2023).

After surgical debridement, a thorough assessment of the vascular status is essential. This may include vascular surgery or endovascular interventions to improve blood flow and support the healing process (Fisher *et al.,* 2010; Rauwerda, 2004).

Once infection is controlled and circulation optimized, reconstruction of tissues follows. The primary objective is to achieve wound closure and limb preservation, a process that frequently necessitates multiple staged surgical interventions (Fisher *et al.,* 2010; Zgonis *et al.,* 2008). Various wound cleaning methods, irrigation, and lavage are employed, followed by techniques for final closure. The use of modern hydrocolloid dressings and biomaterials is also recommended for ulcer closure (Okroyan *et al.,* 2018). Modern methods for treating deep tissue infections, which reduce tissue damage and improve outcomes, include endoscopic-assisted drainage support, cavitation using ultrasound waves to remove necrotic tissue and enhance the healing process, negative pressure wound therapy to assist drainage and accelerate tissue regeneration, and the use of the bactericidal and regenerative properties of ozone in infection treatment (Ivanusa *et al.,* 2023). Despite promising treatment outcomes, there is a lack of sufficient high-quality evidence to support the routine use of adjunctive therapies (Marson *et al.,* 2018).

Effective surgical treatment of DFS is complex and involves a varied, stepwise approach tailored to the specific characteristics of the infection and the patient's condition. The ultimate goal is not only to stop the progression of DFS but also to improve the patient's quality of life.

Negative Pressure Wound Therapy

Negative Pressure Wound Therapy (NPWT) is a widely used approach in the treatment of diabetic foot wounds, including ulcers and post-amputation sites. This technique applies regulated negative pressure to the targeted area, facilitating wound healing by actively extracting excess fluid (exudate), thereby maintaining a clean environment, lowering infection risk, and improving circulation by reducing edema.

NPWT offers significant benefits in treating DFU, primarily by accelerating healing compared to traditional moist wound dressings. NPWT creates a controlled environment that reduces edema, supports angiogenesis, and enhances granulation tissue formation, which promotes wound closure (Armstrong *et al.,* 2005; Chen *et al.,* 2021). Studies consistently show that wounds treated with NPWT have a higher likelihood of achieving complete healing compared to those managed with traditional dressings, providing patients with faster and more durable outcomes (Liu *et al.,* 2017; Liu *et al.,* 2018; Zhang *et al.,* 2014).

Due to its ability to modulate inflammatory processes, NPWT represents an effective therapeutic option that promotes faster and more efficient wound healing, particularly in the case of chronic ulcers, where excessive inflammatory response can hinder regeneration. This mechanism is associated with the regulation of signaling pathways and the reduction of inflammatory marker levels. The MAPK-JNK pathway, which plays a crucial role in regulating inflammatory processes and tissue damage response, is suppressed during the application of NPWT. The reduction in levels of inflammatory markers, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), also limits the intensity of the inflammatory response (Wang *et al.,* 2019).

Studies suggest that NPWT can significantly improve the prognosis of patients with DFS, helping them avoid amputation and enhancing their quality of life. NPWT

has been shown to reduce the incidence of major (above-ankle) amputations, highlighting its therapeutic relevance in advanced DFU management. The impact of NPWT on the frequency of minor amputations, such as toe amputations, remains less clear and requires further research (Liu *et al.,* 2017; Liu *et al.,* 2018; Zhang *et al.,* 2014).

Although NPWT has higher initial costs, it is more cost-effective over the long term. Faster wound healing reduces the overall treatment time, leading to lower hospitalization costs. NPWT requires less frequent dressing changes compared to traditional methods, which reduces material and healthcare staff labor costs. Due to its more effective wound healing, NPWT reduces the risk of complications that may require rehospitalization. The reduced risk of amputation lowers long-term costs associated with rehabilitation, prosthetics, and loss of productivity. As a result, NPWT not only improves clinical outcomes but also leads to significant savings for both patients and the healthcare system (Bogucka *et al.,* 2023; Liu *et al.,* 2017).

NPWT is generally safe, but requires monitoring for complications. Improper application or lack of adequate monitoring may lead to the development of infections at the wound site. In patients with coagulation disorders or improper use of NPWT, there is a risk of excessive bleeding. Incorrect patient selection or improper use of the device can result in tissue necrosis. It is crucial to strictly follow the guidelines for NPWT application, continuously monitor the wound and device status, and carefully select patients, including a thorough analysis of the indications for the proposed treatment approach (Ji *et al.,* 2021; Seidel *et al.,* 2020). NPWT has a safety profile comparable to standard wound care, with no significant increase in adverse events, provided it is used correctly and regularly monitored (Chen *et al.,* 2021; Liu *et al.,* 2017; Zhang *et al.,* 2014).

The effectiveness of NPWT largely depends on the application technique and adherence to standardized treatment protocols. International consensus recommends regular training of medical staff in the application of NPWT and monitoring therapy outcomes to minimize the risk of complications such as infections or damage to surrounding tissues, ultimately leading to better treatment outcomes. Guidelines include detailed instructions on wound preparation, device selection, pressure level, and dressing change frequency. The success of NPWT largely depends on its customization to the individual patient's needs, including the wound's size and depth, the degree of exudate, and the presence of infection (Ji *et al.,* 2021).

Hyperbaric Oxygen Therapy

Hyperbaric Oxygen Therapy (HBOT) aids wound healing through several mechanisms, including enhancing oxygen delivery, promoting angiogenesis, reducing inflammation, and modulating growth factors and reactive oxygen species.

The Hyperbaric Oxygen Therapy in Diabetics with Chronic Foot Ulcers (HODFU) study demonstrated that HBOT significantly increases the rate of complete ulcer healing compared to placebo (52% vs. 29%) (Löndahl *et al.,* 2010). Meta-analyses have confirmed that HBOT increases the healing rate of DFU (relative risk: 1.901) and reduces the frequency of major amputations (relative risk: 0.518) (Zhang *et al.,* 2022). However, studies did not show significant differences in the impact on minor amputations (Brouwer *et al.,* 2020).

HBOT stimulates neovascularization by increasing the expression of markers such as EGF, VEGF, PDGF, FGF-2, and CXCL10. This process is regulated through the activation of growth factors such as HIF-1α, which controls the proliferation and migration of endothelial cells and fibroblasts (Dhamodharan *et al.,* 2019; Huang *et al.,* 2020). By elevating the oxygen partial pressure within tissues, it improves oxygen delivery to the wound, meeting the energy requirements essential for tissue regeneration (Kranke *et al.,* 2015; Tejada *et al.,* 2019). Oxidative stress constitutes

a key regulatory mechanism in the wound healing cascade, and HBOT has shown the ability to modulate it, thereby supporting the regeneration process. HBOT reduces the levels of pro-inflammatory mediators such as TNF-α and IL-1β, thereby contributing to the reduction of oxidative stress and inflammation. The antioxidant response is also crucial in controlling oxidative stress. Enzymes like catalase, superoxide dismutase (SOD), and glutathione peroxidase (GPx) are critical in mitigating oxidative damage (Capó *et al.,* 2023; Paprocki *et al.,* 2020). Reactive oxygen species (ROS) and nitrogen species generated during HBOT exhibit bactericidal effects and enhance the antimicrobial activity of the immune system by influencing processes such as cell recruitment and chemotaxis (Fosen and Thom, 2014; Thom, 2009; Thom, 2011; Zhou *et al.,* 2023). HBOT influences signaling pathways, including ROS/MAPK/MMP, thereby supporting the healing of ischemic wounds by reducing tissue degeneration (Zhang and Gould, 2014).

HBOT shows promising results in improving the healing of DFU and reducing the incidence of major limb amputations. However, the current evidence base is limited by methodological weaknesses, underscoring the need for larger, high-quality studies to validate its efficacy and cost-effectiveness (Barnes, 2006; Wunderlich *et al.,* 2000). Despite these challenges, HBOT remains a valuable adjunctive treatment for selected patients with DFS.

Conclusions

Diabetic Foot Syndrome (DFS) is a common complication of diabetes, often leading to infections, osteomyelitis, or amputations. Treatment includes prompt diagnosis, appropriate antibiotic therapy, surgical procedures, and adjunctive therapies. Diagnosis is based on clinical evaluation along with microbiological and imaging investigations. Antibiotics are prescribed according to culture results, with empirical treatment utilized for severe infections. Surgical management, including wound debridement and improving blood flow, plays a pivotal role in advanced stages. Negative Pressure Wound Therapy (NPWT) and Hyperbaric Oxygen Therapy (HBOT) contribute to healing by improving microcirculation and promoting tissue regeneration. A multidisciplinary, integrated care model may reduce the risk of amputation, optimize clinical outcomes, and enhance health-related quality of life. Ongoing monitoring and individualized treatment are vital for successful management.

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