ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

Impact of Antimicrobial Resistance in Diabetic Foot Infections

Received: 22 October 2022, **Revised:** 29 November 2022, **Accepted:** 30 December 2022

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Keywords
Diabetic foot infection, Diabetic foot ulcer, Antimicrobial Resistance, Sepsis

Abstract
A terrible micro-vascular consequence called diabetic foot ulcers (DFUs) is to blame for a significant rise in morbidity and mortality. DFU is a complex complication of infection, neuropathy, and peripheral artery disorders. Microbial flora causes conditions ranging from superficial cellulitis to chronic osteomyelitis and lower limb amputations due to gangrenous extremities. Antibiotic treatment is not mandatory without soft tissue or bone infection evidences. Bacteria (particularly gram positive coccii) must be treated empirically for infections ranging from mild to moderate, while obligatory anaerobes and aggressive gram-negative aerobes must be targeted by wide spectrum antibiotics for severe infections or infections brought on by drug-resistant organisms. Neuropathic ulceration commonly leads to common diabetic foot infections. Diabetic foot infections can cause osteomyelitis, especially when they are linked to serious and foot ulcers which are chronic in nature. In this study we assessed various published trailsbased on clinical setting for diabetic foot ulcer, infections and drug resistance cumulatively. It is observed diabetes foot infections should receive individualized antimicrobial treatment based on the severity of the condition, the microbial pathogen, and the host for minimizing antimicrobial resistance.

1. Introduction
Diabetes patients who get foot infections suffer serious risk to their health and well-being. Since there are now roughly four times as many people with diabetes as there were 40 years ago, this threat is getting worse [1,2]. According to estimates, those with diabetes who get diabetic foot infections (DFIs) are

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Journal of Coastal Life Medicine

more than 50 times more likely to end up in the hospital. According to estimates, DFIs account for about 1 in 5 hospital admissions in the United States that are connected to diabetes [3]. In addition, individuals with DFIs have an amputation risk that is about 155 times more than in people without diabetes [2]. Amputation makes patients very anxious. A recent study reported that patients with diabetes as well as foot problems are more afraid of amputation than they are of dying. This is in contrast to people with diabetes who do not have foot disease [4]. Once infection occurs, there is a substantial chance of death [5]. It is anticipated that, based on the kind of foot infection, 1 in 4 to 1 in 8 hospitalized patients will pass away after a year [5]. Death rates from Hodgkin lymphoma, breast cancer, and prostate cancer are all lower than the expected 5-year death rate for those with diabetic foot disease (for instance, infections and ulcers) [6,7]. The issue of the increasing occurrence of DFIs is made worse by the growth in antimicrobial resistance (AMR) among common bacterial diseases seen in infected foot [8]. Our understanding of DFI is being expandedby novel moleculartools for the detection of uncultivable microorganisms, which are also forcing doctors toreconsider which microbes should be selected and which are disregarded. In this study, we provide a fresh look at the disease and health outcome measurement of DFIs, highlight important elements of their pathogenesis, talk about issues with antimicrobial resistance, assess accepted practices for the diagnosis and treatment of DFIs (including involvement of bone), and highlight significant side effects of therapy that are important to clinicians.

2. Diabetic Foot Infections - Epidemiology and Pathogenesis

It is estimated that 148 million of the over 435 million people who have diabetes globally may develop a foot ulcer (DFU) during their lifetime. Foot infections are possibly to occur in the lifespan of almost 75 million persons who already have diabetes because more than 50% of DFUs become infected [11,13]. Any inframalleolar infection in a diabetes mellitus patient is referred to as a DFI, broadly speaking [14]. Due to a number of well-known factors, individuals with diabetes are more likely to get foot infections. For diabetics, an open wound—typically a neuropathic DFU—is the greatest risk factor for developing a pedal infection [15,16]. People with type 2 diabetes who have ulcers typically have foot infections first, which greatly increases their chance of dying [17]. In fact, a prospective study predicted that compared to people with undamaged skin, people with foot wounds have > 2000-fold higher risk of contracting an infection [2]. In addition to the wound itself, bare feet, peripheral neuropathy, renal impairment, chronic ulceration (time span greater than 30 days), a history of lower leg amputation, and peripheral arterial disease are additional risk factors for infection [2,18].

DFIs have a complicated and multifaceted etiology [14,19]. The majority of DFIs are caused by the contiguous spread of bacteria (sometimes fungi) that penetrate the standard skin defenses to spread infection. Hematogenous seeding is a less common choice for the lower leg's soft tissues. Contrary to popular belief, while such incidents do occur, the majority of them do not result in DFIs, such as cut of a part of foot by a sharp instrument or stubbing of one's toe on an object. A neuropathic DFU is the primary cause of the majority of DFIs. As a result, one of the early phases in the DFI’s pathogenesis

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Journal of Coastal Life Medicine

is typically the formation of a DFU. Neuropathy (autonomic, sensory, and motor), which is brought on by chronic, improperly controlled hyperglycemia, is the main factor producing DFU risk [20]. Initial signs and symptom of diabetic peripheral neuropathy include a Loss Of Protective Sensation (LOPS), which patient may not be aware of fact. Inadequate ambulatory biomechanics (and inappropriate load bearing) are made possible by sensory neuropathy and LOPS, which leads to osteoarthritis, callous formation, soft tissue necrosis, and ulceration [14,21]. Skin dryness is a factor in autonomic diabetic neuropathy, which raises the chance of a minor cut or crack [14,21]. Cellulitis can be exacerbated and encouraged by peripheral edema. The pathophysiology of disease is complicated by peripheral vascular dysfunction. The lack of oxygen caused by arterial vascular occlusive disease makes tissue more prone to harm and less effective at healing wounds. Additionally, it limits the movement of circulating leukocytes to the infection site [11]. Assessing vascular flow and, where possible, restoring inadequate flow is crucial components of DFI management and prevention, as will be covered later in this article.

When a wound develops in a neuropathy patient, it may get polluted and colonized by bacteria, which can lead to infection. In those with diabetes, the risk of skin infections is increased. The There is no known reason for this arisen vulnerability to infection in the context of diabetes entirely comprehended, although being frequently documented. Numerous immune system flaws have been linked to diabetes [23]. It has been proposed that the fundamental cause of this compromised host defense is hyperglycemia itself [24]. There is no doubt that polymorphonuclearleukocyte (neutrophils) from diabetic patients show a variety of abnormalities, including weakened chemotactic, phagocytic, and microbicidal capabilities [26]. When exposed to a bacterial challenge, monocytes and macrophages derived from diabetes patients showed reduced reactive oxygen species emission and impaired phagocytic ability compared to those from control patients, which led to less efficient microbial death [27]. Additionally, dendritic cells from diabetics showed a decreased capacity to move to local lymph nodes, indicating that both innate and adaptive immune responses are compromised in diabetic individuals. Although it is well established that diabetes-associated hyperglycemia is closely related to these weakened immune cell phenotypes, the precise processes by which this happens are still unknown and the subject of ongoing research. [29,30]

3. Antimicrobial Resistance and its impact

Benjamin Lipsky said that it’s been clear, within time;all antibiotics will eventually lose their effectiveness [31]. Diabetes patients typically receive antimicrobial treatment for foot sores, which promotes the growth of AMR. AMR is an international crisis. Infections caused by microorganisms resistant to antibiotics are predicted to cause more than 10 million deaths annually by 2050, or one death every three seconds, unless current trends are reversed [32,33]. Recent research shows the increase in infections that are multidrug resistant connected with DFIs and their possibly negative outcome [8].

Bacteria with a gram-positive culture almost all clinical signs and symptoms of DFI, including minor paronychia, persistent bone infection, and potentially fatal necrotizing soft tissue infection, are caused by Staphylococcus

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ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

aureus, which is a significant causal culprit [8,34]. Skin and soft tissue infections are now mainly due to Methicillin-resistant S.aureus (MRSA), notably those in the diabetic patients' foot. Patients with diabetes who are hospitalized with MRSA skin and soft tissue infections do not seem to react as well to antibiotic therapy as hospitalized patients without diabetes [35].There is dispute over how MRSA infection may affect other clinical results in DFI. Studies are divided, for instance, on the issue of whether MRSA increases the risk of infection recurrence, duration of antimicrobial therapy, length of hospital stay, mortality prediction, or clinical clearance of the infection [36]. Nearly all classes of currently available agents are now affected by the increasing danger posed by gram-negative bacteria AMR**.** Extensive-spectrum and AmpC beta lactamases are two new types of beta lactamases that have arisen as a form of resistance to advanced-generation cephalosporins [37,38]. Additionally, there has been a sudden loss of susceptibility to carbapenems, which is brought on by a variety of processes, including carbapenemase expression. Enterobacteriaceae that are carbapenem-resistant pose a serious risk the health of people. Alarmingly, DFIs [39] contain gram-negative bacteria that are "pan-resistant," including some isolates of Pseudomonas and Acinetobacter.

Biofilm production is a significant cause in AMR in the context of diabetic foot wounds because it can act as a barrier for microorganisms to antibiotics, dramatically increasing treatment resistance and persistence [40,41]. A crucial traditional treatment for eliminating or disturbing biofilms is surgical debridement of wounds. Although the research and use of novel strategies to address biofilms in DFI stretches outside the purview of this review, their importance will grow.

4. Approaching the patient with a diabetic foot infection initially

Treatment of the wound, the foot, and patient as a whole, that is clinically appropriate for probable DFI is required when evaluating a technique. This method conforms with recommendations made by the Infectious Diseases Society of America (IDSA) and the International Working Group on the Diabetic Foot (IWGDF) [42,43]. The evaluation of active infection signs and symptoms, such as warmth, swelling, discomfort, induration, erythema and purulent discharge, should be a part of wound assessment. While their visibility enhances the chance of this disease, their absence should rule out clinical infection. The foot which is affected should subsequently be examined for any notable signs of infection spreading distally beyond 2 cm from a lesion and for any further foot irritation causes (eg, trauma, fracture, thrombosis, or gout). In addition, a biomechanical, vascular, and neurological examination of the affected foot should be performed to look for any anomalies that could indicate an underlying risk or cause an infection and/or diabetic foot ulcer (eg, LOPS). Last but not least, doctors should examine the entire patient for signs of systemic inflammation and specifically for two SIRS criteria, such as a temperature greater than 38℃ or less than 36℃, a heart rate greater than 90 beats per minute, a respiratory rate greater than 20 breaths per minute or $PaCO_2$ (partial pressure of carbon dioxide in arterial blood) lower than 32 mm Hg, and a white blood cell count greater than 12,000 or less than 4000 cells/mL or 10% immature (band) forms. The Sequential Despite the fact that the definition of sepsis has evolved since the IDSA (Infectious Diseases Society of America) and IWGDF (International Working Group on the Diabetic Foot), the (Sepsis-

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ISSN: 2309-6152 (Online)
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Related) Organ Failure Assessment Score may not always be used [44]. Since sepsis is now understood to be a life-threatening organ failure brought on by a dysregulated host response to infection, doctors should be aware that the prior criteria for "severe" DFIs were tied to this concept. DFI assessments are categorized similarly to how the IDSA and IWGDF did it in the past [42,43]. Both the PEDIS Grade (perfusion, extent, depth, infection and sensation) and the IDSA Infection Severity rating systems are simple to use clinically and offer uniform standards for use in research. Uninfected (PEDIS Grade 1), a mild local infection (PEDIS Grade 2), an advanced local infection (PEDIS Grade 3), a deeper or more complicated infection, or a severe infection with systemic inflammatory signs (PEDIS Grade 3) is possible clinical presentation. Clinical programmers may be able to engage in interdisciplinary and systematic interventions at various levels with the help of a method for DFI assessment that is consistent. There are several classification schemes that could help with different institutional requirements [45]. Once the existence, intensity, and DFI severity have been determined, medical & surgical resources can be prioritized properly. Without further testing or treatment, empiric antibiotic therapy based on likely microbiological pathogens may be provided to patients having acute, mild infections with no complications. Microbial screening and vigorous wound care prior to empiric antibiotic treatment may help in the selection of the right antibiotic as well as treatment length for patients with subacute, chronic, or more difficult mild infections. The most prudent course of action for patients who have signs of a serious illness may be empiric antibiotic medication while immediately organizing a surgical and diagnostic assessment even if this may reduce the yield of the ensuing microbiologic culture [42,43].

5. Diagnosing Osteomyelitis

The ability to diagnose diabetic foot osteomyelitis (DFO) is essential since it influences treatment options and give rise to amputation risk [46]. DFO nearly invariably occurs from direct, continuous extension via an adjacent, infected chronic ulcer. Hematogenous seeding of bone happens less commonly in the foot. The diagnosis should be considered only if the overlying ulcer is greater than 2 cm^2, penetrates to the bone, or when the patient's ESR is higher than 70 mmHg [37]. Furthermore, DFO may be indicated by a high blood C-reactive protein level, which is beneficial for tracking the effectiveness of treatment [47, 48]. The clinical markers of infection that are used to determine bone infection diagnosis should be kept by laboratory, microbiological and radiographic evidence combination [46]. The doctor’s ability to use a blunt metal probe to bone (PTB) through an ulcer item can give aid in the early assessment of DFO; however this is a doubtful issue. PTB test which comes positive is more diagnostic in case of high suspicion, but PTB test resulting negative is not useful [37, 46].

There are some excellent reviews on the radiographic examination for DFO, which is continually evolving [49, 50]. A plain radiograph of the foot is an appropriate imaging test because it identifies radiopaque foreign objects, soft tissue gas, osteolytic bone anomalies, and periosteal elevation [49]. These studies lack specificity, and once an infection begins, such bone abnormalities might take weeks to manifest [49]. Currently, MRI is still the preferred imaging method for researching DFO because to its accessibility and accuracy [49]. Renal insufficiency patients

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
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Journal of Coastal Life Medicine

are allowed to have an MRI without gadolinium contrast since the procedure may reveal anomalies that point to a bone infection (edema). Nuclear medicine tests, such as [18F] fluorodeoxyglucose positron emission tomography/computed tomography and radiolabelled white blood cell scintigraphy (either with 99mTc-hexamethylpropyleneamineoxime or 111In-oxine) [50], are not readily available to many practitioners. Infection-related mid foot Bone-related Charcot neuro-osteo arthropathic changes are difficult to distinguish using standard radiography techniques [51]. DFO can be highly suspicious when radiographic evidence is present alongside a clinically ill ulcer [51]. Mid foot DFO without continuous dissemination from a nearby wound is unusual, according to 386 Chastain et al. The doctor should think about an acute fracture as a potential cause of mid foot erythema, edema, discomfort, and warmth when Charcot alterations are present. Finding a particular microbiological cause of bone infection can enhance therapy results [52]. Because bone cultures frequently differ from cultures obtained from underlying soft tissue or sinus systems, bone cultures are crucial to study [53–55]. A significant, albeit brief, study revealed that when bone biopsy was used to guide treatment for DFO rather just soft tissue swab culture, it was much more successful [52]. It is advised to do a bone biopsy after at least two weeks without taking antibiotics if there is no severe illness and the patient does not require rapid antibiotic treatment [53]. It is planned that the Concordance in Diabetic Foot Ulcer Infection research would compare soft tissue culture-directed treatment to bone culture-directed therapy as part of a larger inquiry [55].

6. Empiric and directed antibiotic treatment for diabetic foot infection

After clinical assessment of DFI, potential antibiotic treatments and microbiological causes may be taken into consideration. A microbiologic test should be conducted prior to beginning of empiric antibiotic therapy if the patient's condition is stable [42, 43]. The presentation severity, the effect of pre-operative antibiotic treatment on later interventions, as well as the diagnostic & therapeutic aims of surgical interventional modification all influence the requirement for antibiotic therapy prior to surgical debridement. Despite the incidence and consequences of DFI, there isn't adequate support for several antimicrobial tactics. This is partly because DFI has such a broad definition, infections can occur in a variety of anatomical and host situations, and there are many different kinds of microorganisms that can infect people. A few key findings from clinical trials dealing with DFI treatment have supported certain broad recommendations; nevertheless, more information is required to guide future guidance [56,57].

It's still debatable which type of the optimum antibiotic treatment for DFI is either oral or intravenous. Despite the fact that topical therapy provides theoretical benefits such direct antibiotic distribution while lowering systemic toxicity, there aren't many good clinical studies that show the efficacy of topical antimicrobial treatment. Topical therapy may have a constant and future role as a preferred or complementary treatment choice, according to further research in this field [58]. As a result, the most popular administration methods for formulations are still oral and intravenous. Although the majority of medical professionals advise intravenous antibiotic therapy for serious infections, at least initially, it is still unclear

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ISSN: 2309-6152 (Online)
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how long intravenous therapy should last for the best results [42,43]. A small but significant body of literature has shown that oral antibiotics are beneficial in treating infections of the skin and soft tissues, such as osteomyelitis. Although detractors claim that oral medication has little empirical backing, there is also a dearth of evidence to demonstrate the superiority of intravenous antibiotics [59]. Emerging studies are encouraging since they suggest that oral or intravenous medication may be just as effective in treating some types of bone and joint infection [60,61]. Other clinical trial findings indicate that oral medication following first intravenous therapy plays at least a little influence [62]. Oral treatment is probably adequate for minor infections. For minor infections, some individuals may benefit from receiving solely oral treatment or brief course of IV treatment, followed by oral treatment. Further clinical evidence will be required before a clear future guideline for treating severe DFI can be developed, but in the intervening time, clinical judgments based on particular patient characteristics will continue to direct treatment decision-making [42, 43]. Gram-positive bacteria like Staphylococcus and Streptococcus are typically blamed for acute, minor illnesses. Empiric antibiotic regimens frequently utilized in diabetic foot infections found clindamycin, cephalexin, and amoxicillin-clavulanate. For DFIs that have not responded to past antibiotic regimens, expanding the antibiotic spectrum of activity to cover, it may be required to use gram-negative bacteria and MRSA. Patients who have particular risk factors for Pseudomonas aeruginosa (such as water exposure, puncture wounds, and warm climates like those in Asia and Africa) could gain from empirical medication targeting this organism. The likelihood of polymicrobial infections increases when they are connected to persistent wounds or when previous antibiotic treatment courses have failed. These infections may call for adequately widened antibacterial spectra of activity. Anaerobic antimicrobial treatment should be employed in cases when anaerobic bacteria are present, such as necrotic or foul-smelling wounds. Patients having severe infections & systemic inflammation may be benefitted from starting therapy with a broad-spectrum intravenous drug, such as a carbapenem or vancomycin combination with a beta-lactam and beta-lactamase inhibitor (e.g., ampicillin-sulbactam, piperacillin-tazobactam) (eg, ertapenem, meropenem). Once there is identification of a microbial pathogen, antimicrobial therapy should be targeted [42, 43]. DFO typically involves a variety of microbes in which Streptococci and staphylococci are frequently engaged [46, 53, 63, 64]. In contrast, gram-negative bacteria like Escherichia coli and Pseudomonasare in warm regions. Staphylococci (such as S aureus and coagulase-negative Staphylococcus) are also frequently present [53]. Studies increasingly point to anaerobic bacteria as the culprits [64]. Therefore, it is best to undertake anaerobic cultures of bone samples whenever possible. DFO therapy options, both empiric and guided, might be chosen accordingly. The length of antibiotic therapy must be decided upon when the necessity for therapy has been established, a route has been chosen, and empiric or directed antimicrobials have been prescribed. The most crucial considerations for healthcare professionals are the degree of infection and the existence of bone or joint infection. Patients with a little soft tissue injury infectionsmay include therapy with one to two weeks of medication, according to suggestions in the guidelines. Patients with moderate soft tissue infections should get

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ISSN: 2309-6152 (Online)
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Journal of Coastal Life Medicine

therapy for one to three weeks, whereas patients with significant soft tissue infections should receive therapy for two to four weeks. The recommended course of antibiotic therapy for bone and/or joint infection can vary depending on the type of surgical regimen, from 2 to 5 days in cases where there is no visible residual infected tissue after surgery to 3 months in cases where there is visible residual dead bone both with and without surgery [43]. To update this professional advice, further information is required. Six weeks of treatment are probably sufficient in the majority of instances forpatients with no necrotic bone or other lingering infection sources [65]. One randomized patient in a prospective study found that patients without peripheral arterial disease (PAD) who stopped receiving antibiotics once clinical manifestations of DFI had subsided fared just as well as those who continued taking them for the full recommended course. This suggests that a patient's clinical response to treatment may have an impact on how long they receive treatment [66].

7. Medical, surgical, and emerging management of diabetic foot infection

Despite the fact that antibiotic treatment is acrucial component of DFI therapy, medical procedures are crucial for infection control. Besides, healing of wound and patient wellness can be counted here too. Although there aren't enough facts to back up the idea that managing diabetes is an important aspect of managing DFI, it is conceivable and remains a good idea for general medical care. Diabetes mellitus medical care should encourage ideal blood glucose control and lessen microvascular and macrovascular consequences [67–69]. As mentioned, PAD is a prevalent concomitant disease in people with diabetes. An appropriate revascularization via endovascular or open surgical procedures, medicinal treatment for this condition, perfusion for antibiotic delivery and wound healingprocedures may be required [70]. An essential and frequently underused component of ulcer therapy is wound off-loading, which can be accomplished with the aid of contact casts, diabetic insoles, or other devices [71]. It is important to emphasize that a small number of patients in a few restricted randomized controlled studies demonstrated equivalent results between the antibiotic-only and conservative surgery groups, showing that conservative treatment may be effective in treating DFI [72]. Direct care of wound and any necessary surgical regimen are still essential for many DFI and DFU therapy programmers. Debridement is a vital step in the treatment and recovery of wounds. Wound care remedies may help with wound debridement. Even if harsh debridement or other involved surgical procedures might accomplish this. Additionally, as more trustworthy data are made available, novel wound dressings and creative wound care treatments including vacuum-assisted wound closure, hyperbaric oxygen therapy, granulocyte colony-stimulating factor, and others may become more important in the management of DFU and DFI [73–77]. Despite best efforts for management of infection, debride wounds and revascularize limbs, partial limb amputation may be necessary when there is gangrene, severe necrosis, or a chronic infection [78–80]. As prior DFU and DFI are highly related with recurrent pathology, more medical advancement following amputation is necessary [81,82].

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ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

8. Complications of medical management of diabetic foot infection

Although antimicrobial medication is still a crucial component of management of DFI, unforeseen outcomes and negative effects do occasionally happen. Adverse effects in Gastrointestinal region, hematologic side effects, renal and liver damage, and drug allergy are examples of direct adverse consequences of antibiotic therapy [83,84]. For the proper dose of some medications, including intravenous vancomycin, both for end organ dysfunction andappropriate laboratory monitoring is necessary (i.e., acute kidney injury) [85]. Prescribers should take into account and keep an eye on any unusual. Medication interactions and adverse consequences, such as rhabdomyolysis with daptomycin or serotonin syndrome with linezolid [86,87]. AMR caused by drug exposure has happened and still happens, as was previously mentioned [88]. The advent of a multidrug-resistant pathogen component of the DFI microbial ecology serves as both a warning against overusing antibiotics and an invitation to adopt more sophisticated treatments when necessary. In addition to microorganisms that are multi-drug resistant, Clostridium difficile infection has also become a hospital and community problem as a result of antibiotic exposure [89]. Providers must distinguish between non-infected and infected wounds in order to choose the right course of action and length of therapy to minimize both the risk to the patient's health and the public health.

9. Conclusion

The global burden of DFIs is rising as a result of the population's ageing and the rising incidence of diabetes. Evaluation of the infected wound, the accompanying limb, as well as the entire patients is all parts of the right clinical treatment for the patient with a suspected DFI. Because it affects treatment and prognosis, bone infection should be taken into account in some individuals. The growing threat of AMR necessitates the use of all suitable treatment modalities, excellent the right choice of empiric and targeted antibiotic therapy, cultures of infected areas,and collaboration across many disciplines.

Reference

[1]. Roglic G. WHO Global report on diabetes: a summary. Int J Noncommun Dis 2016; 1(1):3.

[2]. Lavery LA, Armstrong DG, Wunderlich RP, et al. Risk factors for foot infections in individuals with diabetes. Diabetes Care 2006; 29(6):1288–93.

[3]. Hobizal KB, Wukich DK. Diabetic foot infections: current concept review. Diabet Foot Ankle 2012; 3:1–8.

[4]. Wukich DK, Raspovic KM, Suder NC. Patients with diabetic foot disease fear major lower-extremity amputation more than death. Foot Ankle Spec 2018; 11(1):17–21.

[5]. Fincke BG, Miller DR, Turpin R. A classification of diabetic foot infections using ICD-9-CM codes: application to a large computerized medical database. BMC Health Serv Res 2010; 10(1):192.

[6]. Armstrong DG, Wrobel J, Robbins JM. Guest Editorial: are diabetes-related wounds and amputations worse than cancer? Int Wound J 2007; 4(4):286–7.

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

[7]. Robbins JM, Strauss G, Aron D, et al. Mortality rates and diabetic foot ulcers: is it time to communicate mortality risk to patients with diabetic foot ulceration? J Am Podiatr Med Assoc 2008; 98(6):489–93.

[8]. Saltoglu N, Ergonul O, Tulek N, et al. Influence of multidrug resistant organisms on the outcome of diabetic foot infection. Int J Infect Dis 2018; 70:10–4.

[9]. Malone M, Johani K, Jensen SO, et al. Next generation DNA sequencing of tissues from infected diabetic foot ulcers. EBioMedicine2017; 21:142–9.

[10]. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016; 388(10053):1545–602.

[11]. Armstrong DG, Boulton AJ, Bus SA. Diabetic foot ulcers and their recurrence. N Engl J Med 2017; 376(24):2367–75.

[12]. Lazzarini PA, Pacella RE, Armstrong DG, et al. Diabetes-related lower-extremity complications are a leading cause of the global burden of disability. Diabet Med 2018; 35(9):1297–9.

[13]. Prompers L, Huijberts M, Apelqvist J, et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia 2007; 50(1):18–25.

[14**].** Lipsky BA, Berendt AR, Deery HG, et al, Infectious Diseases Society of America. Diagnosis and treatment of diabetic foot infections.Clin Infect Dis 2004; 885–910.

[15]. Reiber GE, Vileikyte L, Boyko EJ, et al. Chastain et al Causal pathways for incident lowerextremity ulcers in patients with diabetes from two settings. Diabetes Care 1999; 22(1):157–62.

[16]. Noor S, Khan RU, Ahmad J. Understanding diabetic foot infection and its management. Diabetes MetabSyndr 2017; 11(2):149–56.

[17]. Walsh JW, Hoffstad OJ, Sullivan MO, et al. Association of diabetic foot ulcer and death in a population-based cohort from the United Kingdom. Diabet Med 2016; 33(11):1493–8.

[18]. Nikoloudi M, Eleftheriadou I, Tentolouris A, et al. Diabetic foot infections: update on management. Curr Infect Dis Rep 2018; 20(10):40.

[19]. Lipsky BA, Berendt AR, Deery HG, et al, Infectious Diseases Society of America. Diagnosis and treatment of diabetic foot infections.PlastReconstrSurg 2006; 117(7 Suppl):212S–38S.

[20]. Frykberg RG, Cook JJ, Simonson DC. Epidemiology and health care cost of diabetic

foot problems. In: Veves A, Giurini JM, Guzman RJ, editors. The Diabetic Foot. Cham (Switzerland): Humana Press; 2018. P - 3–17.

[21]. Ulbrecht JS, Cavanagh PR, Caputo GM. Foot problems in diabetes: an overview. Clin Infect Dis 2004; 39(Supplement_2):S73–82.

[22]. Joshi N, Caputo GM, Weitekamp MR, et al. Infections in patients with diabetes mellitus. N Engl J Med 1999; 341(25):1906–12.

[23]. Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM). FEMS Immunol Med Microbiol 1999; 26(3–4):259–65.

[24]. Jafar N, Edriss H, Nugent K. The effect of short-term hyperglycemia on the innate immune system. Am J Med Sci 2016; 351(2):201–11.

[25]. Delamaire M, Maugendre D, Moreno M, et al. Impaired leucocyte functions in diabetic patients. Diabet Med 1997; 14(1):29–34.

[26]. Alba-Loureiro TC, Munhoz CD, Martins JO, et al. Neutrophil function and metabolism in individuals with diabetes mellitus. Braz J Med Biol Res 2007; 40(8): 1037–44.

[27]. Turina M, Fry DE, Polk HC Jr. Acute hyperglycemia and the innate immune system: clinical, cellular, and molecular aspects. Crit Care Med 2005; 33(7):1624–33.

[28]. Dejani NN, Brandt SL, Pin˜eros A, et al. Topical prostaglandin E analog restores defective dendritic cell-mediated Th17 host defense against methicillinresistant Staphylococcus aureus in the skin of diabetic mice. Diabetes 2016; 65(12):3718–29.

[29]. Domingueti CP, Dusse LM, Carvalho MD, et al. Diabetes mellitus: the linkage between oxidative stress, inflammation, hypercoagulability and vascular complications. J Diabetes Complications 2016; 30(4):738–45.

[30]. Wada J, Makino H. Innate immunity in diabetes and diabetic nephropathy. Nat Rev Nephrol 2016; 12(1):13–26.

[31]. Lipsky BA. Diabetic foot infections: current treatment and delaying the 'post-antibiotic era'. Diabetes Metab Res Rev 2016; 32:246–53.

[32]. Goff DA, Kullar R, Goldstein EJC, et al. A global call from five countries to collaborate in antibiotic stewardship: united we succeed, divided we might fail. Lancet Infect Dis 2017; 17(2):e56–63.

[33]. O'Neill J. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. London (United Kingdom): Review on Antimicrobial Resistance; 2017.

[34]. U, kay I, Gariani K, Dubois-Ferrie`re V, et al. Diabetic foot infections: recent literature and cornerstones of management. CurrOpin Infect Dis 2016; 29(2):145–52.

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

[35]. Lipsky BA, Itani KM, Weigelt JA, et al. The role of diabetes mellitus in the treatment of skin and skin structure infections caused by methicillin-resistant Staphylococcus aureus: results from three randomized controlled trials. Int J Infect Dis 2011; 15(2):e140–6.

[36]. Zenelaj B, Bouvet C, Lipsky BA, et al. Do diabetic foot infections with methicillinresistant Staphylococcus aureus differ from those with other pathogens? Int J Low Extrem Wounds 2014; 13(4):263–72.

[37]. LaSalvia MT, Karchmer AW. Microbiology and treatment of diabetic foot infection. In: Veves A, Giurini JM, Guzman RJ, editors. The Diabetic Foot. Cham (Switzerland): Humana Press; 2018. p. 267–79.

[38]. Xie X, Bao Y, Ni L, et al. Bacterial profile and antibiotic resistance in patients with diabetic foot ulcer in Guangzhou, Southern China: focus on the differences among different Wagner's Grades, IDSA/IWGDF Grades, and ulcer types. Int J Endocrinol 2017; 2017:8694903.

[39]. Sekhar SM, Vyas N, Unnikrishnan M, et al. Antimicrobial susceptibility pattern in diabetic foot ulcer: a pilot study. Ann Med Health Sci Res 2014; 4(5):742–5.

[40]. Vatan A, Saltoglu N, Yemisen M, et al. Association between biofilm and multi/ extensive drug resistance in diabetic foot infection. Int J ClinPract 2018; 72(3): e13060.

[41]. Mottola C, Matias CS, Mendes JJ, et al. Susceptibility patterns of Staphylococcus aureus biofilms in diabetic foot infections. BMC Microbiol 2016; 16(1):119.

[42]. Lipsky BA, Arago´n-Sa´nchez J, Diggle M, et al. IWGDF guidance on the diagnosis and management of foot infections in persons with diabetes. Diabetes Metab Res Rev 2016; 32(Suppl 1):45–74.

[43]. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2012; 54(12):e132–73.

[44]. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016; 315(8):801–10.

[45]. Game F. Classification of diabetic foot ulcers. Diabetes Metab Res Rev 2016; 32(Suppl 1):186–94.

[46]. Giurato L, Meloni M, Izzo V, et al. Osteomyelitis in diabetic foot: a comprehensive overview. World J Diabetes 2017; 8(4):135–42.

[47]. van Asten SA, Jupiter DC, Mithani M, et al. Erythrocyte sedimentation rate and C-reactive protein to monitor treatment outcomes

in diabetic foot osteomyelitis. Int Wound J 2017; 14(1):142–8.

[48]. Victoria van Asten SA, Geradus Peters EJ, Xi Y, et al. The role of biomarkers to diagnose diabetic foot osteomyelitis.A meta-analysis.Curr Diabetes Rev 2016; 12(4):396–402.

[49]. Peterson N, Widnall J, Evans P, et al. Diagnostic imaging of diabetic foot disorders. Foot Ankle Int 2017; 38(1):86–95.

[50]. Lauri C, Tamminga M, Glaudemans AWJM, et al. Detection of osteomyelitis in the diabetic foot by imaging techniques: a systematic review and meta-analysis comparing MRI, white blood cell scintigraphy, and FDG-PET. Diabetes Care 2017; 40(8):1111–20.

[51]. Rogers LC, Frykberg RG. The diabetic charcot foot. In: Veves A, Giurini JM, Guzman RJ, editors. The Diabetic Foot. Cham (Switzerland): Humana Press; 2018. p. 391–413.

[52]. Senneville E, Lombart A, Beltrand E, et al. Outcome of diabetic foot osteomyelitis treated nonsurgically: a retrospective cohort study. Diabetes Care 2008; 31(4): 637–42.

[53]. Senneville E, Robineau O. Treatment options for diabetic foot osteomyelitis. Expert OpinPharmacother 2017; 18(8):759–65.392 Chastain et al

[54]. Vris A, Massa E, Ahluwalia R, et al. Primary results of bone biopsies in outpatients with neuropathic ulcers: comparison with wound swabs and superficial tissue samples. Foot & Ankle Orthopaedics 2017; 2(3). 2473011417S000078.

[55]. Nelson A, Wright-Hughes A, Backhouse MR, et al. CODIFI (Concordance in Diabetic Foot Ulcer Infection): a cross-sectional study of wound swab versus tissue sampling in infected diabetic foot ulcers in England. BMJ Open 2018;8(1): e019437.

[56]. SelvaOlid A, Sola I, Barajas-Nava LA, et al. Systemic antibiotics for treating diabetic foot infections. Cochrane Database Syst Rev 2015 ;(9):CD009061.

[57]. Tchero H, Kangambega P, Noubou L, et al. Antibiotic therapy of diabetic foot infections: a systematic review of randomized controlled trials. Wound Repair Regen 2018; 26(5):381–91.

[58]. Dumville JC, Lipsky BA, Hoey C, et al. Topical antimicrobial agents for treating foot ulcers in people with diabetes. Cochrane Database Syst Rev 2017; 6: CD011038.

[59]. Spellberg B, Lipsky BA. Systemic antibiotic therapy for chronic osteomyelitis in adults.Clin Infect Dis 2012; 54(3):393–407.

[60]. Li HK, Scarborough M, Zambellas R, et al. Oral versus intravenous antibiotic treatment for bone and joint infections (OVIVA): study

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

protocol for a randomized controlled trial. Trials 2015; 16:583.

[61]. Scarborough M, Li HK, Rombach I, et al. Oral versus intravenous antibiotics for the treatment of bone and joint infection (OVIVA): a multicentre randomized controlled trial in Orthopaedic Proceedings. 2017: The British Editorial Society of Bone & Joint Surgery.

[62]. Schaper NC, Dryden M, Kujath P, et al. Efficacy and safety of IV/PO moxifloxacin and IV piperacillin/tazobactam followed by PO amoxicillin/clavulanic acid in the treatment of diabetic foot infections: results of the RELIEF study. Infection 2013; 41(1):175–86.

[63]. Johani K, Fritz BG, Bjarnsholt T, et al. Understanding the microbiome of diabetic foot osteomyelitis: insights from molecular and microscopic approaches. ClinMicrobiol Infect 2019; 25(3):332–9.

[64]. van Asten SA, La Fontaine J, Peters EJ, et al. The microbiome of diabetic foot osteomyelitis.Eur J ClinMicrobiol Infect Dis 2016; 35(2):293–8.

[65]. Tone A, Nguyen S, Devemy F, et al. Six-week versus twelve-week antibiotic therapy for nonsurgically treated diabetic foot osteomyelitis: a multicenter open-label controlled randomized study. Diabetes Care 2015; 38(2):302–7.

[66]. Chu Y, Wang C, Zhang J, et al. Can we stop antibiotic therapy when signs and symptoms have resolved in diabetic foot infection patients? Int J Low Extrem Wounds 2015; 14(3):277–83.

[67]. Fullerton B, Jeitler K, Seitz M, et al. Intensive glucose control versus conventional glucose control for type 1 diabetes mellitus. Cochrane Database Syst Rev 2014 ;(2):CD009122.

[68]. Paneni F, Luscher TF. Cardiovascular protection in the treatment of type 2 diabetes: a review of clinical trial results across drug classes. Am J Med 2017; 130(6S):S18–29.

[69]. Ueki K, Sasako T, Okazaki Y, et al. Effect of an intensified multifactorial intervention on ardiovascular outcomes and mortality in type 2 diabetes (J-DOIT3): an open-label, randomised controlled trial. Lancet Diabetes Endocrinol 2017; 5(12): 951–64.

[70]. Hinchliffe RJ, Brownrigg JR, Andros G, et al. Effectiveness of revascularization of the ulcerated foot in patients with diabetes and peripheral artery disease: a systematic review. Diabetes Metab Res Rev 016; 32(Suppl 1):136–44.

[71]. Fife CE, Carter MJ, Walker D, et al. Diabetic foot ulcer off-loading: the gap between evidence and practice. Data from the US Wound Registry.Adv Skin Wound Care 2014; 27(7):310–6.

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

[72]. Lazaro-Martinez JL, Aragon-Sanchez J, Garcia-Morales E. Antibiotics versus conservative surgery for treating diabetic foot osteomyelitis: a randomized comparative trial. Diabetes Care 2014; 37(3):789–95. 73.

[73]. Fedorko L, Bowen JM, Jones W, et al. Hyperbaric oxygen therapy does not reduce indications for amputation in patients with diabetes with nonhealing ulcers of the lower limb: a prospective, double-blind, randomized controlled clinical trial. Diabetes Care 2016; 39(3):392–9.

[74]. Huang ET, Mansouri J, Murad MH, et al. A clinical practice guideline for the use of hyperbaric oxygen therapy in the treatment of diabetic foot ulcers. Undersea Hyperb Med 2015; 42(3):205–47.

[75]. Liu Z, Dumville JC, Hinchliffe RJ, et al. Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus. Cochrane Database Syst Rev 2018 ;(10):CD010318.

[76]. Cruciani M, Lipsky BA, Mengoli C, et al. Granulocyte-colony stimulating factors as adjunctive therapy for diabetic foot infections. Cochrane Database Syst Rev 2013 ;(8):CD006810.

[77]. Edmonds M, La´zaro-Martı´nez JL, Alfayate-Garcı´a JM, et al. Sucrose octasulfate dressing versus control dressing in patients with neuroischaemic diabetic foot ulcers (Explorer): an international, multicentre, double-blind, randomised, controlled trial. Lancet Diabetes Endocrinol 2018; 6(3):186–96.

[78]. Callahan D, Keeley J, Alipour H, et al. Predictors of severity in diabetic foot infections. Ann VascSurg 2016; 33:103–8.

[79]. Uysal S, Arda B, Tas,bakan MI, et al. Risk factors for amputation in patients with diabetic foot infection: a prospective study. Int Wound J 2017; 14(6):1219–24.

[80]. Zhan LX, Branco BC, Armstrong DG, et al. The Society for Vascular Surgery lower extremity threatened limb classification system based on Wound, Ischemia, and foot Infection (WIfI) correlates with risk of major amputation and time to wound healing. J VascSurg 2015; 61(4):939–44.

[81]. Dubsky´ M, Jirkovska´ A, Bem R, et al. Risk factors for recurrence of diabetic foot ulcers: prospective follow-up analysis in the Eurodiale subgroup. Int Wound J 2013; 10(5):555–61.

[82]. O rneholm H, Apelqvist J, Larsson J, et al. Recurrent and other new foot ulcers after healed plantar forefoot diabetic ulcer. Wound Repair Regen 2017; 25(2): 309–15.

[83]. Keller SC, Dzintars K, Gorski LA, et al. Antimicrobial agents and catheter complications in outpatient parenteral

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

antimicrobial therapy. Pharmacotherapy 2018; 38(4):476–81.

[84]. Keller SC, Williams D, Gavgani M, et al. Rates of and risk factors for adverse drug events in outpatient parenteral antimicrobial therapy. Clin Infect Dis 2018; 66(1): 11–9.

[85]. Schrank GM, Wright SB, Branch-Elliman W, et al. A retrospective analysis of adverse events among patients receiving daptomycin versus vancomycin during outpatient parenteral antimicrobial therapy. Infect Control HospEpidemiol 2018; 39(8):947–54.

394 Chastain et al

[86]. Papadopoulos S, Ball AM, Liewer SE, et al. Rhabdomyolysis during therapy with daptomycin. Clin Infect Dis 2006; 42(12):e108–10.

[87]. Wigen CL, Goetz MB. Serotonin syndrome and linezolid.Clin Infect Dis 2002; 34(12):1651–2.

[88]. Chatterjee A, Modarai M, Naylor NR, et al. Quantifying drivers of antibiotic resistance in humans: a systematic review. Lancet Infect Dis 2018; 18(12):e368–78.

[89]. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults and children: 2017 update by the infectious diseases Society of America (IDSA) and Society for health care epidemiology of America (SHEA). Clin Infect Dis 2018; 66(7):e1–48.