# DIABETIC FOOT INFECTIONS

## OPPORTUNITIES AND CHALLENGES IN CLINICAL RESEARCH

Diabetic foot infections (DFI) are a frequent and complex secondary complication of diabetes that inflict a substantial financial burden on society and are associated with the potential for serious health consequences. The prevalence of DFI is significant, considering that more than 382 million people are living with diabetes worldwide, of which 25% will experience at least one diabetic foot ulcer and approximately 58% of these are likely to become clinically infected.[1,2] As such, diabetic foot complications continue to be responsible for the majority of diabetes-related hospitalizations and lower extremity amputations as well as pose a serious risk for death related to infection. Unfortunately, guidelines regarding the diagnosis and treatment of DFI are not specific.[1] Additionally, there is a lack of uniformity in clinical trials involving DFI. Differences in design, terminology, and clinical and microbiological outcome measurements pose significant challenges to comparing results among randomized controlled trials (RCT).[3] Thus, research in diagnosis, management, and therapy development, as well as development of standardized guidelines for upcoming studies need to be addressed in order to improve the prognosis of DFI patients.

## AN AT-RISK POPULATION

Infection by invading pathogenic organisms is of particular concern for the diabetic population. Diabetes mellitus, a metabolic condition characterized by prolonged elevated blood sugar as a result of inadequate and/or defective insulin production, triggers many downstream metabolic pathways leading to inflammation, nerve damage, circulatory dysfunction, impaired signaling and an altered immune system. The multifactorial nature of diabetes results in diminished wound healing that predisposes diabetics to foot ulcers with the potential for infection. Specifically, foot ulcers develop from a combination of major risk factors involving primarily neuropathy and ischemia. Neuropathy manifests by altering the autonomic, sensory, and motor divisions of the nervous system. These changes frequently result in dry, cracked feet and a decreased ability of the patient to sense pain and coordinate movement, thereby contributing to foot deformity and disruption of skin integrity. Another contributing factor and a common comorbidity among diabetic patients is peripheral vascular disease (PVD). PVD affects circulation and may lead to inadequate blood flow, especially in the lower extremities, predisposing the patient to ulcer formation and poor wound healing. Albeit present in about 50% of cases, PVD and associated limb ischemia are common exclusion criteria in many clinical trials or not even recorded in some RCT, thereby limiting evidence to support recommendations for treatment in such patients.[1,2,3]

“Disease state awareness is another important factor for successful recruitment,” says Dr. Harrison. “This requires working with the sites to get out into the community — not just your typical advertising campaign but really going ‘boots on ground’ to get into offices to show physicians what they’re missing. Doctors may not change their practice based on one double-blind, randomized, placebo-controlled trial published in Lancet or NEJM, but they will on one anecdotal experience. If we’re able to go into community practices and look at patients they’ve treated for years but they never focused on their liver disease and we show them patients right under their nose are progressing, then that is very powerful and that really revs-up practitioner interest in NAFLD/NASH and subsequently clinical trial recruitment inevitably improves.”

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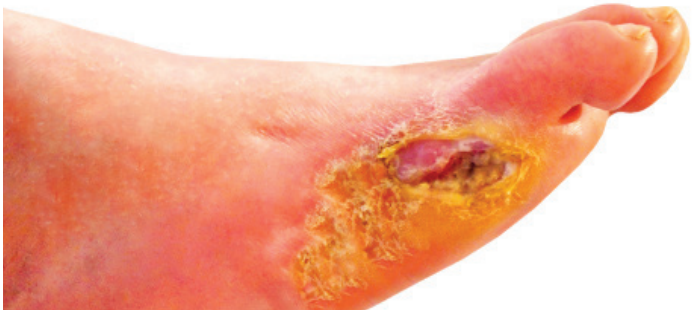

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## R&D AND REGULATORY DIFFICULTIES

Guidelines that provide recommendations on good clinical practice are based in scientific research derived from trials, preferably RCT and prospective studies. In order to justify guidelines that cover the gamut of manifestations for DFI, consistency, clarity, and objectivity are necessary across trials to ensure adequate power and to achieve statistically significant results. Unfortunately, the absence of standardization among past trials is a contributing factor to the current uncertainty regarding the management of DFI.

From a research and development perspective, categorization of ulcer and infection severity has been a major problem in past studies due to the use of varying classification schemes and wound scores, some of which are not validated or based on differing criteria. In addition to providing clinical value, though, the utilization of a standardized classification scheme to characterize DFI in terms of type, severity and outcome is necessary to provide quantitative information.[1,3] Varying timetables pertaining to treatment and evaluation of response to therapy also contribute to the variability among data and ambiguity in comparing results.[3]

From a regulatory standpoint, indications involving diabetic foot infections remain a gray area. The Food and Drug Administration's (FDA) current guidance on acute bacterial skin and skin structure infections (ABSSSI) as well as the European Medicines Society (EMA) recommendation for the treatment of skin and soft tissue infections (SSTI) fail to address drug development for treatment regimens involving DFI. Ongoing discussions concerning the definition of a diabetic foot infection, diagnosis, obtaining microbiological information, and defining clinical cure or failure still exist.[5] Additionally, diabetic foot infections complicated by bone involvement lack FDA guidance and questions regarding drug efficacy and confirming osteomyelitis in diabetic foot infection patients have yet to be standardized.[6,7] This creates regulatory challenges in terms of developing protocols for this indication. For these reasons, patients exhibiting diabetic foot infections are excluded from many clinical study criteria. The complexity of treating diabetic foot infections combined with regulatory uncertainties makes it difficult for pharmaceutical companies to develop drugs against DFI.

| SOURCES OF VARIABILITY IN TRACKING DFI |
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| Lack of standardized classification schemes |
| Wound scoring |
| Timetables for treatments and evaluation of response therapies |

## ADVANCEMENTS IN DIAGNOSIS

The most commonly used method for the identification of microorganisms in a suspected infection relies on standard clinical culture techniques. While this method is widely available at a low cost, it does not allow for the complete identification of bacteria present.[4] Advances in microbial classification through the use of molecular microbiologic techniques and rapid diagnostics would allow for a more comprehensive and less time consuming evaluation of microorganisms populating the wound environment. New technologies using multiplex PCR and gel electrophoresis have revealed that a complex community of microorganisms consisting not only of bacteria, but potentially viruses, protozoans, and fungi exist within a given wound environment. Partly attributable to the diversity and spatial arrangement of pathogens within the wound are biofilms and indeed, research has shown that deep flora are more complex than superficial flora.[4] Therefore, sample collection techniques that only scrape the surface, such as a swab, are not likely to accurately encompass the scope of microbes residing within a DFI.[4] Even so, studies exist whereby swabbing techniques were utilized and proper specimens for culture were not required, in spite of the fact that international guidelines highly recommend sample collection from deep tissue via biopsy or curettage.[1,3,8]

Further, molecular microbiologic techniques provide a more sensitive and specific means to explore and define microbial communities within the setting of DFI.[2] By amplifying and sequencing DNA associated with the wound, information regarding the total number of microbes present, their relative abundance, detection of fastidious organisms not typically revealed by culture, and genes of interest would be available. This is particularly useful as genes encoding resistance can be identified early, allowing for the selection of the most effective antimicrobial therapy. Additionally, because the human body is home to many bacteria, it is difficult to parse out commensal organisms from pathogenic organisms. While debridement attempts to filter these organisms and reduce the microbial load, it is not flawless. Molecular microbial techniques offer a greater degree of granularity in distinguishing colonization from infection and begin to elucidate the microbial interactions contributing to the severity and chronicity of infections.[4] Further research is necessary to better understand the interactions of organisms as they pertain to DFI, the associated deficits in wound healing, and to develop rapid diagnostic tests for diagnosing DFI.

## TREATMENT

The interface of potentially infectious agents in a diabetic population makes diabetic foot infections a challenging target for treatment as well. Current guidelines from the Infectious Disease Society of America (IDSA) and the National Institute for Health and Clinical Excellence (NICE) for the management of DFI include wound debridement and drainage, antimicrobial therapy, pressure offloading, and appropriate wound dressing as the mainstays of treatment. Additionally, providing coordinated management which utilizes multidisciplinary foot teams consisting of a diabetologist, an infectious disease specialist, a surgeon, a podiatrist, and other specialists with skills relevant to managing DFI has been shown to improve outcomes.[1,8] Even with current treatment, diabetic foot ulcers are still a leading cause for amputation, accounting for approximately 85% of all lower extremity amputation cases, with the presence of infection increasing the chance for amputation by 50% compared to patients with uninfected foot ulcers.[1,2]

## CONCLUSION

There are clearly growing opportunities to provide alternative treatments for diabetic patients with foot ulcers and infected foot ulcers. Still, Sponsors who are developing these new options face a challenging landscape in the development program around their product and design of the necessary clinical trials. Lack of clarity around classification schemes and scoring, management of comorbidities, diagnostics, and defining endpoints are some of the complexities. As a result, too many patients who could truly benefit from new treatments are excluded from many clinical trials. Nonetheless, promising therapies are in development. To be successful, companies who are developing products to address the growing needs in this population must develop close working relationships with regulatory authorities, have an in-depth understanding of disease and inherent complexities to drive study design, and have strong site relationships with the ability to recruit patients and manage a successful development program.

## FULL-SERVICE CLINICAL DEVELOPMENT

Medpace is a scientifically-driven, global, full-service clinical contract research organization (CRO) providing Phase I-IV clinical development services to the biotechnology, pharmaceutical and medical device industries. Medpace's mission is to accelerate the global development of safe and effective medical therapeutics through its high-science and disciplined operating approach that leverages local regulatory and deep therapeutic expertise across all major areas including oncology, cardiology, metabolic disease, endocrinology, central nervous system and anti-viral and anti-infective.

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