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Diabetic Foot Infections: Assessment, Clinical Management and Diagnostic Challenges

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❖ **Abstract**

Diabetic foot infections (DFIs) are serious long-term consequences of diabetes, and they provide a diagnostic difficulty since it is exceedingly challenging to distinguish between osteomyelitis (OM), soft tissue infection (STI), and Charcot's osteoarthropathy. However, in order to design the patient's best course of therapy, such a differential diagnosis is essential. However, it would be ideal to have a non-invasive test that is capable of detecting, localising, and assessing the degree of the infection with high accuracy. Currently, the gold standard for diagnosis is the isolation of the pathogen from bone or soft tissues. The best way to treat diabetic patients with infectious problems is through a multidisciplinary approach, although there are currently no definitive diagnostic flow charts available. This review intends to give a general overview of multimodal imaging for the diagnosis of DFI and to provide clinicians with evidence-based responses when they request that radiologists or nuclear medicine (NM) doctors examine their patients.

❖ **Keywords:**

Infection, diabetic foot, imaging, WBC scintigraphy, MRI

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❖ Introduction

A prevalent consequence of long-term diabetes is diabetic foot infection (DFI), which is linked to significant morbidity, an elevated risk of lower limb amputation, and a high death rate [1]. The development of DFI originates from a complicated interplay involving peripheral neuropathy, peripheral arterial disease (PAD), and the immune system.The main risk factor for diabetic foot ulcerations is neuropathy (DFU). Foot abnormalities brought on by damaged motor neurons lead to harm to the foot's tissues and bones. Sensory neurons injury leads to a lack of protective feeling. As a result, individuals with neuropathic conditions may get skin ulcers that go unnoticed for a long time, exposing the nearby soft tissues to the colonisation of bacteria and leading to a soft tissue infection (STI). The infection may spread to the underlying bone and result in osteomyelitis (OM) if it is not immediately found and treated. Since inadequate tissue oxygenation may hinder ulcer healing, PAD further promotes microbial invasion and the quick development to infection by providing the ideal environment for pathogen colonisation.

Additionally, PAD hinders granulocyte migration and antibiotic penetration into the affected area, promoting the progression of the infection and making its therapeutic treatment more challenging. Additionally, individuals with severe PAD are more likely to experience abrupt ischemia brought on by arterial thrombosis, which can lead to critical limb ischemia and a higher risk of amputation [2,3]. Since patients with PAD and infection exhibit more severe comorbidities and worse clinical outcomes in comparison to the traditional "neuropathic foot patients," ischemia and infection are in fact the most crucial determinants in predicting the prognosis of foot ulcerations [4]. Another important factor in the pathophysiology of DFI is uncontrolled hyperglycemia, which impairs both cell-mediated and humoral immune responses. This is mostly shown by altered leukocyte functions, decreased chemotaxis, and altered phagocytosis properties [5,6].For patients' prognostication and for planning the best course of treatment, which typically entails a combination of metabolic control, medical treatment with a specific antibiotic regimen, and surgical approach. Prompt identification of foot ulcers, STI, and OM as well as an accurate assessment of the extent of the infective process are crucial. A single classification system was proposed by the International Working Group (IWGDF) and the Infectious Diseases Society (IDSA) to evaluate the presence and severity of infection [7,8]. This system is currently used to forecast the need for hospitalisation, the likelihood of undergoing lower extremity amputation, and other unfavourable outcomes [9]. Although they may coexist in the same patient, OM and STI have been treated individually in the most recent version of these recommendations because they are two distinct disorders with differing diagnostic, pharmacological, and prognostic consequences [10].The initial steps in the diagnosis of DFI include a thorough history and physical examination, followed by a full laboratory examination, microbiologic analysis, and imaging. The presence of at least two local indicators of inflammation, such as rubor, calor, dolor, tumour, or purulent discharge, is required for the clinical diagnosis of superficial STI. Necrosis, friable or discoloured granulation tissue, and inability of the lesion to heal are examples of other secondary signs that may indicate infection [11]. Abscess, necrotizing fasciitis, and gangrene are some of the clinical signs of acute deep infection. In some circumstances, the infection process may infiltrate one or more foot compartments, necessitating an initial surgical procedure, followed by distal revascularization, to lessen the risk of amputation [12]. One of the most severe and incapacitating effects of diabetes is the emergence of an OM, which is related with extended antibiotic therapy, hospitalisation, increased re-infection rates, and a greater risk of amputations when compared to individuals with STI, leading to large societal expenses [13].The absence of local or systemic symptoms of infection or inflammation, particularly in the case of persistent infections, might make it difficult for doctors to diagnose OM. The occurrence of a bone infection may be predicted by a number of wound features, particularly the breadth and depth of the lesion. For the diagnosis of OM, a lesion with a surface larger than 2 cm^2 has a sensitivity of 56% and a specificity of 92%. Similar to how a deeper ulcer than 3 mm is considerably more likely to have an underlying OM than a shallower one (82 percent versus 33 percent) [14].The ability to use a blunt instrument to probe the bone near the lesion's base, or the "probe-to-bone test," is another diagnostic criteria. The overall diagnostic accuracy of OM is increased when the results of the probe-to-bone test are combined with those of plain radiography [15,16].The bone biopsy, which offers histological and microbiological data and is also helpful in determining the susceptibility to different antibiotics, continues to be the gold standard for the conclusive diagnosis of OM. [7]Bone biopsy is the most accurate method for locating pathogenic microorganisms, but it is an intrusive process that is not always practical. Although a deep soft tissue culture that is in close proximity to the bone does not replace a bone biopsy, it does show a strong association with it in terms of identifying the pathogen that is to blame [17].In addition to physical examinations, laboratory tests, and microbiological analyses, imaging provides a less intrusive way to diagnose DFI. For the physicians to better determine if the patient has a STI, OM, or sterile inflammation that is a characteristic of Charcot osteoarthropathy, for example, a broad panel of modalities may be extremely useful. In order to quickly begin an effective therapy and reduce the need for hospitalisation and the danger of severe amputations, it is imperative to make an accurate differential diagnosis, but there is currently no universal agreement on the diagnostic standards for imaging modalities. This study aims to give a general overview of radiologic and nuclear medicine (NM) techniques capable of making a precise distinction between various types of DFI and directing treatment plans.

❖ **Pathophysiology**

The neuropathic, vascular, and immune system aspects of the pathogenesis of diabetic foot ulcers all have a fundamental connection to the hyperglycemic state of diabetes. [11, 12]Neuropathy is brought on by hyperglycemia, which causes oxidative stress on nerve cells. [11] Glycosylation of nerve cell proteins results in further nerve dysfunction, which worsens ischemia. The motor, autonomic, and sensory aspects of neuropathic foot ulcers exhibit these cellular alterations. An imbalance of flexors and extensors, anatomical abnormalities, and eventually skin ulcerations may result from damage to the motor neurons of the foot musculature. The function of the sweat glands is compromised by autonomic nerve damage, and the

foot may become less able to moisten the skin, resulting in epidermal fissures and skin deterioration. Finally, due to diminished peripheral feeling, patients might not be aware of foot wounds. Chronic ulceration can occur because the blood supply needed to repair a diabetic foot ulcer is larger than the blood supply needed to maintain healthy skin. [9] The vascular alterations that cause diabetic foot ulcers start at the cellular level and are correlated with changes brought on by hyperglycemia in the peripheral arteries of the foot. [11] Vasodilators are reduced as a result of endothelial cell failure, and plasma thromboxane A2 levels are increased. [13] As a result, peripheral arteries experience vasoconstriction and plasma hypercoagulation, which increases the risk of ischemia and ulceration. Immune modifications affect how quickly diabetic foot ulcers heal. Patients with diabetic foot ulcers have been found to have higher T lymphocyte apoptosis, which prevents healing. [14]

❖ **RISK FACTORS**

Risk factors for foot ulcers in patients with diabetes include:

- previous lower extremity amputation
- history of a foot ulcer
- anatomic foot deformity
- peripheral vascular disease
- diabetic nephropathy in those on dialysis
- poor glycemic control
- smoking. [10]

❖ **ASSESSMENT AND DIAGNOSIS**

A standardised programme based on established risk factors should be used to evaluate diabetic patients for vascular insufficiency and neuropathic illness. [9] Take note of any anomalies in the patient's temperature, respirations, heart rate, and blood pressure in both of their extremities. [9] An infected ulcer may be indicated by fever, tachycardia, or tachypnea. By feeling all peripheral pulses and examining the patient's extremities' look and temperature, determine the patient's vascular state. A score of 1 to 1.2 on the arterial-brachial index (ABI) test is considered normal, whereas a value of less than 0.6 suggests claudication. A toe-brachial index (TBI) may be preferable for individuals with medial sclerosis; a score of 0.6 or below implies a need for vascular intervention. Intermittent claudication or limb ischemia, dry, glossy, hairless skin on the afflicted limb, brittle nails, and chilly to the touch skin are all signs of arterial insufficiency. A patient with arterial insufficiency may also have a history of cardiovascular illness or erectile dysfunction. Elevate the leg above the level of the heart and let any pooled blood drain to measure arterial flow. A healthy limb will still be pink; an arterially insufficient limb turns pale. Numbness, paresthesia, and burning sensations are signs of neuropathic illness. Any of the five tests listed below may be used to frequently check on all diabetic patients for protective sensory loss. [15]

- A patient's sensitivity to touch is assessed using the 10-g monofilament test. Touch the monofilament to one or more anatomic locations, including reference sites, while the patient's eyes are closed to check for sensation detection. If the touch cannot be felt at the test site, major nerve fibre function has been lost. Test the distal hallux's plantar surface as well as the first, third, and fifth metatarsal heads.
- A tuning fork with a 128-Hz frequency used to measure vibration. In this test, the vibratory feeling is elicited by holding a tuning fork bilaterally over the toes. Request that the sufferer close their eyes. To perform the test, place the base of a vibrating tuning fork tuned to 128 Hz on the bony surface of each bare toe in turn. The patient will be asked to indicate when the vibration is felt and when it is gone.
- The dorsal part of the hallux is pinprick tested just next to the toenail. An aberrant outcome that denotes neuropathy is the inability to detect the pinprick.
- The patient is tested for Achilles tendon ankle reflexes while seated in a chair or on an examination table. Put the foot in a neutral posture and extend the Achilles tendon just a little. Use a tendon hammer to strike the tendon. Ask the patient to lock his or her fingers together and pull; if the tendon does not respond, repeat the tendon reflex test. An aberrant finding that can suggest peripheral neuropathy is the absence of an ankle response.
- A biothesiometer is used in the vibration perception threshold test to make a semiquantitative evaluation of the patient's vibration perception threshold (VPT). By putting the instrument stylet on the patient's skin and raising the amplitude until vibration is felt, a VPT is recorded at a proximal control location while the patient is lying supine. Then, using the average of three measures for each hallux, VPT measurements are made. The later occurrence of diabetic foot ulcers has been linked to a VPT greater than 25 V. [15]

Inspect, palpate, and probe the patient's feet if they have soft-tissue wounds to gauge the degree of the soft-tissue injury and determine whether there is any bone involvement (osteomyelitis). [16]By the depth of the incision and the degree of infection, diabetic foot ulcers are categorised (Table 1, 2, and 3). [11, 16]

Stage	
A	No infection or ischemia

B	Infection present
C	Ischemia present
D	Infection & Ischemia present
Grade	
0	Epithelialized wound
1	Superficial wound
2	Wound penetrates to tendon or capsule
3	Wound penetrates to bone or joint

Table – 1 : University of Texas Diabetic Wound Classification [11]

The infectious Disease Society of America (IDSA) defines infection as the presence of at least two of the following : Local Swelling or induration ; erythema > 0.5 cm around ulcer in any direction ; Local tenderness or pain ; Local warmth ; purulent discharge , and no other cause of an inflammatory response such as fracture, trauma, or thrombosis.

Clinical Classification (IDSA)	**International Working Group on Diabetic Foot Grade**	**Description**
Uninfected	1	No systemic or local signs or symptoms of infection
Mild infection	2	Infection involving the skin or subcutaneous tissue only or erythema extending < 2 cm in any direction from the wound. No systemic signs or symptoms of infection
Moderate infection	3	Infections involving structures deeper than the skin and subcutaneous tissues or erythema extending > 2 cm from the wound margin. No systemic signs and symptoms of infection.
Severe infection	4	Any foot infection with two or more of the following signs of a systemic inflammatory response syndrome – • Temperature > 38℃ (100.4℉) or < 36℃ (96.8℉) • Heart Rate > 90 beats / minute • Respiratory rate > 20 breaths or $Paco_2$ < 32 mm Hg • White blood cell count > 12000 or < 4000 cells / mm or 10% immature forms

Table 2: Classifying Wound infection [16]

Grade 1	Superficial diabetic ulcer
Grade 2	Ulcer extension involving ligament , tendon , joint capsule , or fascia with no abscess or osteomyelitis
Grade 3	Deep Ulcer with abscess or osteomyelitis
Grade 4	Extensive gangrene of the foot

Table 3: Wagner Ulcer Classification System [11]

❖ **Osteomyelitis (OM)**

If the patient has an ulcer over a bony prominence that doesn't heal with enough pressure relief, suspect osteomyelitis. Probe to bone and erythrocyte sedimentation rate are two diagnostic procedures for osteomyelitis (ESR). A blunt, sterile probe is put into the wound during the probe-to-bone test; a hard, gritty feeling indicates a good result. In a patient with a diabetic foot ulcer, an ESR of more than 70 mm/hour is suggestive of osteomyelitis (the normal range for males and women is 0 to 22 mm/hour and 0 to 29 mm/hour, respectively). [16] A diagnosis of osteomyelitis may also be supported by plain radiographs. Radiographs are between 28 and 75 % sensitive and % specific for osteomyelitis, depending on when they are collected.Bone abnormalities changes are more likely to be seen on plain radiographs in patients who have had diabetic foot ulcers for a longer period of time. Serial radiographs offer a better level of predictability [16]. When it comes to identifying osteomyelitis, MRI has been proven to have a sensitivity range of 77% to 100% and a specificity range of 40% to 100%. [17] With regard to edoema, fluid buildup, and bone abnormalities related to osteomyelitis, MRI also offers extensive soft-tissue detail.Few studies indicate that positron emission

tomography (PET) and CT are highly sensitive (81%) specific (93%), accurate (90%) and specific (93%) for the diagnosis of osteomyelitis. [16] Although CT/PET is a promising approach for osteomyelitis diagnosis, this test may not be feasible or cost-effective. Front-line testing like radiography and MRI should be utilised initially before contemplating tests that could have restricted availability if the practitioner suspects osteomyelitis. If MRI is not available or is inappropriate, a leukocyte or antigranulocyte scan performed in combination with a bone scan is advised as an alternate diagnostic imaging strategy for osteomyelitis in a diabetic foot ulcer. [10]A bone sample may be used to confirm the diagnosis of osteomyelitis if imaging data strongly support it. Pathogens and their antibiotic susceptibility can be determined using bone histology and microbiology cultures. [10, 17] Bone biopsies conducted via the ulcer, however, may lead to false-positive results; samples should therefore be collected through clinically unaffected skin or after meticulous wound cleaning. Similar to this, soft-tissue cultures should be obtained by curettage and aspiration at the deep base of a diabetic foot ulcer and following debridement; this yields the most accurate findings for determining therapy. [16]

❖ **CLINICAL MANAGEMENT**

Patients under their care who have diabetic foot ulcers are likely to be identified by primary care doctors, who may then manage these patients with the necessary multidisciplinary assistance, such as wound care experts. Determine the patient's risk group based on their medical history, physical examination, and diagnosis, then start the right treatment (Table 4). To receive the best surgical care, refer high-risk patients with open ulcers to orthopaedic practitioners.

Risk Category	Definition	Treatment Recommendation	Suggested follow up
0	No loss of Protective sensation or peripheral arterial disease , no anatomic deformity	Patient education on foot care, including information on appropriate footwear.	Annually by generalist or specialist
1	Loss of protective sensation, with or without anatomic deformity	• Prescriptive or accommodative footwear • Prophylactic surgery if deformity cannot be safely accommodated in shoes • Continue patient education	Every 3-6 months by generalist or specialist
2	Peripheral arterial disease, with or without loss of protective sensation	• Accommodative footwear • Consider a vascular consultation for combined follow - up	Every 2 - 3 months by specialist
3	History of ulcer or amputation	• Patient education on foot care • Consider vascular consultation for combined follow-up if patient also has peripheral arterial disease	Every 1 -2 months by specialist

Table 4: Risk classification of diabetic foot ulcers [15]

Patients at low risk who do not have anatomical foot abnormalities should get patient education on proper foot care, recommendations for footwear that will lessen pressure points, and a careful evaluation of their glycemic management. In order to lower the patient's risk of microvascular illness, blood glucose levels should be monitored and optimised with a goal of a haemoglobin A1C level of 7 percent or below. [9] Surgical intervention may be required for individuals with active ulcers or anatomic foot abnormalities who are classified as being at greater risk.

- **Ulcer debridement -**Debridement of ulcers eliminates any surrounding hyperkeratosis, necrotic tissue, and foreign objects like germs. [10] A scalpel is used for precise

debridement to clean the wounds, remove the edges, and reveal a healthy tissue granulation basis for epithelial layer regeneration. Specimens may also be obtained at this time for culture. [9,15,16] The treatment of diabetic foot ulcers has traditionally included selective harsh debridement followed by gauze soaked in saline. [18] When necessary, local anaesthetic can be used to perform superficial ulcer debridement in the clinic or at the patient's bedside. With more severe peripheral neuropathy symptoms, local anaesthetic might not be necessary. Surgery in the OR is necessary for advanced ulcers needing deep tissue debridement in order to get the right specimens for culture. [10] Sharp or mechanical debridement are alternatives to chemical debridement. Debridement of diabetic foot ulcers using clostridial collagenase ointment has been demonstrated to promote healing. [18] In comparison to selective sharp debridement followed by saline-moistened gauze, clostridial collagenase ointment debridement dramatically reduced mean wound area, according to a research by Tallis and colleagues. [18] Clostridial collagenase ointment is also economical in a variety of healthcare settings, according to economic study. Hydrocolloid and hydrogel dressings, which promote autolysis of necrotic wound tissue but cannot be applied to infected wounds, are further debridement techniques. Maggot debridement treatment as well as alginate and silver-impregnated dressings may be necessary. [19] However, proper systemic antibiotic medication, frequent dressing changes, and wound inspection cannot be substituted for effective wound debridement. [20] Based on the findings of the wound culture, patients with infected diabetic foot ulcers should be given a specific antibiotic course. [9] Regularly check the wound to see how the patient is responding to the antibiotic treatment. Deep infections could need up to two months of treatment; mild infections only need two weeks of antibiotic medication. [9] According to a prospective research conducted by Manisha and colleagues, Pseudomonas aeruginosa (30.57%), Klebsiella (22.29%), Escherichia coli (16.56%), and Staphylococcus aureus (16.56%) were the main bacteria (12.74 %). [21] In 55% of the S. aureus cultures, methicillin resistance was found. Ampicillin and sulfobactam, cefepime and tazobactam, and ceftriaxone and tazobactam were all shown to be effective against gram-negative isolates. Teicoplanin, minocycline, and amoxicillin combined with clavulanic acid were shown to be effective against gram-positive isolates. Cefepime with tazobactam, imipenem, and amikacin were determined to be the most appropriate antibiotics to use as empirical therapy. The study also established the polymicrobial nature of infected diabetic foot ulcers and the multidrug resistance of these mixed infections, which represents a significant infection management risk factor. [21] Between infected and uninfected ulcers, Sotto and coworkers discovered significant changes. [22] A positive result in uninfected wounds was related with the presence of two methicillin-sensitive S. aureus clonal complexes, which were present in 86 % of the isolates from uninfected wounds. In addition, a gene that distinguishes between infected and non-infected diabetic foot ulcers was discovered with 96.5 % sensitivity. In addition to providing powerful predictive tools for treating diabetic foot ulcers, the observed clonal complexes and virulence marker may encourage the more prudent use of antibiotics. Negative-pressure wound treatment, which encourages angiogenesis and boosts granulation tissue, and pressure-reducing techniques can also promote wound healing. [23,24] Driver and associates compared the results of transdermal continuous oxygen therapy (treatment group) to conventional debridement, offloading, and moisture therapy for treating wounds (control group). [25] Over the course of 14 to 20 months, wound fluid and weekly measurements were gathered. The fluid samples were examined for proinflammatory cytokine, protease, and macrophage biomarker levels. Indicating that transdermal continuous oxygen therapy reduces inflammation and promotes tissue turnover and repair, patients in the treatment group had considerably greater levels of interleukin-8 and interleukin-6 and much lower levels of macrophages.

- **Vascular grafts or bypasses -** Patients with peripheral arterial disease may benefit from vascular grafts or bypasses. The key to preventing infection and accelerating wound healing is adequate peripheral circulation. Examine the patient's vascular condition and check for flow-limiting vascular leg lesions to decide whether the patient needs revascularization. Doppler ultrasonography, ABI, TBI, duplex ultrasound, MRI angiography, CT angiography, and contrast angiography are

vascular evaluation techniques. [9,26] Before ordering examinations like MRI and CT angiography and contrast arteriography, take into account baseline testing like ABI, TBI, plain radiography, and Doppler ultrasound since patients may experience negative responses to contrast media. Revascularization progress is determined by a variety of variables, including operational risk, arteriographic findings, and the supply of graft material. Patients with acceptable surgical risk, an appropriate life expectancy, and lesions that are either technically unsuitable for endovascular repair or that have failed endovascular treatment are candidates for revascularization surgery. Foot infection, severe foot gangrene, and a nonambulatory state are all reasons to avoid revascularization. [9] The procedure being used—which may be a surgical arterial bypass, endovascular angioplasty stenting, endovascular subintimal angioplasty, or endovascular artherectomy that determines the operative risk of revascularization. [9] In individuals with claudication, endovascular repair methods have demonstrated great success rates. [27] Clinicians can detect flow-limiting lesions and decide on the appropriate repair method with the use of thorough arteriographic examinations. [28] The gold standard in lower extremity revascularization is revascularization utilising a saphenous vein bypass graft. [9] Polytetrafluoroethylene conduit material is a good alternative for patients who do not have a sufficient saphenous vein for grafting. To prevent the loss of good limb tissue and lower the chance of foot amputation, revascularization surgery should be performed as soon as feasible. Amputation or surgical resection may be required for patients in higher risk categories or those who have infections like osteomyelitis. The patient will require foot amputation and, if appropriate, should be given the option of a prosthesis if debridement, antibiotic treatment, or resection fail and a life-threatening infection manifests. [16]

❖ **Surgical Management of Diabetic foot infections (DFI)**

The treatment of these individuals must include surgical care of diabetic foot (DF) deformities and sequelae. The treatment of diabetic individuals with complex feet has been made better thanks to knowledge of the DF "syndrome." The interest in creating less invasive surgical techniques as alternatives to major lower extremity amputation has grown over the past few decades. For neuropathic or neuroischemic complex DF, they concentrate on local resections and the drainage of infected underlying soft tissue, toes, and metatarsal heads [18,19]. Aiming to identify those instances that are candidates for more conservative therapies, imaging is critical in this method for detecting the infection and determining its extent. A risk factor for developing diabetic foot ulcers (DFU) involves structural abnormalities and excessive plantar pressures [20,21,22,23]. Hammertoes, large metatarsal heads, hallux limitus, Charcot foot, and prior toe or partial foot amputations are a few common malformations [24]. In the event of an insensitive DF, each results in high pressures that exacerbate tissue inflammation and ulceration. The goal of foot surgery is to reduce these high pressures by physically realigning or eliminating bony prominences. Surgery becomes a vitally important and essential part of therapy when infection, phlegm, and/or OM are present [25]. The existence of open wounds and their severity are included in a suggested classification system for the various foot surgeries performed on diabetes patients [26]:

- In neuropathic individuals, prophylactic measures are used to lessen the risk of ulcers or recurrent ulceration in the absence of open wounds;
- When cutaneous ulcers are present, curative surgery is frequently undertaken to give a cure by joint resection, the removal of bone prominences beneath the skin (surgical decompression), osteomyelitis, or the draining of underlying abscesses or phlegmons.
- For severe deep or ascending infections (infectious gangrene, necrotizing fasciitis, etc.), urgent measures are carried out to stop the infection's spread. These treatments are carried out in an emergency and typically involve wide-open drainages or small foot amputations.

Since patients typically come at a surgical referral with an ongoing, more or less difficult DFU, curative and urgent treatments are more common in everyday clinical practise.The main strategy for managing surgical infection when dealing with deeply infected cutaneous ulcers is source control. The majority of infected DFUs react well to local debridement, the administration of antibiotics tailored to the particular culture, and unloading the foot using particular footwear. Some exhibit localised tissue necrosis, developing cellulitis, and a systemic inflammatory response as the infection spreads quickly along the tendon sheaths and tissue planes [27].The T.I.M.E. (Tissue, Infection, Moisture, and Edges) approach states that source control entails removing any dead or infected tissue or bones and debriding them in order to prevent fluid stasis [28]. But time also means "do not waste time" when referring patients to experts who can better address their needs. It also means "timing," which

denotes choosing a surgery (such as limb revascularization) for the patient's treatment too early or inadequately (for example). Delay will result in more tissue loss since deep foot infection has the potential to be limb-threatening without prompt treatment. We might say that "Time is Tissue" in this situation.

Endpoints of a curative strategy for osteomyelitis and deep foot ulcers are:

- Treat and cure the infection;
- Reduce pain (not always present because of neuropathy);
- Retain foot and allow best function (rehabilitation);
- Reduce recurrency.

In the event of deep foot infections and OM [29,30], which are challenging to treat and may return, radical surgical excision, including good bone and soft tissue, is occasionally necessary and must take a "oncologic approach."

The biofilm model, which explains the vast range of symptoms, courses, and difficult therapeutic treatment, has significantly enhanced our understanding of the pathogenesis. The pathogens first create a layer of colonies on the surface, which they then expand into to create a three-dimensional structure. As a diffusion barrier, this biofilm structure protects the bacteria from mechanical stressors and hinders the penetration of antibodies, body defence cells, and drugs. The pathogens transition from a planktonic, free-floating stage with a high metabolic rate and quick multiplication to a sessile form with a significantly lower metabolic rate and slower biological processes. Since cellular development within biofilms generates a matrix that shields the pathogens from the immune system and antimicrobial medications, this phenotypic shift renders them more resistant to antibiotics than their planktonic counterparts. It has been estimated that this specific form of growth can decrease an infection's sensitivity to antibiotics by a factor of 103 in OM and prosthesis-related illnesses [31]. A mature biofilm must grow in between 24 and 48 hours [32]. This matrix is effectively disrupted by the mechanical forces of surgical debridement, exposing germs to the effects of drugs and the body's immunological response. In order to clear the wound bed of all instable tissues and biofilm, a sharp debridement should be performed again within the therapeutic window of 1-2 days that can be realised with surgical medicine.Since they might be transmitters of biofilm, all foreign bodies, including screws and sutures, must be removed. To get rid of necrotic and/or diseased tissues, all infected tendons and bone should be cleansed and irrigated. The remaining tissues must be healthy and well vascularized. Since there are no objective standards for determining bone resection boundaries, the surgeon must make this decision on an individual basis. However, in general, it should be up to the point at which the surgical tool touches a hard bone [33]. In certain instances, non-infected bones need to be removed or decreased in size in order to release pressure on the underlying cutaneous plane that has an ulcer. The vascular supply should be assessed and conserved rather than the extent of the defect caused by the surgery. Depending on how extensive the débridement and resection was, the next step will be determined. The treatment of dead space, which, if not handled correctly, may result in an early return of infection and insufficient rehabilitation, especially if it affects the plantar surface of the foot, comes next. The avoidance of any fluid or exudate stasis that could be the cause of chronic bacterial contamination, biofilm, infection, and wound-healing impairment and delay requires surgical drainage [34]. The surgical management of DF problems is difficult, and it necessitates a proper diagnosis in order to accurately pinpoint the issue and swiftly begin an effective and individualised therapy for each patient. It is essential to use a multidisciplinary strategy that results from close cooperation between clinicians, doctors, radiologists, NM doctors, microbiologists, podiatrists, and nurses.

❖ **Radiological Modalities for Imaging DFI**

The presence of clinical and laboratory findings, such as an erythrocyte sedimentation rate (ESR) >70 mm/h and a positive probe-to-bone test result (palpation of bone in the depths of infected pedal ulcers), are largely what determine the diagnosis of diabetes-related OM, even though bone biopsy remains the reference standard [10,11]. However, it should be remembered that

- an ESR over 70 mm/h is highly specific for OM but only has a sensitivity of 28% [35] and
- the reliability of the probe-to-bone test may differ depending on the experience of the performing clinician and the location of the ulcer [10,11,35].

The likelihood that the patient has an OM before the test also has a significant impact on the test's value. A high-risk patient's diagnosis is suggested by a positive probe-to-bone test. A negative test results in a low-risk patient having a low possibility of having OM [36,37]. Therefore, when based solely on clinical and laboratory results, the diagnosis of DFI may be challenging. In addition to helping with diagnosis and delineation of deep or soft-tissue purulent collections, advanced imaging of the foot has increased our capacity to assess the likelihood of OM.

The two radiological modalities that are most often utilised to assess the DF infective consequences are radiography and magnetic resonance imaging (MRI). The IWGDF [10] and the American College of Radiology's diabetic foot recommendations [38] do not presently propose using ultrasounds to guide the aspiration of questionable fluid accumulation or to remove foreign materials. The imaging of diabetic patients with suspected OM or STI of the foot is

limited by computed tomography (CT), despite its higher sensitivity compared to radiography and MRI in detecting cortical erosions, periosteal reaction, small sequestra, soft tissue gas, and calcifications within sites of chronic osteomyelitis [38]. The primary drawbacks of CT are its poor resolution for soft tissue contrast and failure to pick up bone marrow edoema, which is present in the early stages of infection. Post-contrast CT can be utilised to find the development of soft-tissue and osseous abscesses if MRI is contraindicated or not accessible. However, as diabetic nephropathy that progresses to end-stage renal disease is frequently a comorbidity in people with diabetes, the danger of using iodinated contrast in diabetic patients should be considered [39].

- **Radiography**

Since radiographic signs of DF infective consequences can lie undiagnosed for up to four weeks after the start of infection, and since similar changes can be brought on by Charcot osteoarthropathy and other conditions like gout, the sensitivity of radiography in this situation is quite poor [40,41]. But for any patient with a possible infection, radiography ought to be the primary imaging technique used. It is affordable, widely accessible, and highly suggestive of DF infective complications when radiographic findings like demineralization, bone resorption, cortical destruction, periosteal reaction, bowing, or the obliteration of fat stripes and fascial planes, arthropathic changes, the presence of soft tissue gas, and foreign bodies are interpreted by an expert radiologist [10].

- **Magnetic Resonance Imaging (MRI)**

After initial radiography, the preferred method for examining OM and related soft-tissue complications is MRI with fluid-sensitive, fat-suppressed sequences (e.g., short-tau inversion recovery [STIR] or fat-saturated T2-weighted images), which has high sensitivity and high specificity (90 % and 83 %, respectively) in the diagnosis of OM [38,44]. Post-contrast pictures aid in the easier detection of abscesses and sinus tracts, which improves the evaluation of soft tissue pathology [43]. Furthermore, when regular follow-up imaging is expected to be required and the population is young, its radiation-free evaluation becomes especially crucial. However, morphologic sequences, which solely give structural information, are often the only basis for routine MRI. Technical advancements in recent years have made it possible to supplement structural knowledge with functional quantitative data. Utilizing Dixon sequences enhances picture quality and facilitates the identification of intraosseus sequestrums and sinus tracts [45]. With excellent inter-observer agreement, diffusion-weighted imaging and the apparent diffusion coefficient value can aid in differentiating diabetic neuropathic osteoarthropathy from OM [45].

In diabetic individuals with STIs, a normal signal intensity in the bone marrow (BM) rules out the diagnosis of OM. Early OM is characterised by BM edoema with post-contrast enhancement, high marrow signal intensity on fluid-sensitive fat-suppressed sequences, and low marrow signal intensity on T1-weighted pictures.

The presence of BM edoema and post-contrast enhancement in a number of mimics of diabetes-related OM, however, may make it difficult to make a precise MRI diagnosis. Further complicating the process of making an accurate diagnosis are illnesses that may coexist with OM, such as biomechanical stress changes brought on by changed weight bearing, recent post-operative surgery, inflammatory arthritis, and predominantly neuropathic osteoarthropathy. As a result, MRI may not be particularly accurate if marrow edoema is employed as the main diagnostic indicator.

The secondary characteristics of OM often include subtending skin ulcers, sinus tracts, abscesses, tenosynovitis, or septic arthritis. Their presence can increase the accuracy of the diagnosis and strongly implies that osteomyelitis is present [42,46].

- **Skin ulcer**

Focused disruption of the cutaneous line with elevated edges is a hallmark of skin ulceration (secondary to preexisting callus formation). On fluid-sensitive fat-suppressed images, acute ulcers appear hyperintense with prominent peripheral post-contrast enhancement, a feature that is suggestive of granulation tissue near the ulcer's base. Chronic ulcers may be accompanied by fibrous healing, which causes them to show as a mass on T1-weighted imaging and on fluid-sensitive fat-suppressed images with low to moderate signal intensity [42,43,46].

- **Sinus tract and abscess**

Some of the most common symptoms of osteomyelitis are sinus tracts and abscesses. The detection of a sinus tract demonstrated good specificity (on average, 85%) for the diagnosis of osteomyelitis in the neighbouring bone, according to Morrison et alanalysis .'s of the utility of main and secondary OM MRI signals [47]. Sinus tracts are common passageways for infection to migrate from skin ulcers to tendon sheaths, bones, or joints, which can result in abscesses, septic tenosynovitis, and/or osteomyelitis [47]. On fluid-sensitive fat-suppressed images, sinus tracts appear as linear fluid signal intensity, and on contrast-enhanced images, they exhibit a distinctive "tram-track" pattern of the enhancement. These are the MRI features that are most effective in identifying sinus tracts (Figure 3). Due to the presence of granulation tissue, an abscess appears as a focal fluid collection that is hypointense on T1-weighted imaging and hyperintense on fluid-sensitive fat-suppressed images (Figure 3). Distinguishing abscesses from

cellulitis or phlegmons, which exhibit widespread post-contrast enhancement, requires the presence of rim enhancement [42,43,46].

- **Septic tenosynovitis**

The most common cause of septic tenosynovitis is the contiguous spread of infection from a nearby abscess, ulcer, or sinus tract. On an MRI, the tendon sheath exhibits an abnormally high fluid level, and post-contrast imaging may reveal a thick rim enhancement surrounding the tendon, which is caused by inflammatory synovium. The tendon thickens and blurs, losing its steady low signal intensity [42,43,46].

- **Septic arthritis**

Similar to OM and tenosynovitis, contiguous spread from a nearby ulcer, abscess, or sinus tract also causes septic arthritis to develop. There is no single MRI finding that may distinguish between septic and nonseptic arthritis; non-infectious inflammatory arthropathies may likewise show increased joint fluid and thickened synovium with contrast enhancement. In contrast, if an ulcer and an adjacent soft-tissue infection directly border the joint or if a sinus tract penetrates into the joint, the diagnosis of septic arthritis in pedal infections may be more precise. On both sides of the joint and in the surrounding soft tissue, septic arthritis may show edoema with post-contrast enhancement. A superimposed OM should be distinguished from reactive BM oedema, which is related to septic arthritis. The presence of OM is often indicated by poor signal intensity on T1-weighted imaging and proximal extension of subchondral edoema beyond the subchondral bone [42,48].It is a common and challenging clinical and radiological challenge to distinguish OM from neuropathic osteoarthropathy in the absence of subsequent symptoms of infection. Since early OM identification is necessary to start rapid medicinal and/or surgical therapy, a precise distinction is required. The distribution and location of anatomical changes might be useful. In fact, OM mostly affects the calcaneum, malleoli, and forefoot, whereas neuropathic osteoarthropathy often affects the tarsometatarsal and metatarsophalangeal joints [49]. The midfoot is where the major diagnostic issue occurs. Secondary symptoms of infection are quite helpful in identifying the presence of OM in this area where MRI findings may be ambiguous. BM oedema is restricted to juxta-articular regions because neuropathic osteoarthropathy is largely an articular illness, in contrast to OM, which usually often develops as a consequence of an ulcer or abscess in nearby soft tissue and exhibits extensive marrow alterations (Figure 3) [38,50]. Since the radiological and clinical symptoms may be similar, it is still very difficult to distinguish between neuropathic osteoarthropathy that is infected and one that is not. To differentiate between these two disorders, a number of MRI findings may be helpful. Infection that has been superimposed is supported by the creation of sinus tracts, the replacement of soft tissue fat, fluid collections, diffuse marrow abnormalities, diffuse joint fluid augmentation, and joint erosion [43,51]. The lack of infection is indicated by thin-rim increase of effusion, subchondral cysts, or intraarticular structures [19]. Another MRI signal that suggests the existence of a superimposed infection is the "ghost sign," which describes bones that "disappear" on T1-weighted images and then "reappear" on contrast-enhanced or T2-weighted images. The "ghost sign" is missing in simple neuropathic osteoarthropathy because there is bone deterioration but no inflammatory cell infiltration of the marrow, which would cause the "ghost sign" to be absent [42,43,46].

- **Nuclear Medicine Imaging for DFI**

The use of NM methods enables the functional imaging of a process and the early detection of pathological alterations before they are clinically evident. Both single photon emission computed tomography (SPECT) and positron emission tomography (PET) modalities have a variety of radiopharmaceuticals available for imaging infection and inflammation, and the majority of these agents are now used for the diagnosis and follow-up of DFI.

- **Gamma-Camera Imaging for DFI**

Since radiolabelled white blood cells (WBC) scintigraphy precisely targets active granulocytes, which serve as a surrogate sign of bacterial infections, it represents the NM cornerstone for the detection of infection [52]. In order to unify labelling practises, acquisition techniques, and interpretation standards across all institutions, the European Society of Nuclear Medicine (EANM) has produced a number of recommendations [53,54,55]. It is advised to take pictures with timings corrected for isotope decay at three different moments after reinjecting autologous cells in order to offer an in vivo imaging of the physiological dynamic process of granulocyte migration into the infected location. The right interpretation results from comparing the uptake extent and intensity between delayed pictures, collected 20 hours (h) after injection (p.i.), and late photos (3 h p.i.). These guidelines make it simple to distinguish between a sterile inflammation and a bone infection. In fact, the amount and/or intensity of the uptake in the first condition grows with time, but in inflammation, the uptake shrinks or stays constant over time [55,56,57]. This modality achieves a very high accuracy in the diagnosis of an infection by following these suggestions and combining them with SPECT/CT acquisitions for the evaluation of the extent of the process and for the exact localization of the uptake [58]. Data on the application of radiolabelled WBC scintigraphy in DF, however, are quite inconsistent in the literature [60]. Depending on how closely the labelling method is followed, the

interpretation criteria used, and of course the varied acquisition protocols, the sensitivity and specificity of this modality vary from 75% [61] to 100% [62,63,64] and from 67% [64] to 100% [65]. Particularly, a number of articles solely used one-time point pictures, while others used dated acquisition techniques that used set times or a predetermined count, suggesting a significant variation in methodology and outcomes [64,66,67,68,69]. The accuracy of radiolabelled WBC scintigraphy, particularly in separating surface STIs from deeper infections, is greatly influenced by hybrid imaging with SPECT/CT. Although difficult to achieve with only planar pictures, this distinction is essential for the proper care of the patient. In fact, a precise diagnosis of foot complications—specifically, the distinction between sterile inflammation, STI, OM, and Charcot foot with or without a superimposed infection—is essential for a successful therapeutic intervention.Since it gives an in vivo illustration of the pathophysiology behind inflammatory and infectious disorders, radiolabelled WBC scintigraphy is, in this context, the most accurate NM imaging method capable of achieving this differential diagnosis. The district of the foot, however, also affects how well radiolabelled WBC distinguishes between OM and STI [60]. Although prior factors may be used for a proper distinction between these two illnesses in forefoot problems, mid- and hindfoot Charcot osteoarthropaty may also be taken into account. The specificity of this technique would be reduced in this case since radiolabelled WBC uptake may potentially be linked to physiological BM enlargement brought on by chronic inflammation [70,71,72]. The use of nanocolloids in a second bone marrow scintigraphy (BMS) is thus advised in order to get around this restriction and boost the accuracy of WBC scintigraphy. The fact that both radiopharmaceuticals accumulate in BM but only WBC accumulate in infectious foci makes the diagnosis of Charcot the most likely. On the other hand, if there is a mismatch (positive at WBC scintigraphy and negative at colloids), the diagnosis of OM may be made.The adoption of radiolabelled WBC scintigraphy at all centres is sadly constrained by a number of practical and technological challenges, despite the fact that it continues to be the NM gold standard for the diagnosis of infections. In fact, this modality needs trained individuals, suitable labs, and tools. Additionally, since three different time points must be acquired for the photos to be properly labelled, the process takes a long time. The availability of closed and single use kits has made the separation and labelling operations simpler and safer for the operator, but its accuracy in this sector is unmatched [73].As an alternative to radiolabelled WBC scintigraphy, the use of monoclonal antibodies (MoAbs) or antibody fragments (Fab') directed against specific antigens expressed by activated granulocytes has been suggested; however, they also have some drawbacks, most notably their high molecular weight, which limits their diffusion into the infective focus, their long plasma half-life, and their non-specific accumulation into inflamed sites. MoAbs can only be used once in a person's lifetime because they cause human murine antibodies (HAMA) in the host. Additionally, there hasn't been much research done on the function of MoAbs or Fab' fragments in DF, and the results in the literature are primarily based on small patient populations [74,75,76]. Additionally, there are currently no standardised protocols for data acquisition and interpretation, and the scant information available in the literature does not support the recommendation that MoAbs or their fragments should be used instead of radiolabelled WBC scintigraphy to diagnose DF disorders.

- **PET/CT Imaging for DFI**

As particularly outlined in the guidelines issued in 2013 by EANM and Society of Nuclear Medicine and Molecular Imaging (SNMMI) [77], [^{18}F]FDG PET/CT has grown significantly in importance for numerous indications in the field of infection and inflammation.Compared to traditional scintigraphy, [^{18}F] FDG has a number of benefits. It avoids handling potentially infectious blood, has an acquisition time that is significantly faster than radiolabelled WBC, and produces pictures with higher quality resolution than planar scintigraphy. Additionally, the availability of CT co-registration makes it feasible to define anatomical landmarks precisely and assess the extent to which an infection has spread to soft tissues or bone. In contrast, [^{18}F] FDG builds up in all the diseases where glucose is processed as a source of energy, including infections, inflammations, malignancies, reparative processes, and other illnesses.The per-patients-based study in a meta-analysis published in 2013 shown a pooled sensitivity of 74% and a specificity of 91% [78]. Nevertheless, only 4 papers were used in this meta-analysis. Another more recent meta-analysis with 6 trials and 254 patients found that [^{18}F] FDG PET/CT had sensitivity and specificity of 89 and 92 percent, respectively [59]. The accuracy of this imaging modality is obviously greatly influenced by CT co-registration, but it also depends on accurate interpretation criteria for [^{18}F] FDG PET/CT scans, which are regrettably still not clearly defined and standardised. Nawaz et al. examined [18F]FDG PET and MRI in a sizable sample of 110 diabetic individuals with suspected pedal OM. In this series, the first modality performed better than the second in terms of specificity (93 percent vs 78 percent), accuracy (90 percent compared 81 percent), and specificity (81 percent versus 91 percent) [79]. Without doing any semi-quantitative analysis of the highest Standardized Uptake Value, the diagnosis of OM in this study was relied only on visual evaluation of [18F]FDG uptake on bony structures (SUVmax).

Additionally, there was no CT co-registration done in this investigation, which may have had an impact on the relatively poor sensitivity when compared to MRI.On 63 patients with DF diseases, Basu et al. [80] investigated the function of semi-quantitative analysis with SUVmax. SUVmax may be a useful metric for distinguishing between these illnesses since individuals with OM had greater SUVmax values than patients with Charcot and simple DF. Others did not identify a relationship between SUVmax levels and the various DF problems, despite the fact that these results were verified by other researchers [81].Since [18F]FDG currently lacks well-defined interpretation criteria for discriminating infection, inflammation, STI, OM, and Charcot, this particular clinical indication is severely constrained. Although CT co-registration is effective for locating the uptake in bone as opposed to soft tissue, it cannot distinguish between an infection and inflammation or degradation [82]. (Figure 5).WBC have also been tagged with [^{18}F] FDG in an effort to provide a more specialised radiopharmaceutical for PET imaging; however, published research on DF are still lacking in the literature.

❖ **Consensus Statements Emerged from Round Table of 3rd European Congress of Infection and Inflammation**

Several experts that evaluate patients with DF problems presented their presentations on this subject from various angles during the 3rd European Congress of Infection and Inflammation held in Rome in December 2019. In order to offer evidence-based responses to the most typical clinical queries, we have compiled a number of comments that came up during the subsequent round table.

- **Is Radiography Useful in a Patient with Suspected OM?**

When examining for bone involvement in the DF, radiography should be the initial imaging modality used. This method is affordable, widely accessible, and linked to little danger. It offers an anatomical overview of the relevant region and any problems that may affect the choice and interpretation of further imaging modalities. Although there haven't been any studies on the use of serial radiographs to diagnose OM, it is possible to learn important information by taking serial radiographs to find progressive bone changes.

- **Is a Negative Radiographic Examination Enough to Rule Out OM?**

A negative radiographic examination is insufficient to rule out OM from a radiological perspective since it is insensitive to the early phases of acute OM [10]. For up to four weeks following the start of the illness, radiographs could not show anything unusual. Additionally, it may be challenging to correctly interpret radiographic changes of OM, such as demineralization, bone resorption, and periosteal reaction, because similar abnormalities can also be seen in Charcot osteoarthropathy and other conditions, like gout [40]. Therefore, the use of advanced imaging is essential for making a correct diagnosis.

- **Is MRI Indicated Since the First Diagnostic Steps?**

MRI is strongly advised as a second imaging modality after first radiography when OM is suspected but is not appropriate as the first imaging modality to diagnose OM. MRI enables for preoperative mapping of the degree of infection, which helps in limiting the region of resection. It also offers good spatial resolution and accurate anatomical features. Furthermore, it is now widely accessible and less expensive than other imaging modalities, and its radiation-free evaluation becomes particularly significant in the young population and when regular follow-up imaging is required [38].

- **Is MRI Indicated for Therapy Evaluation?**

The use of MRI in the monitoring of DFO is not supported by any pertinent literature. However, this imaging technique can be highly useful for assessing whether patients have recovered from the infection after receiving therapy. This illness shouldn't be deemed "cured" until there has been no indication of recurrence for at least a year [83], given that normal marrow signal consistently eliminates OM [42]. MRI imaging is a highly useful follow-up imaging technique, particularly in young people, because to the radiation-free evaluation and the high sensitivity and specificity for identifying the presence or absence of pedal OM and STI [44].

- **Is WBC Scintigraphy Able to Differentiate between Superficial or Deep Infection?**

Planar NM imaging methods' primary drawbacks are their low spatial resolution and absence of anatomical landmarks, which are particularly problematic in the foot because all of the bony structures there are tiny and near to one another. In fact, an uptake on soft tissues during planar scans may overlap the underlying bone and vice versa, resulting in a misinterpretation of the scan and a mistreatment as a result. As a result, as already noted, the use of hybrid pictures is essential to increasing the diagnostic efficacy of planar images.Numerous researchers have examined the additional benefits of SPECT/CT in the diagnosis [66,67,84,85,86] and therapy monitoring of DFO [87,88]. Despite the various acquisition protocols used in the various studies, all researchers agree that hybrid imaging is able to better localise uptake into bone or soft tissues with an excellent definition of the extent of the infective process. According to Przybylski et al., ^{99m}Tc WBC scintigraphy with SPECT/CT had a sensitivity, specificity, and diagnostic accuracy of 87.5 percent, 71.4 percent, and 80 percent, respectively [85]. In a separate paper, Heiba et al. examined 272 patients using a combined strategy that included ^{111}In WBC scintigraphy and bone scan [66]. They came to the

conclusion that dual isotope SPECT/CT was superior to bone scan or WBC scintigraphy with SPECT/CT alone in differentiating STI from OM, and that this combined strategy is also associated with a shorter hospital stay [67]. In the series examined by Filippi et al. in 2009, the addition of SPECT/CT significantly altered the interpretation of planar images in 52.6 percent of cases, allowing for the exclusion of infection in 6 cases, the diagnosis of OM in 1 case, and a better understanding of the process' extent in 3 cases [86]. Therefore, in order to more correctly localise the infection into bone or soft tissues and to determine the degree of the process, findings from the literature suggest the use of SPECT/CT in addition to planar imaging in the evaluation of DFI.

- **Is It Possible to Perform Radiolabelled WBC Scintigraphy during an Antibiotic Treatment?**

There is considerable disagreement about the possibility that prolonged antibiotic therapy may affect the sensitivity of radiolabelled WBC scintigraphy. According to several articles, the use of antibiotics has no discernible impact on the diagnostic validity of radiolabelled WBC [87,88,91,92]. A large sample of patients with prosthetic joint infections were retrospectively evaluated by Glaudemans et al. in 2013, and they found no appreciable changes in the diagnostic performance of patients getting antibiotic treatment compared to patients who were not receiving medication. This investigation supported the notion that this imaging technique maintained a high sensitivity and specificity in detecting residual illness, regardless of the treatment of antibiotics, while not being specifically focused on DFI [93]. In fact, as stated in most recently released EANM recommendations [55], "patients taking antibiotic therapy should not be eliminated a priori as data about their influence on WBC scintigraphy present a variety of outcomes."However, because to the possibility of false negative scans, not all NM doctors have a lot of faith in doing this screening while taking antibiotics. It is therefore frequently a common practise to delay the radiolabelled WBC scintigraphy until 2 weeks after therapy withdrawal or to repeat the scan in case of uncertainty in patients receiving antibiotics 2 weeks later. This is despite the literature not clearly indicating the ideal timing to perform WBCs scintigraphy following antimicrobial therapy. Although preliminary findings appear to support the use of radiolabelled WBC scintigraphy, particularly with SPECT/CT acquisitions, for the assessment of treatment response, data in the literature on therapy monitoring in DF are primarily based on small series and do not allow drawing firm conclusions [87,88]. Similar to this, [18F]FDG PET/CT might be used to monitor any symptoms of inflammation in the foot that may still be present even when the patient is seen as having healed clinically [94], although there is currently a lack of conclusive data in the literature.

- **Do We Need to Perform a Combined Bone Marrow Scintigraphy in Addition to Radiolabelled WBC Scintigraphy for the Evaluation of Charcot?**

The difficult diagnosis of DFI is made more difficult by a disorder called Charcot osteoarthropathy. Regardless of whether an infection is present or not, radiolabelled WBC uptake in the mid- or hind-foot must always be interpreted cautiously due to the potential for physiologic accumulation into an enlarged BM, which is generally present in a Charcot foot. In order to get a scintigraphic map of the BM and to compare it with WBC pictures, a BMS is strongly advised. The presence of labelled leukocyte uptake without matching activity on marrow imaging and the spatially incongruent distribution of two radiopharmaceuticals are the two criteria Palestro described for diagnosing OM in the context of Charcot's arthropathy [70,71].

Because the uptake in this disease is often quite high and widespread, including all the tarsal and metatarsal joints, indicating the obvious abnormalities in bone architecture typical of this disorder, [18F]FDG also demonstrates numerous limits in the assessment of Charcot. As a result [18F], FDG is unable to distinguish between Charcot with and without an infection.

❖ **WHAT PATIENTS NEED TO KNOW**

- ✓ For diabetic foot ulcers to heal successfully, patients must be aware of and follow best practises for wound care. Reducing the repeated pressure on the foot that led to the ulcer is the first step. There are several pressure-relieving tools and shoe adjustments available. [9]
- ✓ Inform patients that treating limb ischemia's causes will need several doctor visits. Encourage people to quit smoking and to regain control of their hyperglycemia when appropriate. [11]
- ✓ To prevent wound infection, patients must also follow their prescribed antibiotic regimen (which may be modified from time to time). [16] In order to promote the development of healthy granulation tissue and wound healing, patients must also change their wound dressings every day. [16,18]

❖ **Conclusions**

The doctor still has difficulties in correctly identifying and differentiating between various kinds of DFI. Planning the best therapeutic approach for a particular patient requires the use of multimodality imaging and a multidisciplinary strategy. The most relevant radiological and NM methods include [18F]FDG PET/CT, radiolabelled WBC scintigraphy, and MRI, although bigger multicenter investigations

are still required to develop uniform diagnostic flow charts that may be used globally.

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