Diagnosing Foot Infection in Diabetes

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Infection represents the presence of an inflammatory response and tissue injury due to the interaction of the host with multiplying bacteria. The disease spectrum is a consequence of the variability in these interactions. Diabetes, because of its effects on the vascular, neurological, and immune systems, can compromise the local and systemic response to infection, potentially masking the typical clinical features and hindering diagnosis. The early recognition of infection, particularly osteomyelitis, is paramount in the management of diabetic foot disease. Careful clinical appraisal remains the cornerstone of the assessment. Hematologic, biochemical, and radiological investigations are important aids in assessing the severity of infection. Microbiological assessment, particularly in more severe infection, requires good-quality samples, combined with rapid transport in an appropriate medium and effective communication with the laboratory. A focused, systematic approach to the accurate diagnosis and treatment of infection, combined with careful monitoring, ensures the maintenance of optimal management.

Foot infection in diabetic patients can accelerate dramatically with devastating consequences if appropriate treatment is not given promptly. The role of the health professional caring for these individuals is to identify and treat infection as early as possible, along with preventing further episodes. However, diagnosing infection in an ulcerated diabetic foot is not always straightforward. In diabetics, the host inflammatory response to injury or infection may be reduced because of impaired leukocyte function, vascular disease, and neuropathy [1]. Thus, the classical signs of dolor, rubor, calor, and tumor associated with infection may be absent. Further confusing the issue are the effects of diabetic peripheral neuropathy, which can mimic some of these findings. When clinical signs are misleading, we rely on laboratory tests to help us diagnose infection. However, blood tests whose results can suggest infection (i.e., elevations in leukocyte count and erythrocyte sedimentation rate) often yield falsely normal results. Also, in the presence of chronic wounds, microbiological results may be difficult to interpret. Herein we examine definitions related to infection and describe, from our clinical experience, how we diagnose infection in the ulcerated diabetic foot.

DEFINING INFECTION IN THE DIABETIC FOOT

There are many definitions of infection. It is most frequently described as a disease caused by a microbial pathogen that occurs when the presence of replicating organisms is associated with tissue damage. The American College of Surgeons [2] defined infection as the product of the entrance, growth, metabolic activities, and resultant pathophysiological effects of microorganisms in the tissues of the patient. More specifically, White et al. [3] defined infection as the presence of multiplying bacteria in body tissues, resulting in spreading cellular injury due to competitive metabolism, toxins, intracellular replication, or antigen-antibody response (host reaction).

In some situations, such as when established pathogens are isolated from properly obtained specimens of normally sterile fluid or tissues, diagnosing infection is easy. The presence of microorganisms in a wound, however, does not in itself define a clinical infection. It is important to recognize that there is a spectrum, or continuum, of disease (figure 1). All wounds are exposed to skin commensals, and their microflora will

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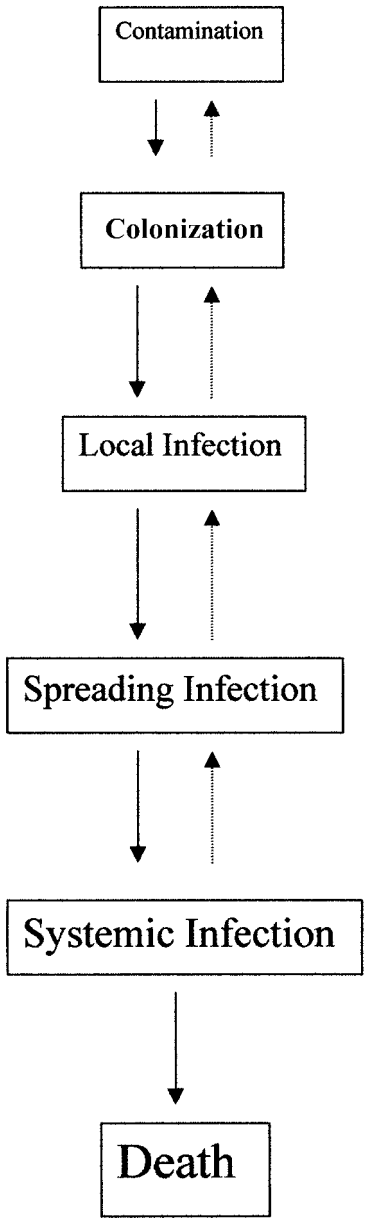

Figure 1. Spectrum of relationships between bacteria and wounds

represent the surrounding environment. These contaminating microbes can quickly become established within a wound, reaching a state of colonization. Colonization is defined as the presence of multiplying bacteria with no overt host immunologic reaction [4]. Diabetic foot ulcers are commonly colonized with multiple species of organisms [5] that do not normally interfere with healing. Multiplication of bacteria within the wound can reach a stage of "critical colonization" [6], in which the host defenses are unable to maintain a balance, thus resulting in delayed healing. Infection results when the invading organisms overwhelm the host defenses, either by their sheer numbers or by impairing the host's immunity.

Infection confined to an ulcer bed can be described as local infection. This is typically manifest as purulent secretions, often accompanied by inflammatory signs. Untreated, local infection can progress to involve the surrounding and deeper tissues. Superficial soft tissue infection may be accompanied by painful spreading erythema, known as cellulitis. Superficial infections involve the skin but do not extend to fascia, muscle, tendon, bone, or joint, as defined by the International Consensus on the Diabetic Foot. Deep infections are those with evidence of abscess, septic arthritis, osteomyelitis, or septic tenosynovitis. The International Consensus on the Diabetic Foot distinguishes bone infections as osteitis, infection of the cortical bone only, and osteomyelitis, in which the bone marrow is involved.

Mechanisms of infection. Although microorganisms are responsible for infection, there is debate as to the exact mechanisms by which they cause their adverse consequences and their effect on a nonhealing chronic wound. Several factors are thought to be involved (figure 2), including the bacterial burden, or load, within a wound. Many authors have reported healing to be delayed in a variety of wounds by an excessive bacterial burden, and the likelihood of infection rises as the bacterial burden increases [7]. Controversy persists over whether the mere presence of a high bacterial bioburden warrants antimicrobial therapy [8]. Some have proposed that a burden of $>10^5$ cfu of bacteria per gram of tissue is required to cause wound infection [7]. However, particularly virulent organisms, such as β-hemolytic streptococci, secrete toxins that allow rapid spread through the host's tissue planes and are capable of producing clinical infection at a lower burden.

As demonstrated by β-hemolytic streptococci, the virulence of the colonizing microorganism correlates with the likelihood

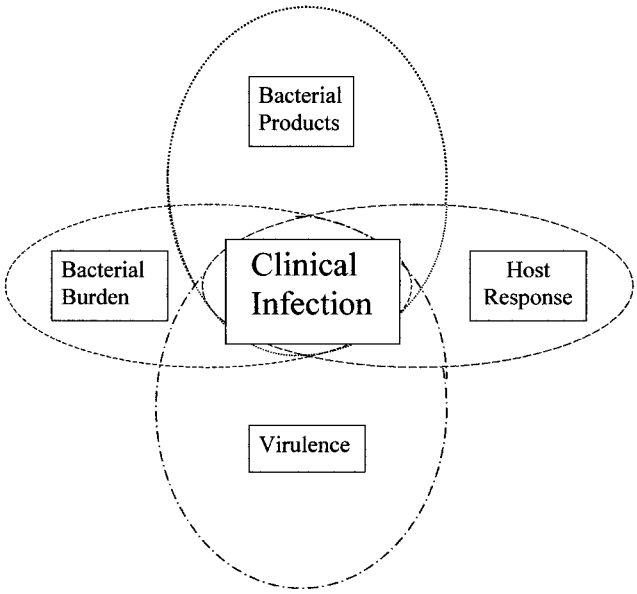

Figure 2. Interactions of factors in infection

of infection. The significance of other individual species of bacteria in a wound is not yet known. In uninfected diabetic foot ulcers, the microflora is likely to be polymicrobial [5]. *Staphylococcus* species are the most frequently isolated organisms, along with *Streptococcus* species, *Pseudomonas aeruginosa,* and various coliform bacteria [9]. When infection ensues, especially in patients who have not recently received antibiotics, aerobic gram-positive cocci are the dominant pathogens [10]. With careful sampling and culturing techniques, some anaerobic bacteria can also be recovered in 74%–95% of more severe diabetic foot infections [11, 12]. A culture with polymicrobial flora from a diabetic foot ulcer does not reveal which microorganisms are pathogens. In fact, bacteria are thought to be synergistic and form biofilms on the surface of chronic wounds. This allows anaerobes to survive on wound surfaces and supports growth of bacteria not normally considered pathogenic [13].

The final factor potentially influencing the manifestation of clinical infection is the host response. In diabetic patients, hyperglycemia reduces the activity of neutrophils and macrophages, the cells responsible for phagocytosis of bacteria and foreign material in the initial inflammatory phase of healing [14]. Ischemia, edema, and neuropathy reduce the capillary vasodilation response to injury, further impairing the host's response to infection. Thus, the interaction between the bacteria present within the wound and the host response determines whether a wound will progress from colonization to infection and how infection will manifest.

DIAGNOSING INFECTION IN THE DIABETIC FOOT

In diabetic foot disease, we should aim to diagnose infection at an early stage before it progresses toward deep infection and damage to underlying tissue. Obtaining a rapid and accurate diagnosis is, however, compounded by several factors. Because the clinical signs of infection and microbiological analysis may be misleading, it is important to combine all information available and not rely on any single laboratory report. Sometimes subtle findings, such as failure of a wound to heal within the expected time frame, may suggest infection.

Microbiological sampling. Traditional methods of sampling to determine the causative agents of a wound infection include rubbing the wound surface with a cotton swab, aspirating purulent secretions, and obtaining tissue by curettage or biopsy. Surface swabbing will collect skin contaminants, which may or may not be pathogenic. Furthermore, routine processing of swabs in clinical microbiology laboratories is rarely sufficient to isolate anaerobic or fastidious bacteria; this results both from the inadequate collection and/or transport method and variations in laboratory processing and incubation [15, 16]. Culture of aspirated fluid or pus is more likely to reveal the pathogenic organism, especially if taken from a deep pocket within the wound. Culture of debrided infected tissue is an excellent method for diagnosis in diabetic foot ulcers [17]. Removing superficial debris before sampling will eliminate surface contaminants and provide more specific results. Tissue biopsy is generally regarded as the reference standard for diagnosing infection [18]. Quantitative analysis of the deep tissue can identify heavily inoculated wounds ($>10^5$ cfu/g of tissue), but the clinical significance of this finding is unclear, because it requires expertise in obtaining the sample and specialist laboratory processing. If osteomyelitis is suspected, a specimen of bone obtained at surgery or by percutaneous biopsy is the most useful sample for culture. Although culture and histological examination of a specimen is the most accurate method for diagnosing infection, it not always easily obtainable. The technique used to obtain a microbiological sample is crucial. Although some methods are clearly superior, those selected sometimes depend on local clinical and laboratory expertise.

Hematologic and biochemical markers. Blood tests, such as WBC count, erythrocyte sedimentation rate, and C-reactive protein level, are commonly requested to aid diagnosis. However, they are neither sensitive nor specific and are unlikely to be elevated in local or superficial infection. Up to 50% of patients with a deep foot infection will not have leukocytosis [19, 20]; therefore, normal results do not preclude infection. Inflammatory blood markers are simple and relatively inexpensive to detect and may help guide the clinician in assessing treatment responses in severe infection, when used in combination with other factors. The erythrocyte sedimentation rate is frequently used to monitor the response to treatment for osteomyelitis. C-reactive protein levels have been demonstrated to be elevated in diabetic foot ulceration, and other acute-phase proteins, such as ferritin, α_1-antitrypsin, and haptoglobulins, are currently under investigation [21]. Blood glucose and hemoglobin A_{1c} levels may rise in infection.

Radiological diagnosis of osteomyelitis. Many imaging techniques have been used to confirm or refute the presence of bone infection. Plain radiographs are useful as an initial evaluation and can be used as comparisons for later assessments. Radiography can also detect gas in soft tissues, which may represent severe soft tissue infection by anaerobic organisms and possible abscess formation. Osteolytic bone changes or periosteal elevation are suggestive of osteomyelitis. However, these changes may not be present in the first few weeks of infection, and their absence does not exclude osteomyelitis. Follow-up radiography is usually done 2–6 weeks later, although there is no agreed best interval. If the diagnosis remains in doubt, further investigations may include an isotope bone scan or labeled WBC scan, infrared thermography, ultrasound, or MRI. Among these, MRI has been found to be more sensitive

and far more specific than bone scans for diagnosis of osteomyelitis in diabetic feet [22, 23].

Clinical diagnosis of infection. The most important diagnostic tool for infection is bedside clinical evaluation. The patient should be asked about an increase in pain, odor, or exudate. Local infection of an ulcer can be difficult for inexperienced clinicians to recognize. Cutting and Harding [24] described signs of infection in a granulating wound: delayed healing, friable tissue, offensive odor, secretion of pus, increase in lesion size, pain or discomfort, and prolonged exudate production. Although symptoms may be absent in the neuropathic foot, the clinical signs of abnormal granulation tissue, such as a change in color from bright red to dark red, brown, or gray and increased fragility and contact bleeding, should alert the clinician to the possibility of infection. Spreading superficial infection, usually represented by warmth, erythema, and edema, may be less obvious in the diabetic foot. Systemic signs, such as pyrexia, chills, and lymphadenopathy, are usually absent. Even if infection is present, it can be difficult to differentiate from acute neuro-osteoarthropathy (Charcot's foot). Radiological and clinical assessments, together with laboratory tests, should aid differentiation of infectious from noninfectious bone lesions.

If bone is visibly exposed within the wound, or can be detected on gentle probing with a sterile instrument, osteomyelitis is likely. In a study of 75 patients with 76 ulcers, osteomyelitis was confirmed in 50 ulcers (66%) [25]. Thirty-three of these ulcers had bone detectable on probing, whereas 4 with underlying osteomyelitis did not, giving a sensitivity of 66%, a specificity of 85%, and a positive predictive value of 89%. Other deep structures exposed within the wound, such as tendon or joint capsule, also signify deep infection. Probing a wound can also detect foreign bodies and sinus tracts. It is essential that a wound is carefully probed with a narrow, blunt instrument able to convey to the user the presence of hard material within the wound. It is among the quickest and easiest procedures to do when evaluating a diabetic foot ulcer, and among the most important.

CONCLUSION

To accurately diagnose infection, a combination of clinical, laboratory, and imaging investigations must be used. Various studies have defined the proper techniques for obtaining and the values of various tests. Determining which diagnostic procedures to order depends somewhat on local expertise and availability. Among the simplest and most important of tests is probing the debrided wound at the base of an ulcer; this should be done on every wound to evaluate its depth and exclude osteomyelitis. If in doubt, it is better to treat potential infection empirically while waiting for a definitive diagnosis than to delay treatment.

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