Letter: Microbiological and clinical mismanagement of non healing diabetic leg ulcers?

Dear Sirs

Diabetic foot ulcers are a major health care problem with more serious consequences, thereby the most common indication for hospital admission in diabetic patients. Peripheral neuropathy, repetitive trauma and peripheral vascular disease are common underlying pathways that lead to skin breakdown, often setting the stage for limb-threatening infections; thus, foot ulcers frequently become infected with potentially disastrous progressions to deeper spaces and tissues, and if not promptly and appropriately treated, diabetic foot infections can become incurable or even lead to septic gangrene, which may require foot amputation (1). Individuals with diabetes who present with foot infection may therefore warrant optimal surgical management to effect limb salvage and prevent amputation, while aggressive short-term and meticulous long-term care plans are also required (2).

According to the hypothesis of functional equivalent pathogroups (FEP), individual members of the pathogenic communities when occurred alone may not cause a disease but when they coaggregate or consort together into an FEP, the synergistic effect provides the functional equivalence of well-known pathogens (3). It was reported that while chronic infections are often polymicrobial (4), many acute infections in patients not previously treated with antibiotics are caused by a single pathogen, usually a Gram-positive coccus (1); diagnosing infection in a diabetic foot ulcer is thus quite necessary, though usually based on clinical signs and symptoms of inflammation but more importantly, proper culturing of an infected lesion can disclose the aetiological pathogens (1). It has therefore been suggested that specimens for microbial culture should be obtained after wound debridement to avoid contamination and optimise identification of aetiological pathogens.

Bacterial flora of diabetic foot wounds/ulcers vary significantly among studies from various countries but the most prominent bacterial flora associated with diabetic foot ulcers include the easily recoverable species like *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus epidermidis*, *Streptococcus*, *Serratia*, *Enterococcus* and *Proteus mirabilis*, while the not easily recoverable pathogens include *Bacteroides*, *Peptoniphilus*, *Fingoldia*, *Anaerococcus* and *Peptostreptococcus* spp. Other diabetic wound-borne bacterial flora also include *Proteus vulgaris*, *Klebsiella pneumoniae*, *Enterobacter* spp., *Acinetobacter* spp. and *Corynebacterium* spp. (1,3,5). In view of the polymicrobial nature of diabetic foot ulcers, Karchmer and Gibbons (6) questioned the need for precise definition of the causative microorganism(s) and suggested that the treatment of infection could be based on a better understanding of the general microbiology of these wounds.

It was suggested that without clinical signs of infection and careful considerations, a wound should not be treated with systemic antibiotics and it is for this reason that all clinical observations must be made prior to treatment (4). The proper use of antibiotics in the treatment of diabetic foot, however, remains contested, with two major views, one proposing that the administration of antibiotics should be only in the presence of clinical infection, while the other proposal was that antibiotics should be freely administered to all patients with ulcers; however, both views agreed that

diabetic patients who have clean ulcers associated with peripheral vascular disease and positive ulcer swabs should be considered for early antibiotic treatment, because diabetic foot is highly susceptible to repeated ulceration, diabetic ulcers being more prone to infection than other ulcers, and furthermore, because untreated infection can lead to amputation (7).

Although appropriate systemic antibiotics are essential for the treatment of deteriorating, clinically infected wounds, debate exists regarding the relevance and use of antibiotics (systemic or topical) and antiseptics (topical) in the treatment of non healing wounds that have no clinical signs of infection, even providing a detailed analysis of wound microbiology, together with current opinion and controversies regarding wound assessment and treatment. However, careful use of broad-spectrum antimicrobial agents is likely to be the most successful treatment in the management of majority of the clinically infected chronic wounds (e.g. leg ulcers, foot ulcers and pressure ulcers). Initial therapy is usually empirical but may be modified according to the culture and sensitivity results and the patient's clinical response. Surgical intervention is also usually required in cases of retained purulence or advancing infection despite optimal medical therapy but if a wound fails to improve after an initial course of topical treatment (e.g. 2 weeks), continued use is not likely to be of benefit (4).

The antibiotic susceptibility of wound isolates observed in the laboratory cannot always be related directly to the clinical situation, as the *in vitro* and *in vivo* conditions vary considerably. It is therefore important to consider that laboratory data may not always translate to therapeutic success (8) but somehow, the fact that most diabetic wound ulcers are not effectively treated with antibiotic therapy should lead to deep curiosity that additional groups of microbial pathogens may be associated with the non healing effects of such therapy, most especially, in cases of more serious debilitating infectious conditions (Ogunshe, personal communication), which ultimately lead to amputation. In addition, several publications have documented a markedly increased incidence of superficial and most importantly, systemic yeast infections, even with increasing spectrum of aetiological agents (9). Infections by yeasts and/or yeast-like fungi most commonly involve mucocutaneous membranes and are associated historically with malnutrition, malignancies and diabetes mellitus. Although complexity of diagnosis has limited chemotherapy, while the association with underlying debilitation adds to the gravity of systemic yeast infections, it is hereby suggested that routine bacteriologic diagnosis should be supplemented with targeted mycological and histopathological methods as earlier advised by Missoni *et al*. (10).

In the study of Mlinarić-Missoni *et al*. (11) as an example, identified fungal species detected from interdigital spaces of the feet (toe webs) of 122 (24%) of the 509 diabetic outpatients using standard mycological diagnostic methods were *Candida*, *Rhodotorula*, *Cryptococcus*, *Trichosporon*, *Saccharomyces*, *Blastoschizomyces*, *Geotrichum*, *Debaryomyces* and *Ustilago*, as well as three species of dermatophytes of the genera *Trichophyton* and *Epidermophyton*. Yeasts were the most common isolates (95/18·7% of the patients), followed by dermatophytic moulds (24/4·7% of the patients), while coexistence of yeasts and dermatophytes was the most infrequent finding (3/0·6% of the patients). The most frequently isolated fungi were *Candida parapsilosis* (59/11·6% of the patients) and *Trichophyton mentagrophytes* (16/3·1% of the patients).

Similarly, in the study of Missoni *et al*. (10), although bacterial isolation was five times as common as that of yeasts, more than 89% of the diabetic foot ulcer patients had a single foot ulcer with fungal or mixed infection, big toe and the plantar metatarsal region in one foot or both feet being the most common sites of ulcer. Fifteen species from the genera *Candida*, *Cryptococcus*, *Trichosporon* and *Rhodotorula* were confirmed to be the causative agents of the fungal and mixed foot ulcer infections, while *Candida* species were the most common fungal isolates with *C. parapsilosis* (in 61·5% of patients) and *Candida albicans* and *Candida tropicalis* (in 10·8% of patients each) being the most common causes of the infections. The study further confirmed that the fungal isolates originated not only from a primarily sterile ulcer sample (biopsy specimen) but also from foot ulcer swabs, confirming that the fungal flora to be the causative agents (not ulcer colonisers or contaminants) of the foot ulcer infection. The pathogenic effect of yeasts in foot ulcer is indicated by the severity of clinical finding, chronic course of infection and infection progression despite antibiotic therapy.

Diabetic extremity ulcers are associated with chronic infections and diabetic foot ulcers are the most common, disabling and costly complications of diabetes and the disease frequently leads to substantial long-term complications, thereby imposing a huge socioeconomic burden on available resources and health care systems (2). Such ulcer infections are too often followed by amputation because there is little or no understanding of the ecology of such infections or how to control or eliminate this type of chronic infection. It is therefore better to understand the polymicrobial nature of chronic diabetic extremity ulcer infections (3). Although the crisis of antibiotic resistance has come rapidly to the (cutaneous) surface (12), it is also apparent that the aetiological agents of the diabetic foot ulcers in many cases may be non-bacterial. In infectious cases, bacterial flora are the most screened for aetiological agents and it is usually during indicative cases of urogenital/vulvovaginal conditions that mycological screening are carried out; thus mycological diagnosis is not common, and even neglected in most cases, especially in cases of diabetic wound infections. Therefore, all attempts should be made to prevent diabetic foot ulceration by treating existing ulcers through multidisciplinary approaches in order to decrease amputations (13).

Long-term efforts have reduced amputation by 37–75% in different European countries for over 10–15 years and indeed, improvement in ulcer healing has been reportedly observed with primary healing rates of 65–85% in mixed series but even when healed, diabetic foot should be regarded as a life-long condition and treated accordingly to prevent recurrence. The majority of the diabetic ulcers among the Nigerian patients are around the ankle but the advise on better understanding of the ulcers are also very appropriate, because amputation and higher mortality rates are more prominent in such cases because of gross lack of appropriate health care support and funding by government. In Nigeria and probably in most developing countries, just as cancer is taken as a no-remedy terminal clinical health condition, so is diabetic foot ulcer taken as an ultimately, no-remedy, amputation-required and terminal wound condition; therefore, it is passionately advised that all microbiological findings including mycological investigations should be taken into consideration before the provision of an expert opinion and follow-up treatments, because the aetiological agents and microbial pathogenicity may be genetic, diet and geographical dependent.

Adenike AO Ogunshe
Applied Microbiology and Infectious Diseases,
Department of Microbiology,
Faculty of Science,
University of Ibadan,
Ibadan, Nigeria
adenikemicro@yahoo.com

REFERENCES

1 Fisher TK, Scimeca CL, Bharara M, Mills JL, Armstrong DG. A stepwise approach for surgical management of diabetic foot infections. J Am Podiat Med Assoc 2010;100:401–5.
2 Dowd SE, Wolcott RD, Sun Y, McKeehan T, Smith E, Rhoads D. Polymicrobial nature of chronic diabetic foot ulcer biofilm infections determined using bacterial tag encoded FLX amplicon pyrosequencing (bTEFAP). PLoS One 2008;3:e3326.
3 Bowler PG, Duerden BI, Armstrong DG. Wound microbiology and associated approaches to wound management. Clin Microbiol Rev 2001;14:244–69.
4 Armstrong DG, Lipsky BA. Diabetic foot infections: stepwise medical and surgical management. Int Wound J 2004;1:123–32.
5 Alavi SM, Khosravi AD, Sarami A, Dashtebozorg A, Montazeri EA. Bacteriologic study of diabetic foot ulcer. Pak J Med Sci 2007;23(pt I):681–4.
6 Karchmer AW, Gibbons GW. Foot infections in diabetics: evaluation and management. Curr Clin Top Infect Dis 1994;14:1–22.
7 Edmonds M, Foster A. The use of antibiotics in the diabetic foot. Am J Surg 2004;187:25S–8S.
8 Washington JA. The role of the microbiology laboratory in antimicrobial susceptibility testing. Infect Med 1999;16:531–2.
9 Ahearn DG. Medically important yeasts. Ann Rev Microbiol 1978;32:59–68.
10 Missoni EM, Kalenić S, Vukelić M, De Syo D, Belicza M, Kern J, Babić VV. Role of yeasts in diabetic foot ulcer infection. Acta Med Croatica 2006;60:43–50.
11 Mlinarić-Missoni E, Kalenić S, Vazic-Babić V. Species distribution and frequency of isolation of yeasts and dermatophytes from toe webs of diabetic patients. Acta Dermatovenerol Croat 2005;13:85–92.
12 Colsky AS, Kirsner RS, Kerdel FA. Analysis of antibiotic susceptibilities of skin wound flora in hospitalized dermatology patients: the crisis of antibiotic resistance has come to the surface. Arch Dermatol 1998;134:1006–9.
13 Vuorisalo S, Venermo M, Lepäntalo M. Treatment of diabetic foot ulcers. J Cardiovasc Surg (Torino) 2009;50:275–91.