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Influence of wound scores and microbiology on the outcome of the diabetic foot syndrome

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ABSTRACT

Aims: To establish if the microbiology and the TEXAS, PEDIS and Wagner wound classifications of the diabetic foot syndrome (DFS) predict amputation.
Methods: Prospective cohort study of 250 patients with DFS from 2009 to 2013. Tissue samples for culture were obtained and wound classification scores were recorded at admission.
Results: Infection was monomicrobial in 131 patients (52%). *Staphylococcus aureus* was the most frequent pathogen (76 patients, 30%); being methicillin-resistant *S. aureus* in 26% (20/76) *Escherichia coli* and *Enterobacter faecalis* were 2nd and 3rd most frequent pathogens. Two hundred nine patients (85%) needed amputation being major in 25 patients (10%). The three wound scales associated minor amputation but did not predict this outcome. Predictors of minor amputation in the multivariate analysis were the presence of osteomyelitis, the location of the wound in the forefoot and of major amputation elevated C reactive proteine (CRP) levels. A low ankle-brachial index (ABI) predicted major amputation in the follow-up. Overall, 74% of gram-positives were sensitive to quinolones and 98% to vancomycin and 90% of gram-negatives to cefotaxime and 95% to carbapenems.
Conclusions: The presence of osteomyelitis and the location of the wound in the forefoot predict minor amputation and elevated CRP levels predict major amputation. In the follow-up a low ABI predicts major amputation.

1. Introduction

Diabetes is a disease with a high prevalence (6% of the general population), which is increased with age (11% after 65 years) (American Diabetes Association, 2000a; Centers for Disease Control, 2000). Among its late complications is the foot ulcer. It is the most frequent cause of hospitalization (25%), with prolonged stays, of the diabetic patients (Relber, Boyko, & Smith, 1995). Between 14 and 20% of this ulcers will require an amputation (American Diabetes Association, 2000b; US Department of Health and Human Services, 1997).

Diabetic foot syndrome (DFS) is defined, according to the World Health Organization, as "ulceration of the foot (distally from the ankle and including the ankle) associated with neuropathy and different grades of ischemia and infection" (Jeffcoate, Macfarlane, & Fletcher, 1993). Recent research also remarks an "adipovascular axis" expression in lower plasma levels of adiponectin and higher plasma levels of IL-6 could be linked to foot ulcers pathogenesis by microvascular and inflammatory mechanisms (Tuttolomondo, Maida, & Pinto, 2015). The DFS implicates immense personal, social, medical and economical costs and should be one of the most preventable long-term complications of diabetes (Boulton, Vileikyte, Ragnarson-Tennvall, & Apelqvist, 2005; Driver, Fabbi, Lavery, & Gibbons, 2010). The burden of the DFS will tend to increase in the future because the contributing factors, such as peripheral neuropathy and vascular disease, are already present when the patient is diagnosed with type 2 diabetes (Boulton et al., 2005).

There are several scales to evaluate the degree of severity of a diabetic ulcer analyzing the characteristics of the ulcer, ischemia and infection. The most used and globally accepted scales are the Wagner scale, University of Texas and PEDIS (Gul, Basit, Ali, Ahmadani, & Miyan, 2006; Lipsky et al., 2012; Sun et al., 2012). These scales have demonstrated their utility correlating their degree of severity with the risk of amputation (Gul et al., 2006; Lipsky et al., 2012; Sun et al., 2012). The Wagner scale is easy to use and evaluates the depth of the wound, with the presence of osteomyelitis in intermediate stages and gangrene in advanced stages. It does not evaluate ischemia specifically, but the gangrene can be due to the infection or ischemia in the advanced stages. The University of Texas scale is a bit more complex, evaluating the presence of ischemia and infection with the

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depth of the wound. The PEDIS scale is the most focused on infection (Mills et al., 2014).

In the moment of the diagnosis of an infected foot ulcer, an empirical antibiotic regimen should be started and then directed according to the ulcer cultures (Blanes et al., 2012; Lipsky, 2004; Lipsky et al., 2012) There are several studies regarding the bacteriology of the DFS, but the results are varied and often contradictory (Aragón-Sánchez et al., 2009; Shanmugam, M, J., & Susan, 2013).

The aim of this study was to establish if the microbiology and the TEXAS, PEDIS and Wagner wound classifications of the diabetic foot syndrome (DFS) can predict amputation.

Secondary aims were to determine other risk factors for amputation, death and prolonged stay and to establish the best empiric therapy.

2. Materials and methods

This was a prospective cohort study of 250 consecutive patients diagnosed of DFS and admitted to the Angiology and Vascular Surgery Unit of the San Cecilio University Hospital in Granada, Spain, between January 2009 and September 2013. The criteria for admission were foot ulcers in diabetic patients with wide soft tissue and/or bone involvement, with infection and/or ischemia signs, that we did not consider candidates for oral antibiotic treatment, but instead intravenous treatment plus possible debridement. Patients with chronic lesions who presented infections 6 months prior to admission were excluded, as well as patients that did not require to be admitted for their treatment. Follow-up was during one year in our outpatient clinic. We did not have any patient lost to follow-up, except for the seven patients who died. The local Ethics Committee approved the study and all the patients signed an informed consent for participation.

Information on demographical and laboratory data and associated risk factors was obtained from the patients' medical records and by direct interview. It included data on age, sex, height and weight, type of diabetes, retinopathy, bone deformities, excessive alcohol intake (35 U or more a week for men, 21 U or more for women), smoking, cardiac disease, renal disease, pulmonary disease, hypertension, stroke, prior amputations and revascularizations.

Data on the current wound were recorded, such as time of evolution, type of wound, type of dressings used and prior use of antibiotics.

The presence of osteomyelitis was assessed using plain radiographs (using the following criteria: periosteal elevation, subcortical demineralization, cortical disruption, sequestra and gross bone destruction) and magnetic resonance when the radiographs were negative. Vascular status was assessed with pulse palpation and ankle brachial index (ABI) plus pulse volume recording (PVR), reserving invasive imaging studies when the previous explorations were abnormal. The decision in performing a revascularization depended on the results of the ABI and the PVR plus the imaging studies, which also helped decide the type of revascularization: open surgery versus endovascular surgery.

Laboratory data were also analyzed, including C reactive protein (CRP) and white blood cell (WBC) count as a measure of infection.

The degree of severity was assessed using the Wagner, University of Texas and PEDIS scales at admission by a staff vascular surgeon.

Cultures of the wounds, after cleaning, were obtained at admission. When possible, samples were taken from tissue biopsy or pus aspiration, trying to avoid swab cultures (taking 3 samples and considering a positive culture when the same bacteria were present in all the samples). We used as empirical antibiotic treatment levofloxacin associated with clindamycin (77%) for mild to moderate infections and vancomycin associated with a carbapenem (15%) for severe infection, based on laboratory data, fever, or systemic response to infection.

Amputations were divided in minor (toe, ray o transmetatarsal) and major (above or below the knee) for the analysis.

2.1. Statistical analysis

Continuous variables are expressed as mean ± standard deviation; categorical variables are presented as percentages. Comparison between quantitative variables was performed using Student's t-test for unpaired observations and 2-tailed and Mann–Whitney U test and for analysis of the qualitative variables, the chi-square and Fisher's exact tests were used. All the risk factors, laboratory data, different bacteria infecting the wounds, location of the wound, ABI, absence of distal pulses, presence of osteomyelitis and the severity of the wounds according to the three scales were included for the univariate analysis. For the analysis we separated as endpoints minor and major amputations and those amputations occurring during the hospital stay and those occurring during the follow-up. The predictive factors were analyzed with logistic regression, including those that were statistically significant in the univariate analysis. Statistical significance was set at $P < .05$. Statistical analysis was performed using SPSS version 20.0 (SPSS, Chicago, IL, USA).

3. Results

Two hundred fifty patients (199 male, 80%) with a mean age of 66 years (SD 11.3) were included in the study. Eighty-eight percent had type 2 diabetes while the remaining 12% had type 1 diabetes. One hundred fifty-four (62%) were current or former smokers, 155 (62%) had arterial hypertension, 106 (42%) had prior amputations and only 88 (35%) had present distal pulses (45% had absent distal pulses and the remaining 20% had absent popliteal or femoral pulse). Mean ABI was 0.7 (SD 0.28). Plain radiographs were performed in 94% of patients, visualizing signs of osteomyelitis in 44%. An additional 14% of patients had an MRI to diagnose osteomyelitis (see Table 1 for complete demographic information and risk factors).

The severity of the wounds according to the Wagner, University of Texas and PEDIS scores is shown in Table 2.

Infection was monomicrobial in 131 patients (52%). *Staphylococcus aureus* was the most frequent pathogen (76 patients, 30%); being methicillin-resistant *S. aureus* (MRSA) in 26% (20/76) *Escherichia coli* and *Enterobacter faecalis* were 2nd and 3rd most frequent pathogens (see Fig. 1 for wound culture results). The sensitivities to the different antibiotics of the microorganisms can be seen in Table 3. Overall, 74% of gram positives were sensitive to quinolones and 98% to vancomycin and 90% of gram negatives to cefotaxime and 95% to carbapenemes.

Two hundred nine patients (85%) needed amputation being minor in 184 patients (75%) and major in 25 patients (10%). Fifty-three patients had a revascularization, with an associated minor amputation in 39 cases and 5 failures, which required a major amputation. Seven patients (3%) died during hospitalization (5 from cardiac disease, 1 from digestive bleeding and 1 from sepsis). After one year of follow-up, 73 patients (29%) were readmitted because of worsening, 58 needed amputation (39 minor and 19 major) and 1 died.

3.1. Univariate analysis

No microorganism was associated with higher severity according to the Wagner, TEXAS or PEDIS scores.

After analyzing the different grades of the classifications, factors associated with minor amputation were Wagner score ≥3 ($P = .001$), TEXAS score ≥2B ($P = .007$) and PEDIS score ≥2 ($P = .046$). Also the presence of osteomyelitis ($P = .000$) and the location of the wound in the forefoot ($P = .000$) were associated with minor amputation. Smoking had a tendency toward significance ($P = .054$). No microorganism was associated with higher rates of amputation. Infection by *S. aureus* and gram-negative bacilli had greater rates of minor amputation, without reaching statistical significance (see Table 4 for complete results of the univariate and multivariate analyses).