# Risk Factors for Foot Infections in Individuals With Diabetes

LAWRENCE A. LAVERY, DPM, MPH[1]
DAVID G. ARMSTRONG, DPM[2,3]
ROBERT P. WUNDERLICH, DPM[4]
M. JANE MOHLER, PHD[5,6]
CHRISTOPHER S. WENDEL, MS[5]
BENJAMIN A. LIPSKY, MD[7]

**OBJECTIVE** — To prospectively determine risk factors for foot infection in a cohort of people with diabetes.

**RESEARCH DESIGN AND METHODS** — We evaluated then followed 1,666 consecutive diabetic patients enrolled in a managed care–based outpatient clinic in a 2-year longitudinal outcomes study. At enrollment, patients underwent a standardized general medical examination and detailed foot assessment and were educated about proper foot care. They were then rescreened at scheduled intervals and also seen promptly if they developed any foot problem.

**RESULTS** — During the evaluation period, 151 (9.1%) patients developed 199 foot infections, all but one involving a wound or penetrating injury. Most patients had infections involving only the soft tissue, but 19.9% had bone culture–proven osteomyelitis. For those who developed a foot infection, compared with those who did not, the risk of hospitalization was 55.7 times greater (95% CI 30.3–102.2; $P < 0.001$) and the risk of amputation was 154.5 times greater (58.5–468.5; $P < 0.001$). Foot wounds preceded all but one infection. Significant ($P < 0.05$) independent risk factors for foot infection from a multivariate analysis included wounds that penetrated to bone (odds ratio 6.7), wounds with a duration >30 days (4.7), recurrent wounds (2.4), wounds with a traumatic etiology (2.4), and presence of peripheral vascular disease (1.9).

**CONCLUSIONS** — Foot infections occur relatively frequently in individuals with diabetes, almost always follow trauma, and dramatically increase the risk of hospitalization and amputation. Efforts to prevent infections should be targeted at people with traumatic foot wounds, especially those that are chronic, deep, recurrent, or associated with peripheral vascular disease.

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Foot wounds are now the most common diabetes-related cause of hospitalization and are a frequent precursor to amputation (1–3). Individuals with diabetes have a 30-fold higher lifetime risk of undergoing a lower-extremity amputation compared with those without diabetes (4,5). An infected foot wound precedes about two-thirds of lower-extremity amputations (6,7), and infection is surpassed only by gangrene as an indication for diabetic lower-extremity amputation (8). Individuals with diabetes have at least a 10-fold greater risk of being hospitalized for soft tissue and bone infections of the foot (9) than individuals without diabetes.

While several retrospective studies address the epidemiology of foot infection in people with diabetes, there are no prospective data addressing this problem. Clinicians, health care organizations, and insurance and funding agencies would benefit from knowing the true incidence, the most common types, the clinical and demographic predisposing risk factors, and the outcomes of these infections. This information could help to predict which patients are at highest risk for diabetic foot infections, thereby helping to plan optimally targeted preventative strategies. We therefore conducted a prospective study of the epidemiology of foot infections, as part of a diabetes disease management program.

## RESEARCH DESIGN AND METHODS

— This report includes data from a cohort of the first 1,666 patients enrolled in a program designed to prevent and treat foot complications in diabetic patients (Fig. 1). The methods used in this analysis have been previously published (10). The disease management program was conducted in cooperation with two large primary care physician groups in south Texas. The patients all participated in a commercial HMO insurance plan or a Medicare replacement HMO insurance program. In the 1st year of the program, we identified people with diabetes (ICD-9-CM code of 250) from inpatient and outpatient administrative databases and confirmed the diagnosis by review of medical, laboratory, and pharmacy records. Of those identified, 74% participated in the screening and risk assessment program and were followed in a diabetic foot clinic. This clinic generally served as the patients' only source for diabetic foot care and for consultations for lower-extremity complications from specialists in vascular surgery or infectious diseases.

All patients (and any interested family members) were educated on basic diabetes and foot care principles in small group sessions when they were enrolled into the program. Patients were then screened for risk factors known to be associated with lower-extremity complications (11) (e.g., peripheral neuropathy, foot wounds, peripheral vascular disease, Charcot arthropathy, or previous foot surgical procedures). A staff podiatrist and nurse evaluated each patient's feet using a defined protocol. We diagnosed peripheral sensory neuropathy by either a vibration

From the [1]Department of Surgery, Scott and White Hospital, Texas A&M University Health Science Center College of Medicine, Temple, Texas; the [2]Dr. William M. Scholl College of Podiatric Medicine, Rosalind Franklin University of Medicine and Science, Chicago, Illinois; the [3]Department of Medicine, Manchester Royal Infirmary, Manchester, U.K.; [4]Diabetex, San Antonio, Texas; the [5]Research Service, Southern Arizona Veterans Affairs Medical Center, Tucson, Arizona; the [6]Epidemiology and Biostatistics Division, College of Public Health, University of Arizona, Tucson, Arizona; and the [7]Department of Medicine, University of Washington and the VA Puget Sound Heath Care System, Seattle, Washington.

Address correspondence and reprint requests to Lawrence A. Lavery, Professor, Department of Surgery, Scott and White Hospital, 703 Highland Spring Ln., Georgetown, TX 78628. E-mail: llavery@swmail.sw.org.

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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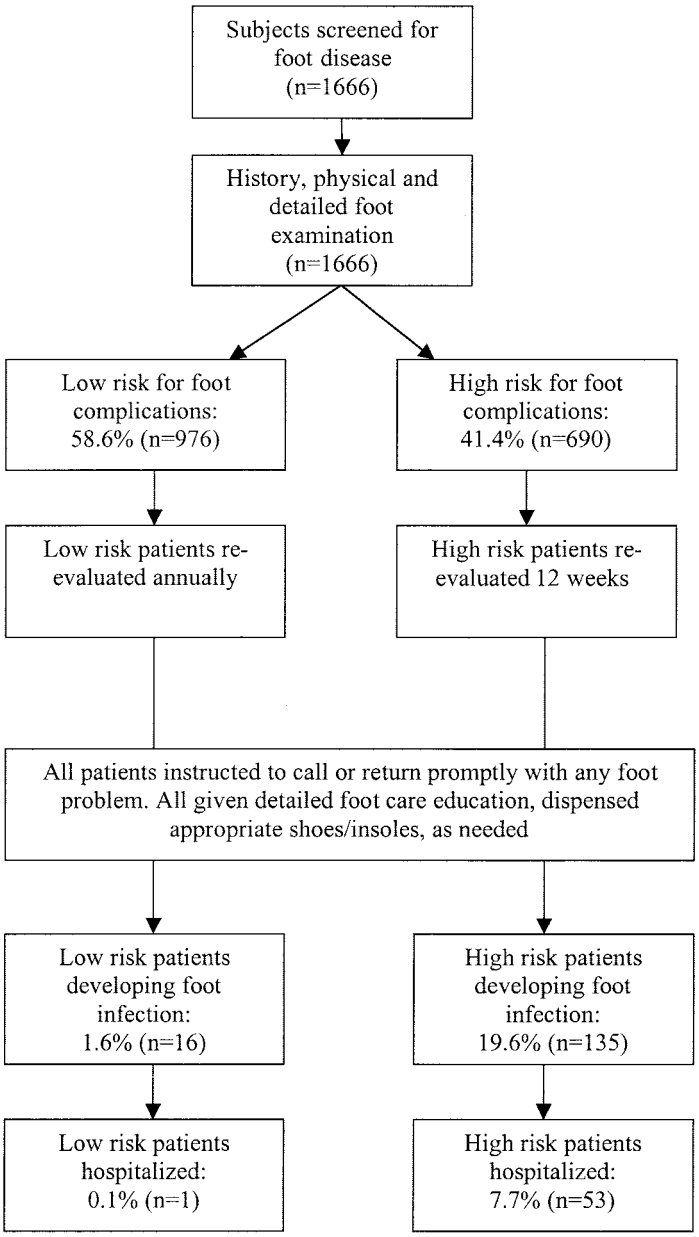


**Figure 1—***Flow chart for patients enrolled in the study.*

perception threshold level of >25 volts (VPT Tester; Xilas Medical, San Antonio, TX) or the inability to accurately perceive pressure at one or more site(s) with the 10-g Semmes-Weinstein monofilament (Touch-Test Sensory Evaluator; North Coast Medical, Morgan Hill, CA) (12). We defined peripheral vascular insufficiency as the absence of arterial foot pulses (both dorsalis pedis and posterior tibial arterial pulse) and an ankle-to-arm systolic blood pressure ratio of <0.80 (13). We evaluated for limited joint mobility, hallux rigidus (<50° dorsiflexion of the first metatarsophalangeal joint), or ankle equinus (dorsiflexion of <0°) (14–18), and foot deformities, e.g., hallux valgus, hammer toes, or claw toes. We measured peak foot pressures on the sole of the foot with the EMED force-plate (Novel, Minneapolis, MN), using a two-step method (19–21).

We constructed a database to record the information obtained in the screening evaluation of the enrolled individuals and to track any foot-related clinical outcomes of interest. We used claims data to verify all hospital admissions and amputations. Based on the results of screening examinations, we stratified patients into risk groups using the International Diabetic Foot Classification System (22–24). Low-risk patients (category 0) were annually rescreened for foot problems. High-risk patients (categories 1, 2, or 3) were examined in the foot clinic at least every 12 weeks and, when needed, were fitted for therapeutic shoes and insoles by a certified pedorthist. Subjects in all risk groups were instructed to call for an appointment any time they had a concern about a foot problem.

During the follow-up period, two staff podiatrists (L.A.L., R.P.W.) evaluated and treated any patient who developed a foot complication. We defined a foot wound as a full skin thickness lesion involving any portion of the foot or ankle (25–27). Using a blunt sterile probe, we evaluated the depth of any wound to determine undermining and whether the wound penetrated to tendon, joint capsule, or bone. We also recorded the duration the wound had been present from the time the patient reported it had started until the wound was healed, the wound necessitated an amputation, or the evaluation period ended. We defined Charcot arthropathy as a foot fracture or dislocation occurring with little or no trauma, in the presence of sensory neuropathy but palpable pulses (28,29). We defined a foot infection by clinical criteria consistent with the International Working Group guidelines (23) (i.e., the presence of purulence or two or more other local signs of inflammation). We evaluated patients with an infection for the extent of soft tissue involved and for evidence of bone involvement (30–32). When bone infection was suspected, the patient underwent an appropriate evaluation; we only diagnosed osteomyelitis when there was a positive culture from a bone biopsy (surgical or percutaneous).

### Statistical analyses

We compared differences in mean values for various à priori selected factors in patients who developed an infection and those who did not, using the $\chi^2$ test for categorical predictor variables and *t* tests for continuous variables. Using infection as the outcome variable, we calculated odds ratios (ORs) and 95% CIs by logistic regression. For categorical variables with more than two levels, such as wound depth or number of missing pulses, we chose one level as baseline and calculated ORs for other levels in comparison to baseline. After the univariate analysis, we used stepwise logistic regression analysis to model the effects of predictors and interactions while simultaneously controlling for potential confounding variables. We included predictors and interaction

**Table 1—*Demographic and clinical characteristics at enrollment for patients with foot wounds or penetrating injuries who did and did not develop a foot infection**

| | Infection | No infection | *P* value | OR (95% CI) |
|---|---|---|---|---|
| *n* | 150 | 97 | | |
| Demographics | | | | |
| Age ≥70 years | 51.3 | 52.6 | 0.85 | 0.95 (0.57–1.6) |
| Percent male | 52.4 | 53.6 | 0.85 | 0.95 (0.57–1.6) |
| Years with diabetes | 13.9 ± 9.9 | 12.8 ± 9.6 | 0.38 | 1.0 (0.99–1.04) |
| BMI (kg/m$^2$) | 30.3 ± 8.4 | 28.9 ± 6.3 | 0.14 | 0.97 (0.94–1.01) |
| Percent ≥30 kg/m$^2$ | 39.3 | 42.3 | 0.65 | 0.89 (0.53–1.5) |
| History of lower-extremity disease | | | | |
| Wound | 53.3 | 41.2 | 0.06 | 1.6 (0.97–2.7) |
| Amputation | 26.5 | 14.1 | 0.03 | 2.2 (1.1–4.4) |
| Lower-extremity bypass | 19.3 | 7.2 | 0.01 | 3.1 (1.3–7.3) |
| Charcot arthropathy | 4.7 | 3.1 | 0.54 | 1.5 (0.39–6.1) |
| Recurrent foot wounds | 41.3 | 22.7 | 0.003 | 2.4 (1.4–4.3) |
| Main cause of foot wound | | | | |
| Neither neuropathy nor peripheral vascular disease | 7.3 | 8.6 | 0.79 | 0.88 (0.34–2.3) |
| Neuropathy | 27.3 | 43.3 | 0.009 | 0.49 (0.29–0.84) |
| Neuroischemic | 31.3 | 18.6 | 0.026 | 2.0 (1.1–3.7) |
| Ischemia | 3.3 | 3.1 | 0.92 | 1.1 (0.25–4.6) |
| Trauma | 24.0 | 14.4 | 0.07 | 1.9 (0.95–3.7) |
| Venous stasis | 6.7 | 12.4 | 0.12 | 0.51 (0.21–1.2) |
| Peripheral neuropathy present | 71.3 | 77.3 | 0.29 | 0.73 (0.42–1.3) |
| Peripheral vascular disease present | 46.0 | 26.8 | 0.002 | 2.3 (1.3 to −4.0) |
| Foot deformity (any) present | 60.7 | 68.0 | 0.24 | 0.72 (0.42–1.2) |
| Hallux valgus | 26.0 | 39.2 | 0.03 | 0.55 (0.32–0.94) |
| Claw or hammer toe | 33.6 | 38.1 | 0.46 | 0.82 (0.48–1.4) |
| Equinus | 15.3 | 14.4 | 0.85 | 1.1 (0.52–2.2) |
| Plantar pressure >87.5 N/cm$^2$ | 65.1 | 66.2 | 0.89 | 0.96 (0.48–1.88) |
| Wound location | | | | |
| Great toe | 32.0 | 23.7 | 0.16 | 1.5 (0.85–2.7) |
| Small toes | 26.0 | 28.9 | 0.62 | 0.87 (0.49–1.5) |
| Metatarsals | 16.0 | 16.5 | 0.92 | 0.96 (0.48 −1.9) |
| Midfoot | 8.0 | 2.1 | 0.07 | 4.1 (0.90–18) |
| Heel | 8.0 | 9.3 | 0.73 | 0.85 (0.34–2.1) |
| Leg | 10.0 | 18.6 | 0.06 | 0.49 (0.23- 0.02) |
| Wound depth | | | | |
| Full thickness | 51.3 | 88.7 | — | 1.0 |
| Deep to fascia or tendon | 20.7 | 7.2 | <0.001 | 4.9 (2.1–11.9) |
| Joint or bone | 28.0 | 4.1 | <0.001 | 11.7 (4.0–34.2) |
| Wound duration (days) | 203 ± 281 | 147 ± 252 | 0.11 | 1.0 (1.0–1.01) |
| Wound duration >30 days | 96.7 | 78.4 | <0.0001 | 8.0 (2.9–22.0) |

Data are means ± SD or percent, unless otherwise indicated. *Of 151 foot infections encountered in the study, all but 1 (150) involved a penetrating wound or ulcer.

terms in a stepwise model based on statistical significance ($\alpha = 5\%$) in the univariate analysis or biological plausibility of an association.

**RESULTS** — Over an 8-month period, we enrolled 1,666 diabetic patients in the disease management program and followed this cohort for an average of 27.2 ± 14.2 months (range 3.9–32.0). During the study period, 151 patients (9.1%) developed 199 foot infections. Table 1 shows a comparison of demographic and clinical characteristics present at enrollment for the patients with a wound or penetrating injury who developed a foot infection and those who did not. The average duration of follow-up for subjects with foot wounds was 25.6 ± 11.5 months (median 30.4). Recurrent foot infections at the same or a different site occurred in 23.2% (35 of 151) of study patients; 24 patients had two, 9 had three, and 2 had four infections. Most infections involved only soft tissue, but 30 (19.9%) patients with foot infection had bone culture–proven osteomyelitis.

Sustaining a lower-extremity wound was the most common precipitating event for a foot infection. All but one of the 151 patients who developed a foot infection had a preexisting lower-extremity wound or penetrating injury. The risk of developing an infection was 2,193 times greater in subject who developed a foot wound than in those without a wound (60.7 vs. 0.07% [95% CI 303.6–15,837.6]; $P < 0.0001$).

During the study period, 69 people were hospitalized for 85 separate lower-extremity–related events. Foot infection was a contributing factor for hospitalization in 71.7% (61 of 85) of these events. Among the patients with a lower-extremity infection, 64.2% (97 of 151) were treated in an outpatient setting, while the rest (35.8%) were admitted for at least one infection-related hospitalization. The risk of hospitalization was 55.7 times greater for people with diabetes who developed a foot infection than for those who did not (95% CI 30.3–102.2; $P < 0.001$). The risk of amputation was 154.5 times greater in patients with diabetes who had a lower-extremity infection than in those who did not (95% CI 58.5–468.5; $P < 0.001$).

Using a stepwise logistic regression model we found several factors were significant independent risks (Table 2). We excluded ulceration from the regression model because of its high degree of colinearity with infection. The dominant remaining independent risk factors were wounds that penetrated to bone (OR 6.7; $P < 0.001$), wound duration of >30 days (4.7; $P < 0.004$), a history of recurrent wounds during the study period (2.4; $P < 0.006$), wounds with a traumatic etiology (2.4; $P < 0.02$), and the presence of peripheral vascular disease (1.9; $P < 0.04$).

**Table 2—*Variables achieving independent statistical significance as risk factors for foot infection by multivariate analysis***

| Variable | Risk ratio (95% CI) | *P* value |
|---|---|---|
| Wound depth to bone | 6.7 (2.3–19.9) | 0.001 |
| Wound duration >30 days | 4.7 (1.6–13.4) | 0.004 |
| Recurrent foot wound | 2.4 (1.3–4.5) | 0.006 |
| Traumatic wound etiology | 2.4 (1.1–5.0) | 0.02 |
| Peripheral vascular disease | 1.9 (1.0–3.6) | 0.04 |

**CONCLUSIONS** — Our search of the literature uncovered no previously published prospective study of this common and important problem. To best define types of and risk factors for foot infections, we conducted a comprehensive prospective study among individuals with diabetes carefully followed in a health management program. This included enrolling consecutive patients in a large cohort study, having specialists examine them thoroughly at baseline, and tracking them carefully during a relatively long follow-up period. The patients received all of their foot care at the site of enrollment. Because the enrolled patients, especially those at high risk for foot wound, made frequent follow-up visits and had ready access to specialty foot care, we likely detected all clinically important infections. We may, however, have missed some mild, self-limited, or patient-treated infections.

The incidence of foot infections in these patients was surprisingly high. Despite being extensively educated, provided with therapeutic shoes and insoles when indicated, followed in a foot clinic, and having ready access to podiatric care, 9.1% of enrolled patients developed a foot infection during just over 2 years of follow-up. As reported in previous retrospective studies (33), infections most commonly involved only the soft tissue, but about one in five extended to the bone.

We identified several risk factors for developing a foot infection in these subjects with diabetes. Sustaining a foot wound was by far the most important antecedent to an infection. In fact, only one infection developed in the absence of a wound or penetrating injury. Since most soft tissue infections occur when pathogens penetrate into the subcutaneous tissue, the association of infection with foot wounds is not surprising. Most (60.9%) foot wounds were clinically infected at presentation, but a substantial minority was not. This is an important distinction, as uninfected foot wounds were not routinely treated with antimicrobial therapy.

By multivariate analysis, we found four statistically significant independent risk factors for foot infection: wounds that penetrated to bone, recurrent wounds, wounds of long duration (30 days), and peripheral vascular disease. It is not surprising that patients with multiple wounds, wounds of long duration, and deeper wounds had a higher risk of infection. Subjects with recurrent wounds during the study period would have had a more prolonged exposure to the primary risk for infection, i.e., a penetrating wound. It is not, therefore, surprising that deeper wounds are associated with slower healing (34,35).

The finding that peripheral vascular disease was associated with an approximately twofold increased risk of foot infection in the multivariate model was unexpected. Foot ischemia certainly appears to be associated with an increased severity of an infection (36). Diabetic patients often have a diminished inflammatory response to injury or infection (37–43); this deficit could be further impaired by ischemia. Diminished blood flow could result in a lack of erythema or induration, visual cues of infection. These deficits, especially in a patient with sensory neuropathy who also lacks the ability to sense pain or warmth, might delay awareness of an infection. In a previous case-control study (43) of patients with an infected puncture wound of the foot, we found that visual cues of inflammation, rather than the pain, were the most frequent presenting complaints in the people with diabetes. The interval from the puncture injury to surgery was also significantly longer in the diabetic individuals, suggesting that their lack of pain perception might delay recognition of a limb-threatening problem (44). The types of traumatic wounds in this study included burns, puncture wounds, blunt trauma, lacerations, and ingrown toenails. The finding that wounds associated with trauma had a high risk of infection may be caused by the fact that these wounds often penetrate to deep structures and inoculate them with bacteria at the time of injury. Traumatic wounds may also be associated with more tissue damage, making it more prone to necrosis and infection.

Risk factors for developing a foot ulcer have been defined in several retrospective and prospective studies (11,14,45–49) We found only one other epidemiological study, however, of foot infections in persons with diabetes. Peters et al. (50) reported a case-control study of 112 patients with diabetes, of whom 68 were hospitalized for a foot infection while the other 44 were hospitalized for other reasons. In this study, neuropathy, peripheral vascular disease, and previous history of amputation were each significantly and independently associated with infection, conferring 3.4-, 5.5-, and 19.9-fold increased risk, respectively. Various social and economic factors were investigated and found not to be risks for infection. These results are similar to those in our study.

The strengths of our study included the fact that it involved a relatively large group of patients, the patients had a thorough and uniform baseline foot examination by experienced podiatrists, and they were then carefully followed for a long period. We also used internationally accepted definitions for foot infections and defined osteomyelitis by bone culture. One limitation of this study is that data on the microbial isolates of the infections were not collected. We rarely take superficial swabs of wounds because they are unreliable culture specimens (51–53). Thus, most of our cultures were of deep tissue and therefore obtained only for the more severe wounds. Another limitation was that we lacked some disease-staging data, such as serial glycated hemoglobin levels, and some information on comorbidities.

The results of this study clearly demonstrate the relatively high incidence of foot infections in people with diabetes, even those who have been subjected to intensive efforts to prevent foot complications. We have also defined the most important risk factors for these infections. Foot infections almost invariably occur in patients who sustain a foot wound, especially if the wound is of long duration and penetrates to underlying bone or if the patient has coexisting peripheral vascular disease or recurrent foot wounds. Finally,

we have demonstrated the high amputation risk associated with foot infections in diabetic patients. Fortunately, the risk factors associated with foot wounds and infection are all easily detected by a simple screening foot examination, allowing preventative efforts to be targeted to those at greatest risk (54). Although foot complications occurred despite our interventions, successful preventative efforts could potentially dramatically reduce the high rate of these potentially devastating problems in individuals with diabetes.

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