Clinical predictors of treatment failure for diabetic foot infections: data from a prospective trial

Benjamin A Lipsky, Peter Sheehan, David G Armstrong, Alan D Tice, Adam B Polis, Murray A Abramson

ABSTRACT

To aid clinicians in selecting the appropriate approach for treating patients with diabetic foot infections, we investigated whether any baseline clinical findings predicted an unfavourable clinical outcome. Using data from a large, prospective treatment trial of diabetic foot infections (SIDESTEP), we assessed the association between clinical treatment failure and baseline history, physical and laboratory findings, by univariate and multivariate logistic regression analyses. Among 402 patients clinically evaluable 10 days after completing antibiotic therapy, baseline factors significantly ($P < 0.05$) associated by univariate analysis with treatment failure were 'severe' (versus 'moderate') University of Texas (UT) wound grade; elevated white blood cell count, C-reactive protein or erythrocyte sedimentation rate; high wound severity score; inpatient treatment; low serum albumin; male sex; and skin temperature of affected foot $>10°C$ above that of unaffected foot. By multivariate logistic regression only severe UT wound grade (odds ratio 2·1) and elevated white blood cell count [odds ratio 1·7 for a 1 standard deviation (2971 cells/mm^3) increase] remained statistically significant. Clinical failure rates were 46% for patients with both risk factors compared with 10% for patients with no risk factors and 16–17% for patients with one risk factor. Increased white blood cell count and severe UT wound grade at baseline, but not other features, were significant independent and additive risk factors for clinical failure in patients treated for a diabetic foot infection.

Key words: Clinical prediction ● Diabetic foot infection ● Treatment outcome ● White blood cell count ● Wound severity

Key Points

- the appropriate approach to treating a diabetic foot infection largely depends on the clinical severity of the infection

INTRODUCTION

Infected foot wounds are a major cause of morbidity in persons with diabetes and the leading cause of lower extremity amputations in developed countries (1–4). The potential severity of these infections and the complex treatments they require have resulted in foot wounds being the most frequent reason for diabetes-related hospitalisation in the United States (5,6). The clinician treating a patient with a diabetic foot infection must immediately address several issues (1,7–11). Key among these are how broad-spectrum the antibiotic regimen should be and by what route it should be administered, when to request urgent surgical or other specialty consultations and whether or not hospitalisation is required. These decisions will affect the cost of care, the likelihood of adverse events and presumably

Authors: BA Lipsky, MD, Veterans Affairs Puget Sound Health Care System, and University of Washington School of Medicine, Seattle, WA, USA; P Sheehan, MD, Cabrini Medical Center and Mount Sinai School of Medicine, New York, NY, USA; DG Armstrong, Scholl's Center for Lower Extremity Ambulatory Research (CLEAR) at Rosalind Franklin University of Medicine and Science, Chicago, IL, USA; AD Tice, MD, John A Burns School of Medicine, University of Hawaii, Honolulu, HI, USA; AB Polis, MA, Merck & Co., Inc., West Point, PA, USA; MA Abramson, MD, MPH, Merck & Co., Inc., West Point, PA, USA
Address for correspondence: Dr BA Lipsky, Veterans' Affairs Puget Sound Health Care System (S-111-GIMC), 1660 S. Columbian Way, Seattle, WA 98108-1597, USA
E-mail: benjamin.lipsky@med.va.gov
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the clinical outcomes. Perhaps the most important factor affecting these decisions is the clinical severity of the infection. (1,12,13). Unfortunately, clinicians currently have little evidence-based guidance for identifying which patients have a severe diabetic foot infection or which clinical findings are associated with a poor outcome (14).

Because providing high-quality care should improve treatment outcomes, it would be useful to know if any patient- or wound-related factors affect the results of treatment for diabetic foot complications (7). This study was designed to determine which, if any, of the many easily assessed baseline clinical findings predict the clinical outcome in patients being treated for a diabetic foot infection. Identifying such risk factors might help clinicians decide on the most appropriate type of care, the need for hospitalisation and the urgency with which various interventions should be undertaken.

RESEARCH DESIGN AND METHODS

Data for this study were derived from a prospective, multicentre, double-blind randomised controlled trial for diabetic foot infections (SIDESTEP) (15) that compared intravenous therapy with ertapenem versus piperacillin/tazobactam (with the option for follow-on therapy in either arm with oral amoxicillin/clavulanate) for a moderate to severe diabetic foot infection. Infection was defined, in accord with the Infectious Diseases Society of America guidelines (1), as the presence of purulent wound drainage or ≥3 designated systemic or local inflammatory findings. The investigators excluded patients who did not require parenteral antibiotic therapy; had necrotising fasciitis or underlying osteomyelitis; or had critical limb ischaemia, extensive gangrene or any indwelling prosthetic material.

At baseline, enrolled patients were stratified based on the University of Texas (UT) diabetic wound classification (16,17). This system, which includes four grades of depth (0–3) and four stages of comorbidity (A = non infected, B = infected C = ischaemic, D = infected and ischaemic), has been shown to predict outcome of a foot wound (17,18). We enrolled patients with stage B or D, and categorised the severity of the wound as either 'moderate' (grade 0 or 1) or 'severe' (grade 2 or 3). The investigators were trained to asses the size, depth and presence and intensity of eight signs and symptoms of infection (related to findings of inflammation and wound discharge). This allowed us to use a custom-developed scoring system to calculate a quantitative wound severity score (the validation of which is the subject of another study) at each visit.

In addition to the efficacy and safety outcomes, we obtained extensive descriptive and clinical characteristics, including patient demographics and medical history; prior and concomitant medications used; physical examination findings, emphasising the foot (including specified neurological and vascular assessments); standard serological and haematological tests and plain foot X rays (and any other imaging tests deemed necessary by the investigators). We also used a dermal thermometer to compare the skin temperature at the site of the infection with temperature at the same anatomic site on the uninfected foot. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines (19) and was approved by each site's institutional review board, and each patient provided written informed consent.

We evaluated the clinical response to treatment based on the changes in signs and symptoms of infection between the baseline visit and the follow-up assessment (FUA), conducted ~10 days after the end of all study-designated antibiotic therapy. We designated the response as 'favourable' if all or most (i.e. more than half) of the pretherapy signs and symptoms of infection (and specifically fever, lymphangitis and purulent drainage) resolved and the patient did not need further antibiotic therapy, and 'failure' if there was persistence, progression or recrudescence of most (i.e. more than half) pretherapy signs and symptoms or the patient required additional systemic antibiotic therapy or surgical or other adjunctive treatments for their foot infection. A patient was clinically evaluable if there were data to assess the clinical response, no confounding factors and ≥48 hours of intravenous antibiotic therapy. Since favourable clinical response rates for evaluable patients at the FUA were statistically equivalent for patients who were treated with ertapenem (87%) and piperacillin/tazobactam (83%), we combined all patients for these analyses.

Key Points

● there are few data on which clinical factors present at baseline correlate with the clinical outcome of treatment for these infections

Key Points

- the SIDESTEP study randomised 586 patients, 402 of whom were clinically evaluable at the FUA
- 342 (85%) had a favourable response and 60 had clinical failures

Statistical analysis

We performed a univariate analysis for each selected baseline parameter to determine if it was related to the clinical outcome. We used logistic regression to determine each parameter's clinical and statistical significance by calculating odds ratios, 95% confidence intervals (CI) and P values (20). For continuous parameters, we standardised the odds ratios to express the risk associated with a 1 standard deviation increase. To examine as many risk factors as possible in the multivariate analysis, we included each baseline parameter with a possible relationship with clinical outcome ($P \leq 0.25$) in the univariate analysis. Using a stepwise method of model selection, we entered and maintained parameters in the multivariate model that had a $P \leq 0.05$. When modelling data, using a higher P value (e.g. 0.25) allows inclusion of factors in the univariate model that are statistically significant ($P \leq 0.05$) as well as those that might become significant within the multivariate model. We assessed the relationship among the parameters included in the multivariate analysis using correlations for continuous parameters, Fisher's exact test for categorical parameters, and one-way analysis of variance tests for the relationship between continuous and categorical parameters (20).

Missing data and multivariate analysis

We assessed patterns of missing data for each variable and used five models to assess the predictors of outcome. Model 1 used no imputation of missing data and excluded patients with any missing data point. Model 2 also used no imputation and excluded patients lacking the parameter with the most missing data points (C-reactive protein). Model 3 imputed data using the mean value of the parameter with the most missing data. Model 4 imputed the parameter with the most missing data using a predicted value based on a separate model-building regression analysis. Model 5 used multiple imputations for missing data for five parameters, using a Markov Chain Monte Carlo method (21). We created a series of ten imputed data sets, conducted logistic regression analyses for each, then combined the estimates from each imputation and performed sequential model building. To determine the independent predictors of outcome and minimise the amount of missing data, we used the model-building identified factors and conducted a logistic regression with no imputation.

RESULTS

The SIDESTEP study randomised 586 patients, 402 of whom were clinically evaluable at the FUA. Among these, 342 (85%) had a favourable response and 60 had clinical failures. The mean duration of antibiotic therapy was similar for patients with a favourable clinical response and those who failed to respond (17·4 versus 17·6 days total therapy, and 10·7 versus 13·8 days just intravenous therapy). Table 1 summarises the continuous and dichotomous parameters selected for analysis as potential predictors of outcome.

Association between clinical failure of treatment and baseline parameters

Univariate analysis

From the univariate analysis, 13 baseline parameters reached a P value of ≤ 0.25 (see Table 2). There was no effect of sex or ethnicity on outcome. Of the dichotomous factors, a severe baseline wound was associated with the highest increase in odds of failure (odds ratio = 2·40, $P = 0.002$, comparing moderate with severe wounds). Clinical failure was noted in 23% of the patients with a severe wound at baseline compared with 11% with a moderate wound. Among the continuous variables, an elevated white blood cell count had the highest association with clinical failure [odds ratio = 1·80, $P < 0.001$, for an increase of 1 standard deviation (2971 cells/mm^3) in white blood cell count]. The overall mean baseline ($\pm$standard deviation) white blood cell count was 8240 ($\pm$2971) cells/mm^3; it was 9977 ($\pm$4235) cells/mm^3 for the patients who failed treatment compared with 7933 ($\pm$2576) cells/mm^3 for those with a favourable clinical response.

Multivariate analysis

We found no relationship between missing data and erythrocyte sedimentation rate or dermal thermometry, but for C-reactive protein, there were more missing data points among patients with a severe baseline wound (54%) than among those with a moderate wound (32%). Women (45%) had more missing values than men (34%), and outpatients had more (43%) missing values than inpatients (31%).

Table 1 Clinical outcome by baseline patient characteristics analysed for association with clinical outcome

Continuous clinical factors (units)	Favourable response		Failure response		Total	
	n	Mean ± SD	n	Mean ± SD	N	Mean ± SD
White blood cell count (cells/mm^3)	339	7933 ± 2576	60	9977 ± 4235	399	8240 ± 2971
C-reactive protein (mg/dl)	204	3·7 ± 6·6	43	9·1 ± 10·1	247	4·6 ± 7·6
Erythrocyte sedimentation rate (mm/hour)	305	41·0 ± 29·9	55	54·4·0 ± 36·4	360	43·0 ± 31·3
Total wound score* [3 (least)−49 (most) severe]	322	15·5 ± 5·6	51	18·0 ± 5·4	373	15·8 ± 5·6
Serum albumin (g/dl)	324	3·8 ± 1·0	58	3·5 ± 0·5	382	3·7 ± 1·0
Serum glucose (mg/dl)	335	196·4 ± 104	59	220·8 ± 127	394	200·1 ± 108
Haemoglobin (g/dl)	339	13·1 ± 2·0	60	12·7 ± 1·7	399	13·0 ± 1·9
Body mass index (kg/m^2)	307	33·4 ± 9·5	58	32·1 ± 8·1	365	33·2 ± 9·3
Serum creatinine (mg/dl)	337	1·3 ± 1·3	59	1·1 ± 0·6	396	1·2 ± 1·2
Systolic blood pressure (mmHg)	339	136·3 ± 19·7	60	134·5 ± 16·3	399	136·0 ± 19·2
Diastolic blood pressure (mmHg)	339	76·1 ± 11·9	60	75·8 ± 10·6	399	76·0 ± 11·7
Haemoglobin A1C (%)	291	8·7 ± 2·3	48	8·7 ± 2·3	339	8·7 ± 2·3
Duration of diabetes diagnosis (years)	330	12·5 ± 9·4	60	12·7 ± 11·1	390	12·5 ± 9·7
Age (years)	342	58·8 ± 13·6	60	58·6 ± 13·5	402	58·8 ± 13·5
Weight (kg)	309	99·0 ± 28·3	58	98·7 ± 26·8	367	98·9 ± 28·0

Dichotomous clinical factors	Favourable response		Failure response		Total	
	N	n (%)	N	n (%)	N	n (%)
Baseline severity by UT† score at baseline	342		60		402	
Severe		96 (28·1)		29 (48·3)		125 (31·1)
Moderate		246 (71·9)		31 (51·7)		277 (68·9)
Outpatient	342		60		402	
Initial treatment, inpatient		114 (33·3)		31 (51·7)		145 (36·1)
Initial treatment, outpatient		228 (66·7)		29 (48·3)		257 (63·9)
Gender	342		60		402	
Male		200 (58·5)		44 (73·3)		244 (60·7)
Female		142 (41·5)		16 (26·7)		158 (39·3)
Dermal thermometry	308		54		362	
≥10°C		32 (10·4)		11 (20·4)		319 (88·1)
<10°C		276 (89·6)		43 (79·6)		43 (11·9)
Previous insulin use	342		60		402	
Yes		197 (57·6)		41 (68·3)		238 (59·2)
No		145 (42·4)		19 (31·7)		164 (40·8)
Wound onset duration (months)	338		60		398	
>6		40 (11·8)		11 (18·3)		51 (12·8)
≤6		298 (88·2)		49 (81·7)		347 (87·2)
Treatment arm	342		60		402	
Piperacillin/tazobactam		162 (47·4)		34 (56·7)		196 (48·8)
Ertapenem		180 (52·6)		26 (43·3)		206 (51·2)
Nylon monofilament test	335		59		394	
≥2		251 (74·9)		48 (81·4)		299 (75·9)
0–1		84 (25·1)		11 (18·6)		95 (24·1)
Dorsalis pedis pulse	338		60		398	
0 to 1+		121 (35·8)		19 (31·7)		140 (35·2)
>1+		217 (64·2)		41 (68·3)		258 (64·8)
Foot X ray	322		55		377	
Abnormal		140 (43·5)		25 (45·5)		165 (43·8)
Normal		182 (56·5)		30 (54·5)		212 (56·2)

SD = standard deviation; n = sample size of the subgroup of the clinical factor; N = sample size of the total group of the clinical factor.

*See text for details.

†UT = University of Texas wound classification.

Key Points

• risk factors for a diabetic patient developing a foot infection are known but there is little information on which, if any, clinical findings predict the outcome of infection

Table 2 Level of association of clinical factors at baseline with clinical treatment failure from the univariate analyses (follow-up assessment clinically evaluable population)

Clinical factor	Odds ratio (OR)	95% confidence interval (CI)	P value
White blood cell count	1·80	1·39–2·32	<0·001
C-reactive protein	1·74	1·31–2·31	<0·001
Baseline severity by UT* score (severe versus moderate)	2·40	1·37–4·19	0·002
Erythrocyte sedimentation rate	1·48	1·13–1·93	0·004
Total wound score	1·51	1·14–1·98	0·004
Outpatient (initial treatment inpatient versus outpatient)	2·14	1·23–3·72	0·007
Serum albumin	0·52	0·33–0·83	0·007
Gender (male versus female)	1·95	1·06–3·60	0·032
Dermal thermometry (≥10°C versus <10°C)	2·21	1·04–4·70	0·040
Serum glucose	1·23	0·95–1·59	0·112
Previous insulin use (yes versus no)	1·59	0·89–2·85	0·121
Wound onset duration (>6 months versus ≤6 months)	1·67	0·80–3·48	0·169
Treatment arm (piperacillin/tazobactam versus ertapenem)	1·45	0·84–2·53	0·185
Haemoglobin	0·85	0·64–1·12	0·243
Nylon monofilament test (≥2 versus 0–1)	1·46	0·73–2·94	0·290
Body mass index	0·86	0·64–1·17	0·335
Serum creatinine	0·79	0·43–1·45	0·454
Systolic blood pressure	0·91	0·69–1·20	0·507
Dorsalis pedis pulse (0 to 1+ versus >1+)	0·85	0·47–1·54	0·597
Foot X ray (abnormal versus normal)	1·08	0·61–1·93	0·785
Diastolic blood pressure	0·97	0·74–1·278	0·833
Haemoglobin A1C	1·03	0·756–1·39	0·875
Duration of diabetes diagnosis	1·02	0·78–1·34	0·876
Age	0·98	0·75–1·29	0·902
Weight	0·99	0·75–1·31	0·937

*UT = University of Texas wound classification. Single logistic regression was used to estimate the OR, 95% CI and P values. OR for the continuous variables represent the increased odds of clinical failure based on a 1 standard deviation increase in the risk factor.

In running five models (see Research design and Methods) to build the final multivariate model, baseline wound severity and white blood cell count were consistently the most predictive of clinical outcome. Dermal thermometry was a significant predictor in Model 5 ($P = 0.04$), which used multiple imputation. Total wound score nearly achieved significance in Models 2 and 4 ($P = 0.06$), both of which imputed C-reactive protein. Differences in skin temperatures by dermal thermometry and the results of the total wound score were not statistically significant predictors of clinical outcome when tested independently in models containing baseline severity and white blood cell count.

The final multivariate model demonstrated that only two features were statistically significant independent predictors of clinical failure: 1) UT wound grade classification of 'severe' compared with 'moderate' (odds ratio 2·1, 95% CI 1/33, 2·2, $P < 0.001$) and 2) elevated white blood cell count [odds ratio 1·7 with an increase in 1 standard deviation (2971 cells/mm³) above the mean, 95% CI 1·2–3·8, $P = 0.01$). The white blood cell count was significantly and directly related at all values to clinical failure rates at the FUA assessment (Figure 1). At baseline, patients with neither independent risk factor had a failure rate of 22/222, or 9·9% (95% CI 6·3–14·6); this increased to 23/144, or 16% (95% CI 19·4–23·0) for patients with one of these risk factors and to 15/33, or 45·5% (28·1, 63·6) for patients with both risk factors.

CONCLUSIONS

Many of the risk factors for a diabetic patient developing a foot infection are known (22,23), but there is little information on which, if any, clinical findings predict the outcome of infection. Among the grading systems developed for classifying diabetic foot wounds (11,16,24–27), only those from the International Working
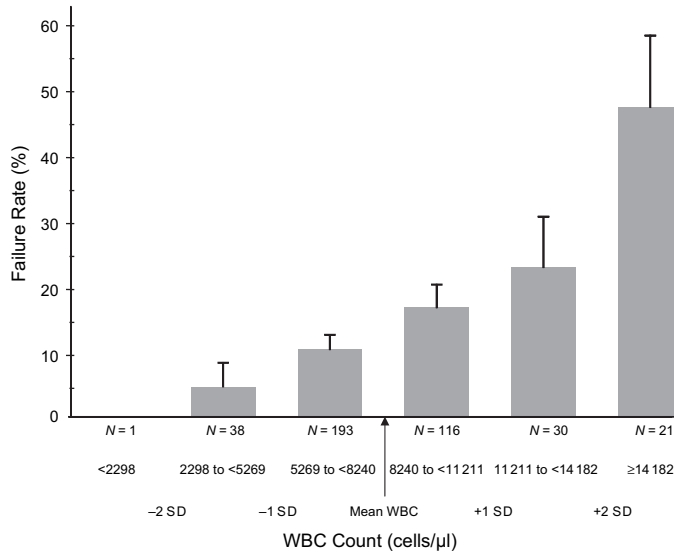
Figure 1. Clinical treatment failure rate by white blood cell count. SD = standard deviation; N = sample size of the group; WBC = white blood cell.

Group on the Diabetic Foot (11,28,29) and the Infectious Diseases Society of America (1) specifically grade the severity of the infection component. Neither of these, however, has yet been validated, and it is unknown if they predict the likelihood of successful treatment. Furthermore, other factors that might potentially help predict the clinical outcome of a diabetic foot infection have not been prospectively analysed.

Knowing which clinical factors predict an unfavourable outcome could help the clinician know when to be especially vigilant and to consider more aggressive diagnostic and therapeutic interventions. The costliest decision in treating a diabetic foot infection is when to hospitalise the patient (30,31). While several medical and psychosocial factors play into this decision, the most important is the severity of the infection (1). A second key decision point is selecting the appropriate antibiotic therapy. Most patients are initially treated empirically while awaiting culture and sensitivity results. Patients with mild to moderate diabetic foot infections can often be treated with relatively narrow-spectrum oral antibiotic agents, but for severe infections it is usually safest to start with broad-spectrum and parenteral agents (3,32).

Our prospective study identified numerous factors by univariate analyses that were associated with a worse clinical outcome with moderate to severe diabetic foot infections.

These included demographic, clinical and laboratory parameters, each of which would be easily assessable at the patient's initial presentation. Among these, we used the nine parameters that achieved statistical significance ($P < 0.05$) and the five parameters with a P value <0.25 level for the multivariate analysis. Our multivariate regression model found that only two baseline parameters, a severe (rather than moderate) wound as determined by the UT grade of depth and a higher white blood cell count, were statistically significantly associated with an unfavourable clinical outcome.

These two parameters have been found to be associated with worse clinical outcomes in previously published retrospective studies, each of which (unlike ours) included some patients with bone infection. In evaluating the UT classification, Armstrong *et al.* found that the risk for high-level limb amputation was 11-fold higher for wounds that penetrated to bone than for those that did not involve deep structures (17). Oyibo *et al.* (18) found that both the UT grade and stage, as well as aspects of the older Wagner classification grade (26), were significantly correlated with the risk of amputation. For UT stage, the risk of amputation significantly increased with the presence of infection, both alone and in combination with ischaemia, but not with ischaemia alone. Increasing stage, regardless of grade, was associated with an increased risk of amputation

Key Points

- using data from a large prospective study, we found that only two factors were significant independent risks for treatment failure: a severe wound by the University of Texas grade and an increased white blood cell count

and prolonged ulcer healing time, and the UT system was a better predictor of outcome than the Wagner system (18). Similarly, Eneroth et al. found, using logistic regression analysis, that a diabetic foot infection deep enough to expose bone was associated with limb amputation (33). Calhoun et al. also noted that more severe or extensive foot infections (by Wagner score) were associated with a higher treatment failure rate than milder infections (24).

Many diabetic patients with a severe infection do not have leukocytosis (34), but our study demonstrated that an elevated white blood cell count should raise special concerns. We found only two other (retrospective) studies with similar findings. The investigation by Eneroth et al. (33) of deep infections found that a white blood cell count of >12 000 cells/mm^3 was an independent predictor of limb amputation. Similarly, Akanji et al. (35) reported that leukocytosis was associated with worse clinical outcomes with diabetic foot infection. In a retrospective cohort study of diabetic foot infections by Pittet et al., however, the neutrophil count was not among the independent factors that predicted treatment failure (36).

Of note is that the results of our large prospective study of diabetic patients with moderate to severe foot infections showed that many factors that might help predict clinical outcome, such as male gender, increased serum inflammatory markers (sedimentation rate and C-reactive protein), long duration of diabetes, poor glycaemic control, elevated serum creatinine, and diminished pedal pulses, did not provide additional information beyond that provided by UT grade of depth and white blood cell count. Previous smaller, retrospective studies, which did not exclude patients with osteomyelitis, have revealed additional factors that correlated with outcome. Pittet et al. reported that independent factors associated with treatment failure were the presence of fever, increased serum creatinine, prior hospitalisation for a diabetic foot lesion and a gangrenous wound (36). Other patient characteristics, however, including various demographic variables, duration of diabetes, neutrophil count or the anatomical site of the lesion, failed to predict outcome (36). Benotmane et al. found that the factors associated with a worse outcome in a group of patients with an infected diabetic foot wound included male gender, delay in proper management,

poor-quality medical treatment, 'negative surgical attitudes' and an inadequate initial amputation level (37). In a study by Eneroth et al., long duration of diabetes and inadequate foot perfusion were also independent risk factors predicting limb amputation (33). Limb ischaemia was the major factor associated with a poor outcome in patients with a severe diabetic foot infection in a report by Diamantopoulos et al. (38). In a prospective antibiotic trial of diabetic foot infections reported by Grayson et al., treatment failure was associated with antibiotic-resistant pathogens and nosocomial acquisition of infection (39). Criado et al., in a retrospective stepwise discriminate analysis of vascular surgery patients, noted that patients most likely to require a major amputation during the initial hospitalisation were those with an absent dorsalis pedis pulse or with a polymicrobial infection (40). In addition, non insulin-dependent diabetic men and those undergoing delayed amputation had worse outcomes (40).

Some of the outcomes from these studies differ from our findings. This may be partly explained by the selection bias that is often introduced by retrospective studies; they are more likely to include sicker patients with several abnormal baseline parameters than in our prospective antimicrobial trial. In addition, unlike these retrospective studies, we excluded patients with osteomyelitis (that was not resected), with critical limb ischaemia requiring surgical intervention or with any immediately life-threatening comorbidity. Although limb ischaemia may be an important predictor of outcomes for diabetic foot infections, our study included too few of these patients to allow any meaningful analysis of this factor. The relatively high cure rate in both arms of our trial also limited our ability to investigate treatment failures. While the mean white blood cell counts for the patients who failed therapy were just within the normal range, an adverse outcome was directly related to the white blood cell count, and a count above ~10 000 appears to predict a poor outcome. Certainly, our findings should be validated by another prospective trial.

In summary, we found that at baseline, a severe wound by the UT grade and an elevated white blood cell count were the only two statistically significant independent predictors of an unfavourable clinical outcome

in diabetic patients with a moderate to severe foot infection. The importance of these clinical parameters is supported by the fact that their risk was more than additive when combined, that the white blood cell count was linearly related to outcome, and the similar findings in some previously published retrospective case series. Of interest is that other factors previously found to be associated with a poor outcome in retrospective studies were not in our prospective study. Knowing which baseline clinical findings predict a worse clinical outcome may help clinicians formulate an effective management strategy for a patient with a diabetic foot infection.

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