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Severity of Diabetic Foot Infection and Rate of Limb Salvage

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Abstract

Background—Foot infections are limb threatening complications in patients with diabetes mellitus (DM) and proper classification of diabetic foot infection (DFI) severity is important in establishing the proper antibiotic regimen, the need for hospitalization and surgery and the risk of amputation. Our hypothesis was that patients with severe DFI would have a longer hospitalization than those with moderate DFI. The purposed of this study was two fold. The first purpose was to define DFI using readily available clinical information and objective parameters outlined by consensus statements. The second purpose of this study was the assess the amputation and limb salvage rates for hospitalized patients with DFI.

Materials and methods—The database of a single academic foot and ankle program was reviewed for patients who were hospitalized for a DFI from 2006-2011. Inpatient and outpatient electronic medical records identified 100 patients. Severe DFI was defined as having two or more objective findings of systemic toxicity and/or metabolic instability at the time of initial assessment.

Results—The length of stay was significantly shorter for patients with a moderate infection than those with a severe infection (median 5 days versus 8 days, p=0.021). A non-significant trend indicating higher rates of limb salvage in patients with moderate infections compared to patients with severe infections was observed (94% versus 80%, p=0.081).

Summary and Conclusion—As hypothesized, patients with severe DFI had a median hospital stay that was 60% longer than patients with moderate DFI. In this sample, 55% of patients with a severe DFI required some type of amputation compared to 42 % of patients with a moderate DFI.

Keywords

diabetic foot infection definition severe

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INTRODUCTION

Foot infections are limb threatening complications in patients with diabetes mellitus (DM) and proper classification of diabetic foot infection (DFI) severity is important in establishing the proper antibiotic regimen, the need for hospitalization and surgery and the risk of amputation.[15] In 2004, a consensus report by the Infectious Disease Society of America (IDSA) described four grades of severity (Table 1).[14] The International Working Group on the Diabetic Foot (IWGDF) also established a virtually identical severity classification (Table 1).[15] The IDSA classification was later validated by Lavery et al.[12] who observed a trend toward an increased risk for amputation, higher-level amputation, and lower extremity-related hospitalization with increasing infection severity.

Severe IDSA (IWGDF 4) infections are distinguished from moderate IDSA (IWGDF 3) infections by the presence of systemic signs of toxicity and/or metabolic instability, however no precise values have been defined as to what constitutes fever, tachycardia, hypotension, leukocytosis, acidosis, severe hyperglycemia or azotemia in patients with DFI (Table 1).[9] Although the validation study by Lavery et al.[12] classified infection severity based on the presence or absence of systemic findings of infection, the authors did not define fever, leukocytosis or metabolic aberration. Similarly, another study evaluating clinical and laboratory testing in DFI utilized the IDSA/IWGDF classifications but did not define the parameters of a severe infection.[7] A recent study of amputations after DFI defined severe infection as a systolic blood pressure < 100 mm Hg, temperature < 96° F or > 100.5° F, pulse <49 or > 125 beats per minute, respiration rate < 10 or >29 breaths per minute or altered mental status.[17] Another study defined severe infection as University of Texas San Antonio (UTSA) Stage 2 and 3 infections, and did not consider systemic signs or laboratory findings.[16] Most recently, an expert panel convened by the IWGDF and IDSA defined a severe (IWGDF 4) infection as any foot infection with ≥ 2 signs of a systemic inflammatory response syndrome.[13,15] These signs included temperature > 38 ° C or < 36 ° C, heart rate > 90 beats/minute, respiratory rate > 20 breaths/min or PaCO < 32 mmHg and white blood cell (WBC) count > 12,000 or < 4,000 cell/mm^3. These reports did not include hyperglycemia, azotemia or acidosis in defining a severe infection in contrast to the previous guidelines. Finally, another recent review reported similar signs with the exception of using a temperature threshold of > 39° C.[23] It is apparent that there is no consensus on the precise definition of systemic toxicity or metabolic instability in patients with DFI.

Our hypothesis was that patients with severe DFI would have a longer hospitalization than those with moderate DFI. The purposed of this study was two fold. The first purpose was to define DFI using readily available clinical information and objective parameters outlined by consensus statements. The second purpose of this study was the assess the amputation and limb salvage rates for hospitalized patients with DFI.

MATERIALS AND METHODS

After approval by our local institutional review board, the database of a single academic foot and ankle program was reviewed for patients who were hospitalized for a DFI from 2006-2011. Both inpatient and outpatient electronic medical records were reviewed and 100 patients were identified who were hospitalized for DFI. While we did not develop the parameters which distinguished moderate from severe DFI according to the IDSA consensus, our goal was to define them based upon clinical information using vital signs and laboratory studies that were readily available. Severe DFI was defined as having two or more objective findings of systemic toxicity and/or metabolic instability at the time of initial assessment (Table 2). We elected to use two or more of these parameters to define a severe DFI based on the recommendations for systemic inflammatory response syndrome (SIRS). We utilized the threshold for temperature, heart rate, respiratory rate and WBC count as described for SIRS.[3,15,24] Sepsis induced hypotension was defined as a systolic blood pressure < 90 based on the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference.[3] Hyperglycemia was defined as serum glucose > 200 mg/dl since patients undergoing non-cardiovascular surgery with values above this level had a twofold increased risk of mortality.[19] Major infections are associated with pre-renal azotemia secondary to decreased renal perfusion and hypovolemia, and we defined azotemia as a blood urea nitrogen/creatinine ratio of > 20 (normal ≤ 10).[18] The primary findings of diabetic metabolic acidosis are a reduction in serum bicarbonate and an increased anion gap. Arterial blood gases were not available in the vast majority of our patients so we defined metabolic acidosis as serum CO_2 levels < 22 mmol/l (normal 22-32) and anion gap > 15 mEq/L (normal 7-15) as determined using serum electrolytes.[25] All infections were assigned a wound grade according to the UTSA classification.[9] All of the hospitalized patients had moderate or severe infections utilizing previously defined parameters.[9]

As part of our academic teaching program, all patients with DM who are evaluated have a thorough neurovascular examination. Peripheral pulses were evaluated and if the dorsalis pedis and/or posterior pulse are not palpable non-invasive studies were obtained. Peripheral artery disease (PAD) was diagnosed if the ankle brachial index was < 0.9 or if the patient had previously undergone open or endovascular surgery[4] Peripheral neuropathy was assessed using the Michigan neuropathy screening index (MNSI) which utilizes monofilament, vibration, reflexes, deformity and ulceration.[26] Neuropathy was defined as MNSI score of ≥ 2.5.

Minor amputations were defined as removal of a part of the foot distal to the transverse tarsal joint with preservation of the talus and calcaneus. Major amputations were defined as a transtibial amputation since none of our patients underwent a Syme amputation. Limb salvage was defined as avoiding an amputation proximal to the transverse tarsal joint (Chopart's) which is consistent with previous reports and equates to a minor or no amputation in this series.[6,20]

Continuous data were inspected to determine if it was reasonable to assume approximate normality. If the distribution of a variable was approximately normal, the mean (standard deviation) was compared between the two groups using a two-sample t-test. If the distribution of a variable was not approximately normal, the median (25th percentile, 75th percentile) was reported and the two groups were compared using a Wilcoxon rank sum statistic. For categorical variables, a chi-square statistic was utilized except for a few count variables where Wilcoxon rank sum statistics were used. SAS Version 9.2 Cary NC was used for statistical analyses. A p-value <0.05 was considered statistically significant.

RESULTS

Using our methods to define infection in hospitalized patients, there were 69 severe infections and 31 moderate infections. Characteristics and demographics of patients with severe and moderate infections are shown in Table 3. Baseline demographic data demonstrated patients with moderate and severe DFI were similar with regard to age, body mass index, gender, duration of DM, type of DM (type 1 or 2), use of insulin, and complications of DM (PAD, neuropathy, Charcot neuroarthropathy and end stage renal disease). An equal number of patients in both groups had osteomyelitis (71%). Baseline laboratory studies demonstrated significant differences between moderate and severe infections with regard to serum albumin, BUN, creatinine, platelet count, anion gap, WBC count, percentage of neutrophils and serum glucose. No significant differences were observed with regard to Hbg A1C, hemoglobin and CO_2 levels.

The majority of wounds were graded as UTSA 3 and there was no significant difference of UTSA class between those with moderate and severe DFI. All patients in this study had peripheral neuropathy and 43% had PAD although there was no difference in the prevalence of PAD in moderate and severe DFI.

Patient outcomes and objective parameters of systemic response to infection are shown in Table 4. The length of stay for the index admission was significantly shorter for patients with a moderate infection than those with a severe infection (median 5 days versus 8 days, p=0.021). (Table 4) In contrast, the number of follow-up admissions did not differ between the two infection groups.

Amputations were more common among of patients with a severe DFI than those with a moderate DFI, but the differences were not statistically significant (p=0.22). (Table 4) In addition, a non-significant trend indicating higher rates of limb salvage in patients with moderate infections compared to patients with severe infections was observed (94% versus 80%, p=0.081). (Table 4) A post hoc power analysis demonstrated that a total sample size of 213 patients would have been required in order to achieve 80% power to detect a significant result with at an alpha level = 0.05 between limb salvage rates of 94% and 80% for moderate and severe infections respectively.

Patients who ultimately required below knee amputation [N=16] had lower serum albumin levels than patients who had successful limb salvage [N=80] (2.1± 0.4 versus 2.8± 0.7, p= 0.001). Serum Albumin levels were lower in patients who required any form of amputation [N=49] (2.5 ± 0.7 g/dl) compared to those who did not require an amputation [N=47](2.8 ± 0.8 g/dl) but the differences were not statistically significant with the numbers available (p= 0.089). Four of the 100 patients did not have preoperative serum albumin levels measured.

DISCUSSION

As hypothesized, patients with severe DFI had a median hospital stay that was 60% longer than patients with moderate DFI. In this sample, 55% of patients with a severe DFI required some type of amputation compared to 42 % of patients with a moderate DFI. A consistent trend towards increased limb salvage was achieved in patients with moderate infections

(94%) compared to patients with severe DFI (80%). Although these differences did not reach statistical significance with the number of patients available for analysis, we feel that the observed differences are meaningful clinically since the rate of major amputation was three times higher in patients with severe DFI (20% compared to six percent). We did not identify significant differences in the distribution of the UTSA classes between the moderate and the severe infection groups, but some trends were evident. The majority of infections in this study were deep infections (UTSA 3B and 3D) which would be expected in hospitalized patients.

Another important finding of this study was that serum albumin level differed significantly between those who had limb salvage and those who had a transtibial amputation (p=0.001). Other studies have reported a relationship between lower albumin levels and treatment failure.[1,16] Serum albumin levels have traditionally been thought of as markers of nutritional status and lower levels have correlated with poor healing at amputation sites.[5,21] Another plausible explanation for this relationship is that serum albumin is a marker of inflammation. During catabolic states such as sepsis, hepatic albumin synthesis decreases and albumin can be lost through peripheral wounds and edema.[10] Our patients with severe infection had significantly lower serum albumin, higher percentage of neutrophils and higher ESR levels than those with moderate infection, findings which are consistent with an increased systemic inflammatory response. It is unlikely that suboptimal nutritional status alone was responsible for this difference given the similar diabetes status and BMI between the two groups.

Of the eight objective signs of systemic toxicity/ metabolic aberrations that were utilized in our study, the findings in descending order of frequency in severe DFI were hyperglycemia (75%), WBC > 12,000 cell/mm^3 (71%), tachycardia (68%), temperature >38 ° C (41%), prerenal azotemia (36%), respiratory rate > 20 (25%), metabolic acidosis (22%) and systolic hypotension (3%). Systolic hypotension was the only factor that did not differ significantly between patients with moderate and severe DFI. Subjective symptoms of nausea, vomiting, chills and anorexia were significantly more common in patients with severe versus moderate DFI and should prompt the clinician to suspect a severe DFI.

A large multicenter study from France demonstrated that 35% of hospitalized patients with DFI underwent amputation during their hospitalization and an additional 19% underwent amputation during the first year after discharge.[22] Their conclusion was that the prognosis for DFI remained poor and that severity of the wound was related to the need for amputation. Another recent study from Korea evaluated limb salvage for patients with severe IDSA infections and reported that limb salvage was accomplished in 98% of cases.[11] They included one case of a Syme amputation as limb salvage although this is not consistent with the definitions of others.[6,20] Similar to other reports, this study did not define what constituted a severe IDSA infection. Their limb salvage rate of 98% may be artificially high since they excluded patients with dry gangrene of the entire foot who required transtibial amputations. Notwithstanding the limitations of that study, the high limb salvage rate illustrates the importance of a multidisciplinary team and advanced technology. Another important finding of that study was that nearly 70% of patients required some type of amputation. The study that validated the IDSA classification reported that 77% of patients with a severe DFI required some type of amputation and that major amputations were performed in nearly 30% of patients.[12] Our overall rate of major and minor amputations of 51% in hospitalized patients with DFI is consistent with the recent literature.

Monitoring clinical signs of infection are important. This article does not address which of these clinical parameters are most important however other studies have addressed this. A leukocytosis of > 11,000 cells/mm^3 has been demonstrated to be associated with a 2.6 increased risk of amputation and fever > 100.5° F (38° C) was associated with a 1.3 increased risk of amputation.[17] Patients with DM may not mount the normal inflammatory response to DFI such as leukocytosis and fever. Nearly 15 years ago Armstrong et al.[2] reported that 54% of patients with DM and acute osteomyelitis of the foot had a normal WBC count and 82% had a normal oral temperature. A more recent study demonstrated that the mean oral temperature of patients who had a poor response to treatment was 99.1° F (37.2 ° C).[7] Another study of 400 patients with moderate or severe DFI demonstrated a mean WBC count of 8240 cells/mm^3 and the mean WBC count of those who failed treatment was 9977 cells/mm^3 compared to 7933 cells/mm^3 who had a favorable response to treatment.[16] Based on these studies we feel that it is important to include other variables in addition to leukocytosis and fever in defining severe infection. The patients in our study demonstrated a positive response to treatment during their hospitalization manifested by a significant decrease between admission and discharge WBC and serum glucose. By the time of discharge there were not any significant differences in WBC or serum glucose levels in moderate versus severe infections. This finding would add credence to our inclusion of hyperglycemia > 200 mg/dl as an objective variable of distinguishing severe from moderate infection. Anecdotally, we have observed that many patients with DFI report a recent worsening in glycemic control as one of the earliest signs of DFI.

Our aim was to incorporate previously identified objective signs of systemic toxicity and / or metabolic instability and to define those parameters based on readily available information such as vital signs, complete blood count and serum metabolic panel. The new consensus statements take a huge step forward by employing the parameters defining systemic inflammatory response syndrome as the criteria for severe infection. Thus far, these new guidelines have not been validated.

This study is limited by its retrospective nature and arbitrary definition of severe infection although we have utilized clinical findings recommended by an expert panel.[14] Another limitation of this study is the high prevalence of severe infections in our patients. Since all of the patients were hospitalized, our cohort included only the sickest patients and excludes those patients with mild infection and some patients with moderate infections. This is analogous to Grayson's study on the probe to bone test where the prevalence of osteomyelitis was high.[8] Since non-hospitalized patients with moderate DFI do not require surgery or amputation, we feel that inclusion of this group would only strengthen our observations regarding the trends in limb salvage. Lavery et al. [12] were able to manage 48% of moderate infections as outpatients. At our medical center surgeons typically don't evaluate mild or non-hospitalized moderate DFIs since they are managed by their primary care team. In addition, some hospitalized patients with moderately severe infections do not receive surgical consultation. Consequently, our cohort of patients is biased towards the most serious of DFIs. Our definition of severe DFI needs to be independently validated, ideally with a prospective study that includes mild, moderate and severe infections (outpatient and inpatient). Patients with DM often do not manifest the classic signs of inflammation and/ or infection, and utilizing eight different objective signs assists in identifying severe infections. It is clear from this study and others that moderate DFIs can also be limb threatening, as six per cent of our moderate infections required transtibial amputations and 36% required a minor amputation.[12] Finally, another limitation of this study is that it is underpowered with regard to identifying a significant difference between limb salvage and amputation rates in patients with moderate and severe DFI. We are continuing this study in an effort to achieve adequate power to definitively determine if there is a significant difference exists.

In summary, using readily available clinical information and objective parameters outlined by consensus statements we were able to classify hospitalize patients with DFI into moderate and severe infections. Patients with DFI who manifested ≥ 2 objective signs of systemic toxicity or metabolic instability required significantly longer hospitalization than patients who manifest < 2 signs. A trend toward increased need for major amputation (reduced limb salvage) was observed in patients with severe infections. Another finding of this study was that all of the patients who presented with wet gangrene or soft tissue emphysema manifested at least two of the previously described objective signs and should immediately be considered severe infections, requiring emergent surgical debridement. Patients who required transtibial amputation had significantly lower serum albumin levels than patients who had successful limb salvage.

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Table 1

Diabetic foot infection classification scheme using the Infectious Disease Society of America (IDSA) and International Working Group on the Diabetic Foot (IWGDF) classifications

Clinical Description	Infectious Diseases Society of America	International Working Group on the Diabetic Foot
Wound without purulence or any manifestations of inflammation	**Uninfected**	**1**
≥ 2 Manifestations of inflammation (purulence or erythema, pain, tenderness, warmth, or induration); any cellulitis or erythema extends ≤ 2 cm around ulcer, and infection is limited to skin or superficial subcutaneous tissues; no local complications or systemic illness	**Mild**	**2**
Infection in a patient who is systemically well and metabolically stable but has ≥ 2 cm; lymphangitis; spread beneath fascia; deep tissue abscess; gangrene; muscle, tendon, joint, or bone involvement	**Moderate**	**3**
Infection in a patient with systemic toxicity or metabolic instability (e.g., fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, hyperglycemia, or azotemia)	**Severe**	**4**

Adapted from Lavery LA et al. *CID*;44:562-5,2007.

Table 2

Objective signs of severe infection Severe infection defined as ≥ 2 of the following

Temperature > 38° Celsius or < 36° Celsius
Heart rate > 90 beats/minute
Respiratory rate >20 beats/minute
White blood cell count > 12,000 cell/mm^3 <4000 cells/mm^3
Systolic blood pressure <90
Hyperglycemia (serum glucose >200 mg/dl)
Prerenal azotemia (Bun/Creatinine ratio >20)
Metabolic acidosis CO^2 < 22 mmol/l and anion gap > 15 mEq/L

Table 3

Patient Characteristics and Demographics by Infection Status

	Overall N=100	Moderate Infection N=31	Severe Infection N=69	P value
Follow up, weeks	39 (13, 65)	46 (13, 69)	31 (14, 55)	0.35
Length of Stay, days	8 (4, 12)	5 (3, 10)	8 (5, 13)	0.021
Age, years	58.0 (11.6)	59.3 (11.6)	57.4 (11.6)	0.45
Males	78%	71%	81%	0.26
BMI, kg/m^2	31.4 (6.6)	31.4 (6.2)	31.5 (6.9)	0.94
Tobacco Use (I)	32%	45%	26%	0.059
Type 1 DM (M) **Type 2 DM (M)**	11% 89%	10% 90%	12% 88%	0.78
Duration of Diabetes (years)	14.9 (9.6)	12.9 (8.7)	15.8 (9.8)	0.16
Insulin use	72%	68%	74%	0.53
MNSI score	7.6 (1.5)	7.2 (1.6)	7.8 (1.5)	0.083
Charcot neuropathy	32%	23%	36%	0.18
Osteomyelitis	71%	71%	71%	1.00
PAD	43%	55%	38%	0.11
End Stage Renal Disease	24%	19%	26%	0.47
Nausea/Vomiting/Chills	36%	13%	46%	0.001
Gangrene	17%	6%	22%	0.60
Albumin (g/dl)	2.7 (0.7)	2.9 (0.7)	2.5 (0.7)	0.012
Anion Gap (meq/l)	11.0 (4.3)	9.1 (3.4)	11.8 (4.4)	0.004
BUN (mg/dl)	20 (13, 33)	16 (11, 24)	23 (15, 34)	0.019
Creatinine (mg/dl)	1.4 (0.9, 1.8)	0.9 (0.8, 1.8)	1.4 (1.1, 1.8)	0.037
BUN/Cr ratio	15.6 (11.6, 19.0)	14.7 (11.7, 17.2)	15.9 (11.5, 20.1)	0.19
ESR (mm/hr)	89.5 (42.6)	73.7 (44.1)	97.2 (40.1)	0.012
Glucose admission (mg/dl)	255 (157, 366)	173 (131, 220)	300 (203, 403)	0.001
Glucose discharge (mg/dl)	150 (123, 198)	153 (131, 195)	150 (121, 198)	0.72
Change in Glucose, %	-37% (-58, 2)	-8% (-37, 9)	-45% (-66, -26)	0.001
Hemoglobin (g/dL)	10.9 (2.1)	10.7 (2.8)	11.0 (1.8)	0.60

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	Overall N=100	Moderate Infection N=31	Severe Infection N=69	P value
Hgb A1c (%)	8.9 (2.4)	8.8 (2.5)	8.9 (2.4)	0.85
Platelet count (K/cc^3)	313 (124)	259 (81)	337 (132)	0.001
Serum CO_2 (mmol/l)	24.4 (3.5)	25.1 (3.3)	24.0 (3.6)	0.17
WBC admission (K/cc^3)	12.0 (8.9, 15.4)	8.8 (7.4, 10.7)	13.1 (11.5, 16.7)	0.001
WBC discharge (K/cc^3)	8.6 (6.9, 10.7)	7.7 (6.5, 9.3)	8.7 (6.9, 11.7)	0.056
Change in WBC,%	-25% (-45, - 12)	-15% (-24, 3)	-33% (-47,-15)	0.001
Neutrophils(%) admission	78 (11)	71 (11)	81 (10)	0.001
Neutrophils (%) discharge	68 (11)	64 (11)	70 (11)	0.025
Systolic blood pressure (mm Hg)	137 (24)	131 (19)	139 (25)	0.11
Heart rate/ min	92 (19)	80 (11)	98 (19)	0.001
Temperature in Celsius	37.6 (0.8)	37.1 (0.3)	37.8 (0.8)	0.001
Respiratory Rate/ min	18.8 (3.1)	17.6 (1.6)	19.3 (3.4)	0.001
Number of organisms				0.31
0	2%	3%	2%	(Wilcoxon)
1	24%	24%	23%	
2	25%	38%	18%	
3	28%	10%	35%	
4	12%	14%	11%	
5	10%	10%	9%	
6	1%	0%	2%	
# Surgery during admission				0.59
0	5%	13%	1%	(Wilcoxon)
1	46%	39%	49%	
2	43%	32%	35%	
3-4	11%	13%	10%	
5-7	4%	3%	4%	
Vascular surgery	12%	10%	13%	0.61
Number of f/u admissions				0.96
0	61%	65%	59%	
1	27%	26%	28%	
2	7%	6%	7%	
3-5	5%	3%	6%	
USTA				0.35

	Overall N=100	Moderate Infection N=31	Severe Infection N=69	P value
1 USTA 2B	7%	13%	4%	
2 USTA 2D	1%	0%	1%	
3 USTA 3B	66%	58%	70%	
4 USTA 3D	26%	29%	25%	

Normally distributed data recorded as mean (standard deviation)

Skewed data recorded as median (25th percentile, 75th percentile)

MNSI= Michigan neuropathy screening index
TMA = transmetatarsal amputation
BKA= below knee amputation
UTSA= University of Texas San Antonio

Table 4

Outcomes and Objective Parameters of Infection Measured in % of Patients Affected

	Overall N=100	Moderate Infection N=31	Severe Infection N=69	P value
Length of Stay, days	8 (4, 12)	5 (3, 10)	8 (5, 13)	0.021**
Any Amputation	51%	42%	55%	0.22
Type of Amputation				0.40
None	49%	58%	45%	
Toe	23%	23%	23%	
Foot/TMA	13%	13%	13%	
BKA	15%	6%	19%	
Limb Salvage	84%	94%	80%	0.081
Admission WBC > 12000 *	50%	3%	71%	0.001**
BUN/CR >20 *	27%	6%	36%	0.002**
BP<90 *	3%	3%	3%	0.93
HR>90 *	51%	13%	68%	0.001**
Glucose >200 *	64%	39%	75%	0.001**
Metabolic Acidosis *	8%	0%	12%	0.048**
T>38(CG) *	28%	0%	41%	0.001**
RR> 20 *	17%	0%	25%	0.002**

* Infection severity score (severe versus moderate) computed from these variables

WBC= White Blood Cell Count, BUN = Blood Urea Nitrogen, CR = Serum Creatinine, BP = Systolic Blood Pressure, HR = Heart Rate, T= Temperature, RR = Respiratory Rate
TMA = transmetatarsal amputation
BKA= below knee amputation

** Denotes significant difference between moderate and severe DFI