The Journal of Foot & Ankle Surgery xxx (2017) 1–8

Contents lists available at ScienceDirect

The Journal of Foot & Ankle Surgery

journal homepage: www.jfas.org

Original Research

# Procalcitonin as a Biomarker for Predicting Amputation Level in Lower Extremity Infections

Matthew M. Reiner, DPM, AACFAS [1], Wissam E. Khoury, DPM, FACFAS [2], Michael B. Canales, DPM, FACFAS [3], Richard A. Chmielewski, MD [4], Kartick Patel, DPM, MHSA [5], Mark C. Razzante, DPM, AACFAS, MA [1], Coleman O. Cloughtery, DPM, AACFAS, MA [1], Douglas Y. Rowland, PhD [6]

[1] *Resident, Postgraduate Year 2, Podiatric Surgical Residency, St. Vincent Charity Medical Center, Cleveland, OH*
[2] *Program Director, Podiatric Surgical Residency, St. Vincent Charity Medical Center, Cleveland, OH*
[3] *Chief, Division of Podiatry, Podiatric Surgical Residency, St. Vincent Charity Medical Center, Cleveland, OH*
[4] *Physician, Infectious Disease, St. Vincent Charity Medical Center, Cleveland, OH*
[5] *Resident, Postgraduate Year 1, Podiatric Surgical Residency, St. Vincent Charity Medical Center, Cleveland, OH*
[6] *Adjunct Faculty, Department of Epidemiology and Biostatistics, Case Western Reserve University School of Medicine, Cleveland, OH*

ARTICLE INFO

*Level of Clinical Evidence:* 3

*Keywords:*
amputation
C-reactive protein
erythrocyte sedimentation rate
PCT
procalcitonin

ABSTRACT

Inflammatory markers are essential tools in the decision-making process for lower extremity infections. When coupled with objective findings, clinicians can more accurately diagnose and treat these entities. Typically, markers such as the white blood cell count, erythrocyte sedimentation rate, and C-reactive protein are used to initially assess these patients or monitor the progression of medical or surgical therapy. Procalcitonin is a newer inflammatory marker that is specific for an infectious process. Originally, procalcitonin was used to monitor antibiotic therapy and sepsis for patients in the intensive care setting, but it has now been expanded to other facets of medicine. The utility of procalcitonin has been described for diagnosing infection or osteomyelitis in diabetic foot ulcers. However, limited research has compared inflammatory marker levels and the level of amputation. A retrospective inpatient medical record review was performed of 156 consecutive patient occurrences during 25 months in which surgical intervention was required for a lower extremity infection and an initial procalcitonin level had been obtained. This initial procalcitonin value was then compared with the level of amputation at the final surgical intervention. A highly statistically significant difference was found when comparing those who underwent a below-the-knee or above-the-knee amputation (median procalcitonin 1.72 ng/mL) and those who did not (median procalcitonin 0.105 ng/mL; $p < .001$). Therefore, patients with higher initial procalcitonin values were more likely to undergo below-the-knee or above-the-knee amputation or require aggressive surgical intervention. Thus, the procalcitonin level can provide valuable initial information to the clinician.



Lower extremity amputation cannot be discussed without mentioning the most common underlying medical conditions associated with nontraumatic amputation and the patient population included in this research. The incidence of diabetes is rapidly increasing, and, according to recent data from the Centers for Disease Control and Prevention, approximately 29 million people have a diagnosis of diabetes mellitus. This accounts for roughly 9% of the U.S. population (1). Diabetes mellitus is known to cause multifaceted complications, including foot ulcerations, which often result in lower extremity amputation. The prevalence of foot ulcerations ranges from 4% to 10% among the diabetic population, which translates to an annual population-based incidence of 0.1% to 4.1%, and the lifetime incidence could be as great as 25% (2).

Diabetic foot ulcers are often complicated by infection and are becoming a major cause of hospital admission (3). Approximately 56% of diabetic foot ulcerations will become infected, and 20% of these patients will require lower extremity amputation (3). These ulcerations account for more than one half of nontraumatic lower limb amputations in the diabetic population (4). Additionally, diabetic patients often present with comorbidities such as peripheral arterial disease, end-stage renal disease (ESRD), and chronic renal failure, which play a major role in the lower extremity amputation rates.

**Financial Disclosures:** None reported.
**Conflict of Interest:** None reported.
Address correspondence to: Matthew M. Reiner, DPM, AACFAS, Orthopedic Associates of Lake County, 7551 Fredle Drive, Concord, OH 44077.
*E-mail address:* mattmreiner@gmail.com (M.M. Reiner).

1067-2516/$ - see front matter © 2017 by the American College of Foot and Ankle Surgeons. All rights reserved.
http://dx.doi.org/10.1053/j.jfas.2017.01.014

Morbach et al (5) found that 51% of diabetic patients who underwent major amputation had underlying severe peripheral arterial disease, with a 46% 5-year mortality rate after the initial amputation. The long-term survival rate among diabetic patients undergoing amputation remains poor, especially among patients with peripheral arterial disease or renal insufficiency.

Diabetic foot ulcerations impose a tremendous medical and financial burden on the healthcare system, along with an associated myriad list of complications. Stockl et al (6) estimated as much as $45,000 of hospital costs per patient. This does not account for the deleterious psychosocial effects on the quality of life due to impaired mobility and the substantial loss of productivity (6). Gil et al (7) studied the cost comparison between limb salvage versus amputee groups for 1 year. The results revealed an average cost of $57,000 in the limb salvage group versus $50,000 in the amputee group (7). With the increasing healthcare costs resulting from lower extremity infections, it might be beneficial to risk stratify patients who are acceptable candidates for limb salvage and those who are not.

However, few guidelines are available to aid in this decision-making process. Among others (8–11), Yu et al (12) and Pinzur et al (13) have evaluated numerous diagnostic tests, including laboratory values, the ankle brachial index, and transcutaneous oxygen measurements, to help surgeons optimize healing after lower extremity amputation. The criterion set forth by Yu et al (12) is used at our institution for patients undergoing various levels of amputation (Table 1). Numerous inflammatory markers have been used to determine the absence or presence of lower extremity infections. Until now, research related to the level of amputation and the correlation with these inflammatory markers, specifically procalcitonin, has been limited.

Procalcitonin (PCT) is a hormone precursor released by the follicular cells of the thyroid and polymorphonuclear cells and is specific for bacterial infection. It is released in response to bacterial toxins by circulating polymorphonuclear cells. It has a much more predictable increase over 12 hours compared with other cytokines (14). PCT also displays rapid kinetics, increasing 3 hours after bacterial infection and peaking at approximately 6 to 12 hours. The half-life of PCT is approximately 24 hours (15). Although no uniform or universal threshold value is available, some guidelines have been established (Table 2) (16).

We retrospectively reviewed the PCT values in a subset of inpatients to correlate a PCT value with various levels of amputation. The purpose of the present research was to guide clinicians in their surgical decision-making process, specifically to help determine whether certain patients would be better candidates for limb salvage or proximal amputation. We hypothesized that a significant difference would be found in the PCT values in patients who required a below-the-knee amputation or above-the-knee amputation (BKA/AKA) and those who did not. We set out to compare the PCT value and amputation level for any patient for whom a PCT value had been obtained and who subsequently required surgery because of a lower extremity infection. If significant, PCT could serve as an important marker for the required amputation level and justify aggressive initial surgical therapy or proximal amputation, especially in the acute setting. In the future, the ultimate goal is to use PCT in a scoring system for predictability of limb salvage or optimal healing.

**Table 1**
Wound healing parameters for lower extremity amputations from Yu et al (12) and Pinzur et al (13)

| Preoperative Requirements and Predictors of Success | Value |
|---|---|
| Ankle brachial index | >0.5 |
| Transcutaneous oxygen pressure (mm Hg) | 30 |
| Total lymphocyte count (/mm) | 1500 |
| Serum albumin level (g/dL) | 3.0 |
| Prealbumin level (mg/dL) | 16 to 35 |
| Serum glucose level (mg/dL) | <250 |
| Highly motivated patient | |
| Access to a highly skilled prosthetist | |

**Table 2**
Interpretation reference chart for procalcitonin level used at our institution

| Procalcitonin Level (ng/mL) | Interpretation |
|---|---|
| ≤0.5 | Systemic infection (sepsis) not likely; local bacterial infection is possible |
| >0.5 but ≤2.0 | Systemic infection (sepsis) possible, but other conditions are also known to elevate procalcitonin |
| <2.0 | Systemic infection (sepsis) likely, unless other causes are known |
| ≥10.0 | Important systemic inflammatory response, almost exclusively due to severe bacterial sepsis or septic shock |

## Patients and Materials

After obtaining institutional review board approval, a retrospective inpatient medical record review identified 175 consecutive instances from December 1, 2012 to January 15, 2015 in which a PCT value was obtained before surgery for a lower extremity infection at a single institution. The inclusion criteria consisted of inpatient subjects with a PCT value obtained and intervention for lower extremity infection. All included patients had been were admitted to the hospital because of the severity of their lower extremity infection. When these patients presented to our institution with a lower extremity infection, a PCT level was obtained. The patients had had an unknown duration of infection before the PCT level was obtained. Each patient was followed up until the end result was a closed wound environment, as determined by the primary author (M.M.R.), or amputation. Patients who experienced multiple lower extremity infections of the same extremity were included as separate data points only if the patient had obtained a closed wound environment for each, as determined by the primary author (M.M.R.). The exclusion criteria consisted of repeated lower extremity infections and PCT levels without a previous closed wound environment or cases in which surgical intervention was performed without an initial PCT value. Patients who died before surgical intervention or final treatment were also excluded. A total of 156 inpatient instances were identified, which included a total of 133 patients. The length of treatment or hospital stay was not recorded. The patients could have undergone multiple surgical procedure before the final level of amputation, and this was recorded. The surgical procedures performed were categorized into 8 subgroups according to the amputation level, and amputation identifiers (Amp IDs) were assigned to facilitate the statistical analysis (Table 2). Amp ID 0 was assigned to patients with surgical intervention, including but not limited to, excisional debridement, hardware removal, incision and drainage, and bone biopsy without amputation. Amp ID 1 was assigned for toe amputation; Amp ID 2, for metatarsal head resection, sparing the digit; Amp ID 3, for ray resection; Amp ID 4, for transmetatarsal amputation; Amp ID 5, for partial calcanectomy, Amp ID 6, for Syme amputation; and Amp ID 7, for BKA/AKA. These groups were determined from the most common subtypes of amputations performed at our facility and as discussed among ourselves. The patients were also divided into these separate groups to facilitate future secondary analyses and to appreciate individual trends when stratified by amputation level and PCT value.

The primary objective of the present retrospective inpatient medical record review was to compare the PCT values of those who underwent BKA/AKA and those who did not (Amp ID 7 versus Amp ID 0 to 6). Our aim was primarily to guide clinicians in their overall surgical decision-making process and to help determine whether certain patients would be better candidates for limb salvage or proximal amputation. This could also aid in justifying aggressive initial surgical therapy or proximal amputation in a patient with a severe infection. Patient comorbidities were also recorded. The comorbidities included diabetes, hemoglobin A1c, ESRD, obesity, body mass index, hepatitis C, and peripheral arterial disease diagnosed by a vascular surgeon from pulse volume recordings and the ankle brachial index and/or the need for surgical intervention. Significant differences in the comorbid conditions among the primary subgroups were compared and calculated using Fisher's exact test for categorical data and the 2-sample Student *t* test for quantitative data.

The PCT outcome data were examined for all patients and for the various Amp ID subgroups of interest. For these data, a full statistical summary is given, including the mean ± standard deviation, counts, and quartiles. The nonparametric descriptive statistics are given as the median and quartiles.

The primary subgroups investigated were Amp ID 7 (BKA or AKA) versus Amp ID 0 to 6 (no amputation or limb-sparing amputation). For each subgroup of interest, the 95% confidence intervals were constructed for the subgroup mean values. For the purposes of statistical testing and because some of the subgroup sizes were small,

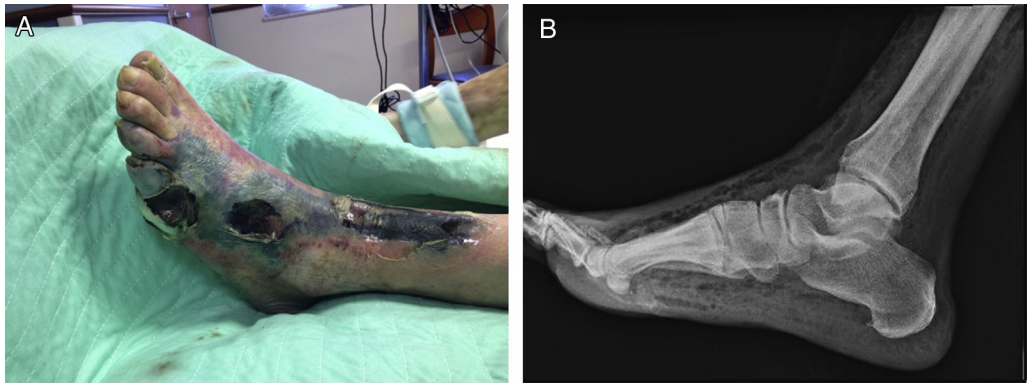


**Fig. 1.** (*A*) Clinical photograph of a patient requiring emergency above-the-knee amputation (AKA) because of severe gas gangrene. The procalcitonin value for this patient was 5.9 ng/mL. (*B*) Corresponding plain film radiograph of this patient showing diffuse soft tissue emphysema that extended to level of the knee.

resulting in the possibility of skewness and/or outliers, the nonparametric Mann-Whitney *U* test was used. The median was the first summary and primary statistic stated, and the *p* value was used to reject the null hypothesis of the equality of distributions. A separate data set was calculated in which 2 outliers were eliminated from Amp ID 7 to maintain a relatively equal distribution. Statistical significance was taken as $p < .05$. Several statistical tests were performed on the data organized into the various subgroups. Also, we included 17 instances from previously examined data of 139 instances to increase the power of data. Even when using the method of Bonferroni, a strict method of correcting *p* values for multiple testing of data, no cases occurred in which the statistical significance of a test was removed by Bonferroni correction.

## Results

A total of 156 instances were identified, which included 133 patients. Of the 133 patients, 109 were male and 47 were female, with an average age of 58.9 (range 22 to 96) years. These 133 patients, who had undergone surgery, had received a diagnosis of ≥1 of the following: gas gangrene, wet gangrene, necrotizing fasciitis, acute limb ischemia, dry gangrene, abscess, infected hardware, postoperative infection, septic arthritis, complicated soft tissue infection, and frostbite. These were all inpatient instances that were investigated. The duration between the initial PCT value and the final surgical intervention was not recorded. The results stratified by Amp IDs were as follows: Amp ID 0 (no amputation), n = 55; Amp ID 1 (toe amputation), n = 29; Amp ID 2 (metatarsal head resection, sparing digit), n = 6; Amp ID 3 (ray resection), n = 16; Amp ID 4 (transmetatarsal amputation), n = 16; Amp ID 5 (partial calcanectomy), n = 7; Amp ID 6 (Syme amputation), n = 1; and Amp ID 7 (BKA/AKA), n = 26. These results are summarized further in Table 2. Some examples of patients and their outcomes are shown in Figs. 1–5.

With or without the 2 outliers, the Amp ID 7 subgroup (BKA/AKA) had a very highly significant different distribution from that of Amp IDs 0 to 6 (no amputation or limb sparing amputation; $p < .001$, Mann-Whitney *U* test). These general relationships were also shown by the 95% confidence intervals, for which distinct intervals (i.e., nonoverlapping 95% confidence intervals) for the subgroup mean occurred when the subgroups had statistically significant distributions. Because of the effect of potential outliers to inflate the sample standard deviations, the 95% confidence intervals were only considered as descriptive results.

The subgroup of patients who underwent BKA/AKA had a median PCT of 1.72 (interquartile range [IQR] 0.81 to 5.51) ng/mL. The difference was statistically significantly ($p < .001$) with greater distributions than for the subgroup of patients who did not undergo BKA/AKA (Amp IDs 0 to 6). The median PCT value for the latter was 0.105 (IQR 0.05 to 0.44) ng/mL. These results are further summarized in Tables 3 to 5.

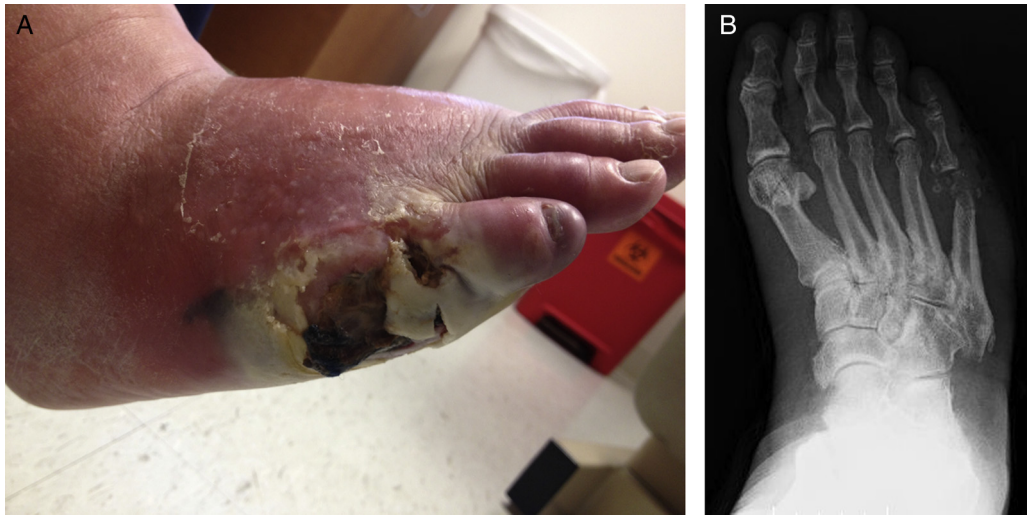


**Fig. 2.** (*A*) Clinical photograph of a patient requiring emergency open transmetatarsal amputation because of gas gangrene. The procalcitonin value for this patient was 7.83 ng/mL; however, this patient subsequently healed despite the high value indicating that aggressive initial surgical intervention might be beneficial to patients with high procalcitonin values. (*B*) Corresponding plain film radiograph of this patient showing soft tissue emphysema diffusely throughout the forefoot.

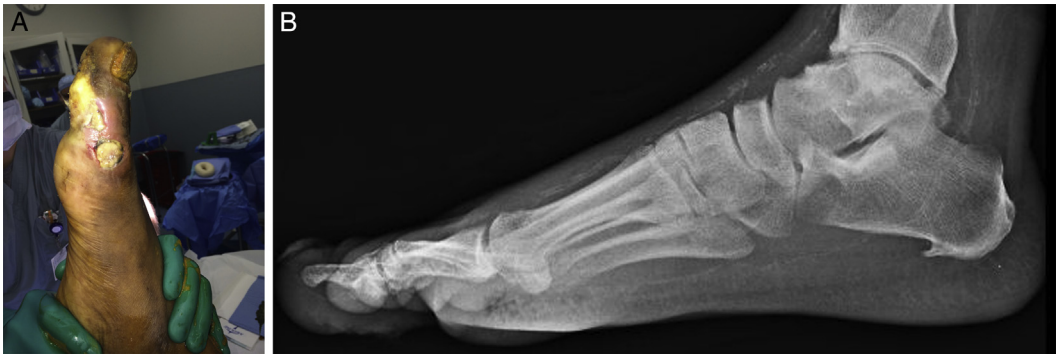


**Fig. 3.** (*A*) Clinical photograph of a patient requiring emergency first ray amputation because of gas gangrene. The procalcitonin value for this patient was 0.5 ng/mL and eventually healed without further amputation. (*B*) Corresponding plain film radiograph of this patient showing soft tissue emphysema plantar to the first metatarsal head.

Of the 156 instances, 12 patient instances (7.7%) resulted in BKA/AKA and the patient had had an initial PCT value of < 1.72 ng/mL. Also, 12 patient instances (7.7%) did not result in BKA/AKA, although with an initial PCT value was >1.72 ng/mL. Finally, 1 patient instance (0.64%) did not result in amputation, although the initial PCT value was >1.72 ng/mL. Using any elevation in the initial PCT value greater than our laboratory threshold of 0.05 ng/mL, 79 of the 156 patient instances (50.64%) resulted in some level of amputation. Only 22 of 156 patient instances (14.10%) resulted in some level of amputation when the PCT value was less than the threshold value of 0.05 ng/mL.

Additional patient comorbid conditions and characteristics are summarized in Table 6. The primary groups analyzed were those who required BKA/AKA (Amp ID 7) and those who did not (Amp IDs 0 to 6). We also evaluated the patient population as a whole (Amp IDs 0 to 7). No statistically significant difference was appreciated among these subgroups other than that the number of patients with ESRD was significantly greater in the group who required BKA/AKA (Amp ID 7; $p = .013$).

## Discussion

A high unpredictability of healing rates after lower extremity amputation remains. Some criteria are available, including clinical examination, diagnostic testing, and laboratory values, which have assisted in predicting the level of healing. Yu et al (12) investigated the healing rates after proximal amputations, in particular, Syme amputations. In a retrospective study of 10 patients with multiple comorbidities, all patients underwent successful Syme amputation without progression to proximal amputations. However, to achieve high success rates, Yu et al (12) advocated that the following factors should be met preoperatively: ankle brachial index >0.5, transcutaneous oxygen measurement >30 mm Hg, total lymphocyte count >1500/mm, serum albumin >3.0 g/dL, prealbumin level of 16 to 35 mg/dL, and serum glucose level of <250 mg/dL (12).

Pinzur et al (13) studied the effects of serum albumin, total lymphocyte count, and ankle brachial index on the healing rate in diabetic patients with peripheral vascular disease undergoing midfoot amputation. An overall 81% healing rate in 64 amputations was found. When all 3 factors were greater than the minimum level, the healing rate increased to 92%. In contrast, when ≥1 of the factors was less than the minimum level, the healing rate decreased substantially to 38% (13). These markers provide predictors of success in amputations healing but do not provide guidance in the acute surgical setting.

Although C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are typically used to aid clinicians in diagnosing lower extremity infections, they are frequently elevated because of other comorbidities, including inflammatory arthropathy, chronic renal insufficiency, and coronary artery disease. At our institution, we use PCT as a routine inflammatory marker, in addition to CRP and ESR. PCT is a prohormone of calcitonin produced by the thyroid gland.

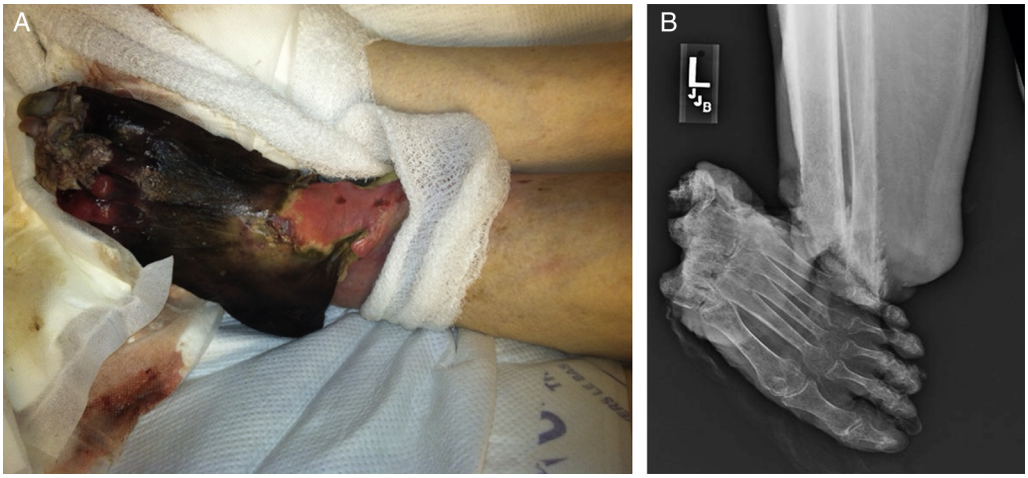


**Fig. 4.** (*A*) Clinical photograph of a patient with a chronic wound that developed into wet gangrene requiring an above-the-knee amputation. The procalcitonin value for this patient was 0.81 ng/mL. This patient had a procalcitonin level less than the median threshold for a foot-sparing amputation; however, the patient clearly required a more proximal amputation, indicating the importance of clinical judgment. (*B*) Corresponding plain film radiograph of this patient.

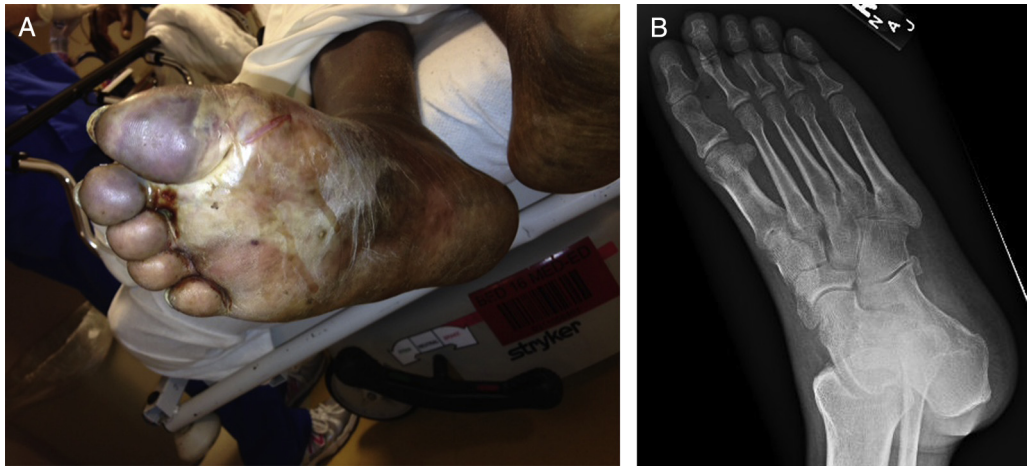


**Fig. 5.** (*A*) Clinical photograph of a patient with gas gangrene who eventually required a below-the-knee amputation. The procalcitonin value for this patient was only 1.08 ng/mL, less than the median threshold for a foot-sparing amputation. However, because of his medical comorbidities, including end-stage renal disease, insulin-dependent diabetes mellitus, peripheral arterial disease, congestive heart failure, and hepatitis C, this patient was better served with a proximal amputation. (*B*) Corresponding plain film radiograph displaying a pinpoint area of soft tissue emphysema in the first interspace.

However, it is also released in response to bacterial toxins by circulating polymorphonuclear cells and is relatively specific for bacterial infection. It has a much more predictable increase over 12 hours, it has rapid kinetics, increasing 3 hours after bacterial infection and peaking at approximately 6 to 12 hours, and has a half-life of approximately 24 hours (14–16).

Originally, PCT was used in the intensive care setting to aid in diagnosing sepsis or guiding antibiotic therapy. In a large meta-analysis of 1075 patients by Prkno et al (17), the hospital and 28-day mortality rates were not different between the PCT-guided therapy and standard treatment groups. The use of PCT-guided therapy reduced the antibiotic duration by 2 days, which could reduce the potential for complications from antibiotic use (17). Regarding sepsis, the CRP level was more effective in predicting localized infection and short-term antibiosis; however, the PCT level was more effective in predicting systemic infection and long-term antibiosis (18). Many investigators have continued to advocate for the routine use of PCT in the intensive or critical care setting to promote antibiotic stewardship and stratify patients according to sepsis severity (17,18).

When comparing the inflammatory markers of systemic inflammatory diseases such as systemic lupus erythematosus and systemic antineutrophil cytoplasmic antibody-associated vasculitis with systemic infection in 394 subjects, PCT was found to be markedly elevated, with a mean value of 1.93 ng/mL in patients with systemic infections (19). PCT values >15.9 ng/mL were shown to predict for positive blood cultures in 422 specimens (20). Patients with a PCT level >149 ng/mL were more likely to be septic secondary to gram-negative rods (21).

**Table 3**
Amputation level with amputation identifier (N = 156 infections in 133 patients)

| Amputation Level | Amp ID | Infections [n (%)] |
|---|---|---|
| None | 0 | 55 (35.26) |
| Level of toes | 1 | 29 (18.59) |
| Metatarsal resection | 2 | 6 (3.85) |
| Ray resection | 3 | 16 (10.26) |
| Transmetatarsal | 4 | 16 (10.26) |
| Partial calcanectomy | 5 | 7 (4.49) |
| Syme | 6 | 1 (0.64) |
| BKA/AKA | 7 | 26 (16.67) |
| Total | NA | 156 (100) |

Abbreviations: Amp ID, amputation identifier; BKA/AKA, below-the-knee amputation/above-the-knee amputation; NA, not applicable.

PCT can also be used to monitor the resolution of infection. In a study of 50 patients, a significant decrease was found from a mean PCT level of 1.4 ng/mL to 0.2 ng/mL from day 1 to 14 with oral or intravenous antibiotic therapy (22). Patients with healing wounds also showed a significant decrease from 0.6 ng/mL to 0.05 ng/mL in the same period (22). In a study of the ratio of PCT from day 1 to day 2 after surgical treatment of necrotizing fasciitis in 38 patients, a ratio of 1.665 was noted to be a significant predictor of clinical success. In the present study, eradication of the infection focus was successful in 84% of patients requiring a mean of 1.9 operations (23). In another study, a PCT clearance of ≥30% at 48 hours after the initial presentation was independently associated with survival (24). We routinely use PCT to monitor progression and resolution of lower extremity infections, most importantly after surgical intervention. PCT determination is ordered daily for the first 3 days after surgical intervention or hospital admission to confirm and correlate clinically with the resolution of infection, similar to the aforementioned studies.

High-quality research pertaining to the reliability of PCT in patients with renal impairment or failure has been performed. When reviewing >201 studies, Lu et al (25) identified 803 patients with renal impairment, totaling 255 bacterial infections, in whom the PCT level was obtained. The pooled sensitivity and specificity was 73% and 88% for diagnosing bacterial infection, respectively. The positive likelihood ratio for bacterial infection was 6.03, making it sufficient as a "rule-in" test. It did have a poor negative likelihood ratio and low sensitivity, indicating that its role as a "rule-out" test is questionable. They further discussed the possibility of delayed decreased renal clearance of PCT of ≤30% to 50% (25,26). However, these same data indicated that despite decreased renal elimination, the plasma clearance rate of PCT was only weakly related to renal dysfunction. Therefore, clinical decisions based on PCT might not be influenced (25,26).

Other potential limitations exist to the use of PCT. The PCT level can be increased in primary inflammation syndromes after trauma such as extensive burns and major surgery, including cardiac procedures, transplantation, and abdominal procedures. However, a rapid decrease will occur in the absence of bacterial infection. Medullary C-cell cancers of the thyroid, pulmonary small cell carcinoma, and bronchial carcinoma can also increase PCT levels. Prolonged circulatory failure such as cardiogenic shock, hemorrhagic shock, and thermal shock can also result in increased levels of PCT. Treatments that can cause a cytokine storm such as muromonab-CD3 and other antilymphocyte globulins can also cause an increase in PCT (27).

**Table 4**
Summary of procalcitonin level statistics stratified by amputation identifier

| Amp ID | Inpatient Instances (n) | Procalcitonin Level (ng/mL) | | | | |
|---|---|---|---|---|---|---|
| | | Mean ± SD | Median | Q1 to Q3 | Maximum | Minimum |
| 0 to 7 | 156 | 1.7916 ± 7.5111 | 0.135 | 0.05 to 0.815 | 82.9 | 0.01 |
| 0 to 7* | 154 | 1.0382 ± 2.3697 | 0.13 | 0.05 to 0.795 | 18.38 | 0.01 |
| 0 to 6 | 130 | 0.5663 ± 1.3255 | 0.105 | 0.05 to 0.44 | 8.33 | 0.01 |
| 7 | 26 | 7.9181 ± 17.1427 | 2.085 | 0.8625 to 6.3275 | 82.9 | 0.13 |
| 7* | 24 | 3.5942 ± 4.4075 | 1.72 | 0.8075 to 5.51 | 18.38 | 0.13 |
| 0 | 55 | 0.2751 ± 0.3822 | 0.1 | 0.05 to 0.345 | 1.92 | 0.05 |
| 1 to 6 | 75 | 0.7799 ± 1.6873 | 0.11 | 0.05 to 0.495 | 8.33 | 0.01 |

Abbreviations: Amp ID, amputation identifier; Q, quartile; SD, standard deviation.
* Two outliers removed.

Uzun et al (28) compared the use of PCT to that of CRP, ESR, and the white blood cell count in patients with diabetic foot ulcerations. A PCT level of 0.08 ng/mL exhibited a sensitivity and specificity of 77% and 100%, respectively, for diagnosing a clinical infection. The area under the receiver operating characteristic curve for infection identification was greatest and was statistically significant for PCT (28).

Jafari et al (29) evaluated PCT as a marker of bacterial infection in diabetic foot ulcers and found that a PCT level of 1.20 ng/mL was statistically significant for confirming clinical infection. They further reported that a threshold PCT value of 0.21 ng/mL exhibited a sensitivity and specificity of 70% and 74%, respectively (29). In reference to PCT in those with chronic osteomyelitis, those with osteomyelitis had a mean PCT level of 0.066 ng/mL and those without osteomyelitis had a mean PCT level of 0.0586 ng/mL (30). They concluded that PCT cannot discriminate between infected ulcers with underlying osteomyelitis and those without underlying osteomyelitis (30). This further stresses the importance that PCT is much more useful in the acute setting of lower extremity infections, because osteomyelitis typically occurs in a more chronic setting. In another small pilot study by Karakas et al (31), PCT failed to predict for amputation in patients admitted with diabetic foot ulcers. Although the mean PCT value was greater for patients requiring an amputation at 1.15 pg/mL compared with 0.079 pg/mL, no statistically significant difference was found. This can be attributed to the small sample size, because only 6 of the 27 patients enrolled in the pilot study required amputation. The interleukin-6 level was a statistically significant predictor of amputation in these patients (31).

At our institution, the PCT level is considered when deciding whether a patient is a candidate for limb salvage. The use of a single laboratory test for this decision is clearly not recommended as a sole entity of the decision-making process; however, it has become a part of our patient evaluation. We routinely find a normal PCT value in patients with osteomyelitis or dry gangrene, likely related to the usual chronic nature of these pathologic entities. Thus, PCT is better used in the acute setting when a patient is septic or a necrotizing infection has been diagnosed. In these patients, the PCT level is crucial for our surgical planning, determining the level of amputation, and the ultimate decision of attempting limb salvage.

The subgroup of patients who underwent BKA/AKA (Amp ID 7) had a median PCT level of 1.72 (IQR 0.81 to 5.51) ng/mL. This difference was statistically significantly ($p < .001$), with greater distributions than the subgroup of patients without BKA/AKA (Amp IDs 0 to 6; median PCT of 0.105 ng/mL, IQR 0.05 to 0.44 ng/mL). Therefore, a patient with a PCT value $\geq$1.72 ng/mL might be better served with a BKA/AKA to reduce the risk of continued sepsis and multiple surgical interventions, because these patients will be more likely to require a proximal amputation. This is especially true for patients with ESRD, because these patients have a significantly greater risk of a BKA/AKA ($p = .013$). If the patient or surgeon opts for limb salvage with a PCT value of $\geq$1.72 ng/mL, each party must know that the probability of successful limb salvage is very low, especially in the presence of ESRD. With a PCT value of $<$1.72 ng/mL, the patient or surgeon can be more confident in opting for a limb salvage procedure, especially with aggressive initial surgical intervention, because these patients will be less likely to undergo a more proximal amputation. Nearly 50% of the patients with any increase greater than the threshold PCT value of 0.05 ng/mL in our study required some level of amputation.

One limitation of the present study was that it was a small and retrospective study performed at 1 facility. The bias remained relatively low by abiding to strict inclusion and exclusion criteria, and no clinical decisions were made based on this value. Some of the patients included in the present study might have undergone additional surgical intervention after data collection ceased. Also, the length of treatment and length of stay were not included, which might have added information regarding the severity of the lower extremity infection. Many patients could have had an infection for a long period before their admission, which could theoretically have caused elevated PCT values that had accumulated throughout the body. Patients could also have been treated with antibiotic therapy on an outpatient basis before their admission to the hospital for a worsening infection or could have received intravenous antibiotics in the hospital before the PCT value was obtained. The study period of the

**Table 5**
Descriptive analysis of procalcitonin levels for selected amputation identifier groups (N = 156 infections in 133 patients)

| Amp Level | Amp ID | Patients (n) | PCT Level (ng/mL) | | Mean Surgical Procedures (n) | Mean Age (yr) |
|---|---|---|---|---|---|---|
| | | | Median | Mean ± SD | | |
| None | 0 | 55 | 0.10 | 0.28 ± 0.38 | 2.00 | 53.78 |
| Level of toes | 1 | 29 | 0.06 | 0.19 ± 0.40 | 1.83 | 62.10 |
| Metatarsal/ray resection | 2 to 3 | 22 | 0.14 | 0.85 ± 1.92 | 1.86 | 62.73 |
| Transmetatarsal | 4 | 16 | 0.63 | 1.87 ± 2.51 | 3.13 | 59.19 |
| Partial calcanectomy | 5 | 7 | 0.15 | 0.61 ± 0.84 | 3 | 57 |
| Syme | 6 | 1 | 0.01 | 0.01 ± NA | 9 | 64 |
| No BKA/AKA | 0 to 6 | 130 | 0.11 | 0.57 ± 1.33 | 2.18 | 58.07 |
| BKA/AKA | 7 | 24 | 1.72 | 3.59 ± 4.41 | 3.04 | 64.33 |

Abbreviations: Amp ID, amputation identifier; BKA/AKA, below-the-knee amputation/above-the-knee amputation; NA, not applicable; PCT, procalcitonin; SD, standard deviation.

**Table 6**
Patient characteristics and comorbid conditions for each occurrence (N = 156 infections in 133 patients)

| Comorbid Condition | BKA/AKA | | All Patients (Amp ID 0 to 7) | *p* Value |
|---|---|---|---|---|
| | Yes (Amp ID 7) | No (Amp ID 0 to 6) | | |
| DM (n) | 21 (81) | 105 (81) | 126 (81) | >.99 |
| HbA1c (%) | 8.2 | 8.49 | 8.45 | .66 |
| ESRD (n) | 7 (27) | 12 (9) | 19 (12) | .013* |
| Obesity (n) | 11 (42) | 60 (46) | 72 (46) | .83 |
| BMI (kg/m$^2$) | 27.94 | 29.79 | 29.48 | .27 |
| Hepatitis C (n) | 4 (15) | 15 (12) | 19 (12) | .53 |

Abbreviations: Amp ID, amputation identifier; BKA/AKA, below-the-knee/above-the-knee amputation; BMI, body mass index; DM, diabetes mellitus; ESRD, end-stage renal disease; HbA1c, hemoglobin A1c.

* Statistically significant difference.

present retrospective inpatient medical record review concluded at 25 months; however, we did not record the interval between the initial PCT value determination and the final surgical intervention. The present study was retrospective in nature; therefore, no biased decision was made for expedited or delayed surgical intervention.

As stated previously, the PCT values can be higher in patients with ESRD owing to reduced clearance, although this is only a minor pathway for PCT elimination. Therefore, it is possible that the ESRD patients might have had falsely elevated levels, creating the higher distributions seen with the Amp ID 7 patients. ESRD, in and of itself, was a significant risk factor for BKA/AKA ($p = .013$), indicating that what might be perceived as a false elevation might actually be an inherent risk factor for lower extremity infections in ESRD patients. It is well-known that limb salvage is favorable in ESRD patients; however, the amputation rates have often been significantly greater and survival significantly lower in some studies (32–35).

Several of our Amp ID groups had a low number of patients, including Amp ID 7, with only 26 patients. Because of the uneven distributions of patients and several low numbers in the subgroups, a nonparametric statistically analysis was implemented. When comparing the subgroups, the median PCT for Amp ID 7 (BKA/AKA) was 1.72 ng/mL and the mean PCT value was 3.59 ng/mL. For Amp IDs 0 to 6 (no amputation or limb-sparing amputation), the median PCT was 0.105 ng/mL and the mean PCT value was 0.57 ng/mL.

Although localized abscess and gas gangrene are markedly different pathologic entities, these patients are routinely admitted to our hospital and require surgical intervention. We did not seek to stratify the severity of infection but to stratify the amputation risk along the spectrum of lower extremity infections encountered in the hospital setting. Patients with gas gangrene or necrotizing fasciitis inarguably have a greater risk of amputation than a patient with an abscess. However, targeting those patients in the “gray area” of difficult limb salvage situations, we have used this data set to the best of our ability to guide clinicians in these difficult situations by appreciating a trend or pattern. Patients who present to us with a simple abscess could be the same patients who would present to us after not seeking treatment for a longer period and, therefore, have developed a fulminating deep space abscess. Both require surgery; however, the PCT value would likely be different in each situation, as would the clinical outcome. Comparing a simple abscess with a fulminating deep space abscess might not be ideal; however, after collecting data on a spectrum of various lower extremity infections, patterns can be realized or extrapolated to predict the outcomes.

In conclusion, future research could include additional evaluation of other inflammatory markers, such as ESR, CRP, and white blood cell count, the percentage of change or ratio of PCT from the initial presentation to surgical intervention, and comorbidities. Calculating the odds ratios or risk ratios in the future might provide clinicians and patients with useful information. PCT could also serve useful in scoring systems to predict for necrotizing fasciitis such as the Laboratory Risk Indicator for Necrotizing Fasciitis or the level of amputation (36). The present study could also be reproduced in a similar fashion as a multicenter retrospective medical record review with a larger population to better normalize the data and subgroup distributions.

## References

1. Centers for Disease Control and Prevention. 2014 National Diabetes Statistics Report. Available at: https://www.cdc.gov/diabetes/data/statistics/2014StatisticsReport.html. Accessed October 28, 2014.
2. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA 293:217–228, 2005.
3. Smith D, Weinberger M, Katz BP. A controlled trial to increase office visits and reduce hospitalization in diabetic patients. J General Int Med 2:232–238, 1987.
4. Dang CN, Boulton AJ. Changing perspectives in diabetic foot ulcer management. Int J Low Extrem Wounds 2:4–12, 2003.
5. Morbach S, Furchert H, Gröblinghoff U, Hoffmeier H, Kersten K, Klauke G, Klemp U, Roden T, Icks A, Haastert B, Rumenapf G, Abbas ZG, Bharara M, Armstrong DG. Long-term prognosis of diabetic foot patients and their limbs: amputation and death over the course of a decade. Diabetes Care 35:2021–2027, 2012.
6. Stockl K, Vanderplas A, Tafesse E, Chang E. Costs of lower extremity ulcers among patients with diabetes. Diabetes Care 27:2129–2134, 2004.
7. Gil J, Schiff AP, Pinzur M. Cost comparison: limb salvage versus amputation in diabetic patients with Charcot foot. Foot Ankle Int 34:1097–1099, 2003.
8. Fife CE, Smart DR, Sheffield PJ, Hopf HW, Hawkins G, Clark D. Transcutaneous oximetry in clinical practice: consensus statements from an expert based panel. Undersea Hyperb Med 36:143–153, 2009.
9. Arsenault KA, Al-Otaibi A, Devereaux PJ, Thorlund K, Tittley JG, Whitlock RP. The use of transcutaneous oximetry to predict healing complications of lower limb amputations: a systemic review and meta-analysis. Eur J Vasc Endovasc Surg 43:329–336, 2012.
10. Wyss CR, Harrington RM, Burgess EM, Matsen FA III. Transcutaneous oxygen tension as a predictor of success after an amputation. J Bone Joint Surg 70:203–207, 1988.
11. Kaur S, Pawar M, Banerjee N, Garg R. Evaluation of the efficacy of hyperbaric oxygen therapy in the management of chronic nonhealing ulcer and role of peri-wound transcutaneous oximetry as a predictor of wound healing response: a randomized prospective controlled trial. J Anaesthesiol Clin Pharmacol 28:70–75, 2012.
12. Yu G, Meszaros A, Schinke T. *Syme's Amputation: A Retrospective Review of 10 Cases*, Podiatry Institute, Decatur, GA, 2005.
13. Pinzur M, Kaminsky M, Sage R, Cronin R, Osterman H. Amputations at the middle level of the foot, retrospective and prospective review. J Bone Joint Surg 68:1061–1064, 1986.
14. Meisner M. Procalcitonin: experience with a new diagnostic tool for bacterial infection and systemic inflammation. J Lab Med 23:263–272, 1999.
15. Brunkhorst FM, Heinz U, Forycki ZF. Kinetics of procalcitonin in iatrogenic sepsis. Intens Care Med 24:888–892, 1998.
16. Harbarth S, Holeckova K, Froidevaux C, Pittet D, Ricou B, Grau C, Vadas L, Pudin J; Geneva Sepsis Network. Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. Am J Respir Crit Care Med 164:396–402, 2001.
17. Prkno A, Wacker C, Brunkhorst FM, Schlattmann P. Procalcitonin-guided therapy in intensive care unit patients with severe sepsis and septic shock—a systematic review and meta-analysis. Crit Care 17:R291, 2013.
18. Hoeboer S, Groenveld A. Changes in circulating procalcitonin versus C-reactive protein in predicting evolution of infectious disease in febrile, critically ill patients. PLos One 8:1–7, 2013.
19. Brunkhorst R, Eberhardt O, Haubitz M, Brunkhorst F. Procalcitonin for discrimination between activity of systemic autoimmune disease and systemic bacterial infection. Intens Care Med 26:199–201, 2000.

20. Arai T, Kumasaka K, Nagata K, Okita T, Oomura T, Hosiai A, Koyama M, Ohta S, Yukioka T. Prediction of blood culture results by measuring procalcitonin levels and other inflammatory biomarkers. Am J Emerg Med 32:330–333, 2013.
21. Nakajima A, Yazawa J, Sugiki D, Mizuguchi M, Sagara H, Fujisiro M, Shibazaki M, Hitani A, To M, Haruki K. Clinical utility of procalcitonin as a marker of sepsis: a potential predictor of causative pathogens. Intern Med 53:1497–1503, 2014.
22. Altay F, Sencan I, Senturk G, Altay M, Guvenman S, Unverdi S, Acikgoz Z. Does treatment affect the levels of serum interleukin-6, interleukin-8 and procalcitonin in diabetic foot infection? A pilot study. J Diabetes Complications 26:214–221, 2012.
23. Friederichs J, Hutter M, Hierholzer C, Novotny A, Friess H, Buhren V, Hungerer S. Procalcitonin ratio as a predictor of successful surgical treatment of severe necrotizing soft tissue infections. Am J Surg 206:368–373, 2013.
24. Nor MBM, Ralib A. Procalcitonin clearance for early prediction for survival in critically ill patients with severe sepsis. Crit Care Res Pract 2014:1–7, 2014.
25. Lu X, Xaio Z, Yang M, Zhu Y. Diagnostic value of serum procalcitonin in patients with chronic renal insufficiency: a systematic review and meta-analysis. Nephrol Dial Transplant 28:122–129, 2013.
26. Meisner M, Lohs T, Heuttemann E, Schmidt J, Hueller M, Reinhart K. The plasma elimination and urinary secretion of procalcitonin in patients with normal and impaired renal function. Eur J Anaesthesiol 18:79–87, 2001.
27. Barnes S. Procalcitonin: contributing to improved clinical decision making. ThermoFisher Scientific Lecture 23, 2013.
28. Uzun G, Solmazgul E, Curuksulu H, Turhan V, Ardic N, Top C, Yildiz S, Cimsit M. Procalcitonin as a diagnostic aid in diabetic foot infections. Tohoku J Exp Med 213:305–312, 2007.
29. Jafari N, Firouzabadi M, Firouzabadi M, Izadi M, Saburi A. Can procalcitonin be an accurate diagnostic marker for the classification of diabetic foot ulcers? Int J Endocrinol Metab 12:e133376, 2014.
30. Mutluoglu M, Ipciaglu O, Ozcan O, Mutlu H, Sildiroglu O, Turhan V, Uzun G, Yildiz S. Can procalcitonin predict bone infection in people with diabetes with infected foot ulcers? A pilot study. Diabetes Res Clin Pract 94:53–56, 2011.
31. Karakas A, Arslan E, Cakmak T, Aydin I, Akgul EO, Demirbas S, Yildiz S. Predictive value of soluble CD14, interleukin-6 and procalcitonin for lower extremity amputation in people with diabetes with foot ulcers: a pilot study. Pak J Med Sci 30:578–582, 2014.
32. Biancari F, Arvela E, Korhonen M, Soderstrom M, Halmesmaki K, Alback A, Lepantalo M, Venermo M. End-stage renal disease and critical limb ischemia: a deadly combination? Scand J Surg 101:138–143, 2012.
33. Deery HG II, Sangeorzan JA. Saving the diabetic foot with special references to the patient with chronic renal failure. Infect Dis Clin North Am 15:953–981, 2001.
34. Edwards JM, Taylor LM, Porter JM. Limb salvage in end-stage renal disease (ESRD): comparison of modern results in patients with and without ESRD. Arch Surg 123:1164–1168, 1988.
35. Meloni M, Giurato L, Izzo V, Stefanini M, Pampana E, Gandini R, Uccioli. Long term outcomes of diabetic haemodialysis patients with critical limb ischemia and foot ulcer. Diabetes Res Clin Pract 116:117–122, 2016.
36. Wong CH, Khin LW, Heng KS, Tan KC, Low CO. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. Crit Care Med 32:1535–1541, 2004.