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

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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.
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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,