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Procalcitonin ratio as a predictor of successful surgical treatment of severe necrotizing soft tissue infections

Jan Friederichs, M.D.[a,*], Martin Hutter, M.D.[a], Christian Hierholzer, M.D.[a], Alexander Novotny, M.D.[b], Helmut Friess, M.D.[b], Volker Bühren, M.D.[a], Sven Hungerer, M.D.[a]

[a]*Trauma Center Murnau, Prof.-Küntscher-Str. 8, Murnau, 82418, Germany;* [b]*Department of Surgery, Klinikum rechts der Isar, Technische Universität München, Munich, Germany*

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Abstract

BACKGROUND: Necrotizing soft tissue infections often are characterized by fulminant presentation and lethal outcomes. Besides critical care support and antibiotic therapy, aggressive surgical treatment is important for the therapy of necrotizing fasciitis. The aim of this study was to develop a procalcitonin (PCT) ratio indicating successful surgical intervention.

METHODS: The study group consisted of 38 patients treated with clinical signs of sepsis caused by a necrotizing soft tissue infection. All patients received radical surgical treatment, and serum levels of PCT and C-reactive protein were monitored postoperatively. The ratio of day 1 to day 2 was calculated and correlated with the successful elimination of the infectious source and clinical recovery.

RESULTS: An eradication of the infectious focus was successfully performed in 84% of patients, averaging 1.9 operations (range 1 to 6) to achieve an elimination of the infectious source. The PCT ratio was significantly higher in the group of patients with successful surgical intervention (1.665 vs .9, $P < .001$). A ratio higher than the calculated cutoff of 1.14 indicated successful surgical treatment with a sensitivity of 83.3% and a specificity of 71.4%. The positive predictive value was 75.8%, and the negative predictive value was 80.0%.

CONCLUSIONS: The PCT ratio of postoperative day 1 to day 2 following major surgical procedures for necrotizing soft tissue infections represents a valuable clinical tool indicating successful surgical eradication of the infectious focus.

Necrotizing soft tissue infections (NSTIs) are rare but fulminant and life-threatening bacterial infections. Since the primary infection affects predominantly the fascia and subcutaneous tissue, the term *necrotizing fasciitis* was defined by Wilson[1] in 1952. Characteristics of this highly lethal infection include clinical symptoms of pain out of proportion, edema, blisters, and erythema with a systemic inflammation syndrome as well as the histopathologic features of fascial necrosis, vasculitis, and thrombosis of perforating veins.[2] Synergistic polymicrobial infections are about as common as monomicrobial fasciitis caused by a multitude of aerobic and anaerobic organisms.[3–5] The location of infection involves mainly the extremities in 50% to 80% of the cases, and the trunk and the perineal region (Fournier's gangrene) account for the rest.[2,5,6] Several classification systems have been used to describe this

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* Corresponding author. Tel.: +49-8841-484731; fax: +49-8841-484678.
E-mail address: Jan.Friederichs@bgu-murnau.de

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heterogeneous disease based on microbial subtype or location, but no validated classification scheme has been correlated with outcome.[6] Mortality of necrotizing fasciitis has dropped from up to 32% in study collectives between 1980 and 1998 to a range of 8.8% to 25% in recent reports. This is most likely due to more aggressive surgical treatment, more effective antibiotic therapy, and adjunctive treatment,[3,6] because advances are based on observational studies and randomized controlled trials are lacking.

Many prognostic predictors of mortality or limb loss have been published. Predictors of outcome include advanced age,[6–9] female sex,[7] advanced Acute Physiology and Chronic Health Evaluation II (APACHE II) score,[6,10] evidence of sepsis and shock upon admission,[7,11] comorbidities,[3,6,11] and malignancies.[12,13] Several hematologic values at the point of hospital admission have been shown to predict mortality, such as lactate[7,9,14] and sodium levels.[14] White blood cell count, creatinine, and hematocrit in combination with clinical parameters such as age, heart rate, and temperature have been used to predict mortality as well as limb loss in cases of infected extremities.[15] This seems extremely important as prompt aggressive surgical treatment is a mainstay of successful therapy of necrotizing fasciitis. A delay of surgical therapy results in increased mortality.[2,6,9] However, despite radical initial surgical debridement and a limb amputation rate up to 20%,[6] surgical control of the infectious source is often not achieved. Tools in deciding whether additional radical treatment such as a proximal amputation is necessary are missing, and the decision is only based on clinical parameters and the experience of the surgeon.

For patients with abdominal sepsis, a marker of successful surgical treatment has been recently described.[16] Based on the finding, that procalcitonin (PCT) in combination with a clinical score (APACHE II) is highly sensitive and specific as a prognostic score for the septic course of abdominal sepsis, Novotny et al[17] identified a cutoff level of the PCT ratio of postoperative day 1 to day 2 indicating a successful surgical treatment as an aid in deciding if further laparotomies were necessary. A PCT ratio below 1.03 represented an unsuccessful operative treatment of the septic focus with a sensitivity of 95%.

The aim of this study was to evaluate postoperative PCT levels as a parameter for the detection of progressing disease in patients with NSTIs to facilitate the decision-making progress for reoperations or major amputations.

Methods

The study population primarily consisted of 38 patients treated with the diagnosis of NSTI in the intensive care unit of the Trauma Center Murnau, Germany, from November 2006 until December 2010. The initial diagnosis of necrotizing fasciitis was based on clinical characteristics[2–5] and intraoperative findings; in all patients, the diagnosis was confirmed by histopathologic examination. All patients included in this study initially required critical care support because of acute sepsis and met the established criteria of sepsis.[18] Patients who did not meet septic criteria were excluded from the study. The study group consisted of 27 (71%) male and 11 (29%) female patients, and the median age was 58.5 years (range 29 to 85 years). A detailed profile of the clinical characteristics of the study group is presented in Table 1.

All patients underwent surgery at least once. For later analysis, surgical interventions were defined as major and minor procedures. Major procedures included amputations, exarticulations, and extensive debulking with resection of necrotic and infected soft tissue, whereas minor procedures comprised of vacuum-assisted closures without resection and wound closures. For this study, successful surgical eradication of the septic focus was defined by negative results in at least 2 consecutive microbiologic examinations, the absence of macroscopic infectious tissue in all further operations, and an uneventful recovery (uneventful healing of all wounds, no reappearance of local infectious signs, and no systemic inflammation). For microbiologic examinations, tissue samples and cultures were obtained during each operative procedure. All patients received critical care support as needed, antibiotic therapy, and, in the absence of contraindications, hyperbaric oxygen therapy.

Medical records of all treated patients were retrospectively reviewed. The variables examined in this study

Table 1 Demographic and clinical data of 38 patients with necrotizing soft tissue infections and sepsis

Demographics and clinical categories	
Sex	
Male	27/38 (71%)
Female	11/38 (29%)
Age	58 years (29–85)*
Location of Infection	
Upper limb	6/38 (16%)
Lower limb	18/38 (47%)
Thoracic	2/38 (5%)
Pelvic	12/38 (32%)
Cause of Infection	
Trauma	11/38 (29%)
Chronic ulcer	4/38 (10%)
Injection	6/38 (16%)
Postoperative	3/38 (8%)
Insect bite	2/38 (5%)
Unknown	12/38 (32%)
Clinical Data	
Hyperbaric oxygen -therapy	32/38 (84%)
Focus eradication	32/38 (84%)
Critical care (days)	22 (1–112)*
Hospitalization (days)	50 (1–173)*
Amputation	17/24 (71%)
Mortality	11/38 (29%)

*Age, duration of critical care, and hospitalization are expressed as mean with range in parentheses.

included age, sex, body mass index, comorbidities, duration of hospitalization and intensive care, site and cause of infection, number and type of surgical procedures, rate of amputation, surgical eradication of the septic focus, and mortality. C-reactive protein (CRP) and PCT were measured at least daily, and statistical evaluation was performed with values of postoperative days 1 and 2. If patients returned to the operating room before day 2 or a PCT value was missing for other reasons, no ratio was calculated. Serum PCT levels were determined using an immunoluminometric assay (LIAISON, BRAHMS AG, Hennigsdorf, Germany), and serum CRP levels were measured with the DIMENSION VISTA System (Siemens Health Care, Marburg, Germany), both according to the manufacturers' instructions.

Statistical analysis was performed using the Statistical Package for the Social Sciences version 19.0 (SPSS, Chicago, IL). Data were analyzed for normal distribution using the Kolmogorov-Smirnov test. Comparisons between groups were performed using the nonparametric Wilcoxon and the Mann–Whitney *U* tests. The probability significance level was set at less than .05. To determine the cutoff level of the PCT ratio, a chi-square test was used, as described elsewhere.[17] Briefly, PCT ratios were sorted in ascending values, and every value was used as a potential cutoff assigning all patients, with a cutoff less than this value to the persisting infection group and all patients with ratios above this cutoff to the eradicated group. This assignment was then compared with the real status, calculating the corresponding chi-square statistics. All resulting chi-square statistics were compared, and the cutoff value with the highest chi-square statistic was used as the optimal cutoff. To investigate the prognostic impact of PCT and CRP ratios of postoperative day 1 to day 2, receiver operating characteristic curves were plotted and the areas under the curve were assessed.

Results

A total of 38 patients presenting in a septic state and treated for the diagnosis of NSTI were included in this study. The study group consisted of 27 (71%) male and 11 (29%) female patients. The median age was 58.5 years (average 58, range 29 to 85 years), the median body mass index was 27.5 (range 19 to 60). The most common preexisting comorbidity was diabetes mellitus, occurring in 17 of the 38 patients (45%), while there was no trend observable for other comorbidities. The average stay in the intensive care unit was 22 days (range 1 to 112 days), the average duration of hospitalization was 50 days (range 1 to 173 days). The location and etiology of all infections are summarized in Table 1.

All patients underwent surgery on the day of admission and were operated on at least once. A median of 6 operations (average 7, range 1 to 25) was performed per patient, 68 (25.6%) of which were classified as major surgical procedures. In this selected patient collective, the amputation rate was rather high, with 17 of 24 (71%) patients with NSTIs of the extremities. Adjuvant hyperbaric oxygen therapy was performed in 84% of patients. An eradication of the infectious focus was achieved in 84% of the patients, averaging 1.9 operations (range 1 to 6) to achieve an elimination of the infectious source. The overall mortality in our study group was 11 of 38 patients (29%), with a mean survival of 18 days. Five patients died of nonseptic complications in the postoperative period after a successful eradication of the infectious focus had been achieved.

Of the 38 patients treated for NSTI, 22 (58%) suffered a monomicrobial infection, and in 16 patients (42%) a polymicrobial infection was detected. In the group of monomicrobial infections, β-hemolyzing streptococci (32%) and *Staphylococcus aureus* (41%) were the most frequent causative organisms, including 1 case of a methicillin-resistant *Staphylococcus aureus*. Anaerobes were detected as causative species in only 2 cases (9%). In the group of 16 patients with a polymicrobial NSTI, the number of organisms isolated in each patient varied from 2 to 5 species, with an average of 2.5. The predominant group of organisms in polymicrobial infections were streptococcal and staphylococcal species. However, a total of 17 different species were detected, as summarized in Table 2.

PCT levels after 63 major operative procedures in the study group of 38 patients were measured on postoperative

Table 2 Microbiologic findings in 38 patients with necrotizing soft tissue infections

Monomicrobial infection (n = 22)		Polymicrobial infection (n = 16)	
Streptococcus group A	7 (32%)	Streptococcus group A	3 (8%)
Streptococcus group B	1 (4.5%)	Streptococcus group B	4 (10.5%)
Staphylococcus aureus	9 (41%)	*Staphylococcus aureus*	4 (10.5%)
Staphylococcus others	2 (9%)	*Staphylococcus epidermidis*	5 (13%)
Pseudomonas aeruginosa	1 (4.5%)	Staphylococcus others	5 (13%)
Anaerobes	2 (9%)	Enterococcus species	5 (13%)
		Escherichia coli	4 (10.5%)
		other gram-negative rods	4 (10.5%)
		Anaerobes	3 (8%)
		Candida species	1 (3%)

day 1 and of 61 major surgical procedures on postoperative day 2, resulting in a total of 58 procedures with calculated PCT ratios. An elimination of the infectious focus was achieved in 30 of these 58 operations (52%), and a persistence of the infectious source was observed in 28 (48%). PCT levels on days 1 and 2 after major surgery were significantly increased above normal, with a mean of 14.3 ng/mL (standard deviation [SD] 32.2 ng/mL) for postoperative day 1 and 12.7 ng/mL (SD 32.1 ng/mL) for postoperative day 2. The change of PCT levels was then expressed by the calculation of the corresponding ratios (day 1/day 2). The PCT ratios of surgical procedures with a successful eradication of the infectious focus were significantly higher (mean 1.67, SD .65) than in the group of 28 operations with persisting infection (mean .9, SD .36, $P < .001$). In contrast, the comparison of the CRP ratios of day 1 with those of day 2 did not reach the significance level ($P = .63$). Additionally, there were no significant differences when primary major surgical procedures were compared with later major operations (data not shown). The results are illustrated in Fig. 1 where corresponding receiver operating characteristic curves with an area under the curve of .872 for the PCT ratio and an area under the curve of .617 for the CRP ratio were calculated. The optimal cutoff value was calculated at 1.14 for the PCT ratio between postoperative days 1 and 2. Ratios higher than 1.14 suggested a successful eradication of the infectious focus, as compared with a persisting infection if the ratio was lower than the cutoff, as demonstrated in Fig. 2. Using this cutoff, a prediction of a successful elimination was possible, with a specificity of 71.4% and a sensitivity of 83.3% resulting in a positive predictive value of 75.8% and a negative predictive value of 80.0%.

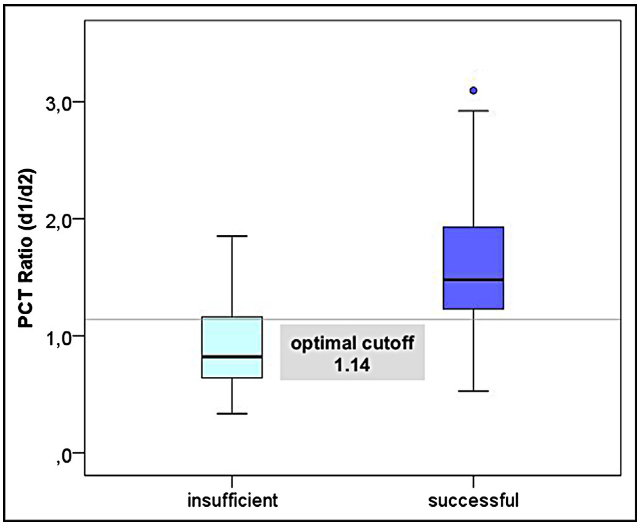

Figure 2 Cutoff value for the procalcitonin (PCT) ratio of postoperative day 1 to day 2 predicting a successful surgical eradication of the infectious focus using classification and regression tree analysis. Ratios higher than 1.14 indicate a successful elimination of the infectious source.

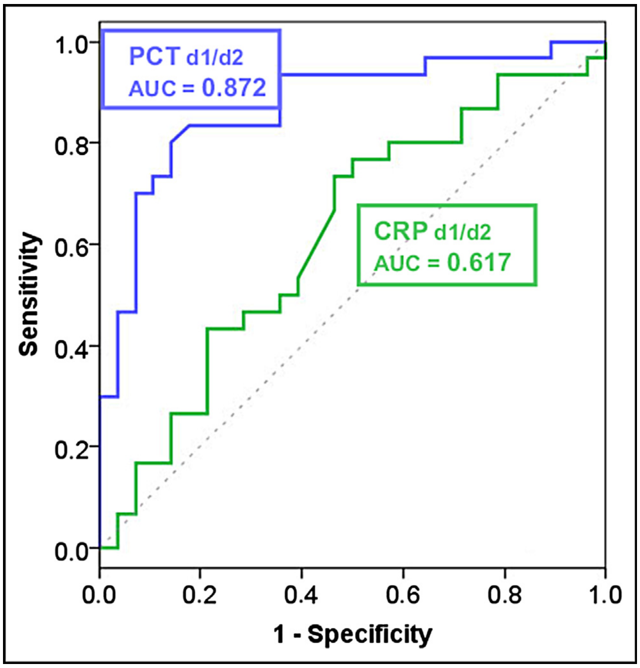

Figure 1 Receiver operating characteristic (ROC) curves of procalcitonin (PCT) and C-reactive protein (CRP) ratio of postoperative day 1 and 2 after a major surgical procedure in 38 patients with necrotizing soft tissue infection. The area under the curve (AUC) ROC for successful elimination of the infectious focus was .872 for the postoperative PCT ratio and .617 for the CRP ratio.

Comments

NSTIs are life-threatening infections with a rapid course of inflammation and often sepsis and shock. Although the reported incidence of .4 cases per 100,000 population[13,19] makes it a rare disease and the treatment of necrotizing fasciitis has improved, its mortality remains high with up to 25% to 32% in recent studies.[6,7,10,13] Compared with recent studies on NSTIs, the mortality rate of 29% found in our study group appears to be rather high. A possible explanation for this finding is that our study included only patients who required critical care support because of acute sepsis and met the established criteria of sepsis.[18] In conclusion, this study group represented only a third of all our patients treated for the diagnosis of NSTI, as an overall of 131 patients received therapy for necrotizing fasciitis. These findings correlate with the recently published findings of Kao et al,[6] where in a collective of 296 patients, vasopressors were only required in 11% to 27% and intensive care in 75% of the patients and the mean length of stay on the intensive care unit was only 0 to 6 days compared with a mean of 22 days in our study group. Another recently published article describes signs of sepsis including tachycardia or hypotension in 25% to 40%.[13] Thus, the selection of only septic patients in need of critical care results in a higher mortality as compared with other studies. The same explanation may be valid when looking at the rate of amputation. Limb loss is reported to reach 17% to

50% of patients with necrotizing fasciitis located on an extremity.[3,13,15,20] In our study, 24 patients suffered an NSTI of an extremity and the amputation rate was as high as 71%. Again, this high rate of amputation is based on the specific collective of patients who were admitted to our institution with all signs of shock and sepsis and therefore differs from the overall amputation rate of 34% in our hospital for patients with necrotizing fasciitis of a limb. According to that, shock has been described as an independent prognostic factor for limb loss.[15]

Several prognostic factors for a favorable outcome of NSTIs have been published. Immediate operative treatment appears to have an important impact on mortality and rate of amputation, as several publications report a delay of surgery being an independent negative prognostic factor.[3,7,20] Wong et al[3] observed a decline in the cumulative survival rate with progressing time between admission and surgery. Our study group consisted entirely of septic patients, and all patients underwent emergency surgery on the day of admission to our hospital. Although our data do not permit us to determine an optimized time point of operation, we believe that immediate surgical treatment is essential for successful therapy.

The importance of radical surgical debridement, resection of all necrotic tissue based on the aggressiveness of the infection, and early amputation of a limb has been described in previous studies. Limited incisions, drainage as a monotherapy, and onetime debridements have been shown to be ineffective and do not decrease mortality.[7] However, aggressive surgical resections are sometimes not radical enough, and extensive reoperations or a more proximal amputation in the further course of disease may be necessary. On the other hand, “overtreatment,” resulting in a loss of noninfected tissue, should be avoided. These decisions are often based on the experience of the surgeon and postoperatively on the clinical state of the patient. Many factors including all septic parameters and laboratory results such as leucocyte count, CRP, interleukin-6,[21] lactate, base deficite,[14] and PCT[16] can be taken into account for the decision to increase or decrease surgical aggressiveness. However, in most cases the decision of the surgeon will be based on the clinical condition of the patient, including all available prognostic markers.

Conclusions

Our study identified the PCT ratio of postoperative day 1 to day 2 as a valuable tool to decide whether the aim of focus eradication has been achieved or if the initial treatment was not radical enough. As described by Novotny et al, PCT represents an appropriate marker as it can easily be measured within less than 2 hours with a commercially available assay. It has favorable kinetics with a rapid increase and a half-life of approximately 20 to 24 hours without prolongation with impaired kidney function.[17,21,22] In our study, a strong decrease of serum PCT was observed from postoperative day 1 to day 2 after a major surgical procedure if the source of infection was eliminated, while the decrease was not significant in patients with persisting infection. This relationship is best expressed by the PCT ratio between postoperative day 1 and day 2, and it was significantly higher after successful surgery ($P < .001$). The calculated cutoff, which was 1.14 in our study, seems to be a practical aid for clinical decisions as it is able to distinguish between successful and unsuccessful surgical eradication of the infectious focus with a high sensitivity and specificity. In the clinical setting, a ratio below the cutoff should especially raise suspicion for persistence of the infectious focus and together with other parameters may lead to an earlier and more radical reoperation or an earlier life-saving amputation.

We are aware that this cutoff only represents an aid for the surgeon, adding one piece of information to the overall clinical impression, and that good surgical judgment still represents the leading factor in decision making. A large prospective study to validate this PCT ratio would be necessary to prove its clinical value, although only a multicenter design can provide enough patients with a fulminant course of necrotizing fasciitis. However, we believe that septic patients with the diagnosis of NSTI may benefit from the proposed method.

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