

The Role of Acute-Phase Reactants in Determining Bacteremia and Evaluation of Diagnostic Benefits of Cultures in Cellulitis Cases

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ABSTRACT

Objective: This study aims to investigate the relationship between bacteremia and the level of acute phase reactants in cellulite cases and to evaluate the value of blood culture and tissue/wound/abscess cultures in determining causal microorganism.

Methods: The adult patients were included in this study, who were hospitalized with a diagnosis of cellulitis between January 1, 2015, and December 31, 2016. Patients' medical records revealed from computer based hospital system, retrospectively. Patients with diabetic foot infections, decubitus infections, cellulite accompanying shingles and other concomitant system infections were excluded from this study. Before antibiotic treatment, patient's body temperature, leukocyte count, c reactive protein level, erythrocyte sedimentation rate, culture results, antibiotic treatment before hospitalization, empirical antibiotic treatment in hospital, treatment duration, comorbidities and clinical response data were collected.

Results: There were 194 patients in this study. Blood cultures collected from 143 patients before antibiotic treatment. Nine of 143 (6.3%) patient's blood cultures were positive. On the other hand, results of the tissue/wound cultures were positive in 17 of the 35 cases (48.6%). Mean white blood cell count at the first admission was $13.9 \times 10^3/\text{mm}^3$ in non-bacteremic group and $15.2 \times 10^3/\text{mm}^3$ in bacteremic group. Mean C-reactive protein level at the first admission was 148 mg/L in non-bacteremic group and 164 mg/L in bacteremic group. There was no statistical significance between these two acute phase marker and bacteremia in cellulitis cases. However, mean erythrocyte sedimentation rate was 92 vs 56.5 mm/h respectively in bacteremic and non-bacteremic patient ($p=0.03$).

Conclusion: In the cases of cellulitis, blood culture did not provide sufficient clinical benefit for the etiology even the presence of fever. It was concluded that taking culture samples from infection site, such as abscess, wound and tissue culture, would be more useful for identification of the etiologic agent.

INTRODUCTION

Microbial invasion of the skin and subcutaneous soft tissue is defined as skin and soft tissue infection. These infections may occur in many different clinical forms. Of these, cellulitis is a clinical entity that occurs with the involvement of the deep layers of the dermis and/or subcutaneous tissue layers, with indetermined borders, redness, swelling and increased temperature.^[1]

The diagnosis of cellulitis is based on the morphological features of the lesion and clinical findings.^[2] Generally, empirical treatment is used. In cases with cellulitis,

detection rates of causative agents in blood cultures are below 5%.^[3,4] Taking an aspiration culture with a needle is not a routine approach in the diagnosis of cellulitis.^[2] However, in different studies performed to investigate the agent microorganism with needle aspiration, the rates of demonstrating the pathogenic agent are much higher than the detection rates based on blood culture positivity.^[5-7] Tissue cultures are important in the diagnosis of cellulitis, while swab cultures are inadequate in determining skin colonization, and isolating the causative pathogen.^[8]

White blood cell counts, C-reactive protein (CRP) levels and erythrocyte sedimentation rates increase in parallel

with the severity of the infection. In our study, we aimed to evaluate the levels of these parameters in the case of bacteremia and the place of the cultures obtained from blood and the infection sites, such as tissue, wound, pus, aspiration culture, in showing the etiological agent.

MATERIALS AND METHODS

Between January 1, 2015, and December 31, 2016, the medical records of patients aged 18 and over who were diagnosed with cellulitis in our clinic were analyzed retrospectively. Patients with diabetic foot infections, decubitus infections, cellulitis accompanying shingles and other systemic infections were excluded from this study. Patients' pre-treatment body temperature, leukocyte count, CRP and erythrocyte sedimentation rate, blood cultures, tissue and wound cultures, antibiotics taken before hospitalization, empirical antibiotic treatments and duration of treatment, comorbid diseases and clinical responses were recorded.

In the recurrent episodes of cellulitis in the same patient, each application was taken as a new episode. Since the procalcitonin test, which is a good and more specific indicator concerning bacteremia, was not studied in our hospital at that time, erythrocyte sedimentation rates, CRP levels and white blood cell counts were measured and evaluated.

Statistical evaluation

Descriptive statistics were presented with percentage, mean, standard deviation, median, minimum and maximum values. The normality assumption was checked using the Shapiro-Wilk Test. In the analysis of the difference between the numerical data of the two groups, Independent Samples- t-test (Independent Two-Sample t-test) was used when the data fit the normal distribution and Mann-Whitney U test was used for the data with the nonnormal distribution. Relationships between numerical data were evaluated using the non-parametric Spearman Correlation Test and parametric Pearson Correlation Test.

Pearson Chi-Square (Pearson Chi-Square) test was used in the analysis of categorical data. The diagnostic positivity limit value (cut-off value) of the acute phase reactants was evaluated by ROC analysis. Analyses were performed with the SPSS 23.0 program. $P < 0.05$ was considered statistically significant.

RESULTS

Demographic and clinical information of 194 patients diagnosed with cellulitis, which meet the inclusion criteria, are given in Table 1.

It was determined that blood cultures were obtained from 143 patients before treatment and only in nine (6.30%) of them bacterial growth was detected. However, in tissue, wound, pus cultures of 17 (48.6%) out of 35 cases, bacte-

Table 1. Demographic and clinical characteristics of the patients

Variables	n=194	(100%)
Age		
Median (min-max)	61	(19–92)
Gender, n (%)		
Male	125	(64.4)
Female	69	(35.6)
Duration of hospitalization/days		
Median (min-max)	7	(1–57)
Most frequently affected region, n (%)		
Lower extremities	97	(50.0)
Types of hospital admission, n (%)		
From emergency service	120	(61.9)
From outpatient clinics	69	(35.6)
Transfer from another service	5	(2.6)
Comorbidities, n (%)		
Tinea pedis, onychomycosis	80	(41.2)
Diabetes mellitus	64	(33.0)
Peripheral vascular/lymphatic disease	53	(27.3)
Implant/prosthesis/graft	26	(13.4)
Malignancy	19	(9.8)
Immobility	14	(7.2)
Chronic renal failure	13	(6.7)
Congestive heart failure (associated with pretibial edema)	12	(6.2)
Immune suppression	9	(4.6)
IV drug addiction	8	(4.1)
Obesity	6	(3.1)
Alcoholism	1	(0.5)

rial growth was observed. Both blood, and tissue, wound and pus cultures were obtained in 17 patients, and in 15 out of these 17 cases, bacterial growth was detected only in tissue, wound and pus cultures, any pathogen was not reproduced in the blood cultures of these patients. In two of these cases, bacterial growth was seen only in blood cultures. The causative agents isolated from blood, tissue, wound, and pus cultures are shown in Table 2.

It was observed that 80 patients (41.2%) used antibiotics before hospitalization. The most frequently used antibiotic therapy in this group was amoxicillin- clavulanate (34.6%), followed by amoxicillin- clavulanate + ciprofloxacin (16%). There was no statistically significant difference between the groups that used and did not use antibiotics before hospitalization regarding bacterial pathogen identification rates in blood and tissue, wound, and pus cultures ($p=0.922$ and $p=0.728$). It was remarkable that 28.7% of the patients who used, and 48.2% of the patients who did not use antibiotics before hospitalization had a fever ($p=0.006$).

Seventy-eight (40.2%) patients had fever at first admission. When the average CRP values were determined at first admission among patients with and without fever, the average CRP value was found to be significantly higher in

Table 2. Pathogenic microorganisms isolated from blood, tissue, wound and pus cultures

Patients	Blood culture	Tissue, wound, pus culture
1	No growth	Methicillin-sensitive Staphylococcus aureus + Streptococcus pyogenes
2	Group G Streptococci	Culture not performed
3	No growth	Methicillin-resistant coagulase negative Staphylococci
4	No growth	Methicillin-sensitive Staphylococcus aureus
5	No growth	Methicillin-sensitive Staphylococcus aureus
6	No growth	Methicillin-sensitive Staphylococcus aureus + Methicillin-resistant coagulase negative Staphylococci
7	Methicillin-sensitive Staphylococcus aureus+ Streptococcus agalactiae	Culture not performed
8	Culture not performed	Group B Streptococci
9	Methicillin-sensitive Staphylococcus aureus	Culture not performed
10	No growth	Morganella morganii + Enterococcus faecalis + Methicillin-resistant coagulase negative Staphylococci
11	Proteus vulgaris	Not available
12	No growth	Methicillin-sensitive Staphylococcus aureus
13	No growth	Methicillin-sensitive Staphylococcus aureus
14	No growth	Methicillin-sensitive Staphylococcus aureus
15	No growth	Methicillin-sensitive Staphylococcus aureus
16	No growth	Methicillin-resistant coagulase negative Staphylococci
17	No growth	Methicillin-resistant Staphylococcus aureus
18	Streptococcus pyogenes	Culture not performed
19	Streptococcus pyogenes	Culture not performed
20	Streptococcus parasanguinis	No growth
21	Methicillin-resistant coagulase negative Staphylococci	Culture not performed
22	No growth	Methicillin-sensitive Staphylococcus aureus
23	No growth	Streptococcus constellatus
24	No growth	Methicillin-resistant coagulase negative Staphylococci
25	Methicillin-sensitive Staphylococcus aureus	No growth
26	Culture not performed	Methicillin-resistant Staphylococcus aureus

patients with fever (115.7 mg/L vs 171.3 mg/L, $p < 0.001$, respectively). From 69 of 78 patients with fever at admission, samples were obtained for blood culture and in five (7.2%) of them bacterial growth was detected, while in four of 74 (5.4%) patients without fever at admission, bacterial growth was observed in the blood cultures ($p = 0.650$).

When all cases were evaluated, the mean values for white blood cell count, CRP and erythrocyte sedimentation rate were $13.2 \pm 5.8 \times 10^3/\text{mm}^3$, 138.07 ± 96.6 mg/L, and 55.05 ± 33.01 mm/h, respectively.

Mean number of white cells (WBC) at first admission were $13.9 \pm 6.2 \times 10^3/\text{mm}^3$ in non-bacteremic, and $15.2 \pm 8.5 \times 10^3/\text{mm}^3$ in bacteremic patients ($p = 0.702$) and WBC counts were, $16.7 \pm 9.3 \times 10^3/\text{mm}^3$ and $13.09 \pm 5.9 \times 10^3/\text{mm}^3$ in patients whose wound, tissue, pus cultures did, and did not demonstrate the presence of bacterial growth, respectively ($p = 0.129$).

The mean CRP values at the first admission were 148 ± 100 mg/L in the non-bacteremic group, and 164 ± 84 mg/L in the bacteremic group, without any statistically significant dif-

ference between groups ($p = 0.839$). The mean CRP value at first admission was 145 ± 73 mg/L in patients whose wound, tissue, pus cultures were positive, while it was 169 ± 93 mg/L in whom wound, tissue, pus cultures were negative ($p = 0.438$).

The mean erythrocyte sedimentation rates at first admission were 92 ± 27 mm/h and 56.5 ± 33 mm/h in the groups with and without bacterial growth in their blood cultures ($p = 0.03$). In addition, it was found that sedimentation values of 67.5 mm/h and above were more significant concerning showing bacteremia by ROC analysis. In the group with bacterial growth in tissue, wound, pus cultures mean sedimentation rate at first admission was found to be higher than the culture negative group, without any statistically significant difference between both groups (61 ± 35 mm/h and 54 ± 25 mm/h, $p = 0.726$, respectively). Mean CRP values, WBC counts, and sedimentation rates in groups with and without bacterial growth in their blood, tissue, wound, and pus cultures are shown in Table 3.

Cellulitis started spontaneously in 142 (72%) of the pa-

Table 3. Mean white blood cell counts, C-reactive protein values, and erythrocyte sedimentation rates

	Overall (n=194)	Patients without bacterial growth in their blood cultures (n=134)	Patients with bacterial growth in their blood cultures (n=9)	p	Patients without bacterial growth in their tissue, wound and pus cultures (n=18)	Patients with bacterial growth in their tissue, wound and pus cultures (n=17)	p
Mean white blood cell counts at first admission ($\times 10^3/\text{mm}^3$)	13.2 \pm 5.8	13.9 \pm 6.2	15.2 \pm 8.5	0.702	13.09 \pm 5.9	16.7 \pm 9.3	0.129
Mean C-reactive protein values at first admission (mg/L)	138 \pm 96	148 \pm 100	164 \pm 84	0.839	169 \pm 93	145 \pm 73	0.438
Mean sedimentation rates at first admission (mm/h)	55 \pm 33	56 \pm 33	92 \pm 27	0.030	54 \pm 25	61 \pm 35	0.726

tients without any causative factors as trauma, burn, open wound, insect bite but tineapedis and/or onychomycosis were detected in 44.4% of these patients.

It was observed that ampicillin-sulbactam (64.9%) and tigecycline (22.7%) were started mostly as an empirical treatment in hospitalized patients and the initial empirical antibiotherapy was continued without changing in 148 (76.3%) patients. The average duration of antibiotherapy was 9.3 \pm 6.6 days, and 185 (95.4%) patients were administered oral follow-up treatment after discharge.

During follow-up, 41 patients (21.1%) developed complications, such as abscess, necrosis, fasciitis or need for surgical intervention, and the length of hospital stay was found to be longer in these patients than the patients without complications (14 \pm 10 and 8 \pm 4 days, $p < 0.001$, respectively). Osteomyelitis accompanied cellulitis in the follow-up of 14 patients (7.2%).

DISCUSSION

In the literature, rates of blood culture positivity have been reported to be below 5% in cases of cellulitis derived from different sources.^[3,4] In our study, this rate was found to be 6.3%. Although in the 2014 skin and soft tissue infections guidelines of Infectious Diseases Society of America (IDSA), obtaining routine blood, wound aspiration, skin biopsy or swab cultures for the diagnosis of cellulitis are not recommended,^[9] in different studies conducted to determine the agent with needle aspiration, it is seen that the rates of identifying the bacterial pathogen are much higher than the rates estimated based on blood culture positivity.^[5-7] Similarly, in our study, the rate of bacterial growth in blood cultures of 143 patients was found to be only 6.3%. Although culture material could be obtained from a smaller number (n=35) of patients, the active microorganism could be demonstrated in 48.6% of tissue, wound and pus cultures.

This result shows that in cases presenting with cellulitis,

isolation of the microorganism from the infection site, such as tissue, wound, and pus, is more useful than the blood culture. Because skin colonization and pathogenic microorganism cannot be distinguished in superficial swab cultures, tissue cultures are more valuable in demonstrating the active microorganisms.^[8]

When the effects of empirical antibiotic use before hospitalization on culture results were evaluated, there was no statistically significant difference between the groups using and not using antibiotics regarding rates of bacterial growth in blood and tissue, wound, and pus culture media ($p = 0.922$ and $p = 0.728$). Fever was detected in 28.7% of the patients who used, and in 48.2% of the patients who did not use antibiotics before hospitalization with a statistically significant difference between groups ($p = 0.006$). It was thought that fever at admission decreased with empirical oral antibiotic treatment instituted before hospitalization.

Blood cultures were obtained from 69 of 78 patients with fever at admission and in five of them (7.2%), bacterial growth was seen in their blood cultures, and in four of 74 (5.4%) afebrile patients bacterial growth was observed in blood cultures. These results suggest that the presence of fever is not an adequate clinical finding to demonstrate bacteremia.

Mean WBC counts at first presentation were 13.9 \pm 6.2 $\times 10^3/\text{mm}^3$ in non-bacteremic, and 15.2 \pm 8.5 $\times 10^3/\text{mm}^3$ in bacteremic patients ($p = 0.702$), and WBC counts were 16.7 \pm 9.3 $\times 10^3/\text{mm}^3$, and 13.09 \pm 5.9 $\times 10^3/\text{mm}^3$ in patients with, and without bacterial growth in wound, tissue, and pus culture media, respectively ($p = 0.129$). Mean CRP values at first admission were 148 \pm 100 mg/L in the non-bacteremic and 164 \pm 84 mg/L in the bacteremic group, without any significant intergroup difference ($p = 0.839$). Also, at first presentation, mean CRP values were 145 \pm 73 mg/L, and 169 \pm 93 mg/L in patients whose wound, tissue, pus culture did and did not reveal the presence of bacterial growth ($p = 0.438$).

Although mean CRP values and white blood cell counts did not differ significantly between groups with and without bacterial growth in their blood, wound, tissue, pus cultures, it is noteworthy that the mean erythrocyte sedimentation rate was higher in bacteremic patients than in non-bacteremic patients (92 ± 27 mm/h and 56.5 ± 33 mm/h, respectively; $p=0.03$). In addition, given that although not statistically significant, mean sedimentation rate was higher at first presentation in the group with bacterial growth in their tissue, wound, and pus cultures compared with those without bacterial growth (61 mm/h and 54 mm/h, respectively) is also a valuable finding. Especially values of 67.5 mm/h and over were found to be significant concerning showing bacteremia by ROC analysis.

In another study comparing the diagnostic values of CRP, sedimentation and white blood cell counts in bacteremia, among 265 pediatric cases with bone, and joint infections, mean CRP values in bacteremic and non-bacteremic groups were 93 ± 5 and 77 ± 5 , $p < 0.05$, respectively; While mean white blood cell counts were $11\,900 \pm 500$ and $13\,800 \pm 700$, respectively, $p < 0.05$, without any significant difference concerning mean sedimentation rates between the bacteremic and non-bacteremic groups (53 ± 2 and 47 ± 3 , respectively, $p = 0.10$).^[10]

The development of cellulitis is mostly induced by the presence of skin trauma, open wound or fissure.^[2] In our study, considering the initial form of cellulitis, cellulitis started spontaneous in 142 (72%) of the patients without causative factors as trauma, burn, open wound, insect bite, and it was found that approximately half of these patients (44.4%) had tinea pedis and/or onychomycosis. Similarly, in a study conducted in our country, in which risk factors were evaluated in patients with cellulitis localized at a lower extremity, tinea pedis was detected in 36.4% of cases and this rate increased to 72.7% in cases of recurrent cellulitis.^[11]

In our study, it was found that ampicillin-sulbactam (64.9%) and tigecycline (22.7%) were started mostly as empirical treatment in hospitalized patients and the mean parenteral antibiotic treatment period was 9.3 ± 6.6 days. In two separate studies conducted with cellulitis patients in our country, the most commonly used antibiotic in the treatment of cellulitis was found to be ampicillin-sulbactam, while mean parenteral treatment times were 17 ± 12.4 days in one, and 3-7 days in the other study.^[11,12] Although the basic treatment approach is similar, it is seen that antibiotic treatment times may differ among centers.

During the follow-up, 41 patients (21.1%) developed complications, such as abscess, necrosis, fasciitis or need for surgical intervention, and the length of hospital stay was found to be longer in these patients than the patients without complications (14 ± 10 and 8 ± 4 days, respectively $p < 0.001$). In another study conducted in our country, it was stated that 6.5% of the patients with a diagnosis of cellulitis developed an abscess as a complication, but there was no significant difference in the treatment response compared to the group without complications.^[11]

Cellulitis may rarely arise from the spread of underlying osteomyelitis.^[2] In our study, advanced radiological imaging modalities revealed that osteomyelitis accompanied cellulitis in 14 patients (7.2%) hospitalized with a diagnosis of cellulitis.

In conclusion, it was determined that increased erythrocyte sedimentation rate was found to be a valuable marker in bacteremic cases with cellulitis, and as a result of the ROC analysis, sedimentation rates of 67.5 mm/h and above were more significant concerning indicating bacteremia. In addition, considering the low rate of bacterial growth in blood cultures, it is thought that even if there is fever in patients presenting with the clinical manifestations of cellulitis, taking tissue, wound, pus cultures from the site of cellulitis instead of blood cultures will provide a diagnostic advantage, as well as reducing the loss of labor, cost and time. However, considering the low number of samples demonstrating bacterial growth in cultures in our study, new studies to be conducted in greater number of cases with cellulitis are needed.

Ethics Committee Approval

Approved by the local ethics committee (date: 30.07.2017; no: 6/14.2017- 083).

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: K.D.Ö.; Design: N.Ö., A.S.K.; Supervision: K.D.Ö., F.K.; Fundings: K.D.Ö.; Materials: K.D.Ö.; Data: K.D.Ö., A.S.K.; Analysis: K.D.Ö.; Literature search: F.K., N.Ö., A.S.K.; Writing: K.D.Ö.; Critical revision: N.Ö., F.K.

Conflict of Interest

None declared.

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Selülit Olgularında Akut Faz Reaktanlarının Bakteremiye Belirlemedeki Yeri ve Kültürlerin Tanısal Yararının Değerlendirilmesi

Amaç: Kan kültürlerinin yaklaşık %5 kadarında üreme gösterilebilen selülit olgularında olası baktereminin tedavi öncesi akut faz reaktanlarının düzeyi ile ilişkisinin araştırılması ve kan kültürü ile doku/yara/apse kültürlerinin karşılaştırılarak etken mikroorganizmayı göstermedeki yerinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: 1 Ocak 2015 ve 31 Aralık 2016 tarihleri arasında enfeksiyon hastalıkları ve klinik mikrobiyoloji kliniğinde selülit tanısı ile yatan 18 yaş ve üzeri hastaların medikal kayıtları hastane otomasyon sistemi üzerinden geriye dönük olarak incelendi. Diyabetik ayak enfeksiyonları, dekübit enfeksiyonları, zonaya eşlik eden selülitler ve eşlik eden başka sistem enfeksiyonları olan hastalar çalışmaya dahil edilmedi. Hastaların tedavi öncesi vücut ısısı, lökosit sayısı, C-reaktif protein ve eritrosit sedimentasyon hızı, kültür sonuçları, yatış öncesi aldıkları antibiyotikler, yatışlarında başlanan empirik tedaviler, tedavi süreleri, komorbid hastalıkları ve klinik yanıtları kaydedildi.

Bulgular: Çalışmaya 194 hasta dahil edildi. Yüz kırk üç hastadan tedavi öncesi kan kültürü alındığı ve bunlardan sadece dokuzunda (%6.30) üreme olduğu saptandı. Buna karşılık doku/ yara kültürü alınan 35 olgunun 17'sinde (%48.6) üreme olduğu görüldü. İlk başvurudaki ortalama beyaz küre sayısı bakteremik olmayan hastalarda $13.9 \times 10^3/\text{mm}^3$ iken, bakteremik hastalarda $15.2 \times 10^3/\text{mm}^3$ idi. İlk başvurudaki ortalama C-reaktif protein değeri ise bakteremik olmayan grupta 148 mg/L iken, bakteremik grupta 164 mg/L saptandı. Ancak her iki parametre için de fark istatistiksel olarak anlamlı bulunmadı. Bununla birlikte ilk başvuruda ortalama eritrosit sedimentasyon hızı kanda üreme olmayan ve olan grupta sırasıyla 56.5 mm/h ve 92 mm/h olarak bulundu ($p=0.03$).

Sonuç: Selülit olgularında başvuruda ateş olsa bile kan kültürünün etiyolojiye yönelik yeterli klinik fayda sağlamadığı; bunun yerine apse, yara, bül sıvısı, doku kültürü gibi enfeksiyon bölgesinden kültür örneği alınmasının etiyolojik ajanı göstermede daha yararlı olacağı kanısına varıldı. Laboratuvar göstergelerden eritrosit sedimentasyon hızı yüksekliğinin özellikle 67.5 mm/h ve üzeri değerlerin bakteremiye işaret etmesi açısından daha anlamlı olduğu saptandı.

Anahtar Sözcükler: Akut faz reaktanı; bakteremi; kültür; selülit; yumuşak doku enfeksiyonu.