

## Patients with Positive Blood Cultures in Cellulitis: A Large Single-centre Study

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Cellulitis is a common skin infection primarily caused by group A beta-haemolytic streptococcus, with an estimated occurrence in developed countries of 6.4–24.6 cases per 1,000 person-years (1, 2). It typically presents as a unilateral spreading of erythema in the skin. Other possible symptoms include fever, chills and general malaise. In severe cases, cellulitis can lead to abscess formation, necrotizing fasciitis and septicæmia (2).

The diagnosis of cellulitis is based on clinical assessment, but laboratory tests may be useful to assess the severity of the infection (3). Blood cultures are used to detect bacteraemia (4). Estimates of the rate of positive blood cultures in patients with cellulitis vary between 4% and 21.7% (4, 5). Blood cultures are rarely positive in uncomplicated cellulitis; therefore, there are recommendations against routine application (6, 7). Rather, blood cultures should be reserved for patients with an elevated risk of bacteraemia, such as those of advanced age and those with multiple comorbidities (8).

Although earlier studies have identified some predictive factors for bacteraemia in patients with cellulitis, further research is needed to better clarify its risk profile and to find the patients at highest risk. This study aimed to identify comprehensively potential predisposing factors for bacteraemia in adult patients diagnosed with cellulitis in the secondary outpatient units of Northern Finland.

### MATERIAL AND METHODS

This was a retrospective electronic health record (EHR)-based study that included all patients aged  $\geq 18$  years who were diagnosed with cellulitis and had blood cultures drawn between 2019 and 2023 in the outpatient units of the Oulu University Hospital (OUH), which provides secondary healthcare for approximately 413,000 people. Cases of secondary cellulitis that occurred during the patient's hospitalization for other reasons were excluded. Individuals with cellulitis were identified from the records database with a search query for International Classification of Diseases (ICD-10) code A46 (erysipelas). In Finland, both cellulitis in general and its erysipelas form are diagnosed with the code A46. Data on patient demographics and relevant clinical parameters were extracted from EHRs by authors VK and JK.

Records of blood cultures were also extracted from the EHR. For the purposes of this study, the presence in the EHR of 2 positive blood samples, accompanied by clinically supportive findings, was considered to be indicative of bacteraemia.

Data are presented as means, standard deviation and range, and as proportions for categorical variables. The Mann–Whitney  $U$  test, Pearson's  $\chi^2$  test and Fisher's exact test, when appropriate, were used to test differences between variables. Multivariate logistic regression analysis was used to estimate crude and adjusted odds ratios (aORs) and their 95% confidence intervals (CIs). The following factors were included for adjustment: location of cellulitis, intravenous drug use, any complication of cellulitis that required surgical evaluation, C-reactive protein (CRP) peak level,  $\geq 150$  mg/L, systemic symptoms (fever and nausea), lymphedema, age (categorical; 30–49 years old as a reference) and sex. The data were analysed using the R software, package version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria). A  $p$ -value  $< 0.05$  was considered statistically significant.

### RESULTS

The data query returned 905 cases of retrospectively verified cellulitis. Of those, 790 (87.3%) had blood cultures taken and therefore met the inclusion criteria. Bacteraemia was detected in 11.5% of all cases. Of all positive blood cultures, the majority (49.5%) was caused by *Streptococcus* spp (mainly  $\beta$ -haemolytic *Streptococcus G/C*, 84.4%) and 30.8% by *Staphylococcus* spp (mainly *Staphylococcus aureus*, 75.0%). When patients were stratified by the bodily location of cellulitis, the rate of bacteraemia varied from 0.81% in the facial area to 30.0% in the genital area ( $p < 0.001$ ; **Table I**).

Systemic symptoms at the time of diagnosis were more common in cases with bacteraemia than in those without ( $p = 0.001$ ). A CRP level  $\geq 150$  mg/L was significantly associated with bacteraemia ( $p < 0.001$ ) as were abscesses requiring surgical treatment in the cellulitis area and lymphedema ( $p < 0.001$  and  $p < 0.05$ , respectively). Intravenous drug usage (26.4%) was the most commonly seen among the predefined risk factors for bacteraemia ( $p < 0.002$ ).

**Table I. Demographics and clinical characteristics of patients with negative and positive blood cultures**

	No bacteraemia	Bacteraemia	p-value	Crude OR	Adjusted OR
N	699	91			
Sex					
Female	295 (88.6)	38 (11.4)		Ref	Ref
Male	404 (88.4)	53 (11.6)		1.02 [0.65;1.59]	0.97 [0.59;1.60]
Age, mean, years	57.5 (17.6)	59.6 (17.9)	0.291		
Age group			0.323		
18–29	48 (85.7)	8 (14.3)		1.80 [0.69;4.34]	1.11 [0.35;3.17]
30–49	182 (91.5)	17 (8.54)		Ref	Ref
50–69	264 (88.9)	33 (11.1)		1.33 [0.73;2.52]	2.36 [1.12;5.36]
≥70	205 (86.1)	33 (13.9)		1.71 [0.93;3.26]	3.55 [1.64;8.28]
Location of cellulitis			<0.001		
Shin, calf, knee	304 (88.4%)	40 (11.6%)		1.02 [0.65;1.58]	
Upper extremity	121 (88.3%)	16 (11.7%)		1.02 [0.56;1.78]	
Facial area, auricle, neck	122 (99.2%)	1 (0.81%)		Not feasible	
Toe, foot, ankle	93 (80.9%)	22 (19.1%)		2.08 [1.20;3.48]	1.83 [0.99;3.29]
Thigh, gluteal region	30 (83.3)	6 (16.7%)		1.60 [0.58;3.73]	
Torso	13 (86.7)	2 (13.3%)		Not feasible	
Genital area	7 (70.0)	3 (30.0)		3.45 [0.69;13.0]	
Chest	8 (88.9)	1 (11.1)		Not feasible	
Predisposing factors			0.002		
Trauma in the area	226 (91.1)	22 (8.87)		0.67 [0.40;1.10]	
Tinea pedis	82 (88.2)	11 (11.8)		1.05 [0.51;1.98]	
Previous skin disease	41 (95.3)	2 (4.65)		Not feasible	
Breast cancer	21 (80.8)	5 (19.2)		1.92 [0.62;4.89]	
Surgery in the area	20 (95.2)	1 (4.76)		Not feasible	
Animal bite	13 (92.9)	1 (7.14)		Not feasible	
Obesity	298 (87.9)	41 (12.1)		1.10 [0.71;1.71]	
Diabetes	210 (86.1)	34 (13.9)		1.39 [0.87;2.18]	
Malignancy	123 (86.6)	19 (13.4)		1.24 [0.70;2.10]	
Lymphedema	90 (81.1)	21 (18.9)		2.04 [1.17;3.44]	1.91 [1.02;3.47]
Immunosuppression	90 (85.7)	15 (14.3)		1.34 [0.71;2.39]	
Intravenous drug use	53 (73.6)	19 (26.4)		3.22 [1.77;5.68]	7.92 [3.42;19.18]
Systemic symptoms <sup>a</sup>	269 (83.8)	52 (16.2)	0.001	2.13 [1.37;3.33]	1.79 [1.09;2.96]
Complication of cellulitis <sup>b</sup> that required surgical evaluation	88 (77.9)	25 (22.1)	<0.001	2.70 [1.61;4.56]	1.89 [1.05;3.33]
Cellulitis in patient history (any location)	257 (86.0)	42 (14.0)	0.105	1.61 [0.94;2.27]	
Number of recurrences			0.974		
1	115 (86.5)	18 (13.5)		Ref	
2–3	77 (85.6)	13 (14.4)		1.08 [0.49;2.34]	
>3	65 (85.5)	11 (14.5)		1.09 [0.47;2.43]	
CRP, peak level			<0.001		
≥150	282 (80.1)	70 (19.9)		4.89 [2.98;8.36]	4.02 [3.36;7.10]
<150	417 (95.2)	21 (4.79)		Ref	Ref

Data are presented as n (%) unless otherwise specified.

<sup>a</sup>Fever or nausea at the time of diagnosis; <sup>b</sup>Complication of cellulitis that required surgical evaluation (such as abscessus developed during the cellulitis).

After adjustment, the logistic regression analysis found that the following predisposing factors most increased the risk of bacteraemia: intravenous drug usage, CRP level  $\geq 150$  mg/L, age and cellulitis in the toe, foot or ankle.

## DISCUSSION

In this outpatient secondary care setting performed over a 5-year period, bacteraemia was detected in 11.5% of cases and possible risk factors for it were demonstrated. In the present study, the risk of bacteraemia increased with age. This finding aligns with that of an Israeli study ( $n=757$ ) that showed bacteraemia to be highest in cellulitis patients aged  $\geq 65$  (9). Correspondingly, a Japanese study ( $n=221$ ) reported the highest prevalence of bacteraemia in the oldest age group (4). Taken together, these results offer strong evidence for a correlation between advancing age and

the prevalence of bacteraemia in patients with cellulitis. More intravenous drug usage increased the risk of bacteraemia nearly 8-fold. Very few studies, and none directly comparable to ours, have taken this variable into account (10, 11): In a previous Finnish study, 3 out of 15 intravenous drug users had bacteraemia, but this study included all types of skin infections, not only cellulitis (11). A Spanish study that analysed factors associated with sepsis development in cellulitis patients found that none of the 7 intravenous drug users had sepsis but did not report the bacteraemia rate for these patients (10).

We found that a markedly elevated CRP level increased the risk of bacteraemia 4-fold. In a Swiss study ( $n=250$ ), the mean CRP level among cellulitis patients with bacteraemia was 187.0 mg/L compared with 115.6 mg/L in nonbacteraemic patients (12). However, it is difficult to compare the findings of other studies with our own because of differences in how CRP

was measured. For example, some studies measured CRP at admission (12), while others did not specify the timing (4).

The presence of systemic symptoms was associated with a 1.8-fold greater risk of bacteraemia. Correspondingly, in a Swiss study, fever was detected in 75.0% of bacteraemic patients, and in 39.9% of nonbacteraemic patients 1 h before blood cultures were taken (12). Interestingly, we found that cellulitis in the foot was an independent risk factor of bacteraemia. This contradicts a Spanish study that reported an association between bacteraemia and proximal cellulitis (13). We also demonstrated that the presence of a complication of cellulitis that required surgical evaluation was associated with an elevated risk of bacteraemia, a finding that was also absent from the Spanish study (13).

The main strength of our study is its large cohort, which included all patients who were diagnosed with cellulitis at the OUH and had blood cultures drawn. This design ensures that the findings are relevant to the general population diagnosed at hospital outpatient units. As a limitation, data for some parameters are missing because of the retrospective nature of the study, which relied on medical records. In addition, the hospital setting may have introduced bias towards more severe cases of cellulitis. However, most previous studies were also conducted in hospitals.

In conclusion, we found blood cultures are negative in most cases of cellulitis. Blood cultures are costly and in Finnish clinical practice, 2 sets of cultures are drawn. Our findings further support previous recommendations that blood cultures should not be routinely performed but should rather be administered only to patients with risk factors for bacteraemia (6). Our findings regarding risk factors for bacteraemia in cellulitis help to define the subgroup of patients from whom blood cultures should be drawn.

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*Data availability statement:* Data requests can be submitted to hospital administrative authority.

*Ethical statement:* The approval of the medical director of OUH was received for the study.

*The authors have no conflicts of interest to declare.*

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