JDA Japanese Dermatological Association
The Journal of Dermatology

doi: 10.1111/1346-8138.12922 *Journal of Dermatology* 2015; **42**: 778–785

ORIGINAL ARTICLE

Use of procalcitonin, C-reactive protein and white blood cell count to distinguish between lower limb erysipelas and deep vein thrombosis in the emergency department: A prospective observational study

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ABSTRACT

Early differentiation of erysipelas from deep vein thrombosis (DVT) based solely on clinical signs and symptoms is challenging. There is a lack of data regarding the usefulness of the inflammatory biomarkers procalcitonin (PCT), C-reactive protein (CRP) and white blood cell (WBC) count in the diagnosis of localized cutaneous infections. Herein, we investigated the diagnostic value of inflammatory markers in a prospective at-risk patient population. This is an observational quality control study including consecutive patients presenting with a final diagnosis of either erysipelas or DVT. The association of PCT (μg/L) and CRP (mg/L) levels and WBC counts (g/L) with the primary outcome was assessed using logistic regression models with area under the receiver–operator curve. Forty-eight patients (erysipelas, *n* = 31; DVT, *n* = 17) were included. Compared with patients with DVT, those with erysipelas had significantly higher PCT concentrations. No significant differences in CRP concentrations and WBC counts were found between the two groups. At a PCT threshold of 0.1 μg/L or more, specificity and positive predictive values (PPV) for erysipelas were 82.4% and 85.7%, respectively, and increased to 100% and 100% at a threshold of more than 0.25 μg/L. Levels of PCT also correlated with the severity of erysipelas, with a stepwise increase according to systemic inflammatory response syndrome criteria. We found a high discriminatory value of PCT for differentiation between erysipelas and DVT, in contrast to other commonly used inflammatory biomarkers. Whether the use of PCT levels for early differentiation of erysipelas from DVT reduces unnecessary antibiotic exposure needs to be assessed in an interventional trial.

Key words: cellulitis, deep vein thrombosis, erysipelas, lower limb, procalcitonin.

INTRODUCTION

Erysipelas is an infectious condition of the skin that is predominantly caused by streptococci and frequently affects the lower limb. Well-known risk factors for erysipelas include edema and lymphedema, cutaneous barrier rupture, a history of leg surgery, and superficial or deep venous insufficiency.[1–6] Erysipelas is currently an empiric clinical diagnosis based on the local presentation and systemic signs of infection because more specific microbiological tests have low sensitivity, with blood cultures becoming positive in fewer than 5% of all cases.[7–9] Hence, early differentiation between erysipelas and other causes of painful swelling of the lower limb – such as deep vein thrombosis (DVT) – remains a difficult task for the physician because of the overlap in clinical signs at presentation, including unilateral limb swelling, redness and pain.[10] The current gold standards in DVT diagnosis are duplex sonography, which has high sensitivity and specificity (both ~95%), and duplex sonography in combination with D-dimer testing in low-to-moderate risk subjects, respectively.[11,12] However, the diagnostic accuracy of both sonography and D-dimers may be compromised in the case of skin infections and erysipelas due to false-positive results.[13] Early and accurate differentiation between these two conditions is crucial to make decisions regarding initiation of antibiotic treatment in the case of erysipelas or anticoagulant therapy in the case of DVT.

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Received 3 February 2015; accepted 24 March 2015.

A current approach to the early diagnosis or ruling out of bacterial infections in the emergency department (ED) is the use of concentrations of inflammatory biomarkers such as procalcitonin (PCT).[14] First described in 1993 as an infection marker,[15] serum PCT has emerged as a biomarker for the diagnosis of systemic bacterial infections with greater accuracy compared to clinical characteristics or commonly used laboratory parameters such as concentrations of C-reactive protein (CRP) or white blood cell (WBC) counts in the serum.[16–18] Particularly for respiratory infections, interventional trials and meta-analyses have found significant reductions in antibiotic (over-) use when PCT was used to guide antibiotic stewardship.[19,20] Exclusion of clinically relevant bacterial pneumonia in need of antimicrobial therapy on the basis of low PCT concentrations, for example, in patients with a clinical presentation of lower respiratory tract infection significantly reduces antibiotic exposure without adversely affecting clinical outcomes.[21] For skin infections such as erysipelas, however, clinical studies investigating the diagnostic performance of PCT and other more traditional inflammatory markers for differential diagnosis are currently scarce. To our knowledge, there is one "pilot study" that investigated the correlation of PCT with the alleged severity of skin infection; this study, however, did not include a control group.[22] A very recent study looked at the value of PCT and interleukin-6 in patients with bullous impetigo and staphylococcal scalded skin syndrome.[23] Finally, a review paper discussed the value of PCT in localized skin and skin structure infection, diabetic foot infections, septic arthritis and osteomyelitis.[24]

The aim of our study was to investigate the diagnostic value of PCT levels as compared with CRP levels and WBC counts in a consecutive at-risk population of patients presenting with either erysipelas or DVT of the lower limb to the ED of a tertiary care hospital in Switzerland.

METHODS

Study design

We prospectively included consecutive adult patients presenting to the ED who had a final diagnosis of erysipelas or DVT of the lower limb (as defined below) between 1 March 2013 and 31 March 2014, independent of other medical conditions. After being examined in the ED, adult general medical patients were included in an observational biobanking study that included a blinded 30-day telephone follow up, entitled the TRIAGE study.[25] This study has been registered at the ClinicalTrials.gov registration website (http://www.clinicaltrials.gov/ct2/show/NCT01768494). In view of the fact that it is an observational quality control study, the institutional review board of the Canton of Aargau approved the study and waived the need for informed consent (EK 2012/059).

Definitions

The definition of erysipelas was based on the clinical diagnosis of the treating physician team (i.e, signs of systemic infection with concomitant typical clinical presentation of erysipelas of the lower limb). Microbiological proof of infection (i.e. positive bacterial cultures) was not required. Because of overlapping presentations in diffuse superstitial spreading skin infections of the lower limb, cellulitis and erysipelas may have been used synonymously in clinical practice of the study site. Therefore, we will use the term "erysipelas" possibly referring to both entities in this report.[26,27] For diagnosis of DVT, validation by color-coded duplex sonography was mandatory. Patients with other concomitant bacterial infections ($n = 7$) were excluded from the main analysis.

Clinical assessment

Data on pertinent clinical variables including common risk factors for erysipelas described in the published work (e.g. edema, chronic venous insufficiency, ulceration, tinea pedis, trauma, obesity, white ethnicity and previous erysipelas) were collected upon admission in all patients.[1–6] To estimate the severity of disease, we used adapted systemic inflammatory response syndrome (SIRS) criteria, defined as temperature of less than 36°C or more than 38.3°C, heart rate of more than 90 b.p.m., WBC of less than 4 or more than 12 g/L and oxygen saturation of less than 90%.

Biomarker measurements

As part of the study protocol, CRP levels (mg/L) and WBC counts (g/L) were measured upon admission in all patients as part of the routine laboratory assessments. Concentrations of CRP were determined by an enzyme immunoassay having a lower limit of detection of less than 0.5 mg/L (EMIT; Merck Diagnostica, Zurich, Switzerland). Concentrations of PCT (μg/L) were measured after study termination by a blinded member of the central laboratory using a time-resolved amplified cryptate emission technology assay (Kryptor PCT; Brahms, Hennigsdorf, Germany) with a lower limit of detection of 0.02 μg/L. Collection of blood or tissue cultures was not mandatory and up to the treating physicians.

Statistical analysis

To evaluate differences between groups, the Mann–Whitney *U*-test and Fisher's exact test were used for non-parametric continuous variables and categorical variables, respectively, as appropriate. The diagnostic value of the individual laboratory markers for differentiating between erysipelas and DVT was compared by receiver–operator curve (ROC) analysis. The area under the ROC (AUC) was the measure of the accuracy of the laboratory parameter to distinguish between the two groups. $P < 0.05$ (for a two-sided test) was considered statistically significant. All calculations were performed using statistical software STATA for Windows version 12.1 (StataCorp, College Station, TX, USA).

RESULTS

Study population

Out of a total of 55 patients (35 patients with erysipelas and 20 patients with DVT), seven patients were excluded due to concomitant bacterial infections (urinary tract infection [$n = 3$], gastrointestinal infection [$n = 3$] and osteomyelitis [$n = 1$]). The

final patient population thus comprised 48 patients (31 patients with erysipelas and 17 patients with DVT).

Baseline characteristics of the patients included in the study are presented in Table 1. The median age of the patients was 64 years and 52% were male. Patients had a high burden of comorbidities including hypertension (n = 19), diabetes (n = 12) and chronic renal failure (n = 10). Underlying comorbidities were equally distributed in both groups, except for a higher body mass index in erysipelas patients. Other common risk factors for erysipelas were also not significantly different between the two groups. Blood cultures were collected from 26 (84%) of the erysipelas patients in the ED, with two of them (7.7%) showing positive growth with *Streptococcus dysgalactiae equisimilis* and coagulase-negative staphylococci (possible contamination). Within the 30-day follow-up period, one patient with erysipelas died early after discharge from the hospital.

Clinical presentation and biomarkers in patients with erysipelas and DVT

There was no difference between the two groups with regard to the distribution of SIRS criteria (Table 1). Figure 1(a) shows the levels of the three biomarkers according to the final diagnosis of erysipelas or DVT. Significant differences between the groups were seen only for PCT concentrations but not for CRP concentrations or WBC counts. As shown in Table 2, there was a significant association of logarithmic PCT and erysipelas with an adjusted odds ratio (OR) of 63.04 (95% confidence

Table 1. Baseline patient characteristics

	All	Erysipelas	DVT	*P*
n	48	31	17	
Sociodemographics				
Age, mean (SD)	64 (15)	62 (15)	67 (16)	0.370
Male sex	25 (52%)	18 (58%)	7 (41%)	0.260
BMI*	29.6 (25.6, 34.8)	33.0 (27.5, 35.4)	25.9 (24.8, 31.4)	0.025
Comorbidities (%)				
Coronary heart disease	2 (4)	1 (3)	1 (6)	0.660
Diabetes	12 (25)	9 (29)	3 (18)	0.380
Chronic renal failure	10 (21)	7 (23)	3 (18)	0.690
Hypertension	19 (40)	10 (32)	9 (52)	0.160
Anemia	5 (10)	3 (10)	2 (12)	0.820
Immunosuppression	6 (13)	3 (10)	3 (18)	0.420
Tumor disease	5 (10)	2 (6)	3 (18)	0.220
Vital signs on admission				
Systolic blood pressure, mmHg*	141 (130, 153)	141 (130, 152)	136 (110, 155)	0.550
Diastolic blood pressure, mmHg*	77 (71, 90)	77 (71, 90)	77 (67, 86)	0.360
Pulse, b.p.m.*	87.5 (76, 100)	86 (72, 93)	95 (77, 107)	0.098
Temperature, °C*	37.3 (36.9, 38)	37.6 (37.1, 38.1)	37.1 (36.7, 37.3)	0.071
Oxygen saturation, %*	95 (93, 96)	96 (94, 97)	93 (89, 96)	0.088
Respiratory rate, b.p.m.*	19 (16, 22)	18 (15, 20)	22 (16, 24)	0.250
SIRS (%)				
0 SIRS criteria	18 (38)	13 (42)	5 (29)	0.320
1 SIRS criteria	15 (31)	10 (32)	5 (29)	
2 SIRS criteria	13 (27)	6 (19)	7 (41)	
3 SIRS criteria	2 (4)	2 (6)	0 (0)	
Common risk factors for erysipelas (%)				
Chronic venous insufficiency	4 (8)	3 (10)	1 (6)	0.650
Past history of erysipelas	1 (2)	1 (4)	0 (0)	0.420
Eczema	4 (8)	4 (13)	0 (0)	0.120
Tinea pedis	5 (10)	5 (16)	0 (0)	0.080
Lymphadenopathy/edema	7 (15)	6 (19)	1 (6)	0.210
Edema	22 (46)	14 (45)	8 (47)	0.900
Initial laboratory work-up				
PCT, μg/L*	0.09 (0.07, 0.22)	0.17 (0.08, 0.67)	0.08 (0.07, 0.9)	0.001
CRP, mg/L*	59 (16, 111)	76 (15, 165)	33 (21, 86)	0.200
WBC, g/L*	9.6 (7.6, 12.2)	10.7 (8.2, 13.8)	8.6 (7.4, 11.1)	0.140
Management of patients				
Length of hospital stay, days*	6 (4, 9)	7 (5, 10)	6 (4, 9)	0.370
Death within 30 days	1 (2%)	1 (3%)	0 (0%)	0.450

*Median (interquartile range). BMI, body mass index; CRP, C-reactive protein; DVT, deep vein thrombosis; PCT, procalcitonin; SD, standard deviation; SIRS, systemic inflammatory response syndrome; WBC, white blood cell.

interval [CI], 1.5–2612.1; $P = 0.03$). The OR was adjusted for age, sex and comorbidities (diabetes, immunosuppression, tumors and chronic renal failure). The corresponding OR for CRP and WBC were 1.82 (95% CI, 0.5–6.1; $P = 0.33$) and 1.91 (95% CI, 0.1–50.1; $P = 0.70$), respectively.

Patients with erysipelas had significantly higher concentrations (median, interquartile range [IQR]) of PCT compared with patients with DVT (0.17 μg/L [0.08–0.67] vs 0.08 μg/L [0.07–0.09], respectively; $P = 0.001$, AUC = 0.79) (Table 1 and Fig. 1b). No significant differences were seen between the two groups with regard to CRP concentrations (76 mg/L [15–165] vs 33 mg/L [21–86], respectively; $P = 0.20$, AUC = 0.61) and WBC counts (10.7 g/L [8.2–13.8] vs 8.6 g/L [7.4–11.1], respectively; $P = 0.14$, AUC = 0.63).

Figure 2 shows PCT concentrations in patients with erysipelas and DVT stratified according to SIRS criteria. Concentrations of PCT increased in patients with erysipelas with each additional SIRS criterion being present (ANOVA, $P = 0.02$), while no differences in PCT levels were seen in patients with DVT regardless of the number of SIRS criteria.

Performance of PCT with regard to diagnosis of erysipelas

At a PCT threshold of 0.1 μg/L or more, the specificity and PPV for erysipelas were 82.4% (95% CI, 56.6–96.2%) and 85.7% (95% CI, 63.7–97%), respectively. Both specificity and PPV increased to 100% at the more than 0.25 μg/L and more than 0.5 μg/L thresholds. Sensitivity values at the PCT

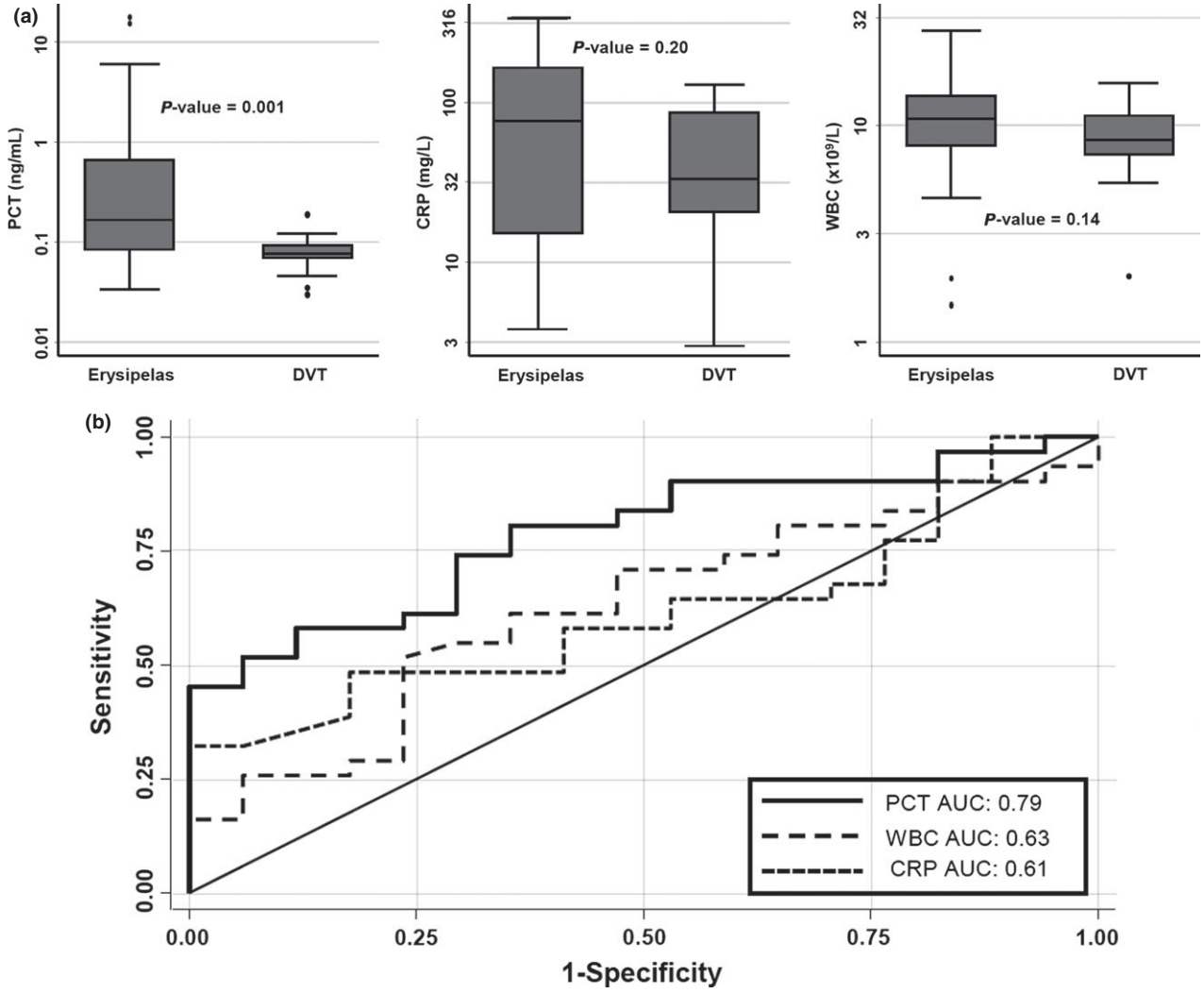

Figure 1. (a) Biomarker levels in patients with erysipelas compared to those with deep vein thrombosis (DVT). Procalcitonin (PCT) shows significantly higher levels in erysipelas patients compared with DVT patients, while levels of C-reactive protein (CRP) and white blood cell (WBC) were similar in these two groups. (b) Results of receiver–operator curve analysis for all biomarkers. Procalcitonin showed the highest discriminatory value as compared with CRP and WBC. AUC, area under the receiver–operator curve.

Table 2. Results of logistic regression analysis

		Unadjusted	Adjusted*	AUC
PCT†	OR	30.28	63.04	0.79
	95% CI	1.7–540.6	1.5–2612.1	
	P	0.02	0.03	
CRP†	OR	1.99	1.82	0.61
	95% CI	0.7–5.9	0.5–6.1	
	P	0.21	0.33	
WBC†	OR	3.09	1.91	0.63
	95% CI	0.3–36.4	0.1–50.1	
	P	0.37	0.70	

*Adjusted for age, sex and comorbidities (diabetes, immunosuppression, tumors and chronic renal failure). †Log transformed. AUC, area under the receiver–operator curve; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; DVT, deep vein thrombosis; OR, odds ratio; PCT, procalcitonin; SD, standard deviation; SIRS, systemic inflammatory response syndrome; WBC, white blood cell.

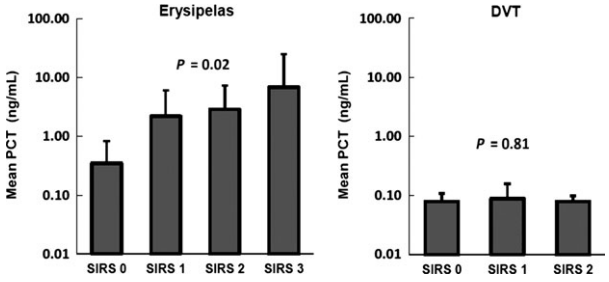

Figure 2. Procalcitonin (PCT) levels according to systemic inflammatory response syndrome (SIRS) criteria in erysipelas and deep vein thrombosis (DVT) patients. Levels of PCT increased with severity of erysipelas patients defined as more SIRS criteria, while no such increase was observed for patients with DVT.

thresholds of 0.1 μg/L or more, more than 0.25 μg/L and more than 0.5 μg/L were 58.1% (95% CI, 39.1–75.5%), 35.5% (95% CI, 19.2–54.6%) and 32.2% (95% CI, 16.7–51.4%), respectively (Table 3).

Performance of PCT in the overall population including patients with concomitant bacterial infection

With inclusion of the seven patients with concomitant bacterial infections, the performance of PCT was slightly inferior (AUC = 0.76 for the overall differentiation). However, sensitivity (62.9%, 37.1% and 34.3%) as well as specificity (75%, 90% and 95%) were still reasonable at the 0.1 or more, more than 0.25 and more than 0.5 μg/L cut-offs, respectively (Table 3).

DISCUSSION

The main findings of this study are threefold. First, circulating PCT levels have a superior diagnostic accuracy for the differentiation of erysipelas from DVT as compared with other routinely used inflammatory biomarkers including CRP concentrations and WBC counts. Second, PCT at a cut-off value of more than 0.25 μg/L showed a high PPV (and specificity) to establish the diagnosis of erysipelas and thus may help to recognize this condition early in ED patients with a clinical presentation of a possible skin infection. Third, a low PCT concentration (<0.1 μg/L) did not ultimately rule out erysipelas (negative predictive value [NPV] = 51.9%). This may be explained by the fact that PCT concentrations remain relatively low in non-severe, localized, non-systemic infections (i.e. early erysipelas), which was mirrored in our study by an association of PCT concentrations with the number of SIRS criteria seen in a patient.

There is currently no reference gold standard for the diagnosis of erysipelas mainly due to the low sensitivity of microbiological tests such as blood and tissue cultures. Failure to correctly identify erysipelas and to prescribe antibiotic therapy can be associated with increased morbidity and even mortality. Many cutaneous conditions – including DVT – may clinically mimic diffuse soft-tissue infections as erysipelas and cellulitis. A recent randomized trial found that dermatology consultation in the primary care setting improved the diagnostic accuracy of suspected cellulitis and decreased unnecessary antibiotic use in patients with "pseudocellulitic" conditions.[28] Thus, it is likely that antibiotic therapy may be misused in this patient population, resulting in unnecessary costs, side-effects and facilitating the emergence of resistant strains of bacteria. Whether inflammatory biomarkers mirroring the extent and severity of bacterial infection may improve the diagnostic work-up has not been systematically investigated. Our data demonstrating a relatively high discriminatory value of PCT levels in distinguishing between erysipelas and DVT are interesting and may open new avenues for future research.

A growing body of evidence supports the use of PCT concentrations to improve diagnosis of bacterial infections and to guide antibiotic therapy for several reasons. First, due to its regulation, PCT is more specific towards bacterial infections than are other inflammatory biomarkers such as CRP and WBC. Moreover, PCT is upregulated by microbial toxins and pro-inflammatory mediators such as interleukin-1β, tumor necrosis factor-α and interleukin-6, and is downregulated as concentrations of these substances subside during recovery. Importantly, PCT expression is attenuated by cytokines typically released during viral infection (e.g. γ-interferon).[29] Therefore, by flagging the presence and tracking the status of systemic bacterial infection, PCT measurements aid in determining the risk and course of sepsis as well as the efficacy of sepsis treatment.[30,31] Second, clinical studies have found PCT to be helpful in identifying the risk of sepsis and bacteremia. A 2007 meta-analysis including 17 observational studies totaling more than 2000 patients found a high discriminatory value of PCT (AUC = 0.84) for bacteremia.[32] In patients with respiratory infections, bacteremic disease was highly unlikely if PCT levels remained below 0.25 μg/L.[33] Patients showing growth of coagulase-negative staphylococci in blood cultures and low PCT concentrations had a high NPV to rule out "true bacteremia" and predict culture contamination.[34] Third, in patients presenting with SIRS, PCT has shown high accuracy in differentiating true infection from other causes. A recent meta-analysis

Table 3. Diagnostic performance of procalcitonin in diagnosing erysipelas

PCT cut-off	Sensitivity (95% CI)	Specificity (95% CI)	LR+	LR−	PPV (95% CI)	NPV (95% CI)
Patients with concomitant infections excluded (n = 48; 31 erysipelas, 17 DVT)						
≥0.1 μg/L	58.1% (39.1–75.5%)	82.4% (56.6–96.2%)	3.3 (1.1–9.6)	0.5 (0.3–0.8)	85.7% (63.7–97%)	51.9% (31.9–71.3%)
>0.25 μg/L	35.5% (19.2–54.6%)	100.0% (80.5–100%)	N/A N/A	0.7 (0.5–0.8)	100.0% (71.5–100%)	45.9% (29.5–63.1%)
>0.5 μg/L	32.2% (16.7–51.4%)	100.0% (80.5–100%)	N/A N/A	0.7 (0.5–0.9)	100.0% (69.2–100%)	44.7% (28.6–61.7%)
Patients with concomitant infections included (n = 55; 35 erysipelas, 20 DVT)						
≥0.1 μg/L	62.9% (44.9–78.5%)	75.0% (50.9–91.3%)	2.5 (1.1–5.6)	0.5 (0.3–0.8)	81.5% (61.9–93.7%)	53.6% (33.9–72.5%)
>0.25 μg/L	37.1% (21.5–55.1%)	90.0% (68.3–98.8%)	3.7 (0.9–14.8)	0.7 (0.5–0.9)	86.7% (59.5–98.3%)	45.0% (29.3–61.5%)
>0.5 μg/L	34.3% (19.1–52.2%)	95.0% (75.1–99.9%)	6.9 (1–48.9)	0.7 (0.5–0.9)	92.3% (64.0–99.8%)	45.2% (29.8–61.3%)

CI, confidence interval; DVT, deep vein thrombosis; LR+, positive likelihood ratio; LR−, negative likelihood ratio; NPV, negative predictive value; PCT, procalcitonin; PPV, positive predictive value.

including 30 high-quality observational studies totaling more than 3200 patients found PCT to have an overall AUC of 0.85 to differentiate sepsis from SIRS in different settings.[35] Results were similar for medical, surgical or pediatric patients, with sensitivities and specificities of 75–80%. These results are in line with the findings of the current study. In addition, PCT-guided disease management has been shown to improve choices regarding initiation and duration of antibiotic treatment in patients with bacterial infections. Evidence from interventional studies demonstrates that in mostly septic patients with respiratory infection, PCT protocols led to dramatic diminution in antibiotic (over-) exposure.[36] Protocols using serially measured PCT concentrations to guide early antibiotic treatment discontinuation have been shown to result in sharp (30–70%) reductions in antibiotic consumption if cut-off ranges adequate for the clinical setting have been applied. A recent individual patient data meta-analysis including more than 4200 ED patients and patients with pneumonia from completed randomized trials found that antibiotic exposure decreased from a median of 8 days to 4 days in PCT arms versus control arms.[19]

In addition to its diagnostic use, PCT has also been found to have prognostic value due to its association with severity of disease and clinical outcome.[37] It has proven to be better than CRP or WBC in detecting serious bacterial infection among children with fever of no apparent source. A US study found an approximately 90% NPV for sepsis mortality when PCT dropped by 80% or more within 72 h of intensive care unit admission.[38] When PCT levels did not decrease or even when they increased, PPV were around 36–48%. A study looking particularly at patients with complicated and uncomplicated skin and skin structure infections also found that PCT showed a good correlation with severity of infection.[22] In line with these findings, we also found a stepwise increase in PCT levels with the number of SIRS criteria being present in patients.

Our study has some limitations. First, the small number of patients included limits the power of this study, as a result of which results may be more hypothesis-generating than definite. Second, due to a lack of a true gold standard, the diagnosis of erysipelas may not have been correct in all patients and we did not seek dermatological evaluation in all patients. Third, follow-up measurements of PCT during hospitalization were not done and could have provided further important kinetic information. Finally, our data is observational and interventional trials are needed to investigate whether PCT-guided therapy would improve antibiotic management of these patients. Towards this aim, we believe that our data provide an interesting first step towards further exploration of this concept.

In conclusion, this study found a high discriminatory value of PCT for differentiation of erysipelas from DVT which was superior to other more routinely used biomarkers such as CRP and WBC. Whether the use of PCT reduces unnecessary antibiotic exposure needs to be assessed in an interventional trial.

ACKNOWLEDGMENTS: We are indebted to the emergency room team (Ulrich Buergi, Petra Tobias and colleagues), medical clinic (nursing department: Susanne Schirlo), the staff of the central laboratory (Martha Kaeslin, Ursina Minder and Renate Hunziker), the study nurses of the TRIAGE study (Katharina Regez, Ursula Schild, Merih Guglielmetti, Zeljka Caldara and Sonja Schwenne), and the staff members of the IT department (Roger Wohler, Kurt Amstad, Ralph Dahnke, Hans Fischer and Sabine Storost) at the Kantonsspital Aarau, Switzerland for their assistance with the conduct of this study. We especially thank the Goldschmidt Jacobson Foundation, Basel, Switzerland, for supporting ACR during the study. Editorial support was provided by Prasad Kulkarni, Ph.D., C.M.P.P. of Asclepius Medical Communications, Ridgewood, NJ, USA and was funded by the authors. This study was supported in part by the Goldschmidt Jacobson Foundation, Basel, Switzerland, the Swiss National Science Foundation (SNSF Professorship, PP00P3_150531/1) and internal funds of the Kantonsspital Aarau. Author contributions are as follows. Knobel and Schuetz had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Rast, Knobel, Faessler, Schuetz, Haubitz, and Mueller. Acquisition, analysis and interpretation of data: Rast, Knobel, Kutz, Steiner,

Felder, Laukemann, Fux, Huber, and Schuetz. Drafting of the manuscript: Rast, Knobel and Schuetz. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Rast, Knobel and Schuetz. Obtained funding: Mueller and Schuetz. Administrative, technical or material support: Huber, Faessler and Haubitz. Study supervision: Fux, Huber, Mueller and Schuetz.

CONFLICT OF INTEREST: Miss Rast was supported by the Goldschmidt Jacobson Foundation, Basel, Switzerland. Drs Kutz, Mueller and Schuetz have received financial support from Thermo Fisher Scientific Biomarkers to attend meetings and fulfill speaking engagements. Drs Mueller and Schuetz have received financial support from bioMérieux to attend meetings and fulfill speaking engagements and have received research grants from both companies. Dr Mueller has served as a consultant to Thermo Fisher Scientific Biomarkers and bioMérieux. All other authors have no financial conflicts of interest to disclose. The funding sources had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1 Cox NH. Oedema as a risk factor for multiple episodes of cellulitis/erysipelas of the lower leg: a series with community follow-up. *Br J Dermatol* 2006; **155**(5): 947–950.
2 Roujeau JC, Sigurgeirsson B, Korting HC *et al.* Chronic dermatomycoses of the foot as risk factors for acute bacterial cellulitis of the leg: a case-control study. *Dermatology* 2004; **209**(4): 301–307.
3 Halpern J, Holder R, Langford NJ. Ethnicity and other risk factors for acute lower limb cellulitis: a U.K.-based prospective case-control study. *Br J Dermatol* 2008; **158**(6): 1288–1292.
4 Bjornsdottir S, Gottfredsson M, Thorisdottir AS *et al.* Risk factors for acute cellulitis of the lower limb: a prospective case-control study. *Clin Infect Dis* 2005; **41**(10): 1416–1422.
5 Mokni M, Dupuy A, Denguezli M *et al.* Risk factors for erysipelas of the leg in Tunisia: a multicenter case-control study. *Dermatology* 2006; **212**: 108–112.
6 Dupuy A, Benchikhi H, Roujeau JC *et al.* Risk factors for erysipelas of the leg (cellulitis): case-control study. *BMJ* 1999; **318**(7198): 1591–1594.
7 Gunderson CG, Martinello RA. A systematic review of bacteremias in cellulitis and erysipelas. *J Infect* 2012; **64**: 148–155.
8 Phoenix G, Das S, Joshi M. Diagnosis and management of cellulitis. *BMJ* 2012; **345**: e4955.
9 Stevens DL, Bisno AL, Chambers HF *et al.* Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. *Clin Infect Dis* 2014; **59**: 147–159.
10 ten Cate-Hoek AJ, van der Velde EF, Toll DB *et al.* Common alternative diagnoses in general practice when deep venous thrombosis is excluded. *Neth J Med* 2012; **70**(3): 130–135.
11 van Gemmeren D, Fobbe F, Ruhnke-Trautmann M *et al.* Diagnosis of deep leg vein thrombosis with color-coded duplex sonography and sonographic determination of the duration of the thrombosis. *Z Kardiol* 1991; **80**(8): 523–528.
12 Tick LW, Ton E, van Voorthuizen T *et al.* Practical diagnostic management of patients with clinically suspected deep vein thrombosis by clinical probability test, compression ultrasonography, and D-dimer test. *Am J Med* 2002; **113**(8): 630–635.
13 Mazzolai L, Haesler E, Milesi I *et al.* D-dimers testing is not recommended for the exclusion of deep vein thrombosis in outpatients with lower limb erysipelas. *Thromb Haemost* 2002; **88**(5): 880.
14 Schuetz P, Aujesky D, Muller C *et al.* Biomarker-guided personalised emergency medicine for all - hope for another hype? *Swiss Med Wkly* 2015; **145**: w14079.
15 Assicot M, Gendrel D, Carsin H *et al.* High serum procalcitonin concentrations in patients with sepsis and infection. *Lancet* 1993; **341** (8844): 515–518.
16 Simon L, Gauvin F, Amre DK *et al.* Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. *Clin Infect Dis* 2004; **39**(2): 206–217.
17 Delevaux I, Andre M, Colombier M *et al.* Can procalcitonin measurement help in differentiating between bacterial infection and other kinds of inflammatory processes? *Ann Rheum Dis* 2003; **62**(4): 337–340.
18 Christ-Crain M, Jaccard-Stolz D, Bingisser R *et al.* Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet* 2004; **363**(9409): 600–607.
19 Schuetz P, Christ-Crain M, Thomann R *et al.* Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA* 2009; **302**: 1059–1066.
20 Schuetz P, Briel M, Christ-Crain M *et al.* Procalcitonin to guide initiation and duration of antibiotic treatment in acute respiratory infections: an individual patient data meta-analysis. *Clin Infect Dis* 2012; **55**: 651–662.
21 Schuetz P, Kutz A, Grolimund E *et al.* Excluding infection through procalcitonin testing improves outcomes of congestive heart failure patients presenting with acute respiratory symptoms: results from the randomized ProHOSP trial. *Int J Cardiol* 2014; **175**(3): 464–472.
22 Eder J, Hlavin G, Haushofer A *et al.* Correlation of serum procalcitonin with the severity of skin and skin structure infections – a pilot study. *J Dtsch Dermatol Ges* 2012; **10**(8): 564–571.
23 Zeng M, Guo Z, Shen S *et al.* Value of serum procalcitonin and interleukin-6 in patients with bullous impetigo and staphylococcal scalded skin syndrome. *J Dermatol* 2014; **41**: 1028–1029.
24 Saeed K, Ahmad N, Dryden M. The value of procalcitonin measurement in localized skin and skin structure infection, diabetic foot infections, septic arthritis and osteomyelitis. *Expert Rev Mol Diagn* 2014; **14**(1): 47–54.
25 Schuetz P, Hausfater P, Amin D *et al.* Optimizing triage and hospitalization in adult general medical emergency patients: the triage project. *BMC Emerg Med* 2013; **13**: 12.
26 Hirschmann JV, Raugi GJ. Lower limb cellulitis and its mimics: part II. Conditions that simulate lower limb cellulitis. *J Am Acad Dermatol* 2012; **67**(2): 177 e1–177 e9; quiz 85–86.
27 Hirschmann JV, Raugi GJ. Lower limb cellulitis and its mimics: part I. Lower limb cellulitis. *J Am Acad Dermatol* 2012; **67**(2): 163 e1–163 e12; quiz 75–76.
28 Arakaki RY, Strazzula L, Woo E *et al.* The impact of dermatology consultation on diagnostic accuracy and antibiotic use among patients with suspected cellulitis seen at outpatient internal medicine offices: a randomized clinical trial. *JAMA Dermatol* 2014; **150**: 1056–1061.
29 Linscheid P, Seboek D, Schaer DJ *et al.* Expression and secretion of procalcitonin and calcitonin gene-related peptide by adherent monocytes and by macrophage-activated adipocytes. *Crit Care Med* 2004; **32**(8): 1715–1721.
30 Schuetz P, Muller B, Christ-Crain M *et al.* Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database Syst Rev* 2012; (9): CD007498.
31 Schuetz P, Christ-Crain M, Muller B. Procalcitonin and other biomarkers to improve assessment and antibiotic stewardship in infections–hope for hype? *Swiss Med Wkly* 2009; **139**(23–24): 318–326.
32 Jones AE, Fiechtl JF, Brown MD *et al.* Procalcitonin test in the diagnosis of bacteremia: a meta-analysis. *Ann Emerg Med* 2007; **50**(1): 34–41.
33 Muller F, Christ-Crain M, Bregenzer T *et al.* Procalcitonin levels predict bacteremia in patients with community-acquired pneumonia: a prospective cohort trial. *Chest* 2010; **138**(1): 121–129.

34 Schuetz P, Mueller B, Trampuz A. Serum procalcitonin for discrimination of blood contamination from bloodstream infection due to coagulase-negative staphylococci. *Infection* 2007; **35**(5): 352–355.
35 Wacker C, Prkno A, Brunkhorst FM *et al.* Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. *Lancet Infect Dis* 2013; **13**: 426–435.
36 Schuetz P, Chiappa V, Briel M *et al.* Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. *Arch Intern Med* 2011; **171**(15): 1322–1331.
37 Auriti C, Fiscarelli E, Ronchetti MP *et al.* Procalcitonin in detecting neonatal nosocomial sepsis. *Arch Dis Child Fetal Neonatal Ed* 2012; **97**(5): F368–F370.
38 Schuetz P, Maurer P, Punjabi V *et al.* Procalcitonin decrease over 72 hours in US critical care units predicts fatal outcome in sepsis patients. *Crit Care* 2013; **17**(3): R115.

