Procalcitonin and cellulitis: Cohort study of the correlation of procalcitonin blood levels with severity and outcome in patients with limb cellulitis

Richard Brindle, Asim Ijaz, Paul Davies,
University of Bristol, Public Health England, Morecambe Bay NHS Trust, University Hospitals Bristol

Background
Procalcitonin is a biochemical marker which is raised in bacterial infections. It has been used to assist in determining whether or not a patient will benefit from antibiotic therapy. Within the context of a clinical trial of antibiotic therapy, we wished to examine the correlation between clinical observations, blood tests and local measurements of skin damage, with serum procalcitonin levels.

Methods
This study used data collected as part of a clinical trial of antibiotic therapy for cellulitis (clindamycin for cellulitis, NCT01876628). A subset of the patients recruited into the trial had procalcitonin levels measured at each visit. Procalcitonin levels were statistically correlated with an array of clinical and laboratory measurements. We then selected the variables most strongly correlated with procalcitonin and evaluated the predictive value of the baseline procalcitonin on the primary trial outcome; improvement at the Day 5 follow up and return to normal activities at the three follow up points.

Results
136 patients (109 trial and 27 non-trial patients) with 139 baseline sets of data (111 trial and 28 non-trial patients) provided 314 procalcitonin values which were correlated with 21 variables. The strongest correlations (Pearson correlation coefficient of >0.5) with procalcitonin were the total affected skin area (0.537), C-reactive protein (0.574) and neutrophil:lymphocyte ratio (0.567). ROC curves demonstrated poor sensitivity and specificity of procalcitonin in predicting primary outcome. Patients with impaired renal function were more likely to have high procalcitonin levels.

Summary
- The neutrophil:lymphocyte ratio was the most strongly correlated with procalcitonin.
- Procalcitonin is a poor predictor of improvement at Day 5 and the return to normal activities at any follow up point.
- We cannot recommend that procalcitonin be used to differentiate cellulitis from other skin disorders which may appear similar to cellulitis.

CONCLUSIONS
Procalcitonin is of little value in the diagnosis or management of cellulitis: baseline levels are generally low, levels may be confounded by impaired renal function and are a poor predictor of improvement of cellulitis.

Figure 1

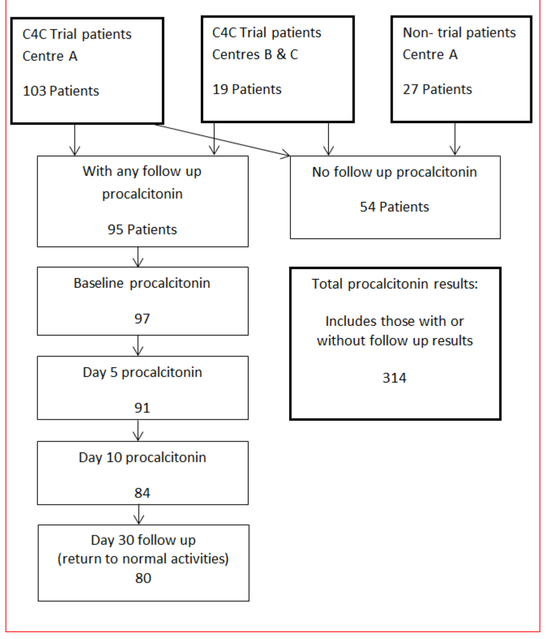


Table 1.
Correlation between the logarithm of serum procalcitonin and other measurements

Variable	Pearson Correlation	P value
Total affected skin area as a percentage of body surface area	**0.537**	0.000
Temperature (°C)	0.321	0.000
Pulse (per minute)	0.090	0.112
Respiratory rate (per minute)	0.096	0.106
Systolic blood pressure (mm Hg)	-0.102	0.075
Diastolic blood pressure (mm Hg)	-00.23	0.000
Difference between the circumference of the affected limb and the unaffected limb (cm)	0.395	0.000
Difference between the surface temperature of the affected limb and the unaffected limb (°C)	0.294	0.000
Pain score (visual analogue scale)	0.150	0.011
Neutrophils (10^9/L) (logarithm)	0.456	0.000
Lymphocytes (10^9/L) (logarithm)	-0.410	0.000
Haemoglobin (g/L) (logarithm)	-0.317	0.000
Platelets (10^9/L) (logarithm)	-0.238	0.000
Urea (mmol/L) (logarithm)	0.267	0.000
Creatinine (µmol/L) (logarithm)	0.289	0.000
Albumin (mg/L) (logarithm)	-0.375	0.000
C-reactive protein (mg/L) (logarithm)	**0.574**	0.000
Alkaline phosphatase (IU/L) (logarithm)	0.055	0.331
Alanine transferase (IU/L) (logarithm)	0.153	0.007
Neutrophil:Lymphocyte ratio (logarithm)	**0.567***	0.000
SIRS score at Baseline (111 values)	0.267	0.005

The size of the correlation coefficient is the degree of correlation between procalcitonin and a variable; the p value gives the degree of statistical likelihood that this correlation is true.
*95% CI 0.486, 0.638

Figure 2.
Primary outcome and ROC curves of neutrophil:lymphocyte ratio, procalcitonin, total affected area and C-reactive protein
A ROC curve with high sensitivity and high specificity would have a large area under the curve (AUC) and the optimum value would be close to the upper left corner of the chart.

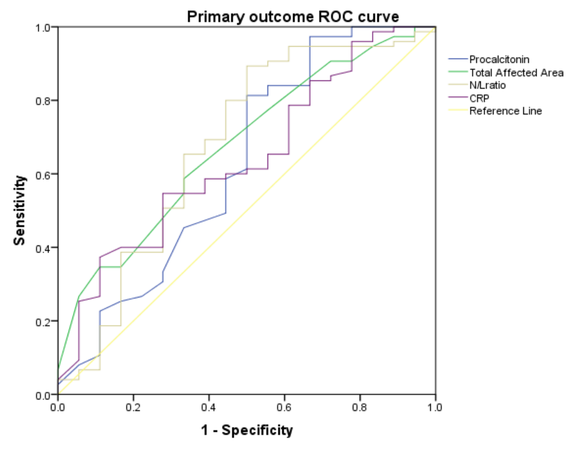


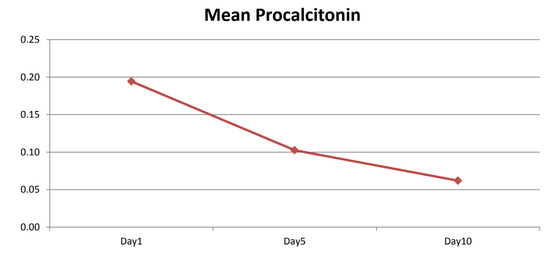
Table 2.
Primary outcome AUCs

Test Result Variables Natural logarithm of	Area under curve	Standard Error*	Asymptotic Significance**	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Total affected area	.676	.068	.021	.542	.810
N/L ratio	.678	.080	.020	.520	.835
CRP	.640	.071	.066	.500	.780
Procalcitonin	.629	.083	.092	.465	.792

*Under the nonparametric assumption, **Null hypothesis: true area = 0.5

Normal activities ROC curves
ROC curves were generated of procalcitonin levels with the patient being back to normal activities at three follow up points; AUCs were for 0.714 Day 5, 0.609 for Day 10 and 0.357 for Day 30.

Mean Procalcitonin



Values at baseline (Day1)
65% of patients had levels below 0.25µg/L at baseline

Renal function
- The arithmetic mean procalcitonin of those patients with serum creatinine levels of ≥100µmol/L was 0.25µg/L compared to 0.10 µg/L for those with creatinine of <100µmol/L.
- The mean creatinine of those patients with procalcitonin levels of ≥1µg/L was 100µmol/L compared to 77µmol/L for those with procalcitonin of < 1µg/L.
- Of the five patients with procalcitonin levels greater than 10µg/L the mean creatinine was 157µmol/L

STRENGTHS AND LIMITATIONS OF THIS STUDY
- This study uses a wide range of data from a controlled clinical trial
- The study allowed follow up over a 10 day period
- There was no control group with other limb skin or soft tissue disorders

ClinicalTrials.gov Identifier: NCT01876628

We would particularly like to thank the coordinating research nurses Chiaki Shioi and Louise Wright, and our trial administrator Lucy Dixon.

Adjunctive clindamycin for cellulitis: clinical trial comparing flucloxacillin with or without clindamycin for the treatment of limb cellulitis

Richard Brindle, Martin Williams, Paul Davies, Tim Harris, Heather Jarman, Alastair Hay, Peter Featherstone
University of Bristol, Public Health England, University Hospitals Bristol, Royal London Hospital, St George's Hospital, Portsmouth Hospitals

OBJECTIVE
Compare flucloxacillin with clindamycin to flucloxacillin alone for the treatment of limb cellulitis.

DESIGN
Parallel, double-blinded, randomised controlled trial.

SETTING
ED attendances and family physician referrals within 20 hospitals in England.

INTERVENTIONS
Flucloxacillin, minimum of 500mg four times per day for five days, with clindamycin 300mg four times per day for two days given orally versus flucloxacillin given alone.

MAIN OUTCOME MEASURES
Primary outcome was improvement at Day 5. This was defined as being afebrile with either a reduction in affected skin surface temperature or a reduction in the circumference of the affected area.

Secondary outcomes included resolution of systemic features, resolution of inflammatory markers, recovery of renal function, reduction in the affected area, decrease in pain, return to work or normal activities and the absence of increased side-effects.

RESULTS
- 410 patients were included in the trial.
- No significant difference was seen in improvement at Day 5 for flucloxacillin with clindamycin (136/156, 87%) versus flucloxacillin alone (140/172, 81%) – OR 1.55 (95% CI 0.81 to 3.01) p=0.174.
- **There was a significant difference in the number of patients with diarrhoea** at Day 5 in the flucloxacillin with clindamycin allocation (34/160, 22%) versus flucloxacillin alone (16/176, 9%) – OR 2.7 (95% CI 1.41 to 5.07), p=0.002.
- **There was no clinically significant difference in any secondary outcome measures.**

CONCLUSIONS
The addition of a short course of clindamycin to flucloxacillin early on in limb cellulitis does not improve outcome.
The addition of clindamycin doubles the likelihood of diarrhea within the first few days.

Figure. C4C CONSORT diagram

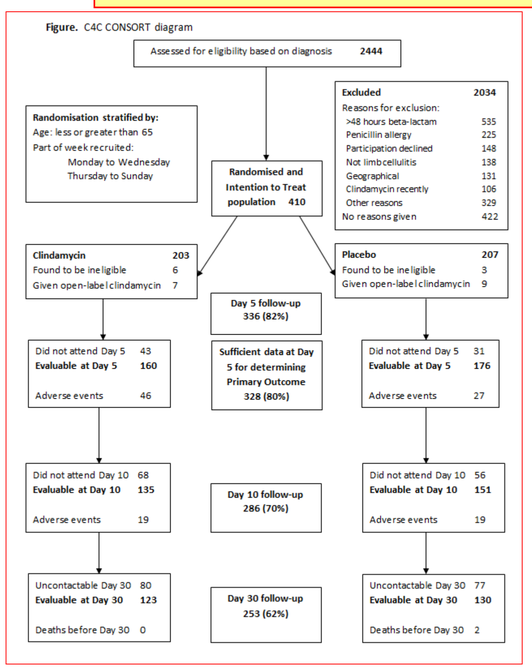


Table 1. Baseline characteristics of the randomised patients. Figures are numbers of patients (percentage) unless otherwise stated.

	Clindamycin (n=203)	Placebo (n=207)
Mean (SD) age in years	47.7 (18.4)	50.5 (16.9)
Leg affected	150 (74)	149 (72)
Duration of local features before starting study drug (days); Median (IQR)	2.1 (2.1)	2.0 (2.1)
Duration of preceding antibiotics before starting study drug (hours); Median (IQR)	1.9 (19.0)	6.5 (23.5)
Affected skin area as percentage of body surface area; Median and IQR	4 (4)	4 (6)
Difference in circumference between affected and unaffected limb (cm) ; Mean (SD)	2.5 (2.1)	2.9 (2.1)
Difference in surface temperature between affected and unaffected limb (°C) ; Mean (SD)	2.5 (1.9)	2.7 (1.6)
Neutrophil (X 10^9/L) ; Median (IQR)	6.3 (4.6)	7.0 (4.9)
Urea (mmol/L) ; Median (IQR)	5.0 (2.1)	4.9 (2.1)
C-reactive protein (mg/L) ; Median (IQR)	23 (80)	54 (119)
Pain score (VAS) ; Median (IQR)	5 (4)	5 (4)
SIRS score ≥1*	83/200 (42)	96/207 (46)

Not every patient had every characteristic recorded
IQR = Interquartile range; SD = Standard deviation
*SIRS criteria: 1 point each for temperature <36°C or >38°C, pulse >90, respiratory rate >20, WBC <4 or >12 X10^9/L
1% of total body skin area is approximately 170 cm^2; 10% of total body skin area is approximately equal to the area of one arm or half the area of a leg.

Table 2. Primary outcome. Figures are numbers of patients (percentage)

	Clindamycin (n=203)	Placebo (n=207)	
Insufficient Day 5 data*	47	35	
Not-improved	20	32	
Improved, as a proportion of those evaluable	136/156 (87)	140/172 (81)	OR 1.55 (95% CI: 0.81, 3.01) P=0.17
Improved, as a proportion of the randomised population	136/203 (67)	140/207 (68)	OR 0.97 (95% CI: 0.63, 1.50) P=0.92

OR=Odds ratio
*Either did not attend follow-up or were missing data.

Table 3. Secondary outcomes. Figures are values at each time-point (means or medians)

	Time point	Clindamycin	Placebo	P value
Affected skin area as percentage of body surface area; Median	Baseline	4	5	
	Day 5	2	2	0.28
	Day 10	1	1	0.67
Difference in circumference between affected and unaffected limb (cm) ; Mean	Baseline	2.67	2.84	
	Day 5	2.04	2.18	0.74
	Day 10	1.42	1.77	0.90
Difference in surface temperature between affected and unaffected limb (°C) ; Mean	Baseline	2.49	2.67	
	Day 5	1.15	1.57	0.24
	Day 10	0.87	1.13	0.65
Neutrophil (X 109/L) ; Median	Baseline	5.97	6.95	
	Day 5	4.24	4.43	0.95
	Day 10	4.18	4.32	0.86
Urea (mmol/L) ; Median	Baseline	5.0	4.9	
	Day 5	4.8	5.0	0.09
	Day 10	4.9	5.2	0.37
C-reactive protein (mg/L) ; Median	Baseline	22	57	
	Day 5	10	16	0.43
	Day 10	5	6	0.20
Pain score (VAS) ; Median	Baseline	4.5	5	
	Day 5	2	2	0.30*
	Day 10	0	1	0.61

Table 4. Adverse events or reactions. Figures are numbers of patients with an adverse reaction or event (percentage)

	Clindamycin	Placebo	P value
Reported at Day 5	n=160	n=176	
Rash	3 (1.9)	8 (4.6)	0.223
Diarrhoea	34 (21.5)	16 (9.3)	0.002
Any adverse event (including rash and diarrhea)*	46 (28.9)	27 (15.6)	0.004
Reported at Day 10	n=135	n=151	
Rash	2 (1.5)	10 (6.7)	0.039
Diarrhea	17 (12.8)	8 (5.3)	0.035
Any adverse event (including rash and diarrhoea)*	19 (14.1)	19(12.6)	0.731

*Other events were: admission to hospital, nausea or vomiting, feeling light-headed or dizzy, lip swelling.
A few patients on both follow up days had missing data.

STRENGTHS AND LIMITATIONS OF THIS STUDY
- This was a double-blind randomised multi-centre study and the first to examine the effect of adjunctive clindamycin with beta-lactam therapy for cellulitis.
- Patients were recruited from general practice, emergency department patients and inpatients and are thus a representative population.
- The study lost 18% of the patients by the first follow-up visit but the characteristics of these patients was similar in both drug allocations.

ClinicalTrials.gov Identifier: NCT01876628

We would particularly like to thank the coordinating research nurses Chiaki Shioi and Louise Wright, and our trial administrator Lucy Dixon.